The use of renin-angiotensin-aldosterone system inhibitors in chronic kidney disease: Is there any doubt?

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Renin-Angiotensin-Aldosterone system (RAAS) is of utmost importance in volume and blood pressure control, as well in sodium homeostasis1. The classical event for RAAS activation is volume depletion. Its presence activates arterial baroreceptors, namely the ones present in the renal afferent arterioles that will lead to renin secretion by the juxtaglomerular apparatus. Renin transforms angiotensinogen in angiotensin I, which is converted in angiotensin II (AngII) by angiotensin-converting enzyme (ACE). In its turn, AngII causes vasoconstriction of renal efferent arteriole, as well as increases in sodium resorption by proximal tubule, and indirectly causes antiuretic hormone release. In the suprarenal cortex, AngII induces the aldosterone synthesis, which acts in the principal cells of collector ducts, causing resorption of sodium and excretion of potassium (through the increased expression of ENaC and ROMK), and increased secretion of prostaglandins1.

Despite its importance, the chronic stimulation of RAAS is deleterious, promoting endothelial dysfunction, inflammation and fibrosis2, and physicians are aware that its blockage is very efficient in controlling high blood pressure.

Nephrologists are also aware of the importance of RAAS inhibition (RAASI) to the preservation of glomerulus health. If we block the vasoconstriction of renal efferent arteriole promoted by AngII, we will diminish the intra-glomerular pressure, and this protects kidneys in the long term. Nevertheless, this system inhibition is not free of complications. The drop in intra-glomerular pressure can precipitate a reduction in the glomerular filtration rate (GFR), which is more likely to happen in a subgroup of patients, namely the ones with chronic kidney disease (CKD) or with heart failure, who are the ones who probably most benefit from RAASI. In addition, RAASI can cause hyperkalemia, and this life-threatening event is more frequent in the presence of CKD.

THE USE OF RAASI IN ADVANCED CKD

Despite possible side effects, the use of RAASI in CKD has been recommended for several years. In 2012 the Kidney Disease | Improving Global Outcomes (KDIGO) guidelines suggested the use of ACEi or ARB in both diabetic and non-diabetic patients with CKD and a urine albumin excretion above 300mg/24h, with a 1B level for the recommendation3.

More recently, in 2020, the KDIGO guidelines for Diabetes in CKD advocated treatment with ACEi or ARB in albuminuric hypertensive patients, with an evidence level of 1B4. The use of those drugs could be considered in the absence of high blood pressure and there seems to be no advantage in its use in the absence of albuminuria4.

This year has seen the launch of the KDIGO guidelines for blood pressure in non-dialysis CKD5. The recommendations for patients with high blood pressure and CKD were different, depending on the presence of diabetes: in diabetic patients, it was recommended to use RAASI in the presence of albuminuria (level of evidence 1B); in non-diabetic patients it was recommended to use RAASI with severely increased albuminuria (A3 – level of evidence 1B) or with moderately increased albuminuria (A2 – level of evidence 2C)5.

The prevention of CKD progression is the goal of all nephrologists. For almost 20 years, we have known the value of RAASI in achieving this goal. The IDNT6 and the RENAAL7 landmark studies were published in 2001 and both showed that, in a population with type 2 diabetes, irbesartan and losartan, respectively, were important in preventing death, end-stage renal disease (ESRD) or duplication of creatinine, with a risk reduction of 20% and 16%, correspondingly. Moreover, the AASK study8, published in 2002, showed the importance of ramipril in the progression of CKD beyond its antihypertensive effects, in African Americans. A further 3 landmark studies, HOPE9, EUROPA10, and PEACE11, showed the importance of ACE inhibitors (ACEi) and angiotensin II receptor blockers (ARB) in cardiovascular protection in patients with and without hypertension, including CKD patients. Nevertheless, those benefits are dependent on the dose we use, and it is very difficult to use full-dose ACEi or ARB in CKD patients.

With the above in mind, are there any studies in the subgroup of patients with advanced kidney disease? Yes, three observational studies have just been published. And I immediately acknowledge a common limitation in these three studies: as they are observational, we cannot infer causality.

The first study I chose to talk about is a nationwide Swedish observational study12, which included a cohort of patients with an estimated GFR (eGFR) below 30 ml/min/1.73 m². The authors compared the introduction of RAASI versus calcium channel blockers and follow 4803 patients for 4.1 years. They verified that those patients with advanced kidney disease benefitted from the introduction of RAASI, as it slowed CKD progression, with no differences in mortality or cardiovascular events.

The same authors published another study based on the same Swedish Renal Registry, including 10,254 patients with an eGFR below
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HYPERKALEMIA WITH THE USE OF RAASI

Currently, the management of RAASI in CKD patients is easier since we have new potassium binders with benefits when compared to the classical/resins.

Patiromer and sodium zirconium cyclosilicate are game changers in the use of RAASI in CKD patients. Patiromer is a non-absorbed drug, which acts mostly in the distal colon through a non-specific cationic-exchange (calcium-potassium). Its action starts within 7 hours, and patients achieve normokalemia mostly in 4 weeks. It is well-tolerated, can cause hypomagnesemia in some patients and may be taken 3 hours apart from the rest of the medication.

Zirconium cyclosilicate exchanges potassium for hydrogen and sodium through the entire gastrointestinal tract. Most patients achieve normokalemia in 24h. It is a well-tolerated drug, although it can cause edema. As with patiromer, it must be taken apart from the rest of the medication, usually with an interval of 2 hours.

With these recent publications and new potassium binders, there is no excuse for letting the old drugs (and the new ones) act for the benefit of CKD patients by blocking RAAS.

References


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