Paper

Efficacy and safety of the direct renin inhibitor aliskiren and ramipril alone or in combination in patients with diabetes and hypertension

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Abstract

Objective. To assess the antihypertensive efficacy and safety of the combination of the direct renin inhibitor aliskiren and ramipril in patients with diabetes and hypertension.

Methods. In this double-blind, multicentre trial, 837 patients with diabetes mellitus and hypertension (mean sitting diastolic blood pressure [BP] > 95 and < 110 mmHg) were randomised to once-daily aliskiren (150 mg titrated to 300 mg after four weeks; n=282), ramipril (5 mg titrated to 10 mg; n=278) or the combination (n=277) for eight weeks. Efficacy variables were cuff mean sitting diastolic BP (msDBP) and mean sitting systolic BP (msSBP); 24-hour ambulatory BP, plasma renin activity (PRA) and plasma renin concentration (PRC) were also assessed.

Results. At week 8, aliskiren, ramipril and aliskiren/ramipril lowered msDBP (mean±SEM) by 11.3±0.5, 10.7±0.5 and 12.8±0.5 mmHg, and msSBP by 14.7±0.9, 12.0±0.9 and 16.6±0.9 mmHg, respectively. Aliskiren/ramipril provided superior msDBP reductions to ramipril (p=0.004) or aliskiren (p=0.043) monotherapy; adding aliskiren to ramipril provided an additional mean BP reduction of 4.6/2.1 mmHg. Aliskiren monotherapy was non-inferior to ramipril for msDBP reduction (p=0.0002) and superior for msSBP reduction (p=0.021). All treatments significantly lowered mean 24-hour ambulatory BP. Aliskiren significantly reduced PRA from baseline as monotherapy (by 66%, p<0.0001) or in combination with ramipril (by 48%, p<0.0001), despite large increases in PRC in all treatment groups. Aliskiren was well tolerated as monotherapy or in combination with ramipril.

Conclusions. Combining aliskiren with ramipril provided a greater reduction in msDBP than either drug alone in patients with diabetes and hypertension.

Introduction

Nearly three-quarters of all patients with diabetes have hypertension,[1] which greatly increases the risk of cardiovascular and renal disease in these patients. Treatment guidelines therefore recommend more stringent blood pressure (BP) targets (e.g. < 130/80 mmHg) for this patient group,[2,3] and more than 60% of diabetic patients require combination therapy with two or more antihypertensive agents to achieve BP control.[4]

The angiotensin-converting enzyme (ACE) inhibitor ramipril is a standard first-line treatment for patients with diabetes and hypertension. Inhibition of the renin system with ACE-inhibitors or angiotensin receptor blockers (ARBs) is an attractive therapeutic approach for this patient group because increased tissue renin system activity may be a major factor in the development of organ damage in diabetes.[5,6] Indeed, clinical trials have shown that ACE-inhibitor or ARB treatment slows the progression of renal disease in patients with type 2 diabetes and hypertension.[7,8]

ACE-inhibitors and ARBs inhibit negative feedback mechanisms, resulting in a reactive increase in plasma renin activity (PRA; the capacity of renin to convert angiotensinogen to angiotensin [Ang] I) that may lead to increased generation of Ang II.[9] The reactive rise in PRA may lead to 'escape' from ACE-inhibitor treatment, because many tissues contain ACE independent pathways for the conversion of Ang I to Ang II.[10] Aliskiren, the first in a new class of orally effective direct renin inhibitors, differs from ACE-inhibitors and ARBs in its ability to lower PRA, thereby inhibiting the production of both Ang I and Ang II.[11] Combination of aliskiren with an ACE-inhibitor would therefore be expected to minimise ACE-inhibitor 'escape'. However, whether this effect might be associated with further decreases in BP than ACE-inhibitor treatment alone has not been tested.

The present study is the first to test this hypothesis and to assess the antihypertensive efficacy and safety of a direct renin inhibitor in patients with diabetes and hypertension. This study assessed whether the combination of aliskiren and ramipril was safe and effective in lowering BP in this patient group, as compared with the respective monotherapies.

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Methods

Patients

Eligible patients were men and women aged ≥ 18 years with type 1 or 2 diabetes mellitus and stage 1–2 hypertension (mean sitting diastolic BP [msDBP] ≥ 95 mmHg and < 110 mmHg) who had been receiving stable doses of hypoglycaemic medication for at least four weeks prior to the start of the study.

Patients whose msDBP was ≥ 110 mmHg were ineligible to participate, as were patients with secondary hypertension, history of severe cardiovascular or cerebrovascular disease, or other severe or life-threatening disease.

All patients provided written informed consent, and the study protocol was approved by local ethical review boards. The study was conducted in accordance with good clinical practice and in compliance with the Declaration of Helsinki (2002) of the World Medical Association.

Study design

This was a randomised, double-blind, parallel group, multicentre trial conducted in 125 centres in Canada, Denmark, France, Germany, Italy, Malaysia, the Netherlands, Norway, Spain, Sweden, Taiwan, Turkey and the United States. The first patient was recruited on 29 November 2004 and the last patient completed on 30 August 2005. This trial is registered at ClinicalTrials.gov with trial identifier NCT00219089.

Following screening and a 1–2 week washout for patients taking antihypertensive therapy (not required for treatment-naïve patients), patients entered a 1–4 week single-blind placebo run-in period to establish BP eligibility. Patients who fulfilled the inclusion and exclusion criteria, and who showed an absolute difference in msDBP < 10 mmHg between the last two visits of the single-blind run-in, were randomised to double-blind, once-daily treatment with aliskiren 150 mg, ramipril 5 mg, or the combination of aliskiren 50 mg/ramipril 5 mg. A randomisation list was produced by Novartis Drug Supply Management using a validated system that automates the random assignment of treatment groups to randomisation numbers in a 1:1:1 ratio. The randomisation scheme was reviewed by a Biostatistics Quality Assurance Group and locked by them after approval. Randomisation was performed using a block size of three and by centre. Randomisation codes were kept strictly confidential until the database was locked. After four weeks of treatment, all patients underwent forced titration to doubled doses of their respective treatments for a further four weeks. No restriction or monitoring of sodium intake was performed in this study.

The 300 mg dose of aliskiren and 10 mg dose of ramipril were selected because (1) the aliskiren dose-response relationship exhibits a plateau for BP reduction above 300 mg,[12] while ramipril 10 mg is a standard first-line treatment for patients with diabetes and hypertension and the ramipril dose-BP response relationship exhibits a plateau above 10 mg;[13,14] (2) the 600 mg dose of aliskiren is associated with an increased incidence of diarrhoea;[15] (3) combination of two renin system inhibitors confers a theoretical risk of exacerbating renal dysfunction, and in the absence of previous data aliskiren 300 mg and ramipril 10 mg were selected as the highest dose to ensure safety in patients with diabetes and hypertension who might have underlying renal disease.

BP, pulse rate, concomitant medications, compliance with study treatment and safety assessments (adverse events [AEs], vital signs and laboratory evaluations) were recorded at baseline (week 0) and during clinic visits at weeks 2, 4, 6 and 8 during double-blind treatment. Blood samples for measurement of biomarkers were taken at baseline and at week 8 at selected sites. During the study, patients were not permitted to take additional drugs indicated for the treatment of hypertension.

Outcome measures

The primary objectives of the study were to compare the change in msDBP from baseline to week 8 end point between (1) the aliskiren 300 mg/ramipril 10 mg combination and the component monotherapies, and (2) aliskiren 300 mg and ramipril 10 mg. We hypothesised that the combination would provide superior BP reduction compared with both monotherapies and that aliskiren would be non-inferior to ramipril.

Secondary efficacy variables were the change from baseline to end point in mean sitting SBP (msSBP), the proportion of patients with a successful response to treatment (trough msDBP < 90 mmHg and/or at least a 10 mmHg reduction from baseline) or achieving BP control (BP < 130/80 mmHg), changes from baseline in 24-hour ambulatory BP monitoring (ABPM) measurements, and changes in biomarkers (plasma renin concentration [PRC], PRA, aldosterone). All efficacy variables were analysed for the intent-to-treat (ITT) population.

BP measurements

Sitting BP was measured at trough (24±3 hours post dose) in the arm in which the highest BP measurement was recorded at the first study visit, using a calibrated standard mercury sphygmomanometer in accordance with the 1988 American Heart Association Committee report on BP Determination. Three sitting BP

measurements were taken at 1–2 minute intervals and the mean value taken as the average BP for that visit. The Principal Investigator and Study Coordinator were trained and certified in proper BP measurement.

Twenty four-hour ABPM

Twenty-four-hour ABPM was conducted in a subgroup of patients at baseline and week 8 (n=173); an ABPM sample of 60 patients per treatment arm was considered sufficient to assess the primary objectives, given the lower variability and relative lack of placebo effect with ABPM compared with office BP measurements. The ABPM device (Spacelabs Model 90207, Spacelabs, Redmond, Washington, USA) was attached to the non-dominant arm of patients between 07:00 hours and 10:00 hours and calibrated to within ±7 mmHg of the mean of three sphygmomanometer readings. Measurements included 24-hour, daytime (06:00 hours to 22:00 hours) and night-time (22:00 hours to 06:00 hours) mean ambulatory BP.

Biomarker assays

PRA was measured by radioimmunoassay of generated Ang I (DiaSorin kit, DiaSorin, Stillwater, Minnesota, USA); PRC (Nichols Direct Renin assay, Nichols Institute, San Clemente, California, USA) and plasma aldosterone (Nichols Advantage Aldosterone assay) were measured by immunochemiluminescence.

Statistical methods

A sample size of 759 patients completing the study was targeted (randomised population 846 patients assuming 10% drop-out rate) with equal randomisation among treatment groups, to provide 90% power to detect a treatment difference in msDBP of 2.5 mmHg for pairwise comparisons of the combination versus aliskiren and ramipril (assuming standard deviation 8 mmHg for msDBP). This sample size gave 80% power to detect (one-sided significance level 0.025) a non-inferiority margin of 2 mmHg (4 mmHg for msSBP) between aliskiren and ramipril.

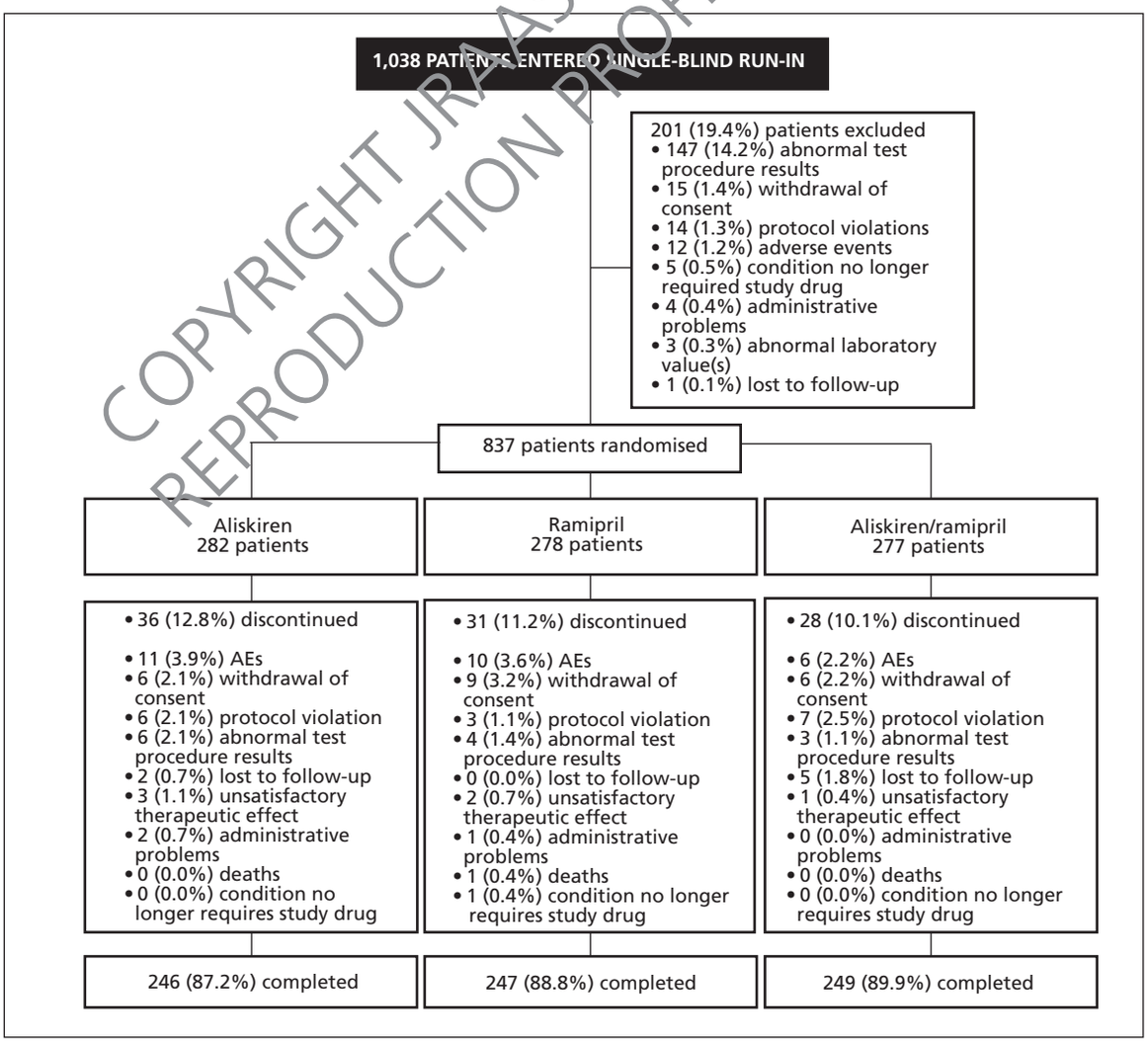

Figure 1

Patient flow diagram. Values are presented as the number (%) of patients unless otherwise stated. AE = adverse event.

Table 1
Patient characteristics (randomised population).

Characteristic	Aliskiren (n=282)	Ramipril (n=278)	Aliskiren/ ramipril (n=277)
Age, years	60.0±9.8	59.9±11.2	59.5±10.2
Sex, n (%)			
Male	157 (55.7)	166 (59.7)	168 (60.6)
Female	125 (44.3)	112 (40.3)	109 (39.4)
Race, n (%)			
Caucasian	256 (90.8)	253 (91.0)	256 (92.4)
Black	5 (1.8)	7 (2.5)	6 (2.2)
Asian	20 (7.1)	18 (6.5)	15 (5.4)
Other	1 (0.4)	0 (0.0)	0 (0.0)
BMI, kg/m^2	31.4±5.9	30.3±5.3	31.3±6.1
Obese patients, n (%)	153 (54.3)	126 (45.3)	154 (55.6)
HbA_{1C} %	7.3±1.4	7.3±1.4	7.2±1.3
Prior medications, n (%)			
Biguanides	131 (46.5)	137 (49.3)	134 (48.4)
HMG-CoA reductase inhibitors	104 (36.9)	88 (31.7)	95 (34.3)
Sulphonylureas	96 (34.0)	84 (30.2)	90 (32.5)
ACE-inhibitor monotherapy	77 (27.3)	78 (28.1)	96 (34.7)
Platelet aggregation inhibitors	71 (25.2)	71 (25.5)	65 (23.5)
Aspirin	66 (23.4)	64 (23.0)	59 (21.3)
Duration of hypertension, years	9.6±8.2	8.4±7.2	9.1±7.9
Mean sitting DBP, mmHg	98.4±3.3	98.2±3.1	98.4±3.5
Mean sitting SBP, mmHg	157.4±12.2	155.9±11.6	156.5±12.2
Sitting pulse, bpm	75.2±10.0	75.9±9.7	75.3±10.6
PRA, ng/mL/h[a]	0.53 (0.41, 0.70)	0.47 (0.37, 0.59)	0.43 (0.32, 0.56)

Key: Data are presented as mean±SD unless otherwise stated. [a] = PRA values are presented as geometric mean (95% confidence interval) for aliskiren (n=79), ramipril (n=74) and aliskiren/ramipril (n=75). Obesity was defined as BMI ≥ 30 kg/m^2. BMI = body mass index; bpm = beats per minute; HbA_{1C} = glycosylated haemoglobin; PRA = plasma renin activity; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Changes in msDBP (or msSBP) between baseline and study end point were compared between treatment groups as described above, using a two-way analysis of covariance (ANCOVA) with treatment and region as factors, and baseline msDBP (or msSBP) as a covariate. Patients who discontinued double-blind treatment before week 8 underwent a final study evaluation, and the last post-baseline measurement during the double-blind treatment period was carried forward as the week 8 end point measurement. Two-sided 95% confidence intervals were calculated for treatment differences.

Responder rates and control rates were compared using a logistic regression model; changes in ABPM measurements and biomarkers (log-transformed PRA, PRC, aldosterone) were compared using ANCOVA models, using the same comparisons as for the study primary objectives. Pairwise comparisons were made at a two-sided significance level of 0.05; testing for both superiority and non-inferiority does not require further significance level adjustment, based on the use of a closed test procedure in which superiority is only tested if non-inferiority has been demonstrated.[16] No interim efficacy analyses were performed. All statistical analyses were performed using SAS software (version 8.2, SAS Institute Inc., Cary, NC, USA) under the responsibility of Hui Fang (Novartis Pharmaceuticals).

Results

Patient characteristics

One thousand and thirty eight patients entered the single-blind placebo run-in period; 837 were randomised to treatment with aliskiren (n=282), ramipril (n=278) or aliskiren/ramipril (n=277). Overall, 95 patients (11.4%) discontinued study treatment before the end of the trial (figure 1); major reasons were AEs (28 patients, 3.3%), withdrawal of consent (21, 3.5%), protocol violation (16, 1.9%) and abnormal test procedure results (13, 1.6%). Rates of and reasons for discontinuation were similar in the three treatment groups. Baseline characteristics showed that the three treatment groups were well balanced, although there were fewer obese patients in the ramipril group (table 1). The majority of patients were Caucasian.

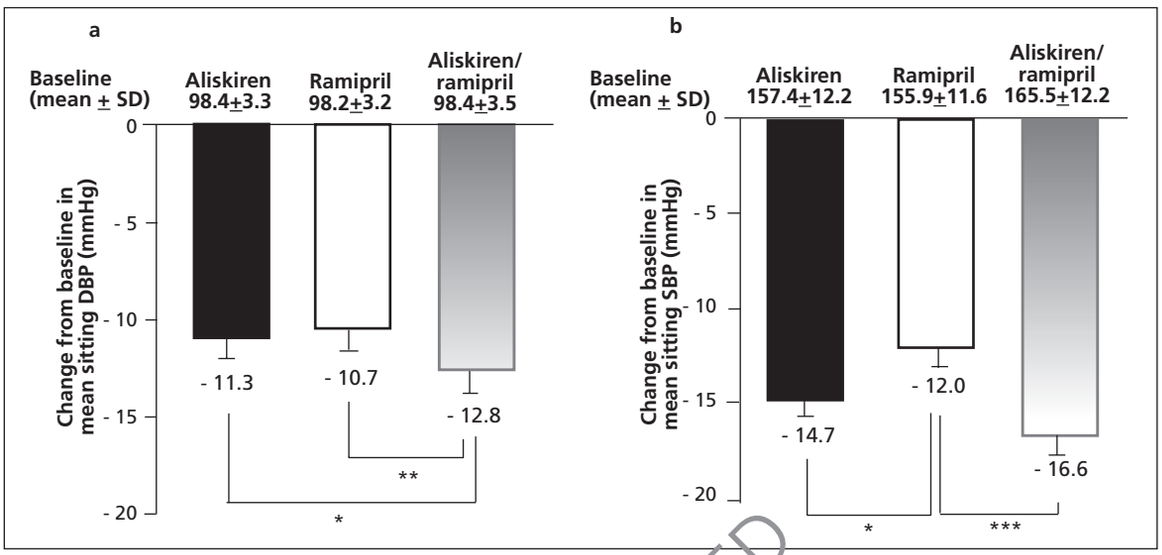

Figure 2
Changes from baseline in (**a**) mean sitting DBP and (**b**) mean sitting SBP at week 8 end point. Graph shows least-squares mean changes from baseline at week 8 end point in patients receiving treatment with aliskiren monotherapy (black bars), ramipril monotherapy (white bars) or aliskiren/ramipril in combination (grey bars). Data are presented as the least-squares mean±SEM; baseline BP values in each treatment group are presented as mean±SD. * = p<0.05; ** = p<0.01; *** = p<0.0001 in pairwise comparisons.

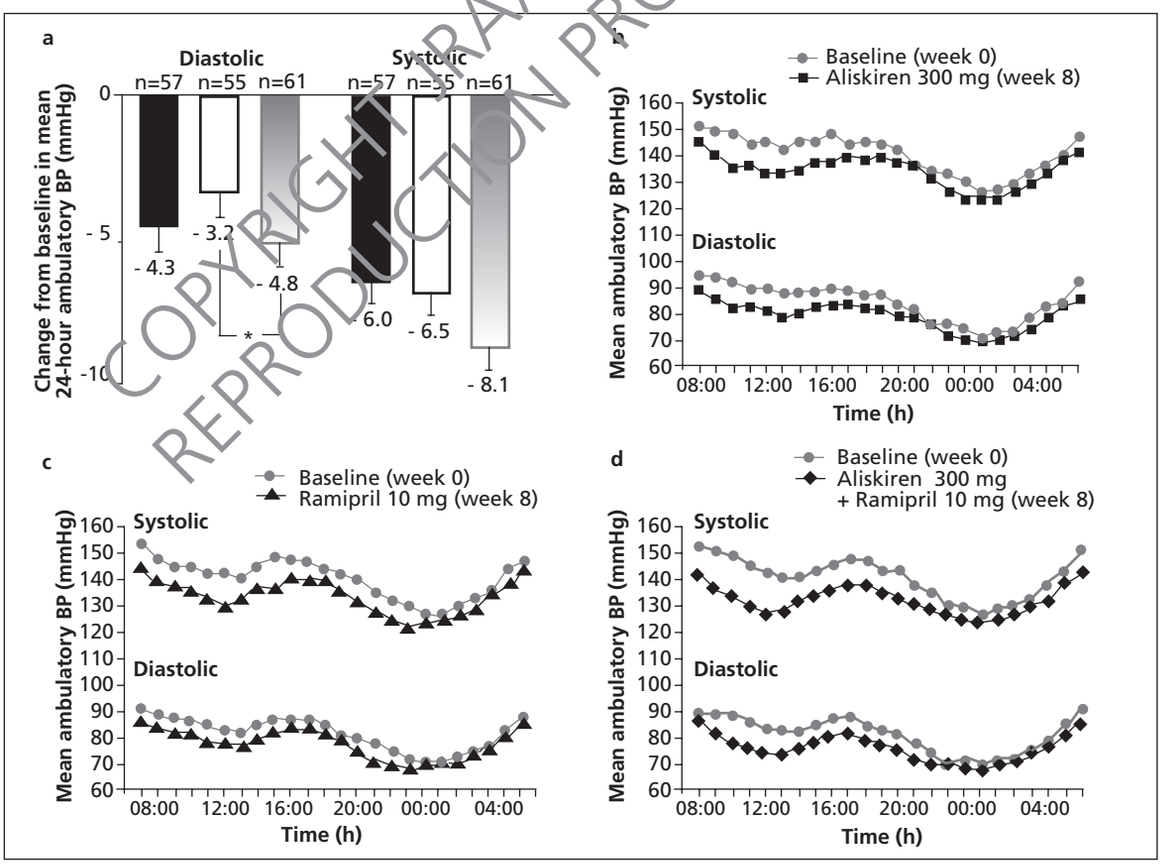

Figure 3
(**a**) Changes from baseline in 24-hour mean ambulatory BP at week 8 end point, and mean 24-hour ambulatory BP profiles for (**b**) aliskiren, (**c**) ramipril; (**d**) aliskiren/ramipril at baseline and week 8 end point. (**a**) Shows least-squares mean changes from baseline in 24-hour ambulatory DBP and SBP at week 8 end point in patients receiving treatment with aliskiren monotherapy (black bars), ramipril monotherapy (white bars) or aliskiren/ramipril in combination (grey bars). (**b**, **c**, **d**) Show mean 24-hour ambulatory BP profiles at baseline and week 8 end point. Data are presented as mean ± SEM in (**a**) and as mean in (**b**, **c**, **d**). * = p<0.05 in pairwise comparisons.

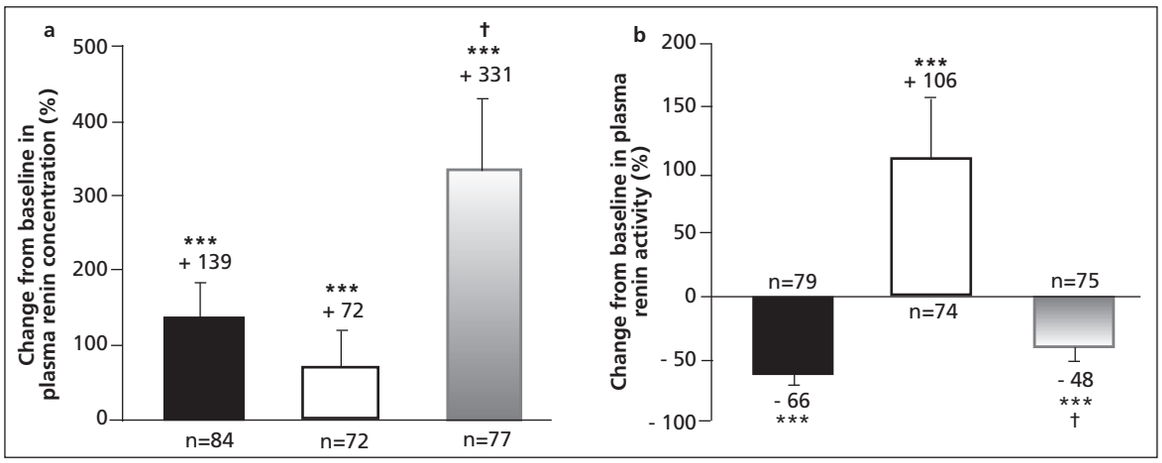

Figure 4

Changes from baseline in (**a**) geometric mean plasma renin concentration (PRC) and (**b**) geometric mean plasma renin activity (PRA) at week 8 end point. Graph shows percentage changes from baseline at week 8 end point in patients receiving treatment with aliskiren monotherapy (black bars), ramipril monotherapy (white bars) or aliskiren/ramipril in combination (grey bars). Data are presented as the percentage change in geometric mean and associated 95% confidence interval. * p<0.05, ** p<0.01, *** p<0.001 vs baseline; † p<0.05 vs aliskiren monotherapy and ramipril monotherapy.

Effect on msDBP and msSBP

At the week 8 end point, treatment with aliskiren/ramipril produced significantly greater reductions from baseline in msDBP than either aliskiren (p=0.043) or ramipril (p=0.004) monotherapy (figure 2a). Aliskiren/ramipril also provided significantly greater mean reductions from baseline in msSBP than ramipril (p<0.0001), but not aliskiren (p=0.088; figure 2b).

Aliskiren 300 mg was statistically non-inferior (p=0.0002) to ramipril 10 mg for the change in msDBP. The least-squares mean treatment difference for aliskiren–ramipril was –0.61 mmHg (95% CI –2.02, 0.80), with the upper bound of the 95% CI (0.80 mmHg in favour of ramipril) smaller than the prespecified non-inferiority margin of 2 mmHg. For the change in msSBP, aliskiren monotherapy was statistically superior (p=0.021) to ramipril.

The proportion of patients with a successful response to therapy at week 8 was similar for aliskiren/ramipril (74.1%) and aliskiren (73.1%); responder rates in both groups were significantly higher (p<0.05) than with ramipril (65.8%). Rates of BP control (< 130/80 mmHg) at week 8 were numerically but not significantly higher with aliskiren/ramipril (13.1%) than either aliskiren (8.2%) or ramipril (8.4%).

24-hour ABPM

Baseline characteristics in the subset of patients with ABPM measurements (n=173) were similar to the overall study population. All treatments lowered mean 24-hour ambulatory BP compared with baseline (figure 3). Aliskiren/ramipril was significantly more effective than ramipril in lowering 24-hour mean ambulatory DBP (p=0.034), and showed non-significantly larger reductions in 24-hour ambulatory SBP compared with ramipril alone (figure 3a). Individual 24-hour ambulatory BP profiles for the three treatments (figures 3b, c, d) suggested a slightly greater BP-lowering effect at the end of the dosing interval with aliskiren and aliskiren/ramipril compared with ramipril.

Markers of renin system activity

PRC increased significantly in all treatment arms (p<0.0001 *vs.* baseline; figure 4a). The increase with aliskiren/ramipril was significantly greater (p<0.001) than that with either monotherapy. Consistent with the reactive rise in PRC, PRA increased with ramipril (p<0.0001 *vs.* baseline). By contrast, aliskiren significantly reduced PRA by 66% (p<0.0001;figure 4b) and in the combination counteracted the effect of ramipril, leading to an overall reduction from baseline (p<0.0001 *vs.* ramipril).

Plasma aldosterone levels at week 8 were not significantly lowered by monotherapy with ramipril (2% reduction from baseline; n=77) or aliskiren (8% reduction, n=83). In contrast, aliskiren/ramipril (n=86) resulted in an 18% reduction (p=0.034 *vs.* baseline).

Glycaemic control

Haemoglobin A_{1C} and fasting plasma glucose levels at week 8 showed no notable changes from baseline in any treatment group.

Safety and tolerability

Aliskiren and ramipril were well tolerated as monotherapies or in combination. Rates of AEs and discontinuation due to AEs were similar in all treatment groups (table 2). The most

Table 2
Safety and tolerability (safety population).

	Aliskiren (n=282)	Ramipril (n=278)	Aliskiren/ramipril (n=277)
Any AE	91 (32.3)	94 (33.8)	83 (30.0)
Any serious AE	8 (2.8)	6 (2.2)	4 (1.4)
Discontinuation due to AE	11 (3.9)	11 (4.0)	6 (2.2)
Most frequent AEs (≥ 2%)			
Headache	9 (3.2)	17 (6.1)	8 (2.9)
Cough	6 (2.1)	13 (4.7)	5 (1.8)
Nasopharyngitis	9 (3.2)	5 (1.8)	3 (1.1)
Diarrhoea	3 (1.1)	7 (2.5)	3 (1.1)
Laboratory abnormalities			
Potassium > 5.5 mmol/L	6 (2.2)	7 (2.6)	15 (5.5)
Potassium ≥ 6.0 mmol/L	3 (1.1)	3 (1.1)	4 (1.5)
Potassium < 3.5 mmol/L	5 (1.8)	7 (2.6)	3 (1.1)
Creatinine > 176.8 µmol/L	3 (1.1)	1 (0.4)	1 (0.4)
BUN > 14.28 mmol/L	3 (1.1)	0	1 (0.4)

Key: AE = adverse event; BUN = blood urea nitrogen. The number of patients with both baseline and post-baseline values for each laboratory parameter was as follows; aliskiren, BUN or creatinine, n=279; potassium, n=277; ramipril, BUN or creatinine, n=274; potassium, n=273; aliskiren/ramipril, n=273 for all parameters above. The safety population comprised all patients who were randomised and received at least one dose of study medication in the double-blind treatment period.

commonly reported AEs were headache, cough, nasopharyngitis and diarrhoea. Notably, cough – a common side effect of ACE-inhibitors – was reported by 4.7% of patients receiving ramipril, but by only 1.8% of patients receiving the aliskiren/ramipril combination (and 2.1% of patients receiving aliskiren), although this difference was not statistically significant (Chi-square test, p=0.08).

One patient in the ramipril group died of ethanol poisoning following excessive alcohol consumption. The incidence of other serious AEs was low and similar in the three treatment groups. For most biochemistry parameters, changes from baseline were small, with no major differences between treatment groups. The proportion of patients with serum potassium elevations above 5.5 mmol/L with the aliskiren/ramipril combination was 5.5%; this was approximately twice the proportion in each of the monotherapy treatment groups. The proportion of patients with elevations above 6.0 mmol/L was similar in the three groups (table 2).

Discussion

This is the first clinical trial to investigate the antihypertensive efficacy of a renin inhibitor in patients with diabetes and hypertension and to compare its effects with those of standard treatment with an ACE-inhibitor and with the combination of both agents. Aliskiren demonstrated non-inferior reductions in msDBP and statistically superior reductions in msSBP compared with ramipril 10 mg (the maximum effective BP-lowering dose), and showed excellent tolerability alone and in combination with ramipril. When used in combination with ramipril 10 mg, aliskiren provided clinically significant additional reductions in both systolic and diastolic BP.

Ramipril 10 mg is a standard first-line treatment for patients with diabetes and hypertension. However, the low proportion of patients achieving BP control (< 130/80 mmHg) with ramipril in the present study exemplifies the fact that monotherapy is rarely sufficient to control BP effectively in this patient group.[4] As there is little difference in trough BP reductions between ramipril 10 mg and 20 mg,[13,14] patients not controlled with ramipril 10 mg generally require treatment with additional antihypertensive drugs. The additional 4.6/2.1 mmHg (systolic/diastolic) reduction in mean sitting BP obtained by adding aliskiren to ramipril 10 mg in the present study is therefore of clinical relevance. Indeed, in the Hypertension Optimal Treatment (HOT) study, the mean additional BP reduction of 3.7/4.0 mmHg achieved in the ≤ 80 mmHg target group (the target for patients with diabetes) compared with the ≤ 90 mmHg target group was associated with a 51% relative reduction in the risk of major cardiovascular events in the subgroup with diabetes.[17]

Consistent with the office BP findings, the aliskiren/ramipril combination led to significantly greater reductions in 24-hour ambulatory DBP

compared with ramipril monotherapy. This probably reflects the fact that, unlike many antihypertensive agents, aliskiren exhibits a long terminal elimination half-life of approximately 40 hours in patients with diabetes.[18] By contrast, the half-life of ramiprilat (the active metabolite of ramipril) is 13–17 hours,[19] hence changes in 24-hour ambulatory BP and office BP measurements taken at trough might be expected to be smaller with ramipril. Nevertheless, the observed differences in BP reduction are likely to have clinical relevance, as it is well established that sustained 24-hour BP control is required for effective protection against end-organ damage and cardiovascular events in patients with hypertension.[20] The present results extend to diabetic patients with the findings of an ambulatory BP monitoring study in patients with hypertension, which demonstrated that once-daily aliskiren treatment provides sustained BP lowering throughout the 24-hour dosing interval.[21] Mean changes from baseline in ambulatory BP were smaller in magnitude than the observed changes in office BP, a finding that probably reflects to some extent the contribution of a placebo effect to the office BP reductions. Further studies, investigating the effect of combining aliskiren with other ACE-inhibitors with longer durations of action than ramipril would be useful to confirm the benefits of this strategy for improving BP control.

Renin system inhibition with aliskiren or ramipril led to a significant increase in PRC, an expected consequence of the disruption of the normal Ang II-mediated feedback inhibition of renal renin secretion.[22] The magnitude of the reactive rise in PRC stimulated by aliskiren/ramipril was numerically greater than the sum of the effects of either monotherapy, indicating synergistic inhibition of the renin system, as demonstrated previously with an aliskiren/ARB combination in healthy volunteers.[23] The reactive rise in PRC stimulated by ramipril was associated with a concomitant increase in PRA, but aliskiren suppressed the rise in PRA in combination with the ACE-inhibitor. This effect of aliskiren may be clinically important, as increased generation of Ang I by renin is associated with 'escape' from ACE-inhibitor monotherapy in patients with diabetes.[24]

Aliskiren was well tolerated alone or in combination with ramipril, consistent with the placebo-like tolerability of aliskiren already demonstrated.[12] The combination of aliskiren with ramipril appeared to reduce the incidence of ACE-inhibitor-induced cough. Cough is a well-known side effect of ACE-inhibitor therapy,[25] and its incidence is not reduced by combination of ARBs with ACE-inhibitors[26] The potential for aliskiren to enhance not just the efficacy of ACE-inhibitor monotherapy, but also its tolerability, would be of considerable therapeutic relevance. However, these findings need to be repeated in subsequent studies, as due to the small number of events in this study our finding was not statistically significant. The mechanism by which aliskiren might reduce the incidence of ACE-inhibitor-induced cough is at present unclear. Increases in serum potassium, a known effect of renin system-blocking agents, were similar with aliskiren and ramipril monotherapy. Elevations in serum potassium > 5.5 mmol/L were more common in the combination treatment group, but were not associated with adverse events and infrequently led to elevations ≥ 6.0 mmol/L; routine clinical monitoring for this population should be sufficient to detect and address them.

This study was designed to investigate the BP-lowering effect of dual renin system blockade by combining aliskiren with ramipril at its maximum effective dose for BP reduction. Similar additional BP reduction may be achieved in a patient with diabetes and hypertension whose BP is not controlled with ramipril 10 mg by addition of a thiazide diuretic. However, the present study showed that aliskiren had no deleterious effect on glycaemic control either alone or in combination with ramipril. Combination of aliskiren with ramipril may therefore have an advantage over add-on treatment with a thiazide diuretic, which may worsen metabolic abnormalities in patients with diabetes.[27] The relative effects of combining aliskiren with an ACE-inhibitor, as compared with combining an ARB with an ACE-inhibitor or a calcium channel blocker with an ACE-inhibitor, were also not investigated in this study. However, the few studies that have investigated the combination of maximum licensed dosages of an ACE-inhibitor and ARB have provided conflicting results regarding the benefits on BP reduction.[24,28,29] In this context, the significant additional BP reduction achieved by combining aliskiren with an ACE-inhibitor is a notable finding.

In conclusion, this study demonstrates that the direct renin inhibitor aliskiren provides additional, significant BP reductions when administered in combination with the highest commonly used dosage of ramipril (10 mg) in patients with hypertension and diabetes. Aliskiren treatment was well tolerated and had no adverse effects on glycaemic control when administered alone or in combination with ramipril. Combination with aliskiren may therefore represent a useful treatment option for patients who do not achieve BP control following first-line treatment with ramipril 10 mg.

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Previous presentation

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