Optimizing the Use of Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease

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https://doi.org/10.71749/pkj.58

Abstract
Chronic kidney disease (CKD) affects millions of people worldwide and is a major public health problem. Renin-angiotensin system inhibitors are the backbone drugs for preventing CKD progression but have potential side effects, such as hyperkalemia or acute decrease in glomerular filtration rate, which can prevent physicians from starting the drugs, or even lead physicians to stop the drug when already in use in advanced CKD patients. In this review, the principal studies performed on this topic are summarized.

Keywords: Angiotensin Receptor Antagonists/therapeutic use; Angiotensin-Converting Enzyme Inhibitors/therapeutic use; Kidney Failure, Chronic/drug therapy; Renal Insufficiency, Chronic/drug therapy

INTRODUCTION
Chronic kidney disease (CKD) affects millions of people worldwide and is a major public health problem, with one in every 10 persons having CKD.[1] This disease will rank the 5th disease in terms of years of life lost in the next few years, after ischemic heart disease, stroke, respiratory infections, and COPD.[2]
In addition to a high mortality rate, other consequences of CKD include disability, cardiovascular (CV) events, and progression to dialysis. According to the European Renal Association Registry, 1040 per million people undergo kidney replacement therapy (KRT) in Europe.[3]
It is important to adopt strategies for delaying disease progression, and simple measures, such as lifestyle modifications, weight loss, regular exercise, smoking eviction, and reduced salt intake help delay CKD progression.[4]
Specific therapies, which are entitled as pillars of CKD management, are crucial for disease control, including the old renin-angiotensin system inhibitors (RASi), the new sodium-glucose transport inhibitors 2 (SGLT2), glucagon-like peptide 1 (GLP1) agonists, and, mineralocorticoid receptor antagonist in diabetic albuminuric patients. With so many new drugs, with impressive data on reducing CKD progression and impressive data on the number needed to treat, there is still room for RASi in CKD management?

RENIN-ANGIOTENSIN SYSTEM (RAS)
In addition to the regulation of blood pressure, RAS is also important for water and electrolyte balance.
Renin, secreted from the juxtaglomerular cells, depending on the sensing mechanisms in response to (low) blood pressure and salt, cleaves angiotensinogen synthetized in the liver (its primary source), to form angiotensin I, which is transformed by angiotensin-converting enzyme (ACE) in angiotensin II (Ang II), the active peptide generated by the renin-angiotensin system.[5] This peptide binds to the Ang II-type 1 receptor on smooth vascular cells and tubules, causing not only vasoconstriction and sodium reabsorption, but also stimulating the activation of the sympathetic nervous system, increasing vascular resistance.[5]
In the kidneys, angiotensin 1 receptors mediate the action of Ang II, causing vasoconstriction mostly in efferent glomerular arterioles, increasing intraglomerular pressure, which maintains glomerular filtration rate (GFR), and increasing sodium reabsorption.[6] In the adrenal gland, Ang II stimulates aldosterone production, a mineralocorticoid that increases sodium reabsorption through the mineralocorticoid receptor.[6]
In summary, the intrarenal RAS contributes to the pathogenesis of hypertension and overstimulation can lead to renal tissue injury. The inhibition of Ang II actions prevents the raised intraglomerular pressure caused by angiotensin

Received: 03/11/2024 **Accepted:** 02/12/2024 **Published Online:** 06/12/2024 **Published:**-
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II–mediated constriction of the efferent arteriole and limits progressive podocyte loss. Additionally, RAS inhibition can impair the inflammatory response to RAS activation.

Numerous drugs are used to block the renin-angiotensin system, and this can be performed at many points in the RAS cascade, including ACE inhibition (ACEi) or angiotensin I receptor blockers (ARB),[7] which are known for their effects in decreasing proteinuria, irrespective of blood pressure control.

RENIN-ANGIOTENSIN SYSTEM INHIBITORS (RASI)

RASi seem to be the backbone drugs for preventing CKD progression, not only in diabetes and hypertension, but also in some glomerulonephritis and hereditary diseases, such as Alport disease.[8]

According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, RASi are a first-line therapy for preventing CKD progression in patients with CKD and proteinuria, with a level of evidence 1A.[9] This level of recommendation exists not only for diabetic kidney disease,[9] where the benefit is superior if the drugs are initiated in earlier stages, but also in CKD patients with hypertension.[10] In these patients, the targets for systolic blood pressure are below 120 mmHg, and an ACEi or ARB should be preferred in albuminuric patients.[10]

Diabetes and CKD

The guidelines on CKD progression in diabetic patients rely on old landmark studies, being 3 of them the most important. One of these studies was performed in 1993, and demonstrated a decrease in kidney events in type 1 diabetes with retinopathy in patients receiving captopril.[11] The study found that captopril treatment reduced the risk of the primary endpoint by 50%, end-stage renal disease by 60%, and death or the need for dialysis by 48%.[8] The beneficial effects of captopril were independent of its antihypertensive effects. The RENNAL trial (Reduction of Endpoints in Non-insulin-dependent diabetes with the Angiotensin II antagonist Losartan) was a randomized trial comparing losartan to placebo in a population of type 2 diabetes with CKD.[12] Patients in the losartan arm had a 16% reduction in the composite outcome (doubling creatinine, KRT initiation, or death).[12] In addition, losartan reduced the incidence of doubled serum creatinine concentration by 25% and end-stage renal disease by 28%. The study also found that losartan did not significantly affect the death rate.

The IDNT study randomized diabetic patients to receive irbesartan or amlodipine or placebo, and the results were very similar to the RENNAL results.[13] Treatment with irbesartan was associated with a 20% lower risk of the primary composite endpoint compared to the placebo group, and a 23% lower risk compared to the amlodipine group. The risk of doubling the serum creatinine concentration was 33% lower in the irbesartan group than in the placebo group, and 37% lower in the irbesartan group than in the amlodipine group. Treatment with irbesartan was associated with a 23% lower relative risk of end-stage renal disease compared with the two other groups. Nevertheless, there were no significant differences among the three groups in the rates of death or the rates of the cardiovascular composite endpoint.

A negative study with both ACEi and ARBs was published, the VA-NEPHRON (Veterans Affairs Nephropathy in Diabetes Study), showing that the use of dual blockade (in this case with lisinopril plus losartan) should not be performed, because of adverse effects (hyperkalemia, acute kidney injury),[14] and it was terminated earlier due to safety concerns. The ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) study showed that patients with diabetes and vascular disease had no benefit from dual blockage.[15] Combination therapy with ramipril and telmisartan did not show any benefit over ramipril alone and was associated with more adverse events, including hypotensive symptoms, syncope, and renal dysfunction.

Proteinuria

The REIN (Ramipril Efficacy in Nephrology) trial was a randomized study that compared patients with CKD treated with ramipril or placebo. This study showed that the decline in GFR was lower in the ramipril arm for patients with proteinuria superior or equal to 3 g, independent of baseline serum creatinine.[16]

Hypertension

The AASK study (African American Study of Kidney Disease & Hypertension) randomized patients with CKD to ramipril versus amlodipine versus metoprolol. The effect of ramipril in lowering the rate of decline of GFR was only significant in patients with a GFR < 40 mL/min, when compared to amlodipine. The presence of proteinuria contributed to the effects of the drugs, and those with proteinuria experienced a reduced risk of CKD progression with ramipril.[17]

Implementation

Despite these recommendations and despite these drugs having been recommended for many years, implementation in clinical practice is still insufficient, as demonstrated by a clinical study where only 39% of patients were under RASi in a potential universe of 78%.[18]

Because of its mechanism of action, the use of ACEi or ARBs in advanced CKD can be associated with undesirable outcomes, such as hyperkalemia or reduction of kidney function due to hemodynamic effects. Therefore, its use in CKD stage 4 (advanced CKD) is not consensual, as in non-dialysis CKD stage 5 patients.

USE OF RASI IN ADVANCED CKD

Initiation of RASi in advance CKD

Considering the acute GFR reduction that is expected to occur after the introduction of ACEi / ARBs, the recommendation is to have a tolerance of up to a 30% increase in serum creatinine before stopping the therapy.

One of the studies that addressed the potential risk of initiating ACEi / ARB therapy in patients with advanced CKD was published in 2006. It was a randomized Chinese study that investigated the renal outcomes of benzipril initiation versus placebo, comparing two groups: one with advanced CKD (serum creatinine – Scr - from 3.1 – 5 mg/dL) and moderated CKD (Scr 1.5 – 3 mg/dL).[19] Globally, the drug was superior to placebo in lowering the number of renal adverse events (such as doubling creatinine, ESKD, or death). Even so, more patients in the advanced CKD group had these outcomes compared to those with moderate CKD, and the authors concluded that a greater benefit is achieved when starting benzipril earlier in the course of the disease.[19]

In a more recent observational study using data from the Swedish Renal Registry, Fu and colleagues compared the effect of initiating a RASi (enalapril, ramipril, candesartan, losartan) versus a calcium channel blocker (amlodipine, felodipine) in advanced CKD (events = dialysis need, kidney transplant, CV events, and all-cause mortality).[20] The authors demonstrated that initiating RAS inhibitor therapy compared with CCBs was associated with a lower risk of KRT, but similar risks for mortality and MACE. It should be indicated that age was observed to be an interaction variable, and older patients did not benefit from the drug (in terms of kidney events). They suggested that the study provided real-world evidence that beginning RASi compared to CCB confers potential kidney benefits with similar CV protection.[20]

Discontinuation of RASi in advance CKD

One of the first studies dedicated to the RASi discontinuation topic was dated 2010. This was a small observational study, including 52 patients, which demonstrated that the negative estimated GFR (eGFR) slope before stopping RAS inhibitors was reversed 12 months after drug withdrawal, among patients with advanced CKD, and this effect persisted for up to 24 months.[21] The authors concluded that discontinuation of RAS inhibition delayed the onset of KRT in most patients.

In a retrospective propensity score-matched cohort study conducted in the United States (US), among a cohort of almost 4 thousand patients, discontinuation of ACEi or ARB therapy in those with advanced CKD was associated with a higher risk of mortality and major adverse cardiovascular events (MACE), with no statistically significant difference in end-stage kidney disease (ESKD) risk.[22]

Another retrospective cohort study of US veterans with non-dialysis-dependent CKD, including a cohort of more than 1 million patients with CKD, among the 141 252 patients who were given a new prescription of ACEI/ARB, its discontinuation was associated with an approximately 2-fold increased risk of death and a 1.5-fold increased risk of ESKD.[23] Based on these findings, the authors concluded that ACEI/ ARB discontinuation has an adverse long-term outcome in patients with CKD. Nevertheless, the study had two major limitations: as it was an observational study, causality could not be proven, and the exact reason for discontinuation was not known. The authors suggest that these findings highlight the importance of careful consideration of factors leading to discontinuation and the potential benefits of continued ACEI/ARB therapy in patients with CKD.

Another retrospective study comparing continuing and stopping RASi was published in the same year. The continuing option was associated with less CV (less mortality, less major CV events, or increased absolute risk of mortality and MACE), but with more kidney events, as the stopping option had a lower absolute risk of KRT.[24]

The STOP ACEi trial was an open-label, multicentre, randomized controlled study of ACEi / ARB withdrawal in patients with advanced kidney disease. It enrolled 411 patients and compared the stopping strategy with the continuing strategy in patients with advanced CKD, with a follow-up of up to 3 years.[25] The study results were surprising, as there were no statistical differences in eGFR slope, ESKD, or a composite of a decrease of more than 50% in eGFR or the initiation of renal replacement therapy, as well as no differences in hospitalization, blood pressure, exercise capacity, and quality of life in both groups. The authors concluded that discontinuation of RASi inhibitors did not lead to a clinically relevant improvement in the eGFR or a change in eGFR long-term rate of decline.[25] There were some limitations, such as the short follow-up period, as we know that 3 years is too short to observe the progression of kidney diseases. In addition, the study population was younger and fitter than the general population nephrologists have in their outpatient clinics.

Recently, a new meta-analysis, including four studies, such as the STOP ACEi trial, was published to examine the effect of RAS inhibitor discontinuation on clinical outcomes in patients with advanced CKD. The pooled analysis showed that cardiovascular events and ESKD were significantly higher in patients in the discontinuation group than in those in the continuation group, with no difference in all-cause mortality.[26] The authors concluded that continuing RAS inhibitors in patients with advanced CKD was associated with a lower risk of cardiovascular events and ESKD.

CONCLUSION

With these contradictory studies on KRT outcomes, but most probably positive results on CV events, my view is that we should not stop ACEi or ARB medication in patients with advanced CKD. While some studies showed no significant difference in all-cause mortality between continuing and discontinuing RAS inhibitors, the overall evidence suggests that the benefits of continuing these medications outweigh the risks.

It is important to note that the decision to discontinue RAS inhibitors should be made on a case-by-case basis, considering individual patient factors, and potential risks and benefits. The factors that may warrant discontinuation include severe hypotension, hyperkalemia, and acute kidney injury. However, in the absence of these contraindications, evidence strongly supports the continuation of RAS inhibitors in patients with advanced CKD to slow disease progression and reduce the risk of cardiovascular complications.

The introduction of these drugs should rely on age, performance status, and previous events or risk of AKI, as well as the rate of GFR decline.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financial Support: This work has not received any contribution grant or scholarship.
Provenance and Peer Review: Not commissioned; externally peer-reviewed.
Consent for Publication: Not applicable.

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