Complete Renin–Angiotensin–Aldosterone System (RAAS) Blockade in High-Risk Patients

Recent Insights From Renin Blockade Studies

Sanjay Rajagopalan, George L. Bakris, William T. Abraham, Bertram Pitt, Robert D. Brook

Online Data Supplement

It has been hypothesized that proximal inhibition of renin may exert complete inhibition of the renin–angiotensin–aldosterone system (RAAS), leading to prevention of recurrent events. In the recently published Aliskiren trial in Type 2 diabetes mellitus using cardioenal end points (ALTITUDE), aliskiren was associated with a trend toward higher composite cardiovascular events (primary end point) compared with placebo. In this review, we provide a summary of the preclinical and clinical data that leads to the development of renin inhibitors and offers perspectives on the findings from ALTITUDE, based on new information on RAAS components and their inhibition.

Rationale and Development of Oral Direct Renin Inhibitors

Theoretically, complete suppression of RAAS by renin inhibition has broad applicability in disease states associated with excess activation of the RAAS and continued production of angiotensin II (ang II) despite angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB) therapy. Pharmacological agents to treat hypertension (HTN) are well known for stimulating plasma renin activity (PRA), and it has been postulated that direct renin inhibitors (DRIs) may have synergistic effects with these agents. Initial attempts to develop DRIs failed because of lack of affinity toward the active site of renin and poor pharmacokinetic properties after oral administration. Aliskiren was synthesized using both crystal structure analysis of renin inhibitor complexes and computational molecular modeling with the intent of addressing issues of solubility and affinity. Aliskiren demonstrated subnanomolar inhibition of human renin (IC50=0.6 nmol/L) with a high degree of distribution in renal glomeruli and small cortical blood vessels. It lowered blood pressure (BP) in marmosets and was subsequently studied in a variety of disease contexts in both animals and humans. Aliskiren was approved for the treatment of HTN by both the US Food and Drug Administration and the European Medicines Agency in 2002. In head-to-head clinical trials, it lowered BP more efficaciously than hydrochlorothiazide and was shown to be noninferior or superior to ACEI/ARB in multiple studies (Table S1 in the online-only Data Supplement). Aliskiren was well tolerated with few adverse effects, rarely resulting in discontinuation and was shown to get patients to goal BP more effectively. Aliskiren is the only DRI developed clinically.

Effects of Aliskiren on Renin Levels and Renin–Prorenin Receptor Signaling

Plasma renin concentrations (PRC) increase with aliskiren, with levels often exceeding those observed during ACEI/ARB treatment. Indeed, it has been suggested that this increase in PRC may lead to a rise in ang II, offsetting the net ability to lower BP. The increase in PRC with DRI may potentially represent an artifact (as opposed to the real increase seen with ACEI/ARB or other vasodilator therapy) attributable to a concomitant rise in prorenin. Assays for PRC do not distinguish between renin and prorenin; this may account for an apparently higher concentration of PRC with renin inhibition. Although PRC did increase in response to DRI, especially in the context of combined ACEI/ARB and renin blockade, it has been suggested that plasma aliskiren levels at clinical doses are more than sufficient to counteract all of the catalytic activity of renin. Differential effects of Aliskiren on BP have been noted in patients based on baseline PRA status, with studies showing that most patients with low PRA and up to 30% of those with medium-high PRA may not appreciably lower BP with this agent. The lack of BP lowering has been suggested to be attributable to ineffective lowering of PRA in response to Aliskiren. Patients who do not demonstrate a satisfactory reduction in PRA have been thought to be prone to a paradoxical increase in BP with Aliskiren. This has been noted in 5% of patients taking aliskiren alone and in 10% when aliskiren was added to an ACEI or ARB.

The discovery of the prorenin receptor by Nguyen et al in 1996 suggested that renin may exert independent effects involving prorenin signaling.

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through pathways unrelated to downstream peptides.\(^{11}\) In a study by Feldman et al.,\(^{12}\) aliskiren exhibited specific binding to the active site of prorenin without altering prorenin binding to its receptor, consistent with earlier observations.\(^{8,13}\) Aliskiren reduced prorenin receptor gene expression in renal glomeruli and tubules of diabetic animals in vivo, an effect that was not seen in cultured mesangial cells. These results further reiterated the notion that renin inhibition may exert differential effects in the kidney, a tissue that is well known for expressing high levels of the prorenin receptor and prorenin.\(^4,12\) Prorenin is typically not expressed in the heart, vasculature, and therefore in these organs, the effects of DRI may reflect downstream effects of decreased Ang I/II signaling alone.\(^11\) Thus, favorable effects on progression of kidney disease and proteinuria in response to DRI have been postulated to result from not only effects of reduction of renin-enzymatic activity but also from the effects of disrupting renin signaling through the prorenin receptor.\(^11\) The lack of expression of prorenin in the heart and vasculature also has implications for nonrenin-mediated conversion of angiotensinogen to Ang II, detailed later in this review.

**Direct Renin Inhibition: Evidence From Experimental Studies**

Aliskiren has been studied in a variety of experimental conditions, including models of HTN, diabetes mellitus (DM), heart failure, and atherosclerosis. In many of these studies, aliskiren was used early during the course of disease, almost exclusively as sole therapy and often at high doses. In almost all reported studies, aliskiren resulted in favorable results that included decreases in BP, amelioration of Type II DM, including renal disease progression, and favorable reduction of atherosclerotic plaque progression in both murine and rabbit models. Table S2 reviews the pertinent preclinical studies on aliskiren in HTN, atherosclerosis, and insulin resistance. These studies collectively suggest that aliskiren exerts favorable effects through mechanisms that involve reduction in oxidative stress, innate immune activation, and fibrosis. In several of these articles, the effects on cardiac fibrosis and renoprotective effects occurred often at doses that were subpressor.\(^{14}\)

**Aliskiren+ACEI/ARB: Insights From Experimental Studies**

In contrast to the studies involving aliskiren monotherapy, studies that have examined aliskiren in conjunction with ACEI/ARB therapy are limited. In a study involving Aliskiren+olmesartan in streptozotocin-induced DM, the combination was superior to either agent alone in ameliorating proteinuria, inflammation, and circulating transforming growth factor β levels. These changes were accompanied by significantly lower BP in the combination group.\(^{15}\) The consistency of the effect of renin blockade on fibrosis across models, including nonhypertensive models such as COL4A3(−/−) mice subjected to ureteral obstruction, suggests that potentiation of antifibrotic effects, when aliskiren is used in conjunction with an ARB, could be a relevant mechanism operational in the kidney. Although these effects may simply relate to reduction in Ang II with the combination, it has also been postulated that renin blockade may disrupt renin–Prorenin receptor signaling pathways in cells such as podocytes that express high levels of the receptor.\(^{4,11,12}\) However, 2 recent studies did not detect favorable effects on fibrosis with combination therapy in the heart and kidneys of hypertensive rats despite greater reduction in aldosterone and BP.\(^{16,17}\) In the only study evaluating a combination of aliskiren with ARB in atherosclerosis in a large animal model by Imanishi et al.,\(^{18}\) plaque area was decreased in Watanabe heritable hyperlipidemic rabbits with combination therapy for 8 weeks versus either agent alone. To our knowledge, there are no studies of Aliskiren with an ACEI in animals.

**Renin Inhibition+ACEI/ARB: Insights From Human Studies**

The preponderant majority of studies that have examined the effects of renin blockade on top of ACEI or ARB therapy have been during a short term (≤24 weeks) and in the setting of HTN and Type II DM. These studies have generally included patients with normal renal function or mild chronic kidney disease (CKD). In general, these studies have shown the following: (1) Less than additive but incremental effect on systolic BP lowering when given on top of ACEI/ARB (2–5 mm Hg). (2) More effective reduction in PRA and plasma aldosterone levels. (3) Incremental reduction in proteinuria in diabetic kidney disease. (4) Low incidence of hyperkalemia, renal impairment, hypotension, and other adverse events primarily in mild CKD and in patient populations without pre-existent cardiovascular disease. Table S1 lists the human studies of Aliskiren with ACEI/ARB with BP as an end point, and Table S3 lists studies of Aliskiren with ACEI/ARB that used surrogate end points other than BP.

In the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study, patients (mean age, 60±10 years) were randomized to receive aliskiren (150 mg followed by 300 mg) or placebo (n=300/group), in addition to losartan (100 mg qd).\(^{19}\) The primary outcome was a reduction in the albumin-to-creatinine ratio at 6 months. Mean baseline systolic BP was 135±12 mm Hg with a nonsignificant reduction of 2 mm Hg in systolic BP with aliskiren. The patients enrolled were those with long-standing Type II diabetics mellitus (mean HbA1c of 8.0 and Stage II CKD, mean glomerular filtration rate [GFR] of 69±26 mL/min per 1.73 m²) with evidence of proteinuria (urinary albumin-to-creatinine ratio of 534 [463–609]). Aliskiren reduced mean urinary albumin-to-creatinine ratio by 20% versus placebo (P<0.001) after adjustment of BP effects. The mean rate of decline in estimated GFR and the rate of adverse events during the 24-week study period were comparable between the 2 groups.

The Aliskiren in Left Ventricular Hypertrophy (ALLAY) study was designed to assess whether the combination of aliskiren and losartan was superior to losartan alone in reducing left ventricular (LV) mass index.\(^{20}\) Patients (mean age of 59±10 years) with a history of or newly diagnosed HTN with left ventricular hypertrophy were randomized to aliskiren 150 mg, losartan 50 mg, or the combination. The mean BP at baseline was 145±14/89±9 mm Hg with a reduction of 7±15 mm Hg in aliskiren, 6±16 mm Hg in losartan and 7±17 mm Hg in the combination. Although all 3 arms reduced LV mass index, there were no differences between the 3 arms (4.9, 4.8, and 5.8 g/m² reduction in aliskiren, losartan, and combination arms, respectively). In a subset analysis, the relationship among diabetic status, degree of left ventricular...
hypertrophy, and response to aliskiren, or combination was evaluated. Combination therapy was associated with greater left ventricular hypertrophy reduction than losartan alone in patients with DM but not in patients without. Plasma aldosterone was reduced to a greater extent in patients with DM with RAAS antagonism ($P=0.004$). When patients were divided into tertiles based on aldosterone reduction, a linear trend toward greater reduction in LV mass was seen with the greatest reduction in aldosterone even after adjusting for covariates. Collectively, these results seemed to suggest that subgroups of patients with clearcut activation of the RAAS cascade defined by plasma aldosterone or disease states associated with activated RAAS cascade (Type II DM) may benefit from Aliskiren.

ALTITUDE was a randomized double-blind, placebo-controlled trial in Type II DM ($n=8561$, mean age of 65±10 years) of aliskiren versus placebo in patients on ACEI or ARB therapy. ALTITUDE enrolled a higher risk, more aged patient population with CKD (mean GFR of 57±22 mL/min per 1.73 m$^2$), most of whom had concomitant established cardiovascular disease (MI or stroke in 30%); >55% of patients had evidence of macroalbuminuria (urinary albumin creatinine ratio ≥200 mg/g and <2000 mg/g). Glycemic control was moderate with mean HbA1C of 7.8±1.6%. The primary outcome was a composite of death from cardiovascular (CV) causes or the first occurrence of cardiac arrest with resuscitation, nonfatal MI, or stroke, hospitalization for heart failure, end-stage renal disease, death attributable to kidney failure, or the need for renal-replacement therapy/doubling of serum creatinine. The trial was prematurely terminated after the second interim efficacy analysis after a median follow-up of 33 months, with an 8% increase in primary outcome measures in aliskiren as compared with placebo (hazard ratio, 1.08; 95% confidence interval, 0.98–1.20; $P=0.12$). All components of the CV outcome, with the exception of hospitalization for heart failure, occurred more frequently in the aliskiren group. Although all-cause mortality did not differ significantly between the groups, the number of sudden deaths was higher in aliskiren (17 excess deaths). BP during the trial increased in the aliskiren arm (1.5 mm Hg), although this increase was less than that noted in placebo. Aliskiren did not have any impact on GFR, although it did reduce proteinuria as evidenced by a 16% (95% confidence interval, 13–18) reduction in urinary albumin creatinine ratio at 6 months, versus 5% with placebo (95% confidence interval, 7–15; $P<0.001$). Interestingly, the effect estimate on proteinuria was identical to that seen in AVOID and in previous trials of ACEI+ARB therapy. Collectively, these results suggest that the mechanisms that drive reduction of microalbuminuria and proteinuria may be responsive to more complete RAAS blockade but reiterate the concept that reduction in proteinuria or microalbuminuria alone may not translate into reductions in cardiovascular and renal hard end points.

Mechanisms of Lack of Benefit of Aliskiren in Light of ALTITUDE

A number of reasons may account for the striking discordance between experimental studies, which almost overwhelmingly have been supportive of a beneficial effect, and large randomized controlled trials assessing hard outcomes such as ALTITUDE. The most obvious of these are differences between experimental animal models and humans, design considerations, lack of experimental equipoise, biological noise, and publication bias, all of which may fail to alert one to possible adverse signals. The short-term nature of almost all of the humans studies using surrogates versus those using hard outcomes, differential responsibility of some end points to RAAS blockade, and the inclusion of patients with advanced CKD represent important additional consideration. In support of CKD status being an important driver of adverse events, studies that have examined the combination of ARB+Aliskiren with milder degrees of CKD have not demonstrated adverse events, despite reductions in ambulatory BP in the combination arm that exceeded monotherapy alone.

What evidence is there that DRI may differ from dual RAAS blockade with ACEI+ARB? In Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), dual blockade with Telmisartan and Ramipril resulted in neither cardiovascular benefit nor harm over monotherapy in any subgroup, including those considered high risk such as those with low GFR and proteinuria. Similarly, in the systolic LV dysfunction and heart failure population assessed as part of the CHARM-Added (Candesartan and Valsartan in Acute myocardial infarction and LV dysfunction), there was no suggestion of an increase in CV mortality.

The combination therapy was shown to reduce BP more effectively in ONTARGET, based on ambulatory BP monitoring. Thus, the lack of benefit cannot be attributed to insufficient lowering of BP, but rather that excess BP lowering may have contributed to more adverse events such as hypotension and acute renal failure. In both ONTARGET and VALIANT, there was an excess of hypotension and hyperkalemia. Thus, dual blockade with an ACEI+ARB may resemble DRI+ACEI/ARB treatment, with more effective suppression of the RAAS and occurrence of renal and BP side effects such as hyperkalemia and hypotension. However, these effects including baseline potassium did not seem to drive propensity to cardiovascular events in trials such as ONTARGET and VALIANT that mostly included patients with preserved renal function. In contrast in ALTITUDE, which included patients with more substantial renal impairment, there was a significant interaction with baseline potassium, with levels of ≥5.0 mmol/L conferring a greater risk for the primary composite cardiovascular outcome (Figure S1). A related question that has been raised is whether more effective RAAS suppression may preferentially benefit patients with CKD and proteinuria (specifically low GFR and very high albumin creatinine ratios, eg, <300 mg/g). In a post hoc analysis of ONTARGET, dual therapy with Telmisartan and Ramipril was evaluated against the respective monotherapy according to higher risk subgroups defined by estimated GFR and the degree of albuminuria. Dual RAAS blockade reduced albuminuria more effectively compared with monotherapy but no improvements in cardiovascular outcomes was found even in the high renal risk group with low GFR (<60 mL/min per 1.73 m$^2$) and high albumin/creatinine ratio (>20 or >28 mg/mmol for men and women, [multiply by 8.84 for mg/g]). However, dual RAAS blockade
was associated with an increase in chronic dialysis and doubling of creatinine in this group. Recently, the VA sponsored NEPHRON-D study, a prospective, randomized, trial testing the efficacy of ACEI+ARB versus ARB alone in patients with Type II diabetes mellitus with albuminuria (>300 mg/g of creatinine) on the composite end point of reduction in estimated GFR/progression to end-stage renal disease or death, was stopped prematurely because of futility. Thus, there is no evidence that combination therapy with ACEI+ARB or ACEI/ARB+aliskiren reduces renal and cardiovascular outcomes across a spectrum of renal disease severity.

Lowering BP to <130 mmHg particularly in those with Type II DM/impaired fasting glucose has been associated with adverse consequences based on meta-analysis of large trials that have recruited those with diabetic hypertension.33 In ALTITUDE, although there were no differences in BP in the main analysis with either aliskiren or placebo, hypotension was more frequent in the elderly (>65 years), those with a pulse pressure below the median (68 mmHg), and patients receiving loop diuretics at baseline (data not shown in the main article). We await further subgroup analysis that would provide insight into whether cardiovascular events were indeed heightened in subgroups at higher risk such as low GFR, lower baseline BP, and those with the most significant on-trial BP lowering with aliskiren. Recent data from a trial with ambulatory BP data in a population with diabetic hypertension with estimated GFR of >60 mL/min per 1.73 m² suggest more robust BP effects of −14.1 mm Hg with the combination compared with −10.1 mm Hg with Valsartan alone.25 The incidence of hyperkalemia and hypotension was also noticeably lower in this study compared with ALTITUDE, suggesting that the degree of baseline renal impairment may be an important driver of adverse events with aliskiren+ARB therapy.

In the only study to date to evaluate the effects of aliskiren on atherosclerosis progression in humans, the effects of aliskiren on atherosclerosis were tested in patients with established cardiovascular disease as part of the Aliskiren Effect on Plaque Progression in Established Atherosclerosis Using High Resolution 3D MRI (ALPINE) trial (NCT01417104).34 After a 2-week single-blind placebo phase, patients in a single center were randomized to receive either placebo (n=37) or 150 mg of aliskiren (n=34), treatment dose was escalated to 300 mg at 2 weeks and maintained during the remainder of the study. Patients underwent dark-blood, 3-dimensional MRI assessment of atherosclerotic plaque in the thoracic and abdominal aorta at baseline and on study completion or termination (up to 56 weeks of drug or matching placebo). On average, patients were >60 years old, and the majority were obese (body mass index >30 kg/m²) with documented previous vascular disease. Baseline sitting clinic systolic BP was 127±13 mmHg in placebo group patients and 125±18 mmHg in Aliskiren, respectively; 60% of the placebo group patients and 61% of the aliskiren group patients were receiving ACEI/ARB therapy. The study’s primary end point was the difference in the normalized total aortic wall volume between the placebo and aliskiren groups in change at the end of the treatment period. The secondary end point was the difference in change in the percentage wall volume in the aorta between baseline and the end of the treatment period between the Aliskiren and placebo groups. The trial was terminated early based on the results of ALTITUDE, resulting in analysis of the MRI measures in 37 patients who completed ≥19 weeks of treatment. There were no significant differences between the 2 groups in any of the hemodynamic measures, including central aortic pressures. Aliskiren use resulted in significant progression of aortic wall volume (normalized total wall volume 5.31±6.57 versus 0.15±4.39 mm³; P=0.03, and percentage wall volume 3.37±2.96% versus 0.97±2.02%; P=0.04) compared with placebo (Figure 1). Further progression was noted only in subjects receiving aliskiren with ACEI/ARB therapy, but not in those who received aliskiren in the absence of background ACEI/ARB therapy.

## Additional Hypothetical Mechanisms of Risk With Renin Blockade + ACEI/ARB

Previous simplistic notions of renin and ACE being the most important rate limiting steps in Ang II generation have been replaced by a more complex and nuanced view of the RAAS with the identification of the angiotensin-converting enzyme 2 (ACE2)/Ang 1-7/Mas system and multiple novel angiotensin peptides.35–37 The primacy of renin-dependent hydrolysis of angiotensinogen has been questioned in both humans and animal models.37 Ang 1-12 formed by nonrenin-dependent pathways may contribute to continued production of both Ang I and Ang II through multiple pathways in tissues (Figure 2).36 Ang 1-12 for instance may represent an important pathway for persistent Ang II generation in tissues such as myocardium and vasculature that lack prorenin transcript.36 ACE2, a mono-carboxypeptidase cleaves Ang I and Ang II to Ang 1-9 and Ang 1-7, respectively, and closely regulates tissue levels of Ang II. ACE2 metabolizes Ang II ≈360-fold more efficiently than Ang I and the conversion of Ang II to Ang 1-7 is believed to be preferred over conversion of Ang I to Ang 1-9.35 Ang 1-7 is the major ligand for the Mas receptor and through this interaction effectively antagonizes many of the Ang II/Type I Ang II receptor effects.40,41 Studies in the ACE-deficient mice (ACE−/−) and ACE2−/− mice show that plasma Ang II is undetectable in the ACE−/− model, although tissue levels of Ang II...
Concomitant renin blockade, while blocking the catalytic activity of renin, may still result in increases in PRC that may exceed that of ACEI/ARB therapy alone as has been previously suggested. This may theoretically result in renin signaling through the renin receptor.

**Conclusions**

There are multiple theoretical advantages of more effectively inhibiting RAAS using DRI with ACEI/ARB. Indeed these combinations do seem to reduce BP favorably and prevent surrogate end points, including cardiac hypertrophy and proteinuria. However, the advantages have not been realized in clinical trials involving patients with cardiorenal disease, with the data in humans suggesting distinct adverse consequences. At this time, the mechanisms remain unclear but may involve adverse hemodynamic, renal, and vascular effects of these combinations. Currently, the use of aliskiren in conjunction with ACEI/ARB is proscribed with no plans to further develop this agent in the context of cardiovascular disease prevention. The ongoing ATMOSPHERE study in patients with LV systolic dysfunction will provide additional perspectives on the role of DRI, although the patients in this study were not receiving ACEI/ARB therapy. Additionally the results of the ongoing Safety and Efficacy of Aliskiren on the Progression of Atherosclerosis in Coronary Artery Disease Patients (AQUARIUS) trial (NCT00853827), which will evaluate the effect of Aliskiren alone (without concomitant ACEI/ARB) on the progression of coronary atherosclerosis in patients with established coronary disease on intravascular ultrasound end points, are likely to provide additional information. Defining the mechanisms of harm and benefit through diligent analysis of these trials and future trials that carefully compare DRI against other RAAS antagonists may be warranted.

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**References**

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Supplemental Figure and Tables

Complete Renin-Angiotensin-Aldosterone System (RAAS) Blockade in High Risk Patients: Recent Insights from Renin Blockade Studies

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**Table S1.** Human studies of aliskiren + ACEI/ARB compared to monotherapy with blood pressures as a surrogate.

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<td>Weinberger MH, et al.</td>
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<td>Geiger H, et al.</td>
<td>Different multi-drug regimens including aliskiren, valsartan, and hydrochlorothiazide (HCTZ) in patients not responsive to HCTZ monotherapy. (N=1249)</td>
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<td>Yarows SA, et al.</td>
<td>Patients with stage 2 HTN require large absolute reductions in blood pressure (BP) to achieve recommended BP goals. (N=1797)</td>
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<td>Chrysant SG, et al.</td>
<td>Open-label study examining the safety and efficacy of the aliskiren/valsartan combination in patients with HTN. (N=601)</td>
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<td>Azizi M, et al.</td>
<td>Efficacy of Renin inhibitor in conjunction with Valsartan in suppressing RAAS in HTN. (N=12)</td>
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<td>Pool JL, et al.</td>
<td>BP lowering effects of aliskiren, alone or in combination with valsartan in HTN patients. (N=1122)</td>
<td>Aliskiren (75, 150, or 300 mg), valsartan (80, 160, or 320 mg) or combination</td>
<td>Aliskiren and valsartan in combination may provide additive BP-lowering effects.</td>
</tr>
</tbody>
</table>
Table S2. Experimental Studies of Renin Inhibition

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Model</th>
<th>Intervention</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood JM, et al. 10</td>
<td>Sodium-depleted marmosets and SHR</td>
<td>In sodium-depleted marmosets, single oral dose of aliskiren (1-30 mg/kg). In SHR, aliskiren (10-100 mg/kg/d via osmotic pump.</td>
<td>Aliskiren is an orally effective, long-lasting renin inhibitor that shows antihypertensive efficacy in animals superior to previous renin inhibitors</td>
</tr>
<tr>
<td>Dechend R, et al. 11</td>
<td>Double-transgenic rat with both human renin and angiotensinogen genes [dTGR].</td>
<td>dTGR at 4 weeks received either Aliskiren at 0.03 mg/kg/day and 3 mg/kg/day (by osmotic minipump) or Losartan 2 mg/kg/day or Los 30 mg/kg/day in food.</td>
<td>Low-dose aliskiren and low-dose losartan effectively reduced mortality and target-organ damage with minimal, non-significant, effects on blood pressure (BP).</td>
</tr>
<tr>
<td>Pilz B, et al. 12</td>
<td>Double-transgenic rat [dTGR])</td>
<td>dTGR at 6 weeks, untreated rats compared with aliskiren (3 and 0.3 mg/kg per day) and valsartan (Val; 10 and 1 mg/kg per day) treatment.</td>
<td>In dTGR, equi-effective antihypertensive doses of Val or aliskiren attenuated end-organ damage.</td>
</tr>
<tr>
<td>Fischer R, et al. 13</td>
<td>Double-transgenic rat [dTGR]) and Sprague-Dawley (SD) controls.</td>
<td>Untreated dTGRs compared to 3-week treatment of n-3 PUFAs ethyl-esters (Omacor; 25-g/kg diet) or aliskiren (3 mg/kg per day by osmotic pumps).</td>
<td>n-3 PUFAs and aliskiren improved electrical remodeling, arrhythmia induction, and connexin 43, despite 70-mm Hg difference in BP and development of cardiac hypertrophy.</td>
</tr>
<tr>
<td>Feldt S, et al. 14</td>
<td>Double-transgenic rat [dTGR]) and Sprague-Dawley (SD) controls.</td>
<td>Vehicle-treated (dTGR), dTGR+aliskiren (3 mg/kg/bp osmotic pum), dTGR+HPR. Because dTGR produce both rat and human renin, rat (NH2-RILLKKMPSV-COOH) and human (NH2-RIFLKRMPSI-COOH) HRP (3.6 µg/kg/d each, co-infused by osmotic pumps) to block pro-renin receptor.</td>
<td>Preincubation with the HRP or aliskiren did not prevent renin- and prorenin-induced extracellular signal-regulated kinase 1/2 phosphorylation, whereas the MAP kinase kinase (MEK1/2) inhibitor PD98059 prevented both. In conclusion, renin inhibition but not treatment with the HRP protects against AngII-induced renal damage.</td>
</tr>
<tr>
<td>Whaley-Connell A, et al. 15</td>
<td>Transgenic (mRen2) 27 rat carrying the mouse Ren-2 gene into the rat genome.</td>
<td>Male Ren2 (6–7 wk of age) and age-matched SD rats w randomly assigned to placebo (Ren2-C and SD ), aliskiren at 50 mg/kg/day, or irbesartan (at 30 mg·kg−1·day−1) via IP injection.</td>
<td>Both renin inhibition and ARB significantly attenuated cardiac functional and structural alterations, although ARB treatment resulted in greater reductions of both BP and oxidative stress.</td>
</tr>
<tr>
<td>Whaley-Connell A, et al. 16</td>
<td>Transgenic (mRen2) 27 and age-matched Sprague-Dawley (SD) controls (age 6-9 wk).</td>
<td>Aliskiren, ARB (irbesartan) or vehicle treatment of mRen-2 (6-9 weeks) for 21 days.</td>
<td>Ren2 rats exhibited increases in SBP, albuminuria, and renal 3-nitrotyrosine content and decrease in podocyte protein nephrin which was attenuated to a similar extent with both treatments despite greater BP lowering with Irbesartan.</td>
</tr>
<tr>
<td>Vanourkova Z, et al. 17</td>
<td>12-week-old Transgenic (mRen2) 27</td>
<td>Ren2 were treated either with losartan (5 mg kg(-1)·day(-1)) or aliskiren (10 mg kg(-1)·day(-1)) for 10 weeks.</td>
<td>Despite similar reductions of MAP and renal ET-1 and ANG II levels aliskiren more effective than losartan in reducing albuminuria</td>
</tr>
<tr>
<td>Rakusan D, et al. 18</td>
<td>Young and Adult heterozygous mRen-2 rats</td>
<td>Aliskiren (10 mg/kg/day in osmotic minipumps) or losartan (5 mg/kg/day in drinking water) for 28 days in young rats and for 70 days in adult rats.</td>
<td>BP and cardiac hypertrophy persistedly reduced with Aliskiren while BP and cardiac hypertrophy rapidly increased after Losartan withdrawal.</td>
</tr>
<tr>
<td>Yamamoto E, et al. 19</td>
<td>Hypertensive endothelial NO synthase-deficient (NOS−) mice subjected to cuffed injury of femoral artery.</td>
<td>5 groups treated with: (1) vehicle; (2) aliskiren (25 mg/kg/d); (3) valsartan (8 mg/kg/d); (4) combined aliskiren (12.5 mg/kg/d) and valsartan (4 mg/kg/d); and (5) hydralazine (10 mg/kg/d) for 4 weeks.</td>
<td>Aliskiren and valsartan suppressed cardiac hypertrophy, inflammation, fibrosis, prevented injury-induced arterial intimal thickening and urinary albumin excretion to a similar extent. Combination of aliskiren and valsartan at half doses exerted superior effects compared to monotherapy via reduction in NADPH oxidase derived oxidative stress.</td>
</tr>
<tr>
<td>van Esch JH, et al. 20</td>
<td>Spontaneously hypertensive rats (SHR) compared to Wistar-Kyoto (WKY).</td>
<td>SHR treated for 1-3 weeks with vehicle, aliskiren, captopril or irbesartan (100, 3 and 15 mg/kg/day respectively) using an osmotic pump and compared to vehicle-treated WKY controls.</td>
<td>For a given decrease in BP, aliskiren improves coronary endothelial function and cardiac hypertrophy to same degree as ACEI or ARB blockade. In addition, aliskiren diminished A II response in the coronary circulation of SHR with better offered long-term cardiac ANG II suppression.</td>
</tr>
<tr>
<td>Rusai K et al. 21</td>
<td>Wistar-Kyoto rats (WKY) and Spontaneously hypertensive rats (SHR).</td>
<td>Serum angiopoietin-1 and angiopoietin-2 was measured in 2-month normotensive WKY and SHR after placebo or renin inhibition (aliskiren: 1</td>
<td>Renin inhibition modulates anti-angiogenesis signaling independently of BP by increasing angiopoietin-1/angiopoietin-2 ratio. This promoted</td>
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<tr>
<td>Study Authors</td>
<td>Study Design</td>
<td>Study Details</td>
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<tr>
<td>Kang et al.</td>
<td>Nonhypertensive mouse model for progressive renal fibrosis</td>
<td>COL4A3(–/–) mice received aliskiren via osmotic minipumps.</td>
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<tr>
<td>Gross O et al.</td>
<td>Three-week-old male SHRs and normotensive Wistar Kyoto control rats.</td>
<td>COL4A3(–/–) mice received aliskiren via osmotic minipumps.</td>
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<tr>
<td>Tain YL et al.</td>
<td>Transgenic (mRen2)27 rat (Ren2).</td>
<td>Aliskiren distributed extensively to the kidneys of normotensive (non)diabetic rats, localizing in the glomeruli and vessel walls after 2 hours exposure. In diabetic TG(mRen-2)27 rats, aliskiren (10 or 30 mg/kg per day, 10 weeks).</td>
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<tr>
<td>Lastra G, et al.</td>
<td>Transgenic (mRen2)27 rat (Ren2) and Sprague-Dawley (SD) controls.</td>
<td>Young (6-9 wk) Ren2 and matched SD were treated with aliskiren (50 mg/kg/d by IP injection) for 21 d. Control mRen2 demonstrated insulin resistance with increased islet insulin, Ang II, and reduced total insulin receptor substrate IRS-1/2 and Akt phosphorylation.</td>
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<tr>
<td>Elrashidy RA et al.</td>
<td>Diabetic nephropathy in rats by unilateral nephrectomy and clipping of renal artery followed by streptozotocin injection.</td>
<td>Pioglitazone (10 mg/kg per day), aliskiren (30 mg/kg per day) or combined pioglitazone and aliskiren for four weeks by gastric gavage.</td>
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<tr>
<td>Kang et al.</td>
<td>lepr–/– mouse model and cultured mesangial cells.</td>
<td>Six-week-old male db/db mice (C57BLKS/J-lepr(−/−)) and male non-diabetic db/m mice (C57BLKS/J-leprd+/+) treated with Aliskiren or placebo for 3 months at 25 mg/kg by osmotic pumps.</td>
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<tr>
<td>Dong et al.</td>
<td>lepr(−/−) mice</td>
<td>db/db mice treated with aliskiren (3 mg/kg per day), valsartan (5 or 10 mg/kg per day), combined aliskiren and valsartan (3 and 5 mg/kg per day), and hydralazine (80 mg/kg per day) for 6 weeks.</td>
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<tr>
<td>Dong et al.</td>
<td>lepr(−/−) mice</td>
<td>db/db mice treated with aliskiren (3, 6, 12 and 25 mg/kg/day or hydralazine (80 mg/kg/day for 6 weeks.</td>
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<tr>
<td>Lu et al.</td>
<td>Ldlr(−/−) fed high fat diet (TD88137), AT1a receptor(−/−) and Renin(−/−) mice used mice served as controls marrow donors</td>
<td>Aliskiren dissolved in PBS (2, 5, 25 and 50 mg/kg/d by osmotic minipump for a total of 12 weeks in Ldlr(−/−) mice. AT1a receptor(−/−) and Renin(−/−) mice used to transplant AT1a receptor and renin deficient marrow to irradiated Ldlr(−/−) mice.</td>
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<tr>
<td>Renin inhibition reduced atherosclerosis in a dose-dependent and BP independent manner in Ldlr(−/−) mice. Renin deficiency in macrophages but not AT1a receptor deficiency reduced atherosclerosis. Monocyte adhesion significantly decreased when HUVECs were co-incubated with macrophages from renin(−/−) mice vs. renin(+/+) mice.</td>
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Stabilization of endothelial cells in SHR, favors pro-angiogenic action resulting in higher capillary density. Nephroprotective effects of the renin inhibitor aliskiren beyond its antihypertensive property in this animal model of progressive renal fibrosis. Aliskiren mitigated increases in plasma ADMA in SHR while renal ADMA levels were lower in high-dose aliskiren versus SHR. Renal neuronal NOS-α and -β levels increased in SHRs fed with high-dose aliskiren. Data suggests that pancreatic functional/structural changes are driven, in part, by tissue renin-angiotensin system-mediated increases in NADPH oxidase and reactive oxygen species generation, abnormalities attenuated with aliskiren. Renin inhibition improved insulin sensitivity, insulin signaling, and glucose transport along with normalization of Ang II. AT(1)R, oxidative stress markers, fibrosis, and mitochondrial abnormalities. Pioglitazone attenuated cardiac lipid peroxidation, oxidative injury and fibrosis. This was associated with up-regulation of TGF-β1 and MMP-2 genes, aliskiren + pioglitazone exerted greater beneficial effect than monotherapy. Aliskiren improved HOMA-IR and triglycerides. Higher levels of SREBP2 and HMG CoA in liver were restored by Aliskiren. Urinary albumin excretion and VEGF levels were attenuated by aliskiren along with suppression of profibrotic and proinflammatory gene expression in kidneys/heart and mesangial cells (in-vitro). All sub-pressor doses of aliskiren attenuated cardiac fibrosis, macrophage infiltration and improved endothelial function. At the 25 mg/kg/day dose it improved glucose intolerance attenuated decrease in glucoregulatory TGFβ, macrophage infiltration, and nephrin expression. Reduced NADPH oxidase derived superoxide.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Model</th>
<th>Treatment</th>
<th>Observations</th>
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<tbody>
<tr>
<td>Imanishi et al.</td>
<td>WHHL rabbits</td>
<td>WHHL treated with vehicle (control), aliskiren, valsartan, or aliskiren plus valsartan for 8 weeks.</td>
<td>Combination therapy reduced atherosclerosis compared to monotherapy. Aliskiren+valsartan co-treatment increased NO production while reducing vascular superoxide generation more than with either aliskiren or valsartan alone. BH4 levels highest in combination group.</td>
</tr>
<tr>
<td>Nussberger et al.</td>
<td>ApoE−/− mice</td>
<td>3 weeks of aliskiren, 50 mg/kg per day via SC minipumps, irbesartan 100 mg/kg/d or atenolol, 120 mg/kg/d or amlodipine 6 mg/kg/d all in drinking water administered 1-week after surgery.</td>
<td>Aliskiren and irbesartan significantly prevented atherosclerosis progression in 2K1C mice. Compared with untreated animals, plaques treated with Aliskiren showed thinner fibrous cap; smaller lipid core; decreased media degeneration, layering, and macrophage content and increased smooth muscle cell content.</td>
</tr>
<tr>
<td>Kühnast S, et al.</td>
<td>ApoE*3Leiden.CETP transgenic mice.</td>
<td>Mice were fed a western-type diet (containing 0.25% cholesterol) alone or were treated with either aliskiren (15mg/kg per day), atorvastatin (3.6mg/kg per day) or a combination of aliskiren and atorvastatin.</td>
<td>Aliskiren inhibited atherosclerosis development and improved plaque stability alone and in combination with atorvastatin, possibly via a mechanism involving T cells.</td>
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</table>
Table S3. Human studies of aliskiren + ACEI/ARB compared to monotherapy examining surrogate outcomes other than blood pressure.

<table>
<thead>
<tr>
<th>Author(s)</th>
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<th>Intervention</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morishita Y et al. 35</td>
<td>Effect of aliskiren on BP, BNP, hs-CRP and diacron-reactive oxygen metabolite (d-ROM) in hypertensive CKD patients. (N=30)</td>
<td>Aliskiren (150 mg) added to existing antihypertensives.</td>
<td>Aliskiren reduced BNP, hsCRP and d-ROM levels in addition to BP lowering.</td>
</tr>
<tr>
<td>Nakamura T et al. 36</td>
<td>Evaluate renal injury parameters with addition of aliskiren to olmesartan in CKD patients. (N=36)</td>
<td>Aliskiren (300 mg daily), olmesartan (40 mg daily), and its combination therapy on urinary L-fatty acid binding protein (L-FABP).</td>
<td>Olmesartan or aliskiren monotherapy for 6 months comparably decreased BP and albuminuria. BP and albuminuria reduced more by combination. Combination therapy produced more reduction in L-FABP compared to monotherapy.</td>
</tr>
<tr>
<td>O’Brien E, et al. 37</td>
<td>24-hour BP lowering and renin suppression with combination of renin inhibitor with ACEI, ARB or HCTZ in HTN patients. (N=67)</td>
<td>25 of HCTZ + 150 mg of aliskiren. 75/150 of aliskiren + 5 mg ramipril. 75/150 of aliskiren+150 mg of irbesartan.</td>
<td>Aliskiren in combination with ACEI, ARB or HCTZ improves RAAS suppression and 24-hour blood pressure control</td>
</tr>
<tr>
<td>Parving HH, et al. 38</td>
<td>Effects of aliskiren + losartan in patients with HTN and type 2 DM with evidence of nephropathy in the Aliskiren in the EVAluation of PrOteinuria In Diabetes (AVOID) study. (N=599)</td>
<td>Patients receiving100 mg of losartan assigned to 6 months of placebo or aliskiren (150 mg daily for 3 months, followed by 300 mg for another 3 months)</td>
<td>Aliskiren + Losartan reduced urinary-albumin creatinine ratio by 40% compared to Losartan alone</td>
</tr>
<tr>
<td>Moriyyama T, et al. 39</td>
<td>Evaluate renin inhibitor+ARB combination in patients with non-diabetic chronic kidney disease (CKD), stage 2-3 and (urinary protein-to-creatinine ratio of 0.3–3.5 g/g. (N=10)</td>
<td>150 mg/day aliskiren while receiving olmesartan (had good BP control at baseline).</td>
<td>Urinary protein-to-creatinine ratio significantly decreased by about 40% at 16 weeks from baseline (( P = 0.0002 )) with the combination Rx.</td>
</tr>
<tr>
<td>Tang SC, et al. 40</td>
<td>Effect of renin-inhibition+ARB on proteinuria in nondiabetic CKD patients with IgA nephropathy and urine protein/creatinine ratio &gt;113 mg/mmol (1000 mg/g) (N=25)</td>
<td>Patients receiving losartan (100 mg daily) received additional treatment with aliskiren for 12 months</td>
<td>Treatment with aliskiren for 12 months reduced mean urinary protein/creatinine ratio by 26.3% (95% confidence interval, 20.1-43.6), with a reduction of ≥ 50% in 24% of patients.</td>
</tr>
<tr>
<td>Persson F, et al. 41</td>
<td>Effect of aliskiren on urinary albumin excretion rate (UAER) in patients with Type II DM.</td>
<td>2-month treatment with placebo or aliskiren 150 mg, 300 mg or 600 mg once daily.</td>
<td>No improved antiproteinuric effect with 600 mg aliskiren daily vs. 300 mg.</td>
</tr>
<tr>
<td>Persson F, et al. 42</td>
<td>Effect of baseline glycemic control on reduction of albuminuria with aliskiren added to losartan in AVOID study (N=599).</td>
<td>6 months aliskiren or placebo added to losartan 100 mg and optimal antihypertensive therapy.</td>
<td>Aliskiren 300 mg once daily added to losartan 100 mg once daily provides reductions in urinary albumin creatinine ratio that are efficacious in all diabetics.</td>
</tr>
<tr>
<td>Solomon SD, et al. 43</td>
<td>Effect of aliskiren, losartan, and their combination on the reduction of LV mass in hypertensive patients. (N=465)</td>
<td>Aliskiren 300 mg, losartan 150 mg, or their combination daily for 9 months.</td>
<td>Aliskiren as effective as Losartan in attenuating this measure of myocardial end-organ damage in hypertensive patients with LV hypertrophy. No additional effects of combination.</td>
</tr>
<tr>
<td>Vardeny O, et al. 44</td>
<td>To evaluate modification (if any) of Diabetes on efficacy of Aliskiren +ARB on LVH (subset of ALLAY). (N=465)</td>
<td>Aliskiren 300mg, losartan 100mg or both for 36 weeks, LVH regression by cardiac MRI</td>
<td>Patients with Diabetes and LVH derive more benefit with combination of aliskiren and losartan with respect to LVH reduction. Diabetic patients older, lower GFR and more obese.</td>
</tr>
<tr>
<td>Pitt B, et al. 45</td>
<td>Concomitant mineralocorticoid receptor antagonists (MRAs) on the safety and neurohumoral effects of renin inhibition (Aliskiren Observation of Heart Failure Treatment (ALOFT) study. (N=302)</td>
<td>Randomized to once-daily, double-blind treatment with aliskiren 150 mg or placebo, added to optimal HF therapy, for 12 weeks.</td>
<td>Aliskiren 150 mg added to standard HF therapy was well tolerated over 12 weeks and provided beneficial changes in neurohumoral biomarkers regardless of concomitant MRA treatment.</td>
</tr>
<tr>
<td>Mihai, et al. 46</td>
<td>Aliskiren Effect on Plaque Progression in Established Atherosclerosis Using High Resolution 3D MRI (ALPINE): A Double-Blind Placebo-Controlled Trial Effect of Aliskiren in patients with established cardiovascular disease (n=71).</td>
<td>Aliskiren 150 mg for 2 weeks followed by 300 mg for 36 weeks. MRI assessment at baseline and at the end of therapy.</td>
<td>Aliskiren use resulted in significant progression of aortic wall volume (normalized total wall volume 5.31±6.57 vs 0.15±4.39 mm³, ( P=0.03 ), and percentage wall volume 3.37±2.96% vs 0.97±2.02%, ( P=0.04 )) compared with placebo. In a subgroup analysis atherosclerosis progression was observed only in aliskiren group receiving ACE/ARB therapy, not in the placebo group.</td>
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Figure S1

Endpoints by potassium < 5.0 and ≥ 5.0 mmol/L and treatment. Plots represent hazard ratios with confidence intervals and p values. Adapted from N Engl J Med 2012; 367:2204-2213.