# Blocking of Renin-angiotensin-aldosterone System and Kidney Disease: an Update

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Chronic kidney disease (CKD) is an increasingly prevalent public health concern and is also associated with a high risk of adverse cardiovascular outcomes. Patients with renal dysfunction and hypertension require therapeutic strategies encompassing control of renal dynamics and appropriate blood pressure (BP) lowering. The various roles of angiotensin II on the kidney and systemic BP suggest that renin- angiotensin- aldosterone system (RAAS) blockade should offer renoprotective benefits by decreasing intraglomerular pressure, minimizing the stressors on the nephron and reducing proteinuria. Inhibition of RAAS provides renoprotection to patients with diabetic and non- diabetic kidney disease with proteinuria. In this patients, RAAS blockers lower BP, reduce proteinuria, slow kidney disease progression, and reduce cardiovascular risk by mechanisms that are additional to lowering BP. However, many individuals with CKD experience loss of renal function despite treatment with angiotensin converting enzyme inhibitors (ACEis) and/or angiotensin receptor blockers (ARBs). Conventional monotherapy with ACEi or ARB may be not enough to attenuate successfully the progression of renal dysfunction in patients with proteinuric CKD.

## The combination of ARBs and ACEis

ACEi and ARBs interfere with the RAAS at different points and each reduces proteinuria and blood pressure in diabetic and non- diabetic kidney diseases. Combination therapy with both drug classes (dual- class therapy) may block the RAAS more effectively than treatment with either ACEI or ARB alone. Many studies reported that the antiproteinuric effect of dual- class therapy was superior to that of ARB or ACEi treatment alone. The COOPERATE trial, a randomized controlled clinical trial, reported improved renal survival with dual- class compared with single-class therapy and attributed this benefit to the additional proteinuria reduction seen with combination therapy. This antiproteinuric effect did not seem to stem from antihypertensive effects, because BP decreases were similar among all treatment groups. Several studies reported that the superior antiproteinuric benefit of combination therapy could result from hemodynamic effect. Potential safety considerations with dual RAAS blockade include hyperkalemia and reduced renal function. Recently completed ONTARGET study, large simple randomized trial of an ARB and an ACEi in patients at high risk for cardiovascular events, reported that the combination of the two drugs was associated with more adverse events without an increased of benefits.

## Adding mineralocorticoid receptor blocker(MRB) to ACEi and/or ARB therapy

Aldosterone, a key hormone of the RAAS not directly targeted by ACE inhibitors or ARBs, may have an important role in the pathophysiological process of progressive CKD. Many clinicians assume secondary suppression of aldosterone after angiotensin blockade, but in clinical trials of ACEis and ARBs, plasma aldosterone levels, after an initial decrease, increase in some patients during the long term, a phenomenon termed aldosterone escape. Targeting the aldosterone component of the RAAS with mineralocorticoid receptor blockers (MRBs), such as spironolactone and eplerenone, may offer benefit additive to therapy with ACEis and/or ARBs. When MRBs were added to ACEi and/or ARBs in patients with proteinuric CKD, the reported proteinuria decreases from baseline ranged from 15 % to 54 %. MRB therapy was also associated with significant decreases in blood pressure and glomerular filtration rate in approximately 40 % and 25 %, respectively in a metanalysis. The exact mechanism of

reduction of proteinuria is still unclear. Major adverse effect of adding MRBs to ACEi and/or ARB therapy in patients with advanced CKD is hyperkalemia. Future research should also examine whether patients who showed aldosterone escape on ACEi and/or ARB therapy should be targeted over nonescapees.

## New class RAAS blocker- Aliskiren

Aliskiren which was approved for hypertension treatment from FDA in March 2007 reversibly binds to the renin catalytic site and prevents renin- mediated cleavage of angiotensinogen. The magnitude of BP reductions during aliskiren therapy is moderate. The reactive rise in plasma renin activity (not the renin proteins conentration but its ability to generate angiotensin I *in vitro*) from an ACEi and ARB is blunted by direct rennin inhibitor- aliskiren. However, renin concentration increases after aliskiren treatment although it blocks renin activity (ability to generate angiotensin I *in vitro*). Combination treatment of aliskiren and other RAAS blockades including ACEis and ARBs may block RAAS activation more effectively than each monotherapy. However, little is known about the functional importance of large reactive increases in renin secretion by aliskiren therapy. Large outcome trials are in progress to address this point later.