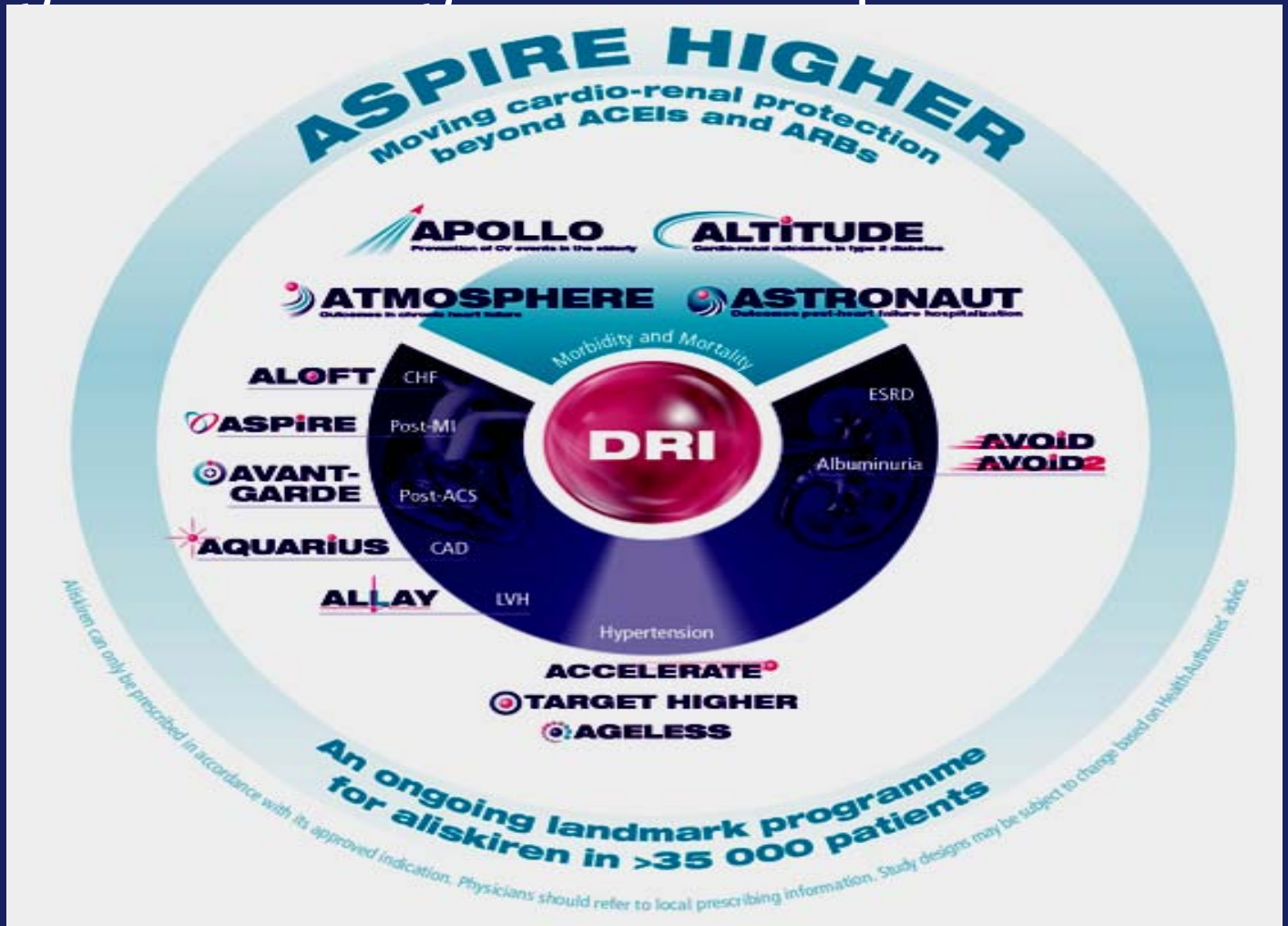
Renin Inhibitors: Protection of Against Target Organ Injury

George Bakris, MD
Professor of Medicine
Director, Hypertensive Diseases Unit
University of Chicago School of Medicine
Chicago, USA

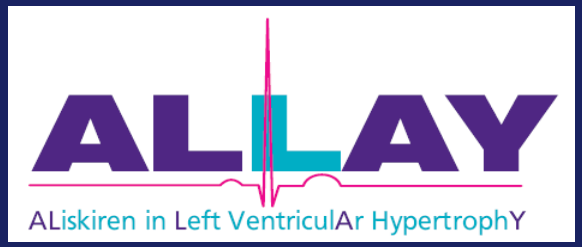
The Rasilez Study Portfolio

- The largest ongoing cardio-renal clinical trial program involving over 35.000 patients



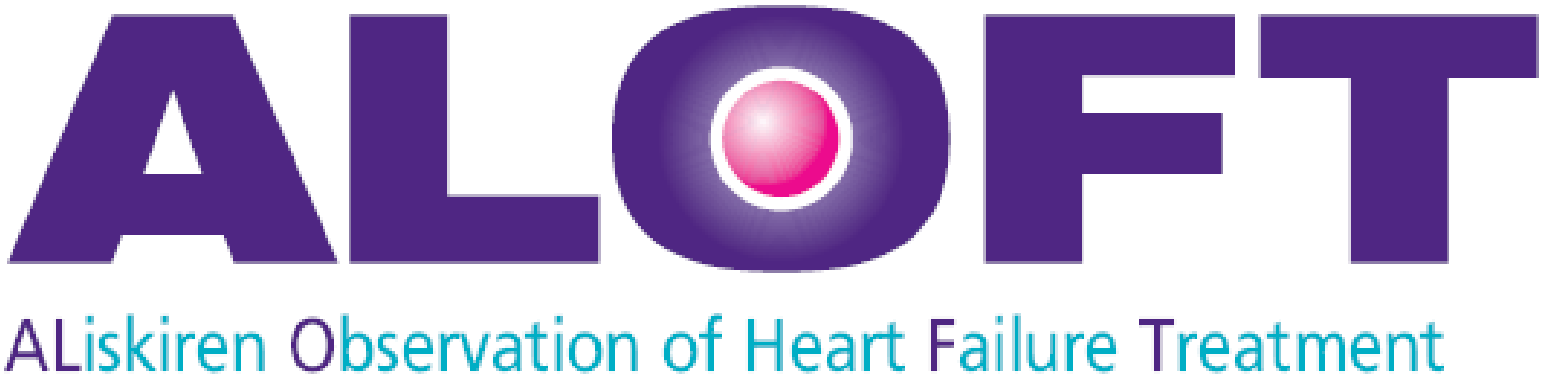
ASPIRE HIGHER
Completed studies

ALiskiren Observation of Heart Failure Treatment



ALiskiren Left Ventricular Assessment of HypertrophY

Aliskiren in the EValuation of PrOteinuria In Diabetes



ALiskiren Observation of Heart Failure Treatment

ALOFT study rationale

- The ALOFT study was designed to evaluate the safety and tolerability of aliskiren in patients with HF when combined with standard HF therapy[1]
- A secondary objective of the study was to evaluate the effect of aliskiren on BNP, NT-proBNP and PRA[1]

HF = heart failure
BNP = brain natriuretic peptide
NT-proBNP = N-terminal pro-BNP
PRA = plasma renin activity

1. McMurray *et al*. Circ Heart Fail 2008;1:17–24
2. Melanson *et al.* Am J Clin Pathol 2005;124:S122–S128
3. Vuolteenaho *et al.* Adv Clin Chem 2005;40:1–34
4. Anand *et al.* Circulation 2003;107:1278–1283

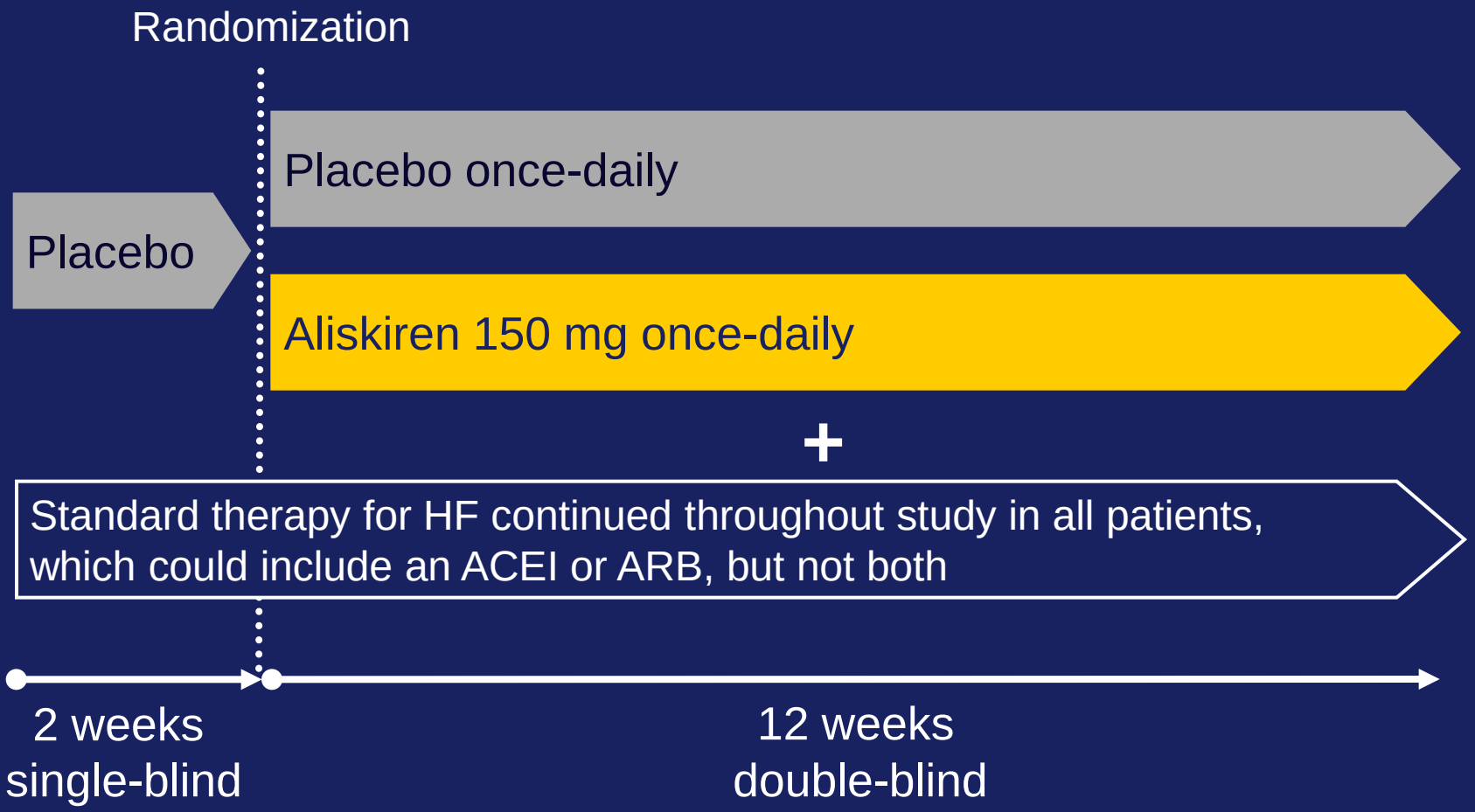
ALOFT population and objectives

Study population included patients with:

- 302 patients with Stable HF, prior or current hypertension
- BNP >100 pg/mL
- Receiving a β-blocker with either an ACEI or an ARB
  (but not both)

McMurray *et al*. Circ Heart Fail 2008;1:17–24

ALOFT study design



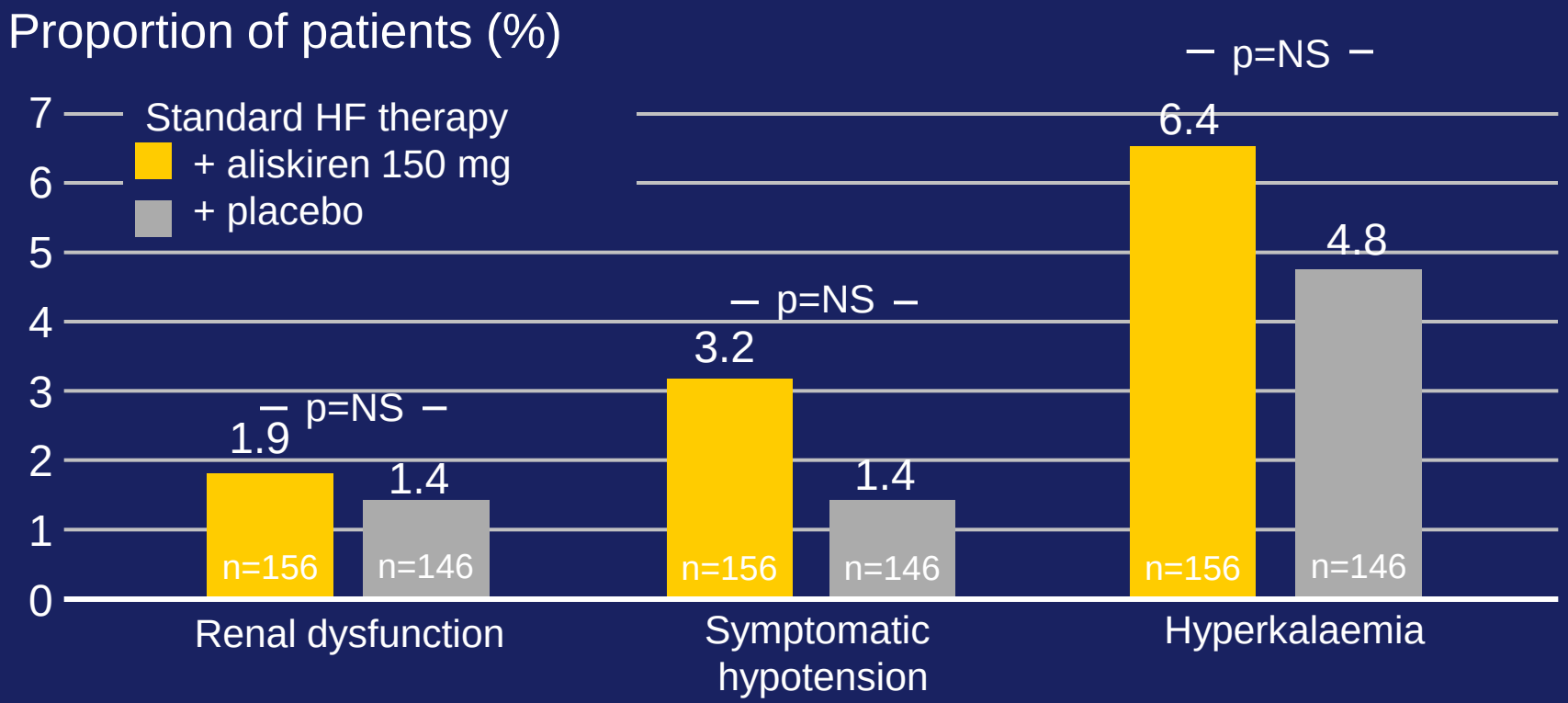
McMurray *et al*. Circ Heart Fail 2008;1:17–24

ALOFT baseline characteristics and concomitant HF therapy

		Aliskiren n=156	Placebo n=146
Clinical characteristics at baseline			
LVEF, n (%)	≤40%	125 (80)	113 (77)
	>40%	31 (20)	33 (23)
NYHA Class II, n (%)		98 (63)	87 (60)
NHYA Class III, n (%)		56 (36)	58 (40)
Concomitant therapy for stable HF			
ARB, %		16	14
ACEI, %		83	84
β-blocker, %		94	95
Aldosterone antagonist, %		33	34

McMurray *et al*. Circ Heart Fail 2008;1:17–24

Aliskiren demonstrates placebo-like tolerability when combined with standard HF therapy



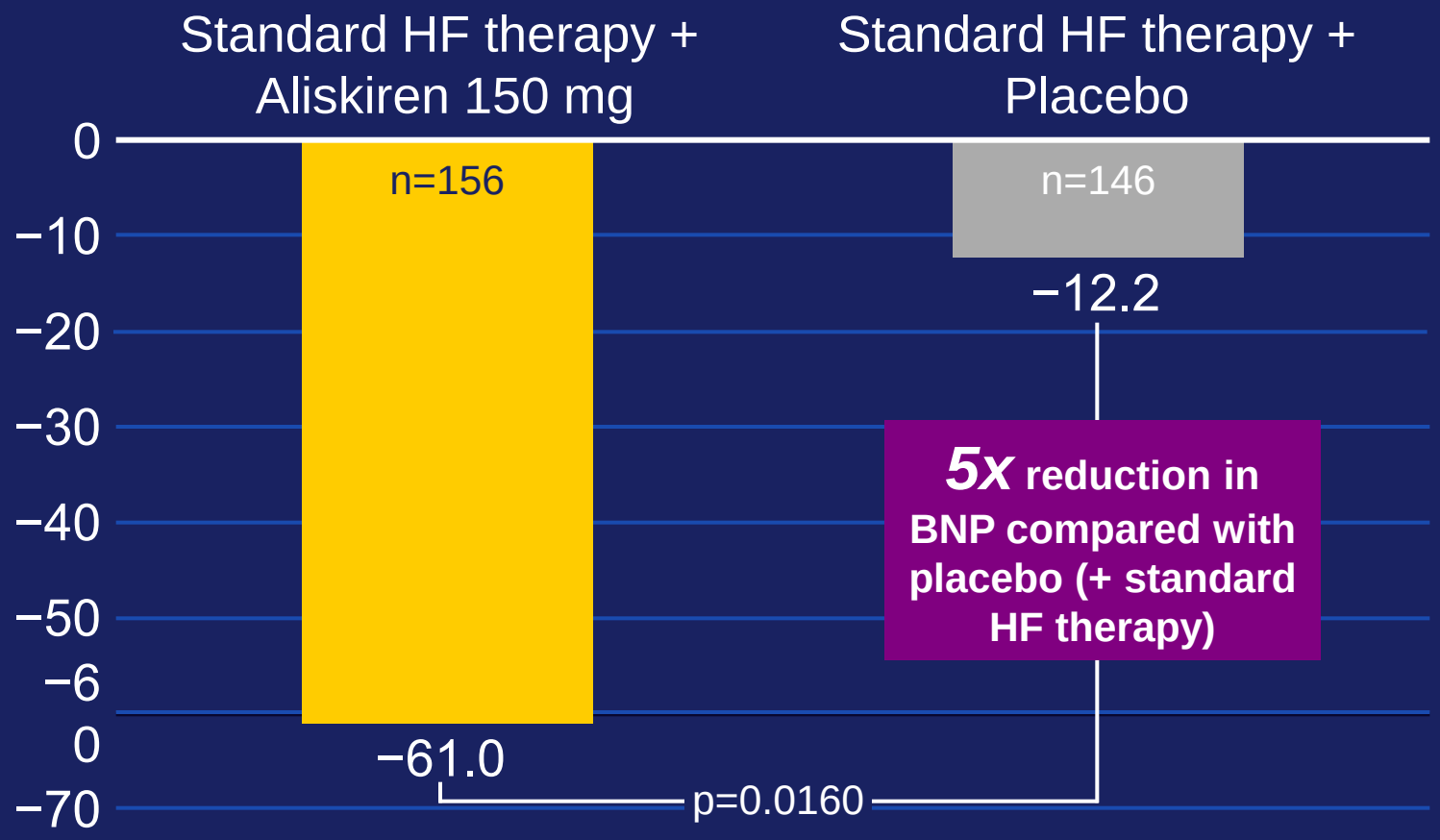
Post-hoc analysis:

- Aliskiren demonstrated comparable tolerability with placebo in the subgroup of patients with diabetes and HF[2]

NS – non-significant

1. McMurray *et al*. Circ Heart Fail 2008;1:17–24
2. Maggioni *et al*. Poster Presentation at ESC 2008

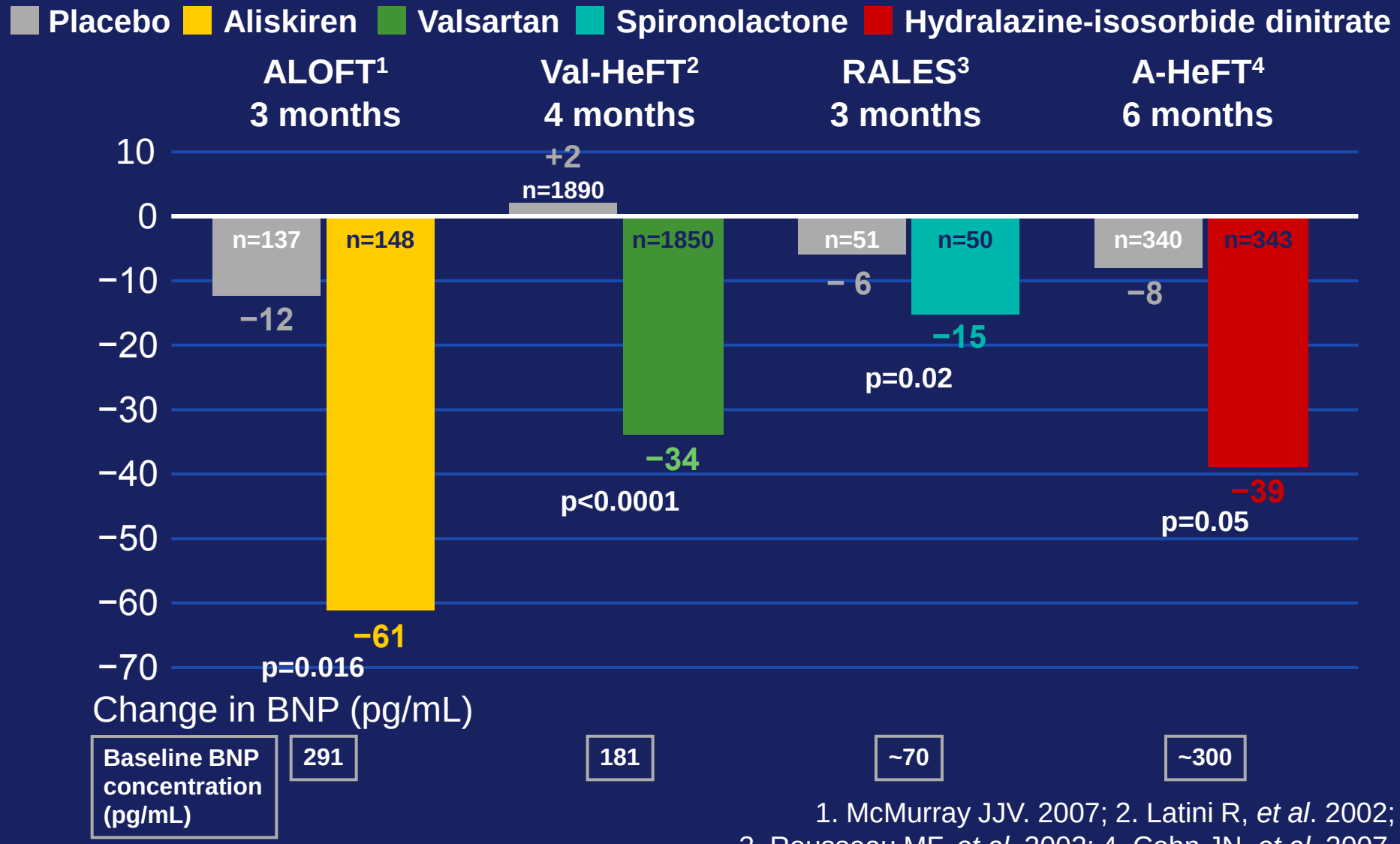
Aliskiren provides significant reductions in BNP levels compared with placebo in patients with HF



Baseline BNP values – aliskiren 301 pg/mL, placebo 273 pg/mL

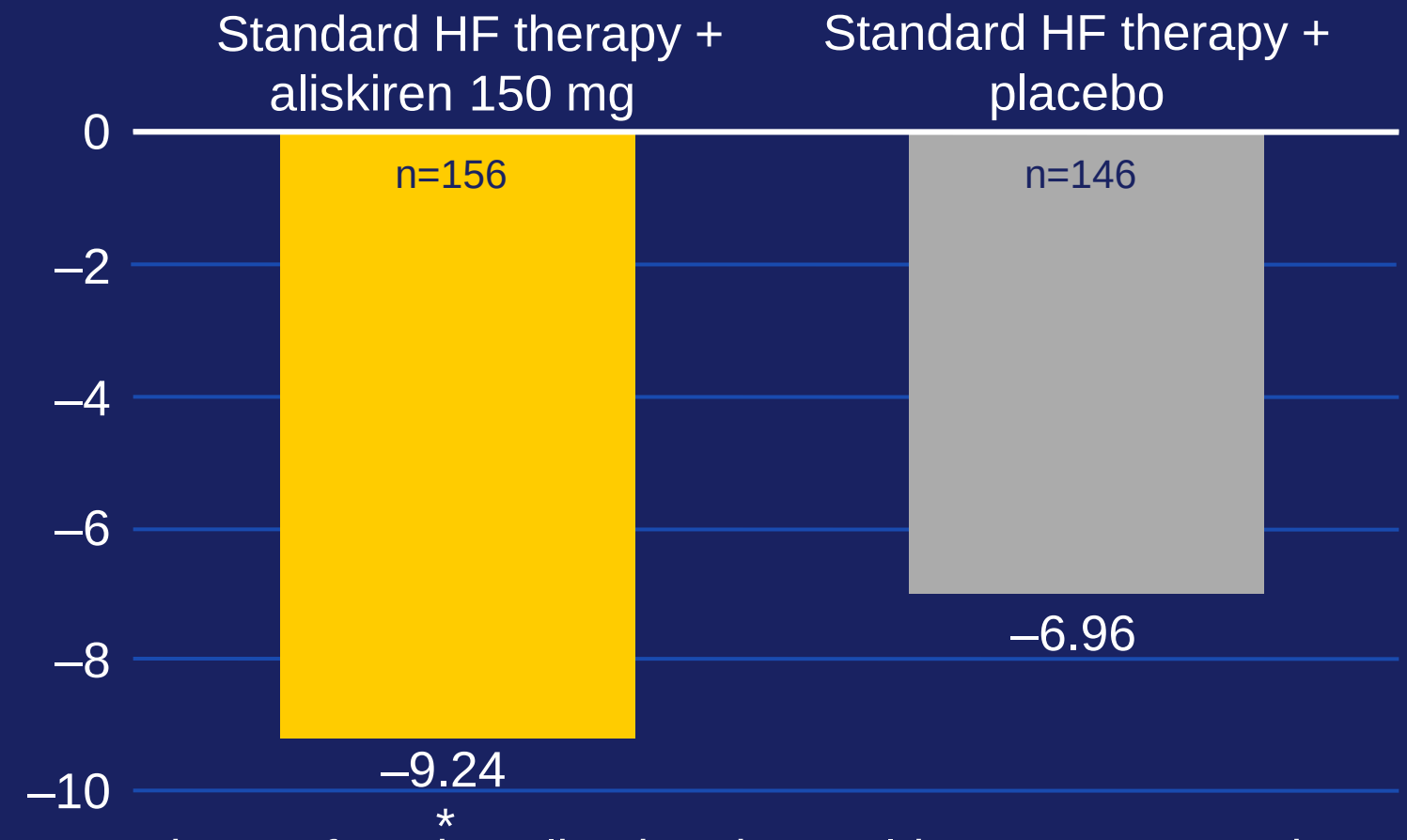
McMurray *et al*. Circ Heart Fail 2008;1:17–24

The effect of aliskiren compared with other antihypertensives on BNP levels in clinical studies



1. McMurray JJV. 2007; 2. Latini R, *et al*. 2002;
3. Rousseau MF, *et al*. 2002; 4. Cohn JN, *et al*. 2007

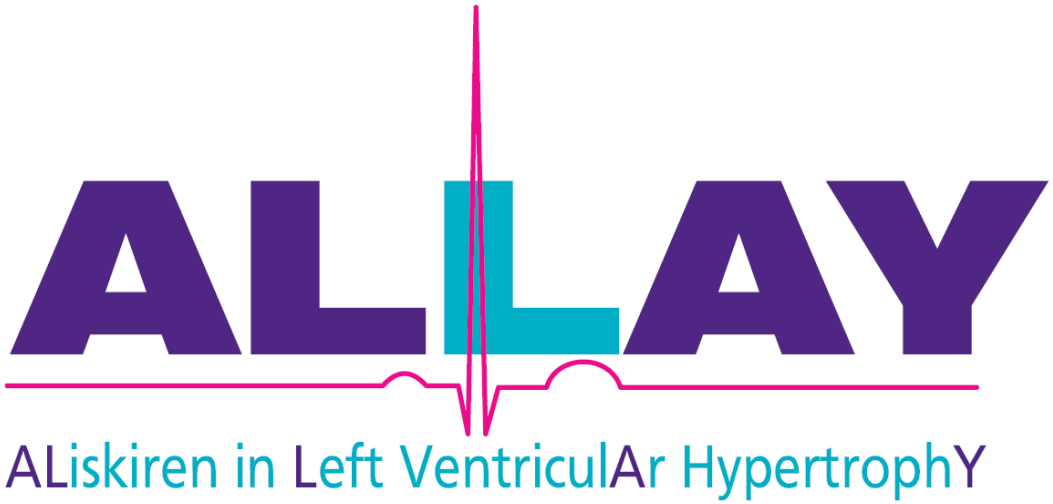
Aliskiren reduces urinary aldosterone levels compared with placebo in patients with HF



Baseline urinary aldosterone values – aliskiren 38 nmol/d, placebo 37 nmol/d

*p<0.05 vs placebo

McMurray *et al*. Circ Heart Fail 2008;1:17–24



ALiskiren in Left VentriculAr HypertrophY

ALLAY population and objectives

Study population included patients with:

- 465 patients with history of hypertension or newly diagnosed hypertension
  - SBP: 140–179 mmHg; DBP: 90–109 mmHg
- Body mass index (BMI) >25 kg/m^2
- Left ventricular wall thickness ≥1.3 cm on echocardiography†

Primary objective:

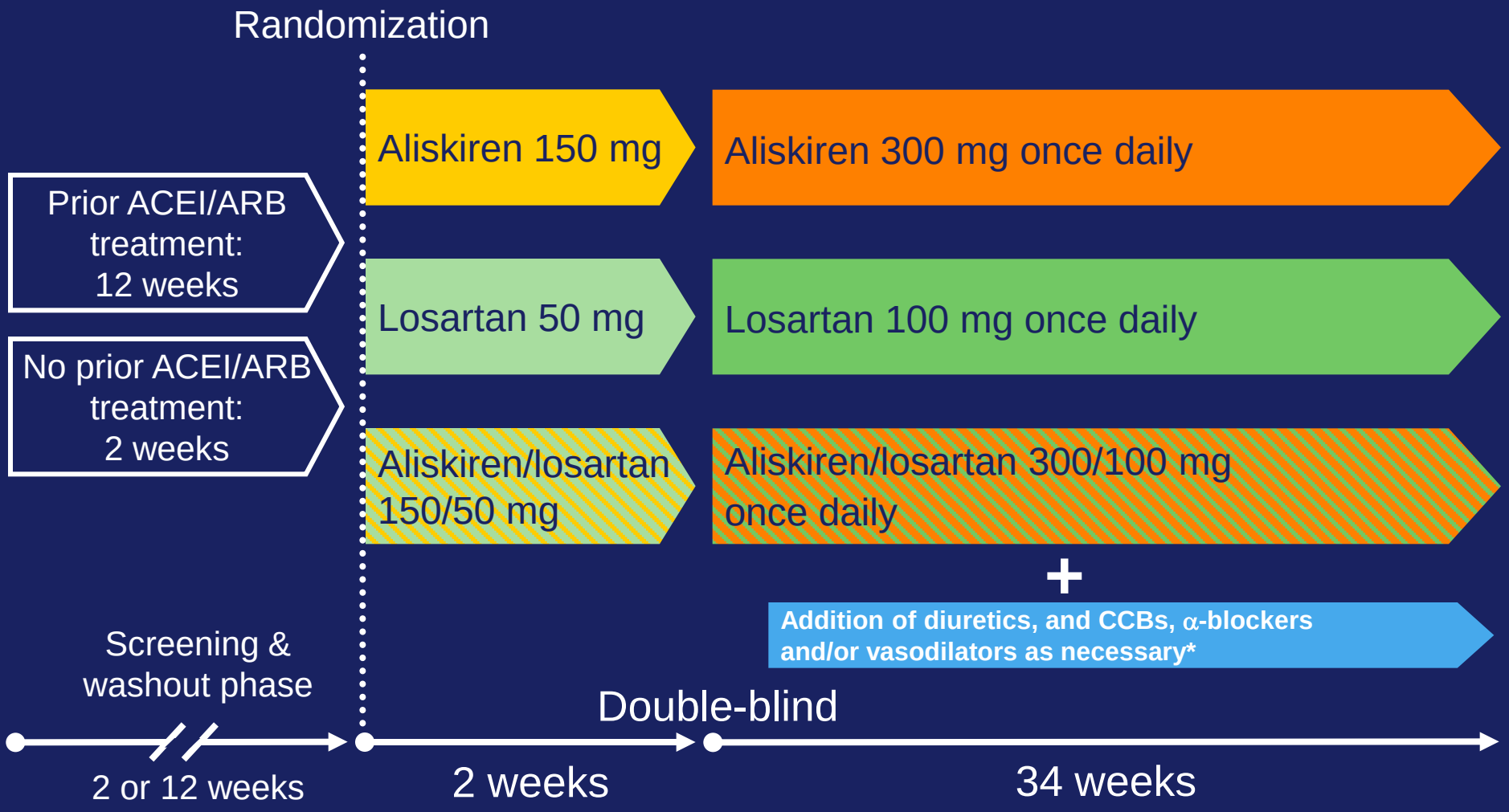
- Evaluate whether aliskiren/losartan combination therapy was superior to losartan monotherapy in reducing LVH by measuring the change in LVMI using CMR

†Confirmed by central echocardiography core laboratory assessments

CMR = cardiac magnetic resonance

Solomon SD *et al.* Oral presentation at ACC 2008

ALLAY study design overview



*To achieve BP <140/90 mmHg
(<130/80 mmHg for patients with diabetes)

Solomon SD *et al.* Oral presentation at ACC 2008

Patient demographics and baseline characteristics were similar in the three treatment groups

	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/m^2	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/ACEI 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

Solomon SD *et al.* Oral presentation at ACC 2008

The degree of LVH, assessed by echocardiography and CMR, was similar in the three treatment groups at baseline

	Aliskiren (n=154)	Losartan (n=152)	Aliskiren/losartan (n=154)
Echocardiography			
LVWT*, cm	1.4 ± 0.1	1.4 ± 0.1	1.4 ± 0.1
LVMI, g/m^2	121.4 ± 24.6	122.7 ± 27.1	125.7 ± 26.2
CMR			
LVWT (antero-septal), cm	1.34 ± 0.2	1.38 ± 0.2	1.38 ± 0.2
LVWT (infero-lateral), cm	0.96 ± 0.2	0.98 ± 0.2	0.98 ± 0.2
LVMI, g/m^2	77.6 ± 17.2	79.4 ± 18.1	78.4 ± 15.8

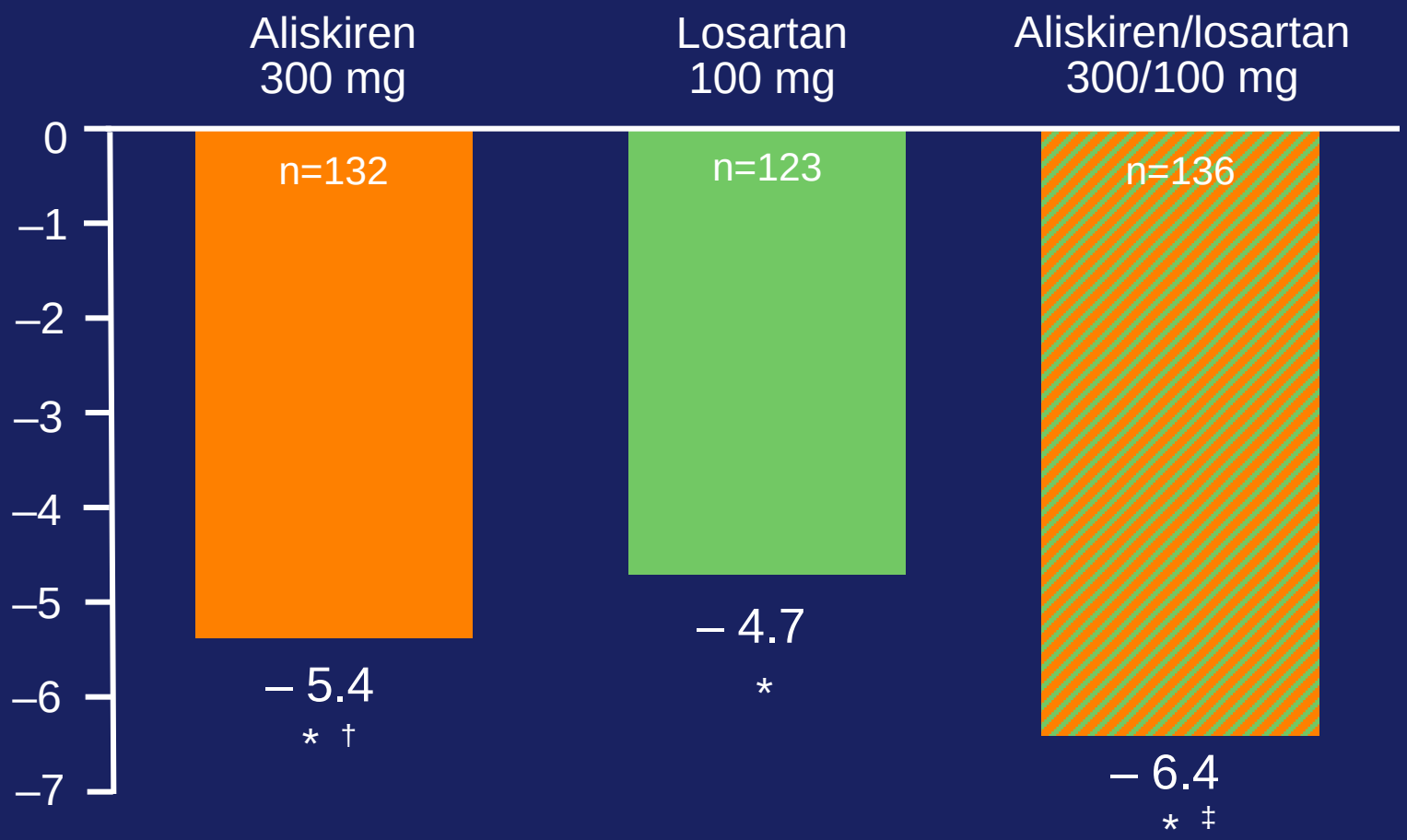
LVWT – LV wall thickness, LVMI – LV mass index

*Baseline LVWT ≥1.3 cm was required for randomization

Data are shown as mean ± SD for the randomized population

Solomon SD *et al.* Oral presentation at ACC 2008

Aliskiren/losartan combination provides an ~20% greater numerical reduction in LVMI from baseline compared with losartan monotherapy

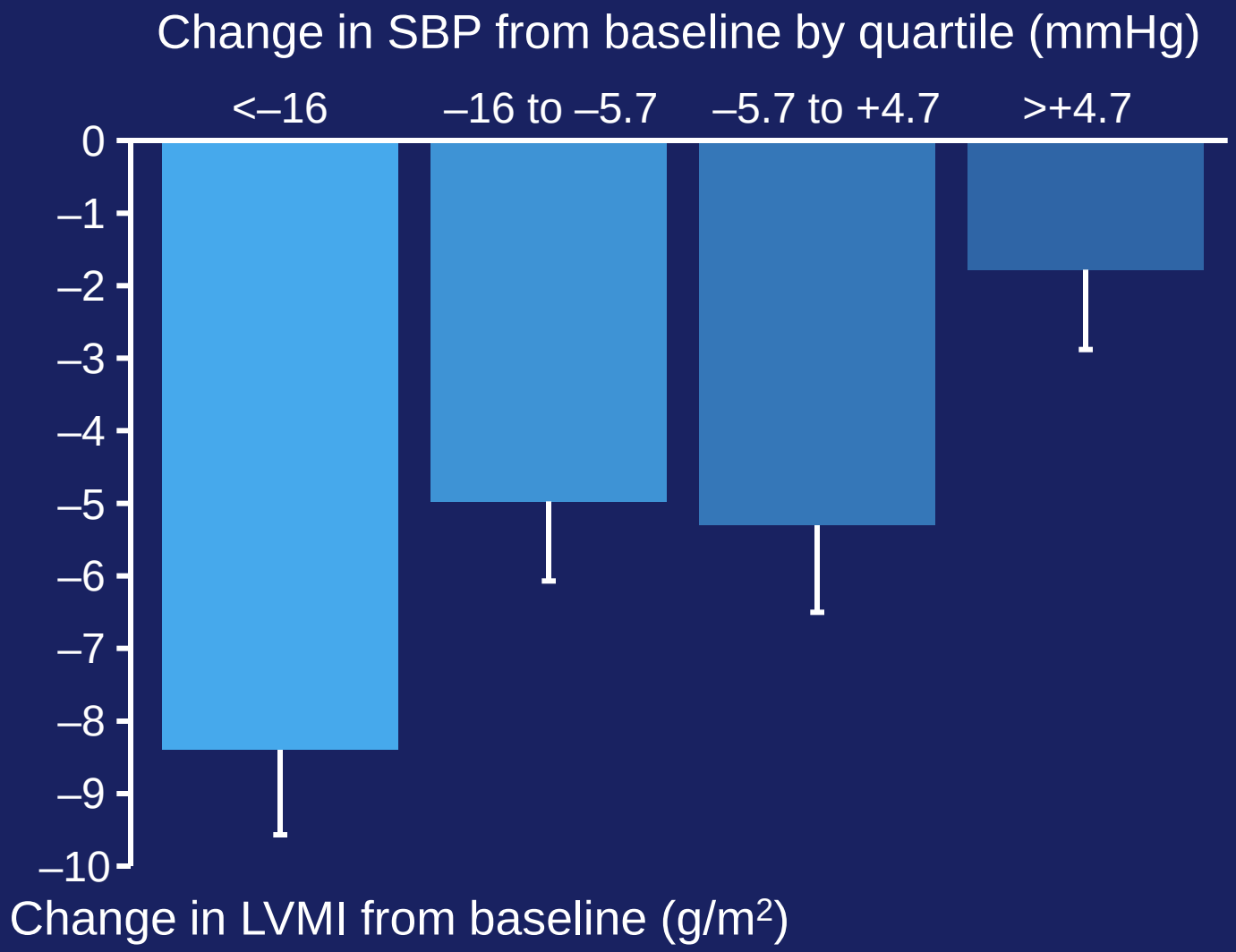


Mean percentage change from baseline in LVMI after 36 weeks' treatment (%)

Between-treatment analyses based on least-squares mean data:
*p<0.0001 vs baseline
†p<0.0001 for non-inferiority vs losartan 100 mg; ‡p=0.52 vs losartan 100 mg

Solomon SD *et al.* Oral presentation at ACC 2008

Greater reductions in SBP are associated with greater reductions in LVMI



Solomon SD *et al.* Oral presentation at ACC 2008

Aliskiren/losartan combination therapy has a similar safety and tolerability profile to aliskiren and losartan monotherapies

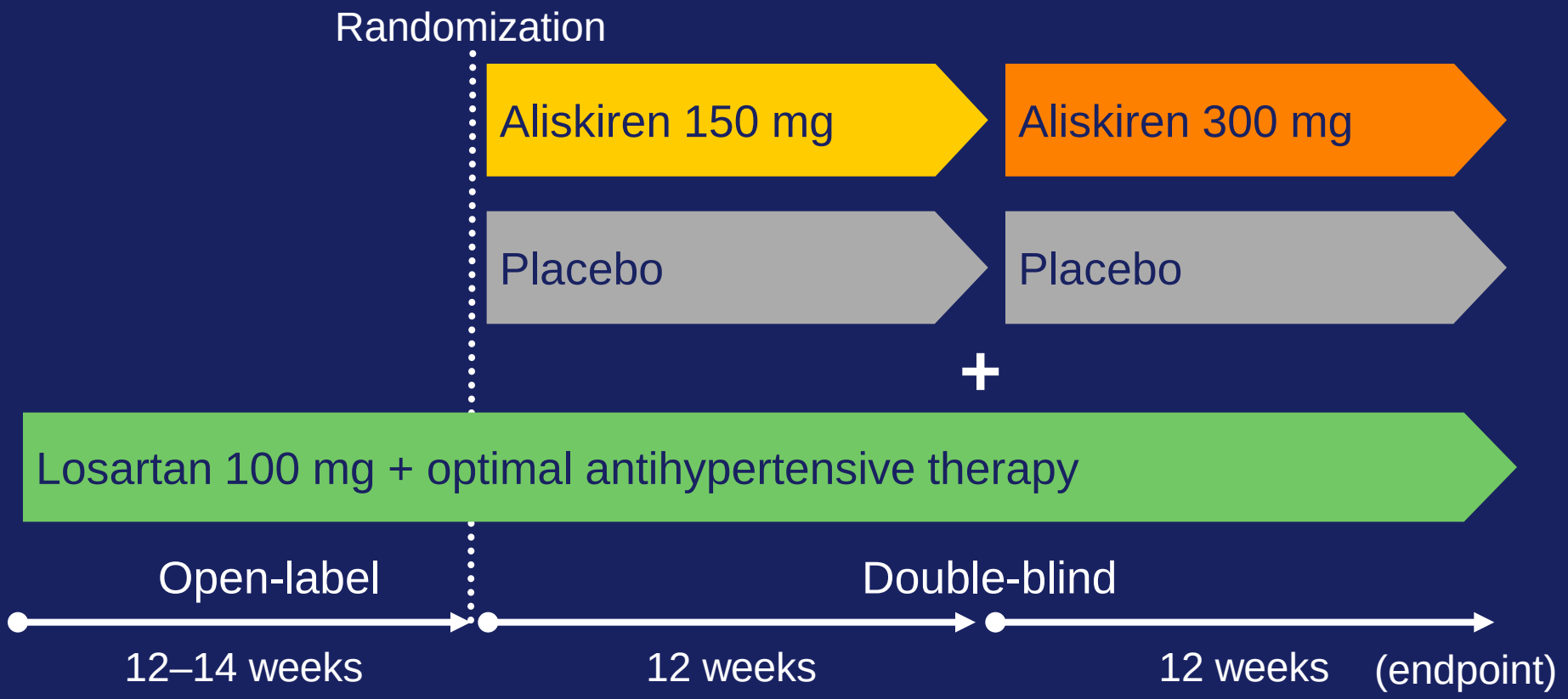
	Aliskiren (n=154)	Losartan (n=152)	Aliskiren/losartan (n=154)
Any AE, n (%)	91 (59.1)	82 (53.9)	86 (55.8)
Discontinuations due to AEs, n (%)	4 (2.6)	10 (6.6)	5 (3.2)
Serious AEs, n (%)	**10 (6.5)**	**13 (8.6)**	**10 (6.5)**
Deaths, n (%)	0	0	0
Headache , n (%)	14 (9.1)	8 (5.3)	10 (6.5)
Nasopharyngitis , n (%)	11 (7.1)	13 (8.6)	11 (7.1)
Bronchitis, n (%)	7 (4.5)	3 (2.0)	3 (1.9)
Diarrhoea, n (%)	6 (3.9)	9 (5.9)	7 (4.5)
Dizziness, n (%)	5 (3.2)	3 (2.0)	8 (5.2)
Hypotension, n (%)	2 (1.3)	2 (1.4)	3 (1.9)

Data are shown for the safety population; AE, adverse events. No significant differences were observed between treatments (p>0.05 for all comparisons)

Solomon SD *et al.* Oral presentation at ACC 2008

Aliskiren in the EValuation of PrOteinuria In Diabetes

AVOID study – Design overview



- All patients continue to receive open-label losartan 100 mg and optimal antihypertensive therapy during the double-blind period
- Patients force-titrated after 12 weeks
- All treatments administered once daily

Parving *et al.* New Engl J Med 2008;358:2433–46

AVOID study – Objectives

Primary objective:

- Change in urinary albumin-to-creatinine ratio (UACR) from baseline to study end with aliskiren when added to losartan 100 mg once daily and optimal antihypertensive therapy, compared with placebo

Secondary objectives included:

- Proportion of patients with ≥50% reduction in UACR at study end
- Effect of treatment on urinary albumin excretion rate (UAER) and eGFR
- Effect of treatment on BP
- Safety and tolerability

Parving *et al.* New Engl J Med 2008;358:2433–46

Baseline characteristics were similar in the aliskiren and placebo groups

Characteristic	Optimal antihypertensive therapy + Aliskiren (n=301)	Optimal antihypertensive therapy + Placebo (n=298)
Age, years	59.8 ± 9.6	61.8 ± 9.6
Male gender, n (%)	206 (68.4)	221 (74.2)
Race, n (%)		
Caucasian	259 (86.0)	261 (87.6)
Black	24 (8.0)	26 (8.7)
Asian	5 (1.7)	6 (2.0)
Other	13 (4.3)	5 (1.7)
Body mass index, kg/m^2	33 ± 7	32 ± 6
Known duration of diabetes, years	13.2 ± 8.4	14.9 ± 8.7
Diabetic neuropathy, n (%)	55 (18.3)	49 (16.4)
Diabetic retinopathy, n (%)	65 (21.6)	82 (27.5)

Data are presented as mean ± SD, unless otherwise stated

Parving *et al.* New Engl J Med 2008;358:2433–46

Baseline laboratory variables were similar in the aliskiren and placebo groups

Variable	Optimal antihypertensive therapy + Aliskiren (n=301)	Optimal antihypertensive therapy + Placebo (n=298)
Mean sitting blood pressure, mmHg		
Systolic	135 ± 12	134 ± 12
Diastolic	78 ± 8	77 ± 9
Geometric mean UACR, mg/g	513 (463–569)	553 (502–609)
Geometric mean UAER, µg/min	495 (440–557)	520 (469–576)
Mean eGFR, mL/min/1.73 m^2	68.5 ± 25.7	66.8 ± 24.5

Data are presented as mean ± SD, except for UACR and UAER, which are shown as geometric mean (95% CI)

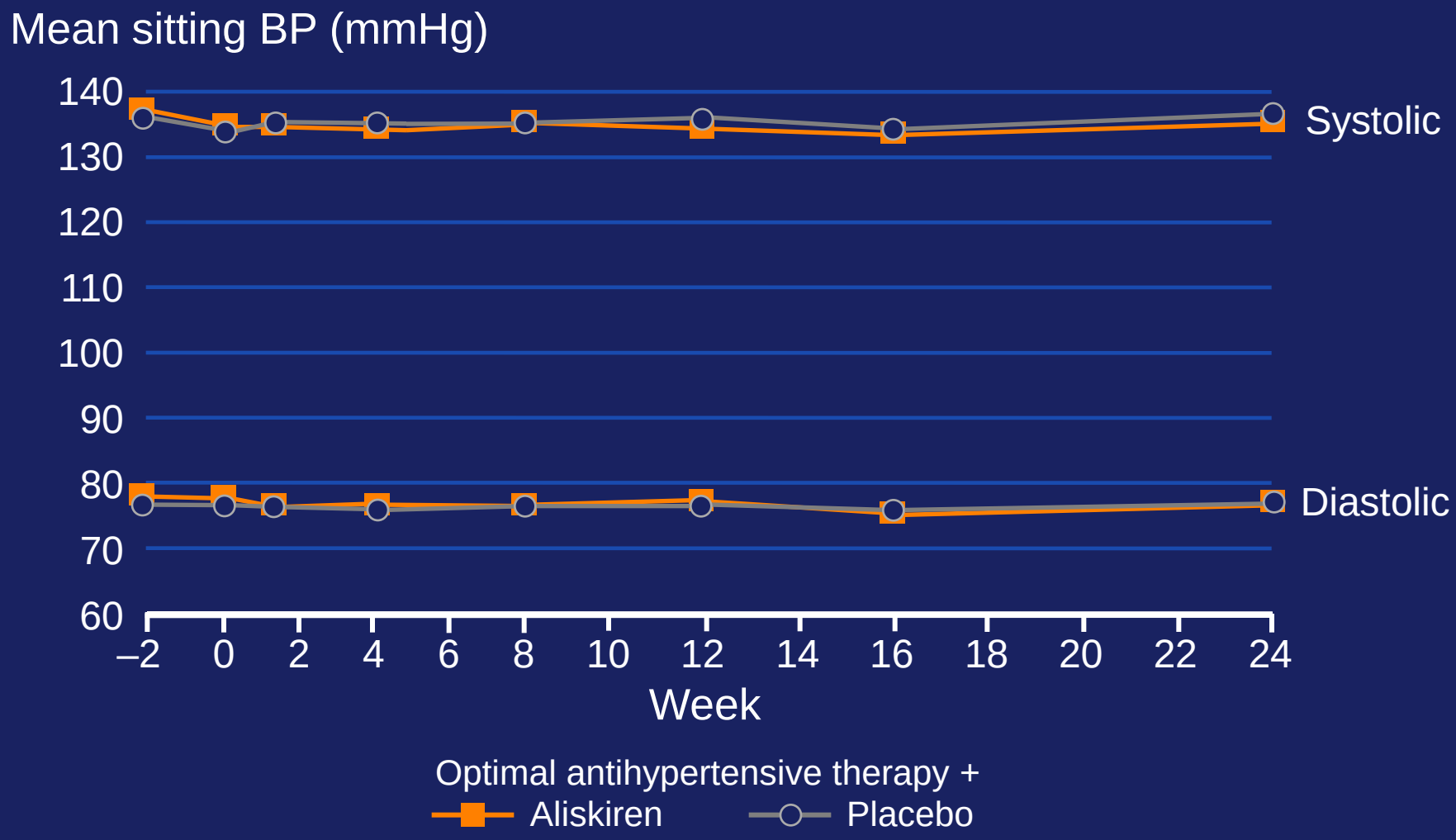
Parving *et al.* New Engl J Med 2008;358:2433–46

Antihypertensive medications initiated prior to the start of the open-label period were similar in the two treatment groups

Drug class	Optimal antihypertensive therapy + Aliskiren (n=301)	Optimal antihypertensive therapy + Placebo (n=298)
Antihypertensive therapies, n (%)		
ACEIs	164 (54.5)	175 (58.7)
ARBs	154 (51.2)	143 (48.0)
Calcium channel blockers (dihydropyridine)	123 (40.9)	147 (49.3)
Thiazide diuretics	109 (36.2)	129 (43.3)
β-blockers	92 (30.6)	90 (30.2)
Loop diuretics	69 (22.9)	73 (24.5)

Parving *et al.* New Engl J Med 2008;358:2433–46

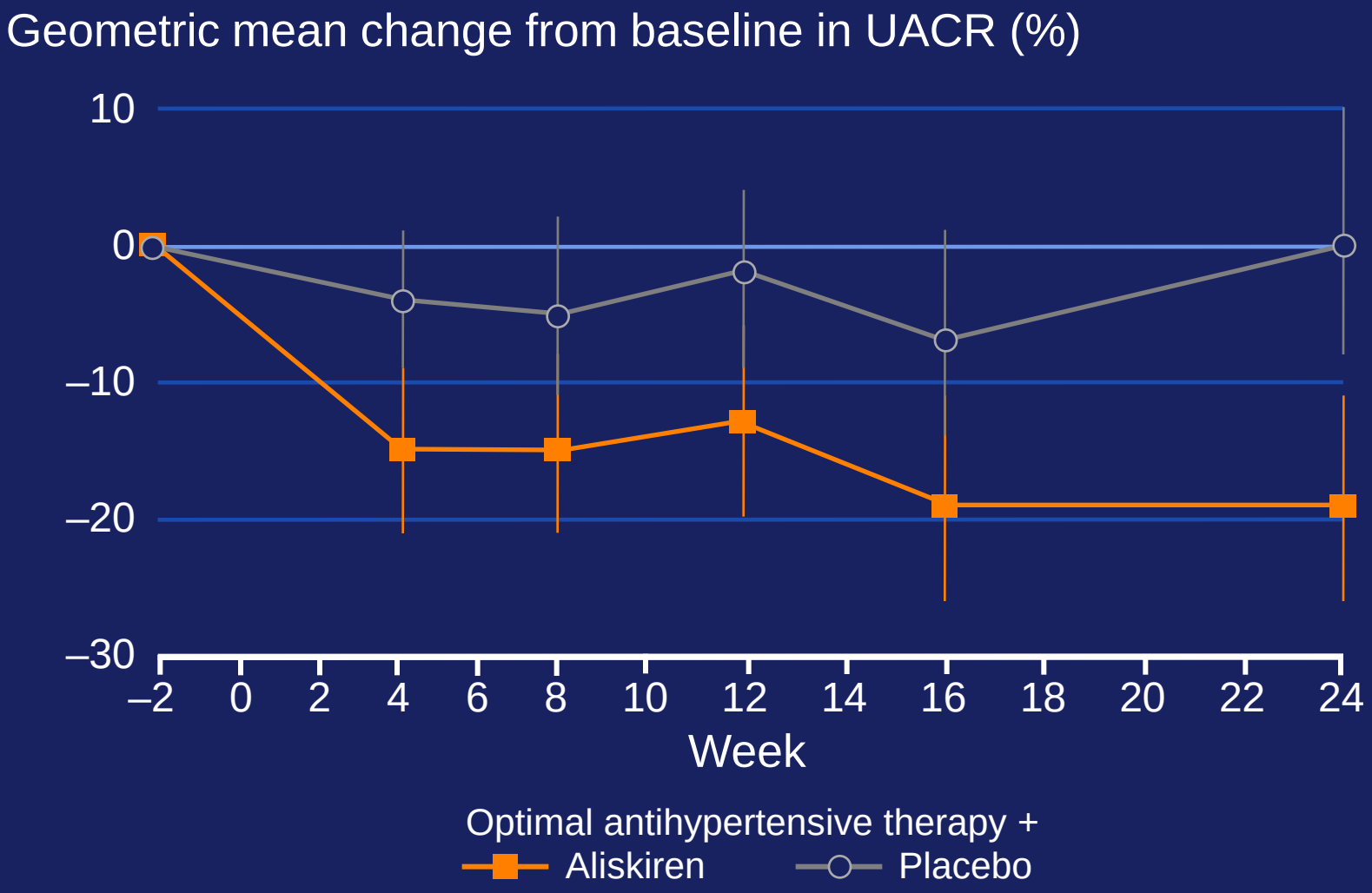
BP remained similar in the aliskiren and placebo groups throughout the course of the study



Baseline was the Week 0 (Day 1) value

Parving *et al.* New Engl J Med 2008;358:2433–46

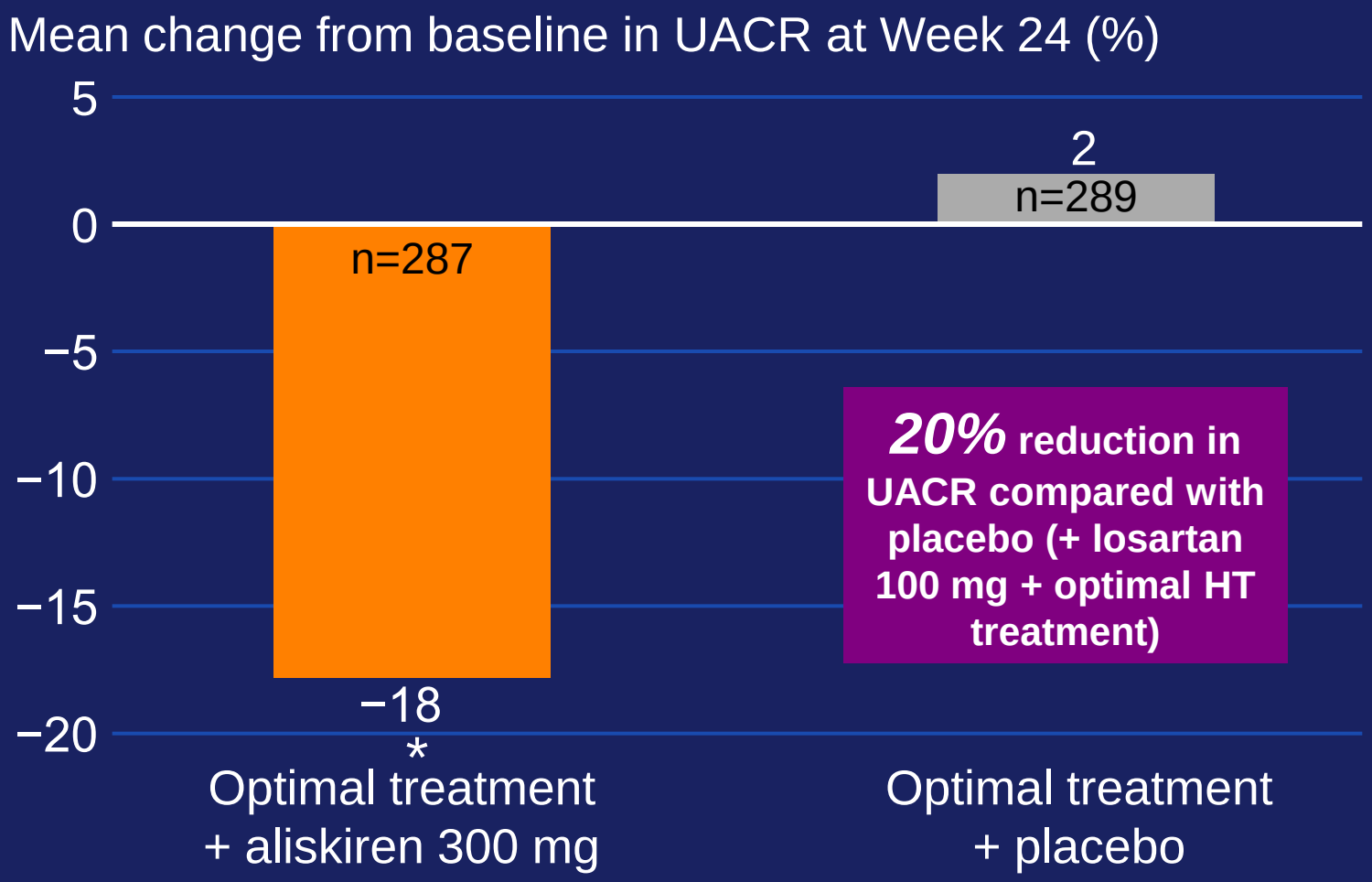
Aliskiren provides greater reductions in UACR from baseline throughout the course of the study compared with placebo



Baseline was the Week –2 value
Data are shown as change from baseline in geometric mean (95% CI)

Parving *et al.* New Engl J Med 2008;358:2433–46

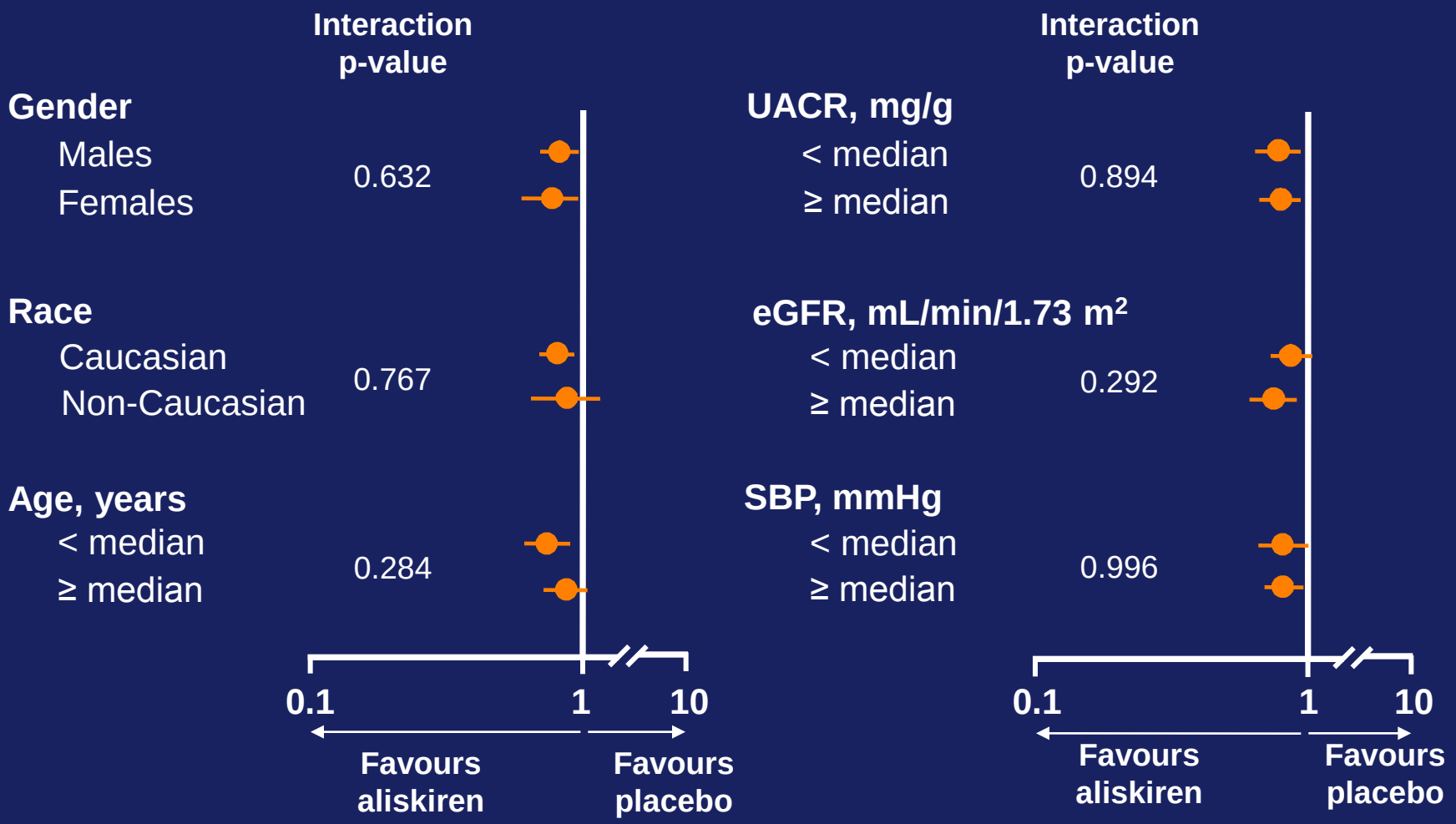
Aliskiren provides significantly greater reductions in UACR compared with placebo



*p=0.0009 vs placebo; data are shown as percentage change in geometric mean; baseline was Week −2 value

Parving *et al.* New Engl J Med 2008;358:2433–46

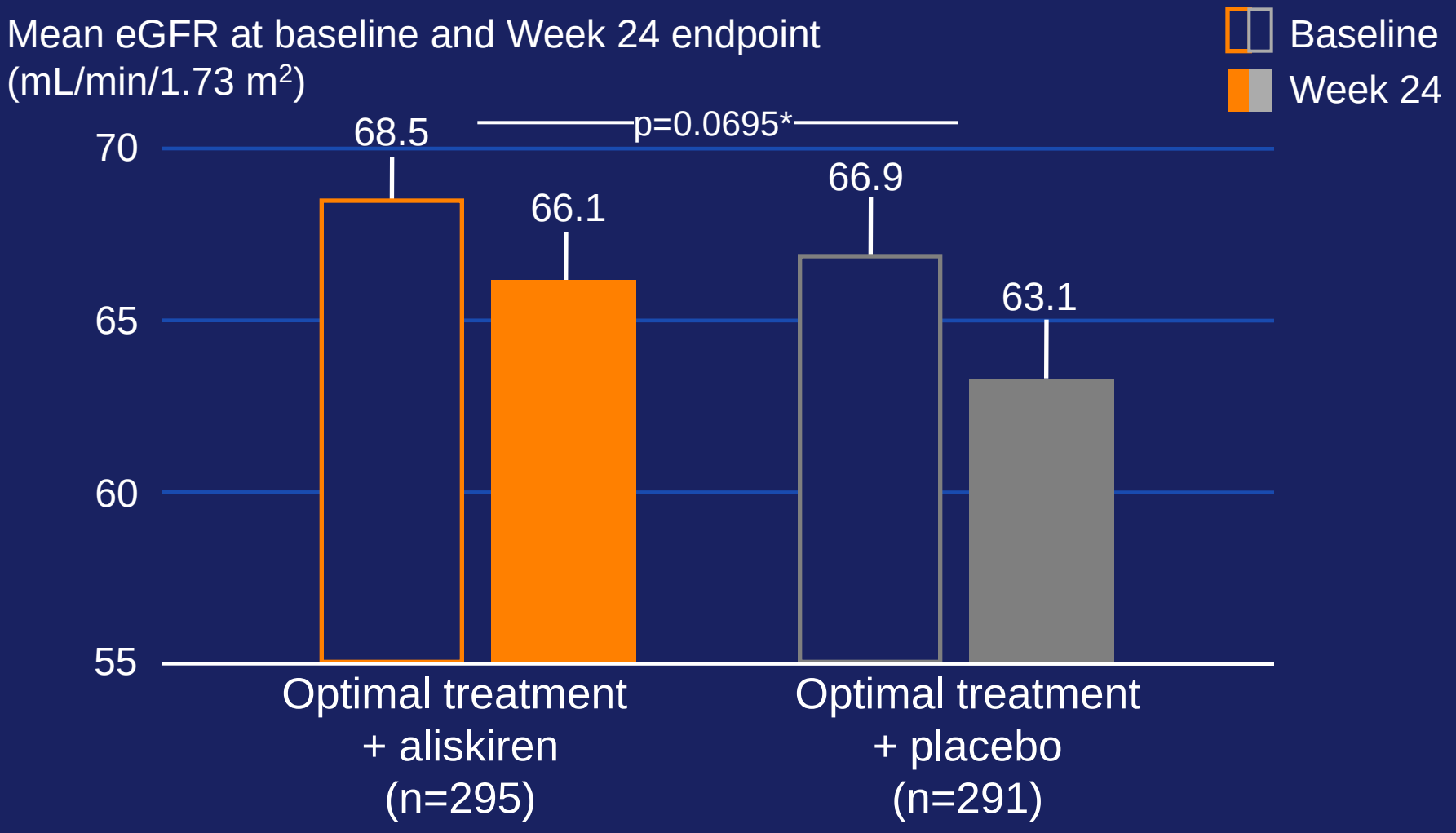
Aliskiren provides greater reductions in UACR than placebo across different patient subgroups



Data are shown as geometric mean with 95% CI
for the ratio of the treatment effect for aliskiren:placebo

Parving *et al.* New Engl J Med 2008;358:2433–46

Aliskiren treatment preserved eGFR during the study



Baseline was Day 1 value; *p value provided for the comparison of change from baseline in eGFR between groups

Parving *et al.* New Engl J Med 2008;358:2433–46

Addition of aliskiren to losartan and optimal antihypertensive therapy was generally well tolerated during the study

	Optimal antihypertensive therapy +	
	Aliskiren (n=301)	Placebo (n=298)
Any adverse event (AE), n (%)	201 (66.8)	200 (67.1)
Any serious AE, n (%)	**27 (9.0)**	**28 (9.4)**
Discontinuations due to AEs, n (%)	**17 (5.6)**	**19 (6.4)**
Deaths, n (%)	0	2 (0.7)
AEs reported by ≥5% of patients in either treatment group, n (%)		
Headache	18 (6.0)	11 (3.7)
Nasopharyngitis	18 (6.0)	15 (5.0)
Dizziness	15 (5.0)	10 (3.4)
Hyperkalaemia	15 (5.0)	17 (5.7)
Peripheral oedema	13 (4.3)	23 (7.7)

Data are shown for the double-blind period

Parving *et al.* New Engl J Med 2008;358:2433–46

Baseline characteristics of patients with elevated serum potassium (≥6.0 mEq/L) during the double-blind period

	Optimal antihypertensive therapy +	
	Aliskiren (n=14)	Placebo (n=5)
Demographic characteristics		
Age, years	64.0 ± 3.8	61.0 ± 11.5
Male gender, n (%)	7 (50.0)	3 (60.0)
Concomitant medication, n (%)		
Diuretic use at baseline	7 (50.0)	3 (60.0)
Diuretic use post-baseline	1 (7.1)	0
Baseline laboratory values		
Potassium, mEq/L	5.2 ± 0.5	4.7 ± 0.2
Creatinine, mg/dL	1.4 ± 0.6	1.2 ± 0.2
BUN, mg/dL	28.0 ± 8.5	27.2 ± 8.7

BUN, blood urea nitrogen
Data are presented as mean ± SEM unless otherwise stated

Parving *et al.* New Engl J Med 2008;358:2433–46

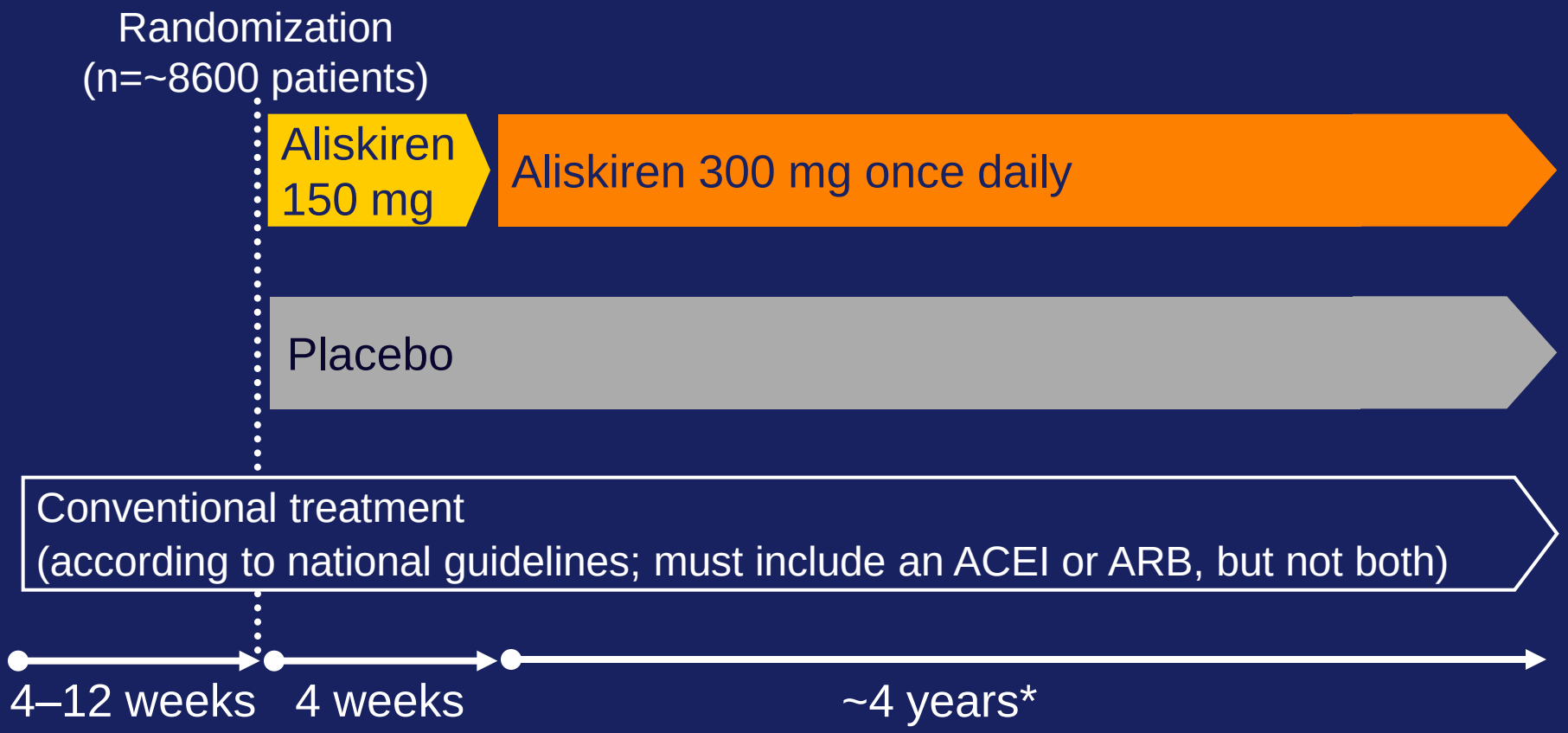
ALiskiren Trial In Type 2 diabetes Using cardio-renal Disease Endpoints

ALTITUDE study – Design

Study design:	Randomized, double-blind, placebo-controlled study
Study population:	~8600 patients
Inclusion criteria:	Type 2 diabetes Proteinuria Mean estimated GFR ≥30 and <60 mL/min/ /1.73m^2 History of CV disease (previous MI or stroke, heart failure [HF], coronary artery disease) Concomitant treatment must include an ACEI or an ARB
Treatment period:	~4 years (event driven [study will conclude when ~1628 patients meet the primary endpoint])
Study status*:	Ongoing
Anticipated completion:	2012

Data on File, Novartis 2007

ALTITUDE – Design overview



Three categories of high-risk patients that will be included are those with either:
(i) albuminuria (UACR >200 mg/g);
(ii) microalbuminuria (UACR ≥20–<200 mg/g) and an eGFR ≥30–<60 mL/min/1.73m^2; or
(iii) a history of CV disease and an eGFR ≥30–<60 mL/min/1.73m^2

*ALTITUDE is an event driven study

Parving H-H, *et al*. 2007 (Study 2337E)

ALTITUDE – Objectives

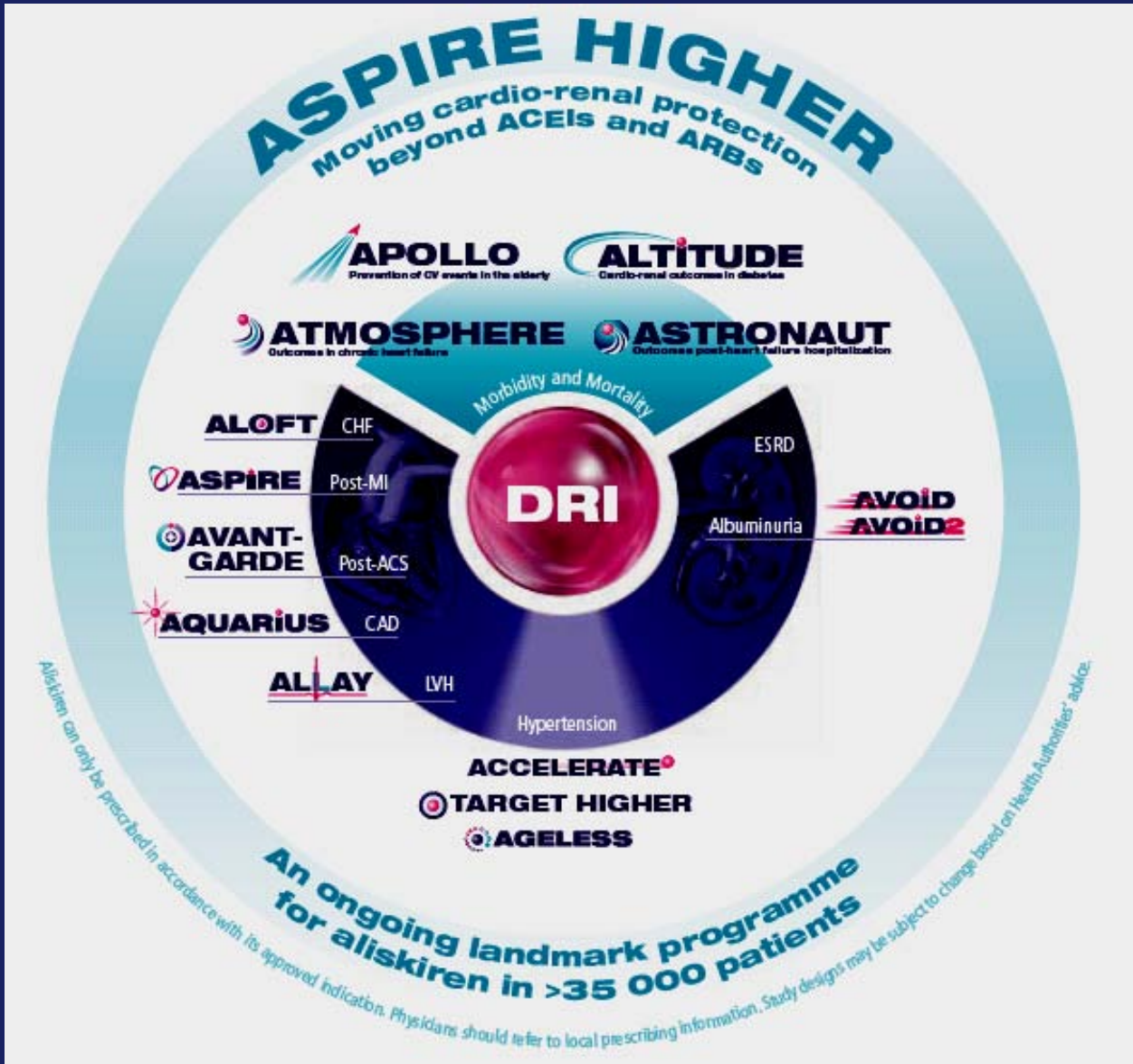
Primary objective:

- To determine whether aliskiren, when added to conventional treatment delays the occurrence of CV and renal complications in patients with type 2 diabetes at high risk for CV and renal events
  - occurrence is defined as the first event of the following composite primary endpoint: (1) CV death; (2) resuscitated sudden death; (3) non-fatal MI; (4) non-fatal stroke; (5) unplanned hospitalization for HF; (6) onset of ESRD or renal death; and (7) doubling of baseline serum creatinine concentration, sustained for at least one month

Parving H-H, *et al*. 2007 (Study 2337E)

ALOFT, ALLAY & AVOID form part of the ongoing ASPIRE HIGHER clinical trial program

- Results from ALOFT, ALLAY & AVOID provide encouraging evidence for potential cardio-renal protection with aliskiren
- The ongoing ASPIRE HIGHER clinical trial programme will potentially confirm these results by providing morbidity and mortality data



Aliskiren QUantitative Atherosclerosis Regression
Intravascular Ultrasound Study

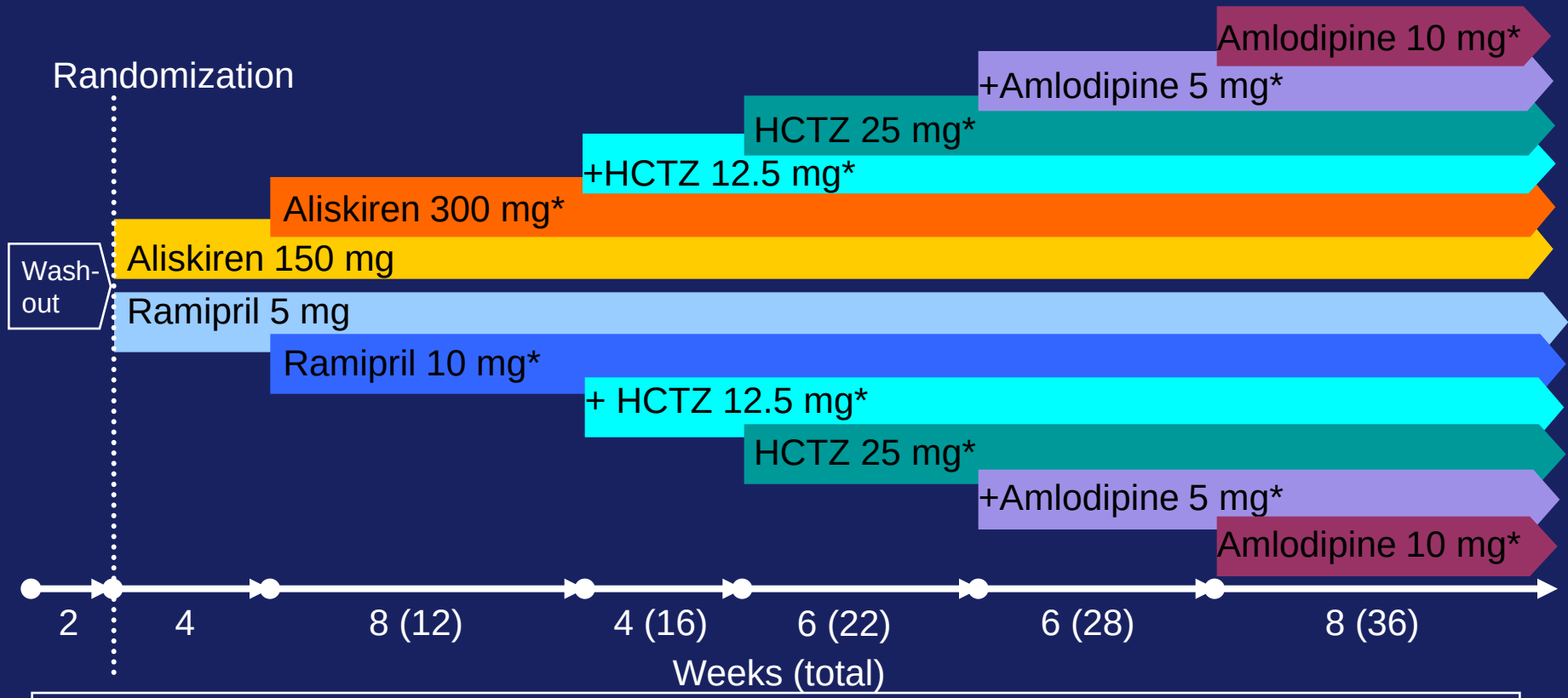
AQUARIUS – Study overview

- In low-density lipoprotein receptor deficient mice, subcutaneous infusion of aliskiren led to near complete removal of atherosclerotic lesions[2]
- The AQUARIUS study is an imaging-based study that will use intravascular ultrasound (IVUS) to evaluate change in atherosclerotic burden for aliskiren compared with placebo in patients with CAD

1. Werner *et al.* 2008; 2. Lu *et al.* 2008.

Aliskiren for GEriatric LowEring of SyStolic hypertension

AGELESS – Study design and objectives



- ~912 patients aged ≥65 years with uncomplicated systolic hypertension (systolic BP 140–<180 mmHg)
- Primary objective: Reduction in systolic BP at Week 12 (i.e. monotherapy stage)
- Additional key objectives: Incidence of cough; effect on quality of life; reductions in BP at Week 36 (i.e. combination therapy stage); safety and tolerability

HCTZ, hydrochlorothiazide. *If SBP ≥140 mmHg

Clinicaltrials.gov 2006.

ASPIRE HIGHER

Moving cardio-renal protection beyond ACEIs and ARBs

An ongoing landmark programme for aliskiren in >35 000 patients

Aliskiren can only be prescribed in accordance with its approved indication. Physicians should refer to local prescribing information. Study designs may be subject to change based on Health Authorities' advice.