Effect of the Direct Renin Inhibitor Aliskiren, the Angiotensin Receptor Blocker Losartan, or Both on Left Ventricular Mass in Patients With Hypertension and Left Ventricular Hypertrophy

Scott D. Solomon, MD; Evan Appelbaum, MD; Warren J. Manning, MD; Anil Verma, MD; Tommy Berglund, MD; Valentina Lukashevich, MD; Cheraz Cherif Papst, MS; Beverly A. Smith, RN; Björn Dahlöf, MD, PhD; for the Aliskiren in Left Ventricular Hypertrophy (ALLAY) Trial Investigators

Background—Left ventricular (LV) hypertrophy, a marker of cardiac end-organ damage, is associated with an increased risk of cardiovascular morbidity and mortality. Inhibitors of the renin-angiotensin-aldosterone system may reduce LV mass to a greater extent than other antihypertensive agents. We compared the effect of aliskiren, the first orally active direct renin inhibitor, the angiotensin-receptor blocker losartan, and their combination on the reduction of LV mass in hypertensive patients.

Methods and Results—We randomized 465 patients with hypertension, increased ventricular wall thickness, and body mass index >25 kg/m^2 to receive aliskiren 300 mg, losartan 100 mg, or their combination daily for 9 months. Patients were treated to standard blood pressure targets with add-on therapy, excluding other inhibitors of the renin-angiotensin-aldosterone system and β-blockers. Patients underwent cardiovascular magnetic resonance imaging for assessment of LV mass at baseline and at study completion. The primary objective was to compare change in LV mass index from baseline to follow-up in the combination and losartan arms; the secondary objective was to determine whether aliskiren was noninferior to losartan in reducing LV mass index from baseline to follow-up. Systolic and diastolic blood pressures were reduced similarly in all treatment groups (6.5±14.9/3.8±10.1 mm Hg in the aliskiren group; 5.5±15.6/3.7±10.7 mm Hg in the losartan group; 6.6±16.6/4.6±10.5 mm Hg in the combination arm; $P<0.0001$ within groups, $P=0.81$ between groups). LV mass index was reduced significantly from baseline in all treatment groups (4.9-, 4.8-, and 5.8 g/m^2 reductions in the aliskiren, losartan, and combination arms, respectively; $P<0.0001$ for all treatment groups). The reduction in LV mass index in the combination group was not significantly different from that with losartan alone ($P=0.52$). Aliskiren was as effective as losartan in reducing LV mass index ($P<0.0001$ for noninferiority). Safety and tolerability were similar across all treatment groups.

Conclusions—Aliskiren was as effective as losartan in promoting LV mass regression. Reduction in LV mass with the combination of aliskiren plus losartan was not significantly different from that with losartan monotherapy, independent of blood pressure lowering. These findings suggest that aliskiren was as effective as an angiotensin receptor blocker in attenuating this measure of myocardial end-organ damage in hypertensive patients with LV hypertrophy. **(*Circulation*. 2009;119:530-537.)**

Key Words: angiotensin ■ hypertension ■ hypertrophy ■ magnetic resonance imaging ■ renin

Left ventricular (LV) hypertrophy (LVH), a marker of cardiac end-organ damage, is present in at least 30% of patients with hypertension[1,2] and is associated with an increased risk of cardiovascular morbidity and mortality.[3–5] LVH is second only to age in predictive power for cardiovascular events.[6] Reduction of LVH has been associated with a lower incidence of cardiovascular events in hypertensive patients.[7,8] Despite current approaches to blood pressure (BP) management, a substantial number of patients with hypertension and LVH remain at risk for cardiovascular morbidity and mortality.

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From the Brigham and Women's Hospital, Boston, Mass (S.D.S., A.V.); Beth Israel Deaconess Medical Center, Boston, Mass (E.A., W.J.M.); Sahlgrenska University Hospital/Östra, Göteborg, Sweden (T.B., B.D.); Novartis Pharmaceuticals Corporation, East Hanover, NJ (V.L., B.A.S.); and Novartis Pharma AG, Basel, Switzerland (C.C.-P.).

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Correspondence to S.D. Solomon, MD, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115. E-mail ssolomon@rics.bwh.harvard.edu

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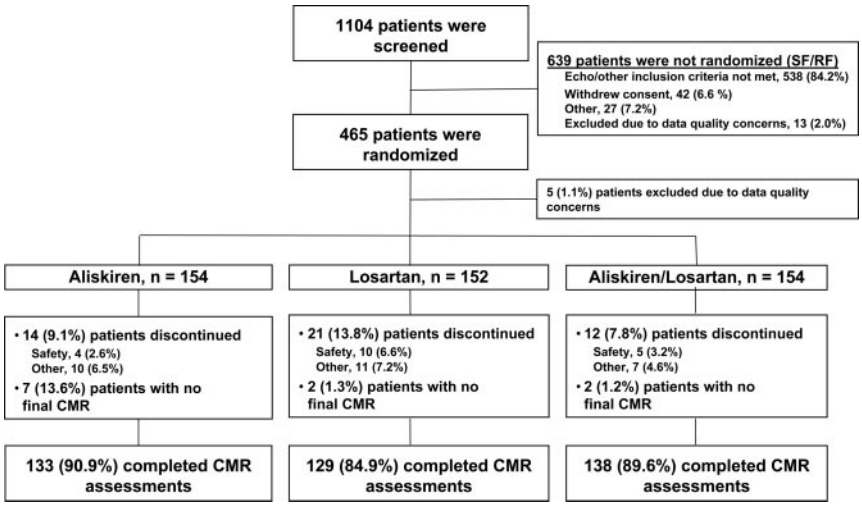

Figure 1. Consort diagram.

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Inhibition of the renin-angiotensin-aldosterone system (RAAS) with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) has been shown to be at least as effective as, and possibly more effective than, other antihypertensive strategies in reducing LVH.[9,10] Aliskiren, the first orally active direct renin inhibitor, represents a novel approach to RAAS suppression by directly inhibiting the system at the rate-limiting proximal step.[11,12] Aliskiren provides BP lowering similar to other inhibitors of the RAAS[13] and additional BP lowering on top of standard therapy in patients already taking ARBs.[14]

The Aliskiren in Left Ventricular Hypertrophy (ALLAY) study was designed to assess primarily whether the combination of aliskiren and losartan was superior to losartan alone in reducing LV mass (LVM) index (LVMI), secondarily whether aliskiren was noninferior to losartan in reducing LVMI, and finally whether aliskiren, alone or in combination with losartan, was safe and well tolerated in patients with hypertension.

Methods

Patients

We studied patients with a history of or newly diagnosed hypertension with systolic BP/diastolic BP ≥140/90 mm Hg but <180/110 mm Hg who had a confirmed LV wall thickness in any wall by a screening echocardiogram of ≥13 mm and a body mass index (BMI) of >25 kg/m^2. We excluded patients with an LV ejection fraction of <40%; those who required continued treatment with an ACEI or ARB; patients treated at entry with an ACEI or ARB who did not complete the 3-month washout period; patients with severe BP elevation, serum creatinine >1.7 mg/dL in men and 1.5 mg/dL in women, serum potassium ≥5.2 mEq/L at visit 1, or severe obesity (BMI ≥42 kg/m^2); patients with pacemakers, implantable cardioverter-defibrillators, or defibrillators; and patients who had a history of myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, transient ischemic attack, or stroke within 6 months of study entry.

ALLAY was conducted in 77 centers across 8 countries. We screened 1104 patients, of whom 639 were not eligible for randomization on the basis of exclusion and inclusion criteria (Figure 1). Of the 465 patients randomized, 5 were excluded from analysis because of data quality concerns, leaving 154, 152, and 154 patients in the aliskiren, losartan, and combination groups, respectively. Of these, 133, 129, and 138, respectively, completed at least 28 weeks of the study and underwent the final cardiovascular magnetic resonance imaging (CMR) evaluation.

Screening echocardiograms were performed at visit 1 according to a standard protocol, and 2-dimensional or M-mode images from the parasternal long axis or short axis were sent to a core laboratory for measurement (A.V.). Patients with LV wall thickness (in any wall) >13 mm, confirmed by the echocardiography core laboratory, were deemed eligible for inclusion.

Patients not on an ACEI or ARB entered a 2-week screening period to complete eligibility evaluations and continued their current antihypertensive medications until randomization. Patients on ACEI or ARB discontinued their current ACEI or ARB but continued with their other current antihypertensive medications during a 3-month washout period. Additional non–RAAS-blocking agents could be prescribed to control BP during the washout phase.

Eligible patients discontinued their current antihypertensive medication at randomization and were randomized into 1 of 3 treatment groups: aliskiren 150 mg, losartan 50 mg, or the combination of aliskiren 150 mg and losartan 50 mg (Figure 2). Randomization numbers were generated with a validated interactive voice response system that automated the random assignment of patient numbers to randomization numbers in an unbiased fashion and concealed randomization codes from patients and investigator staff. Patients, investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment from the time of randomization until database lock using the following methods: Randomization data were kept strictly confidential until the time of unblinding and were not accessible by anyone else involved in the study except the authorized persons, and the identity of the treatments was concealed by the use of study drugs that were identical in packaging, labeling, schedule of administration, and appearance. A double-dummy design was used because the identity of the study drugs could not be disguised as a result of their different forms. Randomization was stratified according to whether a patient was taking an ACEI or ARB within 3 months of visit 1 or at the time of study entry.

BP was assessed for safety within 1 week of randomization. Diuretics could have been added at that point if necessary. After 2 weeks of treatment, all patients were force-titrated to receive aliskiren 300 mg, losartan 100 mg, or their combination for the remaining 34 weeks of the study. For patients not at BP goal (<140/90 mm Hg for nondiabetics, <130/80 mm Hg for diabetics), additional antihypertensive medications, including diuretics, calcium channel blockers, α-blockers, and vasodilators, could be added at any time during the double-blind phase. Patients were not allowed to receive other RAAS inhibitors or β-blockers, which are known to inhibit renin secretion.[15]

BP was measured at each visit with a calibrated standard sphygmomanometer and the appropriate cuff size. The mean of 3 sitting

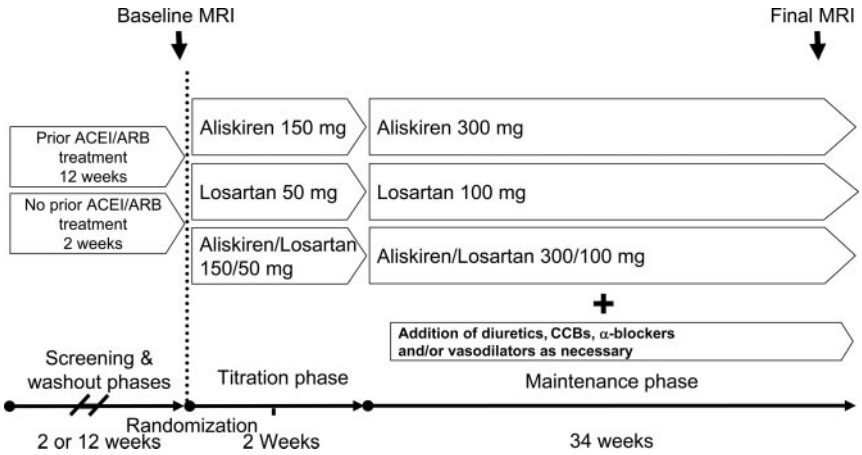


Figure 2. Study design. CCBs indicate calcium channel blockers; MRI, magnetic resonance imaging.

BP measurements was used as the average sitting office BP. Routine laboratory evaluations (hematology and chemistry) were obtained at visits 1, 3, 7, and 11 (or at early termination). An abbreviated chemistry evaluation (including sodium, potassium, chloride, blood urea nitrogen, creatinine, and glucose) was obtained at visits 4, 6, 8, 9, and 10.

Primary Efficacy Assessment

All patients underwent CMR to assess LVMI at the randomization visit and at the end of the study. Only patients who were treated for at least 28 weeks and had both CMR measures were included in the efficacy population. CMR exams were performed with an ECG-gated, breath-hold, 2-dimensional, steady-state free precession cine sequence as previously described.[16] A contiguous LV short-axis stack of images was acquired for each patient 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 (E.A., W.J.M.) by researchers blinded to patient/treatment information and temporal order by manual planimetry of the endocardial and epicardial LV borders (to define the LV myocardial area) 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).[17] LV papillary muscles and trabeculations were excluded from the mass measurement for the primary analysis, although assessment of LVM including papillary muscles and trabeculations was also performed and reported. LVMI was obtained by normalizing LVM to body surface area for the primary analysis. LVM was also indexed to height to the 2.7th power for a secondary analysis to minimize confounding caused by potential weight change during the trial.[18] A reproducibility analysis was performed for change in LVMI using Bland-Altman methods demonstrating within-observer variability of 0.36±2.9 g.

ECGs were recorded at screening (visit 1), baseline (visit 3), day 57 (visit 7), and study completion and sent to a core laboratory for interpretation by investigators blinded to clinical information and temporal order.[7] QRS duration was measured to the nearest 4 ms, and the R-wave amplitudes in leads aVL, V_5, and V_6 and S-wave amplitudes in leads V_1 and V_3 were measured to the nearest 0.5 mm (0.05 mV) with calipers. The Cornell voltage-duration product ($R_{aVL}+S_{V3}$, with 6 mm added in women) times QRS and Sokolow-Lyon voltages ($S_{V1}+RV_{5/6}$) were assessed.

Statistical Analysis

The primary end point, change in LVMI from baseline to week 36, was assessed with an ANCOVA model adjusting for treatment, prior use of ARB/ACEI therapy, country, and baseline LVMI. Baseline characteristics were compared with ANOVA. A sample size of ≈133 patients per treatment arm was estimated on the basis of an SD of 12.5 g/m^2 for the primary outcome, a 5-g/m^2 clinically meaningful difference between groups, and 90% power at a 0.05 significance level to reject the null hypothesis of equal means for combination therapy versus losartan with a 2-sided test. Noninferiority between aliskiren and losartan monotherapies was tested as a secondary objective with a prespecified noninferiority margin of 4.5 g/m^2 and a resulting statistical power of 83% for rejecting the null hypothesis (inferiority of aliskiren monotherapy) in favor of the alternative with a 1-sided significance level of 0.025. Baseline and safety data are presented for the entire randomized population. Efficacy data are presented for the efficacy population that had the final CMR evaluation. A value of $P<0.05$ was considered significant.

The study was designed jointly by the academic steering committee and the sponsor. The sponsor was involved in study management, data collection, and data analysis. At the completion of the trial, all data were transferred to Brigham and Women's Hospital and analyzed by an independent statistician. The manuscript was written by the academic steering committee.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

There were no differences in any of the baseline characteristics by randomization group (Table 1). The average age of the patients was 58.8±10.4 years, 24% were female, and the majority were white. The average BP at baseline was 145±14/89±9 mm Hg. The majority of patients were on antihypertensive medication before enrollment. Approximately 49% of patients were on an ACEI or ARB in the 3 months before the study, with 45% taking RAAS blockers at the screening visit. A similar proportion of patients were taking calcium channel blockers before screening and entering the study: 35% were taking β-blockers, 40% were taking diuretics, and 8% were taking other antihypertensive medications.

Baseline echocardiographic and CMR measurements are shown in Table 2. The average entry maximal LV wall thickness by echocardiography was 1.4 cm, with an LVM of ≈250 g and an LVMI of 123 g/m^2.

Over the course of the study, BP measurements were similar across treatment groups (Figure 3). At the end of the study, sitting BP was reduced by 6.5±14.9/3.8±10.1 mm Hg in the aliskiren group, 5.5±15.6/3.7±10.7 mm Hg in the losartan group, and 6.6±16.6/4.6±10.5 mm Hg in the combination arm ($P<0.0001$ within groups, $P=0.81$ between groups).

We observed highly significant reductions in LVMI from baseline in all treatment groups, with 4.9-g/m^2 (5.4%), 4.8-

Table 1. Baseline Characteristics of Randomized Patients

Characteristics	Randomized Patients		
	Aliskiren 300 mg (n=154)	Losartan 100 mg (n=152)	Combination (n=154)
Age, y	58.4±9.6	59.2±11.0	58.8±10.6
Women, n (%)	42 (27.3)	35 (23.0)	35 (22.7)
BMI, kg/m^2	31.2±4.2	30.7±4.1	31.2±4.0
White, n (%)	144 (93.5)	143 (94.1)	146 (94.8)
Current smoker, n (%)	33 (21.4)	29 (19.1)	19 (12.3)
History of diabetes mellitus, n (%)	35 (22.7)	34 (22.4)	42 (27.3)
Sitting SBP/DBP, mm Hg	145.7±14.1/89.2±9.6	146.1±13.4/89.0±10.0	144.2±13.7/88.4±8.5
eGFR, mL · min^{-1} · 1.73 m^{-2}	87.3±18.1	83.1±17.1	84.8±16.3
Antihypertensive medications at screening visit, n (%)			
Any antihypertensive medication	139 (90.3)	132 (86.8)	130 (84.4)
ACEIs	40 (26.0)	37 (24.3)	38 (24.7)
ARBs	31(20.1)	31 (20.4)	32 (20.8)
CCBs	80 (51.9)	65 (42.8)	60 (39.0)
Diuretics	61 (39.6)	61 (40.1)	62 (40.3)
β-Blockers	56 (36.4)	52 (34.2)	54 (35.1)
α-Blockers	4 (2.6)	6 (3.9)	4 (2.6)
Centrally acting agents	2 (1.3)	6 (3.9)	0
Potassium-sparing diuretics	2 (1.3)	6 (3.9)	10 (6.5)
Aldosterone-receptor blockers	1 (0.6)	1 (0.7)	0

SBP indicates systolic BP; DBP, diastolic BP; eGFR, estimated glomerular filtration rate; and CCBs, calcium channel blockers.

g/m^2 (4.7%), and 5.8-g/m^2 (6.4%) reductions in the aliskiren, losartan, and combination arms, respectively ($P<0.0001$ for all treatment groups; Figure 4). The reduction in LVMI in the combination group was not significantly different from that with losartan alone ($P=0.52$). The difference in LVMI regression between the aliskiren and losartan arms was well within the prespecified noninferiority margin, suggesting that aliskiren was as effective as losartan in reducing LVH ($P<0.0001$ for noninferiority). Similar reductions were found when LVM was normalized for height and height$^{2.7}$ (Table 3).

LV wall thickness in both the anteroseptal and inferolateral walls was reduced significantly in all treatment groups ($P<0.001$; Table 3), with no differences between treatment groups. Similarly, there were no significant differences in the changes in end-diastolic or end-systolic volumes or ejection fraction between treatment groups, although volumes decreased significantly from baseline to follow-up in all treatment groups except LV end-diastolic volume in the losartan arm. No significant differences were observed in LVMI reduction between the combination and losartan arms within any of the prespecified subgroups, including gender, age <65 or ≥65 years, BMI <30 or ≥30 kg/m^2, presence of diabetes, baseline LVMI, or prior ACEI or ARB use (Figure 5).

Table 2. Echocardiographic and CMR Characteristics at Baseline

	Aliskiren (n=154)	Losartan (n=152)	Aliskiren/Losartan (n=154)
Echocardiography			
LV wall thickness, cm	1.4±0.1	1.4±0.1	1.4±0.1
LVM, g	244.6±48.3	246.8±59.3	254.8±53.8
LVMI, g/m^2	121.4±24.6	122.7±27.1	125.7±26.2
LVMI adjusted for height, g/m$^{2.7}$	58.4±13.6	58.5±14.2	60.2±13.9
CMR			
LV anteroseptal wall thickness, cm	1.34±0.22	1.39±0.24	1.38±0.25
LV inferolateral wall thickness, cm	0.96±0.19	0.98±0.23	0.98±0.22
LVM, g	157.9±41.2	160.6±43.2	160.2±37.8
LVM, g (including papillary muscles)	165.1±42.8	169.0±44.8	167.5±39.0
LVMI, g/m^2	77.6±17.2	79.4±18.1	78.4±15.8
LVMI adjusted for height, g/m$^{2.7}$	37.2±8.7	37.8±9.0	37.6±8.2

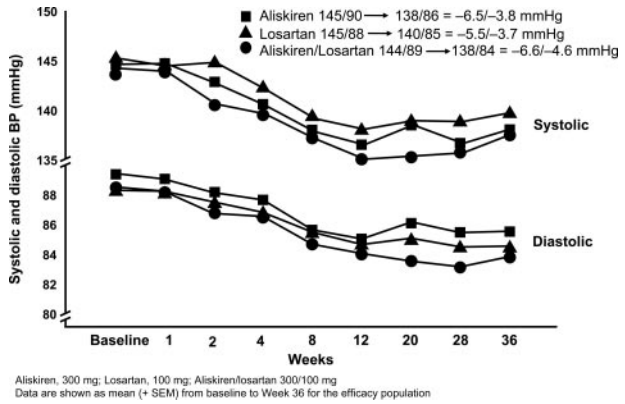


Figure 3. Systolic and diastolic BPs during the course of the trial.

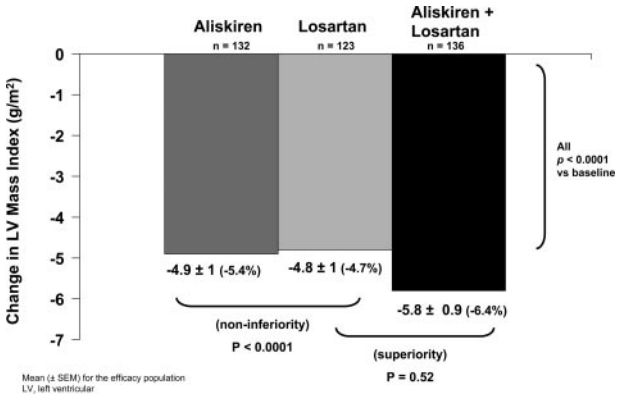


Figure 4. Primary efficacy analysis. Comparison of LVM regression in patients receiving aliskiren, losartan, or their combination. Bars show the mean±SEM for the efficacy population.

Patients with no prior ACEI or ARB use demonstrated a greater reduction in LVM (−7.0±12.4 versus −3.2±10.1 g/m^2; $P<0.001$). ECG assessment at baseline and follow-up showed a significant reduction in both Sokolow-Lyon voltage and Cornell voltage-duration product in all groups (Table 3) and no difference in the degree of reduction between treatment groups. LVMI regression was directly related to the degree of BP lowering across all treatment groups ($P<0.001$; Figure 6) despite relatively modest BP lowering.

Aliskiren alone and the combination of aliskiren plus losartan were well tolerated, similar to losartan alone, with very few overall serious adverse events across the study (Table 4). Of note, there were no imbalances with respect to elevation of serum potassium, blood urea nitrogen, or creatinine or the incidence of hypotension across the groups.

Concomitant antihypertensive medications were used in the majority of patients during the course of the trial and were lower in the combination group (Table 5). More than 2 antihypertensive concomitant medications were used in 29% of patients in the aliskiren group, 30% of patients in the losartan group, and 19% of patients in the combination arm ($P=0.07$).

Discussion

We observed significant and similar reductions in LVM from baseline in overweight hypertensive patients treated with

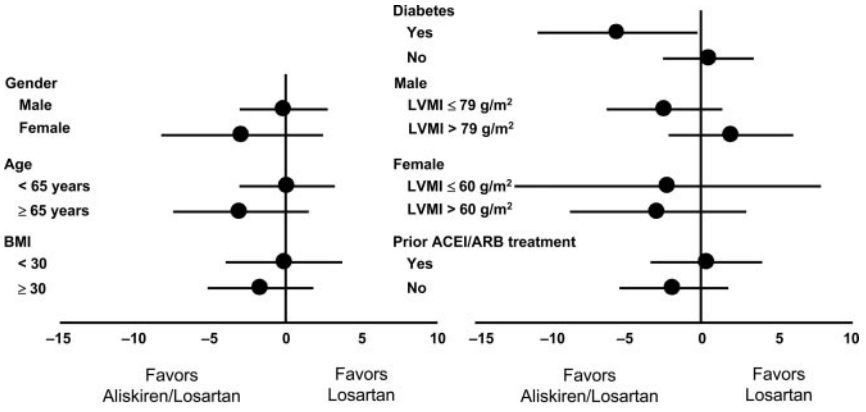
Table 3. Efficacy Measures in Patients Who Underwent Final CMR Assessment

	Baseline				36 Weeks				Change			
	Aliskiren 300 mg (n=133)	Losartan 100 mg (n=129)	Aliskiren+ Losartan (n=138)	*P*	Aliskiren 300 mg (n=133)	Losartan 100 mg (n=129)	Aliskiren+ Losartan (n=138)	*P*	Aliskiren 300 mg (n=133)	Losartan 100 mg (n=129)	Aliskiren+ Losartan (n=138)	*P**
LVMI, g/m^2	76.8±16.5	78.0±17.4	79.1±15.9	0.53	71.9±15.7	73.2±14.3	73.3±15.0	0.78	−4.9±11.7	−4.8±11.9	−5.8±10.9	0.52
P									<0.001†	<0.001	<0.001	
Noninferiority *P*									<0.0001			
LVMI adjusted for height, g/m$^{2.7}$	36.8±8.5	37.3±8.8	37.8±8.3	0.64	34.6±7.9	35.2±7.7	34.9±7.9	0.70	−2.4±5.7	−2.3±5.7	−2.8±5.3	0.50
P									<0.001	<0.001	<0.001	
LVMI including papillary muscles, g/m^2	80.3±17.0	82.2±18.2	82.7±16.5	0.81	77.0±19.1	77.3±15.4	76.7±15.3	0.77	3.8±15.2	−5.1±12.6	−5.5±11.7	0.76
P									0.005	<0.001	<0.001	
LV anteroseptal wall thickness, mm	13.3±2.1	13.7±2.3	13.9±2.5	0.10	12.4±2.5	12.5±2.5	12.7±2.6	0.65	−0.95±2.7	−1.2±2.6	−1.17±2.6	0.69
P									<0.001	<0.001	<0.001	
LV inferolateral wall thickness, mm	9.62±1.9	9.8±2.3	9.8±2.2	0.77	8.7±1.9	8.9±1.9	8.9±1.9	0.68	−0.88±2.0	−0.89±2.1	−0.90±2.2	0.77
P									<0.001	<0.001	<0.001	
LVEDV, mL	158.9±34.7	158.9±38.7	162.2±41.7	0.62	151.9±31.9	154.4±38.5	155.2±42.0	0.92	−7.0±24.1	−4.5±25.1	−7.0±24.9	0.60
P									0.019	0.17	0.037	
LVESV, mL	56.0±19.5	58.5±24.2	60.8±25.0	0.19	52.8±19.2	53.7±22.8	55.7±26.5	0.74	−3.2±16.6	−4.7±15.1	−5.1±15.3	0.86
P									0.035	0.005	0.007	
LVEF, %	65.2±7.9	63.9±9.3	63.3±8.6	0.17	65.8±8.0	65.9±9.0	65.2±9.3	0.81	0.6±7.7	2.0±6.7	1.9±7.0	0.66
P									0.12	0.0018	0.0076	
Sokolow-Lyon voltage, mm	22.4±7.8	22.4±7.9	24.4±8.5	0.07	21.0±6.8	21.5±7.8	22.8±8.0	0.14	−1.2±3.7	−0.9±4.2	−-1.6±3.9	0.50
P									<0.0001	0.02	0.0003	
Cornell voltage-duration product, mm×ms	1894.4±697.1	1833.8±899.9	1963.5±943.8	0.47	1776.4±648.1	1675.4±748.5	1818±850.0	0.39	−118.0±370.2	−158.3±425.9	−145.5±448.7	0.34
P									0.0005	0.0001	0.0002	

LVEDV indicates LV end-diastolic volume; LVESV, LV end-systolic volume; and LVEF, LV ejection fraction.

*Probability value adjusted for baseline measure, ACEI/ARB prior use, and country for the superiority test of the combination versus losartan.

†Baseline vs follow-up.



Data are shown as least-squares mean difference with 95% CI for change in LVMI for aliskiren/losartan vs losartan from baseline to Week 36 endpoint

Figure 5. Comparison of aliskiren plus losartan vs losartan for prespecified subgroups.

aliskiren, a direct renin inhibitor, losartan, an angiotensin receptor blocker, or the combination of both for 36 weeks. The reduction in LVM in the combination group was not significantly different from that with losartan alone. The noninferiority analysis demonstrated that aliskiren was as effective as losartan in reducing LVM in hypertensive patients and was similarly tolerated.

Aliskiren, the first available orally active direct renin inhibitor, is as effective as other RAAS inhibitors at lowering BP, has incremental BP lowering effects when added to an ARB,[14] and is approved for the treatment of hypertension worldwide in doses of 150 and 300 mg/d. Because aliskiren blocks the RAAS proximally, the reactive rise in plasma renin activity that accompanies treatment with downstream inhibitors of the RAAS, including as ACEIs or ARBs, and the resulting increase in angiotensin I and angiotensin II levels are prevented.[13,19–21] Elevation in plasma renin activity is an independent predictor of clinical outcomes, even in patients receiving treatment with a downstream inhibitor of the RAAS,[22] providing a compelling rationale for determining whether aliskiren, either alone or in combination with another RAAS inhibitor, would be of greater benefit than inhibiting the system with a single downstream agent.

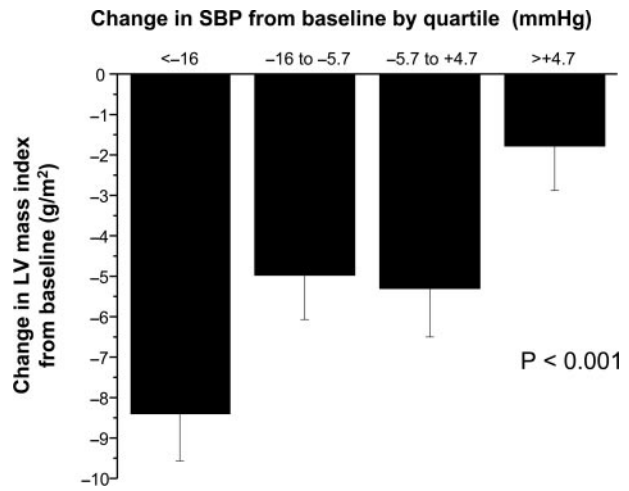


Figure 6. Relationship between change in systolic BP (SBP) and change in LVM. Data are shown for the efficacy population.

The specific effects of aliskiren on end-organ protection in patients with hypertension have been unclear. Aliskiren was associated with a 20% reduction in albuminuria compared with placebo in patients with diabetes on top of losartan therapy[23] and with improvements in brain natriuretic peptide and mitral regurgitation in heart failure patients on optimal background therapy.[24] RAAS inhibitors have been associated with a greater reduction in LVM, the sine qua non of end-organ protection in hypertensive patients, than other antihypertensive agents in meta-analyses,[9] and in the Losartan Intervention for Endpoints Reduction (LIFE) trial,[7] the ARB losartan was associated with greater LVM reduction and greater benefit with respect to outcomes than a β-blocker. We therefore chose losartan as the active comparator in ALLAY to determine whether the combination of aliskiren plus losartan would be associated with greater LVM reduction than losartan alone and whether aliskiren alone would be associated with a benefit similar to that of losartan.

The lack of additional benefit in the combination arm needs to be considered in the context of the study design, in which all groups were treated to standard BP targets with additional antihypertensive medications. Because of this design, we observed similar BP reductions in the combination arm, in which the doses were additive, and in the monotherapy arms, in contrast to prior studies combining aliskiren and an ARB[14] in which BP was not treated to target in all groups. That LVM reduction was directly related to BP reduction is consistent with our prior observations of a similar degree of LVMI regression and improvement in diastolic function in patients with hypertension treated to similar BP levels with an ARB or non-RAAS approaches.[25] These data suggest that even modest BP lowering with RAAS blockade in patients who are only mildly hypertensive at baseline can result in a reduction in LVM and further underscore the potential value of treating hypertension aggressively even within that range. Whether further BP lowering with combined RAAS inhibition or combining a RAAS inhibitor with another agent with an alternative BP-lowering mechanism would have been associated with greater LVMI regression cannot be determined from this study design.

The ALLAY population was distinct from other BP-lowering trials in which LVM regression was observed. In the

Table 4. Adverse Events and Notable Laboratory Values

	Aliskiren (n=154), n (%)	Losartan (n=152), n (%)	Aliskiren/Losartan (n=154), n (%)	*P*
Any AE	91 (59.1)	82 (53.9)	86 (55.8)	0.670
AE discontinuations	4 (2.6)	10 (6.6)	5 (3.2)	0.201
Serious AEs	10 (6.5)	13 (8.6)	10 (6.5)	0.768
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	...
Headache	14 (9.1)	8 (5.3)	10 (6.5)	0.439
Nasopharyngitis	11 (7.1)	13 (8.6)	11 (7.1)	0.882
Bronchitis	7 (4.5)	3 (2.0)	3 (1.9)	0.323
Diarrhea	6 (3.9)	9 (5.9)	7 (4.5)	0.681
Dizziness	5 (3.2)	3 (2.0)	8 (5.2)	0.332
Hypotension	2 (1.3)	2 (1.3)	3 (1.9)	1.000
Serum potassium <3.5 mEq/L	12 (8.1)	11 (7.3)	7 (4.6)	0.418
Serum potassium >5.5 mEq/L	4 (2.7)	5 (3.3)	5 (3.3)	1.000
Serum potassium ≥6.0 mEq/L	3 (2.0)	1 (0.7)	1 (0.7)	0.460
BUN >40.0 mg/dL	1 (0.7)	2 (1.3)	0	0.439
Serum creatinine >2.0 mg/dL	0	1 (0.7)	1 (0.7)	1.000

AE indicates adverse event; BUN, blood urea nitrogen.

LIFE trial, the average starting BP was 20 to 30 mm Hg higher than in ALLAY, in which the average baseline BP was relatively modest (145/89 mm Hg). This difference in the degree of BP lowering between these studies likely accounts for the greater observed LVM regression in LIFE, measured by echocardiography, than in ALLAY over the same time period. Whether a greater reduction in LVM might have been observed in the combination arm if enrolled patients had been more hypertensive, had greater LVM at baseline, or had treatment that extended beyond 9 months remains unknown.

Although CMR has become the de facto gold standard in assessment of LVM, a number of methodological details remain controversial, including whether to include or exclude papillary muscles and LV trabeculae in the LVM estimation[26] and how to best index LVM measurements to body size. Neither including nor excluding papillary muscles and trabeculae resulted in qualitative differences in the overall results, although including papillary muscles resulted in an estimate closer to that obtained with echocardiography. Because patients enrolled in ALLAY were overweight, we have presented LVM data indexed to a function of height in addition to the more standard body surface area assessment,[18] a method that minimizes confounding from significant weight loss changes during the study period (although weight was not significantly different from baseline to follow-up in any group in this study). Similarly, indexing in this manner did not affect the overall study results.

Table 5. Concomitant Antihypertensive Medications in the Efficacy Population Started During the Double-Blind Period

Antihypertensive Medication by Class	Aliskiren (n=133), n (%)	Losartan (n=129), n (%)	Aliskiren/Losartan (n=138), n (%)
Any concomitant antihypertensive	88 (66.2)	84 (65.1)	84 (60.9)
≥2 Concomitant antihypertensive medications	38 (28.6)	39 (30.2)	26 (18.8)
Diuretics	76 (57.1)	75 (58.1)	71 (51.4)
CCBs	52 (39.1)	46 (35.7)	46 (33.3)
α-Blockers	9 (6.8)	8 (6.2)	4 (2.9)
Centrally acting agents	3 (2.3)	6 (4.7)	2 (1.4)
β-Blockers*	3 (2.3)	0	0
Aldosterone receptor blockers*	1 (0.8)	1 (0.8)	0
ACEIs*	1 (0.8)	0	1 (0.7)
ARBs*	1 (0.8)	1 (0.8)	0

*Prohibited by protocol.

We observed a very low number of serious adverse events throughout the trial and no differences with respect to treatment group. Of particular importance is that the incidences of hypotension, hyperkalemia, and renal dysfunction were similar with aliskiren alone, aliskiren combined with losartan, or losartan alone. These findings are both reassuring and consistent with prior observations of aliskiren in addition to standard therapy, including an RAAS blocker, in less healthy populations.[24]

Conclusions

Aliskiren was as effective as losartan in reducing LVM, an important measure of end-organ damage, in overweight hypertensive patients treated for 36 weeks, but the reduction in LVM with the combination of losartan and aliskiren was not significantly different from that achieved losartan alone. Aliskiren alone or in combination with an ARB was tolerated as well as losartan alone. These results suggest that aliskiren is an effective and well-tolerated treatment option in patients with LVH. Ongoing outcome studies will further determine the effects of aliskiren, either alone or in combination, on end-organ protection and on morbidity and mortality beyond BP lowering.

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Disclosures

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CLINICAL PERSPECTIVE

Left ventricular hypertrophy is a marker of cardiac end-organ damage that is associated with an increased risk of morbidity and mortality. Aliskiren is a novel, orally active, direct renin inhibitor that blocks the renin-angiotensin-aldosterone system proximally. To determine whether aliskiren alone or in combination with the angiotensin receptor blocker losartan would be better than losartan alone in regressing left ventricular hypertrophy in hypertensive patients, we randomized 465 to receive aliskiren 300 mg daily, losartan 100 mg daily, or their combination for 9 months and assessed left ventricular mass at baseline and at follow-up using cardiac magnetic resonance imaging. We found a significant reduction in blood pressure and left ventricular mass in all groups. We found no incremental benefit for combination therapy over losartan therapy alone, and we found that aliskiren was as effective as losartan in reducing left ventricular mass. These data suggest that aliskiren is as effective as losartan at reducing this measure of end-organ damage in hypertensive patients.

Effect of the Direct Renin Inhibitor Aliskiren, the Angiotensin Receptor Blocker Losartan, or Both on Left Ventricular Mass in Patients With Hypertension and Left Ventricular Hypertrophy

Scott D. Solomon, Evan Appelbaum, Warren J. Manning, Anil Verma, Tommy Berglund, Valentina Lukashevich, Cheraz Cherif Papst, Beverly A. Smith and Björn Dahlöf
for the Aliskiren in Left Ventricular Hypertrophy (ALLAY) Trial Investigators

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