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ALISKIREN: A DIRECT RENIN INHIBITOR

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Hypertension affects over 1 billion patients worldwide. The World Health Organization (WHO) estimated that poor blood pressure (BP) control is responsible for 66% of the strokes and 50% of ischemic heart disease.[1] New data from the Framingham Heart Study suggests that individuals who are normotensive at age 55 have a 90% lifetime risk for developing hypertension.[2] Even though general awareness and treatment options for hypertension have increased, control rates are still inadequate.

For several decades, renin (rē´ nĭn) and the enzymes that catalyze the renin-angiotensin-aldosterone system (RAAS) have been targets of interest as inhibitors of the RAAS. Inhibition of this system is a viable therapeutic strategy, not only for treatment of hypertension, but also for the clinical benefits that it provides beyond BP reduction, such as in the management of heart failure ad progressive kidney disease.[3] The RAAS can be manipulated at several steps including enzyme inhibition [renin and angiotensin converting enzyme (ACE)] and angiotensin II receptor blockade (ARB) (**Figure 1**). Several peptide-like renin inhibitors have been synthesized in the past, but poor pharmacokinetic properties limited the clinical use of these agents.[5] In April 2006, the FDA accepted the new drug application of aliskiren (ə lĭs´ kər ĭn) by Novartis for the treatment for hypertension both as monotherapy and in co-administration with other antihypertensive agents. Aliskiren (Tekturna® [tek´ tûr nä]) was approved by the FDA on March 6, 2007 for the treatment of hypertension either as monotherapy or in combination with other agents. This approval marks the first new class of antihypertensive to be available in over 10 years. This article will evaluate the clinical pharmacology, pharmacokinetics and review published clinical trials on aliskiren.

Clinical pharmacology

Direct renin inhibitors target the renin system at the point of activation. Aliskiren binds to a pocket in the renin molecule, blocking angiotensinogen cleavage. It is a highly specific inhibitor of renin and has little to no effect on other human enzymes.[5] Currently there are 4 classes of agents that act on the renin system: ACE-inhibitors, ARBs, beta-blockers and aldosterone receptor antagonists. However, ACE-inhibitors and ARBs both activate compensatory feedback mechanisms that result in renin release. Increased plasma renin activity (PRA) stimulates conversion of angiotensinogen to angiotensin I (Ang I) with subsequent conversion to angiotensin II (Ang II) by remaining uninhibited angiotensin converting enzyme (ACE) and ACE independent

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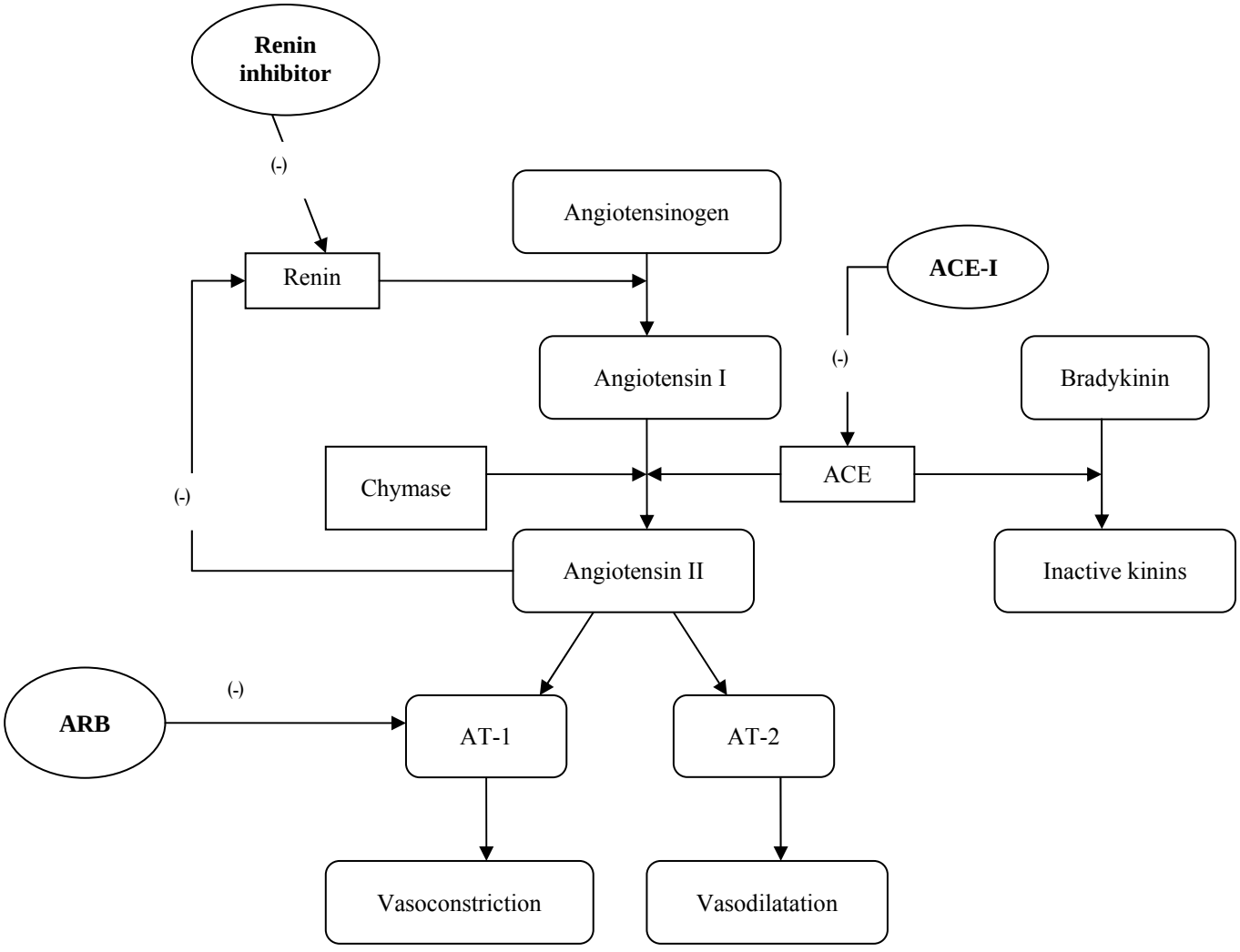
(chymase) pathways. In contrast, renin inhibitors neutralize any compensatory increase in PRA and prevent the formation of both Ang I and Ang II. Kleinhert et al.[6] suggested that blood pressure lowering activity of renin inhibitors must be due, in part, to inhibition of plasma renin activity, but at higher doses, renin inhibitors might also act via other mechanisms, such as inhibition of tissue renin.

In healthy volunteers, after oral doses of 40 to 640 mg/day of aliskiren, plasma alikiren concentration increased with increasing dose, with peak concentrations after 3 to 6 hours. The plasma half-life averaged 23.7 hours (range 20-45 h), allowing once daily administration. Oral bioavailability of aliskiren is very low (2.7%) with plasma steady-state concentrations reached after 5 to 8 days of treatment. When aliskiren is taken with food, AUC is reduced by approximately 62%; whether this is a clinically significant reduction is currently unclear. Volume of distribution is < 2 L/kg and the drug is approximately 50% protein bound.[7] The main elimination route is via biliary excretion as unchanged drug. Less than 1% of the oral drug is excreted in the urine. It is not metabolized by CYP450, does not interfere with the action of warfarin, and shows no clinically relevant pharmacokinetic interactions with lovastatin, atenolol, celecoxib, or cimetidine. Aliskiren displays linear pharmacokinetics across a dose range of 75 to 600 mg.[8]

Clinical Data

Mitchell et al.[9] measured mean 24-hour ambulatory systolic and diastolic blood pressure (SBP, DBP) in patients with mild-to-moderate hypertension (mean sitting DBP ≥ 95 mm Hg and < 110 mm Hg) who had been randomized to receive once-daily al-

Figure 1. Renin-Angiotensin-Aldosterone System (RAAS)



ACE-I = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blocker; AT1 = angiotensin II receptor type 1; AT2 = angiotensin II receptor type 2
(-) = inhibits

Table1. Change from baseline in 24-hour mean ambulatory DBP (MADBP) and SBP (MASBP) [9]

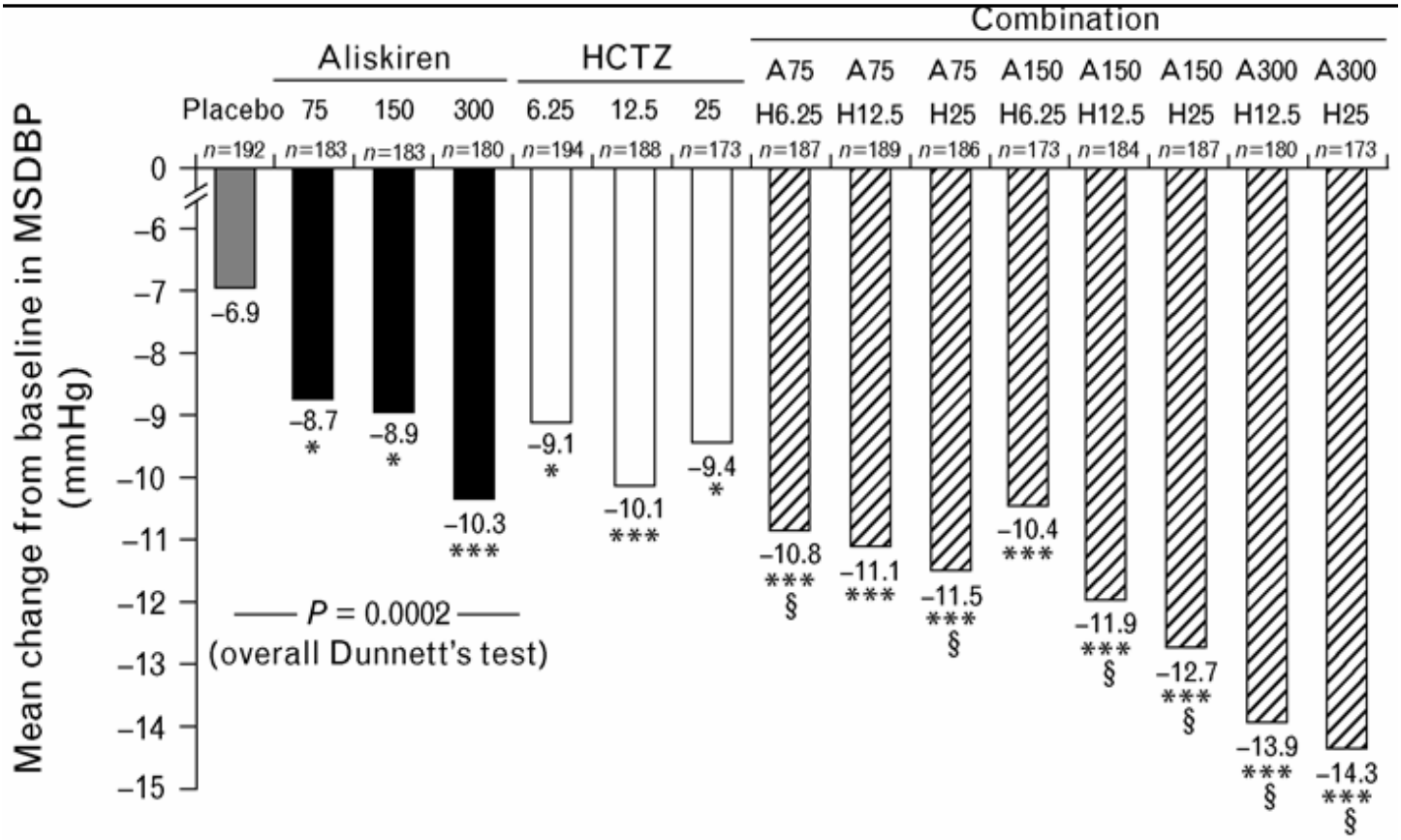
Blood Pressure Measurement	Placebo	Aliskiren ($p < .0001$ vs. placebo)		
		150 mg/day	300 mg/day	600 mg/day
MADBP (mm Hg)	1.61 ± 0.67	-6.55 ± 0.67	-5.96 ± 0,66	-7.43 ± 0.66
MASBP (mm Hg)	1.75 ± 0.95	-9.63 ± 0.96	-8.77 ± 0.94	-9.92 ± 0.93

iskiren 150 mg, 300 mg, or 600 mg or placebo after a 2- to 4-week, single-blind, placebo run-in. The patients were part of a larger cohort participating in an 8-week trial. A subgroup of 216 patients underwent 24-hour ambulatory blood pressure monitoring at baseline and at the end of the study. The authors demonstrated a statistically significant change from baseline in 24 hour mean ambulatory DBP and SBP with all 3 doses of aliskiren compared to placebo($p < 0.0001$ for all 3 doses of aliskiren)[9](**Table 1**).

Aliskiren therapy in combination with HCTZ

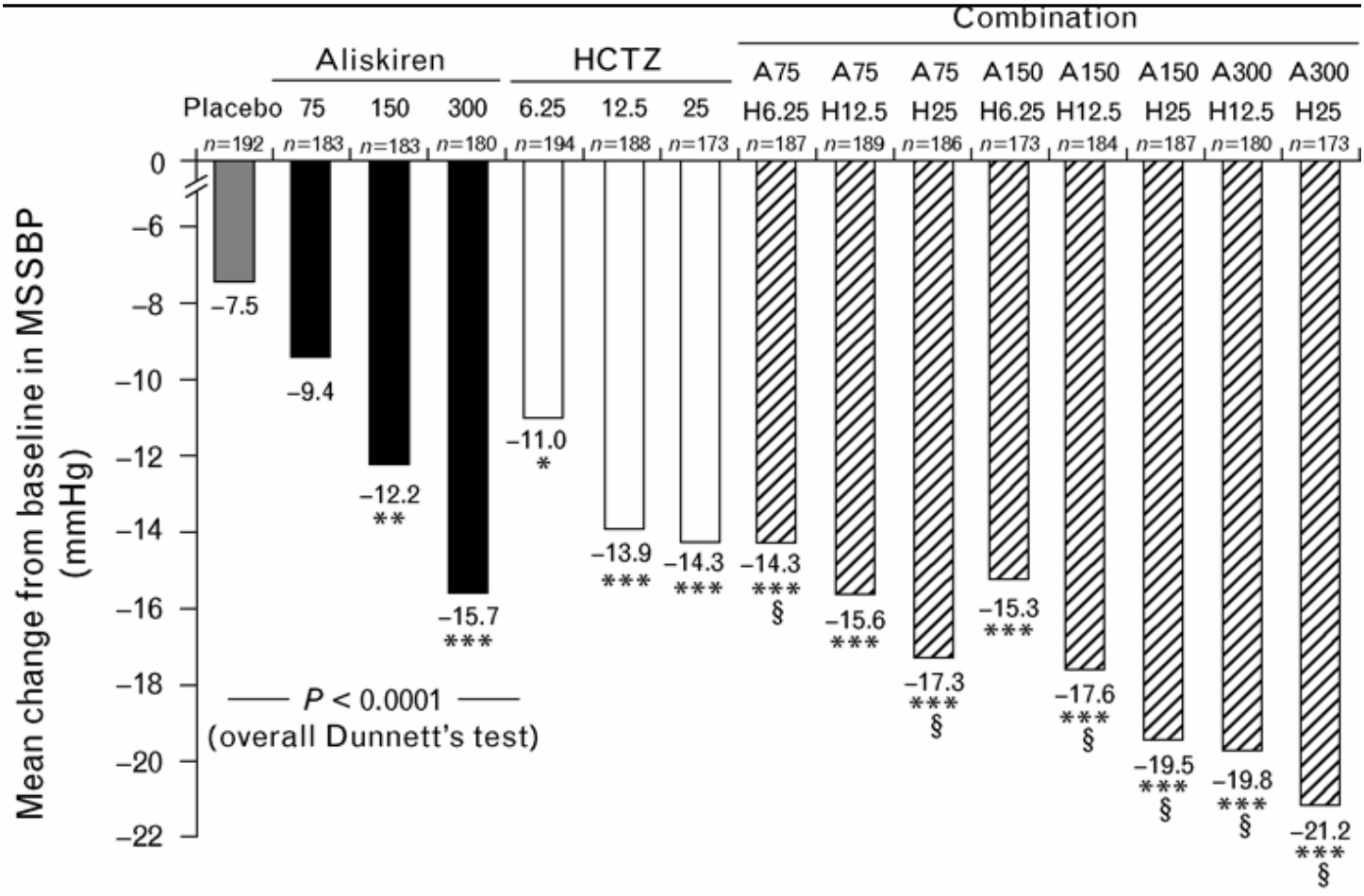
Villamil et al.[10] randomized 2776 patients ≥ 18 years of age with mild-to-moderate hypertension (mean sitting DBP [MSDBP] 95-109 mmHg) to receive 8 weeks of double-blind treatment with once-daily aliskiren (75 mg, 150 mg, or 300 mg), HCTZ (6.25 mg, 12.5 mg, or 25 mg), aliskiren plus HCTZ, or placebo. Aliskiren monotherapy was superior to placebo ($p < 0.001$) in reducing MSDBP and MSSBP. In combination with HCTZ, aliskiren provided significant additional blood pressure reductions (**Fig 2 and 3**). The greatest mean reduction in blood pressure, 21.2/14.3 mm Hg, was seen with aliskiren 300 mg/HCTZ 25 mg. Response rates (patients with MSDBP < 90 mm Hg and/or ≥ 10 mm Hg decrease) were significantly higher with aliskiren 300 mg (64%) and all combinations (58% to 81%)

Figure 2. Mean change from baseline to week 8 in MSDBP with aliskiren and HCTZ monotherapy and combination therapy



Adapted from the original article.[10] *P < 0.05; ** P < 0.001; *** P ≤ 0.0001 versus placebo

Figure 3. Mean change from baseline to week 8 in MSSBP with aliskiren and HCTZ monotherapy and combination therapy



Adapted from the original article.[10] *P < 0.05; ** P < 0.001; *** P ≤ 0.0001 versus placebo

than placebo (46%; all p < .05). Combinations of aliskiren/HCTZ 75/25 mg, 150/25 mg, 300/12.5 mg, and 300/25 mg produced significantly greater response rates than each component monotherapy (all p < .05).

Aliskiren monotherapy and combination with valsartan

Pool et al[11] randomized 1123 patients with mild-to-moderate hypertension (MSDBP ≥ 95 mm Hg) to receive once-daily placebo, aliskiren monotherapy (75 mg, 150 mg, 200 mg) valsartan monotherapy (80 mg, 160 mg or 320 mg), aliskiren and valsartan combination or valsartan/HCTZ (160/12.5 mg). Once-daily oral treatments with aliskiren 300 mg significantly (p < 0.001) reduced MSDBP (-12.3 mm Hg vs. -8.6 mm Hg placebo) and MSSBP (-15.0 mm Hg vs. -10 mm Hg placebo). Aliskiren 75 mg and 150 mg failed to reach statistical significance in comparison to placebo. In comparison to all 3 doses of valsartan monotherapy (80 mg, 160 mg, 300 mg), aliskiren monotherapy (75mg, 150mg, and 200mg) was comparable in SBP and DBP reduction. However, only aliskiren 300 mg, valsartan 160 mg and valsartan 320 mg provided statistically significant reductions in SBP (p < 0.05, p <0.001, p <0.001 respectively) and DBP (p <0.001, p <0.05, p <0.05 respectively). All three aliskiren/valsartan combinations significantly lowered MSDBP and MSSBP compared to placebo (**Table 2**).

Aliskiren in combination with HCTZ, ACEI, or ARB

O'Brien et al.[12] assessed blood pressure in three open-label studies in patients with mild-to-moderate hypertension. Patients were administered aliskiren in combination with HCTZ (n=23), ramipril (n=21) or irbesartan (n=23). In the diuretic combination study, the addition of 25 mg of hydrochlorothiazide to 150 mg of aliskiren daily for 3 weeks significantly lowered daytime pressure, compared with aliskiren monotherapy. In the ACEI combination study, the addition of 75 or 150 mg of aliskiren to 5 mg of ramipril alone for 3 weeks further lowered both daytime and nighttime pressures compared with

Table 2. Summary of major clinical trials with aliskiren

Study	N	Duration of Study	Demographics	Treatment	Δ SBP (mmHg)	Δ DBP (mmHg)
Mitchell et al.[9]	216	Mean 24-hour ambulatory BP over 8 weeks	Mild-mod HTN MDSBP ≥ 95 & MSBP < 110	A150	-9.63$^{\Psi}$	-6.55$^{\Psi}$
				A300	-8.77$^{\Psi}$	-5.96$^{\Psi}$
				A600	-9.92$^{\Psi}$	-7.43$^{\Psi}$
				Placebo	1.75	1.61
Villamil et al.[10]	2776	Mean sitting DBP and SBP over 8 weeks	Mild-mod HTN MSDBP 95-109	A75/150/300	-9.4/-12.2*/-15.7$^{\Psi}$	-8.7*/-8.9*/-10.3$^{\Psi}$
				H6.25/12.5/25	-11.0/-13.9$^{\Psi}$/-14.3	-9.1/-10.7/-9.4
				A75 & H6.25/12.5/25	-14.3$^{\Psi}$/-15.6$^{\Psi}$/-17.3$^{\Psi}$	-10.8$^{\Psi}$/-11.1$^{\Psi}$/-11.5$^{\Psi}$
				A150 & H6.25/12.5/25	-15.3$^{\Psi}$/-17.6$^{\Psi}$/-19.5$^{\Psi}$	-10.4$^{\Psi}$/-11.9$^{\Psi}$/-12.7$^{\Psi}$
				A300 & H12.5/25	-19.8$^{\Psi}$/-21.2$^{\Psi}$	-13.9$^{\Psi}$/-14.3$^{\Psi}$
				Placebo	-7.5	-6.9
Pool et al.[11]	1123	Mean sitting DBP and SBP over 8 weeks	Mild-mod HTN MSDBP ≥ 95	A75/150/300	-12.1/-12.1/-15*	-10.3/-10.3/-12.3**
				V80/160/320	-11.2/-15.5**/-16.5**	-10.5/-11.0*/-11.3*
				A75/V80	-14.5†	-11.3†
				A150/V160	-16.6†	-11.8†
				A300/V320	-18**	-12.1**
				Placebo	-10	-12.9
O'Brien et al.[12]	HCTZ (n= 23) Ramipril (n= 21) Irbesartan (n=23)	24-hour mean daytime systolic and diastolic ambulatory blood pressure over 3 weeks	Mild-mod HTN	A150	-10.4**	-5.8**
				A150/H25	-18.4	-10.6
				R5 & A75/150	-10.5*/-14**	-8.1*/-8.7*
				I150 & A75/150	-14.8*/-13.3*	-8.2*/-6.8*

A75/150/300 = aliskiren 75mg/150mg/300mg daily; H6.25/12.5/25 = HCTZ 6.25/12.5/25; V80/160/320= valsartan 80mg/160mg/320mg; R5= ramipril 5mg; I150= irbesartan 150mg ; DBP = diastolic blood pressure ; SBP= systolic blood pressure
*p <0.05, **p <0.001, †p <0.01, $^{\Psi}$p <0.0001

ramipril monotherapy. In the ARB combination study, the addition of 75 or 150 mg of aliskiren to 150 mg of irbesartan alone, for 3 weeks, resulted in significantly lower night-time pressures compared with irbesartan monotherapy.

Adverse Effects

Aliskiren was well tolerated as either monotherapy or in combination therapy with other antihypertensive agents. Discontinuation occurred in 3.5 to 5 % of the patients.[13] The most common adverse events included headaches (2.7% - 6.1%) and nasopharyngitis (0.5 - 5.4%). Diarrhea occurred in a dose-related manner, with the highest incidence at the 600 mg (9.5% vs. placebo p < .0001).[14,15] The incidence of cough occurring with an ACE inhibitor was reduced when the ACE inhibitor was combined with aliskiren (4.7 % vs. 1.8%).[16] Important adverse effects noted during the clinical trials are summarized in **Table 3**.[17]

Dosing/Cost

Although aliskiren has been approved for the treatment of hypertension, formal dosing recommendations and cost are not available. Doses used in the clinical trials ranged from 37.5 mg to 600 mg once a day. No significant blood pressure reduction was observed with the 37.5 mg daily dose; thus, is not likely

Table 3. Adverse effects observed in clinical trials with aliskiren therapy [17]

	Placebo N = 781	Aliskiren +/- other drugs N = 2598	Aliskiren/CCB N = 187	Aliskiren/ACEI N = 277	CCB N = 357	ACEI N+278
Any Adverse Event	314 (40.2)	1013 (39.0)	59 (31.6)	83 (30.0)	106 (29.7)	94 (33.8)
Headache	68 (8.7)	141 (5.4)	5 (2.7)	8 (2.9)	12 (3.4)	17 (6.1)
Nasopharyngitis	45(5.8)	110 (4.2)	1 (0.5)	3 (1.1)	2 (0.6)	5 (1.8)
Diarrhea	9 (12)	64 (2.5)	3 (1.6)	3 (1.1)	3 (0.8)	7 (2.5)
Dizziness	17 (2.2)	47 (1.8)	2 (1.1)	3 (1.1)	5 (1.4)	5 (1.8)
Fatigue	12 (1.5)	38 (1.5)	2 (1.1)	3 (1.1)	4 (1.1)	3 (1.1)
Back pain	11 (1.4)	32 (1.2)	1 (0.5)	2 (0.7)	1 (0.3)	4 (1.4)
Cough	5 (0.6)	28 (1.1)	1 (0.5)	5 (1.8)	1 (0.3)	13 (4.7)
Peripheral edema	5 (0.6)	24 (0.9)	4 (2.1)	1 (0.4)	26 (7.3)	1 (0.4)
Influenza	5 (0.6)	19 (0.7)	1 (0.5)	3 (1.1)	1 (0.3)	1 (0.4)

Data are presented as the number (%) of patients reporting adverse events.

to be used clinically. Also, an aliskiren dose of 600 mg daily is not associated with additional blood pressure reduction or higher response rates than those seen with the 300 mg dose. The FDA approved the manufacture of 150 mg and 300 mg tablets.

Future studies

There are several ongoing studies that are investigating aliskiren for the prevention of end organ damage, primary prevention of cardiovascular disease, and prevention of microvascular complications in diabetes mellitus. Results from these studies might shed more insight into the long-term effects of aliskiren. Some of the ongoing clinical trials are summarized in **Table 4**.

Summary

Renin-angiotensin-aldosterone system inhibition is a good therapeutic strategy not only for treatment of hypertension, but also for the clinical benefits that it provides beyond BP reduction such as management of heart failure and progressive kidney disease.[4] Aliskiren targets renin, the enzyme catalyzing cleavage of angiotensinogen to angiotensin I (Ang I), the first and rate-limiting step of the renin-angiotensin system (RAS). Studies have shown promising data on BP regulation when aliskiren is used as monotherapy and in combination with the currently available anti-hypertensives. Further studies will be needed to determine the effects of aliskiren on long-term blood pressure regulation and its ability to protect against end-organ damage.

Table 4. Ongoing clinical trials on aliskiren

New studies to test effect of aliskiren on surrogate markers of target organ damage (results to be released in 2007)			Key outcomes studies that will define the role of direct renin inhibition in primary and secondary prevention (anticipated data in 2011)	
ALLAY	**ALOFT**	**AVOID**	**AVIATOR**	**ALTITUDE**
ALiskiren in **L**eft ventricul**A**r Hypertroph**Y**	**AL**iskiren **O**bservation of heart **F**ailure **T**reatment	**A**liskiren in the e**V**aluation **O**f protienuria in **D**iabetes	**A**liskiren in **VI**sceral obesity **AT** risk patients **O**utcomes **R**esearch	**AL**iskiren **T**rial **I**n **T**ype 2 **D**iabetic n**E**phropathy
Aliskiren vs. losartan vs. combination	Aliskiren vs. placebo added to optimal heart failure treatment	Aliskiren vs. placebo added to losartan	Does aliskiren delay the time to first major CV event in high risk patients	Does aliskiren delay time to diabetic complications in patients with Type 2 DM and nephropathy
Primary endpoint: LV mass and geometry as measured by MRI	Primary endpoint: fall in BNP	Primary endpoint: % reduction urinary albumin/ creatnine ratio		

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