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(for the ALLAY Investigators)

Abstract

Hypothesis/Introduction: We investigated whether diabetes modified the effectiveness of renin–angiotensin–aldosterone system (RAAS) inhibition on left ventricular hypertrophy (LVH) regression in hypertensive patients in the Aliskiren in Left Ventricular Hypertrophy (ALLAY) trial.

Materials and methods: Participants ($n=465$) with LVH and a BMI > 25 kg/m² were randomized to aliskiren 300mg, losartan 100mg or both daily for 36 weeks, and LVH regression was assessed by cardiac magnetic resonance imaging. Renin concentration, plasma renin activity and aldosterone were assessed in a subset of patients.

Results: Patients with diabetes mellitus (DM) ($n=111$, 24%) were older (61 ± 9 vs. 58 ± 11 years, $p=0.03$), had higher BMI (32.2 ± 4.2 vs. 30.7 ± 4 kg/m², $p=0.004$), higher systolic blood pressure (148 ± 14 vs. 145 ± 14 mmHg, $p=0.03$) and lower eGFR (79 ± 16 vs. 84 ± 16 ml/min, $p=0.03$) at baseline. Combination therapy with aliskiren plus losartan was associated with greater LVH reduction than losartan alone in patients with DM ($p=0.01$), but not in patients without DM ($p=0.91$; unadjusted interaction $p=0.06$; adjusted $p=0.038$). In a subset of 138 participants, plasma aldosterone was reduced to a greater extent in patients with DM (p -interaction = 0.004).

Conclusions: Patients with DM and LVH may derive differential benefit with dual RAAS inhibition with a combination of aliskiren and losartan compared with losartan alone with respect to LVH reduction. Whether these findings will result in improved outcomes will be further explored in larger studies.

Keywords

Diabetes, left ventricular mass, direct renin inhibitor, angiotensin receptor blocker, aldosterone

Introduction

Type 2 diabetes mellitus (DM) confers an excess risk of microvascular and macrovascular complications, and influences cardiovascular disease (CVD) incidence and severity at any level of blood pressure.^{1–4} Diabetes typically coexists with hypertension,⁵ and the combination of these confers additional risk.⁶ Left ventricular hypertrophy (LVH), a measure of the long-term effect of hypertension on the myocardium, is a powerful predictor of future cardiovascular events,^{7–9} and reduction in left ventricular mass (LVM) with antihypertensive medications results in a lower risk for cardiovascular events.¹⁰

The renin–angiotensin–aldosterone system (RAAS) is known to play a key role in the pathogenesis of DM and its complications,^{11,12} and treatment aimed at reducing RAAS activity has been shown to slow the progression of DM-related nephropathy.^{13–15} Patients with type 1 DM have

been shown to have elevated renin secretion and plasma renin activity (PRA) compared with controls,^{16,17} although PRA levels appear to be similar between diabetics and non-diabetics in the type 2 diabetes setting.¹⁸ Preclinical data supports the concept that renin activity may be enhanced in the setting of hyperglycemia; intracellular levels of renin

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and angiotensin II have been shown to increase in cardiac myocytes exposed to high concentrations of glucose.¹⁹ Moreover, upregulation of the prorenin receptor in the kidney has been associated with concurrent elevation in blood pressure and heart rate in the streptozocin-induced diabetes rat model.^{20,21} Whether RAAS inhibition with a direct renin inhibitor would offer benefits over other approaches to inhibiting the system in patients with DM remains unclear.

The Aliskiren in Left Ventricular Hypertrophy (ALLAY) trial was designed to test the hypothesis that the combination of aliskiren and losartan would be superior to losartan alone, or whether aliskiren would be non-inferior to losartan in reducing left ventricular mass index (LVMI).²² LVMI decreased significantly from baseline in all treatment groups, and aliskiren was non-inferior to losartan at reducing LVMI. We utilized data from ALLAY to assess whether diabetes status modified the effectiveness of aliskiren, losartan or their combination on LVMI reduction. Additionally, we examined whether diabetes modified the effect of aliskiren, losartan or the combination on serum measurements of RAAS activity.

Methods

Participants

ALLAY included patients with a history of or newly diagnosed hypertension, systolic BP/diastolic BP $\geq 140/90$ mmHg and less than 180/110 mmHg. Patients enrolled had a confirmed left ventricular wall thickness in any wall by a screening echocardiogram of at least 13 mm and a body mass index (BMI) > 25 kg/m². Patients were randomly assigned to receive aliskiren 150mg, losartan 50mg or the combination of aliskiren 150mg and losartan 50mg daily for two weeks as previously described.²² Randomization was stratified by a patient's use of an angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) within three months of study entry. After two weeks of treatment, patients were force-titrated to receive aliskiren 300mg, losartan 100mg or their combination daily for an additional 34 weeks. Diabetes was defined as a prior history of diabetes, or having either prior or prior/concomitant use of oral anti-diabetic agents or insulin, or with a fasting plasma glucose ≥ 7 mmol/L or non-fasting plasma glucose ≥ 11.1 mmol/L at study entry. Diabetes was a pre-specified subgroup in the ALLAY study. Detailed inclusion and exclusion criteria have been reported.²²

For patients not at goal per JNC VII guidelines during the study, additional antihypertensive medications could be added anytime during the blinded phase, including diuretics, calcium channel blockers, alpha-blockers and vasodilators. Other RAAS inhibitors or beta-blockers were not allowed during the course of the trial, due to their potential to affect renin secretion. The ALLAY study protocol complies with the Declaration of Helsinki and was approved by

each participating site's institutional review board. All patients provided written informed consent in accordance with established guidelines for the protection of human subjects.

The primary outcome for the ALLAY trial was change from baseline to 36 weeks in LVMI as assessed by cardiovascular magnetic resonance imaging (CMR).^{22,23} CMR exams were performed with an ECG gated, breath-hold, two-dimensional, steady-state free precession cine sequence as previously described. A contiguous left ventricular (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 in a blinded fashion (QMASS MR version 6.16, Medis Inc., Leiden, the Netherlands). LVMI was obtained by normalizing LVM to body surface area, as well as by indexing to height to the 2.7 power, in order to minimize confounding caused by potential weight change during the trial. A Bland-Altman reproducibility analysis demonstrated within-observer variability of 0.36 ± 2.9 g. Left ventricular ejection fraction (LVEF) was calculated in the standard manner as follows: $LVEF = (LV \text{ end diastolic volume} - LV \text{ end systolic volume}) / LV \text{ end diastolic volume}$.

Of the 465 patients randomized, five participants were excluded due to data quality concerns, leaving 460 for this analysis.

Biomarker measurements

Phlebotomy was performed in a subset of fasting subjects who rested for 20 minutes in a supine position, typically between 08:00 and 09:00. Plasma specimens were collected in EDTA, immediately centrifuged and aliquoted into cryotubes stored at -20°C for a maximum of four weeks, then at -80°C without any freeze-thaw cycles until assayed using complete patient sets. The following kits were employed: PRA using RIA kits from DiaSorin (Minneapolis, USA), plasma aldosterone using RIA Coat-a-Count kits from Siemens (Tarrytown, USA) and renin concentration (PRC) using radioimmunoassay Renin III kits from CISbio (Bagnols/Cèze, France).

Statistical analyses

Baseline demographics between participants with and without DM were compared to identify potential differences. Between-group assessments were performed using *t*-tests for normally distributed continuous variables or Wilcoxon rank sum tests for non-normally distributed continuous variables, and Chi-Square or Fisher's exact tests, as appropriate, for categorical variables. Left ventricular mass was indexed both to body surface area and to height to the

2.7. We utilized LVMI indexed to height to the 2.7 for this to minimize confounding caused by potential weight change during the trial. The change in LVM indexed to height to the 2.7 power from baseline to week 36 was assessed with linear regression. As ALLAY was designed and powered to test for superiority between the combination group and those receiving losartan alone, and to test for non-inferiority between the two monotherapy groups, our primary comparison for this analysis was between the combination therapy group and those who received losartan alone. We evaluated for interactions in two separate models: the first assessed the interaction between diabetes status and treatment, adjusting only for baseline LVMI, and the stratification variables of country and prior use of ACE inhibitors or ARBs; the second model included as covariates the additional baseline characteristics that differed between treatment groups or between subjects with and without diabetes with a p -value < 0.10 , including age, BMI, systolic and diastolic blood pressure, eGFR, smoking status and history of cardiovascular events. Linear regression was used to compare mean changes from baseline to 36 weeks in log-transformed levels of plasma renin activity, renin, and plasma aldosterone between treatment arms and between patients with and without DM, adjusting for baseline values. All analyses were conducted using Stata, version 11.

Results

Out of 460 patients included in these analyses, 111 (24.1%) had diabetes at baseline. Baseline characteristics of all the analyzed subjects by DM status are shown in Table 1. Participants with diabetes were more likely to be older (61 ± 9 vs. 58 ± 11 years, $p=0.03$), have a higher BMI (32.2 ± 4.2 vs. 30.7 ± 4 kg/m², $p=0.004$), higher systolic blood pressure (148 ± 14 vs. 145 ± 14 mmHg, $p=0.03$) and lower eGFR (79 ± 16 vs. 84 ± 16 ml/min, $p=0.03$) at baseline compared with patients without diabetes.

Blood pressure (BP) reduction from baseline was similar between individuals with DM and those without DM in the three treatment arms (Table 2). Longitudinal BP analyses between patients with and without diabetes did not reveal evidence of effect modification by diabetes status on BP lowering during the study.

For the primary outcome of LVMI reduction, we noted a weak interaction between diabetes status and treatment assignment (unadjusted except for baseline values, p -interaction=0.059; adjusted model p -interaction=0.038) such that combination therapy with aliskiren 300mg and losartan 100mg daily was associated with greater LVMI reduction than losartan 100mg alone in participants with DM, even following adjustment for degree of blood pressure reduction (LVMI change from baseline $+0.28$ g/m^{2.7} for losartan versus -5.58 g/m^{2.7} for aliskiren + losartan, $p=0.01$). In participants without DM, there were no significant differences

found between losartan and combination therapy (LVMI change from baseline -5.34 g/m^{2.7} for losartan versus -5.13 g/m^{2.7} for aliskiren + losartan, $p=0.91$; Figure 1). We observed numerically less LVM reduction in patients with diabetes compared with patients without diabetes, regardless of treatment (-2.5 g/m^{2.7} vs. -1.4 g/m^{2.7}, $p=0.06$ following adjustment for covariates).

In 138 participants with biomarkers, baseline PRA was higher in those with DM compared with participants without DM (Table 3, $p=0.01$) and baseline plasma aldosterone levels were similar between groups ($p=0.90$). We did not observe an interaction between diabetes and treatment assignment on PRA reduction (Figure 2). In contrast, we noted a significant interaction between diabetes and treatment assignment with respect to plasma aldosterone reduction, such that plasma aldosterone levels were reduced to a greater extent in patients with DM compared with patients without DM (Figure 3; p -interaction = 0.004). Participants with DM randomized to losartan exhibited elevations in PRA and plasma aldosterone levels compared with baseline. We observed no difference in the use of diuretics and calcium channel blockers, which could affect PRA levels, among participants with DM and those without DM throughout the study.

Discussion

Our data suggest that patients with diabetes may derive greater benefit than non-diabetics with respect to LV mass reduction when treated with a combination of aliskiren and

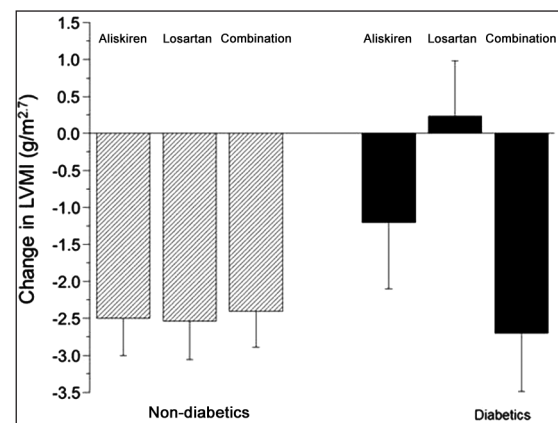


Figure 1. Differences in left ventricular mass index (LVMI) following 36 weeks of treatment by aliskiren, losartan, or aliskiren + losartan. Between group comparisons made with linear regression, adjusting for randomized treatment and diabetes status. Other covariates included age, body mass index (BMI), smoking status, prior use of ACEI inhibitor or ARB, country and baseline LVMI. Patients with diabetes mellitus (DM) exhibited a more pronounced reduction in LVMI with aliskiren and aliskiren + losartan, and patients without DM had similar LVMI reductions with all three treatments. Data are expressed as mean $\pm$ SEM.

Table 1. Baseline characteristics of diabetics versus non-diabetics

Characteristic	All subjects (N=460)	Diabetics (N=111)	Non-diabetics (N=349)	p-value*
Age, years (SD)	59 (10)	61 (9)	58 (11)	0.03
Males, %	348 (76)	78 (70)	270 (77)	0.13
BMI, g/m ² (SD)	31.1 (4.1)	32.2 (4.2)	30.7 (4)	0.004
Caucasian race, %	433 (94)	105 (95)	328 (94)	0.24
Systolic blood pressure, mmHg (SD)	145.3 (14.7)	147.8 (14.1)	144.5 (13.6)	0.027
Diastolic blood pressure, mmHg (SD)	88.9 (9.4)	88.2 (9.2)	89.1 (9.5)	0.2
Medical history (%)				
Tobacco use	81 (18)	13 (16)	68 (19)	0.06
Dyslipidemia	207 (45)	55 (48)	152 (44)	0.27
CV events	35 (8)	9 (8)	26 (7)	0.82
Coronary artery disease	27 (96)	7 (6)	20 (6)	0.82
Chronic heart failure	7 (2)	1 (1)	6 (2)	0.54
Medications (%)				
ACE inhibitors/ARB	184 (40)	40 (36)	144 (41)	0.33
Beta blockers	149 (32)	34 (31)	115 (33)	0.65
Calcium channel blockers	171 (39)	43 (39)	128 (37)	0.83
Diuretic	84 (18)	18 (16)	66 (19)	0.52
Statin	85 (19)	28 (25)	57 (16)	0.047
Laboratory				
Estimated GFR, ml/min per 1.73 m ² (SD)	83 (16)	79 (16)	84 (16)	0.003
Estimated GFR < 60, n (%)	30 (6.5)	6 (5.4)	24 (6.9)	0.58
Left ventricular mass index, g/m ² (SD)	78.5 (17)	76.1 (15.1)	79.2 (17.5)	0.09
Left ventricular mass index, adjusted for height, g/m ^{2.7} (SD)	37.5 (8.6)	37.3 (8.1)	37.6 (8.8)	0.79
Left ventricular ejection fraction, % (SD)	64.2 (8.6)	65.2 (8.1)	63.9 (8.8)	0.16

*Comparison between patients with diabetes mellitus (DM) and patients without DM.

BMI: body mass index; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; GRF: glomerular filtration rate; SD: standard deviation

Table 2. Blood pressure baseline and 36 weeks in the treatment groups by diabetes status

	Aliskiren	Losartan	Combination	p-value between treatment groups (systolic, diastolic)
All patients				
Baseline	145.7 ± 14.1/89.2 ± 9.6	146 ± 13/89.0 ± 10	144.2 ± 13.7/88.4 ± 8.5	
36 weeks	138.4 ± 13.9/85.9 ± 10.4	140.5 ± 15.4/85.0 ± 9.6	138.0 ± 13.4/84.0 ± 8.5	
Change	-6.8 ± 15.5/-3.5 ± 10.7	-5.4 ± 15.7/-4.0 ± 11.2	-6.2 ± 17.0/4.2 ± 10.4	0.73, 0.83
Diabetics (n = 111)				
Baseline	151.9 ± 16.0/89.3 ± 9.7	148.5 ± 10.7/90.3 ± 9.7	143.9 ± 14.0/85.6 ± 7.9	
36 weeks	138.9 ± 15.2/84.3/7.9	142.5 ± 15.1/83.5 ± 9.8	136.1 ± 13.8/82.7 ± 7.9	
Change	-10.9 ± 16.6/-4.9 ± 9.8	-5.9 ± 14.4/6.8 ± 11.4	-7.9 ± 16.8/2.8 ± 9.9	0.44, 0.25
Non- diabetics (n = 349)				
Baseline	143.9 ± 13.1/89.2 ± 9.7	145.4 ± 14.0/88.6 ± 10.2	144.3 ± 13.6/89.4 ± 8.5	
36 weeks	138.2 ± 13.5/86.3 ± 11.0	140.0 ± 15.5/85.4 ± 9.5	138.6 ± 13.2/84.6 ± 8.7	
Change	-5.7 ± 15.1/3.1 ± 11.0	-5.2 ± 16.1/3.2 ± 11.1	-5.5 ± 17.1/4.7 ± 10.6	0.97, 0.44

Data are mean ± standard deviation.

Table 3. Baseline biomarker data for diabetics and non-diabetics

Biomarker	Diabetics	Non-diabetics	p-value
PRA, ng/ml per hour			
Arithmetic mean	5.65 (2.6, 8.7)	3.41 (2.0, 4.9)	0.01
Geometric mean	2.28 (1.4, 3.6)	1.15 (0.87, 1.5)	
Renin, ng/L			
Arithmetic mean	37.0 (21.6, 52.3)	23.8 (12.9, 34.7)	0.2
Geometric mean	19.6 (13.4, 28.7)	9.5 (7.5, 12.2)	
Aldosterone, pmol/L			
Arithmetic mean	268 (223, 313)	272 (241, 302)	0.9
Geometric mean	229 (186, 282)	222 (193, 255)	

PRA: plasma renin activity

Data are mean (95% confidence interval).

losartan compared with losartan alone. Moreover, we observed the greatest reduction in plasma aldosterone concentration in patients randomized to aliskiren or combination therapy compared with losartan alone among those with diabetes. In patients without diabetes, all therapies appeared to reduce LV mass and neurohormone levels similarly.

Patients with concomitant DM and hypertension carry an increased risk for microvascular and macrovascular events, which are often preceded by markers of target organ damage such as left ventricular hypertrophy.^{24,25} In the AVOID study, which enrolled patients with hypertension,

DM and proteinuria who were already receiving the maximal recommended renoprotective treatment with losartan 100mg daily and optimal management of hypertension,²⁶ treatment with aliskiren 300mg daily reduced albuminuria significantly compared with placebo, a benefit that was independent of systemic blood pressure reduction. Likewise, when combined with irbesartan in another study,²⁷ aliskiren reduced albuminuria by 31%.

We observed a similar borderline interaction with respect to diabetes and treatment with aliskiren plus other inhibitors of the RAAS in the Aliskiren Study in Post-MI Patients to Reduce Remodeling (ASPIRE) trial. In ASPIRE,

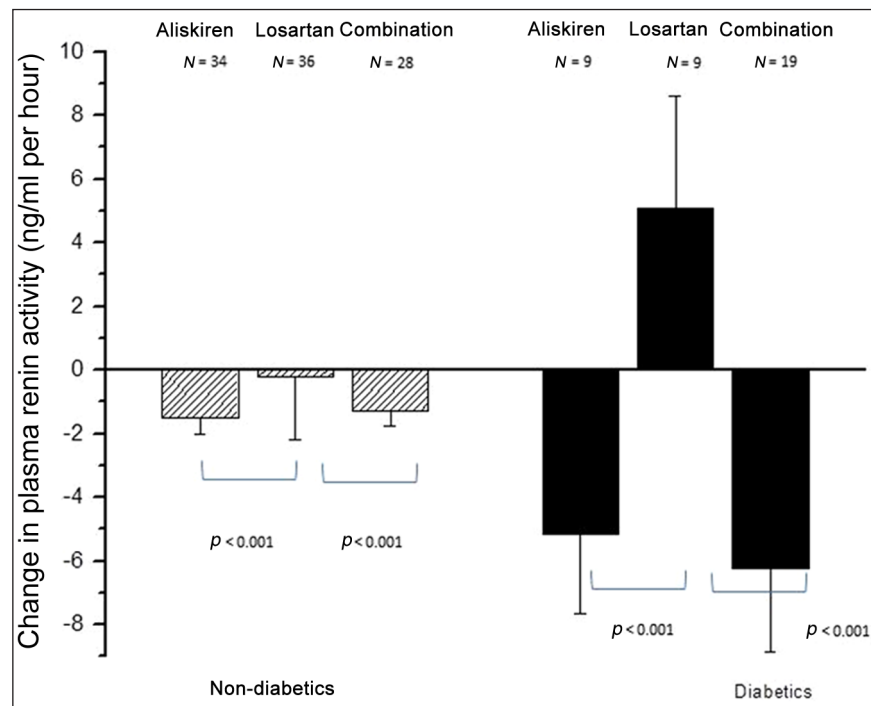


Figure 2. Differences in plasma renin activity following 36 weeks of treatment by aliskiren, losartan, or aliskiren + losartan. Comparisons made with linear regression, adjusting for baseline values. Patients with diabetes mellitus (DM) exhibited a more pronounced reduction compared with patients without DM. Data are expressed as mean $\pm$ SEM.

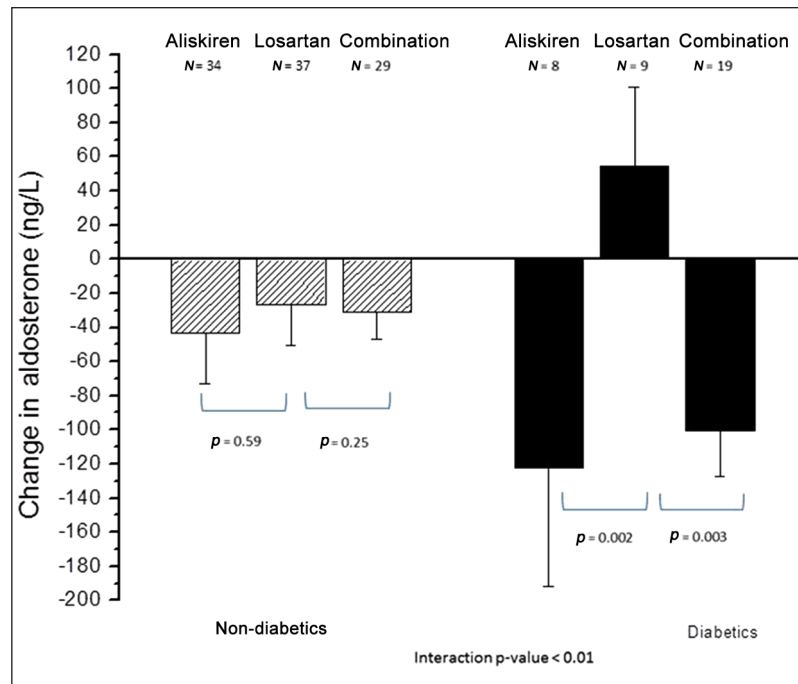


Figure 3. Differences in aldosterone concentrations following 36 weeks of treatment by aliskiren, losartan, or aliskiren + losartan. Patients with diabetes mellitus (DM) exhibited a more pronounced reduction compared with patients without DM. Comparisons made with linear regression, adjusting for baseline values. Data are expressed as mean $\pm$ SEM.

post-myocardial infarction (MI) patients with diabetes treated with aliskiren had greater reduction in the primary endpoint of left ventricular end-systolic volume compared with those treated with placebo (p -interaction = 0.06).²⁸ In ASPIRE all patients were on background therapy of an ACE inhibitor or ARB. In both ASPIRE and ALLAY, diabetes was the only subgroup in which patients receiving aliskiren therapy in addition to another RAAS inhibitor may have derived greater benefit; the likelihood that the diabetes interaction in both trials was due to chance was considerably lower than either trial alone. In support of the primary findings of greater LVMI reduction in diabetic patients treated with combination therapy, we also observed a greater reduction in PRA concentrations and plasma aldosterone with aliskiren and aliskiren plus losartan in participants with DM compared with losartan alone, whereas participants without DM had comparable reductions with each treatment. Participants with DM randomized to losartan exhibited an increase in both PRA and plasma aldosterone levels. Interestingly, we did not observe elevations in PRA in non-diabetic patients who were randomized to losartan, a finding consistent with other reports in which elevations in PRA were observed after administration of captopril or candesartan in patients with DM, but not in healthy controls.^{17,27}

We cannot determine whether the differential effect observed in diabetic patients in the combination group is secondary to the addition of aliskiren or simply the greater overall RAAS inhibition that these patients received. We cannot exclude that increased suppression of the RAAS in diabetic patients may increase risk. Indeed, preliminary

data from the recently stopped ALTITUDE trial raise the possibility that diabetic patients may be more sensitive to RAAS suppression. Of note, patients in ALLAY were healthier than those in ALTITUDE, and the number of adverse events was extremely low. Whether aliskiren alone would offer greater benefits in diabetic patients compared with another inhibitor of the RAAS is being explored in larger trials.^{29,30}

Overall we observed less LVM reduction in patients with diabetes, regardless of treatment. Although the mechanism for this finding is incompletely understood, it is consistent with an analysis of the LIFE study showing less reduction of LVH (detected with ECG) in patients with diabetes following an average of 4.8 years of randomized treatment with losartan or atenolol.³¹ An additional analysis from LIFE demonstrated that while patients without diabetes receiving losartan had more pronounced LVM regression by echocardiography than patients receiving atenolol, the reverse appeared to be true for patients with diabetes, where losartan appeared less effective.³² While LIFE compared losartan with atenolol, and we compared losartan with aliskiren and the combination of aliskiren and losartan, one possible explanation for these findings is that the ARB may stimulate higher plasma renin activity in patients with diabetes compared with those without diabetes.

A number of mechanisms may explain potential differential effects in diabetic patients receiving aliskiren in combination with another inhibitor of the RAAS. While renin secretion is normally inhibited by angiotensin II,

individuals with DM exhibit a blunted renin response to exogenous angiotensin II infusions,³³ as well as an enhanced renin secretion induced by an ARB.³⁴ In several animal studies, renin inhibition was shown to prevent renal injury in a streptozotocin-induced type 1 diabetic transgenic TG(mRen-2)27 rat, and exerted beneficial effects on glucose intolerance and cardiovascular injury in a type 2 diabetic mouse compared with hydralazine, which did not ameliorate cardiovascular injury.³⁵⁻³⁷ Reduction of oxidative stress may partially contribute to aliskiren's benefits in diabetes, as was shown by a reduction in cardiac superoxide levels in one study following treatment with aliskiren.³⁷ Finally, the significant reduction in plasma aldosterone levels with the combination of losartan and aliskiren compared with losartan alone in participants with diabetes may potentially explain a greater reduction in LVM. Aldosterone is a well-recognized contributing factor to cardiac fibrosis, as shown in experimental models.³⁸⁻⁴⁰ Hence, we cannot exclude the possibility that aldosterone antagonists might achieve the same LVH reduction as the combination of aliskiren and losartan.

Some limitations of this study should be noted. The number of diabetic patients in this trial was relatively small and we cannot exclude the possibility that this borderline interaction may have been due to chance as the power to detect an interaction between diabetes and treatment in this trial was low. While biomarker data were available only on a subset of participants, the finding that aldosterone was reduced in parallel with reduction in LVMI data suggests a potential mechanism, although this should be considered speculative. Nonetheless, we've previously shown that the degree of LVM reduction overall was indeed directly related to the degree of aldosterone reduction in ALLAY.⁴¹ Our analysis employed two regression models, one that adjusted for the original ALLAY stratification variables and another that also included as covariates baseline characteristics that differed between diabetics and non-diabetics. Although the interaction between diabetes and treatment with respect to change in LVMI was significant only in the second adjusted model, qualitatively the results were similar in the two models. We therefore interpret these findings as hypothesis generating and await final results of outcomes studies.^{29,42}

In summary, we found that in a cohort of hypertensive, overweight patients, those with DM had a more pronounced reduction in LVM with the combination of aliskiren + losartan compared with treatment with losartan than those without DM. Concordant with these findings, we observed that plasma aldosterone levels were reduced to a greater extent in diabetic patients treated with combination therapy than with losartan alone, with a clear interaction between diabetes status and treatment on plasma aldosterone reduction. These data raise the possibility that patients with DM and LVH may be differentially affected by the addition of aliskiren to another RAAS inhibitor, which may be in part

due to neurohormonal changes. These hypothesis-generating findings will be tested prospectively in outcomes studies in which aliskiren is being compared with or added to other inhibitors of the renin-angiotensin system.

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Conflict of interest

SS, EA and BD have received research support from Novartis and serve as consultants for Novartis. MP and BS are employees of Novartis.

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