Blood Pressure Lowering in Essential Hypertension With an Oral Renin Inhibitor, Aliskiren

Alice Stanton, Chris Jensen, Juerg Nussberger, Eoin OBrien

Abstract—Inhibition of the first and rate-limiting step of the renin-angiotensin system has long been an elusive therapeutic goal. Aliskiren, the first known representative of a new class of completely nonpeptide, orally active, renin inhibitors, has been shown to inhibit the production of angiotensin I and II in healthy volunteers and to reduce blood pressure (BP) in sodium-depleted marmosets. The aim of this randomized, double-blind, active comparator trial study was to assess the BP-lowering efficacy and safety of aliskiren. Two hundred twenty-six patients, 21 to 70 years of age, with mild to moderate hypertension, were randomly assigned to receive 37.5 mg, 75 mg, 150 mg, or 300 mg aliskiren or 100 mg losartan daily for 4 weeks. Dose-dependent reductions in daytime ambulatory systolic pressure (mean change, mm Hg [SD of change]; −0.4 [11.7], −5.3 [11.3], −8.0 [11.0], and −11.0 [11.0], $P=0.0002$) and in plasma renin activity (median change % [interquartile range]; −55 [−64, −11], −60 [−82, −46], −77 [−86, −72], and −83 [−92, −71], $P=0.0008$) were observed with 37.5, 75, 150, and 300 mg aliskiren. The change in daytime systolic pressure with 100 mg losartan (−10.9 [13.8]) was not significantly different from the changes seen with 75, 150, and 300 mg aliskiren. Aliskiren was well tolerated at all doses studied. This study demonstrates that aliskiren, through inhibition of renin, is an effective and safe orally active BP-lowering agent. Whether renin inhibition results in protection from heart attack, stroke, and nephropathy, similar to angiotensin-converting enzyme inhibition and angiotensin receptor blockade, needs to be researched. **(*Hypertension*. 2003;42:1137-1143.)**

Key Words: renin ■ blood pressure ■ hypertension, essential ■ blood pressure monitoring, ambulatory ■ receptors, angiotensin ■ losartan

The renin-angiotensin system (RAS) has well-established roles in both blood pressure (BP) regulation and atherogenesis.[1,2] Recent clinical trial evidence suggests that blockade of the RAS by angiotensin-converting enzyme inhibition or by angiotensin receptor blockade may influence large-vessel atherosclerosis and cardiovascular morbidity and mortality independent of BP lowering.[3,4] As renin catalyzes the first and rate-limiting step of the system and has high specificity for angiotensinogen, blockade of the production of angiotensin (Ang) II by direct inhibition of renin has long been a therapeutic goal. Indeed, intravenous administration of the early renin inhibitors, such as enalkiren and remikiren, did reduce angiotensin levels and lower BP without any important adverse effects.[5–8] However, to date, due to relatively low potency, poor oral bioavailability (<1%), short durations of action, and high costs of synthesis, none of these peptide and peptidomimetic inhibitors has made it to the end of clinical trials.[9]

Aliskiren, an octanamide, is the first known representative of a new class of completely nonpeptide, low-molecular-weight, orally active transition-state renin inhibitors.[10] Designed through the use of molecular modeling techniques, it is a potent and specific in vitro inhibitor of human renin (IC50 in the low nanomolar range), with a plasma half-life of ≈24 hours.[10] Aliskiren has good water solubility and low lipophilicity and is resistant to biodegradation by peptidases in the intestine, blood circulation, and the liver.[10] When administered orally to sodium-depleted marmosets, it caused significant and sustained reductions in arterial blood pressure (unpublished data). In single-dose and multiple-dose tolerability studies in healthy normotensive male volunteers, oral doses up to 640 mg daily for 8 days were well tolerated and did not result in any significant toxicity.[11] Micromolar plasma concentrations were achieved, and aliskiren was shown to cause a dose-dependent decrease in plasma renin activity (PRA), to effectively block the formation of both Ang I and Ang II, and to decrease plasma and urine aldosterone levels.[11]

In this study, we studied for the first time the efficacy, safety, and tolerability of 4 weeks of treatment with 37.5, 75, 150 and 300 mg aliskiren in healthy individuals with mild to moderate hypertension. We compared the effects of these various doses of aliskiren with the effects of 100 mg losartan

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From the Blood Pressure Unit, Beaumont Hospital (A.S., E.O.), Dublin, Ireland; the Department of Clinical Pharmacology, Royal College of Surgeons in Ireland (A.S., E.O.), Dublin, Ireland; Clinical Research, Speedel Pharma AG (C.J.), Basel, Switzerland; and the Division of Hypertension and Vascular Medicine, University Hospital (J.N.), Lausanne, Switzerland.

Correspondence to Dr Alice Stanton, Department of Clinical Pharmacology, Royal College of Surgeons in Ireland, St Stephen's Green, Dublin 2, Ireland. E-mail astanton@rcsi.ie

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once daily and also determined trough plasma concentrations of aliskiren and PRA at baseline and during treatment.

Methods

Participants

The study cohort consisted of men and women, 21 to 70 years of age, with off-treatment average daytime ambulatory systolic BP ≥140 mm Hg, recruited from 5 hospital outpatient clinics in Ireland. Individuals were not eligible if they were unable to withdraw from current antihypertensive medications or if they had secondary hypertension, malignant hypertension, diabetes mellitus, coronary artery disease, or any surgical or medical condition that might significantly alter the absorption, distribution, metabolism, or excretion of aliskiren. All subjects gave written informed consent. The Irish Medicines Board and the appropriate local research ethics committees approved the study protocol, and the research was carried out in accordance with the Declaration of Helsinki (1996) of the World Medical Association.

Study Design

This was a double-blind, active comparator, randomized, parallel-group study. After a 1- to 3-week washout period, a screening 24-hour ambulatory blood pressure monitoring (ABPM) was performed to ensure that off-treatment average daytime ambulatory systolic BP was ≥140 mm Hg. Patients remained off antihypertensive medication for a further week, after which a baseline ABPM was recorded. Patients, stratified by center and by previous antihypertensive therapy, were then randomly allocated to 1 of 5 treatment groups: 37.5 mg, 75 mg, 150 mg, or 300 mg aliskiren or 100 mg losartan. All patients were asked to take the encapsulated study medication, once daily, 30 minutes before eating breakfast. After 4 weeks of treatment, a third (end-of-treatment) ABPM was performed. All study personnel and participants remained blinded to treatment assignment for the duration of the study.

The screening assessment included a complete medical history, physical examination, clinic BP measurement, safety laboratory tests (blood hematology, blood chemistry and urinalysis), and electrocardiography. During each follow-up visit, adverse events, concurrent medication, and compliance with study medication were recorded, in addition to clinic BP measurement, safety laboratory tests, and electrocardiography. To determine trough aliskiren levels and PRA, additional venous blood samples were drawn from the patients while seated, at baseline, and 24 hours after the last dose of randomized study treatment. The plasma was separated and stored at −30°C.

Clinic Blood Pressure and Heart Rate Measurement

Sitting and standing clinic BP and heart rate were measured from the right arm, with the use of a regularly calibrated validated automated sphygmomanometer (Omron HEM-705CP),[12] in accordance with the recommendations of the British Hypertension Society.[13]

Ambulatory BP Monitoring

Ambulatory measurements were made every half-hour throughout the 24-hour period with the use of Spacelabs 90207 monitors.[14] All data were transferred into a specialized software package (DABL), allowing calculation of mean daytime (9 AM and 9 PM) and nighttime (1 and 6 AM) systolic and diastolic blood pressures and heart rates.[15,16] Ambulatory BP monitoring was regarded as satisfactory if there were at least 14 daytime readings and 6 nighttime readings.

Aliskiren Levels and PRA

Aliskiren was measured in 2.5 μL plasma by direct radioimmunoassay.[11,17] PRA was measured by trapping of generated Ang I by antibodies and by subsequent radioimmunoassay.[18]

Statistical Methods

All data analyses were carried out with the use of SAS software (SAS Institute Inc). Analyses concerning tolerability and safety were conducted on the safety population (n=226, all patients who received at least 1 dose of study treatment). Analyses concerning drug efficacy were performed on the intention-to-treat population (n=197, patients of the safety population with valid ABPMs at baseline and at end-of-treatment). Assuming a common standard deviation of 12.5 mm Hg for the change in baseline to end-of-treatment daytime ambulatory systolic BP, a significance level of 0.05 (2-sided), and 40 evaluable patients per treatment group, this study had 80% power to detect 3 mm Hg differences in the primary efficacy parameter, daytime ambulatory systolic BP, between the four aliskiren treatment groups.

ANCOVA was used to test the null hypothesis of no difference between each of the four aliskiren dose groups and to compare the individual doses of aliskiren versus 100 mg losartan. The ANCOVA model included the following factors and covariates: treatment group, center, previous hypertensive therapy (yes/no), and baseline value of DASBP. Pairwise comparisons of the responses to the different aliskiren doses and to losartan were conducted with the use of Scheffé's method for multiple comparisons.

Results

Participants

Of the 345 patients recruited to this study, 226 satisfied all inclusion criteria and were randomly assigned to study treatment. Fourteen patients did not complete the study as planned, and a further 15 patients had invalid ABPMs either at baseline or at end-of-treatment (Figure 1). Baseline characteristics of the remaining 197 patients are shown in Table 1.

The distributions of gender, age, body mass index, lifestyle habits, and cardiovascular risk factors were similar across the 5 treatment groups. Baseline ambulatory BP levels and the proportions of patients in the 5 groups who had previously been exposed to antihypertensive drugs were also similar.

Drug Effects on BP

A clear dose-dependent decrease in the primary end point, the change in daytime ambulatory systolic BP, was observed with increasing aliskiren doses (ANCOVA treatment effect, $P=0.0002$). Figure 2 illustrates that although there was practically no change in daytime ambulatory systolic BP with 37.5 mg aliskiren, a significant decrease was observed for 75 mg of aliskiren, with further reductions in pressure for doses of 150 and 300 mg aliskiren. Pairwise group comparisons showed significant differences between the lowest aliskiren dose group (aliskiren 37.5 mg) and the two highest dose groups; the 95% confidence intervals for the comparisons between 37.5 mg aliskiren with 150 mg aliskiren and 300 mg aliskiren were (0.6, 14.5) and (3.5, 17.5), respectively.

Losartan (100 mg) also significantly reduced daytime ambulatory systolic BP. The mean change from baseline to end-of-treatment in pressure in the group treated with 100 mg losartan was found to differ from that of the group treated with 37.5 mg aliskiren—the 95% confidence interval for difference was (2.3, 18.6)—but not to differ significantly from the changes seen in the groups treated with 75, 150, and 300 mg aliskiren.

ANCOVA showed that whereas there was no difference in effects between the centers ($P=0.79$), the pressure-lowering effects of aliskiren were greatest in patients with higher baseline values of daytime ambulatory systolic BP ($P=0.007$) and in those patients who had not previously received antihypertensive therapy ($P=0.043$).

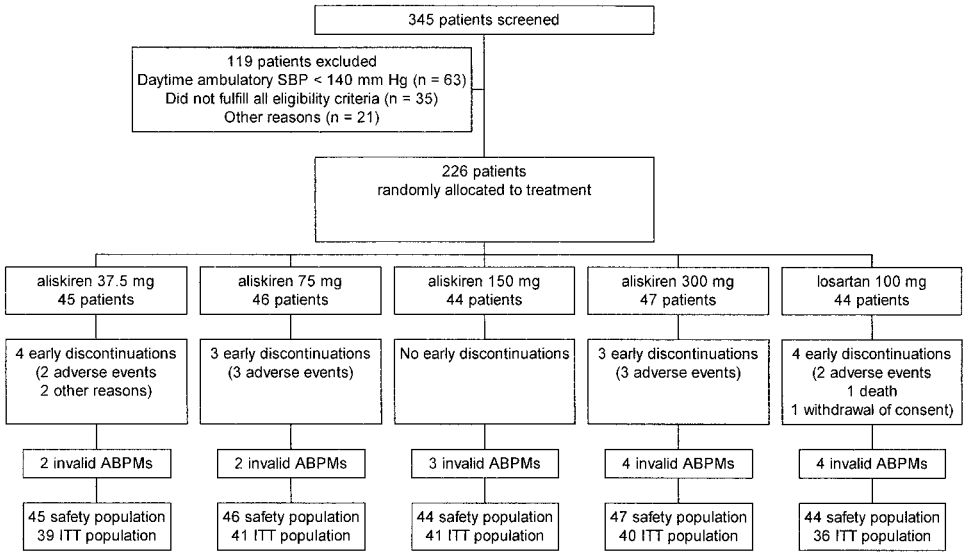

Figure 1. Trial profile.

Figure 3 clearly illustrates that BP lowering with aliskiren was dose-dependent throughout the whole 24 hours. Clinic systolic and diastolic BP, both in the sitting and in the standing positions, again clearly decreased with aliskiren in a dose-dependent manner, whereas heart rate was unaltered (Table 2). The decreases in clinic pressures seen with 100 mg losartan appeared similar to those of 150 mg and 300 mg aliskiren.

Plasma Aliskiren Levels and Plasma Renin Activity

Trough plasma concentrations of aliskiren increased with increasing doses of aliskiren (Table 3). Average baseline PRA was similar among the 5 treatment groups. After treatment with aliskiren, PRA decreased—the percentage reductions in PRA were −55%, −60%, −77%, and −83%, respectively ($P=0.0008$) (Table 3). By contrast, PRA increased by 110% with 100 mg losartan daily. Further exploratory analyses suggested that the obtained on-treatment PRA remained directly related to baseline PRA (Figure 4), and Figure 5 illustrates that treatment with 300 mg aliskiren and with 100 mg losartan resulted in greater reductions in daytime systolic pressures in patients with higher baseline PRA levels.

Compliance, Safety, and Adverse Effects

Compliance, assessed from counts of returned capsules, averaged >95% across all treatment groups. Dosages up to 300 mg of aliskiren were well tolerated. Of the 226 patients in the safety population, 62 patients (27%) had a total of 108 adverse events. The numbers of patients in each of the groups treated with 37.5 mg, 75 mg, 150 mg, and 300 mg aliskiren

TABLE 1. Baseline Demographic and Clinical Characteristics of the 197 Treated Patients

Characteristic	Aliskiren 37.5 mg (n=39)	Aliskiren 75 mg (n=41)	Aliskiren 150 mg (n=41)	Aliskiren 300 mg (n=40)	Losartan 100 mg (n=36)
Gender, M/F	27/12	30/11	27/14	23/17	23/13
Age, y	50.9±10.1	50.7±10.9	52.0±9.3	51.8±10.5	55.9±8.9
Height, cm	169.6±11.9	169±11.2	172±10.4	169.6±10.6	168.8±8.5
Weight, kg	85.4±20.8	88.3±16.6	84.9±16.9	86.2±15.8	80.1±15.3
Body mass index, kg/m^2	29.4±5.5	30.9±6.0	28.5±4.2	29.9±4.4	28.0±4.5
Smoking habit, smoker/ex/never	7/14/18	5/16/20	4/16/21	8/12/20	6/13/17
Alcohol habit, drinker/nondrinker	28/11	33/8	29/12	25/15	26/10
Total cholesterol, mmol/L	5.6±1.0	5.7±1.0	5.8±1.0	6.0±1.1	5.8±0.7
Triglycerides, mmol/L	2.0±2.1	2.1±1.7	2.0±1.1	2.2±1.7	1.9±1.7
Creatinine, μmol/L	96±15	98±14	95±14	95±13	94±13
Daytime ambulatory SBP	153.8±13.1	153.9±11.0	156.2±10.5	152.6±9.7	152.6±10.5
Daytime ambulatory DBP	93.3±12.3	94.5±9.9	96.5±8.4	93.5±8.9	91.1±9.0
Nighttime ambulatory SBP	130.1±17.9	131.9±16.4	132.6±14.9	132.4±13.6	135.1±12.9
Nighttime ambulatory DBP	74.5±11.4	77.6±11.7	78.0±11.5	77.6±9.4	78.6±12.1
Previous antihypertensive therapy, yes/no	27/12	32/9	28/13	29/11	27/9

Data are expressed as mean±SD or proportions as appropriate.
There were no significant differences in demographic and clinical characteristics among the 5 treatment groups at baseline.

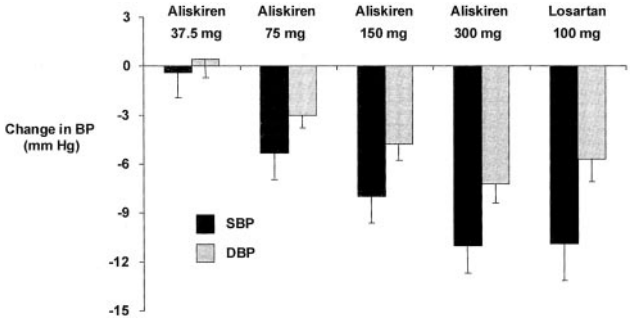

Figure 2. Mean (SEM) change in daytime ambulatory systolic and diastolic blood pressures after 4 weeks of treatment with 37.5, 75, 150, and 300 mg aliskiren and with 100 mg losartan.

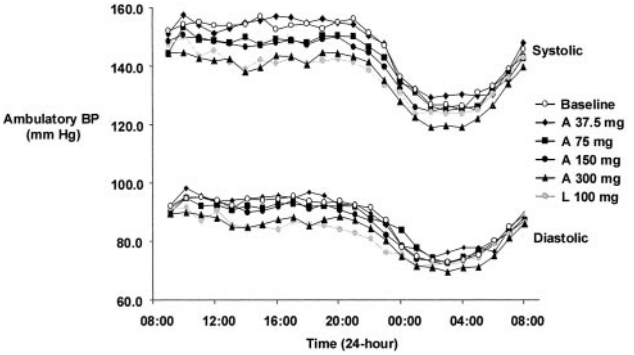

Figure 3. Twenty-four-hour ambulatory BP profiles at baseline and after 4 weeks of aliskiren (A), 37.5, 75, 150, and 300 mg, and losartan (L), 100 mg.

and in the group treated with 100 mg losartan who had adverse events were 10 (22%), 16 (35%), 11 (25%), 11 (23%), and 14 (32%) respectively. The most common adverse events were fatigue or weakness, gastrointestinal disorders, or headaches. No accumulation of adverse events was observed in any of the system organ classes and treatment groups. There was no increase in the number of adverse events when increasing the dose of aliskiren. In general, the incidence of each adverse event was very low.

Three patients had serious adverse events during the active treatment phase. One patient in the group treated with 300 mg aliskiren had chest tightness and electrocardiographic ischemic changes, and another patient in the same treatment group collapsed and was found to be hypotensive. Both patients recovered. A losartan-treated patient died as a result of a ruptured aneurysm of the left common iliac artery. A further 8 patients had adverse events resulting in withdrawal from the study. Of the patients withdrawn from the study because of a serious adverse event or an adverse event, 1 of 2, 3 of 3, 0 of 0, 2 of 3, and 1 of 3 in the 37.5 mg, 75 mg, 150 mg, and 300 mg aliskiren-treated and losartan-treated groups, respectively, had events that were considered by the investigator to be possibly or probably related to the study drug.

The clinical laboratory values remained normal in the majority of patients throughout the study. Shifts from normal values at baseline to abnormal values at the end of the study in some patients in the different treatment groups did not reveal a pattern indicating that any of the study drugs administered might have a marked influence on any of the laboratory parameters. Physical examination findings were normal in the majority of patients at screening and the end of the study. This also applied to the ECG tracings recorded on each of the 5 visits.

TABLE 2. Baseline Clinic Blood Pressures and Heart Rates, and Changes From Baseline With Study Treatment

Hemodynamic Parameter	Aliskiren 37.5 mg	Aliskiren 75 mg	Aliskiren 150 mg	Aliskiren 300 mg	Losartan 100 mg
Sitting SBP					
Baseline	156.8±18.9	158.2±19.4	159.5±18.5	157.6±16.8	159.0±15.5
Change	−4.3±17.8	−4.1±16.9	−10.0±17.0	−11.8±14.9	−11.4±19.2
Sitting DBP					
Baseline	92.7±11.4	93.4±11.4	93.3±9.9	94.1±11.1	95.0±8.1
Change	−1.9±10.5	−0.2±12.4	−2.2±10.0	−5.7±11.0	−5.5±10.7
Sitting HR					
Baseline	71.1±11.0	76.7±13.9	74.0±15.3	73.9±10.7	72.9±11.4
Change	0.3±9.2	−3.9±9.1	−2.4±11.6	1.5±9.9	−2.0±10.1
Standing SBP					
Baseline	158.5±18.4	158.8±23.4	159.1±19.5	161.6±18.7	158.8±18.5
Change	−4.3±15.7	−4.7±12.0	−10.5±18.3	−14.1±14.4	−9.4±21.9
Standing DBP					
Baseline	97.2±13.0	97.0±13.9	97.0±10.7	100.5±11.1	98.8±11.0
Change	−1.9±12.0	−0.6±10.7	−3.5±10.5	−8.2±12.0	−5.7±12.0
Standing HR					
Baseline	72.7±10.0	79.9±15.1	77.1±14.5	77.6±12.0	74.6±11.3
Change	2.5±11.3	−3.3±10.1	−0.6±10.7	2.6±9.4	−0.4±9.9

Data are expressed as mean±SD.

TABLE 3. Trough Plasma Aliskiren Levels and Trough Plasma Renin Activity at Baseline and After 4 Weeks of Treatment

Parameter	Aliskiren 37.5 mg	Aliskiren 75 mg	Aliskiren 150 mg	Aliskiren 300 mg	Losartan 100 mg
Plasma aliskiren on treatment, ng/mL	2.6 (1.6, 3.4)	4.2 (3.2, 6.4)	9.9 (6.5, 14.0)	30.0 (17.5, 50.0)	...
PRA at baseline, ng/mL/h	0.56 (0.25, 0.97)	0.85 (0.38, 1.13)	0.70 (0.42, 1.30)	0.80 (0.48, 1.30)	0.71 (0.36, 1.23)
PRA on treatment, ng/mL/h	0.27 (0.11, 0.61)	0.25 (0.12, 0.49)	0.14 (0.07, 0.32)	0.16 (0.06, 0.31)	1.65 (0.69, 2.90)
PRA percentage change, %	−55 (−64, −11)	−60 (−82, −46)	−77 (−86, −72)*	−83 (−92, −71)*	110 (8, 260)*

Data expressed as median (interquartile range). All available data are shown: plasma aliskiren, baseline PRA, on-treatment PRA, and % change in PRA values were available for 192, 194, 191, and 187 subjects respectively.

Changes in plasma renin activity did vary significantly with aliskiren dose (ANCOVA $P=0.0008$).

*Statistically significant difference from response to aliskiren 37.5.

Discussion

The results of our current study clearly demonstrate, for the first time, that oral aliskiren, once daily, effectively reduces BP in a dose-dependent manner. Previous data on circulating Ang II concentrations in normal volunteers suggested that 150 mg aliskiren would provide equipotent RAS inhibition to 20 mg enalapril.[11] In this study, in patients with mild-to-moderate hypertension, the reductions in daytime and nighttime ambulatory systolic and diastolic blood pressures seen with 75 mg, 150 mg, and 300 mg aliskiren daily were of a similar magnitude to those of the full dose of a currently used antihypertensive agent, namely 100 mg losartan. Both in vitro experiments and normal volunteer studies have suggested that losartan may be a less potent Ang II receptor blocker than other members of the family.[19–21] However, a recent meta-analysis of 43 published randomized controlled trials of losartan, valsartan, irbesartan, and candesartan has demonstrated comparable antihypertensive efficacy within the class.[22] Furthermore, participants randomly assigned to losartan-based antihypertensive treatment in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial had 11% fewer cardiovascular deaths and 25% fewer strokes than those randomly assigned to atenolol-based treatment.[4]

As expected, the antihypertensive effects of both the renin inhibitor and the angiotensin receptor blocker appeared somewhat greater in patients in whom the RAS was activated, as reflected by higher baseline PRA levels. Interestingly, although the achieved on-treatment PRA levels and the percentage inhibition of PRA with 150 mg and 300 mg aliskiren did not appear to substantially differ, there was no appearance of a plateau in the dose-response curve for BP effects. Hence, higher doses of aliskiren may result in further lowering of pressures. Furthermore, on-treatment trough PRA levels may not fully reflect the extent of inhibition throughout the whole 24 hours.[11] Alternatively, local generation of Ang II, contributing to BP elevation,[23,24] may only be effectively inhibited at higher aliskiren doses, with achievement of greater tissue penetration.

We used daytime ambulatory systolic BP as the primary efficacy end point because of the overwhelming evidence of the importance of systolic pressure as a prognostic indicator,[25] the enhanced reproducibility of ambulatory BP parameters over clinic BP measures,[26] and the additional information gained concerning the extent and duration of BP lowering in real-life conditions. This study was an active comparator-controlled trial rather than a placebo-controlled trial. Hence, it was not possible to calculate placebo-corrected BP reductions with each treatment. However, as ambulatory pressures demonstrate little placebo effect, no important error was introduced by the use of absolute BP reductions.[27] The performance of separate screening ABPMs and baseline ABPMs facilitated exclusion of patients with white-coat hypertension[28] and avoidance of regression to the mean.[29]

The other principal finding of this study was that aliskiren was well tolerated across all doses tested. This confirms previous knowledge concerning the safety of aliskiren derived from smaller studies in healthy normotensive volunteers.[11] In contrast to ACE, which acts on bradykinin in addition to Ang I, renin is highly selective for a single naturally occurring substrate, angiotensinogen. Although the increased levels of bradykinin and substance P that occur with ACE inhibition may contribute to BP lowering, they are also held responsible for side effects such as cough and angioedema.[30,31] Given the selectivity of both aliskiren for renin[10] and renin for angiotensinogen, it was not surprising to observe that aliskiren appears to have a side effect profile similar to that of placebo.

In addition to differences in side effect profile, the therapeutic effects of renin inhibitors may differ from those produced by blockade at other levels in the RAS. Alternative pathways to renin cleavage of angiotensinogen are not thought to be of any great physiological importance,[32] whereas a substantial proportion of tissue Ang II is generated by non-ACE pathways.[33,34] Hence, it has been proposed that more effective blockade of tissue Ang II formation may occur with renin inhibition than with ACE inhibition.[35] Further differences between renin inhibition, ACE inhibition, and angiotensin receptor blockade could arise from disparate effects on circulating and tissue levels of bioactive Ang peptides and different patterns of stimulation of the various receptor subtypes.[36–41]

Perspectives

The results of this study show that aliskiren is a safe, orally active renin inhibitor that lowers BP. Despite the wealth of evidence that reduction of BP provides important protection, undertreatment of hypertension is a worldwide problem. Hence, an agent that effectively and specifically blocks the RAS, with a novel mechanism of action, with few side effects, and with a half-life long enough to allow once daily dosage, is to be welcomed. Should further larger trials of a longer duration confirm sustained BP lowering, a placebo-like side effect profile,

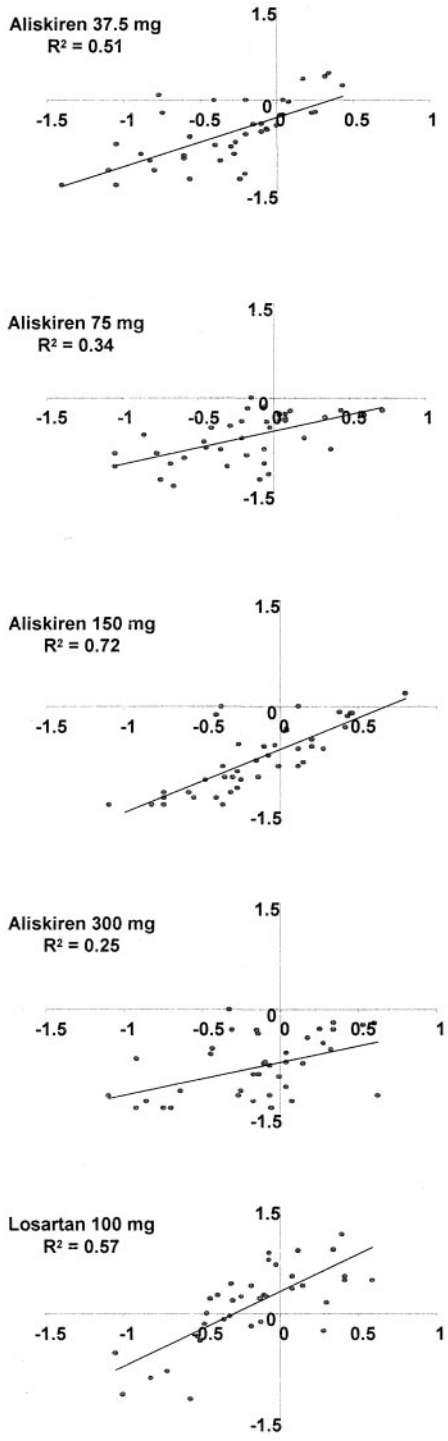

Figure 4. Scatterplots illustrating associations of log baseline PRA (ng/mL per hour, horizontal axis) with log on-treatment PRA (ng/mL per hour, vertical axis) after 4 weeks of treatment with 37.5, 75, 150, and 300 mg aliskiren and with 100 mg losartan. Where PRA was less than the limit of quantification (0.05 ng/mL per hour, n=1 at baseline and n=12 on treatment), a value of 0.04 ng/mL per hour was assigned.

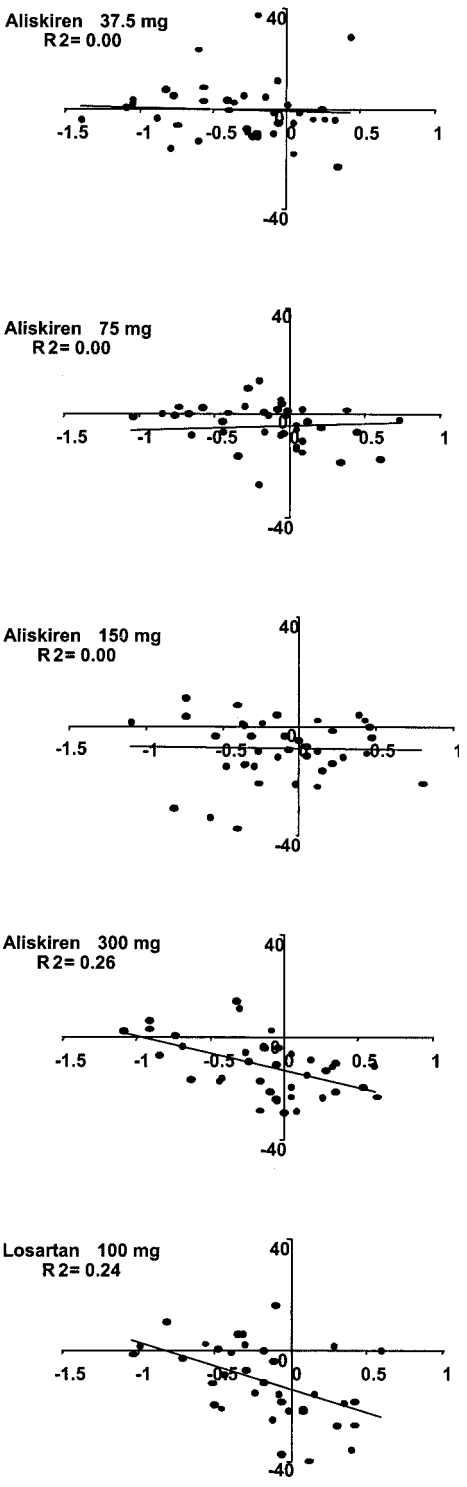

Figure 5. Scatterplots illustrating associations of log baseline PRA (ng/mL per hour, horizontal axis) with changes in daytime ambulatory systolic BP (mm Hg, vertical axis) after 4 weeks of treatment with 37.5, 75, 150, and 300 mg aliskiren and with 100 mg losartan. Baseline PRA was less than the limit of quantification (0.05 ng/mL per hour) in 1 subject, and a value of 0.04 ng/mL per hour was assigned.

and similar or superior effects on intermediate end points, such as left ventricular hypertrophy, carotid intima media thickness, and proteinuria, to those of the established RAS antagonists, renin inhibitors may soon be widely prescribed for essential hypertension. Given the success of ACE inhibitors and angiotensin receptor blockers in reducing morbidity and mortality rates among patients with diabetes mellitus, heart failure, nephropathy, and atherosclerosis, renin inhibitors also have the potential to be beneficial in the same disease states.

Acknowledgments

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References

1. Oparil S, Haber E. The renin-angiotensin system. *N Engl J Med.* 1974; 291:381–401, 446–457.
2. Dzau VJ. Tissue angiotensin and pathobiology of vascular disease, a unifying hypothesis. *Hypertension*. 2001;37:1047–1052.
3. Yusef S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients: the Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342:145–153.
4. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Petersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H, for the LIFE study group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995–1003.
5. Weber MA, Neutel JM, Essinger I, Glassman HN, Boger RS, Luther RR. Assessment of renin dependency of hypertension with a dipeptide renin inhibitor. *Circulation*. 1990;81:1768–1774.
6. Neutel JM, Luther RR, Boger RS, Weber MA. Immediate blood pressure effects of the renin inhibitor enalkiren and the angiotensin-converting enzyme inhibitor enalaprilat. *Am Heart J*. 1991;122:1094–1000.
7. van den Meiracker AH, Admiraal PJ, Derkx FH, Kleinbloesem C, Man in 't Veld AJ, van Brummelen P, Mulder P, Schalekamp MA. Comparison of blood pressure and angiotensin responses to the renin inhibitor RO 42–5892 and the angiotensin converting enzyme inhibitor enalapril in essential hypertension. *J Hypertens*. 1993;11:831–838.
8. Kobrin I, Viskoper RJ, Laszt A, Bock J, Weber C, Charlon V. Effects of an orally active renin inhibitor, Ro 42–5892, in patients with essential hypertension. *Am J Hypertens*. 1993;6:349–358.
9. Fisher ND, Hollenberg NK. Is there a future for renin inhibitors? *Exp Op Invest Drugs*. 2001;10:417–426.
10. Rahuel J, Rasetti V, Maibaum J, Rueger H, Goschke R, Cohen NC, Stutz S, Cumin F, Fuhrer W, Wood JM, Grutter MG. Structure-based drug design: the discovery of novel non peptide orally active inhibitors of human renin. *Chem Biol*. 2000;7:493–504.
11. Nussberger J, Wuerzner G, Jensen C, Brunner HR. Angiotensin II suppression in humans by the orally active renin inhibitor aliskiren (SPP100): comparison with enalapril. *Hypertension*. 2002;39:e1–e8.
12. O'Brien E, Mee F, Atkins N, Thomas M. Evaluation of three devices for self-measurement of blood pressure according to the revised British Hypertension Society Protocol: the Omron HEM-705CP, Phillips HP5332, and Nissei DS-175. *Blood Press Monit*. 1996;1:55–61.
13. Ramsay LE, Williams B, Johnston GD, MacGregor GA, Poston L, Potter JF, Poulter NR, Russell G. British Hypertension Society guidelines for hypertension management. *BMJ*. 1999;319:630–635.
14. O'Brien E, Mee F, Atkins N, O'Malley K. Accuracy of the SpaceLabs 90207 determined by the British Hypertension Protocol. *J Hypertens*. 1991;9:573–574.
15. Atkins N, Mee F, O'Brien E. A customized international database system for storing and analysing ambulatory blood pressure measurements and related data. Abstract. *J Hypertens*. 1994;12:S23.
16. Owens P, Atkins N, O'Brien E. Diagnosis of whitecoat hypertension by ambulatory blood pressure monitoring. *Hypertension*. 1999;34:267–272.
17. Lefevre G, Duval M, Poncin A. Direct micro-radioimmuno-assay of the new renin inhibitor CGP 60536. *J Immunoassay*. 2000;21:65–84.
18. Nussberger J, Fasanella d'Amore T, Porchet M, Waeber B, Brunner DB, Brunner HR, Kler L, Brown AN, Francis RJ. Repeated administration of the converting enzyme inhibitor cilazapril to normal volunteers. *J Cardiovasc Pharmacol*. 1987;9:39–44.
19. Fierens FL, Vanderheyden PM, De Backer JP, Vauquelin G. Insurmountable angiotensin AT1 receptor antagonists: the role of tight antagonist binding. *Eur J Pharmacol*. 1999;372:199–206.
20. Vanderheyden PM, Fierens FL, Vauquelin G. Angiotensin II type 1 receptor antagonists: why do some of them produce insurmountable inhibition?. *Biochem Pharmacol*. 2000;60:1557–1563.
21. Fuchs B, Breithaupt-Grogler K, Belz GG, Roll S, Malerczyk C, Herrmann V, Spahn-Langguth H, Mutschler E. Comparative pharmacodynamics and pharmacokinetics of candesartan and losartan in man. *J Pharm Pharmacol*. 2000;52:1075–1083.
22. Conlin PR, Spence JD, Williams B, Ribeiro AB, Saito I, Benedict C, Bunt AM. Angiotensin II antagonists for hypertension: are there differences in efficacy? *Am J Hypertens*. 2000;13:418–426.
23. Barlucchi L, Leri A, Dostal DE, Fiordaliso F, Tada H, Hintze TH, Kajstura J, Nadal-Ginard B, Anversa P. Canine ventricular myocytes possess a renin-angiotensin system that is upregulated with heart failure. *Circ Res*. 2001;88:298–304.
24. Re RN. The nature of intracrine peptide hormone action. *Hypertension*. 1999;34:534–528.
25. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. *Circulation*. 1999;100:354–360.
26. Stanton A, Cox J, Atkins N, O'Malley K, O'Brien E. Cumulative sums in quantifying circadian blood pressure patterns. *Hypertension*. 1992;19: 93–101.
27. Mancia G, Omboni S, Parati G, Ravogli A, Villani A, Zanchetti A. Lack of placebo effect on ambulatory blood pressure. *Am J Hypertens.* 1995; 8:311–315.
28. Fagard R, Bielen E, Staessen J, Thijs L, Amery A. Response of ambulatory blood pressure to antihypertensive therapy guided by clinic pressure. *Am J Hypertens.* 1993;6:648–653.
29. Yudkin PL. Stratton IM. How to deal with regression to the mean in intervention studies. *Lancet*. 1996;347:241–243.
30. Sunman W, Sever PS. Non-angiotensin effects of angiotensin-converting enzyme inhibitors. *Clin Sci*. 1993;85:661–670.
31. Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angioedema. *Lancet*. 1998;351:1693–1697.
32. Phillips MI, Speakman EA, Kimura B. Levels of angiotensin and molecular biology of the tissue renin angiotensin systems. *Regul Pept*. 1993;43:1–20.
33. Wolny A, Clozel JP, Rein J, Mory P, Vogt P, Turino M, Kiowski W, Fischli W. Functional and biochemical analysis of angiotensin II–forming pathways in the human heart. *Circ Res*. 1997;80:219–227.
34. Hollenberg NK, Fisher NDL. Renal circulation and blockade of the renin-angiotensin system. Is angiotensin-converting enzyme inhibition the last word? *Hypertension*. 1995;26:602–609.
35. Fisher NDL, Allan D, Kifor I, Gaboury CL, Williams GH, Moore TJ, Hollenberg NK. Responses to converting enzyme and renin inhibition: role of angiotensin II in humans. *Hypertension*. 1994;23:44–51.
36. Luque M, Martin P, Martell N, Fernandez C, Brosnihan KB, Ferrario CM. Effects of captopril related to increased levels of prostacyclin and angiotensin-(1-7) in essential hypertension. *J Hypertens*. 1996;14:799–805.
37. Iyer SN, Chappell MC, Averill DB, Diz DI, Ferrario CM. Vasodepressor actions of angiotensin-(1-7) unmasked during combined treatment with lisinopril and losartan. *Hypertension*. 1998;31:699–705.
38. Burnier M. Angiotensin II type 1 receptor blockers. *Circulation*. 2001; 103:904–912.
39. Swanson GN, Harding JW. Discovery of a distinct binding site for angio (3-8), a putative AT4 receptor. *Regul Pept.* 1993;40:409–419.
40. Kerins DM, Hao Q, Vaughan DE. Angiotensin induction of PAI-1 expression in endothelial cells is mediated by the hexapeptide Angiotensin IV. *J Clin Invest*. 1995;96:2515–2520.
41. Mazzolai L, Pedrazzini T, Nicoud F, Gabbiani G, Brunner HR, Nussberger J. Increased cardiac angiotensin II levels induce right and left ventricular hypertrophy in normotensive mice. *Hypertension.* 2000;35: 985–991. (Correction. 2001;37:183.)