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Blood pressure and plasma renin activity responses to different strategies to inhibit the renin-angiotensin-aldosterone system during exercise

Bryan Williams[1], Fabio Baschiera[2], Peter S Lacy[1], Jaco Botha[2], Margaret F Prescott[3] and Patrick Brunel[2]

Abstract

Objective: The effect of two different strategies for renin–angiotensin–aldosterone system (RAAS) blockade; direct renin inhibition (DRI) versus angiotensin receptor blockade (ARB) on blood pressure (BP) and plasma renin activity (PRA) was compared during exercise.

Methods: Hypertensive adults were randomised to aliskiren (300 mg once daily, *n*=33) or valsartan (320 mg once daily, *n*=35). BP and PRA were measured during treadmill exercise (Bruce protocol), at baseline, end of treatment (eight weeks), and after treatment withdrawal (48 hours after last dose).

Results: After eight weeks treatment, Aliskiren inhibited PRA (>80%) at rest and during exercise, with inhibition remaining undiminished 48 hours after treatment withdrawal. In contrast, valsartan increased PRA at rest, and more-so during exercise (>400%). Angiotensin receptor blockade, as indicated by PRA increase, was reduced, 48 hours after valsartan treatment withdrawal, suggesting more sustained RAAS blockade with aliskiren. Despite divergent effects on PRA, similar exercise-induced changes in BP were seen. The primary outcome, the rise in systolic BP from rest to peak exercise (baseline to after treatment withdrawal) did not differ between treatments (p=0.25).

Conclusion: Measurement of PRA is a more sensitive index of RAAS blockade than the BP response during exercise. Furthermore, after treatment withdrawal, aliskiren provides more sustained RAAS inhibition than valsartan at rest and during exercise.

Keywords

Aliskiren, valsartan, exercise testing, hypertension, treatment withdrawal, plasma renin activity, antihypertensive therapy

Introduction

Exercise increases blood pressure (BP) and an exaggerated BP response during exercise predicts the development of hypertension in normotensive and pre-hypertensive adult and adolescent subjects.[1–4] In hypertensive patients, the magnitude of increase in systolic BP (SBP) during exercise is an independent predictor of left ventricular hypertrophy, stroke and death.[5–7] Exercise testing is therefore, a potentially valuable tool for identifying people at risk of developing hypertension, as well as target organ damage and poorer outcomes in those with hypertension.

The rise in BP during exercise is in response to the increased demand for blood flow to muscle which is achieved via an increase in cardiac output and redistribution of blood flow via activation of the sympathetic nervous system and renin–angiotensin–aldosterone system (RAAS).[8,9] During physical exertion, increased sympathetic activity stimulates renin release from the kidney and thus increases RAAS activity. In addition, decreased renal perfusion and reduced sodium load in the macula densa may also play a role in stimulating renin release during exercise.[8,9]

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Few studies have been carried out to examine the impact of BP-lowering drugs on exercise-induced changes in both BP and RAAS activity. Demonstrating differences between treatments in the setting of exercise has been difficult, limited often by the poor statistical power.[10–15] Because exercise is a potent stimulus for RAAS activation, we hypothesised that profiling plasma renin activity (PRA) during exercise and in response to different RAAS- blocking strategies would provide insights into the efficiency of RAAS blockade, both at rest and during the stress of exercise.

Currently there are two main strategies to inhibit RAAS: (a) direct renin inhibition (DRI), i.e. aliskiren, which inhibits the active site of renin and reduces PRA,[16,17] or (b) inhibition of RAAS downstream of renin, i.e., via inhibition of angiotensin-converting enzyme (ACE) or angiotensin receptor blockade (ARB). Both of these downstream RAAS inhibiting strategies result in increased PRA and the magnitude of PRA elevation is an index of their efficiency of RAAS inhibition.[18,19] Thus, the present study compared two different strategies for RAAS blockade, DRI versus ARB, under standardised exercise conditions, in patients with mild-to-moderate hypertension. The objective was to compare the BP responses to exercise with the two different RAAS blocking strategies and the impact on PRA.

Methods

Participants

Eligible study participants were men and women aged ≥50 years with mild-to-moderate hypertension (Stage I / Stage II hypertension, i.e., mean sitting systolic BP (msSBP) ≥140 mm Hg and <180 mm Hg, and mean sitting diastolic BP (msDBP) < 110 mmHg, measured at rest). Participants were either hypertension treatment-naïve, or treated with a single BP-lowering drug which could be withdrawn. Participants were required to be able to reach peak exercise capacity (85% of their predicted maximum heart rate; calculated as (220 – age) for men and (210 – age) for women) during a standard treadmill exercise test conducted according to the standard Bruce protocol.

Key exclusion criteria were secondary hypertension; treatment with more than two classes of antihypertensive agent; history of significant cardiovascular or cerebrovascular disease; known Keith–Wagener grade III or IV hypertensive retinopathy; type 1 diabetes; uncontrolled type 2 diabetes defined as not on stable anti-diabetic medication for at least four weeks before screening; and any condition that may alter the absorption, distribution, metabolism or excretion of the study drugs. Women of childbearing potential were required to use effective contraceptive methods; pregnant or nursing women were excluded.

Exercise testing was conducted using a standard Bruce protocol, according to ACC/AHA[20] and ESC guidelines for exercise testing.[21] Participants exercised on a treadmill (Labtech Ltd. EC-12S Stress Test System or Spacelabs CH2000 Stress Test System). The speed and inclination were gradually increased every three minutes until they reached peak exercise capacity, defined as the point at which they reached 85% of their predicted maximum heart rate. The participants' BP and heart rate were monitored throughout the test and 12-lead electrocardiograms were recorded at the end of each stage of the Bruce protocol and assessed as part of the safety evaluations.

Exercise testing could be terminated for a range of factors including the participant's desire to stop the test, significant ECG changes indicating ischaemia or arrhythmia, a fall in SBP of >20 mm Hg; moderate-to-severe chest pain, dyspnoea or dizziness; or a rise in BP (SBP to >250 mm Hg, DBP to >115 mm Hg).

All study participants provided written informed consent before participating in any study procedures. The study was conducted in accordance with ICH Guidelines for Good Clinical Practice and the Declaration of Helsinki, and received approval from the relevant local and central ethical review boards. This trial is registered with ClinicalTrials.gov (Identifier NCT00819767) and EUDRA CT (2008-005500-10).

Study design

This randomised, double-blind, parallel-group study was conducted at nine study centers in four countries (Czech Republic, Hungary, Singapore, the UK). After the initial screening visit, eligible participants entered a two-week washout period during which their existing antihypertensive medications were withdrawn in accordance with the investigators' instructions and the manufacturers' label. Participants then entered the single-blind, placebo run-in period. After 1 week, eligible participants were randomised to study treatments (Figure 1). Those who did not meet the inclusion criteria were re-assessed after a week, and if they still did not meeting the inclusion criteria they were excluded.

As a safety measure, during the washout and placebo run-in period, all participants were instructed to measure their seated BP twice daily (before dosing and approximately 12 hours after dosing) at home with an automated self-measured blood pressure device (A&D UA-767 plus). BP data were automatically uploaded via GSM transmission to a database (Medifacts International, Rockville, Maryland, USA) viewable to study center staff. If predefined levels for self-measured BP were exceeded at any stage during the washout/placebo run-in phase (SBP≥200 mm Hg; DBP≥120 mm Hg), participants were instructed to attend the study centre for confirmation of their elevated BP by a study physician and an automated alert was sent to the investigator and recorded in a database. If upon subsequently attending the study centre, participants' office-measured BP exceeded

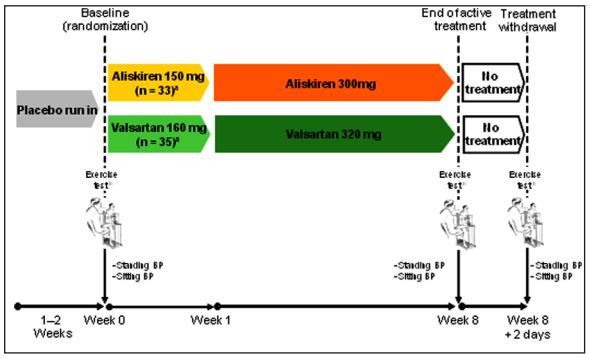

Figure 1. Study design. Participants were randomised to study treatments if they had systolic blood pressure (SBP) ≥140 and <180 mm Hg, diastolic blood pressure (DBP) <110 mm Hg and were able to reach peak exercise capacity (85% of predicted maximum heart rate). All drug doses were administered once daily. BP: blood pressure. [a]Number of randomised participants. [b]Exercise tests were performed according to the standard Bruce protocol to peak exercise capacity (85% of predicted heart rate).

predefined levels for office-measured BP (>180/110 mm Hg), participants were excluded from further participation in the study. No study exclusion decisions were taken on the basis of self-measured BP alone.

After the placebo run-in period (i.e. at baseline), eligible participants underwent a treadmill exercise test (see supplementary material, Figure 1, showing the exercise test procedure) performed according to the standard Bruce protocol. Exercise testing (see above), was also performed at the end of the eight-week active treatment period (before the last dose of medication, Week 8; Figure 1) and 48 hours after the last dose of medication (Week 8+2 days).

Participants were randomly assigned (1:1) to once-daily aliskiren 150 mg or once-daily valsartan 160 mg for one week, followed by forced titration, doubling the initial dose for the next seven weeks (Figure 1). Participants were instructed to take their medication at 08:00 am each day, except on the day of a study visit, when it was to be taken after the completion of study assessments.

Randomisation was generated by Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms. Study participants, study centre staff, people performing the assessments and data analysts remained blinded to treatment from the time of randomisation until after the database lock. A double-dummy design was used to maintain blinding; placebo medication was matched to active aliskiren and valsartan medications.

Study assessments

Blood pressure measurements. Seated BP was measured at screening, washout, randomisation (baseline), after one week and four weeks of treatment, at the end of active treatment (Week 8) and following treatment withdrawal (Week 8+2 days), using a validated mercury sphygmomanometer with the appropriate cuff size. Seated BP was recorded as the mean of three measurements taken 1–2 minutes apart, after the study participant had been sitting for five minutes, after which a single standing BP measurement was taken. Single standing BP measurements were taken throughout the exercise test at baseline, at the end of active treatment and 48 hours after the last dose of study medication. The standing BP measurement (at rest) provided the baseline reference value for assessing the primary end-point of the study because it is only practical to measure BP during treadmill exercise whilst standing. Standing BP was also measured during exercise at the end of each three-minute period, immediately after reaching peak exercise capacity, and then during the recovery period (10, 20, and 30 minutes after peak exercise: see supplementary material, Figure 1 showing the exercise test procedure).

PRA and biomarkers. Blood samples for the measurement of biomarkers (PRA, B-type natriuretic peptide (BNP) and asymmetric dimethyl arginine (ADMA) were taken at rest, at peak exercise and after 30 minutes of recovery during each exercise test at baseline, at the end of active treatment and treatment withdrawal (48 hours after last dosing) (see supplementary material, Figure 1 showing the exercise test procedure). Blood samples were collected into tubes containing EDTA for the measurement of PRA and BNP, and into tubes containing Lithium heparin for the measurement of ADMA. Samples were centrifuged within 10 minutes of collection and plasma was immediately frozen at −20°C for a maximum of four weeks before being shipped to the central lab (Eurofins, Breda, The Netherlands) on dry ice and storage at −70°C prior to analysis. PRA was measured by radioimmunoassay of generated angiotensin I (DiaSorin kit; DiaSorin, Saluggia, Italy). BNP was measured by chemiluminescence immunoassay (Siemens Centaur XP, Malvern, Pennsylvania, USA) and ADMA was measured by HPLC fluorescence.

Safety assessments. All adverse events (AEs) and serious AEs were recorded and assessed for their relationship to study medication. Twelve-lead ECGs were performed at screening and during the exercise test procedures. The ECGs tracings were evaluated locally for safety at the time of the test, and were also assessed at a central laboratory (Medifacts International). Other safety assessments included measurement of vital signs, physical examination, and monitoring of haematology and blood chemistry.

Study objectives

The primary objective was to assess the change in standing SBP from rest to peak exercise, from the pre-treatment baseline, to after treatment withdrawal, comparing aliskiren versus valsartan (Figure 2).

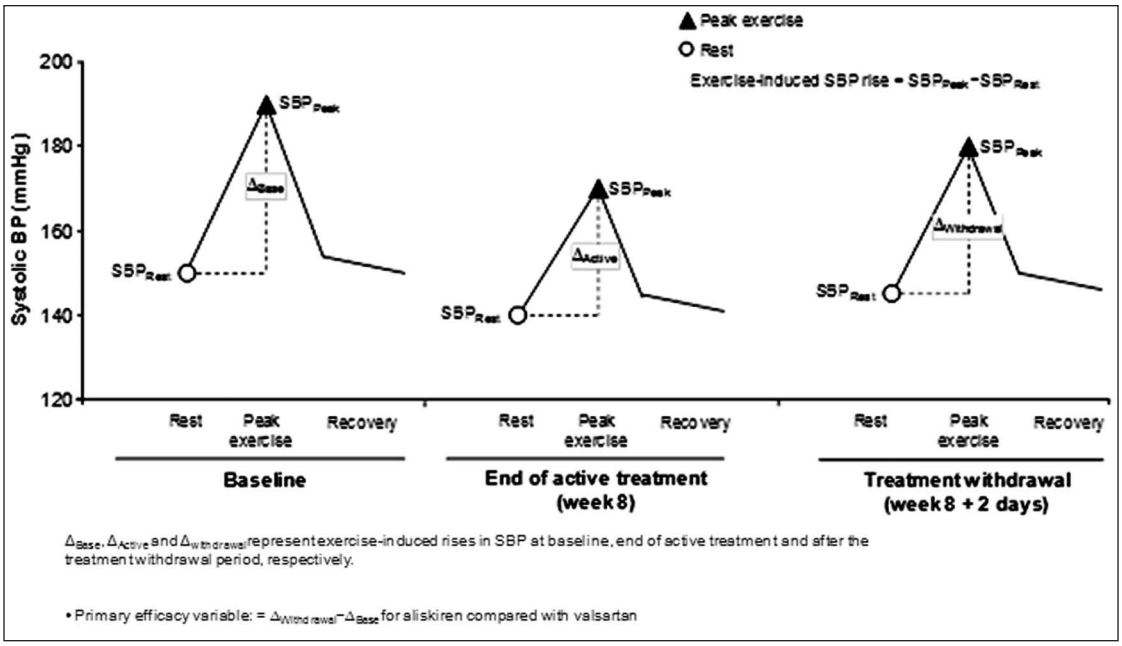

Figure 2. Calculations for the primary endpoint for the change in standing systolic blood pressure (SBP) during exercise testing. Exercise tests were performed according to the standard Bruce protocol. Peak exercise capacity was achieved when 85% of predicted mean maximum heart rate was reached. Maximum predicted heart rate was calculated as 220 – age for men and 210 – age for women.

Secondary objectives included assessment of:

1. RAAS activity, i.e. PRA, cardiac wall stress during exercise, BNP and vasodilatation during the post-exercise recovery period, ADMA. Blood samples were taken for these measurements during the treadmill test (rest, peak exercise and recovery) at baseline, the end of active treatment and following treatment withdrawal.
2. The change in SBP from rest to peak exercise, from the end of active treatment to after treatment withdrawal, for aliskiren compared with valsartan.
3. Standing SBP during the treadmill exercise test at each of the main stages of the Bruce protocol (rest, peak exercise and recovery) comparing (a) baseline to end of active treatment, (b) baseline to after treatment withdrawal and (c) end of active treatment to after treatment withdrawal.
4. Safety and tolerability of study treatments.

Statistical analyses

With regard to the primary end-point, i.e. BP changes, this was, by necessity a pilot study to assess the effects of two different RAAS blocking strategies, i.e. aliskiren versus valsartan during exercise. Estimating the number of participants required to undertake this comparison was difficult due to the limited number of prior studies which were generally small in scale and descriptive rather than direct comparisons of treatment strategies. One of the objectives of the present study was to acquire data on the impact of these treatments during exercise to provide the basis for power calculations for future studies of this kind. A sample size of 30 randomised participants per treatment arm was targeted, assuming a drop-out rate of 20%, a two-sided 95% confidence interval (CI) for the difference of two means would extend by ±7.4 mm Hg from the observed difference in means (assuming that the common standard deviation (SD) is 13.0 mm Hg and that the confidence interval is based on the large sample *z* statistic).

The primary efficacy variable was the change from baseline in the peak exercise-induced rise in standing SBP ($SBP_{Peak} - SBP_{Rest}$) after treatment withdrawal (i.e. $\Delta_{Withdrawal} - \Delta_{Base}$) (Figure 2). Secondary efficacy measures included the changes in the exercise-induced rise in SBP from baseline to end of active treatment ($\Delta_{Active} - \Delta_{Base}$) and from the end of active treatment to after treatment withdrawal ($\Delta_{Withdrawal} - \Delta_{Active}$) (Figure 2). Between-treatment differences for all three variables were assessed by a two-way analysis of covariance model with treatment and center as factors, and rise in SBP from rest to peak exercise at baseline (Δ_{Base}) as a covariate. In addition, changes in sitting BP and standing BP at rest were evaluated between baseline, the end of active treatment and after treatment withdrawal.

Data for PRA, BNP and ADMA are presented as geometric means with SD or 95% CI. Biomarker data are

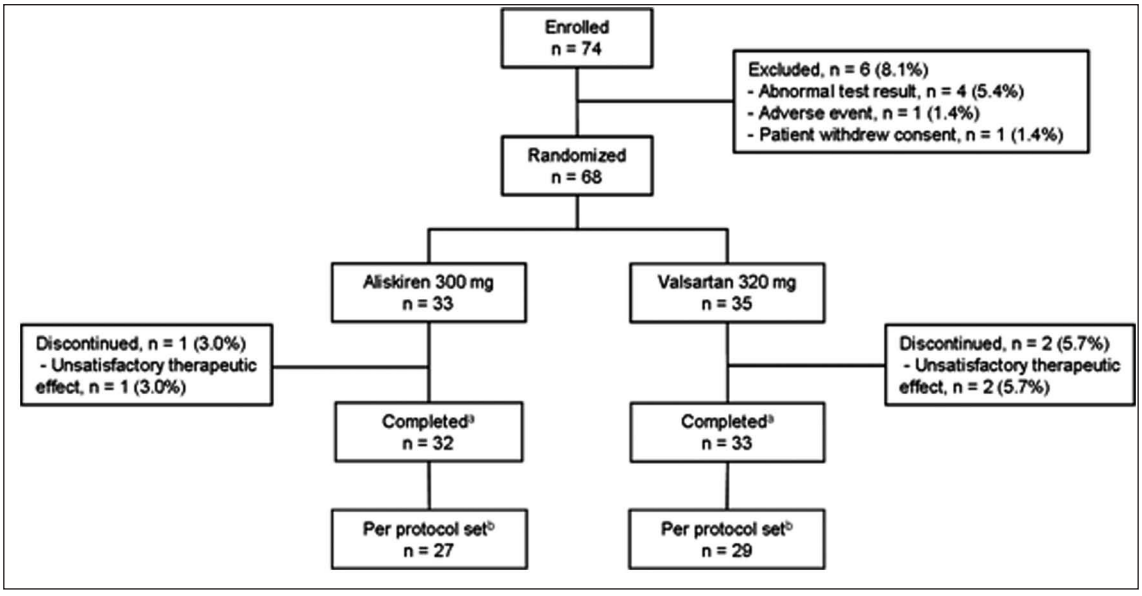

Figure 3. Patient flow diagram.
[a]Includes all patients who were randomised to study treatments and completed the double-blind period. [b]Includes all participants who were randomised to study treatments and completed the double-blind treatment period without any major protocol deviations. protocol deviations were identified by the study monitors. These were usually identified after the event. The study was analysed by intent to treat and therefore all data from participants who completed the study was included in the analysis of exercise testing.

presented for the sensitivity analysis, excluding values from one study site that did not handle blood samples as instructed. Changes from baseline to the end of active treatment and to following treatment withdrawal (for each stage of the exercise test) are shown as ratios of the geometric means at that time point to those at baseline. Comparison between PRA values used unpaired student's *t*-tests.

Efficacy analyses were performed on the full analysis set (defined as all randomised participants), except for the primary efficacy variable, which was performed on the exercise-evaluable set (all participants for whom the treadmill test values for SBP at peak were available at baseline and after treatment withdrawal). All participants who received at least one dose of double-blind study medication were included in the safety analyses (safety set). Baseline data are presented for randomised participants (all participants who received a randomisation number, irrespective of whether they received study medication). All analyses were performed using SAS® version 8.2 or higher (SAS Institute, Inc., Cary, North Carolina, USA).

Results

Participant characteristics

In total, 68 people were randomised to aliskiren (n=33) or valsartan (n=35). Of these, 32 people in the aliskiren group and 33 in the valsartan group completed the study (Figure 3). The three study discontinuations were due to inadequate therapeutic effect as determined by the study physician.

Patient demographics at baseline were broadly similar between the treatment groups (Table 1), although there were more men in the valsartan group versus the aliskiren group (77.1% vs 57.6%). The mean age of participants was 59 years, and most were male (67.6%) and almost all Caucasian (95.6%).

Blood pressure changes during exercise

At baseline, mean standing SBP at rest was 152.7 mm Hg in the aliskiren group and 149.3 mm Hg in the valsartan group. Resting standing SBP values in both treatment groups were lower at the end of active treatment and after treatment withdrawal compared with baseline (end of active treatment, resting standing SBP; aliskiren 137.1±11.8 mm Hg, valsartan 133.8±13.1 mm Hg: after treatment withdrawal, resting standing SBP aliskiren 136.3±12.6 mm Hg, valsartan 135.0±12.9 mm Hg, Figure 4). Resting values for seated blood pressure were also reduced relative to baseline values at the end of active treatment and after treatment withdrawal (see supplementary material, Table 2 showing changes in mean seated BP during the study).

During exercise a similar pattern of BP change was observed with both treatments. The mean standing SBP increased by approximately 40–50 mm Hg at peak exercise and returned to resting levels after approximately 10 minutes of recovery, with a further decrease in BP to below

Table 1. Patient demographics and baseline characteristics.

	Aliskiren 300 mg (*n*=33)	Valsartan 320 mg (*n*=35)
Age, years	58.1±6.3	59.8±8.3
≥65 years, *n* (%)	4 (12.1)	8 (22.9)
Sex, *n* (%)		
Male	19 (57.6)	27 (77.1)
Female	14 (42.4)	8 (22.9)
Race, *n* (%)		
Caucasian	32 (97.0)	33 (94.3)
Asian	1 (3.0)	2 (5.7)
Diabetes, *n* (%)	1 (3.0)	4 (11.4)
BMI, kg/m^2	28.3±2.8	28.3±3.0
Obesity,[a] *n* (%)	8 (24.2)	10 (28.6)
Duration of hypertension,[b] years	8.3±9.1	8.5±8.5
Mean BP at rest, mm Hg		
Standing SBP	152.7±11.5	149.3±11.6
Standing DBP	94.1±7.6	94.1±7.3
Sitting SBP	152.8±9.4	150.3±9.4
Sitting DBP	94.0±7.0	92.5±7.2

BMI: body mass index; BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure. Data are for the randomised set. Values are presented as mean±standard deviation unless otherwise stated. [a]BMI≥30 kg/m^2. [b]Aliskiren, *n*=32; valsartan, *n*=33.

pre-exercise levels during the remainder of the recovery period (Figure 4). At the pre-treatment baseline, participants in the valsartan group had a lower mean standing SBP at rest and a higher mean peak standing SBP than those in the aliskiren group (Baseline: valsartan rest SBP 149.3±11.6 mm Hg, peak SBP 199.6±23.0; aliskiren rest SBP 152.7±11.5, peak SBP 189.7±25.1 mm Hg, Figure 4). Exercise-induced rises in standing SBP at the end of active treatment (Δ_{Active}) were similar with aliskiren (+49.1 mm Hg) and valsartan (+53.8 mm Hg) (Figure 4). The difference between treatments with regard to least-squares mean (LSM) change in exercise-induced rise in standing SBP from baseline to the end of active treatment ($\Delta_{Active} - \Delta_{Base}$) was not statistically significantly (–2.0 mm Hg; $p = 0.654$) (Table 2).

The primary outcome of the study was the mean rise in standing SBP from rest to peak exercise SBP, comparing baseline with data 48 hours after treatment withdrawal (see Figure 2). Participants receiving aliskiren had a mean rise in standing SBP from rest to peak exercise, after treatment withdrawal (48 hours after last dose of study medication; $\Delta_{Withdrawal}$) of 44.9±3.32 mm Hg compared with an increase of 53.2±3.58 mm Hg for valsartan. Thus, the change in LSM exercise-induced standing SBP rise after treatment withdrawal compared with baseline ($\Delta_{Withdrawal} - \Delta_{Base}$; the primary efficacy measure) did not differ between treatments (Figure 4 and Table 2).

When comparing the LSM change in the exercise-induced rises in SBP after treatment withdrawal with those at the end of active treatment ($\Delta_{Withdrawal} - \Delta_{Active}$), similar findings were observed (Table 2). The changes in standing DBP during exercise testing followed a similar pattern (Table 2).

Plasma renin activity

At rest, baseline PRA levels were similar in the aliskiren and valsartan groups (geometric means 0.90 vs 1.10 ng/mL/h; Figure 4 and see supplementary material, Table 3 showing plasma renin activity during the study). Exercise increased PRA compared with rest in both treatment groups ($p<0.05$). Aliskiren significantly reduced PRA from baseline by at least 80% at all exercise time points after eight weeks of treatment ($p<0.001$). Moreover, these reductions in PRA activity at rest and during exercise were sustained 48 hours after treatment withdrawal (Figure 4). In contrast, valsartan markedly and significantly increased PRA both at rest (versus pre-treatment values by 286.1%, $p<0.001$) and during exercise when PRA was 436.9% above pre-treatment values ($p<0.001$), and 194% above resting values on treatment ($p<0.001$). After valsartan treatment withdrawal, resting PRA values were still higher than pre-treatment resting values but 45% lower than resting on treatment values ($p<0.001$). Similarly, the peak PRA during exercise after valsartan treatment withdrawal was 57% of the exercise peak PRA value on treatment with valsartan ($p<0.01$, Figure 4 and see supplementary material, Table 3, showing plasma renin activity during the study).

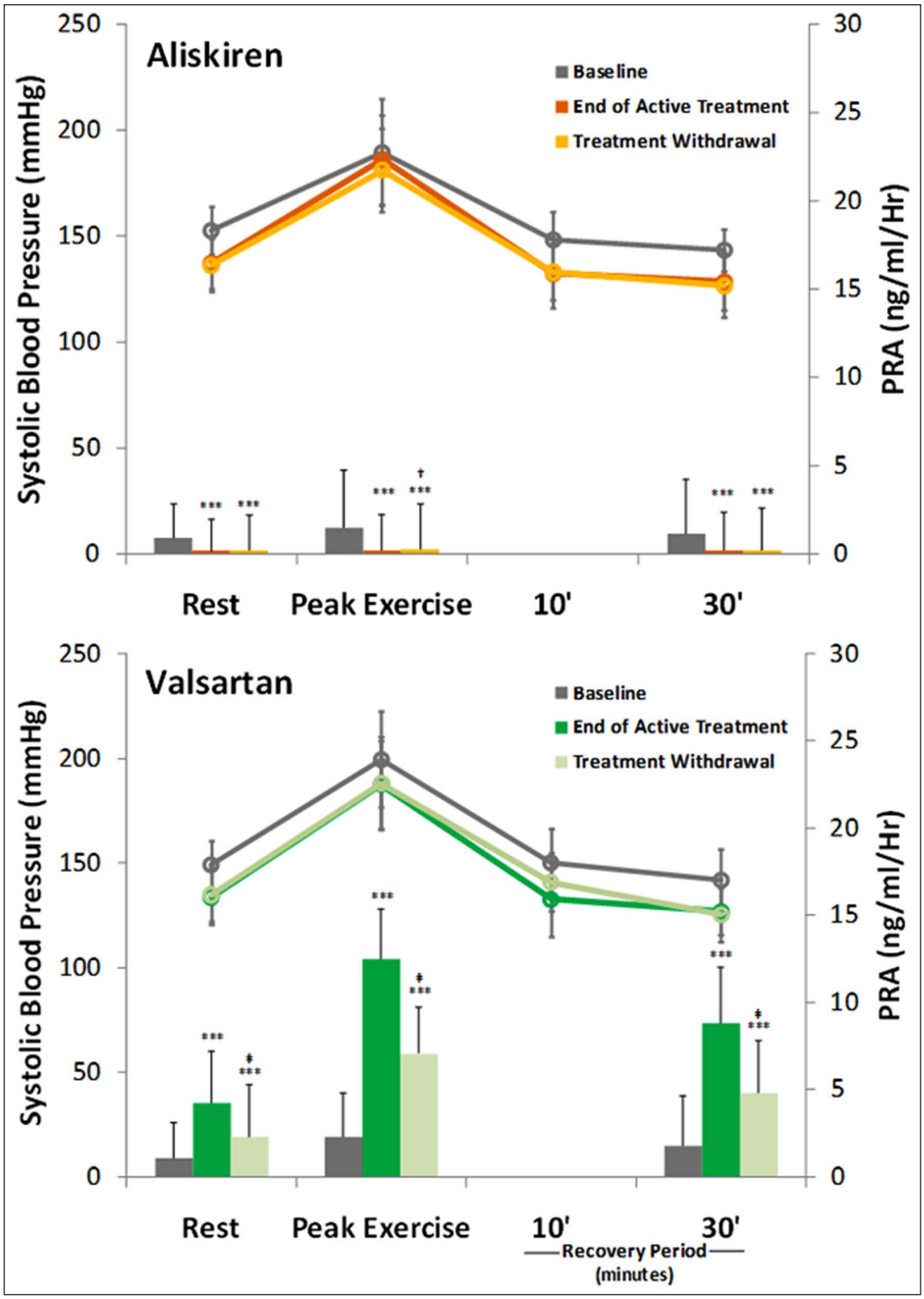

Figure 4. Influence of aliskiren (upper panel) or valsartan (lower panel) on systolic blood pressure (SBP) (lines) and plasma renin activity (bars) during exercise testing at baseline, after eight weeks treatment and following treatment withdrawal. Data are shown as mean±standard deviation (SD) for standing SBP, geometric mean+SD for plasma renin activity (PRA) for the full analysis set. End of active treatment was at Week 8; treatment withdrawal was at Week 8+2 days. Exercise tests were performed according to the standard Bruce protocol. Peak exercise was achieved when 85% of predicted maximum heart rate was reached.
***$p<0.0001$ vs baseline PRA value at each exercise stage. †$p<0.05$ treatment withdrawal vs end of active treatment PRA at each exercise stage. ‡$p<0.01$ treatment withdrawal vs end of active treatment PRA at each exercise stage.

Table 2. Changes in exercise-induced rises in standing blood pressure (BP) between baseline, the end of active treatment and after treatment withdrawal in the aliskiren and valsartan groups.

Assessment	LSM change from baseline±SEM (mm Hg)		LSM difference (mm Hg)[a]	95% CI	*p* value
	Aliskiren 300 mg (*n*=32)	Valsartan 320 mg (*n*=33)			
Systolic BP					
Changes in exercise-induced rises from baseline, mm Hg					
End of active treatment[b] ($\Delta_{Active} - \Delta_{Base}$)	5.8±3.2	7.8±3.2	–2.0	–10.9, 6.9	0.654
After treatment withdrawal[c] ($\Delta_{Withdrawal} - \Delta_{Base}$)	2.6±3.5	8.3±3.5	–5.7	–15.5, 4.1	0.248
Changes in exercise-induced rises from the end of active treatment					
After treatment withdrawal[b] ($\Delta_{Withdrawal} - \Delta_{Active}$)	–4.2±3.3	1.4±3.2	–5.5	–14.3, 3.2	0.211
Diastolic BP					
Changes in exercise-induced rises from baseline, mm Hg					
End of active treatment[b] ($\Delta_{Active} - \Delta_{Base}$)	2.7±1.7	5.7±1.6	–3.0	–7.5, 1.6	0.193
After treatment withdrawal[b] ($\Delta_{Withdrawal} - \Delta_{Base}$)	–0.4±1.6	1.8±1.5	–2.2	–6.5, 2.0	0.299
Changes in exercise-induced rises from the end of active treatment, mm Hg					
After treatment withdrawal[b] ($\Delta_{Withdrawal} - \Delta_{Active}$)	–6.5±1.8	–4.1±1.6	–2.4	–6.9, 2.2	0.304

BP: blood pressure; CI: confidence interval; LSM: least-squares mean; SEM: standard error of the mean. Δ_{Base}, Δ_{Active} and $\Delta_{Withdrawal}$ represent exercise-induced rises in standing BP at baseline, end of active treatment and after treatment withdrawal, respectively (see Figure 2 for explanation). [a]LSM change for aliskiren minus LSM change for valsartan, [b]data are presented for the full analysis set, [c]data are presented for the exercise-evaluable set.

BNP and ADMA

Pre-treatment BNP concentrations at rest were lower in those allocated to treatment with aliskiren (geometric mean 16.0 pg/mL (95% CI, 11.8, 21.7); *n*=25) versus those allocated to treatment with valsartan (geometric mean 23.8 pg/mL (95% CI, 16.2, 35.0); *n*=27).

Pre-treatment ADMA concentrations (geometric mean (95% CI)) were 0.38 µmol/L (0.33, 0.44) and 0.41 µmol/L (0.36, 0.47) in the aliskiren and valsartan groups, respectively.

There were no significant changes in BNP or ADMA levels with either treatment at the end of active treatment, at rest or during exercise testing (see supplementary material, Table 4 showing BNP and ADMA activity during the study).

Safety and tolerability

Overall, four participants (12.1%) allocated to aliskiren treatment and five participants (14.3%) allocated to valsartan treatment experienced an AE during double-blind treatment. No patient discontinued the study because of an AE. The most common AEs were hypertension, headache and bronchitis (see supplementary material, Table 5 showing safety and tolerability data for study treatments). All AEs were mild in severity and none was considered by the investigator to be related to study medication. None of the participants reported any exercise-related AEs during the treadmill exercise tests. There were no deaths, serious AEs, or pre-specified laboratory abnormalities (for serum potassium, serum creatinine or blood urea nitrogen).

Discussion

The main findings of this study are that both aliskiren (300 mg once daily) and valsartan (320 mg once daily) provided similar reductions in BP at rest and similar blunting of the rise in BP during exercise, in people with mild-to-moderate hypertension. The study also provides an unequivocal illustration of the markedly different PRA profiles with these two different RAAS blocking strategies and illustrates that aliskiren markedly inhibited PRA at rest and prevented the exercise-induced rise in PRA both during active treatment and for at least 48 hours after treatment withdrawal. This uniquely shows that aliskiren (300 mg once daily) maintains its inhibition of RAAS in humans during the stress of exercise and that this effect is prolonged well beyond treatment cessation. The use of exercise as a potent stimulus for PRA has helped confirm the sustainability of PRA inhibition. These findings are consistent with the sustained BP-lowering and PRA suppression effect seen with aliskiren

in previous treatment withdrawal studies in patients with hypertension.[22,23]

In contrast, valsartan treatment, as expected, resulted in activation of PRA at rest, which was markedly accentuated during exercise. After valsartan treatment withdrawal, PRA remained elevated versus pre-treatment values but the magnitude of elevation was reduced by approximately one-half versus the corresponding PRA levels at rest or peak exercise. Because PRA responds to the magnitude of angiotensin receptor blockade,[18,19] this novel PRA data suggests that although some blockade of the angiotensin receptor is still evident 48 hours after the last dose of valsartan, it is reduced by almost one-half.

Of interest, there were no meaningful changes in other biomarkers, i.e. BNP or ADMA, as a result of exercise or either antihypertensive treatment.

It is noteworthy that the dose of valsartan used in these studies, i.e. 320 mg once daily is significantly higher than the dose typically used to treat hypertension in clinical practice, which is mainly 160 mg once daily This suggests that higher dose ARBs are required to achieve equivalence to aliskiren 300 mg once daily in terms of BP lowering at rest and during exercise.

The use of exercise to provoke activation of RAAS and the use of PRA as an index of RAAS suppression with treatment provides important data about the potential utility of exercise studies to interrogate the completeness and longevity of RAAS inhibition with different treatment strategies. The effects of exercise on PRA were rapid and substantial. Moreover, PRA remains elevated during recovery from exercise, an effect which is particularly noticeable when treated with an ARB (Figure 4). The mechanisms for the exercise-related rise in PRA have not been fully elucidated but are likely to involve an acute reduction in glomerular filtration rate[8] and sympathetic nervous system activation.[24–26] Previous studies in normotensive people have reported increases in plasma catecholamine levels during exercise[8,24–26] accompanied by a marked increase in PRA and Ang II levels.[8,24–26] Moreover, in these studies, the Ang II levels at peak exercise were increased to a greater extent in individuals with an exaggerated BP response, suggesting that Ang II may play an important role in the BP response to exercise. Other studies have also suggested a potential role for aldosterone.[25] The magnitude of the PRA response to exercise in our study is consistent with those reported in these prior smaller studies.[24,26]

Despite the different effects of aliskiren and valsartan on PRA both at rest and during exercise, there were no significant differences between treatments with regard to BP lowering. Similarly, previous exercise studies in patients with hypertension have shown that the ACE inhibitor fosinopril attenuates the exercise-induced rises in BP, despite increasing PRA.[11,27] The present study extends these observations, providing novel data regarding the effects of aliskiren.

Importantly, RAAS blockade is not sufficient to eliminate the exercise-induced rise in BP, supporting the notion that other factors, especially activation of the SNS and changes in cardiac output, allied to variation in arterial stiffness, play a key role in determining the exercise-related rise in BP.

The final question raised by these studies is whether the divergent effects on PRA of different treatment strategies to inhibit the RAAS has any adverse consequences beyond the impact on blood pressure. This is an important question because of the markedly divergent PRA response when comparing the DRI with ACE-inhibition in previous studies or ARBs in this study. Some prior studies have suggested that elevated PRA may be associated with adverse cardiovascular outcomes.[28–32] However, it remains unclear whether the observed effects in these studies were simply associated with the PRA level or driven by elevated PRA. Ongoing morbidity and mortality studies comparing the DRI aliskiren with other RAAS blocking strategies will hopefully answer this important question.[33,34]

Limitations of the present study

Undertaking complex exercise physiological studies, with repeated testing, is a formidable challenge. This is underscored by the fact that so few studies of this kind have been reported. This was an exploratory study and was ultimately underpowered to detect significant differences in BP between treatments. However, the study does provide important information about the magnitude of BP responses to exercise and the expected standard deviations in response that will assist in the design of future studies of this kind. Based on the findings of this pilot study, assuming 85% power and common SD of 19 mm Hg and a treatment difference for peak vs rest of 5 mm Hg, a sample size of 522 evaluable participants would have achieved a significant difference in the primary end-point. It is unlikely that such complex studies on that scale will ever be undertaken.

Conclusion

In conclusion, the DRI aliskiren (300 mg once daily) produced similar BP reductions as the ARB (valsartan 320 mg once daily) at rest and during exercise in patients with mild-to-moderate hypertension. This was despite the fact that the two different treatment strategies produced markedly different PRA responses to exercise. The pathophysiological significance, if any, of the divergent effects of these two different treatment strategies on PRA, particularly notable during exercise, will be revealed by ongoing morbidity/mortality trials, the results of which are eagerly awaited.

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Conflict of interest

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