Chapter 3

RAAS Blockade as First-Line Antihypertensive Therapy among People with CKD

Panagiotis I. Georgianos, Elias V. Balaskas and Pantelis E. Zebekakis

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Abstract

Hypertension among people with chronic kidney disease is highly prevalent and remains often poorly controlled. To adequately control blood pressure (BP), a combination antihypertensive drug therapy is often required. The choice of the appropriate antihypertensive regimen should be individualized according to the patient clinical characteristics, the severity of chronic kidney disease (CKD), the levels at which BP should be targeted and the presence or absence of proteinuria. In proteinuric CKD, solid evidence from large-scaled randomized trials suggest that agents blocking the renin-angiotensin-aldosterone system (RAAS) should be the antihypertensive therapy of first choice, given their superiority over the other antihypertensive drug classes in reducing proteinuria and delaying nephropathy progression to end-stage-renal-disease (ESRD). In contrast, inhibition of the RAAS is shown to have no additional benefits towards renoprotection in people with non-proteinuric CKD. Combined RAAS blockade as an alternative approach to gain additive reduction in proteinuria and greater retardation of renal function decline is shown to be associated with increased risk of hypotension, serious hyperkalemia and acute kidney injury. In this chapter, we discuss the role of RAAS blockade as first-line antihypertensive therapy among people with proteinuric and non-proteinuric nephropathy, providing an overview of the evidence derived from large-scaled renal outcome trials.

Keywords: hypertension, chronic kidney disease, proteinuria, RAAS blockade, randomized controlled trials

1. Introduction

Hypertension in people with chronic kidney disease (CKD) is very common, often difficult to control and represents an independent predictor of kidney injury progression to end-stage-renal-disease (ESRD) requiring dialysis [1, 2]. Apart from achieving an adequate blood pressure (BP) control as a tool to delay nephropathy progression, the choice of the appropriate antihypertensive regimen may be another factor determining the long-term renal prognosis in people with CKD. In this regard, agents blocking the renin-angiotensin-aldosterone system (RAAS) are considered as the antihypertensive therapy of first choice in people with diabetic or nondiabetic proteinuric CKD on the basis of large-scaled outcome trials showing that these agents are superior to the other antihypertensive drug classes in retarding kidney injury progression over time [3, 4]. In contrast, RAAS blockade in people with non-proteinuric CKD is shown to confer no additional benefits toward renoprotection [4]. Furthermore, the promise that the use of combined RAAS blockade may offer additive anti-proteinuric and renoprotective effects relative to monotherapy is shown to be counteracted by an excess risk of serious hyperkalemia and acute kidney injury [5, 6].

In this chapter, we discuss the use of RAAS blockade for renoprotection in people with proteinuric and non-proteinuric CKD, summarizing the currently available evidence from large-scaled outcome trials in nephrology. We conclude with clinical practice recommendations for the choice of the appropriate antihypertensive regimen in people with CKD and provide directions for future research in this important area.

2. RAAS blockade in patients with proteinuric CKD

Accumulated evidence from large-scaled randomized controlled trials (RCTs) support the notion that inhibition of the RAAS among people with overt diabetic nephropathy confers benefits towards slower progression of kidney injury to ESRD [4]. In the Collaborate Study Group trial, 409 patients with insulin-dependent type 1 diabetes and overt nephropathy (proteinuria >500 mg/day and serum creatinine <2.5 mg/dl) were randomly assigned to receive therapy with the angiotensin-converting enzyme (ACE) inhibitor captopril or placebo for a mean follow-up of 3 years [7]. Compared with placebo, captopril treatment produced a 30% reduction in the level of proteinuria and decreased by 50% the risk of reaching the combined renal endpoint of all-cause death and need for dialysis or renal transplantation [95% confidence interval (CI) 18–70%, $p < 0.01$] [7]. The renoprotective effect of RAAS blockade among people with type 2 diabetes and overt nephropathy is supported by two landmark RCTs, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) [8] and Irbesartan Diabetic Nephropathy Trial (IDNT) [9]. The RENAAL trial enrolled 1513 patients with overt diabetic nephropathy aiming to compare the effect of the angiotensin receptor blocker (ARB) losartan (50–100 mg daily) versus placebo, both administered on top of conventional antihypertensive drug therapy, on a composite renal endpoint of doubling of serum creatinine, ESRD or death [8]. Over a mean follow-up of 3.4 years, losartan reduced by

25% the risk of doubling of serum creatinine (P = 0.006) and by 28% the risk of ESRD requiring dialysis relative to placebo (P = 0.002), but had no impact on mortality [8]. In the IDNT trial, 1715 hypertensive patients with overt diabetic nephropathy were randomized to receive irbesartan (300 mg daily), amlodipine (10 mg daily) or placebo for a mean follow-up of 2.6 years. The level of proteinuria was reduced by 33% in the irbesartan group versus 6% in the amlodipine and 10% in the placebo groups [9]. Compared with placebo, ARB treatment decreased by 20% the occurrence of the combined renal endpoint of doubling of serum creatinine, ESRD or death [relative risk (RR): 0.80; 95% CI: 0.66–0.97]; ARB therapy was also superior to the calcium channel blocker (CCB) amlodipine in improving renal outcomes (RR: 0.77; 95% CI: 0.63–0.93 for the combined renal endpoint) [9].

The renoprotective properties of ACE inhibitors and/or ARBs among patients with diabetic nephropathy are also supported by carefully conducted meta-analyses of RCTs. An earlier meta-analysis by Strippoli et al. [10] showed that compared with placebo, ACE inhibitor use was associated with a trend towards greater reduction in the risk of doubling of serum creatinine (RR: 0.60; 95% CI: 0.34–1.05) and incident ESRD (RR: 0.64; 95% CI: 0.40–1.03). ACE inhibitor use was associated with 55% reduced risk of progression from micro- to macroalbuminuria (RR: 0.45; 95% CI: 0.28–0.71) and 3.42-fold higher rate of regression from micro- to normoalbuminuria among patients with diabetic CKD (RR: 3.42; 95% CI: 1.95–5.99) [10]. Similarly to ACE inhibitors, the combined analysis of RCTs comparing the effect of ARBs versus placebo on nephropathy progression associated the use of ARBs with reduced risk of doubling of serum creatinine (RR: 0.78; 95% CI: 0.67–0.91) and ESRD incidence (RR: 0.79; 95% CI: 0.67–0.93) [10]. The favorable effect of RAAS blockade on nephropathy progression was confirmed in an updated meta-analysis of 24 RCTs showing that compared with placebo, ACE inhibitors reduced by 30% the risk of incident ESRD (RR: 0.70; 95% CI: 0.46–1.05) and by 29% the risk of doubling of serum creatinine (RR: 0.71; 95% CI: 0.56–0.91); ARB use was associated with 22% lower risk of ESRD incidence (RR: 0.78; 95% CI: 0.67–0.91) and 21% lower risk of doubling of serum creatinine (RR: 0.79; 95% CI: 0.68–0.91) [11].

In accordance with the renoprotective action of RAAS blockade among people with diabetic kidney disease, a growing body of evidence supports the notion that ACE inhibitors and ARBs are similarly effective in delaying kidney injury progression in patients with other types of proteinuric nephropathy. In the REIN-2 study (Ramipril-Efficacy-In-Nephropathy-2), 352 nondiabetic patients with CKD and proteinuria of at least 1 g/day were randomized to receive double-blind therapy with ramipril (5 mg daily) or placebo in addition to conventional antihypertensive therapy targeted at achieving a diastolic BP goal of <90 mmHg [12]. The rate of estimated glomerular filtration rate (eGFR) decline, which was the primary trial endpoint, was significantly slower over time in ramipril-treated patients than in placebo-treated patients (0.53 vs. 0.83 ml/min/1.73 m^2, P = 0.03). The proportional reduction in the level of proteinuria among ramipril-treated patients was inversely associated with the rate of eGFR decline and was an independent predictor of the risk of doubling of serum creatinine and incident ESRD during follow-up [12]. In the African American Study of Kidney Disease (AASK), 1094 African-American patients with hypertensive CKD (mean baseline eGFR: 45.6 ml/min/1.73 m^2; mean urinary protein excretion 0.6 g/day) were randomized to achieve goal mean arterial pressure

102–107 mmHg or ≤92 mmHg and to initial BP-lowering treatment with metoprolol (2.5–10 mg daily), ramipril (2.5–10 mg daily) or amlodipine (5–10 mg daily) in a 3 × 2 factorial design [13]. Compared with metoprolol and amlodipine groups, administration of the ACE inhibitor ramipril was associated with 22 and 38% reduction in the risk of reaching the composite renal outcome of decrease from baseline in eGFR by 50% or greater, incident ESRD, or death, respectively [13]. In a subsequent analysis of 224 patients with advanced stage nondiabetic CKD (baseline serum creatinine range: 3.1–5.0 mg/dl and mean proteinuria 1.6 g/day), Hou et al. [14] compared the effect of benazepril (20 mg daily) versus placebo on top of conventional antihypertensive therapy on a composite renal endpoint of doubling of serum creatinine, ESRD or death. Over a mean follow-up of 3.4 years, the risk of reaching the above combined endpoint was by 43% lower in the ACE inhibitor group than in the placebo group. Additional benefits of the ACE inhibitor therapy were an associated 52% reduction in the level of proteinuria along with a 23% slower rate of eGFR decline [14]. Additional support to the renoprotective action of ACE inhibitors is provided by an earlier meta-analysis of 11 RCTs conducted by Jafar et al. [15]. In this analysis, after adjustment for patient and trial characteristics at baseline and changes in BP and proteinuria levels during follow-up, the use of an ACE inhibitor-based antihypertensive regimen was associated with 31% greater reduction in the risk of developing ESRD (RR: 0.69; 95% CI: 0.51–0.94) and 30% decrease in the risk of doubling of serum creatinine or ESRD (RR: 0.70; 95% CI: 0.55–0.88) in comparison with antihypertensive regimens non-including ACE inhibitors [15].

Post hoc analyses of the aforementioned RCTs provided evidence that the higher the level of proteinuria at baseline the higher was the risk of nephropathy progression to ESRD [16–18]. Most importantly, achievement of an early regression of proteinuria under RAAS blockade (i.e., in the first 6 months after drug initiation) was shown to be associated with reduced long-term risk of doubling of serum creatinine, ESRD incidence or death [16–18]. The notion that drug-induced reduction in proteinuria culminates in subsequent improvement in renal outcomes is further supported by a recent meta-regression analysis of 21 RCTs involving a total of 78,342 patients and 4843 incident ESRD events [19]. The placebo-adjusted treatment effect on proteinuria significantly correlated with the treatment effect on ESRD incidence, since each 30% of drug-induced reduction in the level of proteinuria was associated with a 23.7% reduced risk of subsequent kidney injury progression to ESRD (95% CI: 11.4–34.2%, P = 0.001) [19]. Taken together, the above data support the notion that regression of proteinuria is a major target of therapy in order to delay nephropathy progression in patients with both diabetic and nondiabetic proteinuric CKD.

3. RAAS blockade in patients with non-proteinuric nephropathy

Unlike the well-documented benefits of RAAS inhibition among patients with proteinuric CKD, either diabetic or nondiabetic, it remains largely uncertain whether ACE inhibitors and/or ARBs carry with them a similarly beneficial effect in slowing nephropathy progression among patients with non-proteinuric CKD. This issue is of major clinical relevance, given the

fact that high albuminuria or overt proteinuria is present only in a small proportion of the overall CKD population, whereas the vast majority of people with CKD have normoalbuminuria or microalbuminuria [20–22]. For example, the prevalence of CKD among individuals with age >70 years is estimated to be around 40%, but proteinuria is present in approximately 5% of elderly CKD patients. The prevalence of CKD in the general hypertensive population is estimated to be around 15% (ranging up to 30% in those aged >65 years), but again <5% of hypertensives with CKD exhibit macroalbuminuria [20–22]. Regardless of its high clinical significance, there are no data from properly designed RCTs to evaluate the effect of RAAS blockade on "hard" renal outcomes in patients with non-proteinuric nephropathy. The currently available evidence on this issue is derived mainly from secondary analyses of major cardiovascular outcome trials.

The first trial to evaluate the issue of renoprotection with RAAS blockade in patients with non-proteinuric CKD was the appropriate blood pressure control in diabetes (ABCD) [23]. This trial enrolled 470 patients with hypertension and type 2 diabetes, of whom only 18% had overt nephropathy (i.e., macro-albuminuria and/or impaired renal function). Study participants were randomly assigned to nisoldipine or enalapril and intensive or moderate BP control in a 2 × 2 factorial design. The rate of change in creatinine clearance over a 5.3-year-long follow-up was no different between the enalapril and nisoldipine groups [23]. However, the most definite renal endpoint of incident ESRD requiring dialysis was not evaluated in the ABCD study; accordingly, this study cannot provide direct evidence on whether the enalapril-induced reduction in the level of proteinuria would be translated into a slower kidney injury progression in a population predominantly without overt diabetic nephropathy.

The absence of additive renal benefits under RAAS blockade among patients with non-proteinuric CKD is further supported by a secondary analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [24]. This trial enrolled 33,000 hypertensive patients with an age of 55 years or higher and at least one additional risk factor for ischemic heart disease. The exclusion criteria included a serum creatinine >2 mg/dl and therapy with an ACE inhibitor for underlying CKD prior to the study enrolment. Although actual measurements of the level of albuminuria were not included in the protocol procedures, it is reasonable to hypothesize that participants in the ALLHAT trial were mainly hypertensives without high albuminuria. Incidence of ESRD or >50% reduction in eGFR during follow-up, which was the primary composite renal endpoint of this secondary analysis, was no different between amlodipine-treated and chlorothalidone-treated participants (RR: 1.12; 95% CI: 0.89–1.40) [24]. Similarly, the ACE inhibitor lisinopril was not superior to chlorothalidone in reducing the incidence of ESRD or >50% reduction in eGFR (RR: 1.11; 95% CI: 0.89–1.38). When the analysis was stratified according to the level of eGFR at baseline, lisinopril therapy was not associated with a reduced incidence of ESRD relative to chlorthalidone in the subgroups of patients with baseline eGFR of 60–89 ml/min/1.73 m^2 (RR: 1.34; 95% CI: 0.87–2.06) as well as in those with baseline eGFR <60 ml/min/1.73 m^2 (RR: 0.98; 95% CI: 0.73–1.31) [24]. In addition, at 4 years of follow-up, eGFR was 3–6 ml/min/1.73 m^2 higher in amlodipine-treated than in chlorothalidone-treated participants, depending on baseline eGFR stratum. The results of the ALLHAT come in sharp contrast to the clear renoprotective effect of RAAS blockade seen in

trials involving patients with overt diabetic nephropathy (i.e., the aforementioned IDNT). This discrepancy is possibly explained by the different characteristics of patients included in the ALLHAT trial. It is reasonable to hypothesize that the absence of renoprotection with lisinopril therapy and the better retardation of eGFR over time in amlodipine-treated participants was possibly due to the fact that patients enrolled in the ALLHAT were more likely to suffer from ischemic rather than proteinuric nephropathy.

Additional support to for the notion that RAAS blockade is not associated with greater renoprotection in comparison to other antihypertensive drug classes among patients with non-proteinuric CKD was provided by the renal outcomes of Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH trial) [25]. ACCOMPLISH randomized 11,506 hypertensive patients at high cardiovascular risk to receive combination therapy with benazepril plus amlodipine or benazepril plus hydrochlorothiazide. The clear benefit of the benazepril/amlodipine combination in reducing cardiovascular morbidity and mortality led to the premature termination of the ACCOMPLISH trial. Similarly to the cardiovascular benefit, the analysis of the renal outcomes showed the benazepril/amlodipine combination was associated with a slower annual rate of eGFR decline in comparison with the benazepril/hydrochlorothiazide combination (−0.88 vs. −4.22 mL/min/1.73 m^2 per year), despite the fact that proteinuria was less effectively reduced in patients receiving the ACE inhibitor/CCB combination [25]. Most importantly, compared with the benazepril/hydrochlorothiazide combination, the ACE inhibitor/CCB combination reduced by 48% the incidence of composite renal endpoint of doubling of serum creatinine or ESRD requiring dialysis [hazard ratio (HR): 0.48; 95% CI: 0.41–0.65] and by 27% the risk of doubling serum creatinine, need for dialysis or death (HR: 0.73; 95% CI: 0.64–0.84) [25]. The superiority of the ACE inhibitor/CCB combination in delaying the kidney injury progression despite its less pronounced anti-proteinuric effect could be once again explained by the characteristics of the patients participating in the ACCOMPLISH trial. ACCOMPLISH participants were predominantly older than 65 years, had preserved renal function at baseline (mean baseline eGFR of 79 mL/min/1.73 m^2) and macro-albuminuria was present in only 5% of study participants. Accordingly, it seems reasonable that patients with such clinical characteristics are less likely to benefit from a therapeutic strategy targeting on proteinuria remission; in contrast, these patients are prone to acute kidney injury due to dehydration and hypotension.

4. Dual RAAS blockade

Combining an ACE inhibitor with an ARB was suggested as an additional therapeutic tool aiming to enhance the anti-proteinuric effect of single RAAS blockade, generating the hypothesis that this manoeuvre would be translated into a more effective delay in nephropathy progression [4]. Although small RCTs showed an additive effect on proteinuria with combined RAAS blockade relative to mono-therapy [26, 27], large-scaled RCTs evaluating “hard” renal endpoints showed that the use of ACE inhibitors and ARBs in combination is associated with

increased incidence of hypotension, hyperkalemia and acute kidney injury requiring support with dialysis [5, 6, 28, 29].

In the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), 25,620 patients with established cardiovascular disease or high-risk diabetes were randomly assigned to receive double-blind therapy with ramipril (10 mg daily), telmisartan (80 mg daily) or both drugs in combination for a median follow-up of 56 months [6]. Compared with mono-therapy, dual RAAS blockade was associated with a 24% higher risk of dialysis or doubling of serum creatinine [hazard ratio (HR): 1.24; 95% CI: 1.01–1.51]. Excess need for dialysis in the combination group was predominantly due to episodes of acute kidney injury, possibly attributable to the higher incidence of hypotension and hyperkalemia among patients treated aggressively with dual RAAS blockade [6]. In the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (ALTITUDE trial), 8561 type 2 diabetic patients with CKD, cardiovascular disease or both were randomized to receive the direct renin inhibitor aliskiren (300 mg daily) or placebo on top of background therapy with an ACE inhibitor or ARB [30]. The ALTITUDE trial was prematurely terminated due to excess risk of hypotension (12.1 vs. 8.3%, $p < 0.001$) and hyperkalemia (11.2 vs. 7.2%, $p < 0.001$) in the combination group [30].

Another large-scaled RCT investigating the potential additive renoprotective effect of dual RAAS blockade was stopped early owing to safety concerns. This was the VA-NEPHRON-D (Veteran's Administration Nephron-Diabetes Trial), in which 1448 type 2 diabetic patients with overt nephropathy (i.e., urinary albumin to creatinine ratio >300 mg/g and eGFR ranging from 30 to 89.9 ml/min/1.73 m^2) already treated with the ARB losartan (100 mg daily) were randomized to receive add-on therapy with the ACE inhibitor lisinopril (10–40 mg daily) or matching placebo [5]. Once again, compared with monotherapy, combination therapy was associated with 70% excess risk of acute kidney injury (HR: 1.70; 95% CI: 1.3–2.2) and 2.8-fold elevated risk of serious hyperkalemia (HR: 2.8; 95% CI: 1.8–4.3). At the time of this interim analysis, a trend toward a benefit of dual RAAS blockade with respect to the secondary trial endpoint of first occurrence of a decline in eGFR ≥30 ml/min/1.73 m^2 or ESRD was noted (HR: 0.78; 95% CI: 0.58–1.05, P = 0.10); however, this tendency toward slower renal function decline was not sustained over time [5]. The above data suggest that even in patients with typical diabetic nephropathy and macro-albuminuria, any potential long-term renoprotective action of combined RAAS inhibition is counteracted by excess risk of serious adverse events, including hypotension, hyperkalemia and acute renal injury requiring acute dialysis.

Addition of mineralocorticoid-receptor-antagonists (MRAs) might provide renal benefits in patients with proteinuric CKD that potentially extend over and above the renoprotection provided by ACE inhibitors and/or ARBs alone [31, 32]. Add-on MRA therapy was proposed as an alternative option on the basis of data suggesting that conventional therapy with ACE inhibitors and ARBs cannot produce sustained prolonged lowering of plasma aldosterone levels, the so-called aldosterone breakthrough phenomenon. An earlier meta-analysis of 11 RCTs (including 991 patients with proteinuric CKD) showed that compared with placebo, add-on MRA therapy on top of background treatment with ACE inhibitors or ARBs was associated with a significant additive reduction in proteinuria [weighted mean difference (WMD): −0.8 g/day; 95% CI: −1.27 to −0.33 g/day]. This anti-proteinuric effect, however, was not accompanied

by a slower decline in eGFR (WMD: −0.70 ml/min/1.73 m^2; 95% CI: −4.73 to 3.34 ml/min/1.73 m^2), whereas add-on MRA therapy was also associated with a significantly 3.06 times higher risk of developing hyperkalemia (pooled RR: 3.06; 95% CI: 1.26–7.41) [33]. A subsequent updated meta-analysis of 27 RCTs (including 1549 participants) confirmed in a larger frame of data that add-on MRA therapy offers an additive reduction in proteinuria [standardized mean difference (SMD): −0.61; 95% CI: −1.08 to −0.13], but MRA use aggravated the risk of hyperkalemia and gynecomastia [34]. In the albescence of properly designed RCTs evaluating the effect of add-on MRA therapy on nephropathy progression, the wide use of this therapeutic approach in people with proteinuric CKD is not recommended.

A newly introduced, selective, nonsteroidal MRA-named finerenone offers the opportunity for similarly effective anti-proteinuric action as compared with established steroidal MRAs (i.e., spironolactone and eplerenone), having also the advantage of causing less frequently clinically significant hyperkalemia [35]. The efficacy and safety of finerenone among patients with diabetic nephropathy was tested in the recent phase 2b ARTS-DN study (mineralocorticoid receptor antagonist tolerability study–diabetic nephropathy) [36], in which 821 diabetic patients with high or very high albuminuria already treated with an ACE inhibitor or an ARB were randomly assigned to double-blind therapy with finerenone (1.25 up to 20 mg once daily) or matching placebo for 3 months. Finerenone dose-dependently reduced albuminuria up to 33 and 38% in the 15 and 20 mg groups with only small increases in serum potassium (+0.17 ± 0.46 and +0.23 ± 0.37, respectively) [36]. The incidence of hyperkalemia was 4.1 and 2.6%, respectively, and not significantly different from placebo. These results suggest that finerenone may be an effective and safer approach for renoprotection in proteinuric CKD. Properly designed RCTs are warranted to fully elucidate the effect of finerenone on "hard" renal endpoints.

Recent RCTs have provided evidence that the novel oral potassium-binding resins patiromer and sodium zirconium cyclosilicate can effectively normalize elevated serum potassium and maintain in the long-term the potassium levels within the normal range in hyperkalemic patients with CKD already treated with RAAS blockers [37–39]. These emerging potassium-lowering therapies offer promise that the reduction in the risk of drug-induced hyperkalemia may facilitate the administration of RAAS blockade at adequate doses and enhance the cardiovascular and renal protection provided by these agents in people with proteinuric CKD [29].

5. Conclusion

Choice of the appropriate antihypertensive regimen in people with CKD should be individualized according to the patient clinical characteristics, with proteinuria being an important factor that needs to be taken into consideration. Among people with diabetic or nondiabetic proteinuric nephropathy, large-scaled outcome trials provided solid evidence that ACE inhibitors and/or ARBs reduce the level of proteinuria and this anti-proteinuric action is subsequently translated into slower nephropathy progression to ESRD requiring dialysis. In

contrast, there is no "hard" evidence to support the use of RAAS blockers for renoprotection among elderly patients with preserved or mildly impaired renal function as well as in those with non-proteinuric CKD. The use of ACE inhibitors and ARBs in combination as an approach to achieve additive renal benefits relative to monotherapy is contraindicated in light of evidence suggesting that dual RAAS blockade is associated with increased risk of hypotension, serious hyperkalemia and acute kidney injury. Novel potassium-lowering therapies are shown to effective compensate the hyperkalemia risk associated with RAAS blockade use in people with CKD, offering promise for more adequate therapy and greater renal and cardiovascular risk protection in the future.

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Author details

Panagiotis I. Georgianos, Elias V. Balaskas and Pantelis E. Zebekakis*

*Address all correspondence to: pzebeka@med.auth.gr

Section of Nephrology and Hypertension, 1st Department of Medicine, AHEPA Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

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