Direct Renin Inhibition: Focus on Aliskiren

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ABSTRACT

BACKGROUND: Despite the availability of many effective, well-tolerated drugs, a significant proportion of treated hypertensive patients still have uncontrolled high blood pressure (BP) and thus face serious morbidity and mortality. The renin-angiotensin aldosterone system (RAAS) is a key target for BP control and for cardiovascular and renal protection. Renin controls the rate-limiting step in the RAAS cascade and hence is the optimal target for RAAS suppression. Aliskiren is the first direct renin inhibitor (DRI) to be approved by the U.S. Food and Drug Administration and the European Medicines Agency for treating hypertension.

OBJECTIVE: To provide an overview of the pharmacology, pharmacokinetics, preclinical, and clinical efficacy and safety data on the DRI aliskiren.

RESULTS: Approximately 70% of essential hypertension is associated with elevated renin levels. Aliskiren is a potent and highly specific inhibitor of renin, with oral bioavailability of 2.6% and an elimination half-life of 40 hours, making it suitable for once-daily oral administration. Aliskiren dose-dependently reduced BP, inhibited plasma renin activity (PRA), attenuated renal damage in animal models, and showed efficient and longer-lasting blockade of the RAAS in normotensive human subjects compared with other RAAS inhibitors. The clinical efficacy and safety of aliskiren have been evaluated both as monotherapy and in combination with other antihypertensive agents in phase II and phase III trials of patients with mild to severe hypertension. When used as monotherapy, aliskiren led to significant dose-dependent reductions in BP from baseline that were greater than those obtained with placebo and comparable with those achieved with an angiotensin II receptor blocker (ARB). The combination of aliskiren with a diuretic, a calcium channel blocker (CCB), an angiotensin-converting enzyme inhibitor (ACEI), or an ARB generally had greater and longer-lasting BP-lowering efficacy than did single agents alone. Aliskiren also countered the reactive increase in PRA caused by diuretic, CCB, ACEI, and ARB therapy. Once-daily treatment with aliskiren was well tolerated.

CONCLUSIONS: As a DRI, aliskiren blocks the RAAS more completely than do other current downstream RAAS inhibitors. When used once daily, aliskiren is a safe and effective antihypertensive agent that can be used as monotherapy or in combination with other agents to provide additional options to improve BP control.

KEYWORDS: Aliskiren, Antihypertensives, Renin

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The renin-angiotensin aldosterone system (RAAS) is a coordinated hormonal cascade that governs cardiovascular, renal, and adrenal functions by regulating fluid and electrolyte balance as well as arterial pressure.[1] The RAAS regulates blood pressure (BP) via angiotensin release and body electrolyte content via aldosterone release.[2] Angiotensin (Ang) II is the principal effector hormone of the RAAS and is produced when renin acts on angiotensinogen to form Ang I, which is subsequently converted to the biologically active Ang II via the angiotensin-converting enzyme (ACE).[3] The "traditional" concept of the RAAS has expanded over the years to include local tissue RAASs in the heart, brain, kidney, pancreas, and peripheral vasculature, which act as paracrine or autocrine systems that regulate vascular function and cell growth and contribute to the pathogenesis of cardiovascular and renal diseases.[4,5]

Inhibition of RAAS activity with ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) has proven effective for not only controlling hypertension but also delaying the onset of diabetes mellitus, slowing renal damage in patients with hypertension, and reversing left ventricular hypertrophy.[6] However, these agents are no more effective than other antihypertensive agents in reducing major cardiovascular events,[6] which suggests an incomplete blockade of the RAAS. Inhibition of Ang II formation or action via ACEIs or ARBs does not provide optimal suppression of RAAS activity, because a compensatory increase in renin concentrations again increases Ang I and Ang II levels. Ang II can also be formed using pathways that do not involve ACE.[4]

Because it causes the conversion of angiotensinogen to Ang I, which is the rate-limiting step in the RAAS cascade, renin is the main determinant of RAAS activity and has been considered for at least 50 years the optimal target for RAAS suppression.[7] Circulating renin can be taken up by cardiac and coronary tissues, leading to the long-lasting generation of Ang II via ACE and non-ACE activity that is only partially suppressed by an ACEI.[8] Inhibition of renin would favor more complete blockade of the system. The successful production of a highly potent, selective, clinically effective oral renin inhibitor is a major development in the area of RAAS inhibition. This article provides an overview of direct renin inhibition (DRI) and reviews the pharmacologic and clinical profile of aliskiren, the first antihypertensive agent in a new class of drugs approved by the U.S. Food and Drug Administration (FDA) in more than 10 years. Aliskiren also received approval from the European Medicines Agency (EMEA).

Renin

Overactivity of the RAAS with high renin, Ang, and aldosterone levels causes fatal malignant hypertension and renovascular hypertension, whereas overactivity of the RAAS with milder elevations of renin levels has been associated with up to 70% of cases of essential hypertension.[2] Patients with plasma renin activity (PRA) levels exceeding 0.65 ng/mL/h have renin-mediated hypertension, and those with lower PRA levels have salt hypertension, which accounts for the remaining 30% of essential hypertension.[2]

Renin is an aspartyl protease that is synthesized as prorenin, a proenzyme that is transformed into renin by cleavage of a 43-amino-acid segment from the N-terminal end (Figure 1). This activation process, which occurs exclusively in the juxtaglomerular cells of the kidney, is followed by the release of renin into the circulation system.[9] Although it is synthesized in only a few tissues (eyes, adrenal glands, testes, ovaries, and brain), prorenin represents between 70% and 90% of the total plasma renin in individuals without diabetes and as much as 95% of the total plasma renin in individuals with diabetes.[10] The local actions of renin are thus mediated by kidney-derived renin that is released into the circulation system and taken up by tissues. For example, cardiac Ang production depends on the conversion of angiotensinogen in extracellular fluid by plasma-derived renin.[11]

Renin receptors have been localized to glomerular mesangium and vascular smooth muscle cells within the subendothelium of glomerular and coronary arteries.[9] The receptor colocalizes with renin. Cells transfected with receptor cDNA result in the expression of a membrane protein that specifically binds renin and prorenin with high affinity.[9] Labeling studies have demonstrated high-affinity binding (K_d = 0.4 nM) of renin to receptors on cultured human mesangial cells.[12]

The binding of renin to its receptor with a single transmembrane domain has multiple and far-reaching consequences. Receptor binding induces a 4-fold increase in the catalytic conversion of angiotensinogen to Ang I, suggesting that the cell surface is an important site of Ang generation.[9] Once bound, renin triggers a series of intracellular events that culminate in activation of the mitogen-activated protein kinases ERK1 (p44) and ERK2 (p42), which are involved in cell hypertrophy and proliferation.[9] At physiologic levels, renin enhances the incorporation of ^{3}H-thymidine into cells, with no increase in cell numbers; increases transforming growth factor beta in mesangial cells (suggesting upregulation through a receptor-mediated mechanism, independent of Ang II generation or action); and activates the synthesis of plasminogen activator-1 and fibrotic extracellular components such as fibronectin and collagen (suggesting that renin may contribute to fibrotic disease).[13,14] Overexpression of the renin receptor in arterial smooth muscle cells of transgenic rats resulted in high BP levels, increased heart rate, and significant elevation of plasma aldosterone levels, effects that were attributed to local activation of the intraadrenal RAAS.[15]

When bound to the renin receptor, the catalytic activity of prorenin is comparable with that of renin and appears to be of pathologic significance.[9] Elevated prorenin levels have been correlated with microvascular complications of diabetes, and lesions mimicking diabetic nephrosclerosis are present in transgenic rats expressing prorenin.[16] Rats with streptozocin-induced diabetes have high levels of prorenin, Ang I, and Ang II, but not of renin, ACE, or angiotensinogen.[16] Nonproteolytic activation of prorenin to its enzymatically active state occurs through the binding of certain carbohydrate substances or the renin receptor. When nonproteolytic conversion of prorenin was inhibited with a blocking peptide, levels of renal Ang I and Ang II were reduced and the development of nephropathy was attenuated, thus substantiating that prorenin has a role in the progression of diabetic renal damage.[16] How prorenin contributes to the pathophysiology of these complications remains to be established.

Direct Renin Inhibition

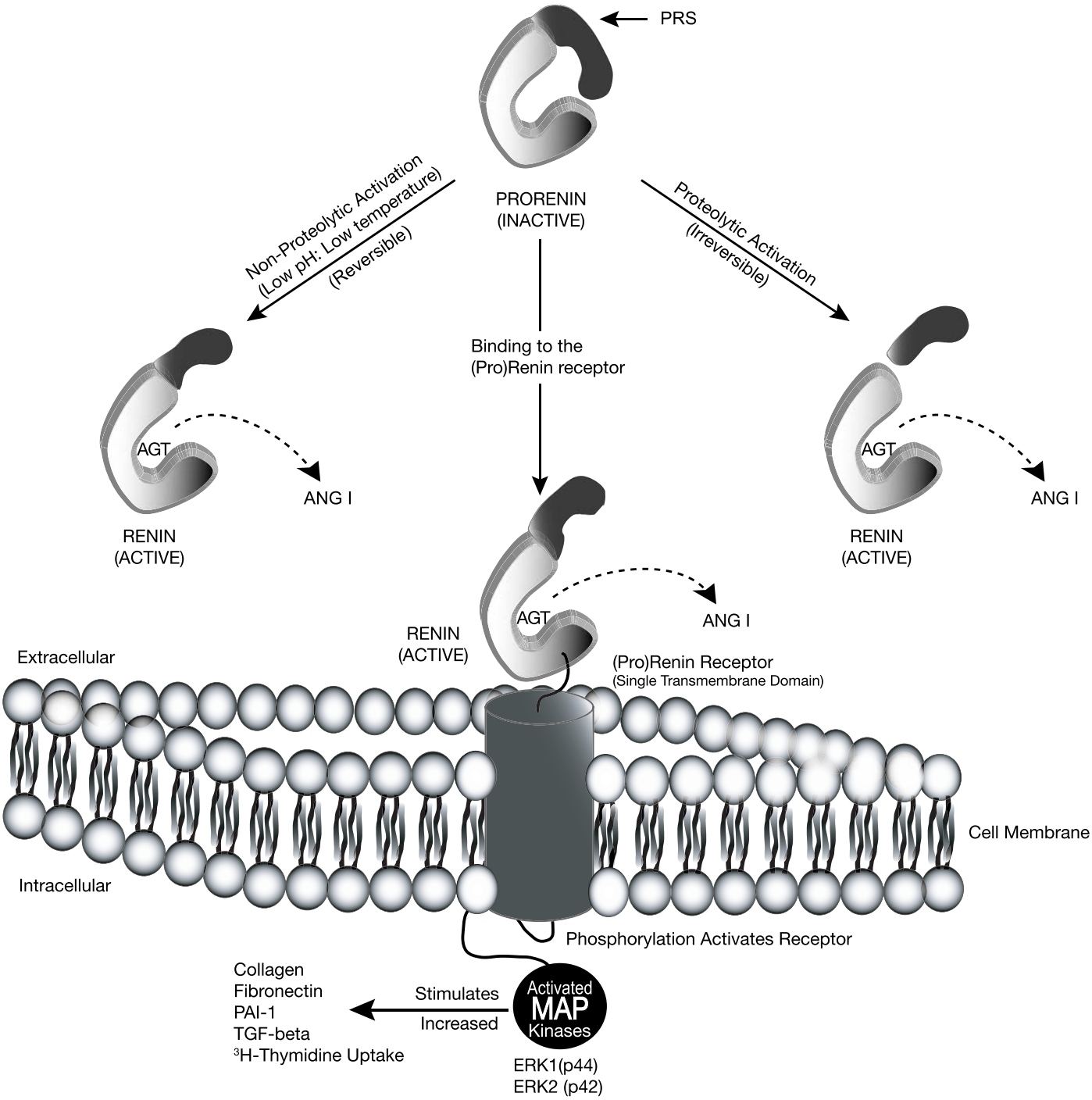
The concept of blocking the RAAS at its origin by inhibiting renin has existed for at least 50 years. The first synthetic renin inhibitor was pepstatin, which was followed by first-generation agents that were active but required parenteral administration.[17] Oral agents that were subsequently developed, such as enalkiren, remikiren, and zankiren, had limited clinical use because they demonstrated poor bioavailability (<2%), short half-lives, and weak antihypertensive activity.[17] Crystal structure analyses of renin-inhibitor complexes and computational molecular modeling were later used to design selective nonpeptide DRIs that lacked the extended peptide-like backbone of previous inhibitors and had improved pharmacokinetic properties.[18] Aliskiren is the first of these new nonpeptide DRIs to be approved by the FDA for the treatment of hypertension. It is administered once daily, either as monotherapy or in combination with other antihypertensive agents. In Europe, aliskiren received approval from the EMEA for the treatment of hypertension.

Aliskiren

Aliskiren is a transition-state mimetic agent with high hydrophilicity, which improves its oral bioavailability.[18] It is a highly potent inhibitor of renin (IC50 = 0.6 nM) with a high affinity for renin and a high species specificity for primate renin. Aliskiren inhibits human, marmoset, and rat plasma renin with IC50 values of 0.6 nmol per L, 2.0 nmol per L, and 80 nmol per L, respectively.[18] Therefore, preclinical testing has been performed in sodium-depleted marmosets and in spontaneously hypertensive rats.

In sodium-depleted marmosets, doses of aliskiren ranging from 0.3 mg per kg to 10 mg per kg caused a dose-dependent reduction in mean arterial BP.[19] All doses of aliskiren completely inhibited PRA within 1.5 hours of administration, and this inhibition was sustained for more than 24 hours with the 3 mg per kg and 10 mg per kg doses.[19] When the 3 mg per kg dose was

FIGURE 1 *Pro(renin) Receptor Binding Initiates Intracellular Signaling; 1 of 3 Mechanisms to Activate Prorenin to Renin*



AGT=angiotensinogen; ANG I=angiotensin I; MAP=mitogen-activated protein; PAI=plasminogen activator inhibitor; PRS=prorenin segment; TGF=transforming growth factor.

administered, BP was reduced by a maximum of 30 mm Hg without any effect on heart rate. The 10 mg per kg dose of aliskiren was more effective than similar doses of either benazepril or valsartan in reducing mean arterial pressure.[19]

Pilz and colleagues compared the effects of subcutaneous aliskiren 0.3 mg per kg per day, 3 mg per kg per day with valsartan 1 mg per kg per day, and 10 mg per kg per day with no treatment on the development of end-organ damage in hypertensive double-transgenic rats with high levels of serum creatinine and albuminuria.[20] Both doses of aliskiren and the higher dose of valsartan reduced renal Ang I and II content, maintained creatinine at normal levels, decreased albuminuria, prevented renal infiltration with inflammatory cells, reduced cardiac hypertrophy, and prolonged survival.[20] However, aliskiren 3 mg per kg per day was significantly more effective than valsartan 10 mg per kg per day in reducing systolic BP (SBP), cardiac hypertrophy, and left ventricular wall thickness ($P<0.05$ for all endpoints).[20] In this model, renin inhibition compared favorably with AT_1 receptor blockade in reversing renal damage.

Subsequent studies in normotensive human subjects demonstrated efficient blockade of the RAAS with aliskiren. In 18 normotensive men with a sodium intake of 100 mmol/day, treatment with aliskiren (40 mg per day to 640 mg per day) for 8 days significantly and in a dose-dependent manner suppressed PRA and plasma concentrations of Ang I and Ang II.[21] Maximal reduction of Ang II occurred within 1 hour of the administration of aliskiren, compared with 6 hours with a 20 mg dose of enalapril. The level of inhibition of Ang II by enalapril (57%) was similar to that with a 160 mg dose of aliskiren (56%).[21] A dose of aliskiren ≥80 mg reduced plasma aldosterone levels within 3 hours of administration and, at the highest dose, these levels remained suppressed for up to 24 hours.[21] In response to the reduction in Ang II level, plasma renin concentrations increased similarly with aliskiren 160 mg and enalapril 20 mg.[21]

A double-blind, placebo-controlled, randomized, 4-period crossover study in 12 normotensive men who were mildly sodium depleted compared a single high dose of aliskiren (300 mg), a standard dose of valsartan (160 mg), and their combination at half doses (aliskiren 150 mg plus valsartan 80 mg).[22] In contrast to valsartan, aliskiren decreased PRA and Ang I and Ang II levels for 48 hours, inhibited urinary aldosterone secretion for a longer period, and resulted in greater and longer-lasting increases in plasma renin levels.[22] In general, the effects of the low-dose combination were similar to those of aliskiren 300 mg than to those of valsartan 160 mg. The combination blunted the valsartan-induced increase in PRA and Ang I and Ang II concentrations, led to greater and longer suppression of urinary aldosterone excretion compared with valsartan alone, and was as effective as either monotherapy in reducing BP.[22] The longer duration of RAAS inhibition by aliskiren compared with valsartan suggested that the effects of Ang II may be reduced more effectively by direct renin inhibition than by Ang receptor blockade.

Aliskiren Pharmacokinetics

The pharmacokinetics of aliskiren deviate from dose linearity, with an overproportional increase in area under the curve (AUC) and C_{max} with respect to the administered dose.[22] The mean terminal half-life is approximately 40 hours after multiple administrations of a single dose, and repeated once-daily administration leads to drug accumulation.[23] The mean absolute bioavailability is 2.6%[24]; administration with a high-fat meal reduces AUC and C_{max} values by 71% and 85%, respectively, of those in the fasting state, so patients should be advised to take aliskiren in the same manner each day with respect to meal times.[25] Peak plasma concentrations are reached 1 to 2 hours after dosing,[23,24] and steady state is reached after 5 to 8 days of once-daily administration.[21]

The main pathway of elimination for aliskiren is via biliary excretion as unmetabolized drug. Less than 1% of an orally administered dose is excreted in urine.[21] Aliskiren is not metabolized by, and does not induce or inhibit, cytochrome P450 enzymes and shows no clinically relevant pharmacokinetic interactions with warfarin,[17] lovastatin,[26] atenolol,[26] celecoxib,[26] cimetidine,[26] amlodipine,[27] valsartan,[27] hydrochlorothiazide (HCTZ),[27] or ramipril.[27] Coadministration of aliskiren with furosemide, a commonly used loop diuretic, reduced the AUC of furosemide by 28% and C_{max} by 49%, but the clinical significance of this remains uncertain.[28] The pharmacokinetics of aliskiren remain unaffected by ethnicity,[24] age,[29] gender,[23] hepatic impairment,[30] renal impairment,[31] and diabetes.[23]

Studies in Patients With Hypertension

Phase II and III clinical trials have demonstrated the efficacy of once-daily administration of aliskiren in the treatment of patients with mild to moderate hypertension (diastolic blood pressure [DBP] ≥95 mm Hg and <110 mm Hg, either as monotherapy or in combination with diuretics, calcium channel blockers [CCBs], ACEIs, or ARBs), or as monotherapy in the treatment of severe hypertension (DBP ≥105 mm Hg and <120 mm Hg). Two trials that evaluated both monotherapy and combination therapy with aliskiren are discussed below in *Combination Therapy*.[32,33] Table 1 provides details of the study design and the main findings of all the trials that are discussed.

Monotherapy

In a 4-week study, aliskiren 37.5 mg, 75 mg, 150 mg, or 300 mg once daily was compared with losartan 100 mg once a day.[34] Dose-dependent reductions from baseline in daytime ambulatory SBP (ASBP) were obtained with all doses of aliskiren ($P=0.0002$ vs. baseline for all doses).[34] The changes in daytime ASBP with the 3 highest doses of aliskiren were similar to those obtained with losartan 100 mg,[34] and the heart rate remained unaltered. All doses of aliskiren also led to significant dose-dependent decreases of PRA between -55% and -83% ($P=0.0008$ vs. baseline), whereas PRA increased by 110% with losartan.[34]

TABLE 1 *Phase II and III Double-Blind Clinical Trials of Once-Daily Aliskiren Treatment in Patients With Mild to Moderate Hypertension*[32-41]

Study	Study Design (Number of Patients Randomized; Mean Age)	Treatments/ Duration*	Effects of Aliskiren on Primary Efficacy Variable (Statistical Significance)
Monotherapy			
Stanton et al.[34] (2003)	r, db, ac (226; 52 years)	Aliskiren 37.5 mg, 75 mg, 150 mg, or 300 mg Losartan 100 mg 4 weeks	Lowers daytime ASBP (P=0.0002 vs. baseline; all doses) No significant difference between aliskiren 75 mg, 150 mg, and 300 mg and losartan 100 mg in mean change in daytime ASBP (all doses: P=NS) Reductions from baseline in: MSSBP/MSDBP (mm Hg) A37.5 mg: -4.3/-1.9 A75 mg: -4.1/-0.2 A150 mg: -10.0/-2.2 A300 mg: -11.8/-5.7 L100 mg: -11.4/-5.5
Gradman et al.[35] (2005)	r, db, pc, ac (652, 56 years)	Aliskiren 150 mg, 300 mg, or 600 mg Irbesartan 150 mg Placebo 8 weeks	Lowers trough MSDBP (P<0.001 vs. placebo, all doses) Aliskiren 150 mg=irbesartan 150 mg Reductions from baseline in: MSSBP/MSDBP (mm Hg) / CR A150 mg: -11.6/-9.8 / 38% A300 mg: -15.8/-11.8 / 50% A600 mg: -15.7/-11.5 / 46% Ir150 mg: -12.5/-8.9 / 34% Placebo: -5.3/-6.3 / 21%
Oh et al.[36] (2007)	r, db, pc, (672; 53 years)	Aliskiren 150 mg, 300 mg, or 600 mg Placebo 8 weeks	Lowers MSDBP and MSSBP (all doses; P<0.0001 vs. placebo) Reductions from baseline in MSSBP/MSDBP levels at 8 weeks, and in RR and CR at 2 weeks postwithdrawal: MSSBP/MSDBP (mm Hg) / RR / CR A150 mg: -13.0/-10.3 / 59% / 36% A300 mg: -14.7/-11.1 / 63% / 42% A600 mg: -15.8/-12.5 / 69% / 46% Placebo: -3.8/-4.9 / 36% / 20%
Strasser et al.[37] (2007)	mc, r, db (183; 55.4 years)	Aliskiren 150 mg/300 mg Lisinopril 20 mg/40 mg (option to add HCTZ) 8 weeks	Mean reductions from baseline in: MSSBP/MSDBP (mm Hg) / RR A300 mg: -20.0/-18.5 / 81.5% L40 mg: -22.3/-20.1 / 87.9%

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In an 8-week placebo-controlled study, Gradman and colleagues randomized patients to once-daily aliskiren 150 mg, 300 mg, or 600 mg; irbesartan 150 mg; or placebo.[35] All doses of aliskiren reduced mean sitting DBP (MSDBP) and mean sitting SBP (MSSBP, P<0.001 vs. placebo for both variables).[35] Antihypertensive efficacy and control rates were comparable in the aliskiren 150 mg and irbesartan 150 mg arms but higher in the aliskiren 300 mg and aliskiren 600 mg arms.[35]

In another placebo-controlled study, Oh and colleagues evaluated the effects of treatment withdrawal after 8 weeks of monotherapy with aliskiren (150 mg, 300 mg, or 600 mg).[36] All doses of aliskiren produced greater reductions in MSDBP and mean MSSBP than did placebo (P<0.0001, Figure 2),[36] as well as daytime and nighttime mean ambulatory DBP (ADBP) and ASBP.[36] The antihypertensive effect persisted for 2 weeks after drug withdrawal, with BP levels lower in the aliskiren groups than in the placebo group.[36]

In an 8-week, active-controlled, parallel-group study, Strasser and colleagues compared the tolerability (primary endpoint) and efficacy of aliskiren 150 mg once daily with lisinopril 20 mg once

Table 1 (continued)—Phase II and III Double-Blind Clinical Trials of Once-Daily Aliskiren Treatment in Patients With Mild to Moderate Hypertension

Study	Study Design (Number of Patients Randomized; Mean Age)	Treatments/ Duration*	Effects of Aliskiren on Primary Efficacy Variable (Statistical Significance)
Combination Therapy			
Villamil et al.[32] (2007)†	r, db, pc (2,776; 55 years)	Aliskiren 75 mg, 150 mg, or 300 mg HCTZ 6.25 mg, 12.5 mg, or 25 mg Aliskiren 75 mg+HCTZ 6.25 mg, 12.5 mg, or 25 mg Aliskiren 150 mg+ HCTZ 6.25 mg, 12.5 mg, or 25 mg Aliskiren 300 mg+HCTZ 12.5 mg or 25 mg Placebo 8 weeks	Lowers MSDBP (P=0.0002 vs. placebo; overall Dunnett's test; all doses) Lowers MSDBP (all combinations, P<0.0001 vs. placebo; most combinations, P<0.05 vs. monotherapy with either component) Reductions from baseline in: MSSBP/MSDBP (mm Hg) / RR A75 mg: -9.4/-8.7 / 52% A150 mg: -12.2/-8.9 / 52% A300 mg: -15.7/-10.3 / 64% HCTZ 6.25 mg: -11.0/-9.1 / 54% HCTZ 12.5 mg: -13.9/-10.1 / 61% HCTZ 25 mg: -14.3/-9.4 / 59% A75 mg/HCTZ 6.25 mg: -14.3/-10.8 / 62% A75 mg/HCTZ 12.5 mg: -15.6/-11.1 / 64% A75 mg/HCTZ 25 mg: -17.3/-11.5 / 70% A150 mg/HCTZ 6.25 mg: -15.3/-10.4 / 58% A150 mg/HCTZ 12.5 mg: -17.6/-11.9 / 70% A150 mg/HCTZ 25 mg: -19.5/-12.7 / 71% A300 mg/HCTZ 12.5 mg: -19.8/-13.9 / 31% A300 mg/HCTZ 25 mg: -21.2/-14.3 / 77% Placebo: -7.5/-6.9 / 46%
Jordan et al.[38] (2007)	r, db (560; 54.1 years)	HCTZ 25 mg 4 weeks Then, for nonresponders to HCTZ: Aliskiren 150 mg, irbesartan 150 mg, amlodipine 5 mg, or placebo; each plus HCTZ 25 mg 4 weeks Aliskiren 300 mg, irbesartan 300 mg, amlodipine 10 mg, or placebo; each plus HCTZ 25 mg 8 weeks	Aliskiren/HCTZ: Lowers MSDBP in obese patients (P<0.0001 vs. placebo/HCTZ); treatment difference of -4.0 mm Hg for MSDBP and -7.2 mm Hg for MSSBP Aliskiren/HCTZ=irbesartan/HCTZ=amlodipine/HCTZ (P=NS for group difference)
Drummond et al.[39] 2007	r, sb then db, parallel-group	Amlodipine 5 mg (sb, 4 weeks) Amlodipine 5 mg, amlodipine 10 mg, or aliskiren 150 mg plus amlodipine 5 mg (db, 6 weeks)	Reductions from baseline in: MSSBP/MSDBP (mm Hg) A150 mg/amlodipine 5 mg: -11.0/-8.5 Amlodipine 5 mg: -5.0/-4.8 Amlodipine 10 mg: -9.6/-8.0 RR Proportion of patients achieving MSDBP <90 mm Hg and/or at least 10 mm Hg reduction from baseline A150 mg/amlodipine 5 mg: 64.2% Amlodipine 5 mg: 45.2% Amlodipine 10 mg: 59.9% CR Proportion of patients achieving BP <140/90 mm Hg A150 mg/amlodipine 5 mg: 42.8% Amlodipine 5 mg: 22.6% Amlodipine 10 mg: 37.9% All outcome measures P<0.005 aliskiren 150 mg plus amlodipine 5 mg or amlodipine 10 mg, compared with amlodipine 5 mg

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Table 1 (continued)—Phase II and III Double-Blind Clinical Trials of Once-Daily Aliskiren Treatment in Patients With Mild to Moderate Hypertension

Study	Study Design (Number of Patients Randomized; Mean Age)	Treatments/ Duration*	Effects of Aliskiren on Primary Efficacy Variable (Statistical Significance)
Combination Therapy (continued)			
Uresin et al.[40] (2006)	r, db (837; 59.8 years) Patients with type 1 or type 2 diabetes	Aliskiren 300 mg Ramipril 10 mg Aliskiren/ramipril 300/10 mg	Reductions from baseline in: MSSBP/MSDBP (mm Hg) A300 mg: -14.7/-11.3 R10 mg: -12.0/-10.7 A300 mg/R10 mg: -16.6/-12.8
Pool et al.[33] (2007)‡	r, db, pc (1,123; 56 years)	Aliskiren 75 mg, 150 mg, 300 mg Valsartan 80 mg, 160 mg, or 320 mg Aliskiren (150 mg, 300 mg, or 600 mg) Aliskiren/valsartan 75 mg/80 mg, 150 mg/160 mg, 300mg/320 mg Valsartan/HCTZ 160 mg/12.5 mg Placebo 8 weeks	Lowers MSDBP (aliskiren 300 mg; $P<0.001$ vs. placebo) Aliskiren = valsartan Lowers MSDBP ($P<0.05$ vs. placebo), aliskiren/valsartan = valsartan/HCTZ (P = NS for group difference) Reductions from baseline in: MSSBP/MSDBP (mm Hg) / RR / CR A75 mg: -12.1/-10.3 / 60% / 36% A150 mg: -12.1/-10.3 / 59% / 31% A300 mg: -15.0/-12.3 / 68% / 42% V80 mg: -11.2/-10.5 / 55% / 38% V160 mg: -15.5/-11.0 / 66% / 47% V320 mg: -16.5/-11.3 / 63% / 42% A75 mg/V80 mg: -14.5/-11.8 / 75% / 43% A150 mg/V160 mg: -16.6/-12.1 / 67% / 37% A300 mg/V320 mg: -18.0/-12.9 / 76% / 50% V160 mg/HCTZ12.5 mg: -18.9/-13.5 / 79% / 55% Placebo: -10.0/-8.6 / 8% / 28%
Oparil et al.[41] (2007)	r, db, pc (1,797; 52.3 years)	Aliskiren 300 mg Valsartan 320 mg Aliskiren/valsartan 300 mg/ 320 mg Placebo 8 weeks	Week 8 reductions from baseline in: MSSBP/MSDBP (mm Hg) / MASBP/MADBP (mm Hg) / CR A300 mg: -13.0/-9.0 / -9.8/-7.1 / 37% V320 mg: -12.8/-9.7 / -10.1/-7.1 / 34% A300 mg/V320 mg: -17.2/-12.2 / -14.4/-10.3 / 49% Placebo: 4.6/-4.1 / -1.3/-1.1 / 17%

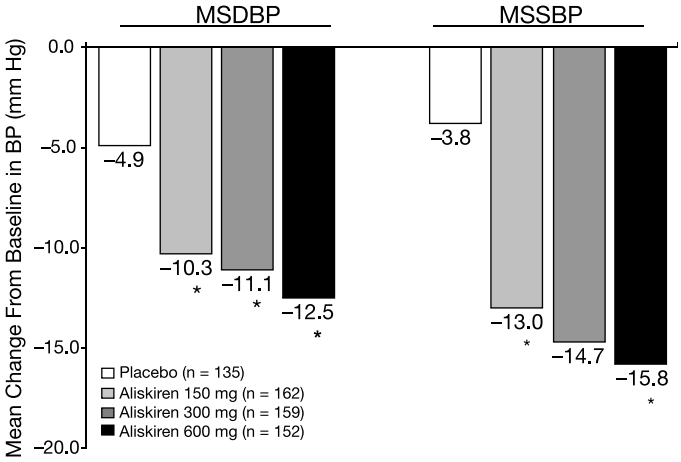
**All treatments were administered once daily.*

†This trial evaluated the efficacy of aliskiren as monotherapy and in combination with HCTZ. A total of 2,776 patients were randomized to placebo (n = 195); aliskiren 75 mg, 150 mg, 300 mg monotherapy (n = 184, 185, 183); HCTZ 6.25 mg, 12.5 mg, 25 mg monotherapy (n = 194, 188, 176); or combination aliskiren/HCTZ therapy (75 mg/6.25 mg, n = 188; 75 mg/12.5 mg, n = 193; 75 mg/25 mg, n = 186; 150 mg/6.25 mg, n = 176; 150 mg/12.5 mg, n = 186; 150 mg/25 mg, n = 188; 300 mg/12.5 mg, n = 181; 300 mg/25 mg, n = 173). The total number of patients given in the table includes the placebo group.

‡This trial evaluated the efficacy of aliskiren as monotherapy (primary objective) and in combination with valsartan (secondary objective). A total of 1,123 patients were randomized to placebo (n = 177); aliskiren 75 mg, 150 mg, 300 mg monotherapy (n = 179, 178, 175); valsartan 80 mg, 160 mg, 320 mg monotherapy (n = 58, 59, 60); combination aliskiren/valsartan (75 mg/80 mg, n = 80; 150 mg/160 mg, n = 60; 300 mg/320 mg, n = 58); or combination valsartan/ HCTZ 160 mg/12.5 mg (active control; n = 59). The total number of patients given in the table includes the placebo group.

A = aliskiren; ac = active controlled/active comparator; ASBP = ambulatory systolic blood pressure; CR = control rate; db = double blind; HCTZ = hydrochlorothiazide; Ir = irbesartan; L = losartan; MADBP = mean ambulatory diastolic pressure; MASBP = mean ambulatory systolic pressure; MSDBP = mean sitting diastolic blood pressure; MSSBP = mean sitting systolic blood pressure; NS = not significant; pc = placebo controlled; R = ramipril; r = randomized; RR = responder rate; sb = single blind; SBP = systolic blood pressure; V = valsartan.

FIGURE 2 Effects of Aliskiren Monotherapy Versus Placebo on Blood Pressure in Patients with Mild to Moderate Hypertension After 8 Weeks of Treatment[36]



**P<0.0001 versus placebo.*
MSDBP=mean sitting diastolic blood pressure; MSSBP=mean sitting systolic blood pressure.

daily in the treatment of uncomplicated severe hypertension (MSDBP ≥105 mm Hg and <120 mm Hg).[37] If additional BP control was required, the dose of aliskiren or lisinopril could be doubled, with the option of adding HCTZ 25 mg once daily to the regimen. Titration to the higher dose of the antihypertensive occurred in 74% and 66% of the aliskiren and lisinopril groups, respectively. Rates of add-on therapy with HCTZ were similar between groups (aliskiren 54%, lisinopril 45%). Similar reductions in MSDBP were observed in the aliskiren and lisinopril groups.

Combination Therapy

Although BP may be controlled in some patients with aliskiren monotherapy, there is greater likelihood that combination therapy will be required to control BP in the majority of patients.

Two trials have evaluated the antihypertensive efficacy of aliskiren in combination with HCTZ,[32,38] and 4 trials have studied the efficacy of dual RAAS inhibition with aliskiren and a CCB,[39] an ACEI,[40] or an ARB.[33,41]

Villamil and colleagues evaluated treatment with once-daily aliskiren 75 mg, 150 mg, or 300 mg; HCTZ 6.25 mg, 12.5 mg, or 25 mg; or their combinations (aliskiren/HCTZ: 75 mg/6.25 mg, 75 mg/12.5 mg, 75 mg/25 mg, 150 mg/6.25 mg, 150 mg/12.5 mg, 150 mg/25 mg, 300 mg/12.5 mg, and 300 mg/25 mg) in an 8-week placebo-controlled study.[32] Aliskiren 150 mg and 300 mg, all doses of HCTZ, and all combinations were superior to placebo in reducing MSDBP levels ($P<0.0001$).[32] All combinations, with the exception of aliskiren/HCTZ 150 mg/6.25 mg and 75 mg/12.5 mg, were also more effective than either monotherapy in reducing MSDBP and MSSBP levels ($P<0.05$).[32] Responder rates (the proportion of patients with MSDBP <90 mm Hg or ≥10 mm Hg decrease from baseline) were significantly higher with aliskiren 300 mg ($P=0.0005$), HCTZ 12.5 mg and 25 mg ($P<0.02$), and with all combinations ($P<0.05$) than with placebo.[32] Responder rates for all combinations of aliskiren with HCTZ 25 mg and aliskiren/HCTZ 300 mg/12.5 mg were significantly higher than for their respective monotherapies ($P<0.05$). A higher proportion of subjects achieved BP control (MSSBP/MSDBP <140/90 mm Hg) with combination therapy than with aliskiren or HCTZ monotherapy.[32] Combinations containing higher doses of 1 or both drugs (aliskiren 150 mg or 300 mg or HCTZ 25 mg) yielded significantly higher control rates compared with monotherapy.[32] Treatment with aliskiren resulted in a reduction of PRA of up to 65% from baseline. An increase in PRA of up to 72% with HCTZ was averted with the aliskiren/HCTZ combination.[32] Plasma renin concentrations increased with aliskiren, with HCTZ 25 mg, and with all aliskiren/HCTZ combinations.[32] An additional effect of combination therapy was a reduction in the incidence of hypokalemia compared with the patients receiving HCTZ monotherapy.[32]

The effects of adding aliskiren 150 mg once daily to amlodipine 5 mg once daily in patients whose hypertension was not fully controlled with CCB monotherapy was compared with continuing treatment with amlodipine 5 mg or 10 mg once daily alone.[39] At 6 weeks, patients who were treated with aliskiren 150 mg plus amlodipine 5 mg had significant additional reductions in MSDBP and MSSBP compared with patients who were treated with amlodipine 5 mg alone (mean change, in mm Hg, -8.5 and -4.8 for MSDBP, respectively, and -11.0 and -5.0 for MSSBP, respectively; $P<0.0001$).[39] The proportion of patients who achieved a MSDBP of <90 mm Hg and/or at least a 10 mm Hg reduction from baseline was significantly greater for those treated with aliskiren 150 mg plus amlodipine 5 mg compared with amlodipine 5 mg alone (64.2% and 45.2%, respectively, $P=0.0005$). In addition, a significantly greater proportion of patients who were treated with aliskiren 150 mg plus amlodipine 5 mg achieved BP levels of <140 mm Hg/90 mm Hg compared with amlodipine 5 mg alone (42.8% and 22.6%, respectively, $P<0.0001$).[39] The additional efficacy resulting from adding aliskiren to amlodipine therapy was comparable with that achieved by doubling the dose of amlodipine to 10 mg, but combination therapy was not associated with the increased incidence of edema that was reported with high-dose amlodipine treatment.[39]

The effect of 12 weeks of add-on therapy with once-daily aliskiren 300 mg, irbesartan 300 mg, or amlodipine 10 mg, or placebo was studied in hypertensive obese patients who were unresponsive to 4 weeks of initial treatment with HCTZ 25 mg.[38] At 8 weeks, the aliskiren/HCTZ combination reduced MSDBP and MSSBP significantly more than did HCTZ (mean

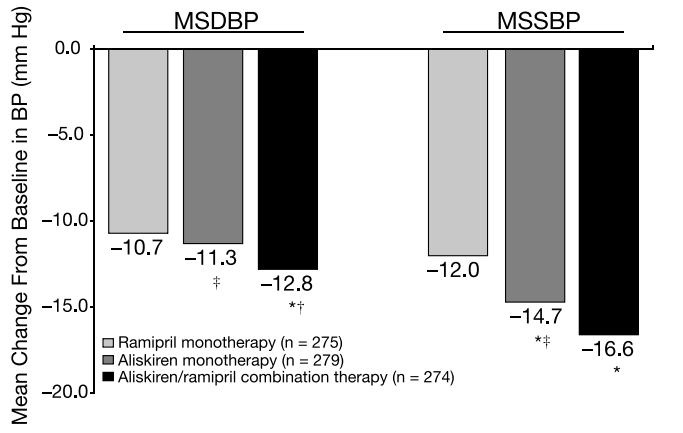
treatment difference, -4.0 mm Hg and -7.2 mm Hg, respectively; $P<0.0001$).[38] Reductions in BP with the combination regimen of aliskiren and HCTZ were comparable with reductions with irbesartan and HCTZ or with amlodipine and HCTZ.[38] Responder rates and BP control rates were higher in patients who were switched to the aliskiren/HCTZ combination than in those continuing on HCTZ alone (week 12 responder rate of 76% vs. 58% [$P=0.004$] and control rate of 58% vs. 33% [$P=0.0001$]).[38]

A phase III study evaluated the use of aliskiren alone or in combination with the ACEI ramipril for managing hypertension in patients with type 1 or 2 diabetes mellitus.[40] Patients were randomized and forced-titrated to receive once-daily aliskiren 300 mg, ramipril 10 mg, or aliskiren/ramipril in combination 300 mg/10 mg for 8 weeks. Reductions in MSSBP and MSDBP with aliskiren, ramipril, and aliskiren/ramipril were 14.7 mm Hg/11.3 mm Hg, 12.0 mm Hg/10.7 mm Hg, and 16.6 mm Hg/12.8 mm Hg, respectively (Figure 3a). A reactive increase in PRA of 111% after ramipril treatment was countered by aliskiren in patients receiving combination therapy, leading to an overall 44% reduction in PRA. These findings suggest that aliskiren, by enhancing RAAS blockade when added to an ACEI, provides additional antihypertensive efficacy in patients with diabetes and hypertension.

Pool and colleagues[33] studied the first-ever combination of a DRI and an ARB. In a primary safety and tolerability study, the once-daily antihypertensive efficacy of aliskiren alone (75 mg, 150 mg, and 300 mg), valsartan alone (80 mg, 160 mg, and 320 mg), aliskiren/valsartan combinations (75 mg/80 mg, 150 mg/160 mg, and 300 mg/320 mg), and valsartan/HCTZ (160 mg/12.5 mg) was evaluated.[33] Aliskiren 300 mg once daily significantly reduced MSDBP and MSSBP levels compared with placebo ($P<0.0001$). The magnitude of BP reduction was similar for aliskiren and valsartan across all dose ranges.[33] Reductions in MSDBP and MSSBP levels were comparable for the aliskiren/valsartan combinations and their respective component monotherapies.[33] Responder rates with aliskiren monotherapy ($P<0.05$, aliskiren 75 mg and 150 mg; $P<0.001$, aliskiren 300 mg) and for all aliskiren/valsartan combinations ($P<0.05$, aliskiren 150 mg/valsartan 160 mg; $P<0.001$, aliskiren 300 mg/valsartan 320 mg) were significantly greater than with placebo. Responder rates for most combinations did not differ from those for their respective monotherapies.[33] The reduction in BP and the responder rates with the 2 highest dose combinations were similar to those with the valsartan/HCTZ combination. Rates of BP control did not differ between the aliskiren/valsartan combinations and their component monotherapies.[33]

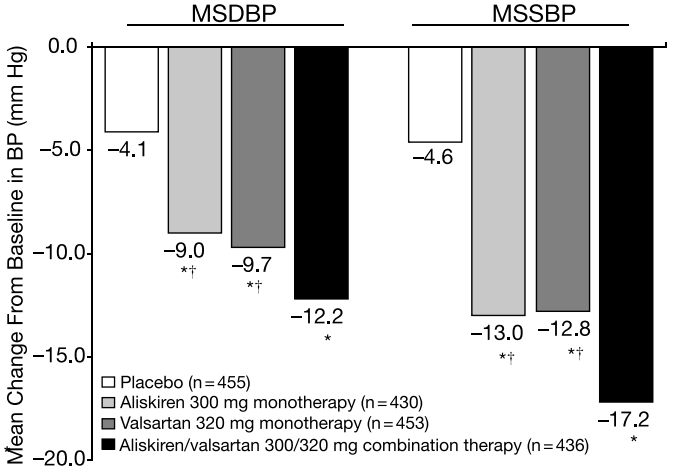
A phase III study was conducted in 1,797 patients with mild to moderate hypertension who were randomized to once-daily aliskiren 150 mg, valsartan 160 mg, aliskiren/valsartan 150 mg/160 mg, or placebo for 4 weeks; followed by forced titration to double the dose for another 4 weeks.[41] At both 4 and 8 weeks, reductions in MSDBP and MSSBP were significantly greater with all active treatments than with placebo ($P<0.0001$) (Figure 3b). The aliskiren/valsartan combination was significantly more effective than either component alone in reducing MSDBP and MSSBP ($P<0.0001$), 24-hour mean ADBP and

FIGURE 3a Efficacy of Ramipril or Aliskiren Monotherapy, or Combination Therapy, at 8 Weeks in Patients with Mild to Moderate Hypertension[40]



*$P<0.05$ for superiority versus ramipril monotherapy.
†$P<0.05$ for superiority versus aliskiren monotherapy.
‡$P<0.05$ for non-inferiority for aliskiren monotherapy versus ramipril monotherapy
MSDBP = mean sitting diastolic blood pressure; MSSBP = mean sitting systolic blood pressure.

FIGURE 3b Efficacy of Valsartan or Aliskiren Monotherapy, or Combination Therapy, at 8 Weeks in Patients with Mild to Moderate Hypertension[41]



*$P<0.0001$ versus placebo.
†$P<0.0001$ versus aliskiren/valsartan combination.
MSDBP = mean sitting diastolic blood pressure; MSSBP = mean sitting systolic blood pressure.

ASBP ($P<0.0001$), and daytime and nighttime mean ADBP.[41] The aliskiren/valsartan combination provided significantly smoother BP control for a 24-hour period (smoothness index 1.2 vs. 0.9 with either aliskiren or valsartan alone; $P<0.05$), with a trough to peak ratio of 0.79. The combination thus provided additional BP reductions that were maintained for 24 hours.

Safety and Tolerability

A pooled safety analysis has been conducted on data from 7 randomized double-blind multicenter studies in 4,704 patients with mild to moderate hypertension (monotherapy, 2,598; combination therapy, 2,106) treated with aliskiren (75 mg to 600 mg) for 6 to 8 weeks.[25] In 5 placebo-controlled trials, the overall incidence of adverse events after 52 to 55 days of treatment was similar for aliskiren monotherapy and placebo (39.8% vs. 40.2%, respectively).[25] Rates of discontinuation due to adverse events were low and were reported as between 1.7% and 2.6% with aliskiren 75 mg to 600 mg, respectively, and 3.5% with placebo.[25] Overall, the most frequently reported adverse events with aliskiren and placebo were headache (5.7% vs. 8.7%; $P<0.01$ vs. placebo), nasopharyngitis (4.4% vs. 5.8%; $P=$ NS), diarrhea (2.6% vs. 1.2%; $P<0.05$ vs. placebo), dizziness (1.8% vs. 2.2%; $P=$NS), and fatigue (1.6% vs. 1.5%; $P=$NS).[25] Increased rates of diarrhea were reported mainly for the 600 mg dose of aliskiren (9.5% vs. 1.2; $P<0.0001$) and not at lower doses.[25] Consequently, the highest recommended dose for aliskiren is 300 mg once daily because of a relatively flat BP response and increased incidence of adverse events with doses higher than 300 mg a day.

In the treatment of patients with severe hypertension, both aliskiren and lisinopril were well tolerated and no differences were noted between groups in the proportion of patients who reported an adverse event, the type of adverse event, or the rate of discontinuation due to an adverse event.[37]

The addition of aliskiren 150 mg or 300 mg to valsartan, amlodipine, HCTZ, or ramipril therapy did not alter the frequency or type of adverse events compared with their respective monotherapies.[25] In fact, some adverse effects may be avoided with aliskiren therapy when used in combination with other antihypertensive agents. The addition of aliskiren to ramipril therapy reduced the rate of cough (1.8%) compared with ramipril alone (4.7%);[25] in patients receiving aliskiren 150 mg as add-on therapy to amlodipine 5 mg, the rate of edema was reduced to 2.1% compared with a rate of 11.2% with amlodipine 10 mg.[25]

Place in Therapy of Pharmacologic Direct Renin Inhibition

Control of hypertension to below-target BP levels is crucial for reducing rates of adverse cardiovascular events. The National Health and Nutrition Examination Survey (1999–2004) showed an overall prevalence of hypertension (BP ≥140/90 mm Hg or use of antihypertensive medication) between 2003 and 2004 of 29.3%.[42] For the same period, rates of BP control were 33%, 64%, and 33%, respectively, for all patients with hypertension, treated patients, and treated patients with diabetes, indicating that the treatment of hypertension remains suboptimal.[42]

Aliskiren administered once daily provides another effective and safe option for the treatment of hypertension as monotherapy.[32,34-37] However, approximately 70% of patients with hypertension, particularly high-risk patients with lower BP goals and patients whose BP exceeds SBP or DBP target values by ≥20 mm Hg or ≥10 mm Hg, respectively, will require combination therapy to achieve BP control.[43] Aliskiren, which acts at the rate-limiting step in the RAAS pathway, is a logical component of combination therapy, because it enhances RAAS suppression and attenuates the reactive increase in PRA when added to other classes of antihypertensive agents.[32] Combining agents (such as diuretics, ACEIs, and ARBs) that increase PRA with an agent (such as aliskiren) that neutralizes this activity appears to be a rational approach for optimizing BP control. Combined RAAS inhibition may allow the use of lower doses of each component to achieve more effective and durable RAAS suppression with potentially fewer adverse effects.[32,33] Patients with severe hypertension, especially those with renal failure, may theoretically benefit from even more intensive RAAS inhibition through the blockade of additional steps of the pathway, but this approach needs further exploration. Table 2 lists some potential therapeutic roles for DRIs in the management of hypertension and its sequelae.

Clinical studies have provided convincing evidence that aliskiren controls RAAS activity, reduces BP significantly, and displays good tolerability. Additionally, as with other RAAS inhibitors, RAAS blockade via direct renin inhibition has the potential to provide organ protection independent of BP reductions.[44] A robust clinical development program is ongoing to evaluate the renoprotective and cardioprotective effects of aliskiren in which surrogate markers and major clinical outcomes will be analyzed as primary endpoints (Table 3). What may be on the horizon is the use of dual RAAS blockade, which includes

TABLE 2 Potential Therapeutic Role of Direct Renin Inhibitors[22,32,33,44]

- Monotherapy for hypertension
- Component of combination therapy for hypertension, with a diuretic, a CCB, an ACEI, and/or an ARB
- Alternative to ACEIs or ARBs in the management of hypertension and the prevention of organ damage
- Alternative to ACEIs in patients with diabetic nephropathy or cardiovascular disease
- Use in patients with diabetic nephropathy or in African American hypertensive patients, in whom intrarenal angiotensin II formation occurs via ACE or non–ACE-dependent pathways

ACE = angiotensin-converting enzyme; ACEI = ACE inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker.

TABLE 3 *Aliskiren Clinical Development Program: Evaluating Surrogate Markers and Clinical Outcomes*

Trial Name	N	Objective of Trial	Length of Trial	Primary Endpoint
AGELESS Aliskiren versus ramipril for BP control in the elderly	912	Compare the efficacy of aliskiren versus ramipril in lowering SBP in patients ≥65 years of age with systolic hypertension	36 weeks	Reduction from baseline in MSSBP
AVOID* Aliskiren in the evaluation of proteinuria in diabetes	754	Determine the effect of adding aliskiren or placebo to background losartan treatment on proteinuria in diabetic patients	24 weeks	Percent reduction in UACR
ALLAY Aliskiren left ventricular assessment of hypertrophy	480	Determine the effect of aliskiren alone or in combination with losartan on the regression of left ventricular mass in overweight hypertensive patients	34 weeks	Change in left ventricular mass
AVANT GARDE (TIMI 43) Aliskiren and valsartan versus placebo in lowering NT-proBNP in patients stabilized following an ACS	1,152	Determine whether aliskiren, valsartan, or combination therapy will improve ventricular remodeling in high-risk patients who have been stabilized following ACS	9 weeks	Reduction of NT-proBNP from baseline
ASPIRE Aliskiren in post-MI patients to reduce remodeling	860	Determine whether aliskiren attenuates pathological left ventricular remodeling in high-risk post-MI patients when added to standard therapy	36 weeks	Change in LVESV by echo
ALOFT* Aliskiren observation of heart failure treatment	320	Determine the safety and tolerability of adding aliskiren or placebo to standard heart failure treatment in patients with chronic heart failure	12 weeks	Tolerability and safety of aliskiren; change in BNP
ALTITUDE Aliskiren in type 2 diabetes using cardiorenal disease endpoints	8,400	Determine whether aliskiren with conventional treatment reduces cardiovascular and renal morbidity and mortality in high-risk patients with type 2 diabetes	4 years	Time to diabetic complications (secondary prevention trial)

**Study completed, results pending.*

ACS = acute coronary syndrome; BNP = B-type natriuretic peptide; BP = blood pressure; echo = echocardiography; LVESV = left ventricular end systolic volume; MI = myocardial infarction; MSSBP = mean sitting systolic blood pressure; NT-proBNP = N-terminal proB-type natriuretic peptide; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio.

a DRI, as several trials will investigate whether combination therapy provides enhanced protection and improved outcomes over monotherapy.

Summary and Conclusions

The DRI aliskiren is a new orally available, highly specific, and effective inhibitor of RAAS activity. Both as monotherapy and in combination with a thiazide diuretic, a CCB, an ACEI, or an ARB, aliskiren reduces BP in patients with mild to moderate hypertension. Aliskiren has antihypertensive efficacy comparable with that of these other classes of antihypertensive agents, and counters the reactive increase in PRA when used in combination with these agents. In the treatment of patients with severe hypertension, aliskiren is comparable with lisinopril. Aliskiren has a tolerability profile similar to that of placebo and ARBs and is well tolerated when used in combination with other agents. Further studies will explore its potential as monotherapy or in combination with other antihypertensives, and for uses beyond BP reduction, such as renoprotection and cardioprotection.

DISCLOSURES

The author discloses no potential bias or conflict of interest relating to this article.

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