

**Aldosterone breakthrough during Diovan (valsartan), Tekturna (aliskiren), and combination (valsartan + aliskiren) anti-hypertensive therapy for proteinuric kidney disease**

**Objectives:** To measure the frequency of aldosterone breakthrough during angiotensin receptor blocker (ARB), direct renin inhibitor (DRI), and combination (ARB + DRI) anti-hypertensive therapy in patients with proteinuric kidney disease, and to determine whether aldosterone breakthrough is associated with refractory proteinuria in these patients.

**Study Rational:** Interruption of the renin-angiotensin-aldosterone system (RAAS) with angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs), alone and in combination, has become a leading therapeutic strategy in slowing the progression of chronic heart and kidney disease. This is an effective but not perfect approach given the significant numbers of patients who progress despite this therapy. In clinical trials of ACE-Is, ARBs, and their combination (i.e. ACE-Is + ARBs), plasma aldosterone levels, after an initial decline, have been shown to increase in some patients over the long-term. This phenomenon, termed “aldosterone breakthrough,” may carry important clinical consequences given aldosterone’s non-epithelial, profibrotic actions on diverse organ systems, including the heart and kidney.

Our central hypothesis is that aldosterone breakthrough is due to override physiology – specifically, blockade of the RAAS leads to accumulation of active precursor substances, most notably angiotensin II, produced in response to the “speed bump” posed by ACE-inhibitors and ARBs. *Because renin inhibitors suppress the RAAS proximally, this new class of anti-hypertensive medications may minimize accumulation of active precursor substances and thereby limit the breakthrough phenomenon compared to conventional RAAS blockade with ACE-Is and/or ARBs.*

**Study Design:**

- Randomized, open-label, three-arm study comparing Diovan (valsartan, an ARB), Tekturna (aliskiren, a DRI), and the combination of valsartan + aliskiren (i.e. ARB + DRI).

- 120 subjects (40 per arm) with proteinuric kidney disease and blood pressure above goal (i.e. 130/80 mm Hg) will be treated with Tekturna, Diovan, or a combination of both drugs for 9 months on top of their usual antihypertensive treatment.

- Changes in urinary aldosterone excretion will be monitored during therapy to measure the incidence of aldosterone breakthrough.

- Changes in urinary protein excretion will also be monitored alongside the urinary aldosterone levels to determine whether aldosterone breakthrough is associated with refractory proteinuria.

**Population:** 120 patients

- Inclusion criteria:
  
  o proteinuria > 500 mg/day and ≤ 3500 mg/day

  o eGFR ≥ 50 ml/min/1.73m²

  o systolic BP >130 mm Hg or diastolic BP >80 mm Hg

  o diagnoses of diabetic nephropathy, hypertensive nephrosclerosis, IgA nephropathy, focal segmental glomerulosclerosis, and obesity-associated glomerulopathy
Exclusion criteria:

- concomitant use of immunomodulatory drugs (e.g. steroids, mycophenolate mofetil, azathioprine, calcineurin inhibitors)
- inability to undergo 6 week washout period if already on RAAS-blocking drug(s) (includes renin inhibitor, ACE-inhibitor, ARB, and mineralocorticoid receptor blocker)
- eGFR < 50 ml/min/1.73m²
- urine protein excretion ≤ 500 mg/day or > 3500 mg/day
- serum K ≥ 5.0 mEq/l
- SBP ≥ 170 mm Hg or ≤ 120 mm Hg after washout period, DBP ≥ 110 mm Hg or ≤ 70 mm Hg after washout period
- congestive heart failure NYHA class III and IV; history of any cardiovascular events (stroke, TIA, MI, unstable angina, CABG, PCI, CHF hospitalization) in 3 months prior to study visit 1; 2nd or 3rd degree heart block without a pacemaker or other uncontrolled arrhythmia; clinically significant valvular disease, known renal artery stenosis
- any concurrent life threatening condition with a life expectancy less than 2 years
- pregnant or nursing (lactating) women, and women of child-bearing potential unless postmenopausal for at least 1 year, surgically sterile, or using effective methods of contraception

**Evaluation schedule:** 5 outpatient clinic visits to the Center for Glomerular Diseases at Columbia University over 9 months.