

**Effect of the Direct Renin Inhibitor Aliskiren,
Either Alone or in Combination With Losartan,
Compared to Losartan, on Left Ventricular Mass
in Patients With Hypertension and Left
Ventricular Hypertrophy: The ALiskiren Left
Ventricular Assessment of HypertrophY (ALLAY)
Trial**

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Disclosures

- Drs Solomon, Applebaum, Manning, Dahlöf and Berglund have received research support from Novartis. Drs Solomon and Dahlöf have consulted for Novartis. Dr Lukashevich, Ms Cherif-Papst and Mr Carten are employees of Novartis.

Background

- LV hypertrophy, a marker of cardiac end-organ damage, is present in approximately 30% of patients with hypertension² and is associated with an increased risk of cardiovascular morbidity and mortality.³ LV hypertrophy is second only to age in predictive power for cardiovascular events⁴
- Regression of LV hypertrophy is associated with lower overall cardiovascular risk, independent of BP lowering⁵
- Despite current approaches to blood pressure management, a substantial number of patients with hypertension and left ventricular hypertrophy (LVH) remain at risk for cardiovascular morbidity and mortality.

Rationale for the Aliskiren Left ventricular Assessment of hypertrophy (ALLAY) study

- RAAS inhibition is a highly effective treatment strategy for reducing cardiovascular morbidity and mortality in patients with hypertension and LV hypertrophy, and may be associated with greater regression of LV mass than other approaches to lowering blood pressure¹
- Aliskiren, the first direct renin inhibitor (DRI), blocks the RAAS proximally at the rate-limiting step²
- The ALLAY study was designed to compare aliskiren, alone or in combination with losartan, with losartan alone on LV hypertrophy in overweight patients with hypertension and LV hypertrophy

ALLAY study objectives

- Primary objective
 - Assess whether the combination of aliskiren and losartan was superior to losartan monotherapy in reducing LV mass index, as measured by cardiac magnetic resonance imaging (CMR), in hypertensive overweight patients
- Key secondary objectives
 - Evaluate whether aliskiren monotherapy was non-inferior to losartan monotherapy in reducing LV mass index
 - Safety and tolerability of study treatments

Key inclusion and exclusion criteria

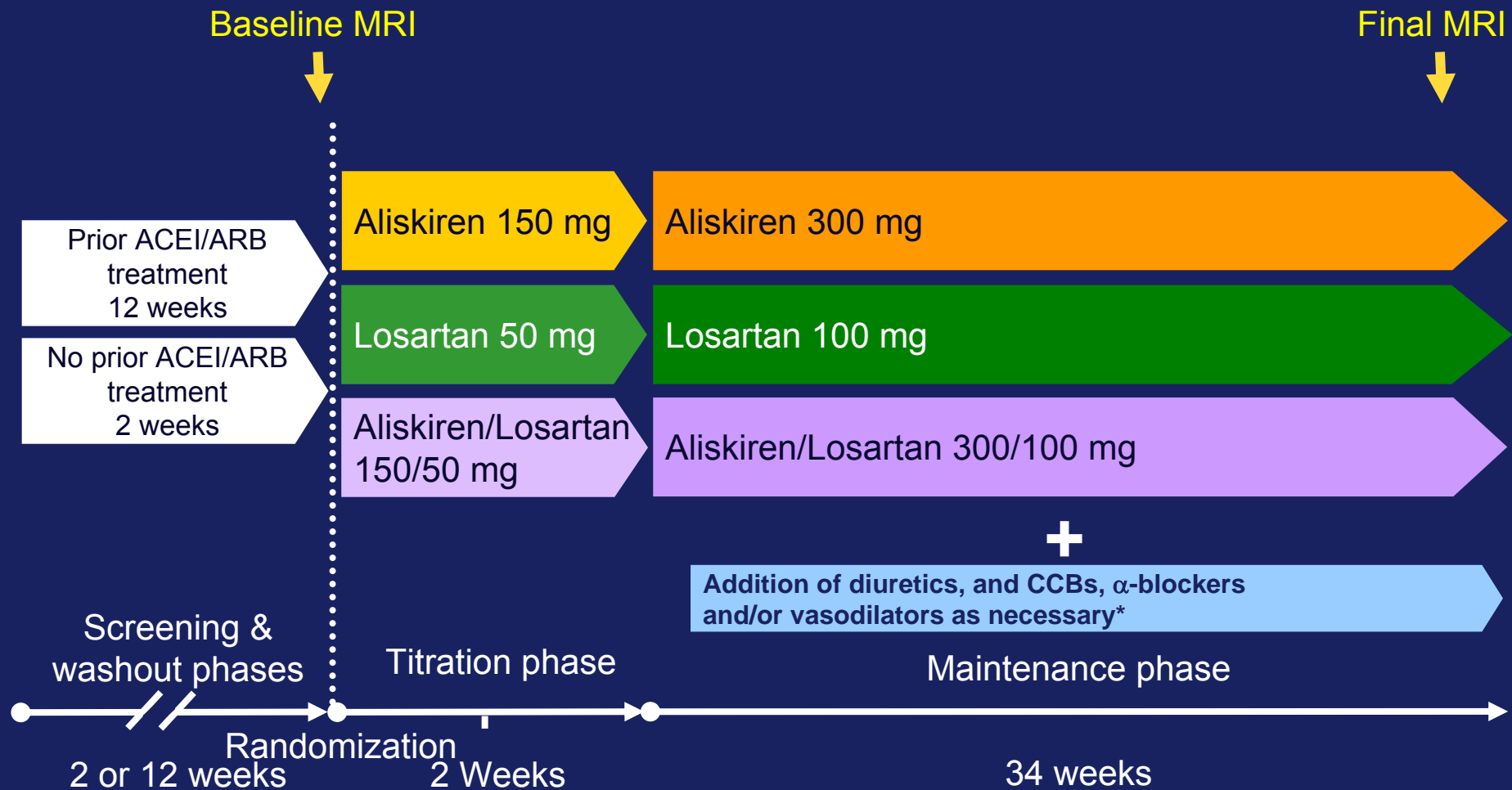
- Inclusion criteria

- History of hypertension or newly diagnosed hypertension
- LV wall thickness ≥ 1.3 cm (as confirmed by ECHO Core Lab)
- Body mass index > 25 kg/m²

- Exclusion criteria

- LV ejection fraction $< 40\%$
- Required continued treatment with ACE inhibitor and/or ARB
- msSBP > 180 mmHg or msDBP > 110 mmHg during the study
- Body mass index ≥ 42 kg/m²
- Myocardial infarction, coronary artery bypass graft, percutaneous intervention, transient ischemic attack or stroke within 6 months of study entry

A double-blind, randomized, active-controlled trial in overweight patients with hypertension and LV hypertrophy



*To achieve BP target of < 140/90 mmHg (< 130/80 mmHg for patients with diabetes)
CCBs, calcium channel blocker; LV, left ventricular

CMR for LV mass

BASE

Slice 1

Slice 2

Slice 3

Slice 4

Slice 5

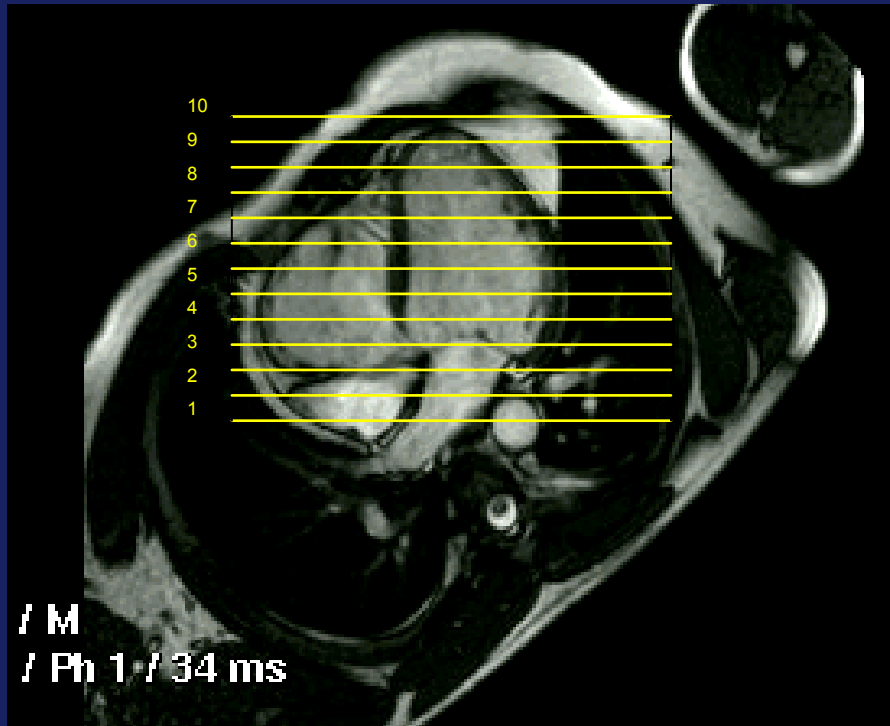
Slice 6

Slice 7

Slice 8

Slice 9

Slice 10



ED short axis stack

Four-chamber end-diastole (ED)

slice thickness	10 mm
spatial resolution	2.0 mm x 2.0 mm
temporal resolution	30-50ms

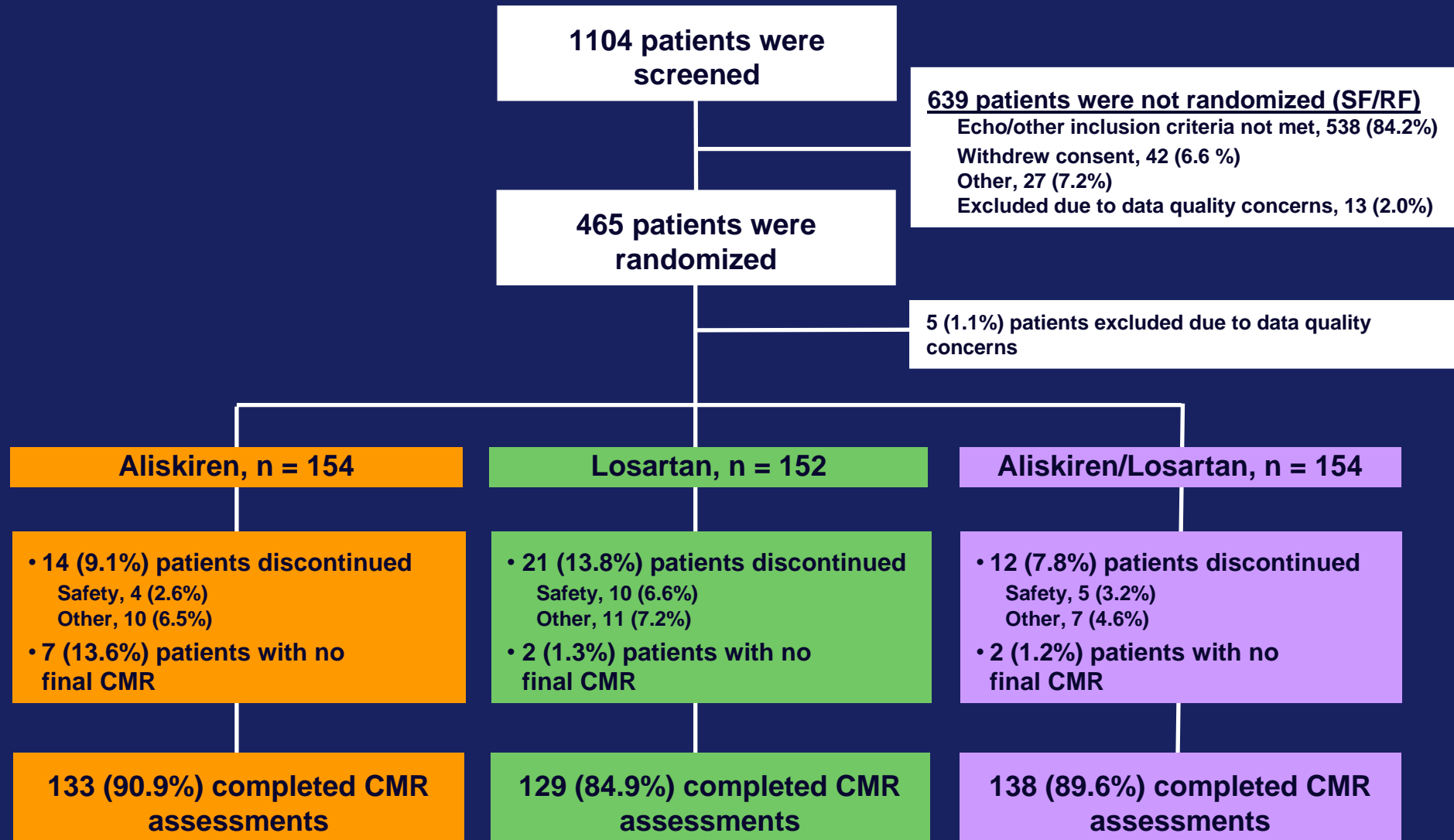
APEX

LV, left ventricular; CMR, cardiac magnetic resonance

Statistical methods

- Change in LV mass index from baseline to Week 36 endpoint was assessed using an ANCOVA model with treatment, prior use of ARB/ACE inhibitor therapy and country as factors, and baseline LV mass index as covariate
- Using the ANCOVA model:
 - Aliskiren and losartan combination vs. losartan monotherapy were compared with a test of superiority
 - Aliskiren monotherapy vs. losartan monotherapy were compared with a test of non-inferiority (Non-inferiority limit (Δ) = 4.5 g/m²)

Patient flow diagram



CMR, cardiac magnetic resonance

Patient demographics and baseline characteristics

	Aliskiren (n = 154)	Losartan (n = 152)	Aliskiren/Losartan (n = 154)
Age, years	58.4 ± 9.6	59.2 ± 11.0	58.6 ± 10.6
Gender – male, n (%)	112 (72.7)	117 (77.0)	119 (77.3)
Race – Caucasian, n (%)	144 (93.5)	143 (94.1)	146 (94.8)
Body mass index, kg/m²	31.2 ± 4.2	30.7 ± 4.1	31.2 ± 4.0
Overweight, %	41.6	48.7	40.3
Obese, %	57.1	50.0	58.4
Diabetes, n (%)	35 (22.7)	34 (22.2)	42 (27.3)
No prior ARB/ACE inhibitor treatment, n (%)	78 (50.6)	79 (52.0)	79 (51.3)
Sitting SBP/DBP, mmHg	145.7/89.2	146.1/89.0	144.2/88.4

Values are shown as mean ± SD unless otherwise stated
Data are shown for the randomized population

Antihypertensive medications at screening visit

	Aliskiren (n = 154)	Losartan (n = 152)	Aliskiren/Losartan (n = 154)
Any antihypertensive medication, n (%)	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)
Beta-blockers	56 (36.4)	52 (34.2)	54 (35.1)
Alpha 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

CMR and echocardiography parameters at baseline

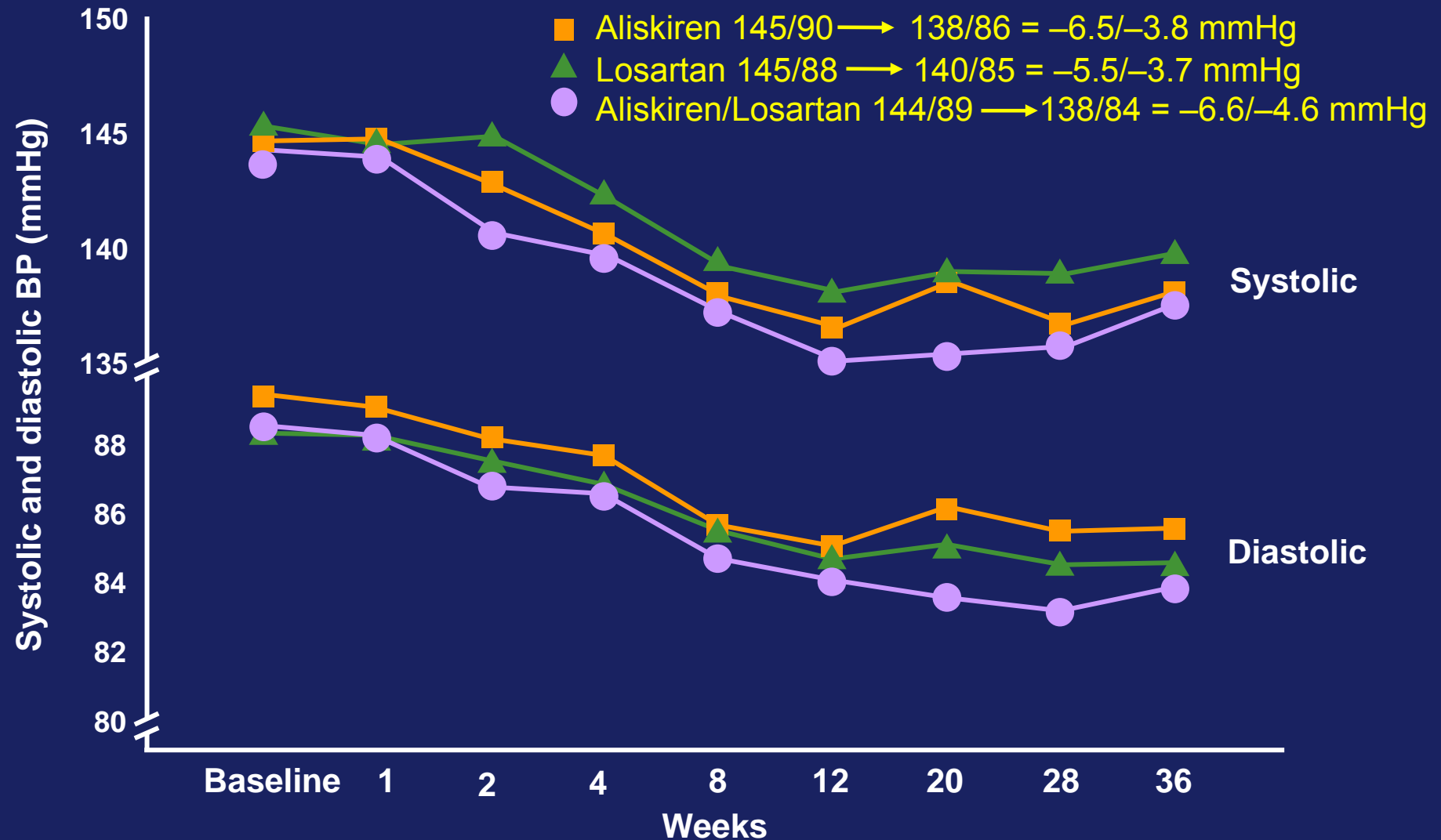
	Aliskiren (n = 154)	Losartan (n = 152)	Aliskiren/Losartan (n = 154)
Echocardiography			
LV wall thickness*, cm	1.4 ± 0.1	1.4 ± 0.1	1.4 ± 0.1
LV mass, g	244.6 ± 48.3	246.8 ± 59.3	254.8 ± 53.8
LV mass index, g/m ²	121.4 ± 24.6	122.7 ± 27.1	125.7 ± 26.2
LV mass index adjusted for height, g/m ^{2.7}	58.4 ± 13.6	58.5 ± 14.2	60.2 ± 13.9
Left ventricular hypertrophy, %	71	81	80
CMR			
LV antero septal wall thickness, cm	1.34 ± 0.2	1.38 ± 0.2	1.38 ± 0.2
LV infero lateral wall thickness, cm	0.96 ± 0.2	0.98 ± 0.2	0.98 ± 0.2
LV mass, g	157.9 ± 41.2	160.6 ± 43.2	160.2 ± 37.8
LV mass index, g/m ²	77.6 ± 17.2	79.4 ± 18.1	78.4 ± 15.8
LV mass index adjusted for height, g/m ^{2.7}	37.2 ± 8.7	37.8 ± 9.0	37.6 ± 8.2

*Baseline LV wall thickness ≥ 1.3 cm was required for randomization

Data are shown as mean ± SD for the randomized population

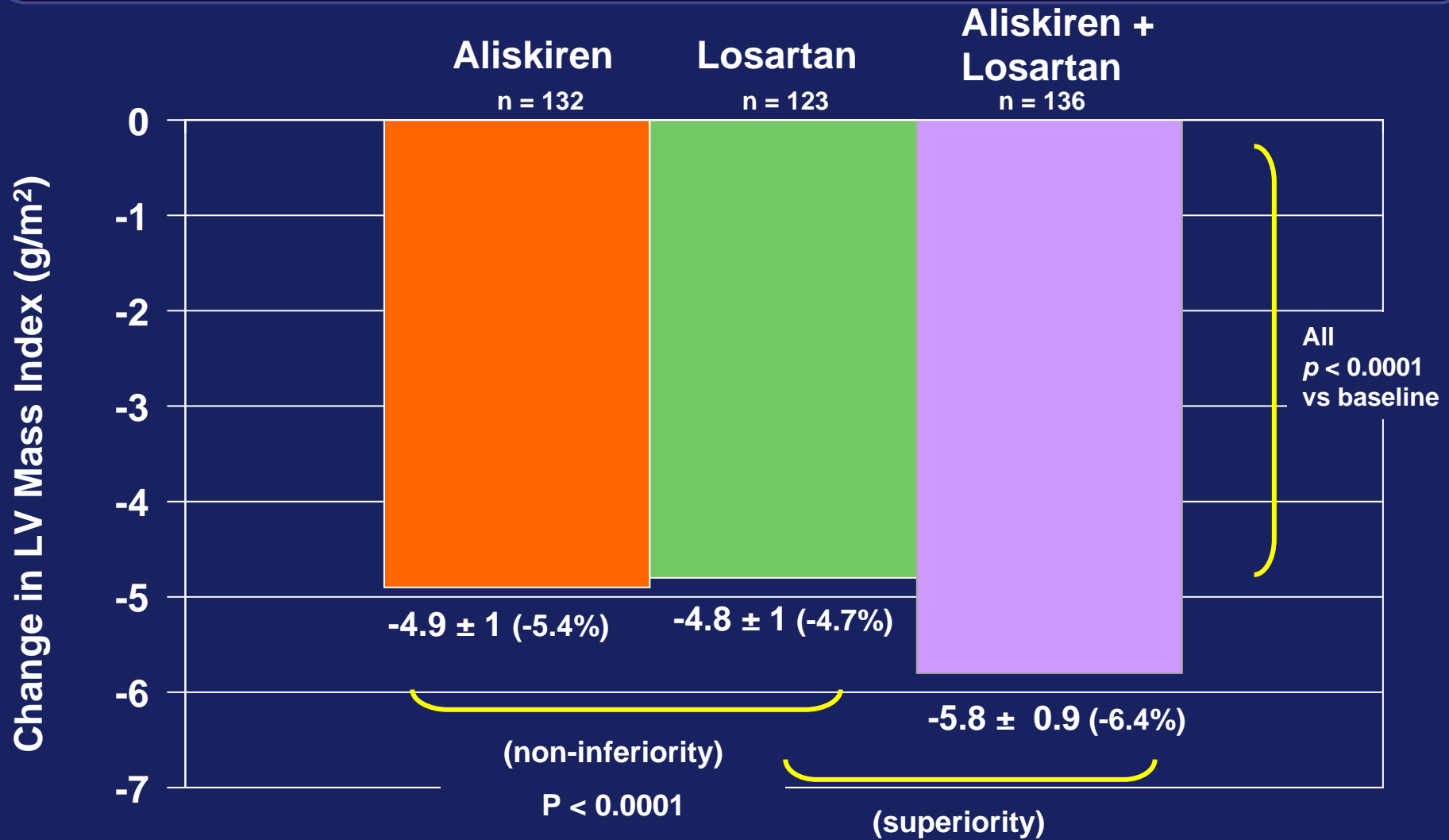
ECG, electrocardiogram; LV, left ventricular; CMR, cardiac magnetic resonance

Effect on mean sitting BP of aliskiren and losartan alone or in combination from baseline to Week 36



Aliskiren, 300 mg; Losartan, 100 mg; Aliskiren/losartan 300/100 mg
 Data are shown as mean (+ SEM) from baseline to Week 36 for the efficacy population

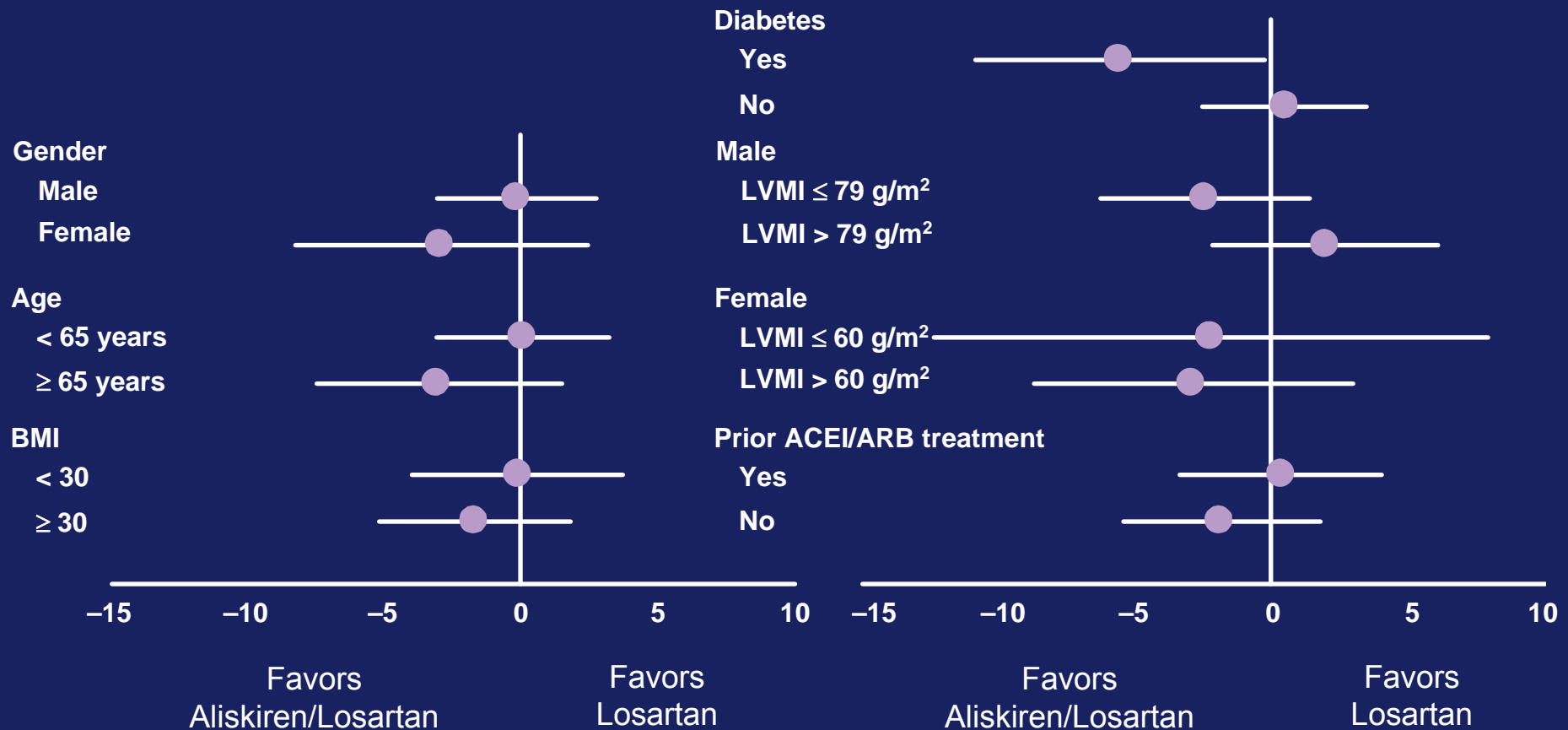
Effect on LV mass index of aliskiren alone or in combination with losartan from baseline to follow-up



Mean (± SEM) for the efficacy population
LV, left ventricular

Change in LV mass index across different patient subgroups

Aliskiren/Losartan vs Losartan



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
 BMI, body mass index; LVMI, left ventricular mass index

Safety and tolerability of study treatments

	Aliskiren (n = 154)	Losartan (n = 152)	Aliskiren/Losartan (n = 154)	P-values
Any adverse event, n (%)	91 (59.1)	82(53.9)	86(55.8)	0.670
AE discontinuations, n (%)	4 (2.6)	10 (6.6)	5 (3.2)	0.201
Serious AEs, n (%)	10 (6.5)	13 (8.6)	10 (6.5)	0.768
Deaths, n (%)	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

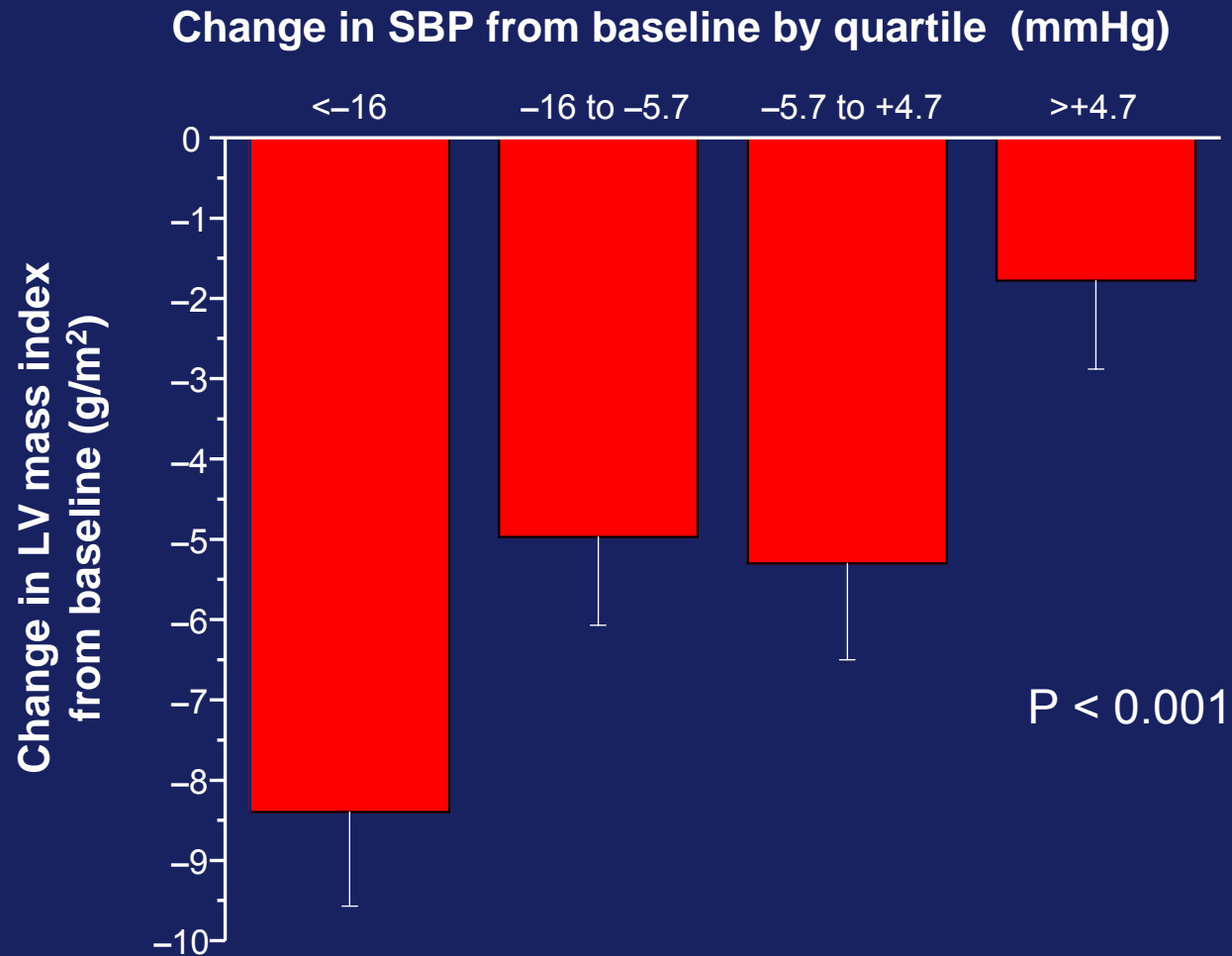
Data are shown for the safety population
 AE, adverse events; BUN, blood urea nitrogen

Concomitant antihypertensive medications started during the double-blind period

	Aliskiren (n = 133)	Losartan (n = 129)	Aliskiren/Losartan (n = 138)
<i>Patients starting concomitant antihypertensives during the double-blind period, n (%)</i>			
Any concomitant antihypertensive	88 (66.2)	84 (65.1)	84 (60.9)
Diuretics	76 (57.1)	75 (58.1)	71 (51.4)
CCBs	52 (39.1)	46 (35.7)	46 (33.3)
Alpha-blockers	9 (6.8)	8 (6.2)	4 (2.9)
Centrally acting agents	3 (2.3)	6 (4.7)	2 (1.4)
Beta-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
≥ 2 Concomitant antihypertensive medications	38 (28.6)	39 (30.2)	26 (18.8)

Data are shown as number (%) of patients who started concomitant antihypertensive therapies during the double-blind period in the efficacy population

Relationship between change in sitting SBP and regression of LV mass index



Data are shown for the efficacy population
LV, left ventricular; SBP, systolic blood pressure

Considerations

- Patients enrolled in ALLAY were relatively well-controlled hypertensives; hence, the overall degree of BP reduction observed in this trial was lower in magnitude than in other LV mass regression studies
- Treating patients to pre-defined BP targets minimized BP differences between therapy groups
- Whether greater LV mass reduction would have been observed – particularly in the combination group – if patients were initially more hypertensive or were followed for a longer period of time remains to be determined

Summary and conclusions

- Aliskiren was as effective as losartan in reducing LV mass, a measure of end-organ damage, in overweight hypertensive patients, over 36 weeks of treatment
- The reduction in LV mass with the combination was not significantly greater than with losartan alone.
- Aliskiren alone or combined with an ARB was safe and well tolerated
- This study demonstrates that aliskiren is an effective and safe treatment option in patients with LV hypertrophy. Ongoing outcome studies will further determine the benefits of aliskiren on end-organ protection beyond BP lowering



Back-up slides

Back-up slides

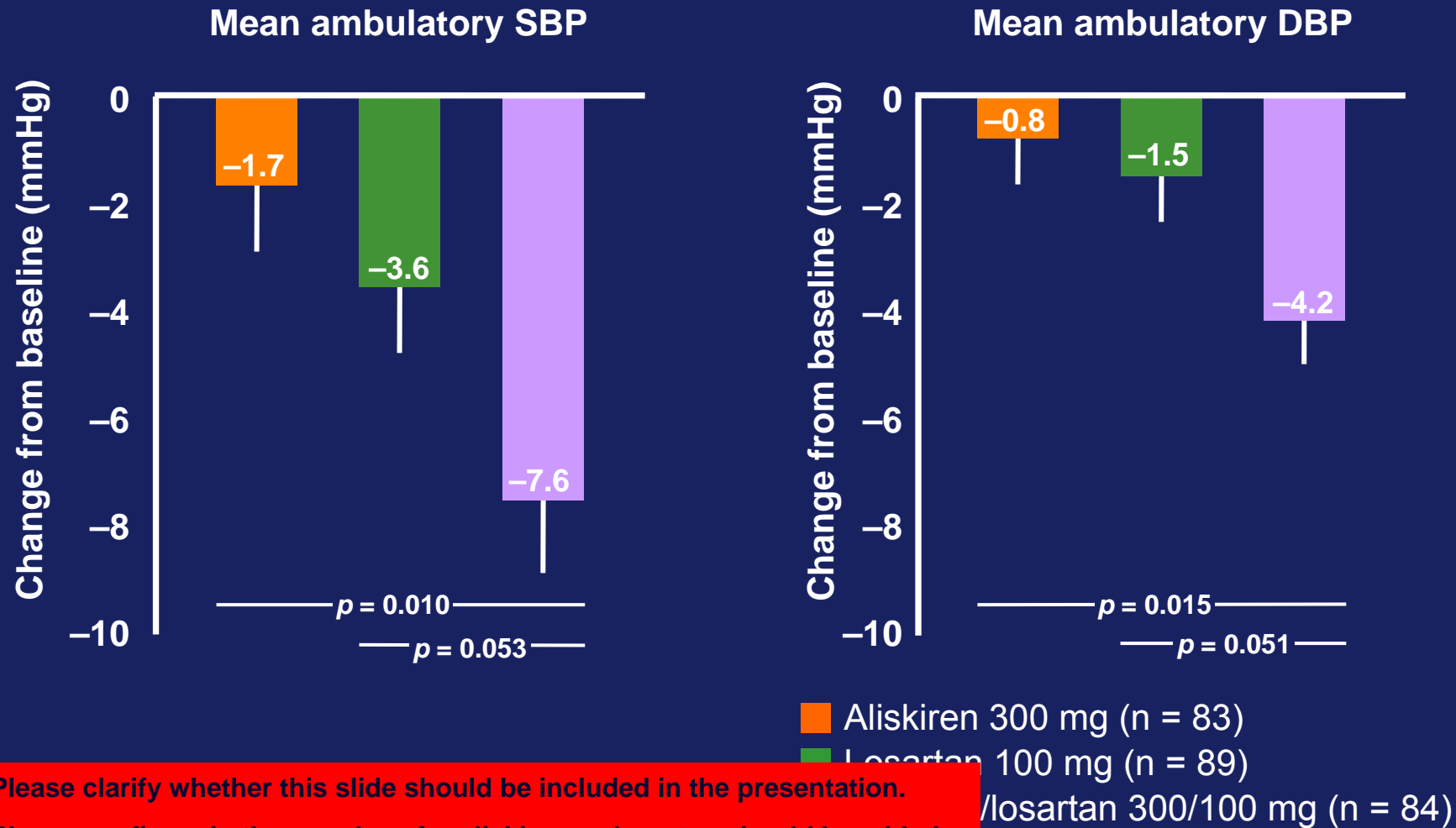
LIFE

- Baseline LV mass index gm/m² (LIFE) 123 ± 26
- Delta LVMI gm/m² over 12 months 14 {11.4% change from baseline}
- HRs per 1-SD (25.3) decrease in intrtreatment LVMI were 0.74 (95% CI, 0.65-0.91; *P*=.003) for the composite end point after the first year of treatment
- Or 26% RRR per 25.3 gm/m²
- Or 26% RRR per 20.6% change in LVMI
- Thus for a 11.7% change in LVMI during the first year of treatment in LIFE we can assume a 14.8% RRR

ALLAY

- Baseline LV mass index gm/m² (from MRI) 77.9 ± 16.5
- Delta LVMI gm/m² over 9 months 5.2 {6.7 % change from baseline}
- Or Delta LVMI gm/m² over 12 months 6.9 {8.9 % change from baseline}
- Extrapolating from LIFE in ALLAY a 8.9% reduction in LVMI would amount to 11.3% RRR

Effect on mean ambulatory BP of aliskiren and losartan alone or in combination at Week 36 endpoint

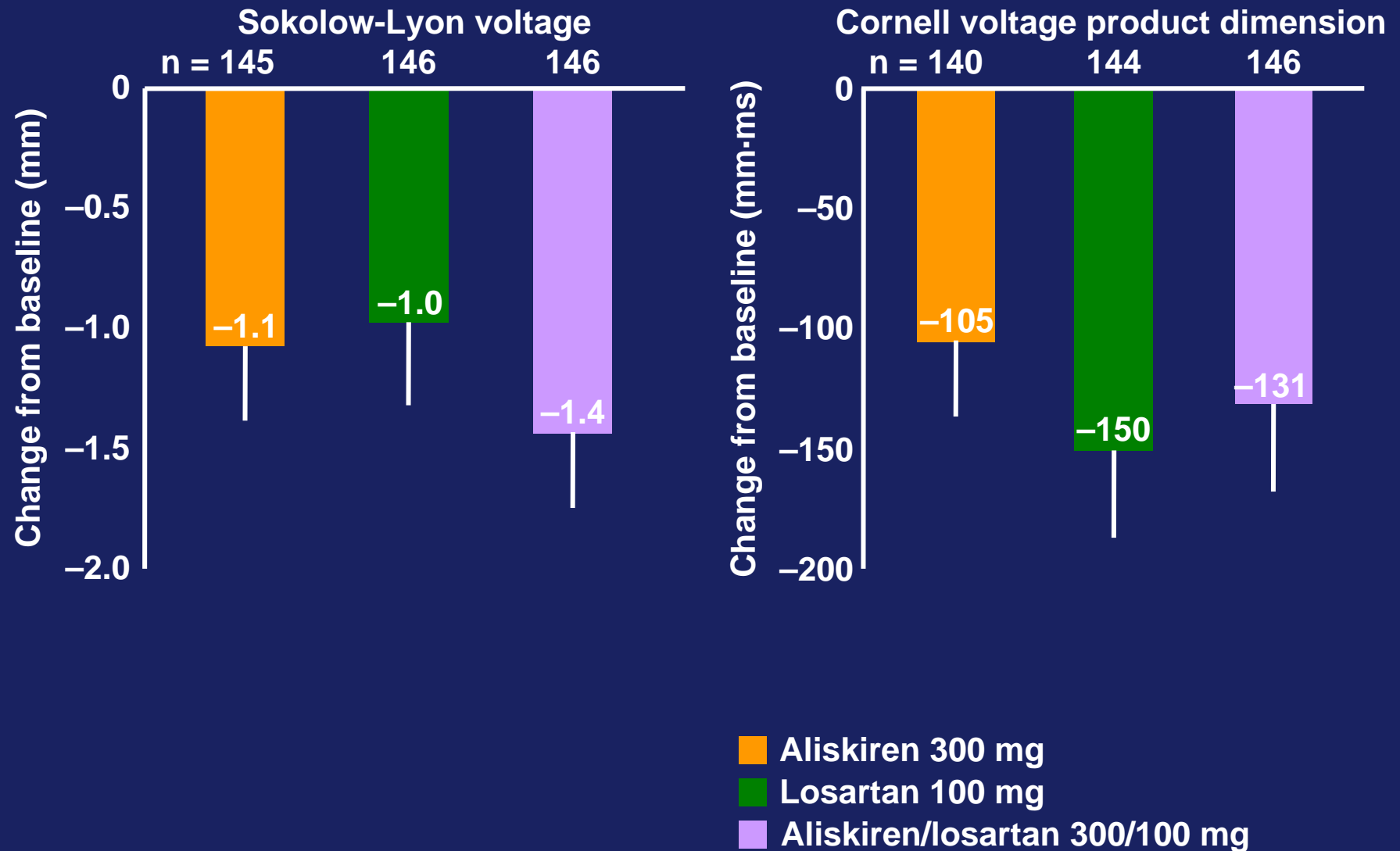


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Please confirm whether p-values for aliskiren vs losartan should be added.

Data are shown as mean (+ SEM) change from baseline to Week 36 endpoint for the ABPM completer population
Between-treatment analyses were based on least-squares mean data
DBP, diastolic blood pressure; SBP, systolic blood pressure

Effect of aliskiren and losartan alone or in combination on ECG parameters



Data are shown as mean (+ SEM) change from baseline to Week 36 endpoint for the ITT population