

Aliskiren: A New Idea in Blood Pressure Management

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CE FOR PHARMACISTS ONLY.

Aliskiren hemifumarate (Tekturna[®], Novartis) is the first renin inhibitor approved in the U.S. and Europe for the treatment of hypertension.¹ While this category of antihypertensive medications is new to current health care professionals, the concept of inhibiting renin to lower blood pressure has been a focus of over 50 years of research.² Previous first generation renin inhibitors, enalkiren, remikiren, and zankiren, had problems with low potency, poor bioavailability, and short durations of action.³ Unlike its predecessors, aliskiren has a high affinity for the renin receptor, demonstrates a long plasma half-life, and is orally active. In addition to discovering aliskiren, Speedel, a Swiss biopharmaceutical company, has three more renin inhibitors currently undergoing phase I and II trials.⁴

MECHANISM OF ACTION: RENIN INHIBITION

The renin-angiotensin system (RAS) is a hormonal cascade that plays a key role in blood pressure regulation through the action of angiotensin II. Renin is secreted by the kidneys in response to decreases in blood volume and renal perfusion. Renin cleaves angiotensinogen to form angiotensin I. Angiotensin I is further converted to angiotensin II by the angiotensin I-converting enzyme (ACE). Angiotensin II then binds with the angiotensin II type I receptor in arteries to produce vasoconstriction, which leads to increases in peripheral vascular resistance, and ultimately an elevation in blood pressure.

The renin-angiotensin system has been a popular drug target for blood pressure control, as renin is the main determinant of RAS activity. Overactivity of RAS has

been associated with approximately 70% of cases of essential hypertension.⁵ Inhibition of RAS with ACE inhibitors (ACEI) and angiotensin II receptor blockers (ARB) has proven to be effective for lowering blood pressure. However, these agents do not provide complete suppression of RAS, as they cause a compensatory increase in renin release, plasma renin activity, and angiotensin I and II levels. Renin inhibitors neutralize plasma renin activity and prevent the formation of angiotensin I and II, which leads to a more complete blockade of this system.⁵ (Figure 1)

ALISKIREN PHARMACODYNAMICS: REVIEW OF THE CLINICAL TRIALS

Aliskiren was approved for the treatment of hypertension based upon data from six randomized, double-blind, placebo-controlled trials.⁶ However, only five of these trials have been published.^{2,8-11}

When results from these studies are combined, these trials demonstrate marked blood pressure lowering with aliskiren in more than 3900 patients with mild to moderate hypertension. (Table 1)

ALISKIREN MONOTHERAPY

The first trial to demonstrate the antihypertensive effects of aliskiren in mild to moderate hypertension was published by Gradman, et al in 2005.⁸ After a two-week washout period, 652 patients from

the U.S., Germany, Belgium and Switzerland were randomized to receive aliskiren 150 mg, aliskiren 300 mg, aliskiren 600 mg, irbesartan 150 mg, or placebo once daily for 8 weeks. Patients were instructed to take the study drug daily with water at 8 a.m. All aliskiren doses and irbesartan significantly lowered mean sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared to placebo ($p < 0.001$ and $p < 0.05$, respectively). The degree of blood pressure lowering was similar between the aliskiren 150 mg and irbesartan 150 mg treatment arms ($p = 0.69$), while higher aliskiren doses (300 mg and 600 mg) lowered blood pressure more than irbesartan ($p < 0.05$). However, the authors noted a plateau effect on blood pressure lowering with aliskiren doses > 300 mg/day. Aliskiren therapy was well tolerated at all doses; the incidence of adverse events and study discontinuations was similar with all treatment arms. The most common adverse events included headache, dizziness, and diarrhea. Higher doses of aliskiren (300-600 mg per day) were associated with more complaints of diarrhea than the other treatment arms. While clinical laboratory values remained normal in the majority of study patients,



Objectives. 1) Explain why inhibition of the renin-angiotensin system is important in the control of blood pressure and discuss the effectiveness of current pharmacologic inhibitors of this system; 2) Identify targets within the renin-angiotensin system for the following antihypertensive agents: ACE inhibitors, angiotensin receptor blockers and renin inhibitors; 3) Discuss the advantages and disadvantages of using a direct renin inhibitor as monotherapy or in combination for the treatment of hypertension; 4) Specify the approved dosing of aliskiren therapy, list potential side effects that have been associated with aliskiren, identify potential drug interactions and provide recommendations to minimize complications from concomitant therapies; 5) Explain future uses of renin inhibitors in the primary and secondary prevention of cardiovascular diseases.

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Target Audience: Pharmacists

it is not clear if any cases of hyperkalemia developed in those receiving aliskiren or irbesartan. An important limitation of this study is the homogenous patient population enrolled ($> 70\%$ Caucasian), as racial differences in response to antihypertensive therapies and renin activity have been previously reported.

To address the efficacy and safety of aliskiren in Asian populations, Kushiro, et al randomized 455 Japanese adults with essential hypertension to receive aliskiren 75 mg, aliskiren 150 mg, aliskiren 300 mg, or placebo once daily for eight weeks.³ Each dose of study drug was taken daily between 6 a.m. and 10 a.m., at least 30 minutes before a meal. All doses of aliskiren significantly reduced both mean sitting SBP and DBP compared to placebo ($p < 0.001$). The reductions in blood pressure from baseline after 8 weeks of aliskiren 150 mg and 300 mg per day (8.7/7.8 mmHg and 14.7/10.7 mmHg, respectively) were similar to the reductions reported in the Gradman et al study (11.4/9.3 mmHg and 15.8/11.8 mmHg, respectively),⁸ where the same aliskiren doses were administered to a predomi-

nately Caucasian Western population. The percentage of patients whose blood pressure reached goal ($< 140/90$ mmHg) was higher in the aliskiren treatment arms than the placebo arm ($p < 0.05\%$). Attainment of goal blood pressure increased in a dose dependent manner from 23.5% to 41.6% of subjects. Interestingly, the reductions in mean sitting DBP from aliskiren treatment were sustained at one week following treatment withdrawal, demonstrating the drug's long half-life and reduced risk of rebound hypertension after discontinuation of treatment. Adverse events were similar in all treatment arms; however, there was no evidence that higher aliskiren doses increased the incidence of adverse events, particularly diarrhea. Two cases of hyperkalemia (defined as $\geq 20\%$ increase in potassium concentrations from baseline) were reported in the aliskiren 75 mg treatment arm.

In a final study that demonstrated the antihypertensive efficacy of aliskiren monotherapy, Oh et al randomized 672 Korean and American patients with mild to moderate hypertension to receive aliskiren 150 mg, aliskiren 300 mg, aliskiren 600 mg or placebo for eight weeks.⁹ Study drug was taken at approximately 8 a.m. daily without regards to meals. All aliskiren doses significantly lowered mean sitting SBP and DBP compared to placebo ($p < 0.0001$). While aliskiren 600 mg caused larger blood pressure reductions than the 300 mg dose, this difference was not statistically significant. Blood pressure lowering with aliskiren was not equal in all patients. Compared to Caucasians ($n = 408$), Black patients ($n = 79$) experienced smaller reduction of both SBP ($p < 0.0004$) and DBP ($p < 0.0001$).

All aliskiren doses were well tolerated and there were no differences in the number of adverse effects reported among the four treatment arms. The most common adverse effects included headache and nasopharyngitis. Similar to the report by Gradman et al,⁸ a higher number of patients reported diarrhea in the aliskiren 600 mg arm than the 150 mg and 300 mg groups (11.4% vs 1.2% and 1.8%, respectively; $p < 0.0001$). The authors did not report the incidence of hyperkalemia in aliskiren-treated subjects.

Several conclusions can be drawn from the results of the aliskiren monotherapy trials. While all aliskiren doses successfully lower BP, the evidence does not support using the 600 mg dose for further antihypertensive effect.^{8,9} The benefit of using aliskiren 600 mg/day is also limited by complaints of diarrhea.^{8,9} A major limitation of all three trials is the short treatment course (eight weeks) that prohibits any correlation between aliskiren's antihypertensive effects and end-organ protection (i.e. heart and kidney) or reduction in cardiovascular events – outcomes well documented with ACE inhibitor and ARB therapies. Another important point that requires further clarification is the use of aliskiren in patient populations other than Caucasians and males who were under-represented in these trials.

The remaining two trials submitted for aliskiren's FDA approval examined the blood pressure lowering effects of aliskiren as both monotherapy and in combination with other antihypertensive agents.^{10,11} The first of these two trials compared aliskiren therapy to valsartan.¹⁰ Eleven hundred twenty-three patients from the U.S., Germany, France, Denmark and Poland with mild to moderate hypertension were randomized to one of eleven treatment arms after a 3 to 4-week placebo run-in. Treatment arms included aliskiren 75 mg, 150 mg, and 300 mg monotherapy; valsartan 80 mg, 160 mg, and 320 mg monotherapy, increasing doses of aliskiren in combination with valsartan; valsartan with hydrochlorothiazide; and placebo. Study drugs were to be taken daily at 8 a.m. for eight weeks without regards to meals. Due to a large placebo effect in this trial, the only aliskiren monotherapy arm that significantly reduced both SBP and DBP compared to placebo was the

FIGURE 1. DRUG TARGETS TO INHIBIT THE RENIN-ANGIOTENSIN SYSTEM

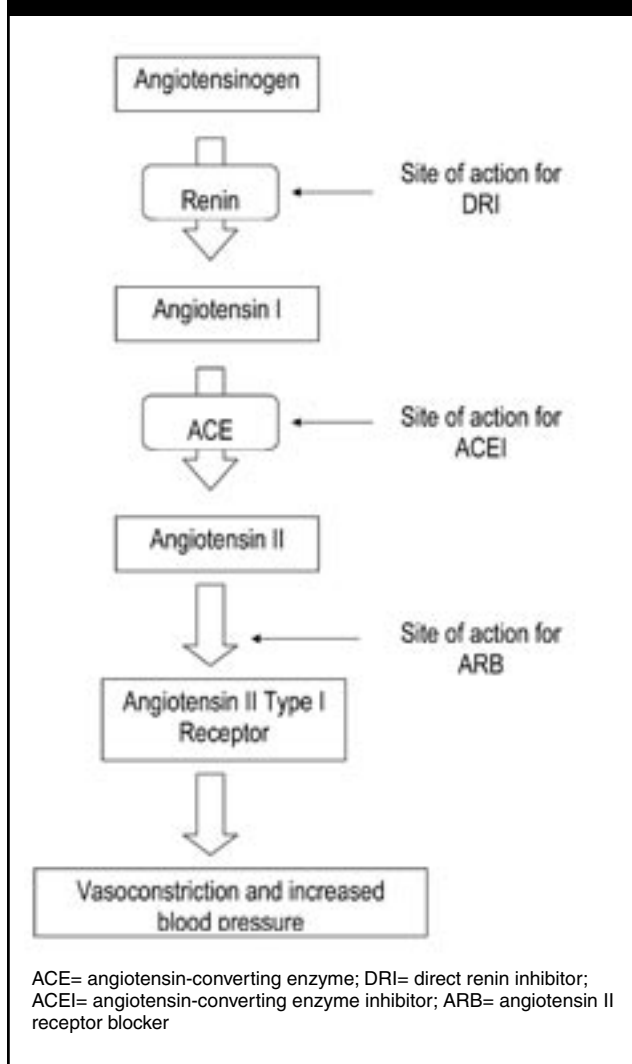


Table 1 Clinical Trials of Aliskiren Treatment for Hypertension

Study	Patient Population	Study Design	Treatment Arms and Duration	Mean BP (mmHg) at Baseline	Mean Decrease in SBP (mmHg) After Treatment	Mean Decrease in DBP (mmHg) After Treatment	Patients Reaching BP Goal (%)
Gradman et al. ¹ (2005)	652 adults with mild to moderate hypertension; mean age 56 yrs; approximately 74% Caucasian and 50% male	Randomized, double-blind, placebo controlled, parallel group; conducted in the U.S., Germany, Belgium Switzerland	Aliskiren 150 mg Aliskiren 300 mg Aliskiren 600 mg Irbesartan 150 mg Placebo 2-week washout, 2-4 week placebo run-in, 8 weeks treatment	151.3/98.8 152.1/98.8 152.6/99.1 152.8/99.4 152.3/98.9	-11.30* -15.76* -15.73* -12.5* -5.29 * p<0.001 compared to placebo	-9.28* -11.77*† -11.57*† -8.88‡ -6.34 # p<0.05 compared to placebo; † p<0.05 compared to irbesartan	37.8‡ 50‡† 45.7‡† 33.8‡ 20.8 # p<0.05 compared to placebo; † p<0.05 compared to irbesartan
Kushiro et al. ² (2006)	455 adults with essential hypertension; mean age 52 yrs; approximately 70% male	Randomized, double-blind, placebo controlled, parallel group; conducted in multiple centers in Japan	Aliskiren 75 mg Aliskiren 150 mg Aliskiren 300 mg Placebo 4-week washout, 8 weeks treatment, 1 week withdrawal	152.7/99.4 155.6/99.5 155.9/99.6 155.4/99.4	-8.57‡ -8.72‡ -14.09‡ -2.85 # p<0.05 compared to placebo	-7.22‡ -7.75‡ -10.72‡ -3.26 # p<0.05 compared to placebo	47.8* 48.2* 63.7* 27.8 * p<0.001 compared to placebo
Oh et al. ³ (2007)	672 adults with mild to moderate hypertension; mean age 53 yrs; approximately 61% Caucasian and male	Randomized, double-blind, placebo controlled, parallel group; conducted in the U.S. and Korea	Aliskiren 150 mg Aliskiren 300 mg Aliskiren 600 mg Placebo 2-week washout, 2-4 week placebo run-in, 8 weeks treatment, 2-week withdrawal	152.2/99.7 153.1/99.7 151.9/99.4 151.9/99.4	-13+ -14.7+ -15.8+ -3.8 + p<0.0001 compared to placebo	-10.3+ -11.1+ -12.5+ -4.9 + p<0.0001 compared to placebo	35.9* 41.6* 46.4* 20.3 * p<0.001 compared to placebo
Pool et al. ¹⁰ (2007)	1123 adults with mild to moderate hypertension; mean age 56 yrs; approximately 93% Caucasian and 55% male	Randomized, double-blind, placebo controlled, multifactorial, parallel-group; conducted in 94 centers in the U.S., Germany, France, Denmark and Poland.	Aliskiren 75 mg Aliskiren 150 mg Aliskiren 300 mg Valsartan 80 mg Valsartan 160 mg Valsartan 320 mg A/V 75mg/80 mg A/V 150mg/160 mg A/V 300mg/320 mg V/H 160mg/12.5 mg Placebo 3-4 week placebo run-in, 8 weeks treatment	152.9/98.7 154.1/99.3 152.9/99.1 152.4/99 154.5/99 153.4/98.9 152.7/99.4 153.9/98.7 153.9/98.8 153.98.9 152.6/98.7	-12.1 -12.1 -15‡ -11.2 -15.5‡ -16.5‡ -14.5‡ -16.6‡† -18‡ -18.9‡ -10 # p<0.05 compared to placebo; ‡ p<0.05 compared to aliskiren 150 mg	-10.3 30.5 42.3‡ 37.9 46.6 41.7 43.3‡ 36.7 50‡ 55.2*† 27.8 * p<0.001 compared to placebo; ‡ p<0.01 compared to each component; † p<0.05 compared to A/V 150/160 mg	

Table 1 Clinical Trials of Aliskiren Treatment for Hypertension continued . . .

Author (Year)	Study Population	Study Design	Interventions	Primary Endpoints (Mean Change)	Secondary Endpoints (Mean Change)	Significance	Other Findings
Williams et al. ¹¹ (2007)	2776 adults with mild to moderate hypertension; mean age 55 yrs; approximately 80% Caucasian (of those 25% were Hispanic) and 55% male	Randomized, double-blind, placebo-controlled, multifactorial, parallel-group; conducted in the U.S. and Argentina	Aliskiren 75 mg Aliskiren 150 mg Aliskiren 300 mg HCTZ 6.25 mg HCTZ 12.5 mg HCTZ 25 mg A/H 75 mg/6.25 mg A/H 75 mg/12.5 mg A/H 75 mg/25 mg A/H 150 mg/6.25 mg A/H 150 mg/12.5 mg A/H 150 mg/25 mg A/H 300 mg/12.5 mg A/H 300 mg/25 mg Placebo 1-week washout, 2-4 week placebo run-in, 8 weeks treatment	153.2/99.4 153.4/98.8 154.4/99.3 153.4/99.3 153.4/99.1 154.5/99.1 154.5/98.9 154/100 152.0/99 153.3/99 154.1/99.1 153.2/98.4 153.2/99.5 154.6/99.3 152.7/99.3	-9.4 -12.2# -15.7# -11# -13.9# -14.3# -14.3#E -15.6# -17.3#E -15.3# -17.6#E -19.5#E -19.8#E -21.2#E -7.5	# p< 0.05 compared to placebo; E p<0.05 compared to each component	Percentages for individual treatment arms not reported
O'Brien et al. ¹² (2007)	87 adults with mild to moderate hypertension; 100% Caucasian and approximately 75% male	3 open-label studies; conducted in Ireland and Switzerland	1. Aliskiren 150 mg, A/H 150 mg/25 mg 2. Ramipril 5 mg, A/R 75 mg/5 mg, A/R 150 mg/5 mg 3. Irbesartan 150 mg, A/I 75 mg/150 mg, A/I 150 mg/150 mg 7-10 day wash out, 3 weeks monotherapy, 3 weeks combination, 3 weeks high dose aliskiren combination	150/88.8 156.2/88.8 Recorded as ambulatory blood pressure measurements (ABPM)	-10.4 -18.4* -6.1 -10.5* -14† -11.4 -14.8 -13.3	# p< 0.05 compared to placebo; E p<0.05 compared to each component	Not reported
Jordan et al. ¹³ (2007)	560 adults with mild to moderate hypertension; mean age 54 yrs; approximately 100% Caucasian and 45% male	Randomized, double-blind, placebo-controlled; conducted in 69 centers in Belgium, France, Germany, Israel, Norway, Russia and Spain	H= hydrochlorothiazide A= aliskiren, R= ramipril, I= irbesartan HCTZ 25 mg x 4 weeks Aliskiren 150 mg/H 25 mg, Aliskiren 300 mg/H 25 mg Amlodipine 5 mg/H 25 mg, Amlodipine 10 mg/H 25 mg Irbesartan 150 mg/H 25 mg, Irbesartan 300 mg/H 25 mg Placebo/H 25 mg 2-week wash out, 4 weeks HCTZ, 4 weeks low dose combination, 8 weeks high dose combination	149.5/97.2 149.4/96.8 149.8/96.7 149.1/96.6	-9.4 -15.79* Not reported -13.55* Not reported -15.44* -8.62	* p<0.001 compared to aliskiren; † p<0.05 compared to ramipril; ‡ p<0.01 compared to ramipril	# p<0.0005 compared to placebo/HCTZ

300 mg dose ($p < 0.05$). The placebo effect was also noted in a higher percentage of patients reaching blood pressure goal with placebo therapy than was reported in previous aliskiren studies.^{8,9} The antihypertensive effect of aliskiren 75 mg to 300 mg was equivalent to that of valsartan 80 mg to 320 mg. When the aliskiren/valsartan combinations were compared to placebo, all three combinations significantly lowered blood pressure ($p < 0.05$). When combination therapy was compared to the respective component monotherapies, only small differences were noted ($p = \text{NS}$), except for the aliskiren 150 mg treatment arm ($p < 0.05$). Both antihypertensive agents were well tolerated as monotherapy or in combination. The incidence of adverse effects and study discontinuation was similar among all treatment arms. The most commonly reported adverse effects included headache, fatigue, back pain, and diarrhea. Five cases of mild hyperkalemia (serum potassium concentration > 5.5 mEq/L) were reported, one each in the placebo, aliskiren 75 mg, aliskiren 300 mg, aliskiren 150 mg/valsartan 160 mg, and aliskiren 300 mg/valsartan 320 mg groups. Not only was the large placebo effect a limitation of this study, but the patient population recruited was predominately middle-aged, Caucasian males. What this study adds to the growing knowledge concerning aliskiren is the apparent safety of using a renin inhibitor with an ARB, as the number of adverse effects was not statistically different among the combination arms and the respective monotherapy arms.

The last study evaluated the antihypertensive efficacy of aliskiren alone and in combination with hydrochlorothiazide.¹¹ A total of 2776 patients with mild to moderate hypertension were enrolled in this trial; the majority were Caucasian ($> 80\%$), with 25-30% being Hispanic, and few were Asian or Black. Patients were randomized to receive aliskiren (75 mg, 150 mg, or 300 mg), hydrochlorothiazide (6.25 mg, 12.5 mg, or 25 mg), a combination of aliskiren with hydrochlorothiazide, or placebo after a one-week washout period. The study drug was administered daily for eight weeks. No information was provided on dosing time of day or relationship to food ingestion. While all three aliskiren doses signifi-

cantly lowered DBP compared to placebo ($p < 0.05$), the aliskiren 75 mg dose failed to significantly lower SBP versus placebo. All combinations were superior to placebo ($p < 0.0001$) and most combinations were superior to the individual monotherapies. The greatest blood pressure reduction occurred in the aliskiren 300 mg/hydrochlorothiazide 25 mg group. A higher percentage of patients receiving combination therapy achieved the blood pressure goal (37.4-59.5%) compared to those receiving either aliskiren or hydrochlorothiazide monotherapies (29-46.7%, 32.5-37.8%, respectively). The most common adverse effects were headache and nasopharyngitis.

ALISKIREN COMBINATION THERAPIES

Although aliskiren monotherapy controls blood pressure in patients with mild to moderate hypertension, many patients will require two or more antihypertensive agents to attain blood pressure goals. Earlier trials demonstrated further blood pressure lowering when aliskiren was administered with valsartan¹⁰ and hydrochlorothiazide¹¹ compared to the individual drugs alone. More recent studies have confirmed the benefit of combining aliskiren with a thiazide diuretic,^{12,13} an ACEI,¹² an ARB,^{12,13} and a calcium channel blocker¹³ to treat hypertension.

Aliskiren with a diuretic or calcium channel blocker. In an open-label study conducted by O'Brien et al, hydrochlorothiazide 25 mg was added to Caucasian patients (approximately 75% males) who continued to have blood pressure readings $> 135/85$ mmHg after three weeks of aliskiren 150 mg/day.¹² Patients were asked to take all study drugs daily, 30 minutes prior to eating the morning meal. Following three weeks of combination therapy, patients had a significant decrease in daytime SBP and DBP as compared to aliskiren monotherapy ($p = 0.007$ and $p = 0.0006$, respectively). Changes in nighttime SBP and DBP had similar trends but did not reach statistical significance ($p = 0.06$ and $p = 0.09$, respectively).

The results from the study conducted by Jordan et al further demonstrate the benefit of adding aliskiren to hydrochlorothiazide.¹³ Four hundred eighty-nine patients from Belgium, France, Germany, Israel, Norway, Russia, and Spain, all of whom were receiving hydrochlorothiazide

25 mg/day with a DBP ≥ 95 and < 110 mmHg, were randomized to one of the following treatment arms: aliskiren 150 mg/hydrochlorothiazide 25 mg, irbesartan 150 mg/hydrochlorothiazide 25 mg, amlodipine 5 mg/hydrochlorothiazide 25 mg and hydrochlorothiazide 25 mg monotherapy. After four weeks of therapy, the doses of aliskiren, irbesartan and amlodipine were doubled and treatment continued for another eight weeks. Aliskiren/hydrochlorothiazide combination therapy produced significant decreases in both SBP and DBP as compared to hydrochlorothiazide monotherapy ($p < 0.0001$). While the aliskiren/hydrochlorothiazide combination produced greater reductions in blood pressure than the other combinations, the decrease was not statistically significant. All study treatments were well tolerated. The amlodipine/hydrochlorothiazide combination had a higher incidence of adverse effects, mainly peripheral edema. Five patients (4.1%) developed hyperkalemia (potassium concentration > 5.5 mEq/L) while receiving aliskiren/hydrochlorothiazide.

Aliskiren with an ACEI. The second arm of the O'Brien et al study added aliskiren 75 mg to ramipril 5 mg after three weeks of monotherapy.¹² Significant reductions in daytime SBP occurred in the ramipril/aliskiren group versus those receiving ramipril alone ($p = 0.003$). When the aliskiren dose was increased to 150 mg after three weeks, daytime SBP was further reduced compared to ramipril alone ($p = 0.0006$). However, there were no significant differences between SBP reductions comparing aliskiren 150 mg/ramipril 5 mg to aliskiren 75 mg/ramipril 5 mg. Both therapies were well tolerated; the maximum individual serum potassium concentration was 5.3 mEq/L when aliskiren was added to ramipril.

Aliskiren with an ARB. In the final treatment arm of the O'Brien et al study, aliskiren 75 mg was added to irbesartan 150 mg after three weeks of monotherapy.¹² While the addition of aliskiren 75 mg did not produce significant reductions in daytime SBP or DBP, it did cause significant reductions in nighttime SBP and DBP compared to irbesartan alone ($p < 0.05$). When the aliskiren dose was increased to 150 mg after three weeks, there was a trend for both daytime and

nighttime blood pressure measurements to increase rather than decrease. As with the other treatment arms, both medications were well tolerated; the maximum individual potassium concentration following the addition of aliskiren to irbesartan was 5.5 mEq/L.

ALISKIREN PHARMACOKINETICS

Aliskiren is poorly absorbed in the small intestine with an oral bioavailability of approximately 2.5%.⁷ After oral administration, peak plasma concentrations are reached within one to three hours. Food may cause variability in drug absorption. In the clinical trials where aliskiren was administered without regards to meals, fatty meals decreased the area-under-the-concentration time curve (AUC) and maximum concentration (C_{max}) by 71% and 85%, respectively. The half-life of aliskiren is 24 hours and steady state concentrations are reached in seven to eight days. One-quarter of an administered dose is excreted unchanged in the urine, but how much of the absorbed dose is actually metabolized remains unclear. In vitro studies indicate aliskiren is primarily metabolized by the cytochrome P450 3A4 enzyme.

ALISKIREN DOSING AND ADMINISTRATION

The usual recommended starting dose of aliskiren is 150 mg once daily and may be increased to 300 mg once daily based on patient response; however, these doses may not be appropriate for all patient populations.⁷ For example, in patients >65 years of age with mild to moderate hypertension, there was a better blood pressure response to lower aliskiren doses (75-150 mg) than in younger patients.¹ Caucasians responded well to all aliskiren doses used in the clinical trials (75-600 mg) while African Americans had a lesser response with all doses. Asians had a better response to the 75 mg dose with no added benefit noted in blood pressure lowering when the doses were increased to 300-600 mg. However, the manufacturer states that pharmacokinetic differences between Caucasian, Asian, and Black patients are minimal.⁷

An important area requiring further clarification is whether the appropriate

doses of aliskiren were approved for marketing.¹ Since elderly patients had better blood pressure responses to lower doses in the clinical trials and, given the potential for adding aliskiren to other antihypertensive agents, higher aliskiren starting doses could result in symptomatic hypotension in these patients. Also, while aliskiren is approved for use as monotherapy or in combination with other agents, no studies have been conducted using maximal doses of ACEI. Therefore, further studies are needed to determine if lower aliskiren doses, such as 37.5 mg and 75 mg, would be equally effective but safer to use as monotherapy or in combination with doses of ACEI commonly used in patients with comorbid conditions such as heart failure. Currently the prescribing information for aliskiren does not recommend any dosage adjustments for the elderly, for patients with mild to moderate renal impairment or patients with mild to moderate hepatic impairment.⁷

Patients should be instructed to take aliskiren once a day, at the same time each day, with or without food. However, patients should establish a routine for taking aliskiren with regards to meals, as fatty meals will affect the absorption of the drug.⁷

DRUG INTERACTIONS

Although aliskiren does not inhibit or induce cytochrome P450 enzymes, the drug can be affected by other medications that do.^{1,7} Medications commonly prescribed to patients for treatment of hypertension and diabetes were selected to test for potential interactions with aliskiren. Concomitant lovastatin, atenolol, warfarin, digoxin, celecoxib, hydrochlorothiazide, ramipril, valsartan, metformin and amlodipine did not affect aliskiren pharmacokinetics.⁷ Aliskiren's effect on warfarin pharmacokinetics has not been well studied in clinical trials, so caution should be used when adding aliskiren to warfarin therapy. Interactions with aliskiren include a 50% reduction in C_{max} after routine dosing with irbesartan, a 50% increase in both AUC and C_{max} by atorvastatin, and an 80% increase in aliskiren plasma levels by ketoconazole 200 mg twice daily. Aliskiren can decrease the AUC and C_{max} of furosemide by 30% and 50%, respectively. Since few

drug interactions have been documented or studied at this time, few dosage adjustments for aliskiren are recommended.¹ For patients receiving a non-topical form of ketoconazole, it is recommended that the aliskiren dose be decreased by 50%.⁷ For patients taking furosemide, no dosage adjustments are recommended when aliskiren therapy is added,⁷ but patients should be monitored for side effects and the furosemide dose should be decreased if necessary.

ALISKIREN SIDE EFFECTS

In the clinical trials, aliskiren therapy was relatively safe and associated with minimal serious side effects. The most commonly noted side effects were gastrointestinal (GI) complaints, mainly diarrhea. In clinical trials, diarrhea was reported in 2.3% of patients receiving 300 mg/day and the percentage of patients who experienced this side effect increased as the dose was increased. Women and patients >65 years of age were also more likely to experience diarrhea with the 150 mg/day dose than men and younger patients. Other GI side effects, such as abdominal pain, dyspepsia, and GI reflux, were experienced by patients taking 600 mg per day. These side effects were considered to be mild and rarely led to the discontinuation of aliskiren.^{2,8,9} The manufacturer recommends that doses >300 mg/day should not be used, as there is no increased response to blood pressure at higher doses and the risk for diarrhea increases.⁷

Hypotension rarely occurred in the clinical trials whether patients were receiving aliskiren alone (0.1%) or in combination with other antihypertensive agents (<1%).⁷ The manufacturer does warn that if starting aliskiren in patients who are volume or salt depleted, these conditions should be corrected before initiating aliskiren to prevent symptomatic hypotension.⁷

There is a slight risk for increased serum uric acid concentrations, kidney stones, and gout with aliskiren.⁶ While the incidence is less than that associated with hydrochlorothiazide, these effects may be additive when the two are used in combination.

As with other inhibitors of RAS, aliskiren therapy has a slightly higher rate of cough than placebo (1.1% vs 0.6%,

respectively), but this incidence is approximately one-third to one-half of that reported with ACEI.⁷ Patients rarely discontinued aliskiren therapy due to cough during the clinical trials. Aliskiren may lower the incidence of ACEI-induced cough when the two are used in combination, but this has not yet been proven in studies.¹ Another potential side effect from inhibiting the RAS system is hyperkalemia. Increases in serum potassium >5.5 mEq/L were infrequent in patients treated with aliskiren monotherapy compared to placebo (0.9% vs 0.6%, respectively). However, the percentage of patients with elevated potassium increased to 5.5% in the clinical trials, particularly in diabetic patients taking aliskiren with an ACEI.⁷ Routine monitoring of serum potassium and renal function is recommended in these patients. Aliskiren therapy has rarely been associated with the development of angioedema (0.06%).⁷

Since other medications that inhibit the RAS have been found to be harmful to the fetus (i.e. ACEI and ARB), aliskiren is not recommended for use in pregnant women.⁷ The FDA-approved labeling for aliskiren was revised in August 2007 to advise prescribers and patients of the risk for fetal/neonatal morbidity and mortality with aliskiren therapy.

CURRENT STUDIES

Blockage of RAS activity by aliskiren has the potential to provide organ protection independent of its blood pressure effects. Other medications that inhibit the RAS have been proven to slow and prevent the end-organ damage associated with longstanding hypertension.^{5,9,12} There are several ongoing trials investigating the benefits of aliskiren alone or in combination with an ACEI or ARB on enhanced end-organ protection and improved outcomes.

Avant-Garde-Timi 43. "Aliskiren and Valsartan to reduce N-Terminal prohormone brain natriuretic peptide (NT-proBNP) via renin-angiotensin-Aldosterone-system blockade" is studying whether aliskiren monotherapy, valsartan monotherapy, or combination therapy will improve ventricular remodeling by reducing the levels of NT pro-BNP in 1152 hospitalized patients who have been stabilized following acute coronary syndrome.^{5,14}

Aspire. "Aliskiren Study in Post-MI patients to reduce Remodeling" will determine if aliskiren, when added to standard post-myocardial infarction therapy, will reduce the remodeling of the heart as determined by left ventricular end systolic volume in 860 high-risk post infarction patients.^{5,14}

Avoid. "Aliskiren in the eValuation of proteinuria In Diabetes" is evaluating whether aliskiren, in combination with losartan 100 mg/day and optimal antihypertensive therapy, will decrease proteinuria in patients who have both hypertension and type 2 diabetes with proteinuria.^{5,14} This study has been completed and results from the 754 patients enrolled in the trial are pending.⁵

Aloft. "ALiskiren Observation of heart Failure Treatment" will determine the safety and tolerability of aliskiren when added to standard heart failure therapy in patients with stable heart failure (NYHA class II-IV).^{5,14} This study has also been completed and results from the 320 patients enrolled in the trial are pending.⁵

Allay. "ALiskiren in Left ventricular hypertrophy" will compare the effects of aliskiren in combination with losartan to losartan alone on left ventricular hypertrophy regression in 754 obese patients with hypertension.^{5,14}

Ageless. The "aliskiren versus ramipril for blood pressure control in the elderly" study will compare the antihypertensive effects of aliskiren to ramipril in 912 patients ≥65 years with systolic hypertension.⁵

Altitude. The "ALiskiren in Type 2 diabetes Using cardiorenal Disease End-points" study will determine if aliskiren can reduce cardiovascular and renal morbidity and mortality when combined with conventional treatments in 8,400 high-risk patients with type 2 diabetes.⁵

CONCLUSION

Aliskiren is a new antihypertensive drug in a novel therapeutic class. It has been proven to effectively lower blood pressure as well as other antihypertensive agents with a placebo-like side effect profile. It has also been shown to be effective in combination with other agents when blood pressure goals have not been reached with monotherapy. Aliskiren should be considered as

add-on therapy for patients who remain above blood pressure goal on hydrochlorothiazide, an ACEI, or an ARB, as these medications can cause a reactive rise in plasma renin concentrations. The potential role of aliskiren in the elderly, patients with heart disease, heart failure or diabetes will be more clearly defined after the results of multiple clinical trials are available. However, aliskiren is a patent drug without a generic equivalent, so the cost of this medicine may limit its usefulness, as other equally effective blood pressure medications already exist in less expensive generic forms. ●

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Aliskiren: A New Idea in Blood Pressure Management

1. Which of the following is secreted by the kidneys in response to low plasma volume or decreased renal perfusion and is the main determinant of renin-angiotensin system activity?
 - a. Angiotensinogen
 - b. Angiotensin II
 - c. Angiotensin-converting enzyme
 - d. Renin
2. Which of the following statements concerning the renin-angiotensin system is correct?
 - a. Angiotensin I is a potent vasoconstrictor that increases peripheral vascular resistance.
 - b. Angiotensinogen is the active precursor of both angiotensin I and angiotensin II.
 - c. Angiotensin-converting enzyme is required to convert angiotensinogen to angiotensin I.
 - d. Renin is required to convert angiotensinogen to angiotensin I.
3. While current antihypertensive medications such as ACE inhibitors and angiotensin receptor blockers effectively lower blood pressure, they do not completely suppress the renin-angiotensin system.
 - a. True
 - b. False
4. What percentage of patients with essential hypertension has overactivity of the renin-angiotensin system?
 - a. 25%
 - b. 50%
 - c. 70%
 - d. 90%
5. Which of the following ethnic patient populations was underrepresented in the aliskiren trials and may experience less blood pressure lowering from aliskiren therapy?
 - a. Asians
 - b. Blacks
 - c. Caucasians
 - d. Hispanics
6. Which of the following adverse effects was reported most frequently by patients taking aliskiren in the clinical trials?
 - a. Angioedema
 - b. Headache
 - c. Hyperkalemia
 - d. Hypotension
7. Which patients are at higher risk for developing diarrhea from aliskiren?
 - a. Elderly (>65 years of age)
 - b. Males
 - c. Patients taking aliskiren doses >150 mg/day
 - d. Patients taking concomitant ACE inhibitors or angiotensin receptor blockers
8. Which of the following statements regarding aliskiren pharmacokinetics is correct?
 - a. Aliskiren has good absorption in the gut with an oral bioavailability of 80%.
 - b. Approximately 50% of an aliskiren dose is excreted unchanged in the urine.
 - c. Peak plasma concentrations are reached within 4-6 hours after oral administration.
 - d. Steady-state plasma concentrations are reached within 7-8 days of therapy.
9. Which of the following statements regarding aliskiren dosing is correct?
 - a. Aliskiren should be initiated at 150 mg once daily and can be titrated up to 600 mg/day if clinical improvement in blood pressure is not seen.
 - b. Aliskiren doses >300 mg/day provide further blood pressure lowering with minimal complaints of gastrointestinal side effects like diarrhea.
 - c. For patients taking oral ketoconazole, the starting dose of aliskiren should be doubled to account for cytochrome P450 enzyme induction.
 - d. The furosemide dose should not be adjusted when starting aliskiren but the patient should be watched closely for signs of toxicity.
10. Which of the following counseling points should be discussed with a patient beginning aliskiren therapy for hypertension?
 - a. Aliskiren absorption may be affected by fatty meals, so she/he should take aliskiren consistently with regard to meals.
 - b. Aliskiren should be avoided if a female patient is planning to become pregnant, as this medication may cause fetal complications or death.
 - c. Patients with a history of gout who are also taking hydrochlorothiazide should have uric acid levels monitored after aliskiren is started.
 - d. All of the above
11. When aliskiren is added to warfarin therapy, the patient should be monitored closely for signs of bleeding or warfarin failure as little data is available on aliskiren's effect on warfarin pharmacokinetics.
 - a. True
 - b. False
12. Based on data from the aliskiren trials, which of the following antihypertensive medications can be safely added to aliskiren if a patient fails to reach his/her blood pressure goal?
 - a. Amlodipine
 - b. Hydrochlorothiazide
 - c. Valsartan
 - d. All of the above
13. A reduction in cardiovascular events, such as myocardial infarction and stroke, has not been associated with aliskiren therapy.
 - a. True
 - b. False
14. Which of the following clinical outcomes are being assessed in ongoing studies with aliskiren?
 - a. Decreased cardiovascular and renal morbidity and mortality
 - b. Decreased proteinuria in patients with hypertension and diabetes
 - c. Decreased ventricular remodeling after myocardial infarction
 - d. All of the above
15. How do you rate this lesson?
 - a. Very Good
 - b. Good
 - c. Poor
16. Did it meet the learning objectives?
 - a. Yes
 - b. No
17. How long did it take you to complete this lesson?

Creative Budgeting

Most of us could easily spend every penny we make and more. Saving doesn't mean making radical changes in your lifestyle. Just becoming more conscious of where your money is being spent should help you find ways to save.

Complete a spending plan worksheet to take a look at where you're spending your money over a three-month period. Start taking notes about where your money is going, or consider using your debit card to help you keep track. You'll be amazed at the waste patterns you spot, and recognizing them is the key to changing.

Before you start investing your new savings, make sure you have an adequate emergency fund. Most experts recommend that you set aside three to six months worth of living expenses in a money market account or CDs that will be easily accessible in an emergency. Having an adequate emergency account will put you at ease about investing for the future.

Then be creative about ways you can save; view it as a challenge and you may find you're having fun along the way. Here are a few relatively painless ways to tighten your belt a notch or two:

- Raise your insurance deductibles (and drop the towing on your auto insurance – it costs more in increased premiums over time than you'll pay to the tow truck operator). With what you'll save in premiums, you'll usually cover any cash outlay you might have to make.
- Don't over-withhold on your taxes. As nice as it is to get a refund, the government is using your money interest-free while you could have been investing it. If you got a refund last year,

adjust your withholding to eliminate it and allocate the extra to your IRA or 401(k). Just be sure not to under-withhold, or you could be liable for penalties and interest.

- Use your 401(k) or IRA account to save money by cutting taxes and generating earnings tax deferred. For example, if you're in the 28% tax bracket, one dollar out of every four dollars you put into a pre-tax retirement account is paid for by reduced taxes – not reduced take-home pay. Also be sure to take full advantage of your employer's match by investing enough to qualify for that important benefit. If you don't, it's like turning down free money.
- Avoid late fees on credit cards or video rentals. It's just money down the drain.
- Avoid ATM surcharges. Use your debit card, plan ahead to use your own bank's ATM or get cash back when you grocery shop.
- Shop around for the lowest long-distance telephone carrier – or better yet – use email when you can.
- Comparison shop among airlines. Watch for sales and utilize e-saver online specials. If possible, be flexible about your departure/arrival cities – 30 miles or less between cities can sometimes save you hundreds of dollars in fares.
- Pay your bills online or use auto-withdrawal to save on the cost of postage.
- Have your hair cut every five weeks instead of every four weeks and you can save two haircuts a year. ●

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| 2) a b c d | 11) T F |
| 3) T F | 12) a b c d |
| 4) a b c d | 13) T F |
| 5) a b c d | 14) a b c d |
| 6) a b c d | 15) a b c |
| 7) a b c d | 16) a b |
| 8) a b c d | 17) _____ |
| 9) a b c d | |

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