

# Inhibition of the Renin-Angiotensin System in Chronic Kidney Disease: A Critical Look to Single and Dual Blockade

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## Key Words

Chronic kidney disease · Hypertension · Proteinuria · Angiotensin-converting enzyme (ACE) inhibitors · Angiotensin II receptor blockers · Dual blockade

## Abstract

The clinical benefits of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) are well established in chronic kidney disease (CKD) patients with diabetic and non-diabetic nephropathies. But despite appearance, the magnitude of this effect has been questioned particularly in mild, proteinuric nephropathies. Given that the single agents can achieve only partial and not durable suppression of the renin-angiotensin system (RAS), it has been hypothesized that dual blockage with ACE inhibitors and ARBs would be most beneficial in the management of progressive CKD than either agent alone. Available evidence indicates significant anti-proteinuric effect, but long-term data in CKD patients are lacking. Recently, the findings of the ONTARGET trial even questioned the safety of this therapeutic approach. Given that preventing cardiovascular complications is extremely important in CKD and RAS inhibition may be useful in this setting, benefits of RAS blockade must be weighed against its possible adverse effects particularly in elderly patients.

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Given that elevated blood pressure above established guidelines and proteinuria are probably the major factors contributing to the progression of chronic kidney disease (CKD), effective antihypertensive therapy is currently considered the single most important treatment in CKD patients. Given that the renin-angiotensin system (RAS) is a major contributor involved in the progression of renal diseases, and that its activation can promote intraglomerular and systemic hypertension, and thus contribute to hemodynamically-mediated renal injury, angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs) are considered the gold standard of treatment.

In this review, we will critically review the efficacy of these 2 classes of agents given alone or in combination and try to give an answer to a number of unanswered questions.

## Are the Benefits of ACE Inhibitors and Angiotensin II Receptor Blockers Well Established?

ACE inhibitors or ARBs significantly reduce proteinuria and the rate of loss of renal function in diabetic and non-diabetic CKD; this effect is greatest in patients with

substantial proteinuria at baseline [1–4]. Similarly, ARBs are effective in reducing the progression of type 2 diabetic nephropathy [5, 6]. However, single trials have been somehow criticised. In overt type 1 diabetic nephropathy, Lewis et al. [1] were the first to clearly demonstrate a lower risk of progression towards the doubling of serum creatinine or end-stage renal disease (ESRD) in patients receiving captopril compared to those receiving placebo. However, the control group had significantly higher proteinuria at baseline and an unexpected fast progression rate compared to the experimental one. The ACE Inhibition in Progressive Renal Insufficiency Study (AIPRI) tested the effect of benazepril in 583 patients with non-diabetic nephropathies and showed a relative risk reduction of nearly 50% of the doubling of serum creatinine or the need of dialysis in those receiving the ACE inhibitor [2]; even if the doubling of serum creatinine is quite predictive of subsequent ESRD, these findings were criticised because of a relative lack of hard end-points (only very few patients needed dialysis or died during the study). Also blood pressure control was substantially better in the ACE inhibitor group. Similarly, the Ramipril Efficacy in Nephropathy Study (REIN) tested the efficacy of ACE inhibition in chronic non-diabetic nephropathies [3]. However, the authors were able to demonstrate a significant effect of treatment on the rate of glomerular filtration rate (GFR) decline, which was the primary study end-point, only in patients with proteinuria in the nephrotic range. In this subgroup (n = 166) the randomisation code was broken after the second interim analyses; it is then possible that the findings were somehow flawed by the fact that nearly 30% of the patients were excluded from the analysis because of inadequate follow-up. In addition to this, another 35 subjects (30%) withdrew from the study because of adverse events or other reasons. In patients with proteinuria below 3 g/day, despite no difference in the progression rate between the 2 groups, those treated with ramipril had a significant lower risk of reaching ESRD. This inconsistency may be partially explained by the fact that the study was possibly underpowered. More recently, Hou et al. [7] confirmed the efficacy of benazepril in nearly 400 patients with CKD of different severity; the accuracy to the study has been questioned by data published in duplicate reporting different sample sizes (see editorial comment).

Altogether, these data support effectiveness of ACE inhibitor or ARB therapy in delaying CKD progression at least in proteinuric nephropathies.

### **Is It a Matter of RAS Inhibition or Is It Just Lowering Blood Pressure?**

In the majority of published trials, patients treated with ACE inhibitors or ARBs achieved lower blood pressure values than those in control groups and blood pressure values during 24 h were not recorded. However, renoprotective efficacy of RAS inhibition seems to be partially independent of blood pressure reduction, since the treatment effect remained significant in almost all of the multivariate models. Anyway, caution is always needed when interpreting ‘adjusted’ results. A biological effect such as reduction of risk associated with improved blood pressure control may not always translate into statistical certainty.

### **Do These Effects Apply to All CKD Patients?**

The magnitude of their efficacy has been questioned recently, particularly in patients with hypertensive kidney disease. Similarly, while the combination treatment with ACE inhibitors and ARBs may have additive renoprotective effects, this may not be true in patients with mild or no proteinuria, in whom it can be even deleterious on renal function.

This raises the question whether RAS inhibition can delay the progression of hypertensive kidney disease, which is the second cause of ESRD worldwide and is characterised by mild proteinuria in the majority of cases. This is of particular relevance in the elderly, in whom mild or no benefit of RAS inhibition should be balanced with a higher risk of deterioration of renal dysfunction secondary to treatment because of the high prevalence of atherosclerotic renal artery stenosis. Further complicating the scene, it is possible that responsiveness to RAS inhibition of hypertensive kidney disease may vary in different races. Indeed, the African American Study of Kidney Disease and Hypertension (AASK) study showed superiority of ramipril compared to amlodipine or metoprolol on the progression of hypertensive nephrosclerosis in 1,094 African Americans despite the fact that they had only mild proteinuria [8]. However, the progression rate of CKD seems to be very slow in subjects older than 65 years [9]. It is then possible that the follow-up of the majority of randomised trials testing the effect of RAS inhibition may be relatively inadequate to study hypertensive kidney disease at least in Caucasians.

Moreover, looking in more depth to the findings of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) [6] and the Irbesartan Diabetic Nephropathy Trial (IDNT) [5] studies, the reduction in the relative risk of reaching the combined primary endpoint of the doubling of serum creatinine, ESRD or death is quite modest (only 16% and 20% in the IDNT and RENAAL studies, respectively). This suggests that RAS inhibition may be less effective in type 2 compared to type 1 diabetes. One possible reason of this is that differing from type 1 diabetic nephropathy, type 2 diabetes kidney disease is a more heterogeneous condition and renal damage can be independent from diabetes or, when due to diabetes, may coexist with other nephropathies, such as hypertensive and ischemic kidney disease.

Despite the fact that the RAS contributes to hypertension and cyst growth in autosomal dominant polycystic kidney disease (ADPKD), it is still unclear whether ACE inhibitors are effective in this disease [10, 11]. However, the majority of the studies have been undertaken in relatively advanced stage of cyst growth. Moreover, ACE inhibitors alone may be insufficient in blocking completely the RAS system. The ongoing HALT-PKD study will test whether the combination of an ACE inhibitor and ARB will delay the progression of renal disease compared with ACE inhibitor alone in 1,020 subjects with early (GFR >60 ml/min) or more advanced (GFR 25–60 ml/min) ADPKD [12].

Another point which deserves attention is glomerulonephritis. In the majority of clinical trials testing ACE inhibitors and/or ARBs, single entities such as immunoglobulin A nephropathy, membranous glomerulonephritis or focal segmental glomerulosclerosis, have been grouped together, despite possible differences in responsiveness among single glomerulonephritis. However, it is unlikely that this gap in knowledge would be ever filled, since glomerulonephritis patients are relatively rare and not using RAS inhibition in proteinuric nephropathies would be considered unethical today.

Altogether, these considerations suggest that the renoprotective effect of RAS inhibition may not apply to all nephropathies.

### **Does RAS Inhibition Reduce the Number of Patients Starting Dialysis?**

According to the encouraging findings obtained by trials testing ACE inhibitors and ARBs in CKD, it has been suggested that the recent decrease in the number of

patients reaching ESRD may be partially due to the increasing administration of drugs blocking the RAS.

However, this interpretation of recent epidemiological data seems too optimistic. Indeed, looking in depth at the findings of the RENAAL and IDNT studies, a relatively high number of patients have to be treated to avoid 1 event (16 and 29 in the IDNT and RENAAL studies, respectively). Even if the findings of the 2 studies are highly concordant, the number of patients needed to treat is higher in the RENAAL than in the IDNT trial. Analysing the inclusion criteria and baseline characteristics, we can observe that the patients in the IDNT trial had higher proteinuria than those in the RENAAL trial. Thus, their kidneys were more likely to be deranged by the metabolic consequences of diabetes than by hypertension.

Even if it is likely that a RAS blockade slows down CKD progression in a number of patients, and thus may reduce the number of patients starting dialysis, epidemiological data about incident dialysis patients are influenced by so many other aspects that it makes it impossible to single out this peculiar aspect.

### **Are the Benefits of ACE Inhibitors and ARBs Confirmed by Meta-Analyses?**

A large meta-analysis evaluating the efficacy of ACE inhibitors in non-diabetic renal disease found that treatment effect was not significant in patients with proteinuria below 0.5 g/day [2]. Further doubts were raised in 2005 by another large meta-analysis showing the benefit to depend, to a large extent, on blood pressure reduction [13]. Even if both agents were proven significantly effective, only a small reduction was seen in the risk of ESRD in favour of either ACE inhibitors or ARBs (relative risk 0.87, confidence interval (CI) 0.75–0.99;  $p = 0.04$ ). In patients with diabetic nephropathy, no benefit was seen in comparative trials of ACE inhibitors or ARBs on ESRD (0.89, CI 0.74–1.07). These results are largely influenced (and their value reduced) by a single study, the ALLHAT trial [14], in which there was no evidence for a greater beneficial effect of ACE inhibitors in the CKD population. The peculiar aspect of this trial is that it is likely that the selected patient population with hypertensive kidney disease had only mild proteinuria (unfortunately not measured), possibly explaining why ACE inhibitors did not work.

Overall, data coming from meta-analyses are conflicting, probably because of the differences in study selection and the quality of some of the studies included.

### **Do ACE Inhibitors and ARBs Equally and Fully Suppress the RAS?**

Both agents act on selective pathways of the RAS system. This implies that none achieve complete blockade. Indeed, ACE inhibitors cannot block alternative pathways of ACE activation. For this reason the initial decrease in angiotensin II and aldosterone levels often gradually returns to pre-treatment level. This 'escape' may be of importance in explaining a modest reno-protective effect observed in some patients in the long-term.

The action of ARBs seems to be more lasting. However, their use causes an increase in angiotensin II levels because of an angiotensin II receptor 1 (AT1) blockade; the actions of angiotensin II on angiotensin II receptor 2 (AT2), which is not blocked by ARBs, are still partially unknown.

Head-to-head comparisons of the 2 classes of drugs are scanty [15, 16]. Barnett et al. [15] made a double-blind trial on 250 subjects with type 2 diabetes and early nephropathy who were randomly assigned to receive either telmisartan or enalapril. After 5 years, the rate of GFR decline was similar in the 2 groups, showing non-inferiority of telmisartan to enalapril. However, these findings do not necessarily apply to patients with more advanced nephropathy or non-diabetic CKD. Shoda et al. [16] studied 68 non-diabetic patients with CKD and proteinuria, showing again no difference among the 2 classes of drugs. Unfortunately, the value of these findings is limited by the fact that study treatment was quite heterogeneous in the 2 groups.

Recently, 2 arms of the Ongoing Telmisartan Alone in Combination with Ramipril Global Endpoint Trial (ONTARGET) compared the effect of ramipril and telmisartan monotherapy on cardiovascular mortality in 25,620 patients with vascular disease or high-risk diabetes [17]; a secondary analysis found non-inferiority of telmisartan to ramipril on the risk of reaching the primary renal outcome (a composite of dialysis, doubling of serum creatinine, and death) [18].

While keeping in mind the limitations of this study, these results give evidence of comparable renal effects of the 2 drug classes.

### **Is It a Class Effect or May Single Molecules Have Distinct Actions?**

All ACE inhibitors or ARBs molecules act in similar way and it is likely that all the molecules of a class share similar renoprotective effects. However, single molecules may have distinct properties that can add further advantage or conversely reduce effectiveness in blocking the RAS system; agents with a longer half-life are more likely to obtain a sustained effect lasting until the following administration. Moreover, some molecules have additional properties beyond RAS inhibition. Indeed, some ACE inhibitors have been found to increase uricosuria mildly by lowering the net reabsorption of uric acid in the proximal tubule [19]; telmisartan also has peroxisome proliferator-activated receptor-gamma-modulating activity [20].

In order to investigate this issue, very recently, Bakris et al. [21] published the findings of a large, double-blind, randomised study comparing telmisartan (a highly lipophilic agent with a long half-life) to losartan (with low lipophilicity and short half-life) in 860 patients with type 2 diabetes and overt nephropathy (urinary protein-to-creatinine ratio  $\geq 700$ ). After 52 weeks of follow-up, telmisartan was found superior to losartan in reducing proteinuria, despite a similar reduction in blood pressure. Given the relatively short follow up, no information is available on hard endpoints.

Conversely, Galle et al. [22] were unable to find any difference between telmisartan and valsartan on proteinuria in 855 hypertensive patients with type 2 diabetes and overt nephropathy.

Even if single molecules have distinct properties, in our opinion, it is unlikely that this translates into significant clinical differences among drugs of a single class.

### **Does Dual Blockade with ACE Inhibitors and ARBs Have Additive Renoprotective Effects?**

Given that single blockade with ACE inhibitors or ARBs can achieve only partial and not-durable suppression of the RAS system, it has been hypothesized that dual blockage with ACE inhibitors and ARBs would be most beneficial in the management of progressive CKD than either agent alone. The adding of an ARB reduces the effects of angiotensin II on AT1, which is escaped from ACE inhibition, whereas ACE inhibitors reduce the rise in angiotensin II secondary to the blockade of

AT1, reducing its partially unknown effects on AT2. Starting from these theoretical advantages, a number of studies, many of them of low methodological quality and/or sample size, tested the dual blockade in CKD patients.

### **Does Dual Blockade Reduce Proteinuria?**

The COOPERATE study found that combination treatment significantly reduces proteinuria compared with monotherapy in non-diabetic nephropathies [23]. These observations are in line with the results of a meta-analysis of 1,079 patients with or without diabetes and microalbuminuria or proteinuria; as with monotherapies, the treatment effect was influenced by the severity of baseline protein excretion [24]. The authors decided not to include the COOPERATE study because of serious implausible occurrences (in particular, an unusual balance in the distribution of 3 key variables at baseline and a high drop-out rate exceeding those expected in a population of relatively healthy and young CKD patients) [25].

Another meta-analysis restricted the search only to patients with primary glomerulonephritis and proteinuria ranging between 0.8 and 7.9 g/day [26]. The COOPERATE study was not included in this analysis either as it enrolled a mixed population of CKD patients [23]. In this particular setting, dual blockade reduced proteinuria more than ACE inhibitor or ARB monotherapy. Significant heterogeneity of the antiproteinuric effect was found among the studies, mainly due to differences in average proteinuria at baseline. Combination therapy invariably decreased blood pressure more than either monotherapy; this complicates the quantification of the anti-proteinuric effect, which may be partially due to the reduction of blood pressure.

Recently, the Irbesartan in the Management of Proteinuric Patients at High Risk for Vascular Events (IMPROVE) [27] study, which is a large randomised controlled trial, questioned the antiproteinuric effect of this therapeutic strategy. Four hundred and five patients at high cardiovascular risk, most with diabetic kidney disease, were randomised to receive either ramipril plus irbesartan or ramipril alone [27]. Despite a better blood pressure control in patients receiving the combination regimen, after 20 weeks of follow-up, the changes in the geometric mean of albumin excretion rate from baseline were similar in the 2 groups. Unfortunately, the study was underpowered to detect differences in the primary

endpoint because of unanticipated and substantial variability in albuminuria, particularly among the majority of participants who had microalbuminuria (70%) [28]. Patients with macroalbuminuria ( $\geq 200 \mu\text{g}/\text{min}$ ) tended to have a greater response to dual blockade, but the difference was not statistically significant. However, even in this subgroup, the albumin excretion rate was quite mild. This may be another explanation of the lack of additional anti-proteinuric effect of dual blockade in this study.

Altogether, our answer to this question is yes, dual blockade reduces proteinuria more than ACE inhibitor or ARB monotherapy.

### **Does Dual Blockade Reduce the Risk of Hard Endpoints?**

The majority of the studies testing dual blockade had inadequate follow-up for evaluating a hard endpoint, such as the need for dialysis or death. Some years ago, the COOPERATE study [23] showed that combination therapy significantly reduce the risk of the doubling of serum creatinine or ESRD compared with monotherapy. Unfortunately, despite adequate sample size and follow-up, its methodological quality has been seriously questioned [25].

More recently, the ONTARGET study compared the effect of ramipril and telmisartan monotherapy and their combination on cardiovascular mortality in 25,620 patients with vascular disease or high-risk diabetes [17]. Quite unexpectedly, in this precise population the primary renal outcome (dialysis, doubling of serum creatinine, and death) occurred more frequently in patients receiving dual blockade than either monotherapy (13.4%, 13.5%, 14.5% for telmisartan, ramipril and dual blockade, respectively) [18]. The same held true for the renal endpoints (doubling of serum creatinine and dialysis) [18]. When the 3 endpoints were considered separately, they did not reach statistical significance. These findings were associated with a much higher percentage of patients receiving dual blockade who discontinued study treatment because of hypotensive symptoms.

Overall, these results are of difficult interpretation, also considering that the majority of the patients had normal renal function at baseline and only less than one-fifth had microalbuminuria.

Altogether, available evidence does not support the notion that dual RAS blockade reduces the risk of hard endpoints.

### Is Dual Blockade Really Harmful?

First of all, it is important to remember that results of secondary analyses should always be interpreted with caution. In addition, it is true that previous long-term experience with dual blockade is quite small, with the exception of the COOPERATE trial [23]. However, today this therapeutic approach is widely used in everyday clinical practice and it does not appear so harmful on kidney function. Thus, it is more likely that dual blockade can worsen CKD in selected patients, as it was the case of those enrolled in the ONTARGET trial [17]. These patients were selected for having vascular disease or high-risk diabetes and had coronary artery disease in a high percentage. Considering that those receiving the combination therapy had more frequently hypotensive symptoms than those receiving monotherapy, it is possible that some of them suffered from unappreciated chronic heart failure; excessive hypotension may have caused the acute worsening of renal function. Indeed, the meta-analysis by Jafar et al. [4] showed clearly a 'J-curve' effect on renoprotection related to lower blood pressure values (systolic blood pressure <110 mm Hg). This hypothesis appears likely since the worsening of renal function in the 3 groups of the ONTARGET study is much more frequent than in trials studying the renoprotective effects of ACE inhibitors or ARBs in CKD patients [2]. Moreover, acute hypotension may increase the risk of myocardial ischemia in patients with narrowed coronary vessels.

Ischemic nephropathy due to bilateral renovascular disease is increasingly recognised as a cause of CKD stage V in the elderly. It is possible that in this high-risk population some of the patients had unknown stenosis of the renal artery or increased intra-renal vascular resistance. In this situation, dual blockade may have precipitated acute renal failure.

### Are Maximal Monotherapy Doses an Alternative to Dual Blockade?

It is still matter of debate whether maximising the inhibition of the RAS system with high doses of a single agent may achieve a more complete suppression of the system and obtain more renoprotection. Even if a number of studies have been made on this topic in recent years, many of them had a small sample size and their findings were not always consistent [29]. Often, the greater anti-proteinuric effect was not proportional to dose increase or the benefit was lost after adjustment for changes in blood

pressure [30, 31]. In other cases, the benefit was quite modest, despite ultra-high doses [32]. In a large sample of patients with type 2 diabetes and urinary albumin excretion rate of 20–700  $\mu\text{g}/\text{min}$ , Hollenberg et al. [33] demonstrated a highly significant albuminuria fall with high valsartan doses (320 and 640 mg) compared with the conventional 160 mg; interestingly, this difference became evident only after the first month of therapy.

The Renoprotection of Optimal Antiproteinuric Doses (ROAD) study [34] is the only trial with adequate follow-up to obtain information about hard endpoints (i.e. the doubling of serum creatinine or ESRD). Three hundred and sixty patients with non-diabetic, proteinuric CKD were titrated on benazepril (median 20 mg/day; range 10–40) or losartan (median 100 mg/day; range 50–200) to optimal antiproteinuric doses. After a median follow-up of nearly 4 years, compared with the conventional dosages, optimal anti-proteinuric dosages of benazepril and losartan were associated with a 51% and 53% reduction in the risk for the doubling of serum creatinine or ESRD and achieved a greater reduction in proteinuria. Interestingly enough, nearly half of the patients obtained maximal proteinuria reduction at conventional doses.

Altogether, available data suggest that maximal doses of RAS inhibitors have increased anti-proteinuric effect compared to standard doses.

### Are Maximal Monotherapy Doses More Effective than Dual Blockade?

At present it is not possible to give a definite answer to this question, since complete evidence is lacking about the effectiveness of both dual blockade and ultra-high doses of a single agent. Recently, a prospective study of 86 patients with chronic glomerulonephritis compared the effects of candesartan (4–12 mg/day) to its combination at 4 mg/day with benazepril (2.5–10 mg/day) [35]. Despite comparable blood pressure values, dual blockade decreased proteinuria more than single blockade with ARB (–42.3 vs. –60.5%). Unfortunately, the authors did not include a third arm testing the effects of benazepril alone.

### How to Reconcile All These Findings and Use Them in Everyday Clinical Practice?

ACE inhibitors and ARBs are effective therapeutic strategies to slow down CKD progression in diabetic and non-diabetic proteinuric nephropathies. Data about dual

blockade are less strong, but suggest a significant anti-proteinuric effect. However, single and even more dual RAS blockade should be reconsidered in elderly or high cardiovascular-risk patients [36]. This population is more likely to be affected by low proteinuric nephropathies (i.e. hypertensive kidney disease) and may receive limited benefit from such intervention. They may also be at higher risk of deterioration of renal dysfunction secondary to treatment because of the high prevalence of atherosclerotic renal artery stenosis or increased intrarenal vascular resistance. On the other hand, preventing cardiovascular complications is extremely important in CKD and

RAS inhibition may be useful in this setting. Benefits of RAS blockade must be weighed against its possible adverse effects particularly in elderly patients. Bearing in mind the experience of the ONTARGET study [17, 18, 37], treatment success may be increased by starting with low doses and adding a second agent with caution only in selected patients (proteinuric patients are more likely to benefit from dual blockade) using an individualized approach. This more cautious approach should be validated by large, randomized, controlled trials, but these are unlikely to be designed after the negative results of the ONTARGET study.

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## Editorial Comment

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This minireview by Locatelli and colleagues offers the readers a critical appraisal of the literature relating to the inhibition of the renin-angiotensin-aldosterone system (RAAS) in CKD. It gives a balanced well-informed view of the literature on the subject. It shows that data interpretation of studies on RAAS inhibition in CKD is confounded by: (1) the impact of ACE inhibitors/ARBs on blood pressure control, (2) unblinded and partially blinded studies, and (3) underpowered studies and posthoc analyses of clinical trials. It is also alarmingly confounded by trials of questionable quality such as COOPERATE [1] and others where the same authors report the same study in different journals with differing power and results [2, 3]. Locatelli and co-authors also comment on the published meta-analyses on the subject; some appear to draw conclusions and recommendations such as a beneficial effect of ACE inhibitors/ARBs in CKD with proteinuria >0.5 g/24 h in the absence of strong supportive data. Suffice to say that in non-diabetic CKD the only reasonably valid study, REIN, showed benefit in CKD patients whose proteinuria was in the nephrotic range. Locatelli

and co-workers also remind us that inhibition of the RAAS can be potentially harmful especially in the growing group of elderly CKD patients. It is high time nephrologists read original publications with a critical mind rather than unquestionably accept sound bites and abstracts headlines and even medical spin! I urge you to ask yourself whether you have read any of the key publications mentioned in this review that guide your daily management of CKD patients?! It is not always easy to jump off a bandwagon such as 'ACE inhibition for all', but some have the courage and knowledge to ask pertinent questions. The authors of this minireview certainly do.

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