RESEARCH ARTICLE

The Impact of Elective Withdrawal of Long-Term Renin Angiotensin Aldosterone System Blockade in Chronic Kidney Disease Patients with Progressive Acute Kidney Injury: A Prospective 40-Months' Single-Unit Cohort Study

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ABSTRACT

Introduction: There is general consensus that Renin Angiotensin Aldosterone System (RAAS) blockade is renoprotective for both diabetic and non-diabetic proteinuric chronic kidney disease (CKD). Nevertheless, there remains considerable debate and controversy regarding renal and cardiovascular (CV) outcomes after discontinuation of concurrent RAAS blockade in patients with advanced CKD. There have been discordant reports on renal and CV outcomes following RAAS blockade discontinuation. Whereas there is some agreement that there may be improved estimated glomerular filtration rate (eGFR) following such discontinuation, most studies reported increased mortality with worse CV outcomes. Conversely, fewer reports have shown renal benefits without adverse mortality and CV outcomes.

Method: Prospective Cohort Analysis conducted at a single site in Burlington, Vermont, USA. In a Nephrology Office at the University of Vermont Medical Center, in Burlington, Vermont, USA, over 40 months, February 2018 – May 2021, concurrent RAAS blockade was electively discontinued in all patients who presented with progressive and >25% increase in baseline serum creatinine. Kidney function was followed prospectively.

Results: 71 patients, 69 Caucasians, 1 African American and 1 Hispanic, 42:29 (M:F), mean age 69.4 (37-95) years, were in the cohort. Medical co-morbidities included diabetes mellitus (37) and hypertension (66). They were mostly asymptomatic. Mean duration of follow up since drug discontinuation was 580 (17-1245) days. Lisinopril was the commonest agent in 40 (56%) patients. Mean duration of RAAS blockade before discontinuation was 2057 (112-4043) days. Baseline serum creatinine was 1.38 ± 0.49 (0.66 - 2.7) mg/dL, n=70. Peak serum creatinine at presentation was 2.31 ± 1.09 (1.1 – 8.3) mg/dL, n=67, $P<0.0001$, t=6.4872, df=135. Nadir serum creatinine after discontinuation of RAAS blockade was 1.49 ± 0.45 (0.84 – 3.3) mg/dL, n=54, $p<0.0001$, t=5.1805, df=119. There were 4 (6%) deaths – bowel obstruction (1), cardiac arrest with pulseless electrical activity (1), metastatic renal cancer (1), and progressive ischemic cardiomyopathy (1), despite improved renal function. Kidney failure progressed despite drug discontinuation in 12 (17 %), and 4 (6%) needed renal replacement therapy, 8-30 months after drug discontinuation. Hyperkalemia in 34 (48%) and hyperphosphatemia in 13 (18%) resolved with improved kidney function. A 71-yo hypertensive man on Olmesartan 20 mg daily for 6 years was listed for kidney transplantation following acute kidney injury (AKI) with serum creatinine up to 2.9 mg/dL. Serum creatinine improved to 1.54 mg/dL, 8 months after drug withdrawal and he was delisted from the kidney transplant list.

Conclusion: This is the largest and longest prospective cohort analysis of renal outcomes in patients presenting with AKI on CKD following withdrawal of RAAS blockade. The elective withdrawal of concurrent RAAS blockade in CKD patients who presented with progressive acutely worsening AKI on CKD generally exhibit clearly improved renal outcomes. Our study did not show worse mortality or CV outcomes. We posit that in selected CKD patients with progressive AKI such as in our study, RAAS blockade discontinuation indeed is the correct next step in their management for both improved renal and CV outcomes.

Keywords: Acute kidney injury (AKI), Cardiovascular (CV) outcomes, Chronic kidney disease (CKD), Estimated glomerular filtration rate (eGFR), RAAS blockade, Serum creatinine.

INTRODUCTION

There is general consensus and agreement about the evidence-based concept of renoprotection with Renin Angiotensin Aldosterone System blockade for both diabetic and non-diabetic proteinuric chronic kidney disease (CKD).[1-5] Nevertheless, there is substantial disagreement regarding the renal and cardiovascular outcomes after the discontinuation of RAAS blockade in patients with advanced CKD.[6-8] A recent Swedish Renal Registry study examined the impact of stopping versus continuing RAAS inhibitor therapy in 10,254 prevalent RAAS inhibitor users (median age 72 years, 36% female) with new-onset eGFR <30 ml/min per 1.73 m2, 1553 (15%).[6] Median eGFR was 23 ml/min per 1.73 m^2.[6] The discontinuation of RAAS blockade was associated with a higher absolute 5-year risk of death (40.9% versus 54.5%) and major adverse cardiovascular events (47.6% versus 59.5%), but with a lower risk of kidney replacement therapy (KRT) (36.1% versus 27.9%).[6] Conversely, a Canadian population-based retrospective cohort study investigated the effect of discontinuing RAAS inhibitor in older adults (n=49,571; mean age 79 years) who had developed hyperkalemia (potassium ≥5.3 mEq/L) while on a RAAS inhibitor.[7] The discontinuation of RAAS inhibitor was associated with the lowest risk of recurrent hyperkalemia, with no apparent increase in short-term risks for cardiovascular events or all-cause mortality.[7] We had in a recent editorial commentary in the American Journal of Medicine raised the concerns that such debate and controversy about cardiorenal outcomes following the discontinuation of RAAS blockade in advanced CKD remain unsettled.[8]

Furthermore, we had earlier described the syndrome of late onset renal failure from angiotensin blockade (LORFFAB) and had demonstrated generally improved renal outcomes in patients presenting with progressive AKI after discontinuation of concurrent RAAS blockade without overt CV consequences.[9,10] The first author had therefore undertaken to complete a prospective study of similar patients with acutely presenting AKI on CKD following the elective withdrawal of concurrent RAAS blockade after moving to the University of Vermont, Burlington, VT in the US Northeast coast.

METHOD

A Prospective Cohort Analysis was conducted at a single site in Burlington, Vermont, USA. Setting - a Nephrology Office at the University of Vermont Medical Center, in Burlington, Vermont, USA. The study period was over 40 months, February 2018 – May 2021. CKD patients on a stable dose of the same RAAS blockade for >90 days who presented with progressive >25% increase in baseline serum creatinine were followed up following the discontinuation of the RAAS blockade. Baseline serum creatinine was defined as the last available for each patient before presentation with increasing azotemia, usually within 3 months of presentation.[10] Kidney function as measured by serum creatinine was rechecked 1-4 weeks after drug discontinuation, and then subsequently every 2-3 months. Estimated glomerular filtration rate (eGFR) was derived from the CKD-EPI equation and was concurrently reported in the electronic medical record. Patients were excluded from this analysis if they had an increase in the dose of RAAS blockade in the previous 3 months, or evidence of hypotension, or volume depletion, or overt infections and other acute medical conditions, the presence of hydronephrosis on renal sonogram where available, or heart failure exacerbation, or concurrent exposure to NSAIDs and peri-operative patients.[9-15] The primary care providers (PCP) followed up with the patients after drug discontinuation for close monitoring of the blood pressure. Anti-hypertensive therapy was adjusted as indicated with the substitution of kidney-friendly agents such as calcium channel blockers, beta blockers, alpha blockers, and the vasodilators, Hydralazine and Minoxidil.

Statistical Analysis

For all continuous variables, the results are reported as means ± SD, with ranges shown in parenthesis. Differences between means were calculated using the Student's t test method, and a p value of <0.05 was considered to be statistically significant. Paired Student's t test was used to compare differences within groups following an intervention whereas unpaired t test was used to compare differences between groups. Data was presented as straight-line graphs, figures and tables. The changes in serum creatinine and estimated glomerular filtration rate

(eGFR) by CKD-EPI equation over time are depicted as straight-line graphs.

RESULTS

Seventy one patients, 69 Caucasians, 1 African American and 1 Hispanic, 42:29 (M:F), mean age 69.4 (37-95) years, were in the cohort. Medical co-morbidities included diabetes mellitus (37) and hypertension (66). They were mostly asymptomatic. Mean duration of follow up since drug discontinuation was 580 (17-1245) days. Lisinopril was the commonest agent in 40 (56%) patients. Mean duration of RAAS blockade before discontinuation was 2057 (112-4043) days. Baseline serum creatinine was 1.38 ± 0.49 (0.66 - 2.7) mg/dL, n=70. Peak serum creatinine at presentation was 2.31 ± 1.09 (1.1 – 8.3) mg/dL, n=67, P<0.0001, t=6.4872, df=135. Nadir serum creatinine following discontinuation of RAAS blockade was 1.49 ± 0.45 (0.84 – 3.3) mg/dL, n=54, p<0.0001, t=5.1805, df=119 (Figure 1). There were 4 (6%) deaths despite improved renal function – bowel obstruction (1), cardiac arrest with pulseless electrical activity (1), metastatic renal cancer (1), and progressive ischemic cardiomyopathy (1). Kidney failure progressed despite drug discontinuation in 12 (17 %), and 4 (6%) patients needed renal replacement therapy, 8-30 months after drug discontinuation. Hyperkalemia in 34 (48%) patients and hyperphosphatemia in 13 (18%) patients resolved with improved kidney function. Kidney biopsy was available in 4 patients and demonstrated advanced diabetic nephropathy in 3 (75%) and tubular atrophy with global and segmental glomerulosclerosis in 1 (25%).

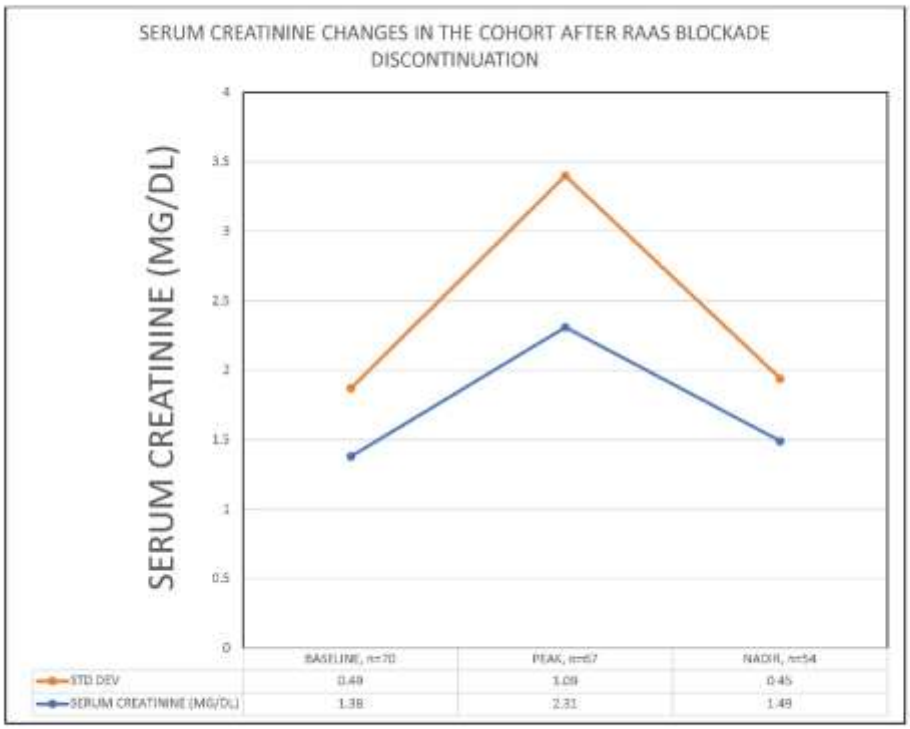

Fig 1. Schematic diagram showing baseline, peak and nadir serum creatinine values with the standard deviations for the cohort of 71 CKD patients.

A 71-year old hypertensive man on Olmesartan 20 mg daily for 6 years had been listed for kidney transplantation following acute kidney injury (AKI) with serum creatinine up to 2.9 mg/dL. Serum creatinine improved to 1.54 mg/dL, 8 months after drug withdrawal and he was delisted from the kidney transplant list (Figure 2). Representative graphs of two other patients' serum creatinine trajectories following RAAS blockade discontinuation are shown in Figures 3 and 4.

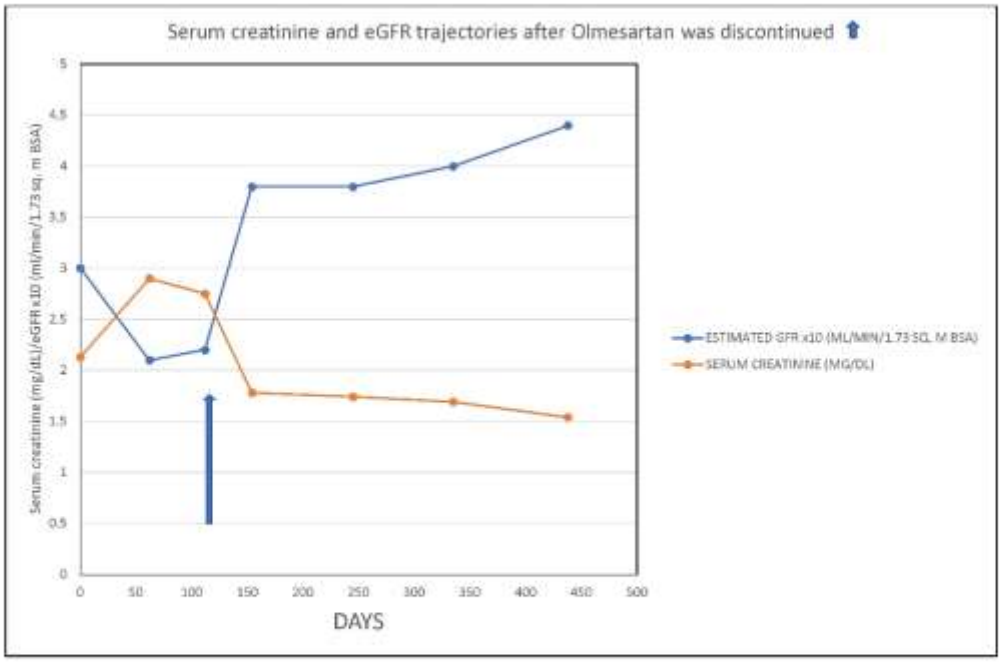

Fig 2. Serum creatinine and estimated glomerular filtration rate in a 71-year old male patient following the elective withdrawal of the ARB, Olmesartan.

Fig 3. Serum creatinine trajectory in a then 72-year old male CKD patient following the discontinuation of Lisinopril 10 mg daily in December 2018, through to March 2021.

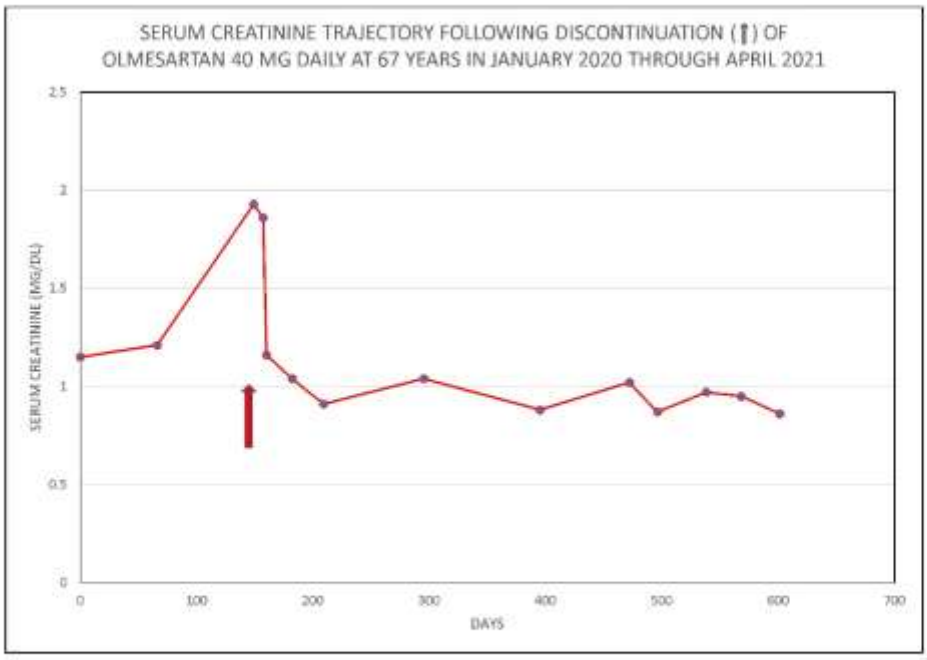

Fig 4. Serum creatinine trajectory in a then 66-year old female CKD patient following the discontinuation of Olmesartan 40 mg daily in December 2020, through to April 2021.

DISCUSSION

The evidence-base is well established regarding renoprotection with preservation of kidney function with RAAS blockade for both diabetic and non-diabetic proteinuric chronic kidney disease (CKD).[1-5] There remains an ongoing debate as to the appropriateness or otherwise of discontinuing or continuing RAAS blockade in patients with advanced CKD and this controversy is addressed below. In this prospective study, we rather examined renal outcomes in patients with all stages of CKD, diabetic and nondiabetic, who presented with progressive acutely worsening AKI while on RAAS blockade and without the classic known precipitating factors of AKI, and the RAAS blockade was discontinued. Prompt discontinuation of RAAS blockade led to significant and sustained improvement in kidney function in 59 of 71 (83%) patients in the cohort (Figures 1-4). There were 71 patients, 69 Caucasians, 1 African American and 1 Hispanic, 42:29 (M:F), and mean age 69.4 (37-95) years. Medical co-morbidities included diabetes mellitus (37) and hypertension (66). They were mostly asymptomatic. Mean duration of follow up since drug discontinuation was 580 (17-1245) days. Lisinopril was the commonest agent in 40 (56%) patients. Mean duration of RAAS blockade before discontinuation was 2057 (112-4043) days. Baseline serum creatinine was 1.38 ± 0.49 (0.66 - 2.7) mg/dL, n=70. Peak serum creatinine at presentation was 2.31 ± 1.09 (1.1 – 8.3) mg/dL, n=67, P<0.0001, t=6.4872, df=135. Nadir serum creatinine after discontinuation of RAAS blockade was 1.49 ± 0.45 (0.84 – 3.3) mg/dL, n=54, p<0.0001, t=5.1805, df=119. There were 4 (6%) deaths – bowel obstruction (1), cardiac arrest with pulseless electrical activity

(1), metastatic renal cancer (1), and progressive ischemic cardiomyopathy (1), despite improved renal function. Kidney failure progressed despite drug discontinuation in 12 (17 %), and 4 (6%) needed renal replacement therapy, 8-30 months after drug discontinuation. Hyperkalemia in 34 (48%) and hyperphosphatemia in 13 (18%) resolved with improved kidney function.

This is the largest and longest prospective cohort analysis of renal outcomes in patients presenting with AKI on CKD following withdrawal of RAAS blockade. The elective withdrawal of concurrent RAAS blockade in CKD patients who presented with progressive acutely worsening AKI on CKD generally exhibit clearly improved renal outcomes. Our study did not show worse mortality or CV outcomes.

Finally, we would once again revisit the concept of microvascular renal artery stenosis.[10] We submit that microvascular renal arteriolar narrowing, or what we have termed microvascular renal artery stenosis (mRAS), within renal capillaries and arterioles is capable of stimulating a state of enhanced angiotensin II production from the renal juxtaglomerular apparatus in the same way as large renal artery renal artery stenosis lesions do.[16,17] Notably, these microvascular renal arteriolar and capillary lesions would tend to be more prevalent in the elderly patients.[16] The mean age of the patients in our study was 69.4 (37-95) years. Arguably, as patients get older, these microvascular renal changes would only get more prominent leading to even more angiotensin II dependence and therefore an ever increasing susceptibility for renal function deterioration as a result of derangement of renal hemodynamic homeostasis by continued RAAS blockade.[10]

The strengths of our report include the prospective nature of the work, the strict inclusion and exclusion criteria, the relatively large size of the patients studied, the long period of RAAS blockade before presentation, the availability of a very comprehensive detailed individual patient-level content of demographics and a long and continuing real-time follow up clinical data. The limitations of our work include that it was a single-center study, our patients were mostly Caucasian thus raising the question of applicability of the study results to other races and ethnicities, the availability of kidney biopsy in only 4 patients, the possible role of unknown or unidentified confounders and the fact that our study was not randomized.

CONCLUSION

This study has reaffirmed our previous observations that elective withdrawal of concurrent RAAS blockade in CKD patients who present with progressive worsening AKI, despite the absence of the usual precipitating factors, still generally demonstrate clearly improved renal outcomes.[9,10] The majority of the patients in this study demonstrated improved renal outcomes and there was no evidence for increased mortality or worse CV outcomes (Figures 1-4). We posit that in selected CKD patients with progressive AKI such as in our study, RAAS blockade discontinuation indeed is the correct next step in their management for both improved renal and CV outcomes.

Self-selected CKD patients with rapidly progressing acutely worsening AKI on CKD must therefore be seen as a distinct group of patients, clearly different and distinct from simply patients with advanced CKD. Once the well-known precipitating factors that are known to precipitate AKI on RAAS blockade such as volume depletion, renal artery stenosis, dehydration, infections, NSAIDs and over diuresis, are ruled out and/or addressed, we herein very strongly argue that in all such scenarios, the provider is mandated to simultaneously consider the discontinuation of RAAS blockade.[11-15] This necessary and clinically sound next step should be seen as no different from the warranted discontinuation of Coumadin in a patient with active life-threatening GI bleed irrespective of the indication for anticoagulation or the mandated need to discontinue oral hypoglycemic agents or insulin in a diabetic patient with life-threatening hypoglycemia.

Raine in 1990 had in an editorial commentary in the Quarterly Journal of Medicine, suggested that the presence of overt renal artery stenosis evident on conventional angiography or the equivalent presence of fixed stenosis of the renal arterioles would explain some of the ACEI-associated AKI observed in clinical practice.[16] In our previous reports on the syndrome of late onset renal failure from angiotensin blockade (LORFFAB), we had

further hypothesized that a state of heightened renin-dependent high angiotensin II mileu, secondary to fixed stenosis in the renal microcirculation, a pathologic state that we had then dubbed microvascular renal artery stenosis (mRAS)[10], would then explain this observation: that in older patients, over the years, with progressive and worsening mRAS that is not evident on conventional renal angiography, a subsequent high angiotensin II state would then predispose the patient to RAAS blockade renal disequilibrium and therefore AKI.[10,17] If sustained for a very long time, we would argue that potentially irreversible acute tubular necrosis may indeed result. This may explain our observation in prior studies, studies from other centers, and again evident in this study, that sometimes the AKI associated with LORFFAB is reversible and sometimes it is not.[9-10,12,13,15] Kidney biopsy, available from 4 patients in our study had demonstrated advanced diabetic nephropathy in 3 (75%) and tubular atrophy with global and segmental glomerulosclerosis in 1 (25%). Of course, there would be other concomitant causes of AKI in such patients that are not related to RAAS blockade such as advanced diabetic and/or hypertensive renal disease and other renal diseases.

The STOP ACEI Trial Revisited

The STOP-ACEI Trial is an ongoing European randomized controlled comparison of cardiorenal outcomes in patients with advanced CKD - CKD IV and CKD V - on concurrent RAAS blockade, in whom RAAS blockade is either continued or discontinued.[18] While the results of this 3-year trail are awaited, we must contrast our study with The STOP-ACEI Trial.[18] Our prospective cohort study is a non-randomized cohort follow up evaluation of renal outcomes after elective withdrawal of RAAS blockade in CKD patients, of all CKD stages, who had exhibited evidence of acutely worsening AKI as defined above at the time of drug withdrawal. It is worth noting that El Nahas et al in the United Kingdom had conducted non-randomized discontinuation of RAAS blockade in advanced CKD patients over ten years ago and had generally demonstrated improved renal outcomes.[19,20]

Finally, it is evident from our study that RAAS blockade can indeed, especially in older (>65-yo) CKD patients, produce potentially reversible renal failure in the absence of previously described precipitating factors such as volume depletion, hypotension, heart failure exacerbation, NSAIDs exposure and renal artery stenosis. Our study has reaffirmed our previous work at the Mayo clinic Health System in Northwestern Wisconsin and the work of El Nahas et al in the United kingdom from several years ago.[9,10,19,20] The ongoing controversy regarding whether or whether not to discontinue RAAS blockade in advanced CKD will continue. The results of the ongoing STOP ACEI Trial may contribute to the ongoing debate.[18,21] Nevertheless, we must continue to argue that in all patients with acutely worsening AKI on CKD on RAAS blockade, there is hardly any ethically justifiable rationale to simply "continue to administer RAAS blockade". Evidence, albeit anecdotal and/or observational, have shown a strong biologically plausible relationship between RAAS blockade and AKI including ESRD.[9,10, 19-23] Moreover, there is evidence that despite all other evidence to-date supporting RAAS blockade in renoprotection strategies,[1-5] providers must accept the commonsense argument that angiotensin II has some significant critical physiological roles to play in the human body including involvement in kidney homeostasis, kidney hemodynamics and in kidney repair mechanisms.[17] Besides, Zhang et al had in experimental animals demonstrated a critical role for angiotensin II in renal repair following injury.[24]

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