Supplemental Table 5. Clinical trials involving RAAS suppression in people with proteinuric kidney disease. Studies are presented in chrological order.

Disease	Treatment(s) Used in Experiments	Outcomes
Evaluation of renal outcomes from patients in the ONTARGET trial (coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage), follow-up ~5 years	Dual therapy with ACEI and ARB compared to mono-therapy with either ACEI or ARB	Dual therapy was shown to result in a greater reduction in proteinuria, yet was also associated with *worsening* of major renal outcomes (need for dialysis, increasing creatinine, and fall in estimated GFR).[1,2]
Meta-analysis of studies of IgA nephropathy	Dual therapy with ACEI and ARB compared to mono-therapy with either ACEI or ARB	Patients receiving dual therapy experienced a greater reduction in proteinuria that patients on mono-therapy. There was, however, no difference in glomerular filtration rate between patients receiving monotherapy and those receiving dual therapy. Therefore, a reduction in proteinuria may not translate to protection from progression or improvement in renal or cardiovascular function in *all* patients or types of proteinuric renal disease.[3,4]
Type-2 diabetic nephropathy, follow-up ~33 months	Dual therapy with DRI and either ACEI or ARB compared to mono-therapy with placebo and either ACE or ARB	This trial was stopped early as more patients in the DRI groups reached the composite endpoint (included time to cardiovascular death, and multiple indices of worsening cardiovascular and kidney function. Patients in the DRI groups also had an increased risk of hyperkalemia and hypotension.[5]
Type-2 diabetic nephropathy, follow up – 42 months	Dual therapy with ACEI and ARB compared to mono-therapy with ARB and placebo	Dual therapy with an ACEI and ARB was associated with an increased incidence of hyperkalemia and acute kidney injury, when compared to therapy with an ARB alone, resulting

		in early termination of the study. There was no benefit in either mortality or cardiovascular events at study termination.[6]
Diabetic nephropathy, treatment duration –18 months	Addition of spironolactone to ARB compared to placebo and ARB and ACEI	Reduction in the urine albumin to creatinine ratio was significantly greater in the spironolactone group; both groups had similar declines in estimated GFR.[7]
Chronic heart failure with reduced ejection fraction and mild to moderate chronic kidney disease	Finerenone compared to spironolactone	Finerenone was associated with lower incidences of worsening renal failure and hyperkalemia; both MRAs led to reduction in B-type natriuretic peptide (BNP), amino-terminal proBNP, and albuminuria.[8]
Systemic hypertension without diabetes, treatment duration –52 weeks	Addition of low-dose eplerenone to ACE and/or ARB compared to placebo and ACE and/or ARB	Percent reduction in the urine albumin to creatinine ratio was significantly greater in the eplerenone group.[9]
Chronic heart failure with reduced ejection fraction and type-2 diabetes mellitus and/or chronic kidney disease, treatment duration – 90 days	Finerenone compared to eplerenone	Finerenone was associated with a greater reduction in N-terminal proBNP, and fewer clinical events (death from any cause, cardiovascular hospitalizations, or emergency presentation for worsening heart failure) when compared to eplerenone.[10]

ACEI, angiotensin converting enzyme inhibitor; ARB angiotensin II type-1 receptor blocker; BNP, B-type natriuretic peptide; DRI direct renin inhibitor; GFR glomerular filtration rate; MRA, mineralocorticoid receptor antagonist

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