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ORIGINAL ARTICLE

Comparative efficacy and safety of aliskiren and irbesartan in patients with hypertension and metabolic syndrome

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Metabolic syndrome, a cluster of risk factors that increase the risk of cardiovascular morbidity and mortality, is common in patients with hypertension. Chronic renin–angiotensin–aldosterone system (RAAS) activation, shown by elevated plasma renin activity (PRA), is implicated in many of the features of metabolic syndrome. The direct renin inhibitor aliskiren may be of benefit in this patient group as aliskiren targets the RAAS at the rate-limiting step. In this double-blind study, 141 patients with hypertension (mean baseline BP 155/93 mm Hg) and metabolic syndrome (modified National Cholesterol Education Program ATP III criteria) were randomized to aliskiren 300 mg or irbesartan 300 mg once daily. Patients treated with aliskiren 300 mg had their mean sitting blood pressure (BP) lowered by 13.8/7.1 mm Hg after 12 weeks, significantly greater ($P \leqslant 0.001$) than the 5.8/2.8 mm Hg reduction observed in patients treated with irbesartan 300 mg. A significantly greater proportion of patients treated with aliskiren achieved BP control to <135/85 mm Hg (29.2 vs 16.7% with irbesartan; $P = 0.019$). Aliskiren treatment led to a 60% decrease in PRA from baseline, whereas irbesartan increased PRA by 99% (both $P < 0.001$). Aliskiren and irbesartan had similar effects on glucose and lipid profiles and on a panel of biomarkers of inflammation and cardiovascular risk. Both aliskiren and irbesartan were well tolerated. Collectively, these results suggest that aliskiren 300 mg may offer treatment benefits compared with irbesartan 300 mg for BP reduction in patients with hypertension and metabolic syndrome.
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Keywords: aliskiren; direct renin inhibitor; irbesartan; metabolic syndrome; plasma renin activity

Introduction

Approximately one-third of patients with hypertension have metabolic syndrome,[1,2] a cluster of risk factors including high blood pressure (BP), central adiposity, dyslipidaemia and impaired fasting glucose that result in increased cardiovascular morbidity and mortality.[3] Chronic activation of the renin–angiotensin–aldosterone system (RAAS) is implicated in many of the key features of metabolic syndrome, including hypertension, insulin resistance and abdominal obesity.[4–6] Human adipocytes express mRNA and protein of many components of the RAAS, including angiotensinogen, angiotensin-converting enzyme and angiotensin receptors.[7] The local generation and release of angiotensin II (Ang II) by adipose tissue may therefore contribute to hypertension and can also influence adipocytokine secretion, thereby having a potential role in the development of features of the metabolic syndrome.[5] Guidelines from the European Society of Hypertension recommend that RAAS inhibition with angiotensin-converting enzyme inhibitors should be preferred over calcium channel blockers, β-blockers and thiazide diuretics for anti-hypertensive therapy in patients with metabolic syndrome.[8] However, despite current anti-hypertensive treatment approaches, patients with obesity and metabolic syndrome still have greater difficulty achieving BP control compared with patients with hypertension who do not have these additional risk factors.[9] This reflects the more complex pathophysiology, in particular the involvement of insulin resistance and low-grade inflammation.

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Aliskiren is the first direct renin inhibitor approved for the treatment of hypertension.[10] It is the only RAAS agent that directly inhibits the activity of renin and thereby lowers plasma renin activity (PRA), in contrast to angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers (ARBs), which increase PRA.[11] Several studies have shown an association of elevated PRA with an increased risk of cardiovascular events.[12–14] Given the importance of RAAS overactivation in metabolic disorders, direct renin inhibition may be of particular benefit for patients with metabolic syndrome. Previous studies have shown that aliskiren-based treatment is superior to thiazide diuretic treatment for BP control in patients with hypertension and obesity.[15,16] Indeed, aliskiren added to hydrochlorothiazide provided significant additional BP reductions over hydrochlorothiazide monotherapy in patients with grade 3 obesity (body mass index (BMI) $\geqslant 40\,kg\,m^{-2}$).[17] Moreover, a pooled analysis of 7219 patients from 10 randomized trials showed that aliskiren monotherapy (150 or 300 mg once daily) lowered BP effectively and with similar good tolerability in patients with or without metabolic syndrome.[18]

We report the results of a 12-week, double-blind, randomized, multi-centre trial conducted to compare the effects of direct renin inhibition with aliskiren and ARB monotherapy with irbesartan on BP, RAAS activity, and a panel of biomarkers of inflammation and cardiovascular risk in patients with hypertension and metabolic syndrome.

Materials and methods

This was a randomized, double-blind, parallel-group trial of 141 men and women aged 40–75 years with hypertension and metabolic syndrome. It was conducted in 27 centres in Germany. All patients entered into the study had metabolic syndrome according to the modified National Cholesterol Education Program ATP III criteria:[3] elevated BP (mean sitting systolic BP (msSBP) $\geqslant$ 130 mm Hg and/or mean sitting diastolic BP (msDBP) $\geqslant$ 85 mm Hg), central obesity (waist circumference $\geqslant$102 cm for men, $\geqslant$88 cm for women), and elevated triglyceride levels ($\geqslant 1.7\,mmol\,l^{-1}$), and/or fasting plasma glucose ($\geqslant$5.6 and $<7.0\,mmol\,l^{-1}$). Patients with msSBP $\geqslant$ 180 mm Hg and/or msDBP $\geqslant$ 110 mm Hg were excluded, as were those with secondary hypertension, angina pectoris requiring pharmacological therapy, heart failure, valvular heart disease or diabetes (type I or type II), and those with a history of hypertensive encephalopathy, myocardial infarction or stroke.

Each patient provided written informed consent before study entry. The study design was approved by the independent ethics committee or institutional review board at each centre, and was conducted in accordance with Good Clinical Practice and in compliance with the Declaration of Helsinki Principles.

Following screening, patients entered a 21-day washout period before randomization to once-daily treatment with aliskiren 150 mg or irbesartan 150 mg. Randomization was performed by Novartis Drug Supply Management using a validated system to randomly assign treatment groups to randomization numbers. Aliskiren and irbesartan were identical in packaging and labelling, and all patients received one tablet and one capsule to maintain the double-blind protocol. After 2 weeks of treatment, doses in both groups were increased to 300 mg (Figure 1).

Study objectives

The objective of this study was to assess changes from baseline in a panel of biomarkers of inflammation and other markers associated with cardiovascular risk and/or metabolic syndrome. These included BP and markers of RAAS activity, inflammation, fibrosis, coagulation/thrombosis, immunomodulation, oxidative stress and metabolism, neurohormones, adipocytokines and lipoproteins.

Changes from baseline in msSBP and msDBP at each time point, the proportion of subjects attaining BP control ($<$135/85 mm Hg) at day 85, changes from baseline in biomarkers at day 85 and safety and tolerability of study treatments in patients were assessed for each treatment group and compared between treatment groups.

BP measurements

Sitting and standing BP measurements were taken according to American Heart Association guidelines[19] using an automatic BP device (OMRON 705IT (HEM-759-E); Omron Medizintechnik, Mannheim, Germany) and an appropriately sized arm

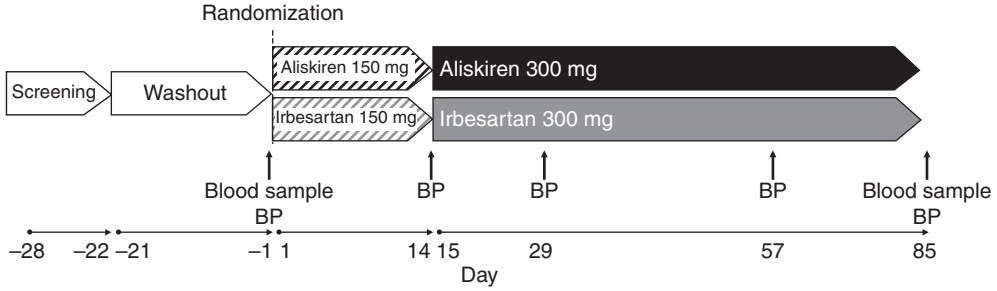

Figure 1 Study design. BP, blood pressure.

cuff at screening, baseline and on days 14, 29, 57 and 85 (Figure 1).

Biomarker assessments

Blood and urine samples were collected at baseline and at week 12 to assess a panel of biomarkers. For measurement of biomarkers of RAAS activity, two 6 ml samples of blood were taken by venepuncture and plasma extracted into EDTA tubes. Biomarkers measured were PRA (measured by the trapping of generated angiotensin I by high-affinity antibodies and by subsequent radioimmunoassay[20]), plasma renin concentration (PRC; IRMA kit; Cisbio, Gif sur Yvette, France), prorenin (measured as the difference between measured PRC and total renin measured by Cisbio IRMA following 'activation' of all prorenin by incubation of plasma for 48 h at 4 °C in the presence of 10 000 nmol l^{-1} aliskiren) and aldosterone (solid-phase radioimmunoassay; Diagnostic Products Corporation, Los Angeles, CA, USA). RAAS biomarkers were measured at the Erasmus Medical Center, Rotterdam, the Netherlands.

For analysis of serum resistin (enzyme-linked immunosorbent assay; R&D Systems Inc., Minneapolis, MN, USA) and high-sensitivity C-reactive protein (immunoturbidimetry; Roche Diagnostics, Mannheim, Germany), two 6 ml samples of blood were taken and serum was collected into plain tubes. For analysis of insulin (chemiluminescence immunoassay; Diagnostic Products Corporation), samples were allowed to clot for at least 30 min but no longer than 60 min, and were then centrifuged and the serum was aliquoted into cryotubes and frozen at $\leqslant -20$ °C. Resistin, high-sensitivity C-reactive protein and insulin were measured at CRL.Medinet, Breda, the Netherlands.

Void urine samples for determination of urinary albumin, creatinine and sodium were collected, the total volume was measured and a 30 ml sample was stored at $\leqslant -20$ °C until analysis of urinary albumin/creatinine ratio at CRL.Medinet. Urine samples for spot urine analysis of F_2 isoprostanes were taken and immediately frozen at $\leqslant -20$ °C until analysis (enzyme-linked immunosorbent assay) at CRL.Medinet.

For all other biomarkers, 1 ml of blood was sampled after overnight fasting by venepuncture and plasma was extracted into EDTA tubes, aliquoted and frozen at −70 °C. Samples were shipped on dry ice to Rules-Based Medicine Inc. (RBM, Austin, TX, USA) for testing for multiplexed analysis of a panel of biomarkers as described previously.[21] Briefly, at RBM each sample was thawed at room temperature, vortexed, spun at 13 000 *g* for 5 min for clarification and 40 µl was removed for Multi-Analyte Profile (MAP) analysis into a master microtitre plate. Using automated pipetting, an aliquot of each sample was introduced into one of the capture microsphere multiplexes of the DiscoveryMAP. These mixtures of sample and capture microspheres were thoroughly mixed and incubated at room temperature for 1 h. Multiplexed cocktails of biotinylated reporter antibodies for each multiplex were then added robotically and after thorough mixing were incubated for an additional hour at room temperature. Multiplexes were developed using an excess of streptavidin–phycoerythrin solution, which was thoroughly mixed into each multiplex and incubated for 1 h at room temperature. The volume of each multiplexed reaction was reduced by vacuum filtration and the volume was increased by dilution into matrix buffer for analysis. Analysis was performed in a Luminex 100 instrument using proprietary data analysis software. Biomarkers assessed by RBM were:

- Adipocytokines: adiponectin, leptin
- Lipoproteins: apolipoprotein-A-1, -CIII, -H, lipoprotein (a)
- Pro-inflammatory: epithelial neutrophil activating peptide (ENA)-78, eotaxin, intercellular adhesion molecule (ICAM)-1, interleukin (IL)-1 (α and β), -5, -6, -8, -16, lymphotactin, monocyte chemoattractant protein-1, macrophage inflammatory protein (MIP)-1 (α and β), regulated upon activation, normal T cell expressed and secreted (RANTES), tumour necrosis factor (TNF; α and β), TNF RII, vascular cell adhesion molecule (VCAM)-1,
- Anti-inflammatory: IL-2, -4, -10, -13, -12 (p40 and p70)
- Matrix degradation/fibrosis: α-1 antitrypsin, matrix metalloproteinase (MMP)-2, -3, -9, tissue inhibitor of matrix metalloproteinase (TIMP)-1
- Coagulation/thrombosis: fibrinogen, plasminogen activator inhibitor (PAI)-1, tissue factor, von Willebrand factor
- Immunomodulatory: granulocyte macrophage colony-stimulating factor, IL-1 (α and β), -2, -3, -5, -6, -7, -15
- Oxidative stress: myeloperoxidase (MPO)
- Neurohormone: endothelin-1

Safety and tolerability assessments

Safety and tolerability were assessed by recording all adverse events, electrocardiograms and standard clinical laboratory tests at baseline and throughout the course of the study. The safety analysis included all patients who received at least one dose of study medication.

Statistical analysis

Sample size was estimated based on the available information for variability of biomarkers, including: C-reactive protein, tumour necrosis factor-α, IL-6 and monocyte chemoattractant protein-1 and an intra-subject coefficient of variation (CV) of 30–65%.[22] Assuming a CV of 30%, it was determined that 100 completed patients (50 per group) would provide 90% power to detect a 20% difference between patient groups, whereas a CV of 50% would provide 50% power to detect the same change.

Statistical analysis of BP changes from baseline was performed using a mixed-effect model with

treatment (aliskiren or irbesartan) and day (14, 29, 57, 85) as fixed factors, and subject (nested in treatment) as a random factor. The number of patients with overall control of BP (defined as $<135/85$ mm Hg) was analysed using a logistic regression model with treatment as a fixed factor and baseline msSBP and msDBP as covariates.

Log-transformed measurements of biomarkers were analysed using a model including treatment (aliskiren or irbesartan), day (baseline and day 85), and treatment by day as fixed factors and subject (nested in treatment) as a random factor. For each biomarker, day 85 vs baseline ratio was estimated for each treatment group and compared between aliskiren- and irbesartan-treated groups.

Correlations between changes from baseline in msSBP or msDBP and baseline BMI were assessed using Spearman's correlation coefficient. All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC, USA).

Results

Patient disposition and baseline characteristics

A total of 141 patients with hypertension and metabolic syndrome were enrolled in the study, and were randomized to monotherapy with aliskiren ($n=75$) or irbesartan ($n=66$). At study end, 63 patients receiving aliskiren monotherapy (84%) and 58 receiving irbesartan (88%) had completed 12 weeks of treatment (Figure 2). Baseline and demographic characteristics were well matched between the two treatment groups (Table 1).

Blood pressure

Least-squares mean reductions from baseline in msSBP and msDBP were significant in both treatment groups at all time points following dose titration on day 14 ($P<0.001$; Figure 3). Patients treated with aliskiren 300 mg had significantly greater BP reductions than patients treated with irbesartan 300 mg on day 57 (13.1/7.7 vs 6.8/4.1 mm Hg, $P=0.006$ and 0.009 for msSBP and msDBP respectively; Figure 3) and end of treatment (day 85; 13.8/7.1 vs 5.8/2.8 mm Hg, $P<0.001$ and 0.001 respectively).

At study end (day 85), 29.2% of patients treated with aliskiren achieved BP control ($<135/85$ mm Hg), a significantly higher proportion than that observed for patients treated with irbesartan (16.7%, $P=0.019$).

No significant correlations were observed between baseline BMI or waist circumference and changes in msSBP or msDBP (from baseline to day 85) for patients treated with either aliskiren or irbesartan (data not shown).

Biomarkers

In patients treated with aliskiren, geometric mean PRA was significantly decreased from baseline by

Table 1 Patient baseline and demographic characteristics

Parameter	*Aliskiren* (n = *75*)	*Irbesartan* (n = *66*)
Age (years)	58.6 ± 8.9	59.2 ± 9.1
Male, *n* (%)	48 (64.0)	43 (65.2)
Race, n *(%)*		
Caucasian	71 (94.7)	65 (98.5)
Other	4 (5.3)	1 (1.5)
Weight (kg)	94.9 ± 16.5	92.3 ± 18.5
BMI (kg m^{-2})	31.3 ± 3.8	31.0 ± 4.8
Waist circumference (cm)	109.6 ± 10.7	107.2 ± 9.5
Elbow breadth (cm)	7.9 ± 1.7	7.8 ± 2.0
msSBP (mm Hg)	155.8 ± 12.1	154.2 ± 13.8
msDBP (mm Hg)	94.1 ± 7.8	91.5 ± 9.9
Sitting pulse rate (b.p.m.)	73.1 ± 10.4	73.6 ± 12.2
Triglycerides (mmol l^{-1})	2.4 ± 1.9	2.2 ± 1.6
Fasting plasma glucose (mmol l^{-1})	5.8 ± 0.6	5.7 ± 0.6

Abbreviations: BMI, body mass index; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure.
Values are presented as mean ± s.d. unless otherwise stated.

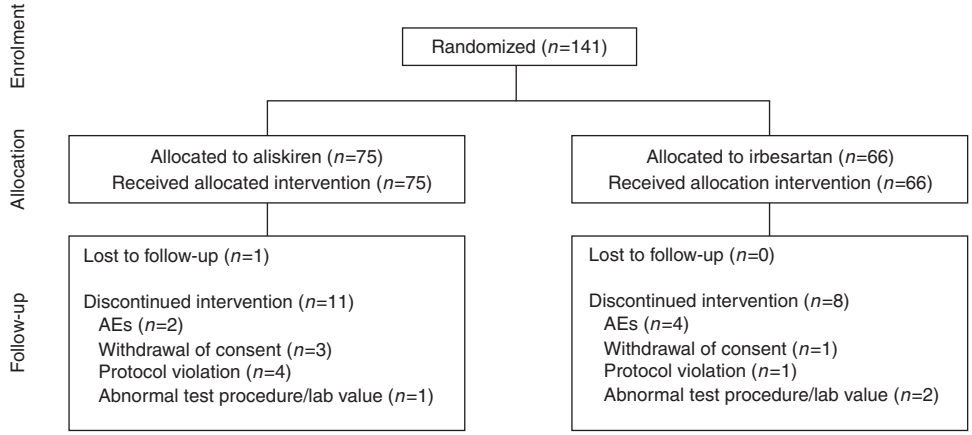

Figure 2 Patient flow diagram. AEs, adverse events.

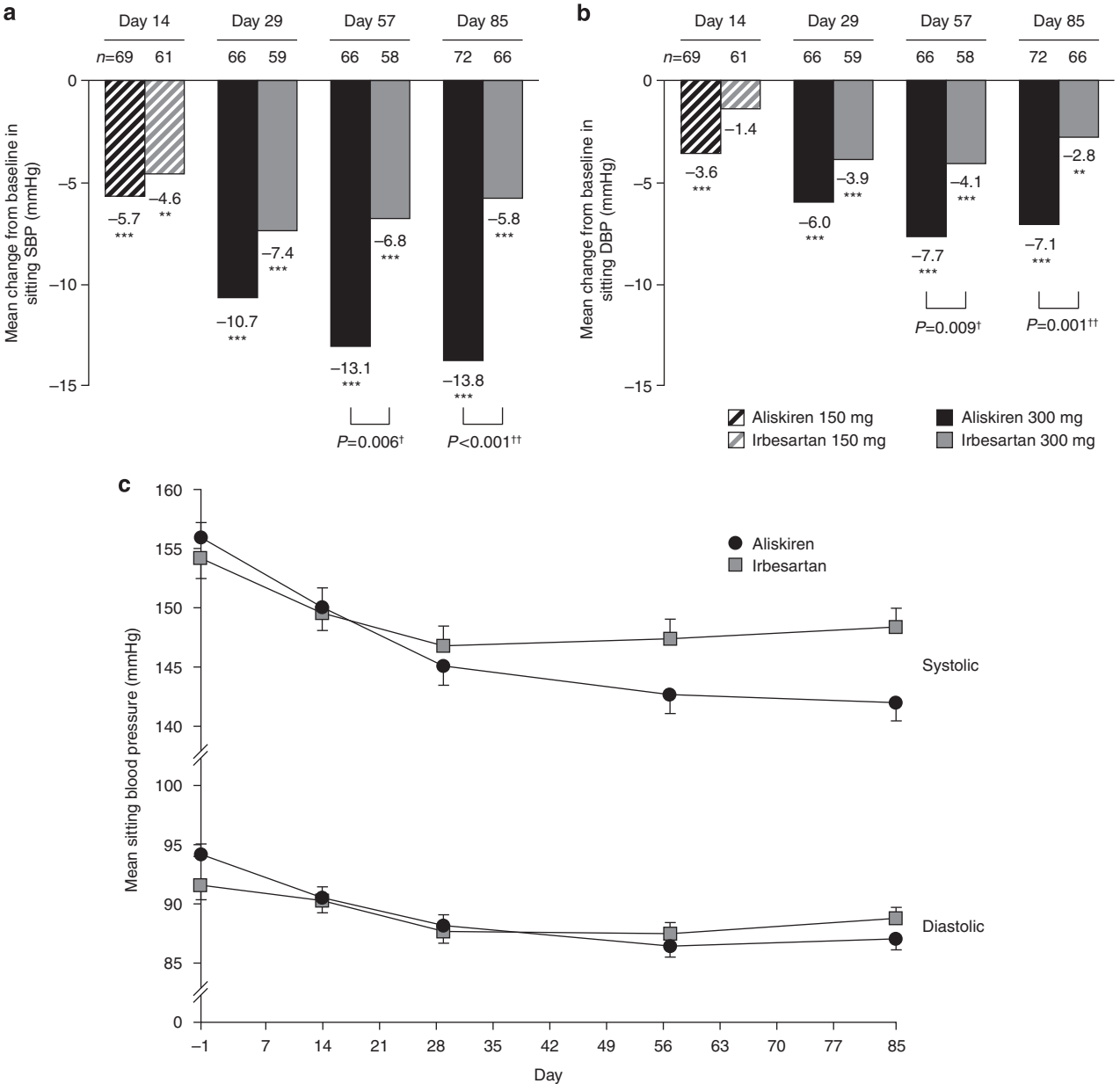

Figure 3 Changes from baseline in mean sitting (**a**) systolic blood pressure and (**b**) diastolic blood pressure and (**c**) absolute mean blood pressure values with aliskiren or irbesartan monotherapy. Within-treatment change from baseline: $^{**}P<0.01$, $^{***}P<0.001$ (**a**, **b**). Between-treatment differences: $^{\dagger}P<0.01$, $^{\dagger\dagger}P\leqslant0.001$ (**a**, **b**). Data are presented as least-squares mean change from baseline (**a**, **b**), and mean ± s.e.m. over time (**c**). DBP, diastolic blood pressure; SBP, systolic blood pressure.

60%, whereas patients treated with irbesartan had their PRA increased by 99% (both $P<0.001$; Table 2). PRC was increased above baseline in both the aliskiren and the irbesartan groups, with a larger increase observed in aliskiren-treated patients (425 vs 157%; $P<0.001$). Small but significant increases in prorenin were observed with aliskiren and irbesartan (both +27%, $P<0.001$ vs baseline).

Changes in biomarkers of inflammation and cardiovascular risk from baseline were generally small and not statistically significant, and were similar in patients receiving aliskiren or irbesartan (Table 2). Small ($\leqslant$30%) although statistically significant changes from baseline in levels of some of the measured plasma biomarkers (endothelin-1, IL-4, IL-12 p40 and IL-13) were observed in patients treated with aliskiren, but not irbesartan, monotherapy. However, the only statistically significant between-treatment difference was observed for the pro-inflammatory marker eotaxin (significant 18% increase with irbesartan vs 1% decrease with aliskiren; $P=0.036$). Levels of the oxidative stress marker F_2 isoprostane were significantly reduced from baseline in both treatment groups ($P=0.029$ and 0.035 for the aliskiren and irbesartan groups

Table 2 Changes in selected biomarkers from baseline and between treatment groups

Parameter	*Aliskiren vs baseline*		*Irbesartan vs baseline*		*Between-treatment comparison* P-*value*
	% change	P-*value*	*% change*	P-*value*	
PRA	−60	<0.001	+99	<0.001	<0.001
PRC	+425	<0.001	+157	<0.001	<0.001
Prorenin	+27	<0.001	+27	<0.001	0.995
Eotaxin	−1	0.925	+18	0.006	0.036
Endothelin-1	−28	0.009	−22	0.073	0.633
F_2 isoprostane	−13	0.029	−13	0.035	0.968
GM–CSF	+25	0.002	+9	0.241	0.183
IL-4	+17	0.017	+6	0.412	0.301
IL-12 p40	+14	0.023	+6	0.354	0.379
IL-13	+18	0.005	+5	0.397	0.196
IL-3	+15	0.022	+8	0.269	0.449
IL-7	+15	0.010	+4	0.525	0.189
Lymphotactin	+20	0.033	0	0.970	0.137
TNF-α	+19	0.007	+3	0.629	0.130
TNF-RII	+8	0.008	+5	0.163	0.417

Abbreviations: GM–CSF, granulocyte macrophage colony-stimulating factor; IL, interleukin; PRA, plasma renin activity; PRC, plasma renin concentration; TNF, tumour necrosis factor.
Only biomarkers showing a significant change from baseline are presented.

Table 3 Safety and tolerability

Category	*Aliskiren* (n = *75*)		*Irbesartan* (n = *66*)	
Adverse events	n (%)		n (%)	
Any adverse event	26 (34.7)		24 (36.4)	
Discontinuations due to adverse events	2 (2.7)		4 (6.1)	
Metabolic parameters	n	*Mean (s.d.)*	n	*Mean (s.d.)*
Fasting plasma glucose (mmol l⁻¹)				
Baseline	75	5.8 (0.6)	66	5.7 (0.6)
Study end	73	5.8 (0.7)	65	5.9 (0.6)
HbA_{1C} (%)				
Baseline	75	5.8 (0.5)	66	5.8 (0.3)
Study end	72	5.9 (0.5)	64	5.8 (0.3)
Total cholesterol (mmol l⁻¹)				
Baseline	75	5.8 (1.0)	66	5.7 (0.9)
Study end	72	5.8 (1.0)	66	5.6 (0.9)
HDL (mmol l⁻¹)				
Baseline	75	1.3 (0.3)	66	1.3 (0.3)
Study end	72	1.3 (0.3)	66	1.3 (0.3)
LDL (mmol l⁻¹)				
Baseline	74	3.7 (0.8)	66	3.6 (0.9)
Study end	72	3.7 (0.8)	65	3.5 (1.0)
Triglycerides (mmol l⁻¹)				
Baseline	75	2.4 (1.9)	66	2.2 (1.6)
Study end	72	2.3 (1.3)	66	2.6 (2.9)

Abbreviations: HbA_{1C}, glycosylated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

respectively; Table 2), with no significant between-treatment difference.

Safety and tolerability

Of the 141 patients who entered the study, 50 (35.5%) experienced adverse events (Table 3), all of which were mild or moderate in intensity. The proportion of patients experiencing adverse events was similar for aliskiren and irbesartan (34.7 vs 36.4% respectively), and there were no serious adverse events or deaths. Headache was the most frequently reported adverse event, and was more common in irbesartan-treated than aliskiren-treated

patients ($n=5$ compared with $n=1$ respectively). Diarrhoea was the only other adverse event that occurred in more than two patients in any treatment group (irbesartan, $n=2$; aliskiren, $n=3$).

No patient in either group showed clinically relevant changes in levels of serum potassium, blood urea nitrogen or serum creatinine at any time point during the study, and there were no clinically relevant changes in electrocardiogram recordings or vital signs. Neither aliskiren nor irbesartan treatment had any notable effect on markers of blood glucose or lipid levels (Table 3).

Discussion

This is the first study to compare the effects of the direct renin inhibitor aliskiren and an ARB in patients with hypertension and metabolic syndrome, and it showed that aliskiren 300 mg was well tolerated and superior to irbesartan 300 mg for both SBP and DBP reduction in this patient group. Patients treated with aliskiren had their PRA markedly reduced, whereas patients treated with irbesartan showed a large reactive rise in PRA. With the exception of PRA and eotaxin, aliskiren or irbesartan treatment were associated with generally similar changes in a predefined panel of biomarkers of inflammation and cardiovascular risk. Neither treatment had any effect on other traits of the metabolic syndrome, in contrast to the adverse effects of β-blockers and diuretics on glucose and lipid metabolism.[23]

Although previous studies have shown that aliskiren is an effective and well-tolerated antihypertensive agent in patients with metabolic syndrome,[18] this is the first study to show that aliskiren is superior to an ARB for lowering BP in this patient group. Patients who were treated with aliskiren showed significantly larger BP reductions (13.8/7.1 vs 5.8/2.8 mm Hg; $P\leqslant 0.001$) and were more likely to achieve BP control ($<135/85$ mm Hg) at day 85 than those treated with irbesartan. The BP reductions reported with aliskiren 300 mg in this study are similar to those observed in a *post hoc* analysis of patients with metabolic syndrome, in which, after 8 weeks of treatment, aliskiren 300 mg monotherapy provided similar ($P>0.2$) BP reductions in patients with (13.4/9.3 mm Hg; $n=827$) and without metabolic syndrome (12.8/8.9 mm Hg; $n=944$); baseline BP (154.0/100.3 mm Hg) in the *post hoc* analysis was similar to baseline BP in the present study.[24] The combination of aliskiren 300 mg and the ARB valsartan 320 mg reduced BP by 17.1/12.4 mm Hg in patients with metabolic syndrome, significantly greater than the reductions observed with either aliskiren 300 mg or valsartan 320 mg monotherapy ($P<0.05$).

The lack of correlation between aliskiren-induced changes in BP and baseline BMI or waist circumference in this study showed that aliskiren lowered BP effectively independent of the presence of obesity. Previous studies in obese patients with hypertension have shown that aliskiren provides highly effective BP reductions as monotherapy[15] or in combination with hydrochlorothiazide.[16,17] Indeed, a study in obese patients with hypertension showed that aliskiren added to hydrochlorothiazide provided higher rates of BP control in patients with grade 3 obesity (BMI $\geqslant 40\,kg\,m^{-2}$) than in patients with less severe obesity; by contrast, the ARB irbesartan was less effective in grade 3 obese patients.[17] Aliskiren-based therapy (with optional addition of amlodipine) has also been shown to provide superior long-term BP reduction to hydrochlorothiazide-based therapy in obese patients with hypertension.[15] Aliskiren may therefore offer treatment benefits compared with ARBs for BP reduction in patients with hypertension and metabolic syndrome or obesity—perhaps because of its distribution to adipose tissue, as adipocytes may contribute to BP elevation in obesity-related hypertension through the generation of Ang II.[5,25] More studies are required to investigate further the effects of aliskiren in patients with hypertension and metabolic disorders.

Biomarkers of RAAS activation showed that direct renin inhibition with aliskiren reduced PRA by 60%, whereas angiotensin receptor blockade with irbesartan increased PRA by 99%. Both treatments were associated with a rise in PRC, which was significantly larger with aliskiren than irbesartan (425 vs 157% increase over baseline levels). These results are similar to a previous study in patients with uncomplicated hypertension, in which aliskiren 150 mg reduced PRA by 69% and increased PRC by 157%, whereas irbesartan 150 mg increased PRA by 109% and PRC by 105%.[26] All RAAS inhibitors increase PRC by interrupting the negative feedback loop by which Ang II normally inhibits renin release from the kidney.[11] It should be noted, however, that at least part of the increase in PRC observed during aliskiren treatment may be the result of an assay artefact related to the ability of aliskiren to bind to and alter the conformation of prorenin, which would then be measured as renin by the standard PRC immunoassay.[27–29] This artefact does not occur with ARBs and might account for some of the observed between-treatment differences in PRC. Levels of prorenin were significantly increased from baseline to a similar extent with both irbesartan and aliskiren treatments, an expected consequence of any chronic stimulus of renin release.[30]

Measurements of a large panel of biomarkers of inflammation and cardiovascular risk showed few statistically significant differences from baseline levels. Only the inflammatory mediator eotaxin[31] showed a statistically significant between-treatment difference, but the clinical significance of this finding is uncertain. Both aliskiren and irbesartan reduced levels of F_2 isoprostane (a marker of oxidative stress) and endothelin-1 (a potent vasoconstrictor). Consistent with these findings, RAAS

inhibition with the ARB losartan has previously been shown to reduce levels of F_2 isoprostanes in patients with type II diabetes and hypertension.[32] However, considering the small magnitude of the changes, large variability in the data and lack of statistically significant between-treatment differences in the present study, it is unlikely that the observed differences are of clinical relevance. It should be noted that a normal range in healthy volunteers has not been established for many of these biomarkers, and so it is unclear to what extent regression to the mean might have explained some of the observed changes from baseline with drug treatment. The limitations in using plasma biomarkers as indicators of effects at the tissue level must also be noted, as the relationship between plasma markers and tissue actions may be complex.[33]

Treatment with either aliskiren or irbesartan monotherapy was well tolerated and not associated with any clinically significant changes in routine blood chemistry and haematologic tests, urinalysis, vital signs or electrocardiogram. The only notable adverse event was headache, which was observed in both treatment groups (more frequently in irbesartan-treated patients). Neither aliskiren nor irbesartan treatment was associated with changes in blood glucose or lipid profiles, a particularly important consideration for the treatment of patients with metabolic syndrome. This property of RAAS inhibitors compares favourably with β-blockers and diuretics, which are known to have potentially harmful effects on glucose and lipid metabolism.[23]

Overall, these results suggest that aliskiren provides effective and significant BP reduction compared with irbesartan in patients with metabolic syndrome, without adverse effects on blood glucose or lipid profile. Aliskiren 300 mg and the ARB irbesartan 300 mg showed generally similar effects on biomarkers of cardiovascular risk and inflammation, although aliskiren provided significant reductions in PRA that were not observed with irbesartan. Aliskiren lowered BP independent of the presence of obesity and provided BP control superior to irbesartan 300 mg.

What is known about this topic

- Approximately one-third of patients with hypertension have metabolic syndrome, a cluster of risk factors that result in increased cardiovascular morbidity and mortality. Chronic activation of the renin–angiotensin–aldosterone system is implicated in many of the key features of metabolic syndrome.
- Despite current treatment approaches, patients with metabolic syndrome still have greater difficulty achieving BP control than those without metabolic syndrome. This reflects the more complex pathophysiology, particularly the involvement of insulin resistance and low-grade inflammation.
- The direct renin inhibitor aliskiren, which is approved for the treatment of hypertension at once-daily doses of 150 and 300 mg, provides effective BP reduction and is generally well tolerated across a broad range of patient groups.

What this study adds

- In patients with hypertension and metabolic syndrome, 12 weeks of aliskiren 300 mg monotherapy provided significantly greater BP reductions than the angiotensin receptor blocker (ARB) irbesartan 300 mg (13.8/7.1 vs 5.8/2.8 respectively); BP control rates were also significantly higher with aliskiren compared with irbesartan.
- Aliskiren and irbesartan had generally similar effects on biomarkers of cardiovascular risk and inflammation, although aliskiren provided significant reductions in plasma renin activity, which were not observed with irbesartan. Both treatments were generally well tolerated; there were no notable effects on blood glucose or lipid profile.
- Direct renin inhibition with aliskiren may therefore offer additional benefits compared with ARB treatment for hypertension in patients with metabolic syndrome.

Conflict of interest

WK has received honoraria from MSD Sharp & Dohme, Takeda, Sanofi, Daiichi Sankyo, and has an advisory board relationship with MSD Sharp & Dohme and a research grant from Bayer Healthcare. MB and IR (Novartis Institutes for Biomedical Research, Basel, Switzerland), C-MY and MFP (Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) and WPD (Novartis Institutes for Biomedical Research Inc., Cambridge, MA, USA) are employees of Novartis and are therefore eligible for Novartis stock and stock options. MH, H-FM and TJ declare no conflicts of interest.

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WK, MB, IR, MF, C-MY and WPD participated in the design of the original study and approval of the final protocol. All authors were involved in the collection, analysis and interpretation of the data, and in the writing of the article, and approved the final version. The authors take full responsibility for the content of the paper but thank Dr Richard White (Oxford PharmaGenesis Ltd) for medical writing support, editorial assistance, and collation and incorporation of comments from all authors. This work was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. A full list of investigators can be found in the Appendix.

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Appendix

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