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Dual RAAS Blockade in CKD: Does the Hype have Teeth?

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The mere mention of the renin-angiotensin-aldosterone system (RAAS) is enough to get the average nephrologist salivating with excitement, like Pavlov’s proverbial pet. Medications that block the RAAS have been the cornerstones of treatment for the prevention of chronic kidney disease (CKD) progression for decades. Nephrologists had hoped by combining the power of RAAS blocking agents we could further improve our patients’ chances of decelerating glomerular filtration rate (GFR) loss, but did we bite off more than we could chew? Our enthusiasm has been gnawed away by a series of studies that have failed to show any added benefit of combining RAAS blockade treatments, while even suggesting potential harm. Are angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs) and/or mineralocorticoid receptor (MRA) blockers combined potential for improving cardiovascular and kidney outcomes truly toothless?

Since their introduction in 1977, ACEi have been widely used for hypertension, heart disease and chronic kidney disease. The effects of ACEi on the kidneys are modulated by both the glomerular actions of angiotensin II (AG II) and their effects on autoregulation of glomerular blood flow.[1] AG II constricts both the afferent and efferent arterioles at the glomerulus, with preferential increase in efferent resistance. The net effect is that the intraglomerular pressure is increased to maintain GFR. The associated decline in GFR induced by ACEi glomerular efferent arteriole dilation occurs within the first few days of initiation of therapy, as AG II levels are rapidly reduced. The decline in GFR that occurs with ACEi is indicative of decreased glomerular pressure, a probable mechanism for glomerular protection. In patients treated with either ACEi or ARBs, when compared to other blood pressure lowering agents, there has been noted to be a reduction of kidney disease progression especially when albuminuria is present.[2]

ARBs effects on the human kidney are broadly similar to ACEi. Many studies have looked at their effects in patients with proteinuria, with and without diabetes. In IDNT patients with type 2 diabetes and CKD were treated with irbesartan, which slowed the progression of diabetic kidney disease independent of its anti-hypertensive effects. There was a 23% improvement in the primary endpoint (doubling of baseline creatinine, end stage kidney disease [ESKD], all-cause mortality) compared with amlodipine.[3] In
RENNAL, patients with DKD similarly showed that losartan decreased proteinuria (35%), doubling of serum creatinine (25%) and progression to ESKD (28%), but did not provide a mortality benefit. Patients in RENNAL were excluded if they were on ACEi.[4]

There are at least some physiological reasons why the combination of ACEi and ARBs might have proven to be better than either medication alone. There is substantial evidence that upregulation of the RAAS plays a key role in CKD progression and suppression of this complex pathway seems unlikely to hinge on a single element. Renin is a proteolytic enzyme stored in the juxtaglomerular cells and is normally released in response to reduced kidney afferent blood flow or increased sympathetic tone. Renin cleaves angiotensinogen into angiotensin I which in turn is converted to AG II by ACE. ACEi as solitary agents, though high up in the enzymatic cascade, provide incomplete blockade of the RAAS (Figure 1). Additionally, with chronic ACE inhibition there is evidence of partial escape of ACE, reflected by a shortened duration of AG II suppression.[5] Furthermore, the efficacy of ARBs may be compromised with chronic use by compensatory increases in AG II levels. Finally, the efficacy of either ACEi or ARBs may be limited by their tissue penetration, with effective dosing improved by combination therapy.[6]

Long term efficacy and tolerability of combination therapy was demonstrated in non-diabetic nephropathy in the COOPERATE study.[7] Those in the combination group had a 60% lower rate of doubling of serum creatinine or ESKD compared with those only receiving a single RAAS inhibiting agent. The COOPERATE study was eventually retracted, however, due to questionable patient consent practices and the lack of verifiable data. Next, the CHARM-Added study, conducted with 2,548 CHF patients, added candesartan to ACEi. There was an associated 15% reduced risk of cardiovascular death or hospitalization despite increased hyperkalemia and acute kidney injury (AKI).[8] Furthermore, Val-HeFT added valsartan to ACEi (in 93% of study patients) with reduction in the risk of death or cardiovascular morbidity by 13.2%.[9] Unfortunately, these early favorable studies started to lose their bite with the completion of ONTARGET (2008) and VA NEPHRON D (2013).
In ONTARGET telmisartan was given to patients with cardiovascular disease or diabetes.[10] The study concluded telmisartan was at least as good as ramipril in preventing death, MI, and stroke. Patients taking the combination had no added benefit but did have increased adverse events. Elevated medication doses used in the study, at least in part, were blamed for some of the harmful effects. Furthermore, in the VA-NEPHRON-D trial in patients with CKD stage 2-3, diabetes, and albuminuria, it was shown that dual RAAS blockade had no added impact on GFR, ESKD, or death. VA NEPHRON D was criticized, however, for also having high doses of study medications with aggressive titration and having no female participants. It was also noted participants had non-nephrotic range proteinuria (median proteinuria 2.1 grams in the combination group), which might not have even warranted dual blockade. In the LIRICO study, patients with diabetes and albuminuria were placed on dual RAAS blockade for 2.7 years and had the same cardiorenal events and albuminuria reduction as either agent alone.[11] This lack of improved albuminuria with dual RAAS blockade in the LIRICO study may have been due once again to medication dosing. Finally, in the VALIANT and ONTARGET studies, patients on dual RAAS blockade had lower sustained blood pressures.[12] It is possible that periods of hypotension were responsible for adverse events such as AKI, and if hypotension was avoided results might have been more encouraging. Another possibility is that AKI events induced by the combination of ACEi and ARBs are not entirely negative. Elevated creatinine induced by combination RAAS inhibition may be hemodynamic and protective and not represent actual histological injury to the nephron. Additionally, it is speculated, had the studies been longer, we might have detected additional cardiovascular and kidney benefits. Based on the current evidence, ACEi and ARBs may have the same efficacy in patients with diabetes, albuminuria, and high cardiovascular risk, but the benefits of the combination therapy for mortality and cardiorenal protection remain unproven.

Mineralocorticoid receptor antagonists (MRAs) have also been considered in dual RAAS blockade therapy. A review of the Cochrane database that included 44 studies of patients with CKD and MRAs (mostly spironolactone and eplerenone) observed that adding MRAs to ACEi or ARBs reduced albuminuria by 51%, with no effects on cardiorenal events or mortality. Similar to studies where ACEi were added to
ARBs there was a 2-fold increased risk of AKI and hyperkalemia. [13] Finerenone is a new non-steroidal MRA that blocks mineralocorticoid receptor mediated sodium reabsorption and overactivation. It has demonstrated anti-inflammatory and anti-fibrotic effects as well. It is potentially more potent and safer than spironolactone, but steroidal and non-steroidal MRAs have not been compared head-to-head in recent studies. [14] The FIDELITY study jointly analyzed two Phase III RCTs (FIDELIO and FIGARO) in 13,026 patients with CKD G3a, albuminuria, diabetes, and serum potassium <4.8 mmol/L taking RAAS inhibitors (99.8%) at optimized doses. The efficacy outcomes were a composite cardiovascular outcome of time to cardiovascular death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure. The kidney specific outcomes included onset of kidney failure, sustained >57% decrease in eGFR, or renal death. The composite kidney outcomes were ESKD or a sustained decrease in eGFR to <15 cc/min or kidney transplantation. The study population included elderly patients (median 65 years), with prior cardiovascular disease (45%) and moderate albuminuria (median UACR 515mg/gr), that is, patients with a high cardiovascular and kidney risk. This population approximates the patients commonly seen in nephrology clinics that would be considered for dual RAAS blockade.

Patients were randomized to receive finerenone or placebo for 3 years. The finerenone group had a 14% reduction in composite cardiovascular events, a 23% reduction in the composite renal outcomes, and a 20% reduction in ESKD. Patients on finerenone had twice the risk of developing hyperkalemia.[15] The finerenone group had a reduction in GFR in the first 4 weeks (-3.18 mL/min compared to placebo -0.73 mL/min), but after 44 weeks the finerenone group lost less GFR (-2.66 mL/min compared to placebo -3.97ml/min) demonstrating its potential long term positive effect on kidney function. After review of this study, it is likely that finerenone will be used more and more, consequently we will accumulate further data from phase IV studies and real-world use, broadening our picture of its benefits and risks.

Finally, before we start gnashing our teeth about recent studies lacking strong positive evidence for dual RAAS inhibition, let’s examine clinical trials from a pragmatists point of view. It has been observed that the populations studied in clinical trials are not the same as those seen in clinical practice. The results of randomized
clinical trials tend to overestimate the relative risk of adverse events because of higher than usual drug dosing and increased laboratory tests frequency. A meta-analysis showed that in patients not involved in RAAS blockade studies, ~20% abandoned dual RAAS blockade, similar to most antihypertensive regimens. Curiously, these patients had negligible changes in potassium and eGFR, suggesting that these events were not the main reason for abandonment.[16] The truth is that most nephrologists consider the failure of studies to show the benefits of combination RAAS inhibition may be because these studies don’t represent the timing, dosing, indications, and demographics of patients that are routinely encountered in clinical practice. It is still reasonable to consider double RAAS blockade (either by combining ACEi with ARB or with MRAs) in certain patients with CKD, significant albuminuria, and high cardiovascular risk. Unfortunately, we don’t have all the answers and still have much to chew on.

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Figure 1.

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CHF, chronic heart failure; CKD, chronic kidney disease; DRI, direct renin inhibitors; MRA, mineralocorticoid receptor antagonist; NS-MRA non-selective mineralocorticoid receptor antagonist; RAAS renin-angiotensin-aldosterone system; UACR, urine albumin-creatinine ratio.
