Suppression of aldosterone mediates regression of left ventricular hypertrophy in patients with hypertension

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Suppression of aldosterone mediates regression of left ventricular hypertrophy in patients with hypertension

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Abstract

Background: High circulating aldosterone levels stimulate myocardial fibrosis and left ventricular hypertrophy (LVH). However, it is not clear whether suppression of aldosterone directly contributes to LVH regression in hypertensive patients.

Methods: The Aliskiren in Left Ventricular Hypertrophy (ALLAY) trial randomised 465 hypertensive overweight subjects with LVH to the direct renin inhibitor aliskiren 300 mg, losartan 100 mg or the combination and followed patients for 9 months. All patients were treated to standard blood pressure targets. Left ventricular (LV) mass index (LVMI) and LV wall thickness (LVWT) were assessed by cardiac magnetic resonance. A subset of 136 patients who had plasma aldosterone concentration (ALDO) measured at baseline and study end was analysed.

Results: At baseline, plasma ALDO was modestly related to systolic blood pressure, LVMI, and wall thickness (all, $p < 0.05$). Aliskiren, either alone or in combination, was associated with a significantly greater reduction from baseline to 9 months in plasma aldosterone than losartan alone ($p < 0.02$). Reduction in ALDO was related to reduction in LVMI even after adjustment for baseline ALDO, BP reduction and treatment group (p for trend = 0.042).

Conclusion: In hypertensive patients with increased LVWT, aliskiren alone or in combination with the angiotensin receptor blocker losartan provides greater reduction in aldosterone compared to losartan alone. Moreover, suppression of aldosterone was associated with reduction of LVH, independently of the change in SBP, suggesting that suppression of aldosterone, a known mediator of LVH, may be particularly important for LVH regression and as a target for therapy.

Keywords

Aldosterone, hypertension, left ventricular hypertrophy

Introduction

Left ventricular hypertrophy (LVH) is the most frequent cardiac complication of arterial hypertension[1] and has been shown to be attributable to not only pressure overload but also to humoral factors such as angiotensin II and aldosterone.[2–4] Aldosterone plays an essential role in salt–water balance and elevation of arterial pressure by acting on epithelial mineralocorticoid receptors. Increasing evidence suggests that aldosterone may be a unique trigger for myocardial fibrosis and LVH, independently of blood pressure.[4–8] Several studies have demonstrated correlations between aldosterone level and increased left ventricular mass in hypertensive patients,[9–14] in healthy populations[15] as well as in patients with aldosterone-producing tumours.[16]

Reversal of LVH is an important goal of antihypertensive therapy since LVH is a well-known cardiovascular risk factor associated with increased incidence of heart failure, myocardial infarction and sudden cardiac death.[1,17–21] However, all antihypertensive agents are not equally effective at reducing LVH.[22,23] Interruption of the renin–angiotensin–aldosterone system (RAAS) with angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blocker (ARBs) has been extensively explored as therapeutic strategies to treat arterial hypertension and reduce LVH. Yet, ACE inhibitors and ARBs only transiently suppress

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aldosterone production[24–27] and the beneficial effects of these traditional RAAS inhibitors may be attenuated by 'aldosterone escape'.

We utilised data from the Aliskiren in Left Ventricular Hypertrophy (ALLAY) Trial[28] to assess the effects of the direct renin inhibitor aliskiren alone or in combination with the angiotensin receptor blocker losartan, on circulating aldosterone and plasma renin activity in overweight hypertensive patients with LVH, as compared with losartan alone, and to evaluate the relationship between changes in aldosterone levels and LVH regression.

Methods

Patient population

The ALLAY trial randomised 465 overweight subjects (body mass index ≥ 25 kg/m^2) with hypertension and LV hypertrophy to the direct renin inhibitor aliskiren 300 mg, losartan 100 mg or the combination and followed patients for 9 months. LVH was defined as an increased anterior LV wall thickness (≥ 13mm) at screening echocardiogram. The details of the patient population and the protocol, including inclusion and exclusion criteria, have been reported previously.[28] All patients were treated to standard blood pressure targets with add-on therapy (excluding renin–angiotensin system antagonists or beta-blockers) as directed by protocol. LV mass index (LVMI) and LV wall thickness (LVWT) were assessed by cardiac magnetic resonance (CMR) at baseline and 36 weeks. Only patients who were treated for at least 28 weeks and had both CMR measures were included in the efficacy population. CMR examinations were performed with an electrocardiogram (ECG)-gated, breath-hold, two-dimensional, steady-state free precession cine sequence. A contiguous LV short-axis stack of images was acquired from above the base of the LV to below the apex of the LV with a slice thickness of 10 mm (no interslice gap), spatial resolution of 2.0_2.0 mm, field of view of 32 cm, and a temporal resolution of 50 ms. LVM was measured at a central CMR core laboratory by manual planimetry of the endocardial and epicardial LV borders and then summing of the product of the area of each slice at end diastole by the slice thickness and myocardial density (QMASS MR version 6.16; Medis Inc, Leiden, the Netherlands), as previously described.[28] A subset of patients with plasma aldosterone concentration measured at baseline and study end was analysed.

Neurohormone measurements

Plasma aldosterone and plasma renin activity (PRA) were analysed in a subset of 136 patients on an outpatient basis. Evaluation included an early morning (typically 8 a.m. to 9 a.m.) phlebotomy performed following 20 min of rest in a supine position. Specimens were stored at −20°C for a maximum of 4 weeks at the clinical sites, and then shipped on dry ice to the central laboratory (Clinical Research Laboratories, Lenexa, KS, USA) for storage at −80 deg C. The central laboratory measured the following biomarkers using plasma samples: plasma renin activity (PRA) using RIA kits from DiaSorin (Minneapolis, MN, USA), and aldosterone using RIA Coat-a-Count kits from Siemens (Tarrytown, NY, USA)

Table 1. Baseline demographic and clinical characteristics

Characteristic	ALDO group (n = 136)	Non-ALDO group (n = 324)	p value
Age (years)	58.3 ± 9.4	59.0 ± 10.8	0.53
Male (%)	111 (81%)	237 (73%)	0.06
White (%)	136 (100%)	297 (92%)	0.007
Diabetes (%)	36 (26%)	75 (23%)	0.45
Current smoker (%)	23 (17%)	58 (18%)	0.79
BMI (kg/m^2)	30.3 ± 3.9	31.4 ± 4.2	0.013
eGFR (ml/min/1.73 m^2)	86.6 ± 16.4	84.5 ± 17.6	0.23
SBP (mmHg)	143.7 ± 12.5	146.0 ± 14.2	0.09
DBP (mmHg)	89.6 ± 9.3	88.6 ± 9.5	0.33
LVMI (g/m^2)	75.6 ± 15.9	79.7 ± 17.4	0.019
LVAWT (mm)	13.2 ± 2.4	13.9 ± 2.3	0.005
LVIWT (mm)	9.8 ± 2.2	9.7 ± 2.1	0.69

Data are expressed as mean ± standard deviation, n (%).
BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LVAWT, left ventricular antero-septal wall thickness, LVIWT, left ventricular infero-lateral wall thickness; LVMI, left ventricular mass index; SBP, systolic blood pressure.

Statistical analysis

Baseline data are presented in the entire group; other analyses were performed in the efficacy population. Continuous variables were expressed as mean ± SD and were compared with Student's t-test. Categorical variables were compared using the Chi-square test. Given that baseline and follow-up plasma aldosterone and PRA measurements were not normally distributed, we applied a log-transformation, calculated mean and corresponding 95% confidence intervals and transformed them back to original scale. We thus reported geometric means with 95% confidence interval. Eight patients have very low aldosterone concentrations that are identical; this is because of the lower limit of the aldosterone assay. Spearman's rank correlation coefficient was used to test the relationship between continuous variables at baseline or their differences between baseline and follow-up. We used the paired t-test for all the comparisons between the baseline value and week 36. We assessed the effect of treatment on changes in aldosterone and PRA with an ANCOVA model adjusting for baseline values, ACEI or ARB use and country, as previously described.[28] We categorised the patients in quartiles according to the percentage of reduction in aldosterone concentration from baseline

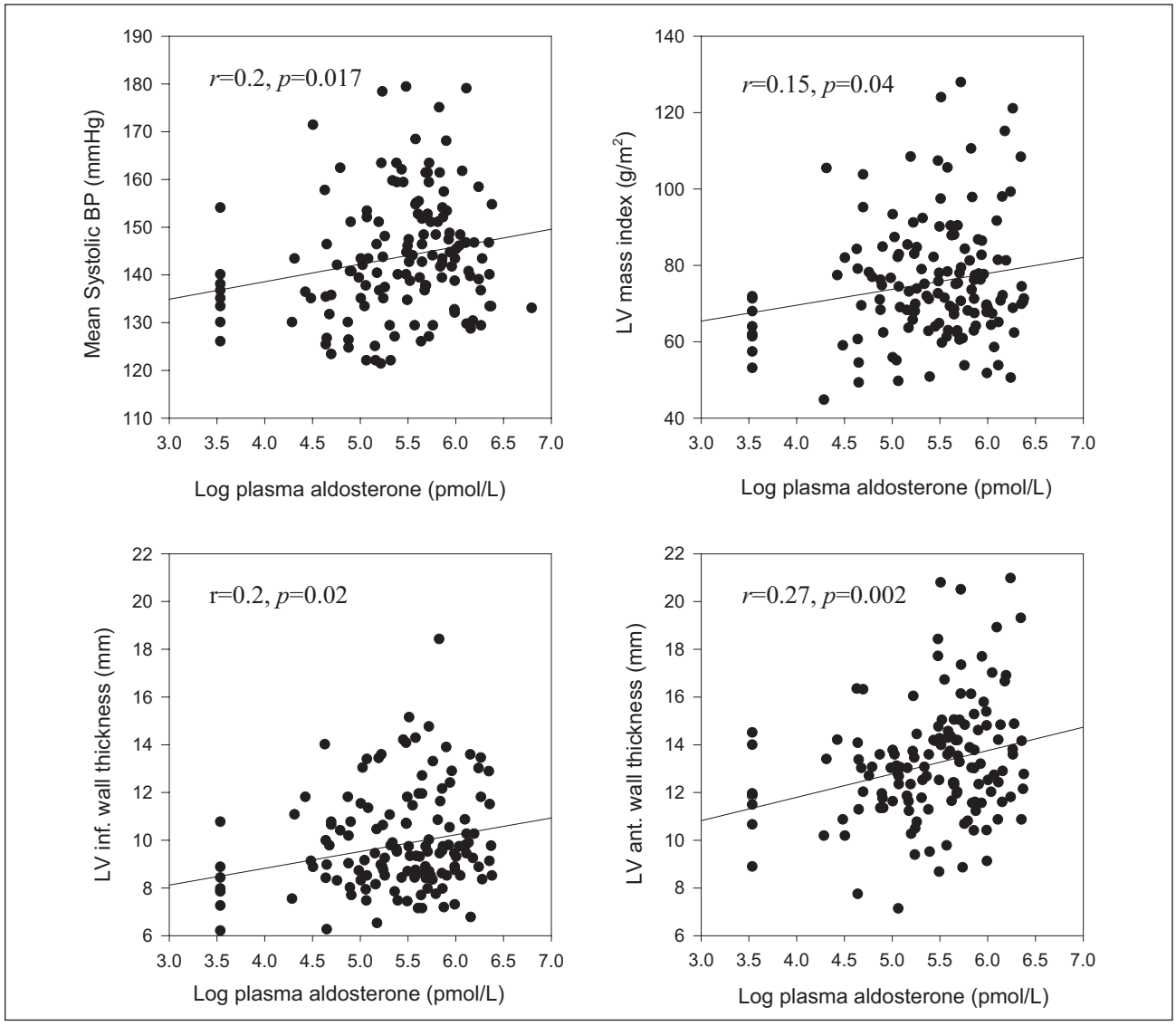

Figure 1. Relationship between plasma aldosterone and systolic BP, LV mass index, infero-lateral and antero-septal LV wall thickness at baseline.

and applied a trend test across the ordered group. We used percentage of change of variables to reduce a potential regression to the mean effect. We looked at potential factors associated with the reduction in LVMI in univariate analysis. The adjusted model included baseline aldosterone, change in systolic blood pressure, and treatment. A more fully adjusted model was repeated by adding variables from the univariate analysis. A p-value (two-sided) < 0.05 was considered statistically significant. All statistical analyses were performed using STATA 10.1 (Stata Corporation, College Station, TX, USA).

Results

Patients who had aldosterone measurements performed during the study were comparable to the other patients in the trial with respect to age, gender, history of diabetes, smoking status, estimated glomerular filtration rate (eGFR), systolic and diastolic blood pressure, and infero-lateral LVWT (Table 1). However, patients from this cohort had lower body mass index, LV mass index, and antero-septal LVWT, and there were more white patients in this group. At baseline, plasma aldosterone concentrations were modestly related to SBP ($r = 0.2$, $p = 0.017$), LVMI ($r = 0.15$, $p = 0.04$), inferior ($r = 0.20$, $p = 0.02$) and anterior LVWT ($r = 0.27$, $p = 0.002$) (Figure 1). The correlation between aldosterone and LVMI did not persist after adjustment for baseline systolic blood pressure ($p = 0.12$), but remained significant for inferior ($p = 0.024$) and anterior ($p = 0.006$) LVWT.

Aliskiren alone ($p = 0.018$) or in combination with losartan ($p = 0.0011$) was associated with a significantly greater reduction in plasma aldosterone than losartan alone (Figure 2a). PRA was significantly reduced in the aliskiren

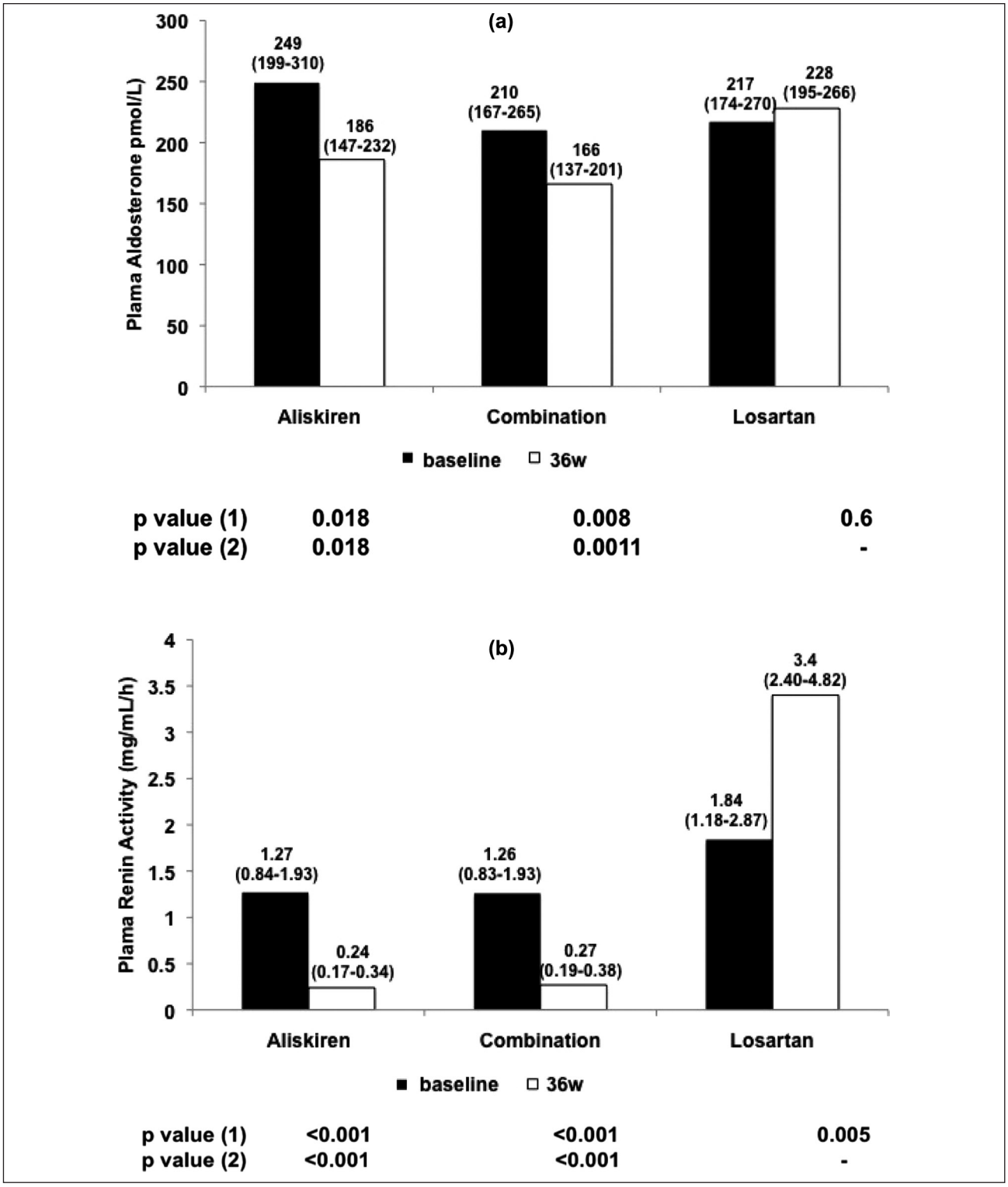

Figure 2. (a) Changes in plasma aldosterone from baseline to study-end in the aliskiren, aliskiren and losartan combination and losartan groups. (b) Changes in PRA from baseline to study-end in the aliskiren, aliskiren and losartan combination and losartan groups. In both (a) and (b), *p* value (1) is the comparison between baseline and week 36 (paired *t*-test). *p* value (2) is the comparison of change from baseline between losartan and aliskiren, and losartan and combination (ANCOVA model adjusted for baseline biomarker, ACE inhibitor or ARB use and country). Data are expressed as geometric means (95% CI).

Table 2. Demographic and clinical characteristics of patients by quartiles of change in aldosterone (%) from baseline to study-end

Characteristic	Aldosterone change (%) in quartiles				*p* trend
	< −10%	−10 to −3%	−3 to +5%	> +5%	
Age (years)	58.1 ± 8.4	58.4 ± 9.9	57.5 ± 8.6	59.2 ± 10.8	0.64
Male (*n*)	30	29	27	25	0.059
Diabetes (*n*)	13	5	10	8	0.50
Current smoker (*n*)	29	30	27	27	0.50
BMI (kg/m^2)	30.6 ± 4.5	31.1 ± 3.9	30.5 ± 3.9	29.1 ± 2.7	0.18
Aliskiren	15	8	7	12	0.23
Combination	13	14	15	6	0.17
Losartan	6	12	12	16	0.012
Baseline aldosterone (pmol/l)	333 (283–393)	315 (278–358)	181 (136–243)	126 (97–164)	<0.0001
Baseline SBP (mmHg)	145.1 ± 12.6	145.1 ± 12.6	140.3 ± 10.0	144.3 ± 14.4	0.53
Baseline DBP (mmHg)	89.3 ± 8.3	89.3 ± 10.7	88.4 ± 8.4	91.3 ± 9.8	0.54
Baseline LVMI (g/m^2)	78.9 ± 15.7	77.9 ± 16.3	73.0 ± 14.6	72.7 ± 16.4	0.003
Baseline LVIWT (mm)	10.5 ± 2.7	9.9 ± 2.1	9.8 ± 1.9	9.0 ± 2.0	0.007
Baseline LVAWT (mm)	13.8 ± 2.7	13.4 ± 2.6	13.4 ± 2.1	12.4 ± 2.2	0.017
% Reduction SBP	−6.0 ± 9.1	−3.8 ± 12.5	−0.3 ± 10.4	−6.0 ± 10.9	0.75
% Reduction LVMI	−10.8 ± 11.8	−7.1 ± 12.7	−6.5 ± 9.3	−5.0 ± 15.9	0.044
% Reduction LVIWT	−17.6 ± 17.1	−10.4 ± 16.9	−6.7 ± 17.7	−5.8 ± 22.5	0.005
% Reduction LVAWT	−10.8 ± 21.3	−8.3 ± 17.3	−8.5 ± 16.6	−8.3 ± 20.0	0.73

n = 34 in all quartiles.

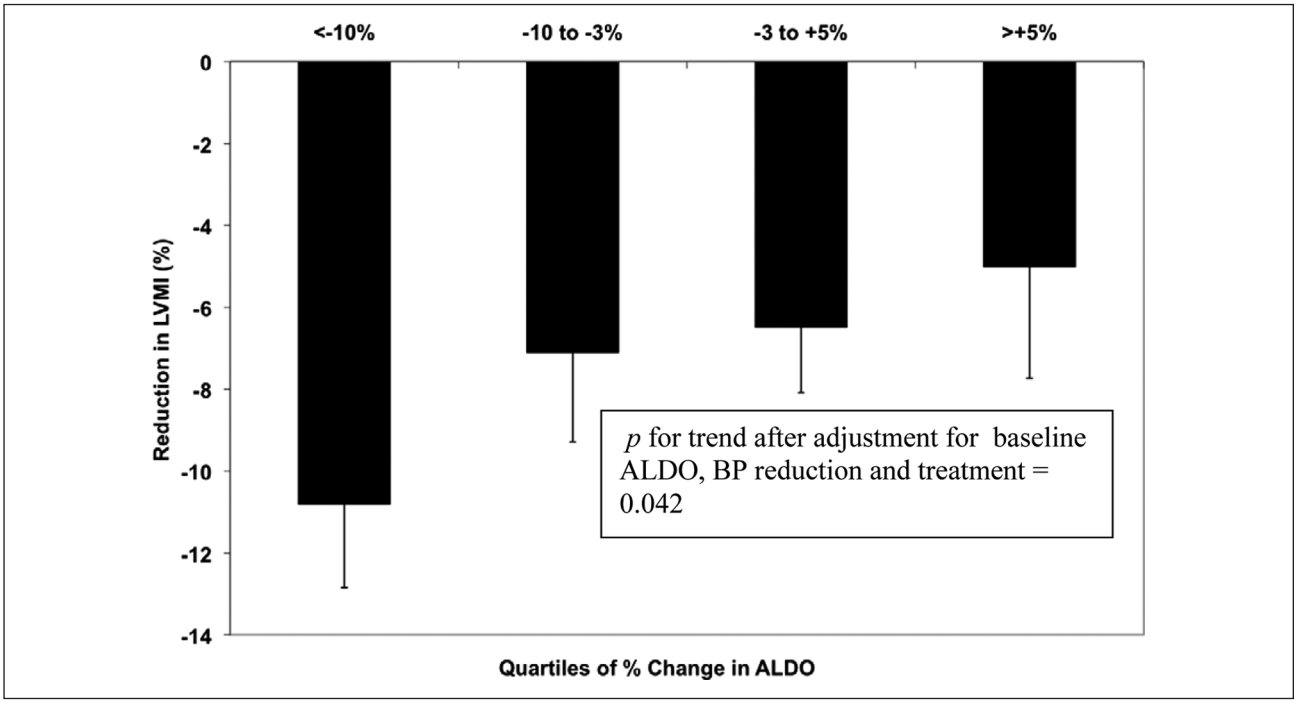

Figure 3. Relationship between change in LV mass index and change in aldosterone.

($p < 0.001$) and the combination groups ($p < 0.001$) compared to losartan alone (Figure 2b). Reduction in aldosterone was also related to reduction in PRA ($r = 0.4$, $p < 0.0001$).

In patients with measured aldosterone values, we observed a significant decrease in SBP (143.6 ± 12.7 vs. 137.1 ± 12.4 mmHg; delta, −6.5 ± 15.5 mmHg; $p < 0.0001$), LVMI (75.3 ± 14.7 vs. 68.3 ± 11.7 g/m^2; delta, −7.0 ± 10.6 g/m^2; $p < 0.0001$) as well as in infero-lateral (9.8 ± 2.1 vs. 8.6 ± 1.6 mm; delta, −1.2 ± 2.0 mm; $p < 0.0001$) and anteroseptal (13.2 ± 2.3 vs. 11.8 ± 2.4 mm; delta, −1.4 ± 2.7mm; $p < 0.0001$) LVWT from baseline to study end. The magnitude of the reduction in LVMI was comparable across the three treatment groups (respectively, −5.7 ± 10.6 g/m^2, −5.4 ± 10.8 g/m^2, −7.9 ± 9.6 g/m^2 for aliskiren, losartan and the combination of both, $p > 0.05$ in a ANCOVA model adjusting for treatment, prior use of ARB/ACEI therapy, country and baseline LVMI as in the main ALLAY study).

Patients were comparable across the four quartiles in percentage of aldosterone reduction from baseline with respect to demographic and clinical characteristics such as age, gender, diabetes, smoker status, body mass index, systolic and diastolic blood pressure but there was a trend for aldosterone, LVMI and LWT to be higher at baseline in the patients who experienced greater aldosterone reduction during the trial (Table 2). In univariate analysis, diabetes ($p = 0.043$), change in SBP ($p = 0.005$), baseline LVMI ($p < 0.001$), previous use of ACE inhibitors or ARBs ($p = 0.011$) and change in aldosterone ($p = 0.04$) were associated with the percent change in LVMI. We observed a linear trend towards greater reduction in LV mass (per cent change from baseline) with the greatest reduction in aldosterone (Figure 3) even adjusting for baseline aldosterone, BP reduction and treatment group ($p = 0.042$). This remains true after adjusting for baseline aldosterone, BP reduction, treatment group, baseline LVMI, diabetes, smoking status and previous use of ACE inhibitors or ARBs (p for trend 0.043). The percentage of reduction in aldosterone was modestly related to the percentage of reduction in infero-lateral LVWT ($r = 0.22$, $p = 0.015$) when assessed continuously (data not shown).

Discussion

We observed that aliskiren alone or in combination with the angiotensin receptor blocker losartan was associated with greater reduction in plasma aldosterone compared to losartan alone in overweight hypertensive patients. We further found that reduction of aldosterone concentration was associated with regression of LVMI and inferolateral LVWT, independently of the change in SBP and treatment.

Although inhibition of the RAAS is an effective approach to reduce blood pressure and LVH, a considerable proportion of patients remain relatively resistant to therapy. Indeed, ACE inhibitors and ARB only transiently suppress aldosterone production. The inability of traditional RAAS blockers to induce a sustained suppression of aldosterone, a phenomenon termed aldosterone escape, attenuates these benefits.[26,29] Our findings suggest that RAAS blockade with a direct renin inhibition may provide greater aldosterone reduction than a haemodynamically similar dose of an ARB, with a similar control of blood pressure, and may provide further reduction in aldosterone in combination with an ARB. These findings are consistent with the numerically, though not statistically, greater reduction in LV mass in patients receiving combination therapy in ALLAY.[28]

Our results also suggest that suppression of aldosterone may be an important mediator of LVH regression. While arterial blood pressure is traditionally thought of as the principal mechanism related to the development of LVH, longitudinal studies suggest that an elevation of cardiac mass may precede the onset of hypertension.[30,31] Furthermore, discrepancies between the level of arterial pressure and the degree of LVH have been shown in hypertensive populations.[19,32,33] Indeed, aldosterone concentration, even within a normal range, has been associated with myocardial fibrosis and LVH, independently of blood pressure, in both experimental models[5–8] and clinical studies.[9,16,34] The Effects of Eplerenone, Enalapril, and Eplerenone/Enalapril in Patients with Hypertension and LVH (4E) trial[35] reported a poor correlation between reduction in BP and reduction in LV mass and the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE)[36] study showed that reduction in LV mass by angiotensin II blockade was independent of blood pressure reduction. These studies indicate that inhibition of RAAS had added benefit beyond blood pressure control. However, we can not consider this in a cause–effect fashion but rather as an association. Our results offer a potential mechanistic explanation and could be considered as hypothesis generating, highlighting the need for further studies.

We can only speculate why the LVMI and infero-lateral LVWT appeared to be better correlated with the aldosterone effects than the anterior LVWT. As LVMI integrates multiple slices of the LV, this variable is less prone to random noise. Still, given the complex geometrical structure of the LV walls, we cannot rule out from our data that the interplay between aldosterone effects and blood pressure effects could vary across various regions of the ventricle.

Some limitations of our study should be noted. Aldosterone measurements in plasma were planned to be performed only in a subset of patients. Urinary aldosterone from a 24-h collection, which reflects aldosterone load over the last day, was not available. Several patients had aldosterone level at the lower detection limit of the assay. Potential selection bias must be noted since all patients were overweight and had an increased anterior LV wall thickness at baseline. Our study is limited to patients with a relatively limited range of LVMI (anterior LVWT ≥ 13 mm at baseline). Finally, our data only provided information at two time points: baseline and study end.

In summary, in overweight hypertensive patients with increased LVWT, aliskiren alone or in combination with losartan provides a greater reduction in plasma aldosterone compared to losartan alone. Moreover, suppression of aldosterone was associated with reduction of LVH independently of the change in SBP, suggesting that aldosterone, a known mediator of LVH, may be a particularly important target for therapy.

Clinical trial registration information

Unique identifier: NCT 00219141.

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Conflict of interest

Drs Solomon, Applebaum and Dahlöf have received research support from Novartis. Drs Solomon and Dahlöf have consulted for Novartis. Drs Prescott and Lukashevich and BA Smith are employees of Novartis. All other authors have nothing to declare.

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