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Comparative effects of aliskiren-based and ramipril-based therapy on the renin system during long-term (6 months) treatment and withdrawal in patients with hypertension

Karl Andersen,* Myron H Weinberger; Christian M Constance,* Mohammed A Ali,* James Jin,* Margaret F Prescott,* Deborah L Keefe*

Abstract
Introduction. This subgroup analysis assessed the effects of treatment based on the direct renin inhibitor, aliskiren, or the angiotensin-converting enzyme inhibitor, ramipril, on plasma renin activity (PRA), plasma renin concentration (PRC) and other biomarkers in a 26-week randomised, double-blind trial. Changes in PRA and PRC after stopping treatment were also assessed.

Methods. After placebo run-in, 842 patients (mean sitting diastolic blood pressure (BP) 95–109 mmHg) were randomised to aliskiren 150 mg or ramipril 5 mg. Dose titration and hydrochlorothiazide addition were allowed after Week 6 and 12, respectively, for inadequate BP control. Patients completing active treatment were re-randomised to current regimen or placebo during a 4-week post-treatment phase.

Results. BP reductions were independent of baseline PRA at Week 12, were greater with aliskiren- than ramipril-based therapy at Week 26 (17.9/13.3 vs. 15.2/12.0 mmHg, p<0.05) and persisted for longer after stopping aliskiren. Aliskiren-based therapy reduced geometric mean PRA (~63%, p<0.05; n=103), while ramipril-based therapy increased PRA (+143%, p<0.05; n=100) at Week 26; PRC increased in both groups (aliskiren: +224% [n=33], ramipril: +145% [n=39], both p<0.05). Four weeks after stopping aliskiren-based therapy, PRA remained 52% below pre-treatment baseline; PRA returned to baseline 2 weeks after stopping ramipril-based therapy.

Conclusions. Aliskiren-based therapy produced sustained BP and PRA reductions over 26 weeks; ramipril-based therapy lowered BP and increased PRA. PRA reductions persisted 4 weeks after stopping aliskiren, suggesting an inhibitory effect beyond the elimination half-life of the drug.

Introduction
The renin system is key to blood pressure (BP) regulation and inhibitors of the system, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB), are widely used in the treatment of hypertension. The renin system is regulated by a negative-feedback mechanism, in which angiotensin (Ang) II inhibits the release of renin from the kidney, thereby reducing plasma renin concentration (PRC), plasma renin activity (PRA), the capacity of renin to convert angiotensinogen to Ang I and the production of Ang I and Ang II. Both ACE inhibitors and ARBs suppress this negative-feedback loop: ACE inhibitors lower Ang II levels by blocking its enzymatic generation from Ang I, whereas ARBs block the activity of Ang II at the Ang II type 1 receptor. ACE inhibitors and ARBs therefore increase renin release from the kidney, raising PRC and PRA. In the case of ACE inhibitors, plasma levels of Ang I increase, and conversion to Ang II can occur via ACE-independent mechanisms such as the chymases. The therapeutic potential of these drug classes may therefore be limited by increased levels of PRA and incomplete suppression of Ang II generation.

Aliskiren is the first in a new class of direct renin inhibitors (DRI) and has been approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of hypertension at once-daily oral doses of 150 mg and 300 mg. By directly targeting the renin enzyme, aliskiren inhibits the renin system at the point of activation, blocking the conversion of angiotensinogen to Ang I and decreasing levels of Ang I and Ang II. Aliskiren decreases PRA by approximately 50–80% in patients with hypertension, and provides similar reductions when administered in combination with drugs known to increase PRA such as the...
ACE inhibitor ramipril, the ARB valsartan or the diuretic hydrochlorothiazide (HCT). Elevated PRA has been identified as an independent predictor of morbidity and mortality (p=0.0025) in a large-scale trial of 4,300 patients with congestive heart failure. Moreover, in a study of 699 patients with congestive heart failure, PRA levels were independently associated with cardiovascular events despite the continued use of ACE inhibitors and ARBs. However, the full clinical implications of the different effects of antihypertensive agents on PRA are not yet known.

We have previously reported the results of a randomised, double-blind study comparing the efficacy, safety and tolerability of aliskiren- and ramipril-based regimens during a 26-week active-controlled-treatment period and a 4-week, randomised, placebo-controlled post-active-controlled-treatment period in patients with mild- to-moderate hypertension. Here we present the effects of aliskiren- and ramipril-based treatment on PRA, PRC and other biomarkers.

**Patients and methods**

This was a randomised, double-blind, multicentric, active- and placebo-controlled study, conducted at 92 study centres in nine countries (Belgium, Canada, Hong Kong, Denmark, Iceland, Slovakia, South Africa, Spain and the USA). The study was performed in accordance with good clinical practice and adhered to the ethical principles of the Declaration of Helsinki of the World Medical Association. The study protocol was reviewed and approved by the Independent Ethics Committee or Institutional Review Board for each study centre, and patients provided written informed consent before participating in the study. The study design and patient population have been described previously.

**Patients**

Patients aged ≥ 18 years with mild-to-moderate hypertension (defined as mean sitting diastolic BP [msDBP] ≥ 90 mmHg and < 110 mmHg) were eligible for inclusion. The main exclusion criteria included severe hypertension (msDBP ≥ 110 mmHg) and/or mean sitting systolic BP [msSBP] ≥ 180 mmHg); secondary hypertension; type 1 or type 2 diabetes mellitus with fasting glycosylated haemoglobin (HbA1c) > 9%; history of severe cerebrovascular or cardiovascular disease; and any condition that may affect the evaluation of efficacy or safety data, or alter the absorption, distribution, metabolism or excretion of study drugs.

**Study design**

A detailed description of the study design has been published elsewhere. Briefly, following a 2–4-week placebo run-in period, patients were randomised equally to double-blind treatment with aliskiren 150 mg or ramipril 5 mg once daily. For patients not achieving BP control (< 140/90 mmHg), dose titration to aliskiren 300 mg or ramipril 10 mg was permitted from Week 6; addition of HCT to the titrated monotherapy dose was permitted from Week 12 in sequential steps (figure 1). The maximum daily dose of ramipril in this trial (10 mg) was chosen based on the results of the HOPE trial and label recommendations in Europe, stating 10 mg as the maximum maintenance dose for ramipril. The aliskiren dose-response relationship exhibits a plateau for BP reduction above 300 mg, while the ramipril dose-response relationship similarly exhibits a plateau above 10 mg.

Patients completing the 26-week active-controlled-treatment period were re-randomised equally to either their current regimen or placebo for a 4-week, double-blind post-active-controlled-treatment period.

**Assessments**

**BP measurements**

Clinic BP was evaluated at randomisation, then every 3 weeks for Weeks 3–21 and at Week 26 during the active-controlled-treatment period. BP was assessed weekly during the 4-week post-active-controlled-treatment period. BP was measured at trough (24±3 hours after dosing) using a sphygmomanometer, and three sitting BP measurements, taken at 1–2-minute intervals, were averaged to give the mean value for that visit.

Changes in msSBP and msDBP during the 26-week active-controlled-treatment period were determined in the intent-to-treat (ITT) population, and were analysed for non-inferiority (and superiority if non-inferiority was achieved) of aliskiren-based therapy versus ramipril-based therapy. During the post-active-controlled-treatment period, mean changes in msSBP and msDBP from post-treatment baseline (Week 26) to Week 30 endpoint were analysed for treatment superiority.

BP changes were analysed using an analogy of covariance model with treatment and region as factors and baseline BP as covariate. Analysis of covariance was used to determine the differences in BP changes between the two treatments. The 15-mg dose of aliskiren was chosen as the study drug for this analysis.

Changes in msSBP and msDBP during the 26-week active-controlled-treatment period were determined in the intent-to-treat (ITT) population, and were analysed for non-inferiority (and superiority if non-inferiority was achieved) of aliskiren-based therapy versus ramipril-based therapy. During the post-active-controlled-treatment period, mean changes in msSBP and msDBP from post-treatment baseline (Week 26) to Week 30 endpoint were analysed for treatment superiority.

BP changes were analysed using an analogy of covariance model with treatment and region as factors and baseline BP as covariate. Analysis of BP changes with aliskiren or ramipril monotherapy at Week 12 endpoint was carried out according to subgroup of baseline PRA; low PRA level...
defined as ≤ 0.65 ng/ml/h and medium/high PRA level defined as > 0.65 ng/ml/h.

**Biomarkers**

Plasma/serum samples for the measurement of biomarkers were obtained from patients at approximately 50% of study centres in the USA and Canada. Biomarkers evaluated were PRA, PRC, high-sensitivity C-reactive protein (hs-CRP), high-sensitivity interleukin-6 (hs-IL-6), monocyte chemoattractant protein-1 (MCP-1), soluble intercellular adhesion molecule-1 (sICAM-1) and plasma aldosterone. Biomarkers were evaluated at randomisation and at Week 26. In addition, PRA and PRC were assessed during the post-active-controlled-treatment period (Weeks 28 and 30). Urine samples for the assessment of urinary albumin:creatinine ratio (UACR) were collected at all study centres in the USA and Canada at randomisation and Week 26.

PRA was measured by means of radioimmunoassay of generated Ang I (DiaSorin kit; DiaSorin, Stillwater, MN, USA). PRC and plasma aldosterone concentrations were measured by immunochemiluminescence (Nichols Direct Renin and Nichols Advantage Aldosterone assays; Nichols Institute, San Clemente, CA, USA). Reagents for the PRC assay became unavailable part way through the study and the remaining plasma samples were insufficient to re-test using a different assay. PRC data are therefore available for only a limited number of patients (n=72). The lower limits of quantification (LLOQ) were 0.2 ng/ml/h for PRA, 0.8 mU/L for PRC and 69 pmol/L for plasma aldosterone. hs-CRP concentration was measured by a high-sensitivity immunoturbidimetric method (Roche Diagnostics, Basel, Switzerland; LLOQ 0.11 mg/L). MCP-1, hs-IL-6 and sICAM-1 were measured by enzyme immunoassay (R&D Systems, Minneapolis, MN, USA; LLOQ 62 ng/L, 0.16 ng/L and 60 μg/L, respectively).

Samples for the measurement of biomarkers were collected after the patient had been in the supine position for a minimum of 20 minutes. Samples were collected between 07.00 and 10.00 h at the first visit, and ±1 h of the first collection time at subsequent visits. In order to avoid cryoactivation of plasma prorenin, blood samples for the determination of PRA, PRC and aldosterone were collected into EDTA tubes and stored at ambient temperature prior to processing. Within 10 minutes of collection, blood was centrifuged at room temperature at 2,500 g for 10 minutes. Plasma samples were frozen immediately at −20°C or lower prior to shipping at −70°C. Samples were shipped on the day of collection; samples that could not be shipped on the day of collection were stored at −70°C and shipped on the next
working day. For the determination of serum hs-CRP, MCP-1, hs-IL-6 and sICAM-1, blood samples were left to clot for 30–60 minutes, and then centrifuged at room temperature at 2,500g for 10 minutes. Serum samples were stored and shipped in the same manner as plasma samples.

Descriptive statistics of baseline value, post-baseline value and change from baseline for each biomarker were summarised by treatment group and visit in the active-controlled-treatment period and the placebo-controlled post-active-controlled-treatment period. All biomarker data are presented as geometric means and 95% confidence intervals (CI). The 95% CIs were calculated by anti-log transformation of the 95% CIs of log-transformed biomarker measurements. Statistical differences at the 5% level were determined as 95% CIs that did not span unity. A post hoc analysis assessed change from baseline in UACR in the subset of patients with proteinuria (defined as baseline UACR ≥ 3.5 mg/mmol) or microalbuminuria (baseline UACR 3.5–30 mg/mmol). Changes in UACR for the ITT population and the subset of patients with microalbuminuria were analysed by paired t-test. Week 26 values for PRA and PRC were used as post-active-controlled-treatment baseline for the placebo-controlled post-active-controlled-treatment period.

Safety and tolerability
Adverse events (AE) were monitored and recorded at each study visit. Other safety assessments, which included measurement of vital signs, physical examination, 12-lead electrocardiogram and monitoring of haematology, blood chemistry and urine test values, were performed at regular intervals throughout the study.

Results

Patient demographics and disposition
In total, 842 patients were randomised to once-daily treatment with aliskiren 150 mg (n=420) or ramipril 5 mg (n=422). Patient demographic characteristics at baseline were similar in the two groups. Overall, 687 patients (81.6%) completed the 26-week active-controlled-treatment period, 675 of whom entered the double-blind post-active-controlled-treatment period and were re-randomised to their existing aliskiren-based regimen (n=170) or placebo (n=163) or their existing ramipril-based regimen (n=165) or placebo (n=177).

During the active-controlled-treatment period, addition of HCT for BP control was required more frequently in the ramipril group (n=209, 49.5%) than in the aliskiren group (n=193, 46.1%), although the difference was not statistically significant (p=0.334). Up-titration to HCT 25 mg was required in a significantly larger proportion of ramipril-treated patients (n=132, 31.3%) than aliskiren-treated patients (n=92, 21.9%; p=0.0024).

Biomarker data were available at both baseline and endpoint (Week 26) of the active-controlled-treatment period for 203 randomised patients (aliskiren, n=103; ramipril, n=100). Demographic characteristics for this patient

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and baseline characteristics of the subgroup of patients with biomarker data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aliskiren (n=103)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>54.2±11.2</td>
</tr>
<tr>
<td>≥ 65 years n (%)</td>
<td>18 (17.5)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60 (58.3)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>87 (84.5)</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>31.1±5.7</td>
</tr>
<tr>
<td><strong>Obese, n (%)</strong></td>
<td>56 (54.4)</td>
</tr>
<tr>
<td><strong>Metabolic syndrome, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>13 (12.6)</td>
</tr>
<tr>
<td>Duration of hypertension, years</td>
<td>9.2±9.0a</td>
</tr>
<tr>
<td><strong>msSBP, mmHg</strong></td>
<td>151.7±11.4</td>
</tr>
<tr>
<td><strong>msDBP, mmHg</strong></td>
<td>98.3±3.0</td>
</tr>
<tr>
<td><strong>PRA, ng/ml/h</strong></td>
<td>0.83 (0.68, 1.00)</td>
</tr>
<tr>
<td><strong>PRC, mU/L</strong></td>
<td>14.9 (11.3, 19.7)</td>
</tr>
</tbody>
</table>

**Key:** PRA and PRC data are presented as geometric mean (95% confidence interval) for patients with both baseline and post-dose PRA data. All other data are presented as mean±SD, unless otherwise stated.

Obesity was defined as BMI ≥ 30 kg/m². Metabolic syndrome was defined as three or more of the following: waist circumference > 102 cm for men or > 88 cm for women; triglycerides ≥ 150 mg/dL (≥ 1.69 mmol/L); high-density lipoprotein cholesterol < 40 mg/dL (< 1.04 mmol/L) for men or < 50 mg/dL (< 1.29 mmol/L) for women; systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg; fasting glucose ≥ 110 mg/dL (≥ 6.1 mmol/L). BMI = body mass index; msSBP = mean sitting diastolic blood pressure; msDBP = mean sitting systolic blood pressure; PRA = plasma renin activity; PRC = plasma renin concentration.
Increased more gradually after stopping aliskiren-based therapy (by +5.2+/−2.4 mmHg at Week 27). Indeed, 1 week after stopping treatment, the msSBP/msDBP-lowering effect was maintained at 73%/83% after stopping aliskiren-based therapy compared with 55%/66% after stopping ramipril-based therapy. In patients who stopped aliskiren-based therapy, median BP did not exceed the target of 140/90 mmHg 4 weeks after stopping treatment (BP at Week 30, 138.7/90.0 mmHg). By contrast, median BP reached 140.0/90.0 mmHg 1 week after stopping ramipril-based therapy, rising to 143.0/90.7 mmHg 4 weeks after stopping treatment. The differences between each active treatment group and its placebo were statistically significant at Week 30 endpoint (\(p<0.0001\)).

Mean changes in msSBP and msDBP were minimal in patients re-randomised to their existing regimen during the post-active-controlled-treatment period (figure 2). After 4 weeks (Week 30), msSBP/msDBP had increased by 0.8/0.4 mmHg and 1.4/1.6 mmHg in patients who continued aliskiren- and ramipril-based therapy, respectively.

**PRA and PRC**

*Active-controlled-treatment period*

Geometric mean PRA at baseline (Week 0) was 0.83 and 0.96 ng/ml/h in the aliskiren and ramipril treatment groups, respectively (table 1). During the active-controlled-treatment period, aliskiren-based therapy reduced PRA by 63% from baseline to Week 26 endpoint, whereas ramipril-based therapy increased PRA by 143% from baseline to Week 26 endpoint, whereas ramipril-based therapy increased PRA by 143% at this timepoint (table 2).

The analysis of BP changes by baseline PRA (≤0.65 or >0.65 ng/ml/h) showed no influence of PRA on the BP-lowering effect of aliskiren monotherapy at Week 12 endpoint (interaction \(p=0.791\) for msSBP and \(p=0.491\) for msDBP). The between-treatment differences for the aliskiren monotherapy and ramipril monotherapy groups were consistent across patients with low baseline PRA (≤0.65 ng/ml/h) and patients with medium/high baseline PRA (>0.65 ng/ml/h) (table 3).

Geometric mean PRC at baseline was 14.9 and 14.4 mU/L in the aliskiren and ramipril treatment groups, respectively (table 1). PRC increased significantly (\(p<0.05\)) from baseline to Week 26 endpoint with both the aliskiren (+224%) and ramipril (+145%) based regimens during the active-controlled-treatment period (table 2).
Table 2
Mean PRA and PRC during the active-controlled and post-active-controlled-treatment periods

<table>
<thead>
<tr>
<th></th>
<th>Geometric means for PRA (ng/ml/h)</th>
<th>Geometric means for PRC (mU/L)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Active-controlled-treatment period</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aliskiren (n=103)</td>
<td>Ramipril (n=100)</td>
</tr>
<tr>
<td>Week 0</td>
<td>0.83</td>
<td>0.96</td>
</tr>
<tr>
<td>Week 26</td>
<td>0.30*</td>
<td>2.33*</td>
</tr>
<tr>
<td>% change from Week 0</td>
<td>−63%</td>
<td>+143%</td>
</tr>
<tr>
<td>Post-active-controlled-treatment period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aliskiren Placebo Ramipril Placebo Aliskiren Placebo Ramipril Placebo</td>
<td>Geometric mean change from Week 0 at Week 30</td>
<td>Geometric mean change from Week 26 at Week 30</td>
</tr>
<tr>
<td>Week 0</td>
<td>0.91</td>
<td>0.79</td>
</tr>
<tr>
<td>Week 26</td>
<td>0.30</td>
<td>0.31</td>
</tr>
<tr>
<td>Week 30</td>
<td>0.29</td>
<td>0.37</td>
</tr>
<tr>
<td>Geometric mean change from Week 0 at Week 30</td>
<td>0.32*</td>
<td>0.48*</td>
</tr>
<tr>
<td>Geometric mean change from Week 26 at Week 30</td>
<td>0.98</td>
<td>1.16</td>
</tr>
</tbody>
</table>

Key: *p<0.05 vs. baseline (Week 0); †p<0.05 vs. Week 26. Geometric means were calculated from the logarithm of the biomarker data. Percentage change values were derived from the ratio of the geometric means. PRA (plasma renin activity) was measured in a subset of 203 patients. PRC (plasma renin concentration) was measured in a subset of 72 patients.

Table 3
Analysis of change from baseline in mean sitting systolic and diastolic blood pressure with aliskiren or ramipril monotherapy by subgroup of baseline PRA at Week 12 endpoint

<table>
<thead>
<tr>
<th></th>
<th>Least squares mean change in BP from baseline (mmHg)</th>
<th>Between treatment difference (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aliskiren (n=414)</td>
<td>Ramipril (n=418)</td>
<td>Aliskiren (n=44)</td>
</tr>
<tr>
<td>msSBP ITT population</td>
<td>−14.0</td>
<td>−11.3</td>
<td>−13.0</td>
</tr>
<tr>
<td>Baseline PRA ≤ 0.65 ng/ml/h</td>
<td>−2.7 (−4.4, −0.9)</td>
<td>0.050*</td>
<td></td>
</tr>
<tr>
<td>Baseline PRA &gt; 0.65 ng/ml/h</td>
<td>−4.4 (−8.5, −0.3)</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>msDBP ITT population</td>
<td>−11.3</td>
<td>−9.7</td>
<td>−12.5</td>
</tr>
<tr>
<td>Baseline PRA ≤ 0.65 ng/ml/h</td>
<td>−1.6 (−2.7, −0.5)</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>Baseline PRA &gt; 0.65 ng/ml/h</td>
<td>−2.7 (−5.3, −0.1)</td>
<td>0.043</td>
<td></td>
</tr>
</tbody>
</table>

Key: *p=0.0503.

n = number of patients in ITT population with PRA value at baseline. BP = blood pressure; CI = confidence interval; ITT population = intent-to-treat population; msDBP = mean sitting diastolic blood pressure; msSBP = mean sitting systolic blood pressure; PRA = plasma renin activity.


Post-active-controlled-treatment period

In patients who continued active treatment, there was little change in either PRA or PRC levels during the 4-week post-active-controlled-treatment period (figure 3). In patients who continued aliskiren-based therapy, PRA had decreased by 68% from pre-treatment baseline (Week 0) at the end of the 4-week post-active-controlled-treatment period (Week 30; p<0.05; figure 3a), whereas PRA increased by 215% in patients who continued ramipril-based therapy (p<0.05).

In patients who switched from either aliskiren- or ramipril-based therapy to placebo, PRC decreased rapidly, returning to pre-treatment baseline 2 weeks after stopping treatment (Week 28; figure 3b). Despite the rapid decrease in PRC in patients who switched from aliskiren-based therapy to placebo, PRA levels increased only gradually during the post-active-controlled-treatment period and remained 52% below pre-treatment baseline 4 weeks after stopping aliskiren-based therapy (Week 30; p<0.05; figure 3a); this equates to a maintenance of 89% of the PRA-lowering effect. In contrast, PRA rapidly decreased over the post-active-controlled-treatment period in patients who stopped ramipril-based therapy, returning to pre-treatment baseline levels 2 weeks after stopping treatment (Week 28).

Other biomarkers

Geometric mean values for UACR were in the normalbuminuric range at baseline in both
treatment groups (1.3 and 1.4 mg/mmol for aliskiren and ramipril groups, respectively). Aliskiren-based therapy showed a 22% reduction in UACR (geometric mean ratio 0.78 [0.60–1.02], p=0.078), whereas there was no change with ramipril-based treatment (mean ratio 1.00 [0.80–1.25], p=0.979; figure 4).

Sub-analysis of patients with proteinuria (defined as baseline UACR > 3.5 mg/mmol) showed that aliskiren-based therapy (n=15) significantly reduced UACR from baseline by 62% (mean ratio 0.38 [0.21–0.70], p<0.05); ramipril-based therapy (n=19) lowered UACR by 50% (mean ratio 0.50 [0.30–0.83], p<0.05). In patients with microalbuminuria (defined as baseline UACR 3.5–30 mg/mmol), UACR was reduced by 66% (mean ratio 0.34 [0.17–0.70], p=0.007) with aliskiren-based therapy (n=13) and 51% (mean ratio 0.49 [0.27–0.91], p=0.027) with ramipril-based therapy (n=17), respectively.

In the overall population for whom biomarker data were available, decreases were observed in mean MCP-1 values with both treatment regimens (−8% and −5% for aliskiren and ramipril, respectively), with the decrease approaching significance with aliskiren-based therapy (mean ratio 0.92 [0.85–1.00]). Baseline plasma aldosterone values were in the low normal range (geometric mean 157.6 and 181.1 pmol/L for aliskiren and ramipril, respectively), and did not change significantly with either treatment regimen during double-blind therapy. Baseline hs-CRP levels were within the mild-to-moderate risk range (1.5 and 2.0 mg/L for aliskiren and ramipril, respectively), but no significant changes in hs-CRP, sICAM-1 or hs-IL-6 were observed during active treatment.

Safety and tolerability

Active-controlled-treatment period

In the overall patient population, most AEs were mild or moderate in intensity. The rate of AEs was similar in the aliskiren and ramipril treatment groups (257/419 patients [61.3%] and 255/422 [60.4%, respectively), as was the rate of discontinuations due to AEs (24/419 [5.7%] and 20/422 [4.7%, respectively). Cough occurred more frequently with ramipril than aliskiren (9.5% vs. 4.1%). The incidence of serum potassium levels > 5.5 mmol/L was higher with aliskiren than ramipril (1.9% vs. 1.0%), but few patients in either treatment group had serum potassium levels ≥ 6.0 mmol/L (0.5% and 0.2%, respectively).

Post-active-controlled-treatment period

The incidence of AEs was similar in patients who switched from aliskiren-based therapy to placebo (19.0%) and those who continued aliskiren treatment (22.4%). The incidence of AEs was higher in the ramipril group, whether patients had switched to placebo (29.4%) or continued active treatment (29.7%). There were no clinically meaningful differences between active-treatment groups in the incidence of serum potassium levels > 5.5 mmol/L (aliskiren 0.6%, ramipril 1.9%).

Discussion

This paper reports biomarker data from the first long-term study to compare the efficacy, safety and tolerability of treatment regimens based on the DRI aliskiren and the ACE inhibitor ramipril, at the maximum commonly-used dose, in patients with mild-to-moderate hypertension.17 Our results show that aliskiren-based therapy provided long-term control of PRA, and importantly, continued to provide PRA control and prolonged BP reductions 4 weeks after stopping treatment.

At the end of the active-controlled-treatment period (Week 26), PRC levels were increased with both aliskiren-based (+224%) and ramipril-based (+145%) treatments, due to loss of Ang II-mediated feedback inhibition of renal renin release. Despite the increase in PRC, aliskiren-based therapy lowered PRA by 63% (whereas ramipril-based therapy significantly increased PRA by +143%), demonstrating that aliskiren-based therapy provides long-term control of PRA. The reduction in PRA with aliskiren-based treatment is particularly noteworthy as just under half (46%) of patients were receiving concomitant HCT, an agent that is known to increase PRA. Previous clinical studies have also demonstrated effective control of PRA when aliskiren is used in...
combination with HCT, as well as during co-administration with the ACE inhibitor ramipril or the ARB valsartan, drug classes that also increase PRA. Despite the differential effect of aliskiren and ramipril on PRA, it should be noted that neither treatment affected aldosterone levels in this study. However, this might reflect the fact that mean plasma aldosterone levels were not elevated at baseline in this patient population, or that plasma aldosterone is much less sensitive than urinary aldosterone measurements for detecting treatment-induced changes.

It should be noted that reagents for the PRC assay became unavailable during the study and the remaining plasma samples were insufficient to re-test using a different assay. As a result, the number of patients with PRC data was low, and therefore these data should be interpreted with some degree of caution. During the post-active-controlled-treatment period, PRC rapidly decreased in patients who switched from either aliskiren- or ramipril-based therapy to placebo, returning to baseline levels 2 weeks after stopping treatment. In patients who stopped ramipril-based therapy, changes in PRA mirrored those of PRC. However, in patients who switched from aliskiren-based therapy to placebo, PRA increased only gradually over the 4-week post-active-controlled-treatment period, remaining 52% below pre-treatment baseline levels at endpoint. The findings of the present study suggest that the increase in PRC that occurs during aliskiren-based therapy does not lead to increases in PRA when treatment is stopped. In a recent study comparing two different PRC assays, both the Nichols direct renin assay (which was used in the present study) and the Cisbio assay overestimated PRC in vitro in the presence of different renin inhibitors. Moreover, the Nichols direct renin assay gave a larger overestimate than the Cisbio assay. This overestimation of PRC is likely to be due to the conformational change in prorenin that occurs in the presence of high concentrations of DRIs. In such circumstances, monoclonal antibodies erroneously measure prorenin as renin molecules; therefore in the presence of aliskiren, PRC assays measure not only the true concentration of renin but also prorenin molecules to which aliskiren has bound.

During the post-active-controlled-treatment period, BP changes in patients who stopped active treatment paralleled changes in PRA. Thus, most of the BP-lowering effects of ramipril-based treatment were lost 1 week after stopping therapy, such that median BP values were no longer below the target BP of 140/90 mmHg 1 week after stopping treatment. By contrast, median BP values did not exceed 140/90 mmHg 4 weeks after stopping aliskiren-based therapy. Indeed, msSBP/msDBP-lowering efficacy was maintained at 75%/83% 1 week after stopping aliskiren-based therapy compared with only 55%/66% after stopping ramipril-based therapy. The gradual return of BP towards baseline levels observed after stopping aliskiren-based therapy reflected the prolonged effects of aliskiren on PRA. The long-term suppression of PRA after aliskiren withdrawal might be explained by renal accumulation of aliskiren, which has been shown to be up to 50-fold in animal studies. In vitro studies indicate that aliskiren is taken up by renin secretory cells and binds intracellularly to stored renin, thus inhibiting renin activity of this enzyme before its secretion. This effect, and the gradual partitioning of aliskiren from the kidneys after stopping treatment, might explain the persistent effects of aliskiren on PRA beyond the half-life of the drug. The prolonged PRA suppression might reduce BP fluctuations following missed doses and may be seen as clinically beneficial. There are no data to support that such long-term suppression of PRA might have deleterious effects. However, PRA is only one marker of renin-angiotensin-aldosterone system activity and the clinical effects of its suppression are at present unknown.

The findings of the present study provide no evidence that responses to aliskiren may be poor or absent in patients with suppressed baseline PRA levels, as has previously been suggested. PRA levels can be classified as low (< 0.65 ng Ang I/ml/h), medium (0.65–4.5 ng Ang I/ml/h) or high (> 4.5 ng Ang I/ml/h). Baseline PRA levels in the present study were therefore in the low-to-medium range (geometric mean 0.83 and 0.96 ng/ml/h for aliskiren and ramipril groups, respectively). Subgroup analysis of BP responses according to baseline PRA showed no significant influence of baseline PRA on the antihypertensive effect of aliskiren monotherapy. In a previous study of aliskiren in 569 patients with mild-to-moderate hypertension, regression analysis showed no significant correlation between baseline PRA and SBP change following 8 weeks’ treatment with once-daily aliskiren 150–600 mg, suggesting that the ability of aliskiren to lower BP is effectively independent of baseline PRA.

In the present study, neither aliskiren- nor ramipril-based treatment significantly changed levels of the inflammatory biomarker hs-CRP during the active-controlled-treatment period. Previous studies with ramipril monotherapy have shown significant reductions in hs-CRP across...
different patient populations. The lack of effect of either treatment regimen on hs-CRP levels in the present study may be due to co-administration of HCT, which was received by nearly half of patients, or to the relatively low baseline levels of hs-CRP.

In the subgroup of patients with proteinuria or microalbuminuria, aliskiren-based therapy provided numerically, but not significantly, greater reductions in UACR than ramipril-based therapy, at the maximum commonly-used dose. In the recently completed AVOID study (Aliskiren in the Evaluation of PrQteinuria In Diabetes), aliskiren 150 mg significantly lowered UACR by a further 20% compared with add-on placebo (p<0.001) in patients with hypertension, type 2 diabetes and kidney disease who were already receiving optimal antihypertensive treatment. Furthermore, in a separate study in patients with type 2 diabetes, hypertension and micro or macroalbuminuria, aliskiren 300 mg monotherapy significantly lowered UACR from baseline by 44% (p<0.001) after 4 weeks of treatment.

It is important to note the limitations of the present study. First, the clinical implications of the different effects of treatment on markers such as PRA and PRC are not yet known. Secondly, data for PRC were available for only a limited number of patients, and so these results should be interpreted with caution. Thirdly, although UACR was measured, this was a secondary endpoint and the study design did not incorporate control of intake of sodium, and other biomarkers. Finally, the renin assay used in the present study is likely to overestimate PRA in the presence of sodium, and other biomarkers. It showed that some commercial assays may overestimate renin inhibition when a renin inhibitor is present; the antibody-trapping assay should therefore be used to measure PRA. In the present study, the authors take full responsibility for the content of the paper, but thank Drs Felicity Sellers and Ann Taylor (Oxford PharmaGenesis Ltd.) for assistance in preparing an initial draft of the manuscript from the final clinical study report and collating and incorporating comments from all authors and other named contributors on this and additional drafts to produce a final draft manuscript for submission. This work was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. MAA, JJ and DLK are employees of Novartis Pharmaceuticals Corporation, and are therefore eligible for Novartis stock and stock options.

Conclusions
In conclusion, aliskiren-based therapy (with optional add-on HCT) provided reductions in BP and PRA that were sustained over 6 months of treatment. The antihypertensive effect of aliskiren monotherapy was essentially independent of baseline PRA. Nearly 90% of the PRA-lowering efficacy was maintained 4 weeks after stopping aliskiren treatment, suggesting that the inhibitory effects of aliskiren on PRA extended beyond the elimination half-life of the drug. These results indicate that aliskiren-based treatment offers sustained control of PRA and effective BP lowering during long-term therapy in patients with hypertension.

References