Where are we with RAS blockade? New Targets.

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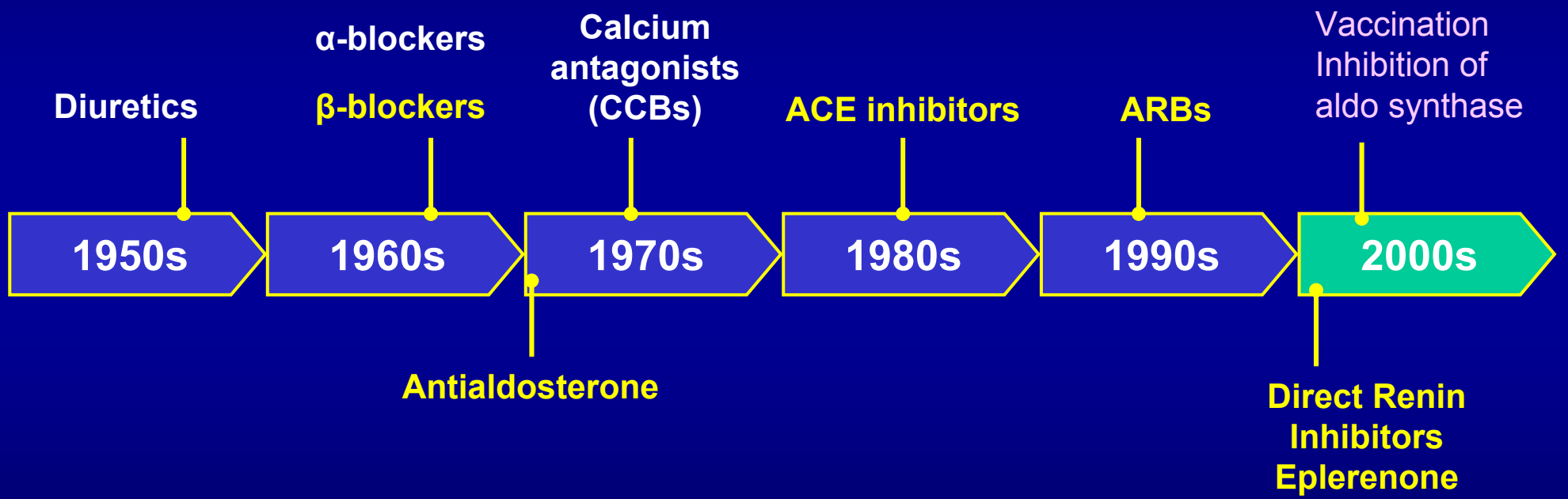
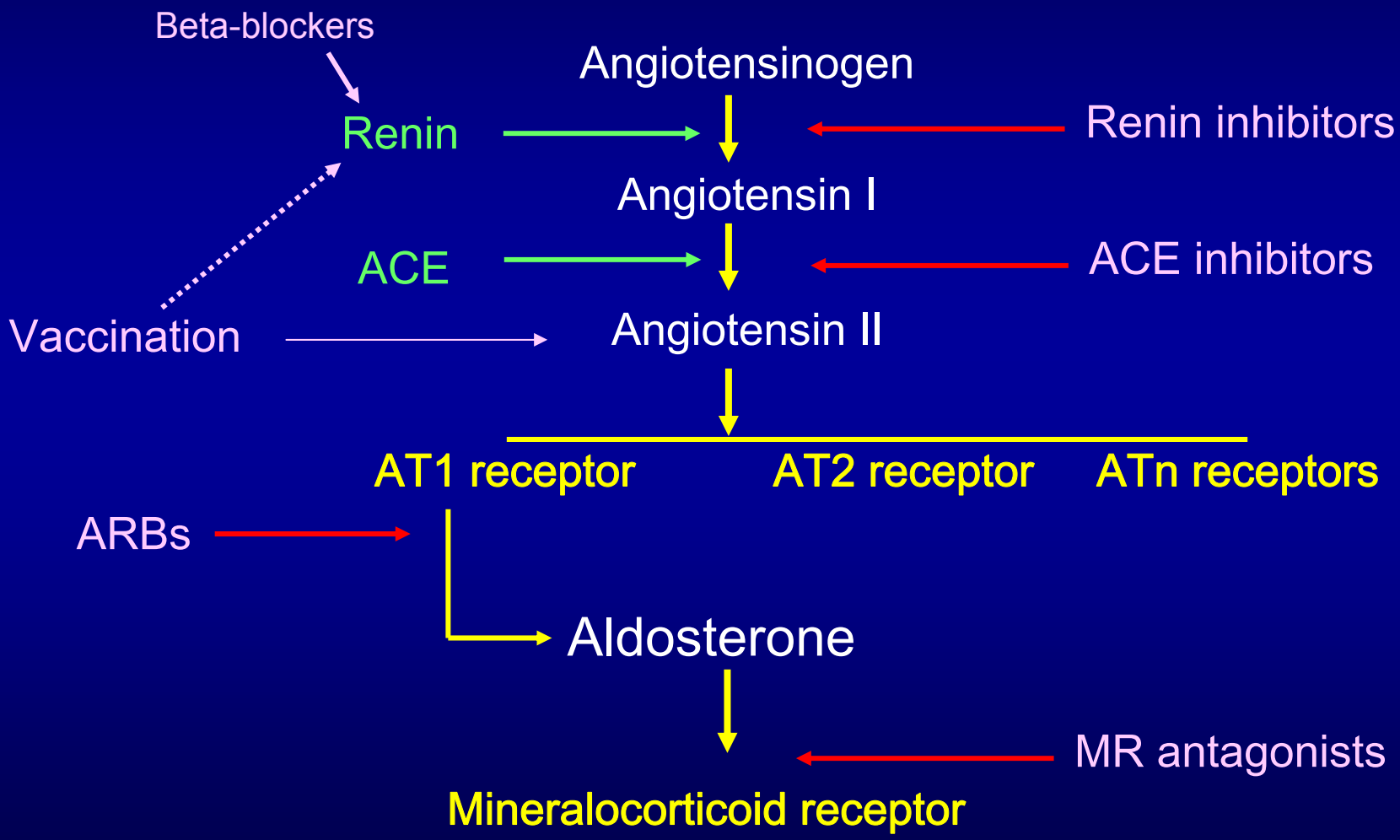
Introduction of new antihypertensive classes

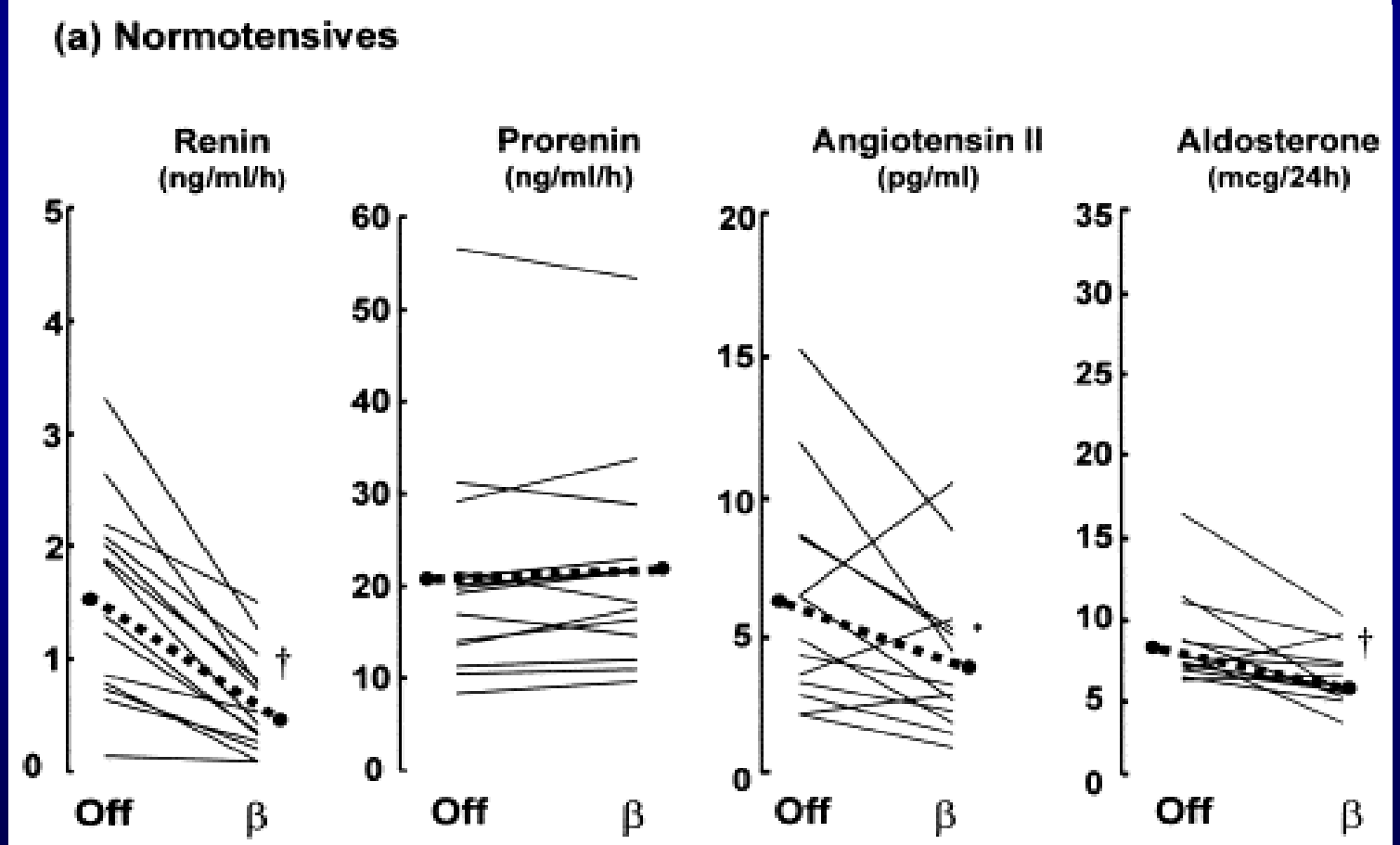


The renin-angiotensin system and aldosterone…



What about beta-blockers and renin inhibition ?

Renin system hormones before and during β-blockade in individual patients



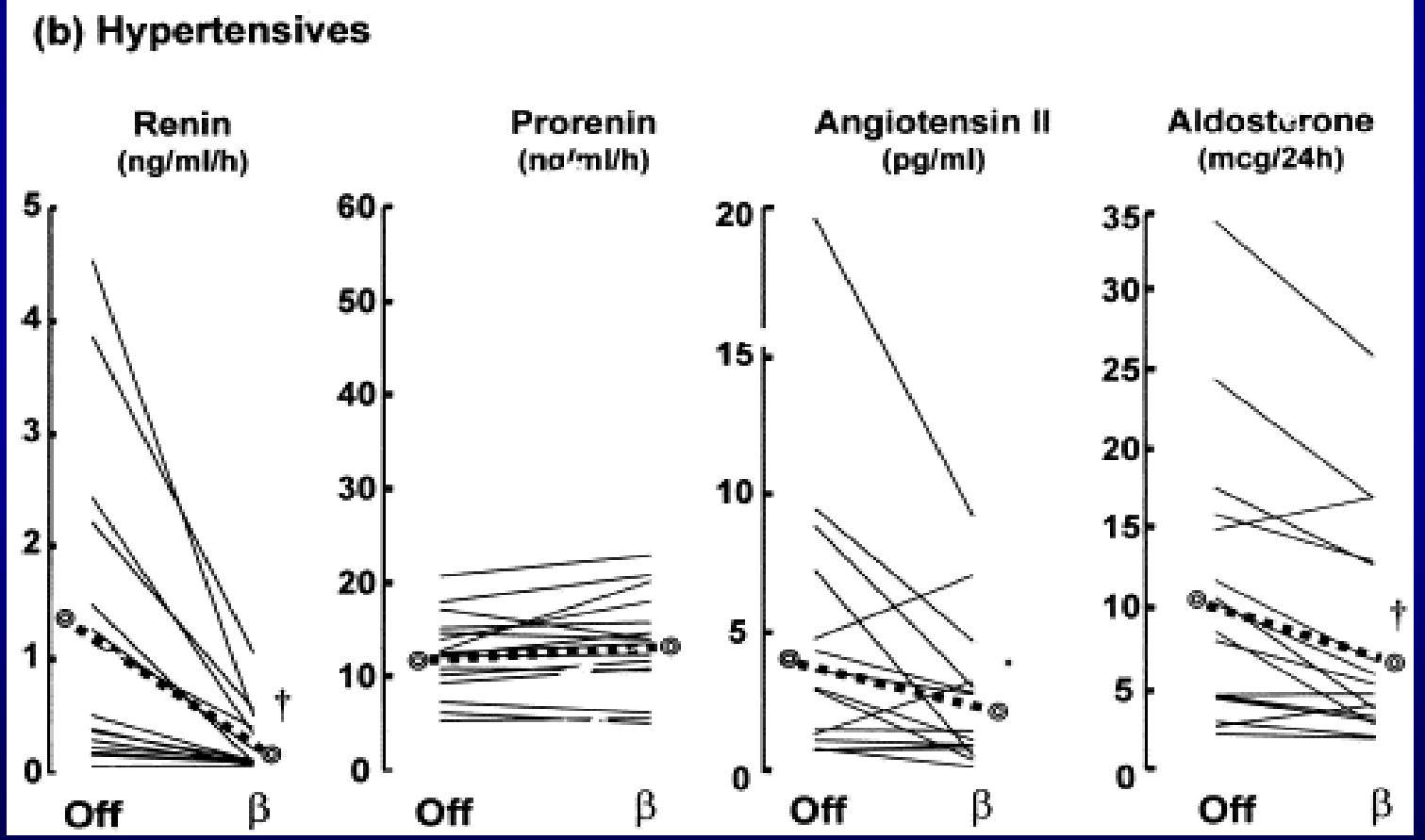
N= 14 subjects
One week administration

4 different β-blockers

Blumenfeld et al, Am J Hypertens, 1999

What about beta-blockers and renin inhibition ?

Renin system hormones before and during β-blockade in individual patients

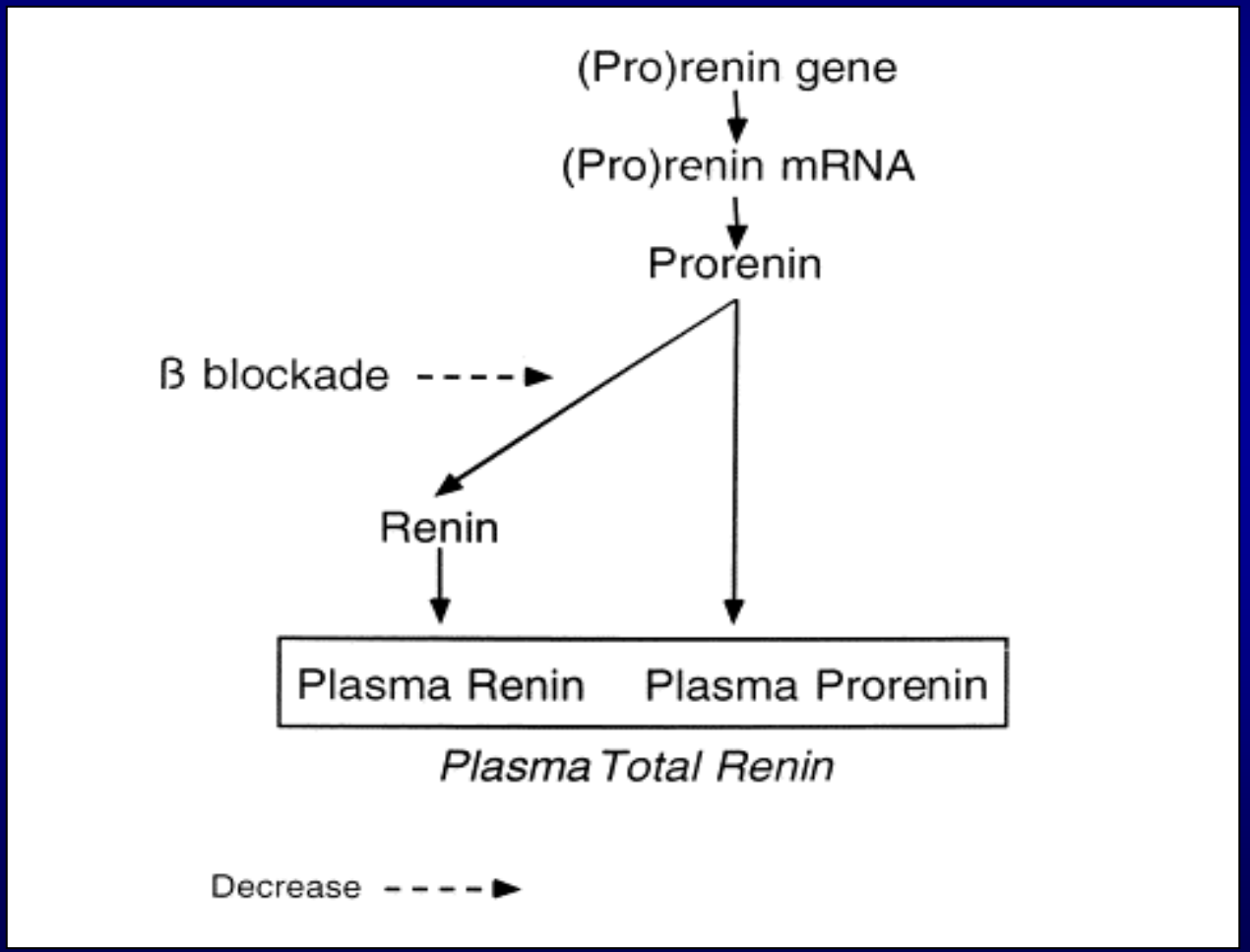


N= 16 hypertensives
One week
Administration

4 different β-blockers

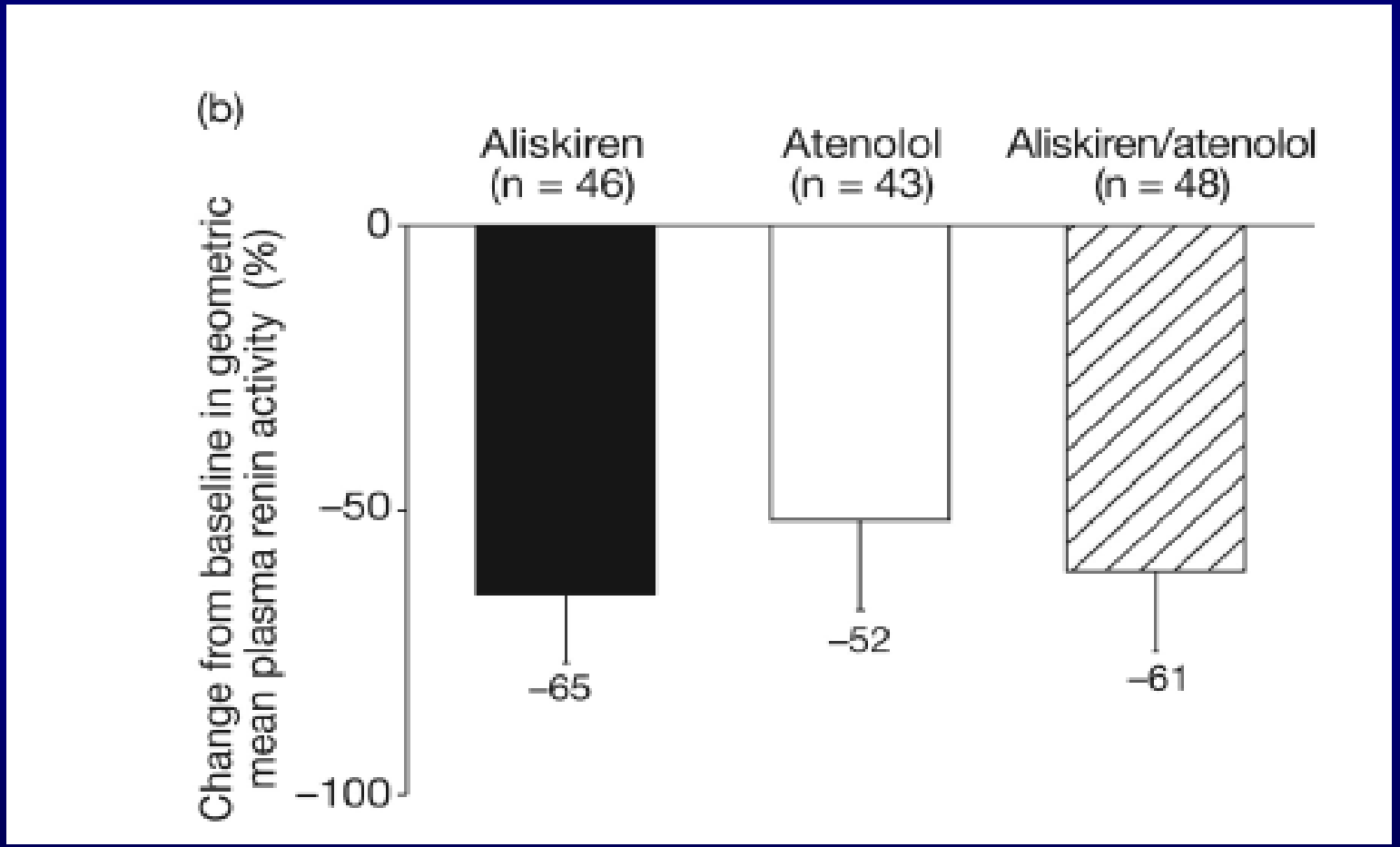
Blumenfeld et al, Am J Hypertens, 1999

Mecanism whereby beta-blockers affect renin
According to Blumenfeld et al



Blumenfeld et al, Am J Hypertens, 1999

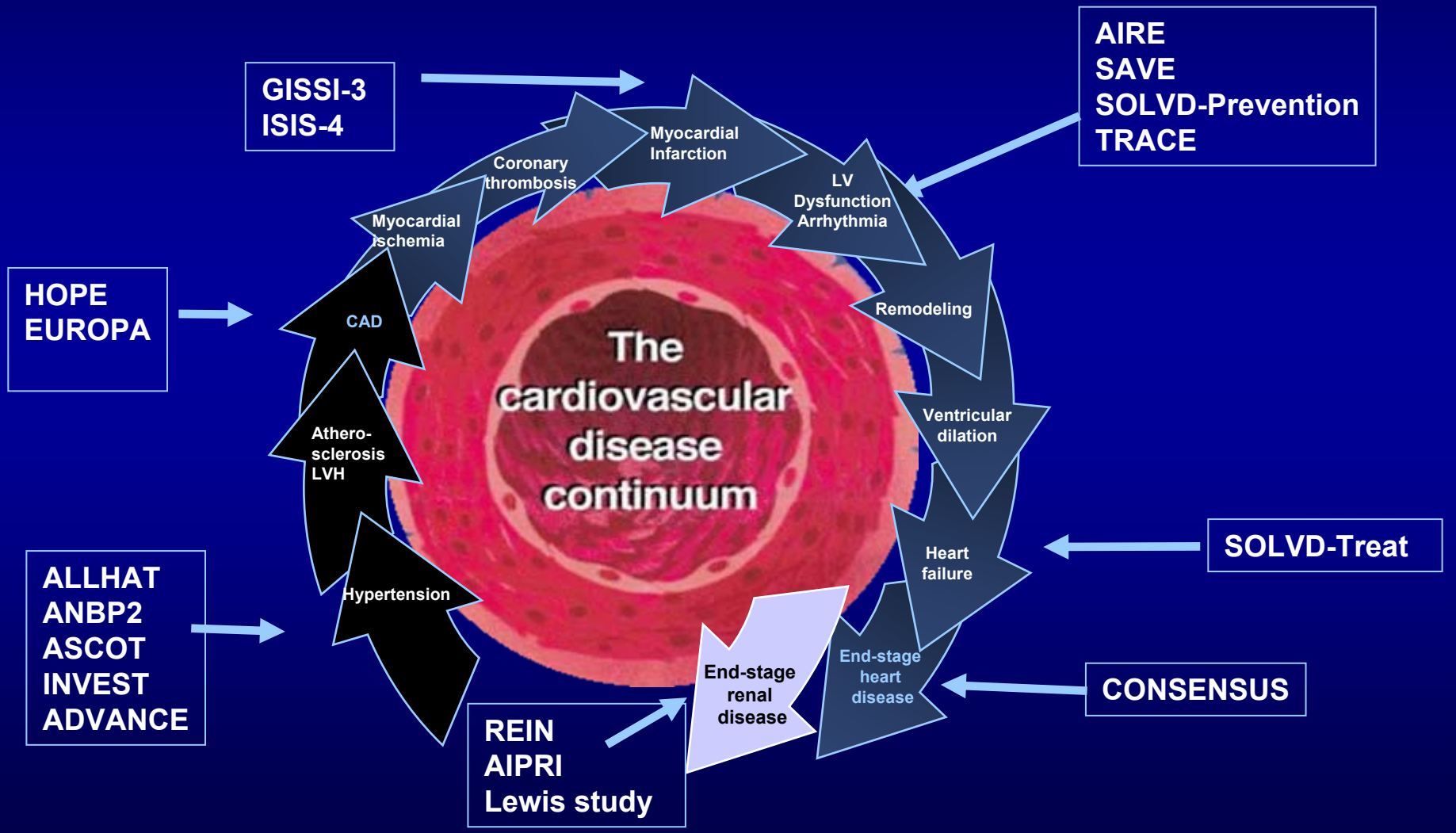
Comparison of a direct renin inhibitor and a beta-blocker in hypertensive patients



Aliskiren 150 mg vs atenolol 50 mg or the combination
PRA measured at week 12.

Dietz et al, JRAAS, 2008

Studies investigating effects of ACE inhibitors on CV disease outcomes



Adapted from: Dzau V, et al. *Am Heart J*. 1991;121:1244-1263.

But…

- **ACE inhibitors are not specific**

  → **Side effects (cough, angioedema)**

- **ACE inhibitors do not block the RAA system completely**

  → **Production of angiotensin II**

- **There are alternative pathways for the production of Ang II**

  → **Ang II production**

Conditions favoring use of ACE inhibitors in the European Guidelines

ACE Inhibitors

Heart failure

LV dysfunction

Post-myocardial infarction

Diabetic nephropathy

Non-diabetic nephropathy

LV hypertrophy

Carotid atherosclerosis

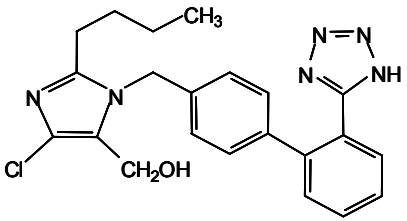
Proteinuria/ Microalbuminuria

Atrial fibrillation

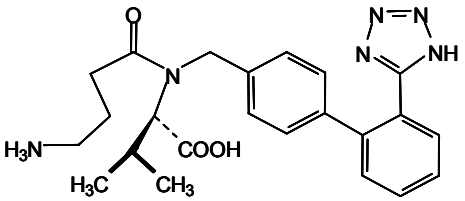
Metabolic syndrome

ESH Guidelines, 2007

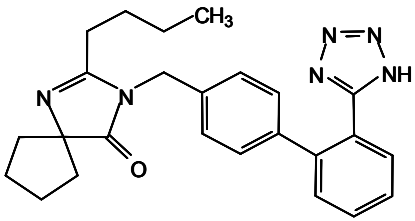
Angiotensin II receptor antagonists



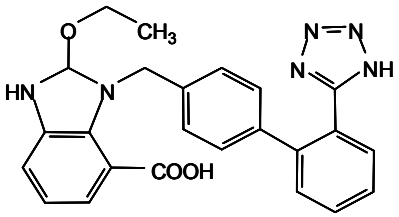
Losartan



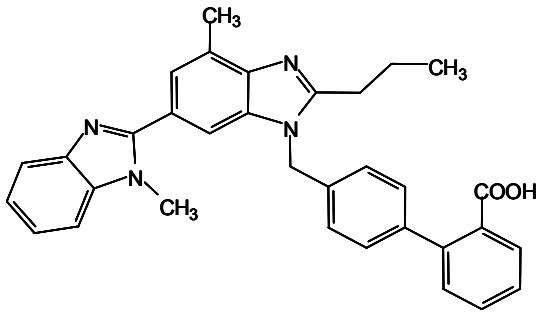
Valsartan



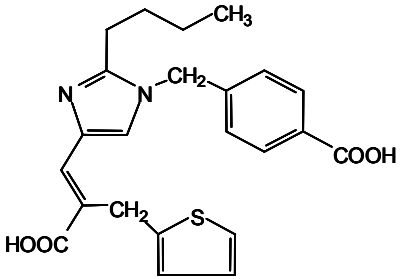
Irbesartan



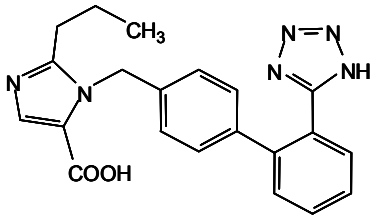
Candesartan



Telmisartan



Eprosartan



Olmesartan

From Maillard M and Burnier M.

Tolerability profile of antihypertensive drugs

	AT_1 antagonists	ACE inhibitors	Diuretics	Ca antagonists	Beta-blockers
Headache	–	–	–	+	–
Flush	–	–	–	+	–
Edema	–	–	–	+	–
Dyspnea	–	–	–	–	+
Bradycardia/arythmia	–	–	–	–	+
Fatigue	–	–	+	–	+
Cold extremities	–	–	–	–	+
Impotence	–	–	+	–	+
Gout	–	–	+	–	–
Cough	–	+	–	–	–
Orthostatic hypotension	–	–	+	–	–

Why is PRA important?

- In the 1970s, PRA was identified as a potential risk factor for heart attacks and stroke in patients with hypertension[1]
- More recently, studies have identified associations between PRA and:
  - myocardial infarction (MI)[2,3]
  - heart failure[4,5]
  - LVH[6,7,8]
  - impaired renal function[9,10]
  - development of hypertension in obese individuals[11]
- Animal studies have shown a link between PRA reductions and reduced organ damage[12]
- In humans, it is not known whether reductions in PRA independently and directly lead to reductions in organ damage

[1]Brunner *et al.* New Engl J Med 1972;286:441–9; [2]Alderman *et al.* New Engl J Med 1991;324:1098–104; [3]Alderman *et al.* Am J Hypertens 1997;10:1–8; [4]Francis *et al.* Circulation 1993;87:VI40–8; [5]Latini *et al.* Eur Heart J 2004;25:292–9; [6]Muscholl *et al.* Am Heart J 1998;135:58–66; [7]Aronow *et al.* Am J Cardiol 1997;79:1543–5; [8]Malmqvist *et al.* J Intern Med 2002;252:430–9; [9]Baldoncini *et al.* Kidney Int 1999;56:1499–504; [10]Yeyati *et al.* Am J Nephrol 1996;16:471–7; [11]Licata *et al.* J Hypertens 1995;13:611–18; [12]Volpe *et al.* Hypertension 1990;15:318–26

Development of renin inhibitors 1980-1995

- Several products have been developed during the last 15 years: H142, R-PEP-27, ditekiren, enalkiren, zankiren and remikiren

- However, all these compounds have not been brought to their late phase of development because of:
  - a low bioavailability
  - a low efficacy
  - a short duration of action
  - and a high cost of production

Luther RR et al. *Clin Nephrol*. 1991;36:181–186
Fisher and Hollenberg. JASN 2005; 16: 592

Overview of key studies examining the link between PRA and CV outcomes

	Population	Follow-up	Outcome
Rouleau JL, *et al.* (SAVE)	Patients post-MI	38 months	Elevated PRA associated with increased CV morbidity and mortality
Latini R, *et al.* (Val-HeFT)	Moderate–severe HF	23 months	Elevated PRA associated with increased CV morbidity and mortality
Vergaro G, *et al.*	Patients receiving optimal treatment for HF	22.6 months	Elevated PRA associated with increased incidence of CV events
Bair TL, *et al.* (Intermountain Heart Registry)	Pre-existing CAD	60 months	Elevated PRA associated with CV events

Rouleau *et al.* J Am Coll Cardiol 1994;24:583–91; Latini *et al.* Eur Heart J 2004;25:292–9; Vergaro *et al.* Eur Heart J 2008;29(Suppl.):393 [Abstract]; Bair *et al*. J Am Coll Cardiol 2009;53:A383 [Abstract]

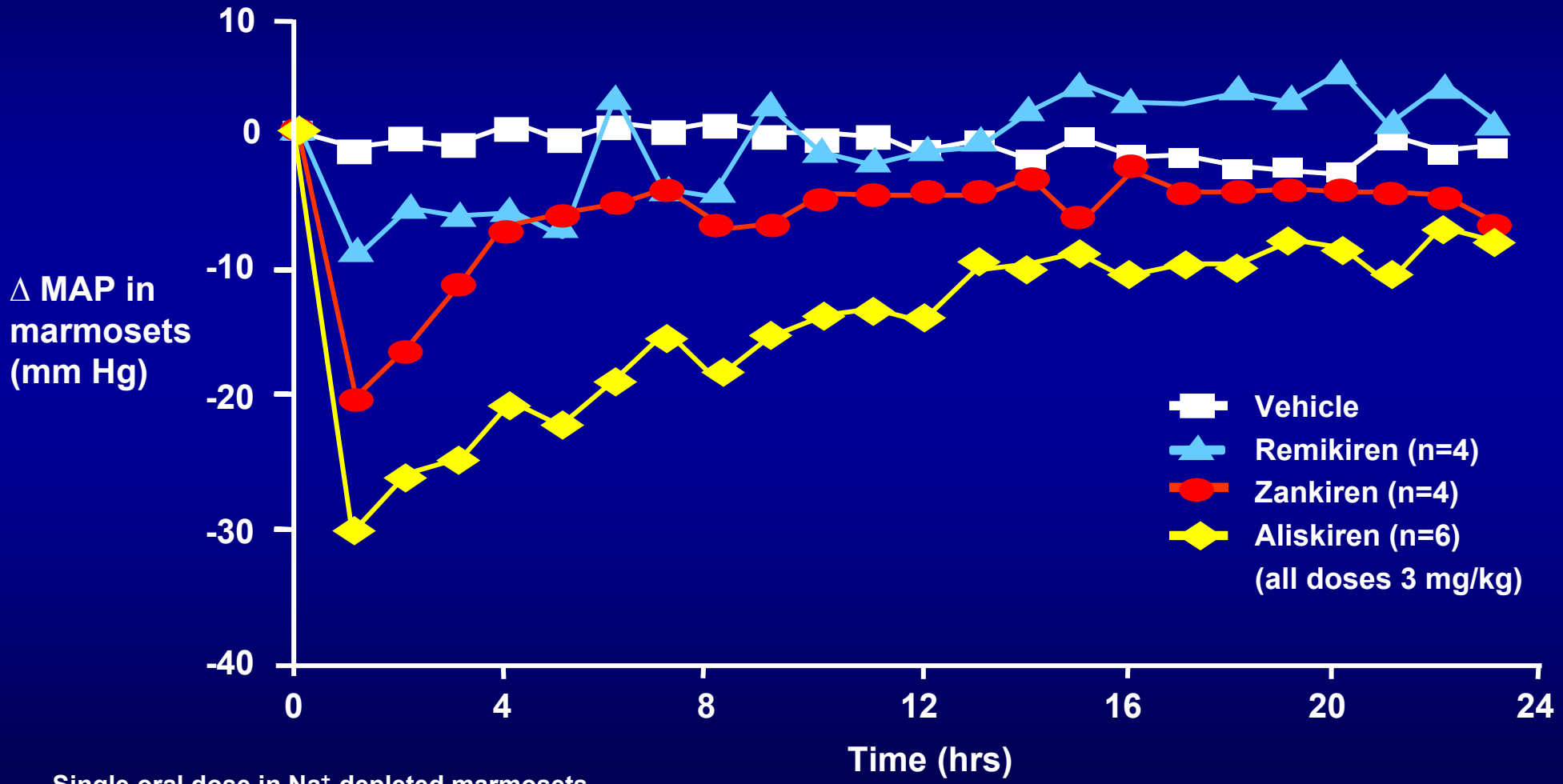
Aliskiren has a high specificity for human renin

Renin isoform	IC_{50} (nM)
Human	0.6
Marmoset	2
Dog	7
Rabbit	11
Guinea pig	63
Rat	80
Pig	150
Cat	8500

- Aliskiren has a high specificity for human renin and is thus challenging to study in animal models
- Animal model developed to test human renin inhibitors: *double TransGenic Rat (dTGR)*
  - expresses genes for human renin and human angiotensinogen
  - animals develop severe hypertension and end-organ damage

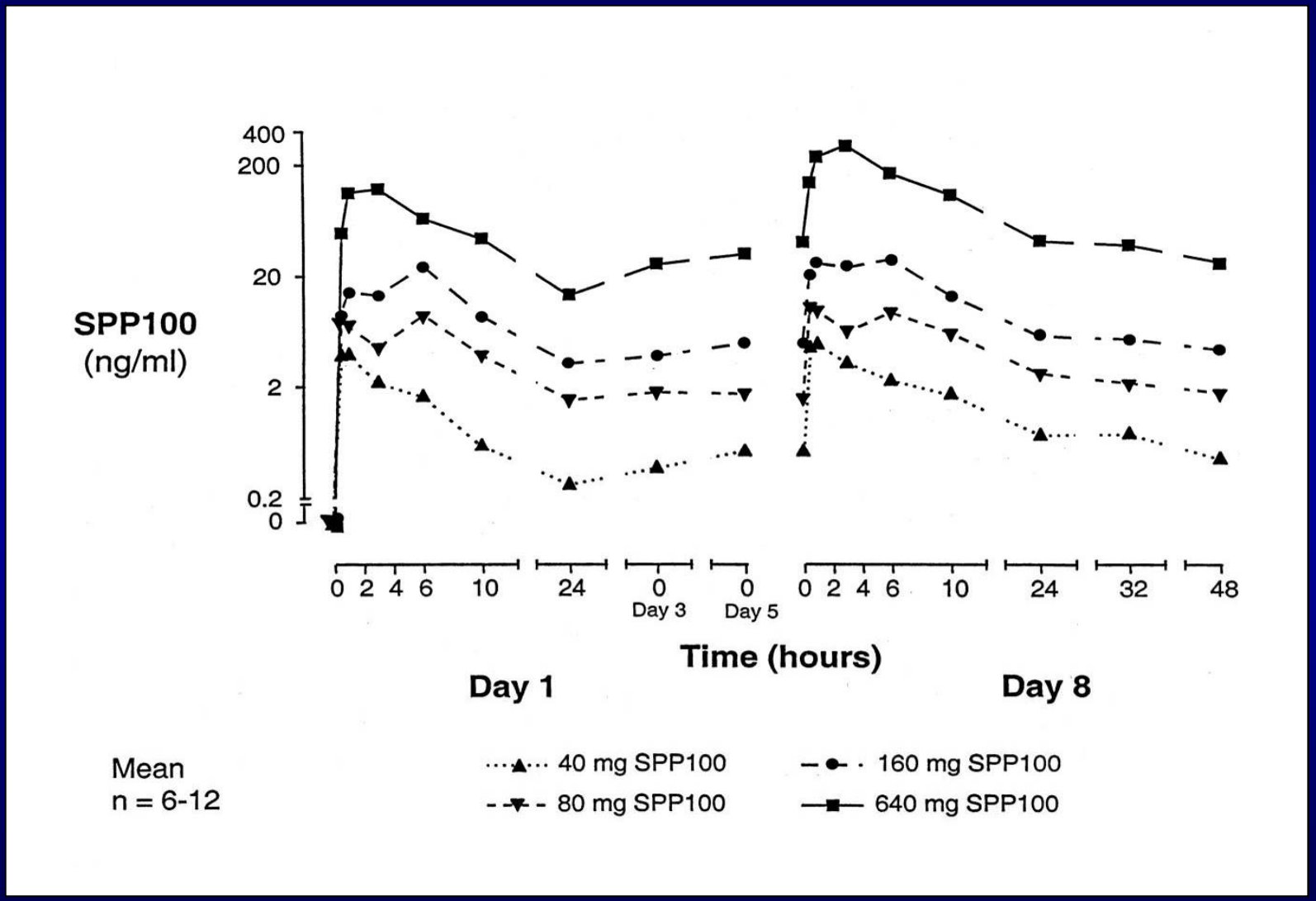
Wood JM, *et al*. 2003; Bohlender J, et al. 1997

Effects of aliskiren on blood pressure in salt-depleted monkeys.



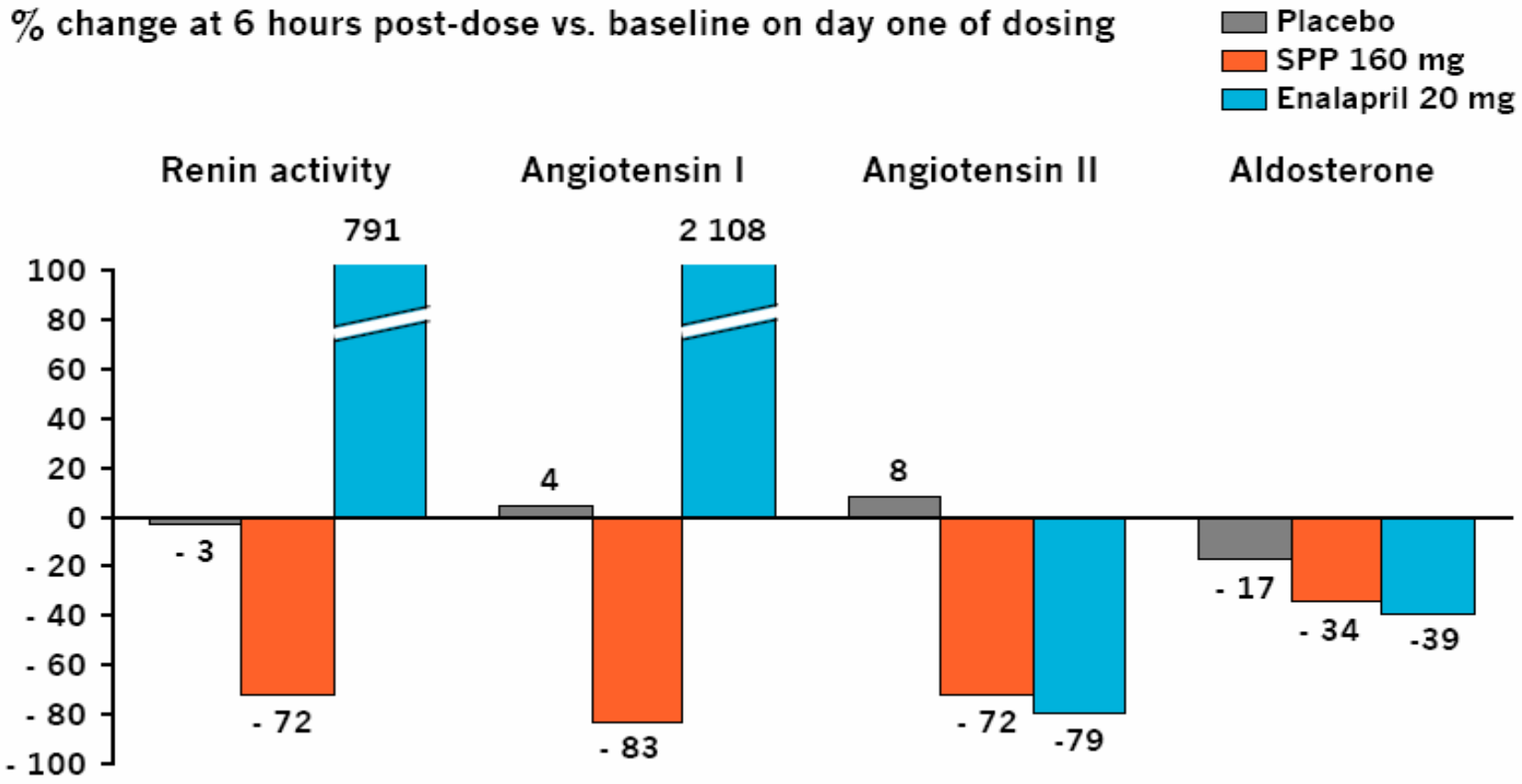
Single oral dose in Na^+-depleted marmosets.
MAP, mean arterial pressure.
Wood JM et al. *J Hypertens*. 2005;23(2):417-26.

Plasma concentrations of the renin inhibitor in healthy men after acute and sustained administration of aliskiren



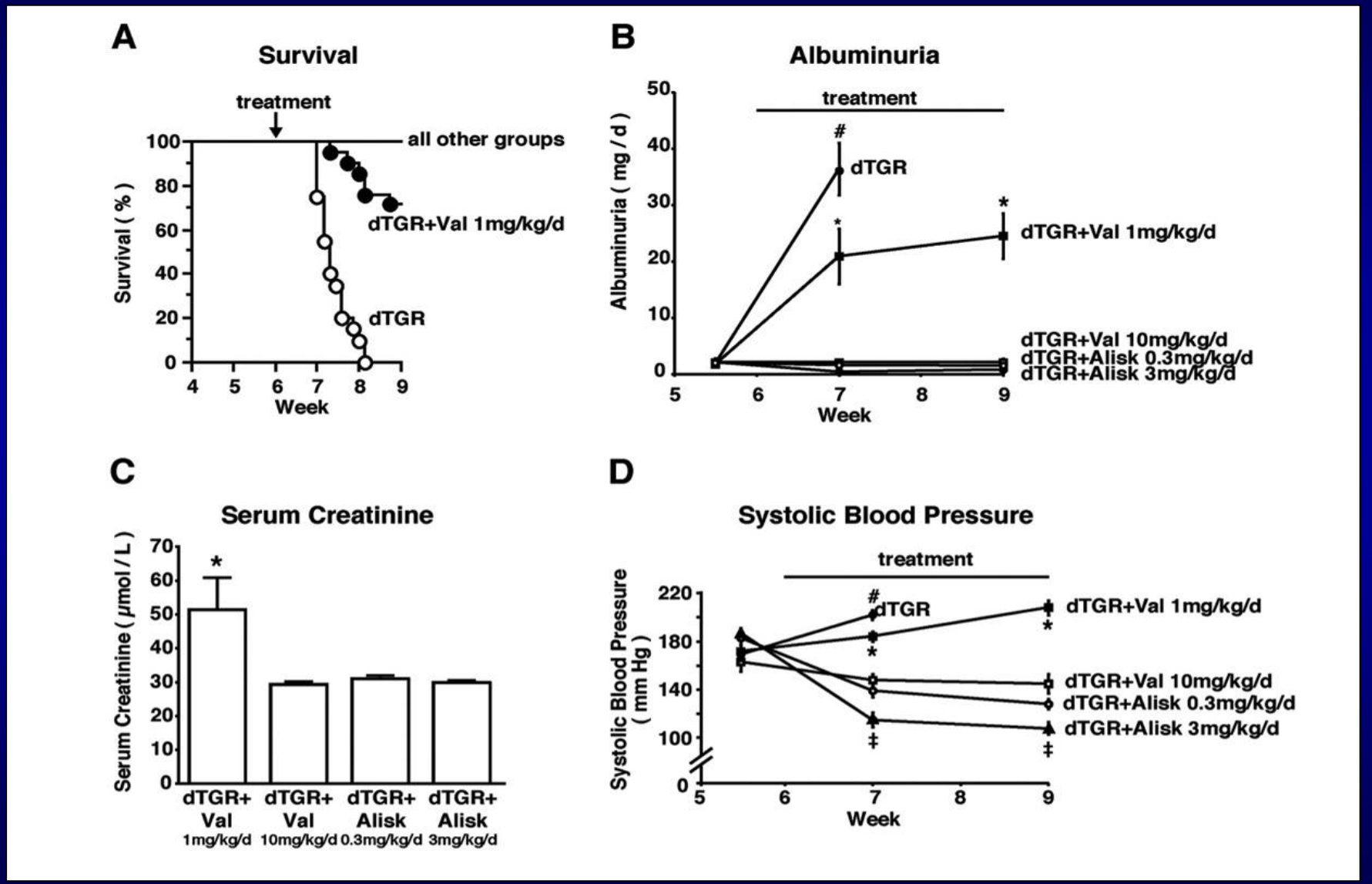
Nussberger, J. et al. Hypertension 2002;39:e1-8e

Enalapril Significantly Increases Plasma Renin Activity Unlike SPP100



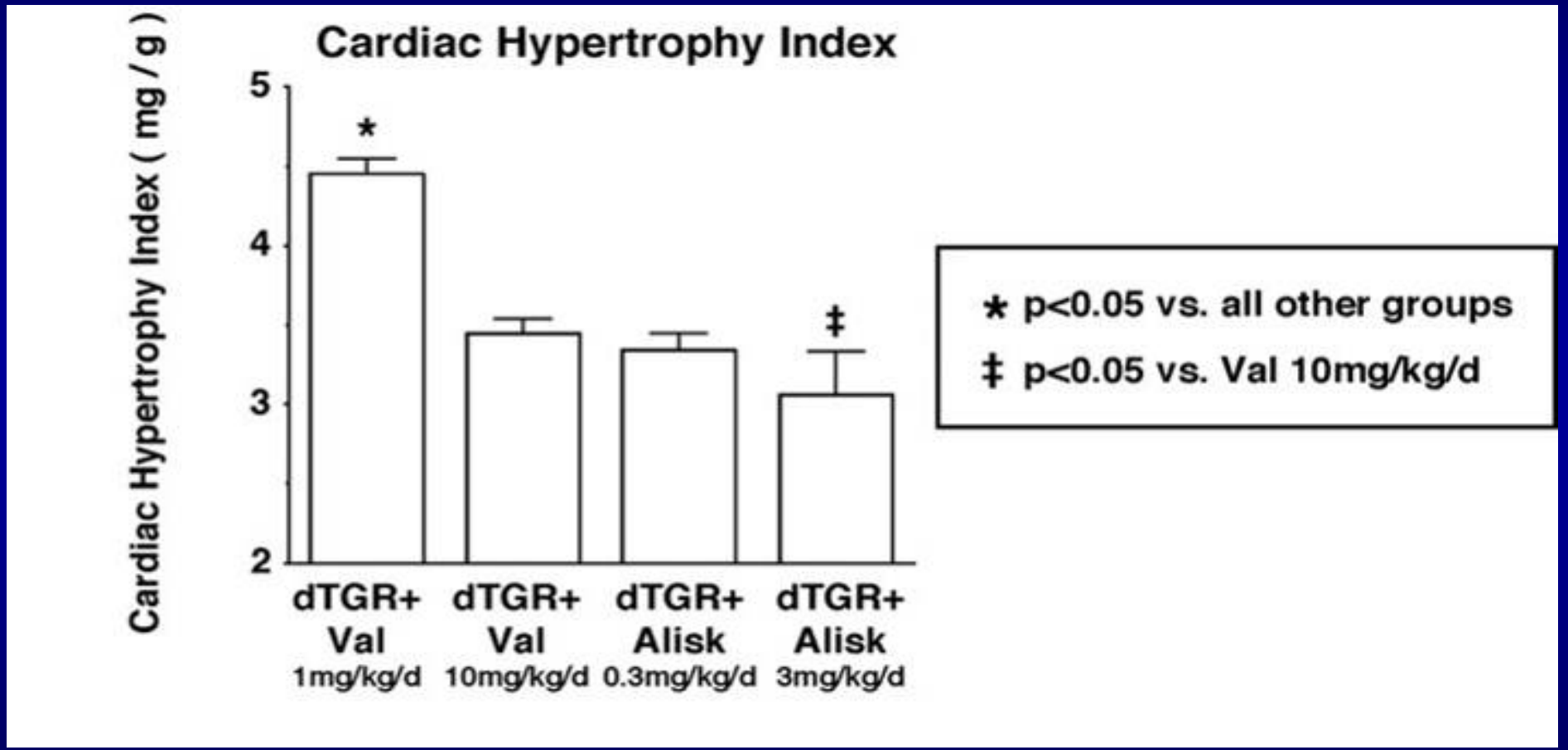
Nussberger et al, Hypertension, 2002

Survival of dTGR treated with aliskiren, valsartan or vehicle



Pilz, B. et al. Hypertension 2005;46:569-576

dTGR treated with aliskiren or valsartan: cardiac effects



Pilz, B. et al. Hypertension 2005;46:569-576

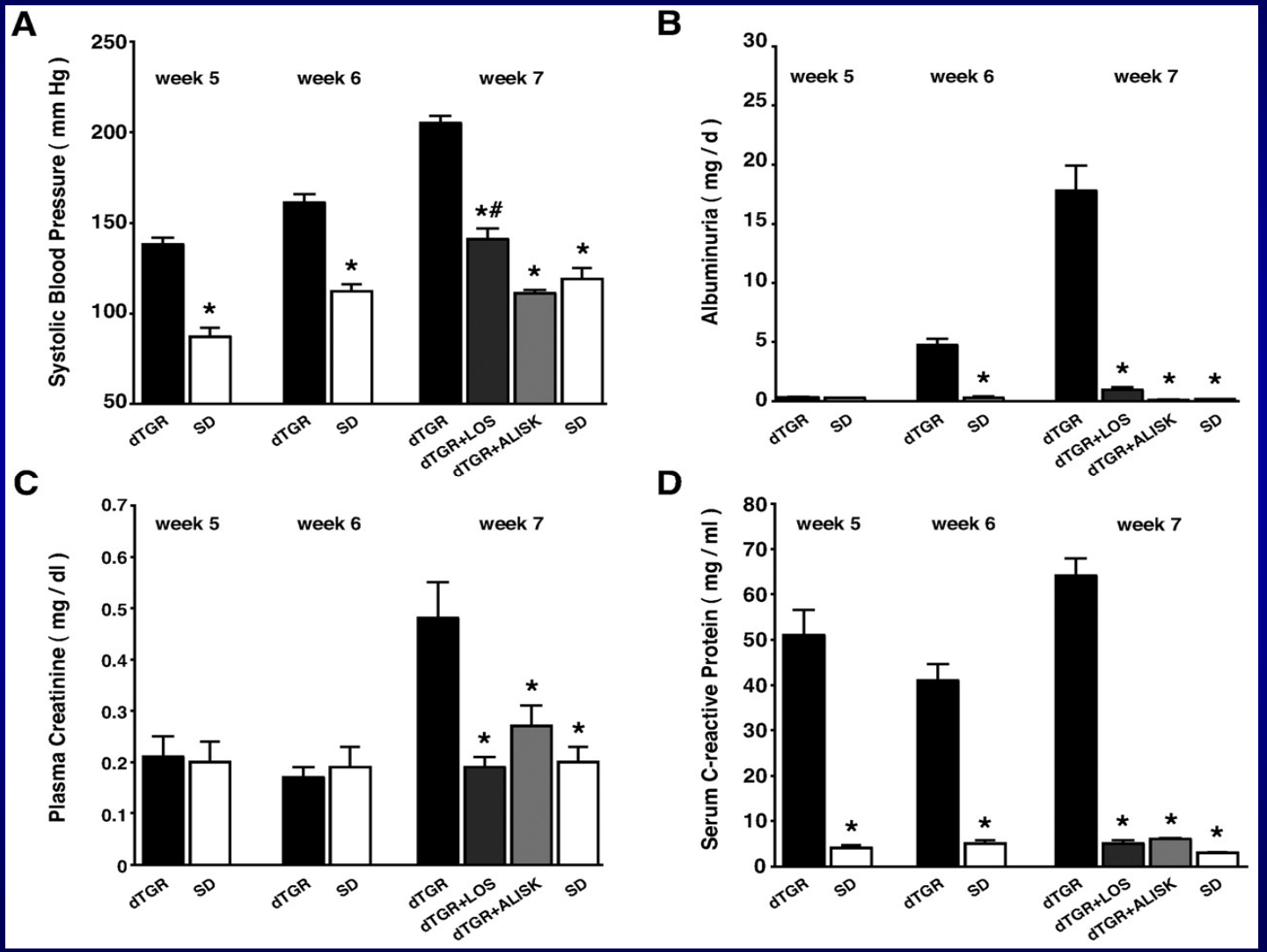
Comparative renal effects of Losartan and Aliskiren in dTGR and age-matched SD control rats

Systolic BP

Albuminuria

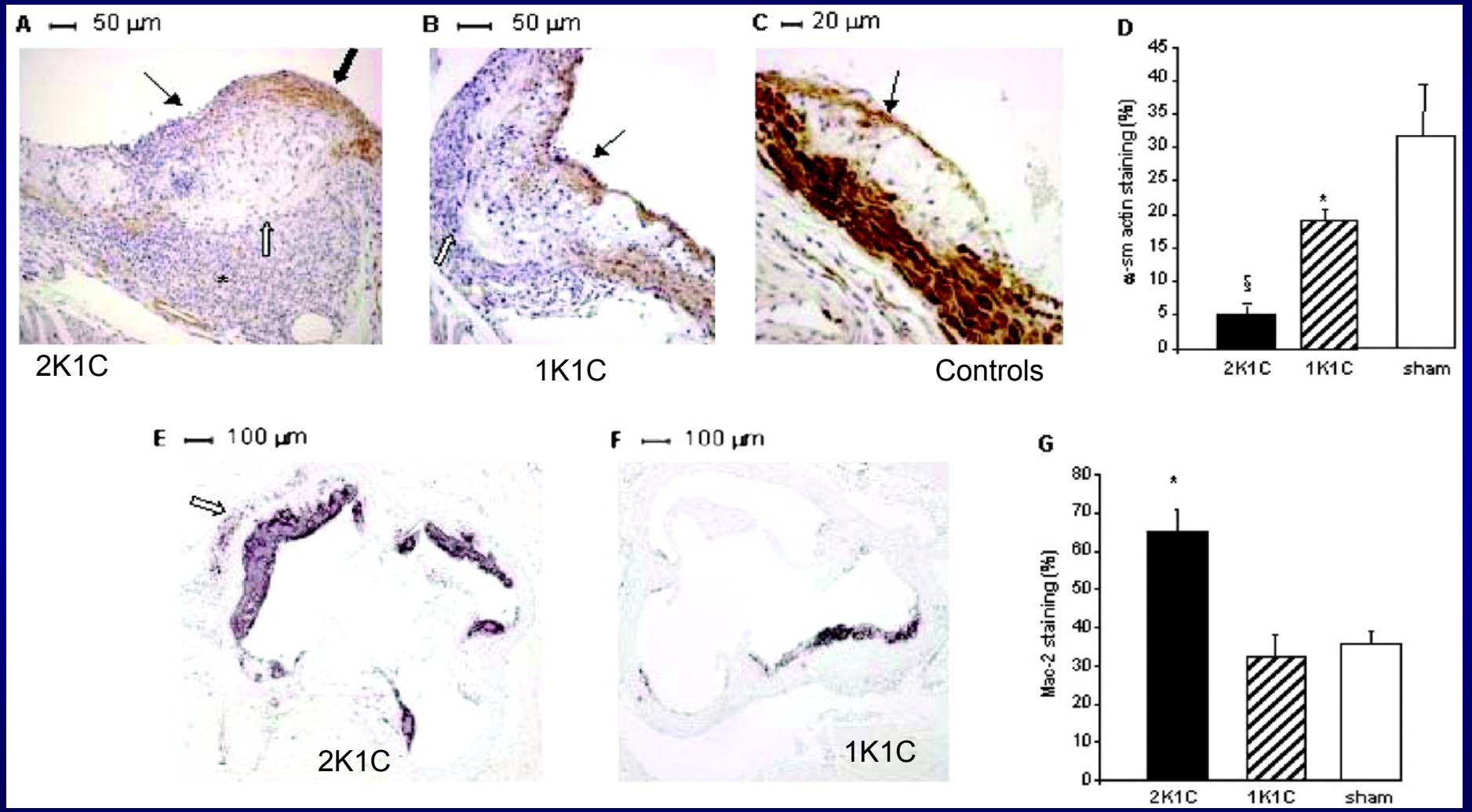
Creatinine

CRP



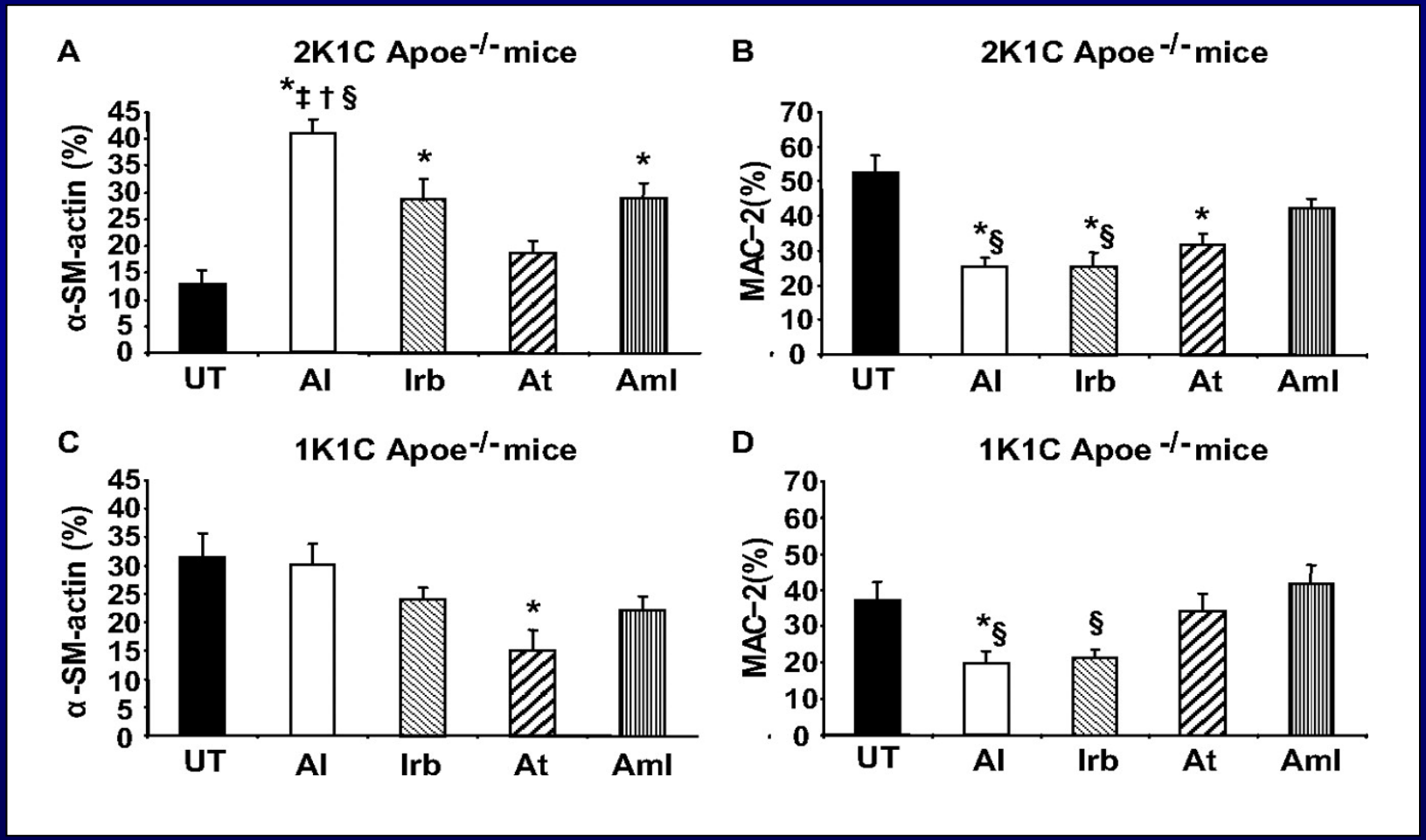
Shagdarsuren, E. et al. Circ Res 2005;97:716-724

Angiotensin II and the vulnerable plaque
In the Apoe knockout mouse



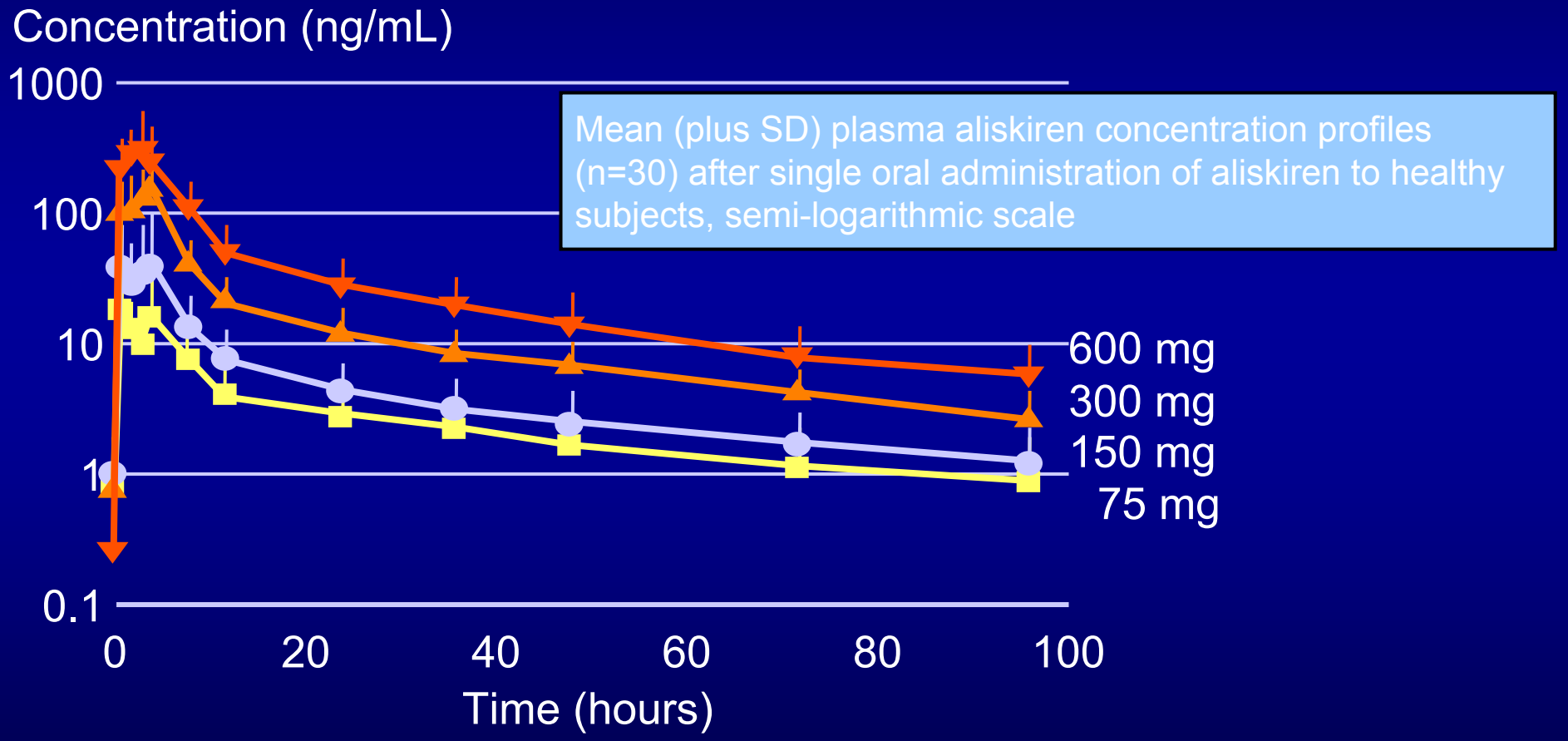
Mazzolai, L. et al. Hypertension 2004;44:277-282

Plaque SMC and macrophage content assessed by α–SM actin and MAC-2 on different treatments



Nussberger, J. et al. Hypertension 2008;51:1306-1311

Aliskiren has a half-life of approximately 40 hours, making it suitable for once-daily dosing



Vaidyanathan S, *et al*. 2006

Aliskiren has a low potential for drug interactions

Effects of aliskiren on other drugs:

Co-administration of aliskiren did not significantly affect the pharmacokinetics of lovastatin, digoxin, valsartan, amlodipine, metformin, celecoxib, atenolol, atorvastatin, ramipril or hydrochlorothiazide.

When aliskiren was co-administered with furosemide, the AUC and C_{max} of furosemide were reduced by about 30% and 50%, respectively

Dieterle W, *et al*. 2004; Dieterle W, *et al.* 2005; Agarwal A, *et al*. 2007; Vaidayanathan S, *et al*. 2007
Dietrich H, *et al.* 2006; Valencia J, *et al.* 200; Reynolds C, *et al*. 2007; Zhao C, *et al*. 2007

Pharmacokinetic of aliskiren

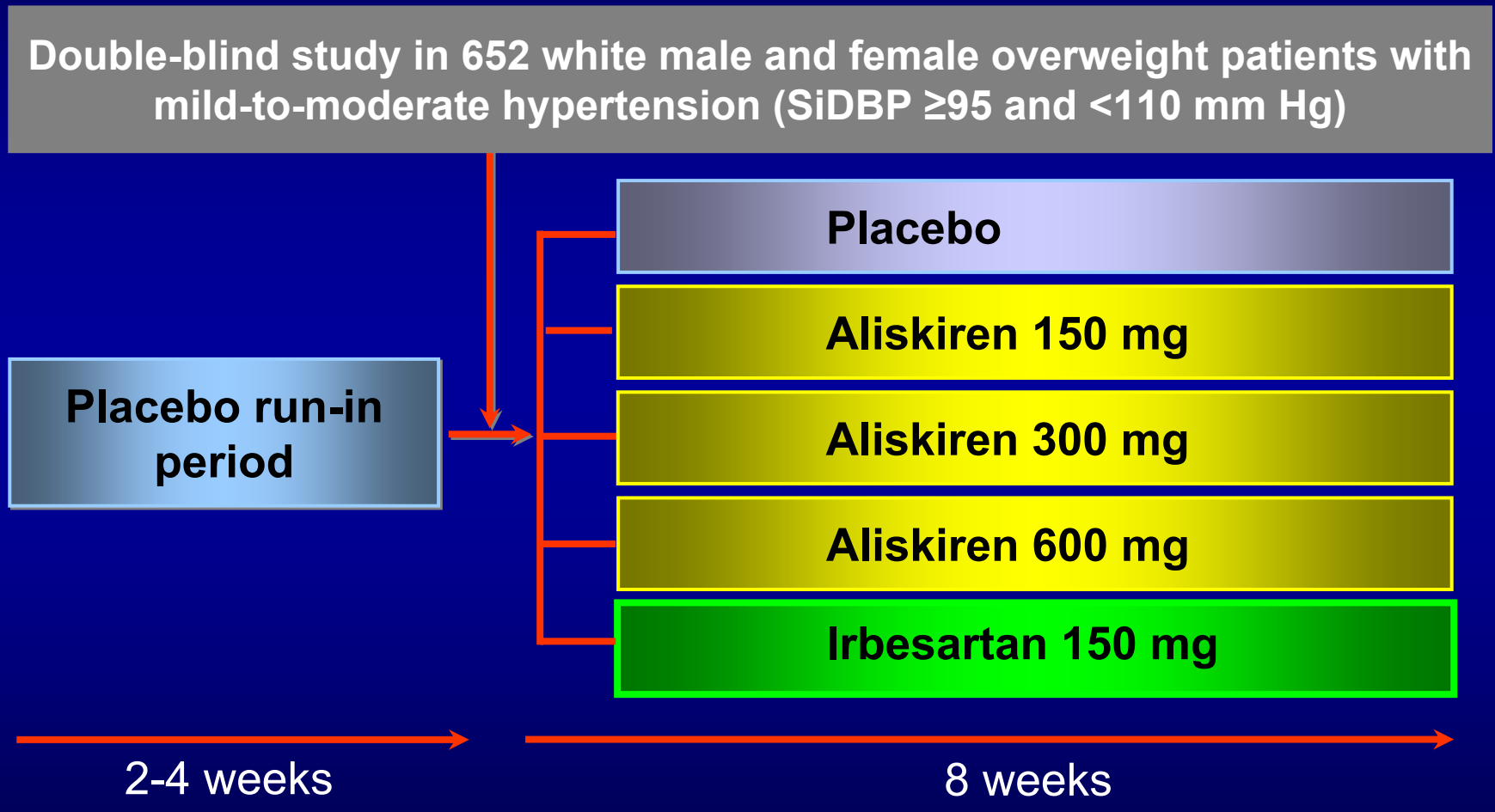
No adaptation of the doses in patients with renal insufficiency

No adaptation of the doses in patients with hepatic insufficiency

Aliskiren and BP control

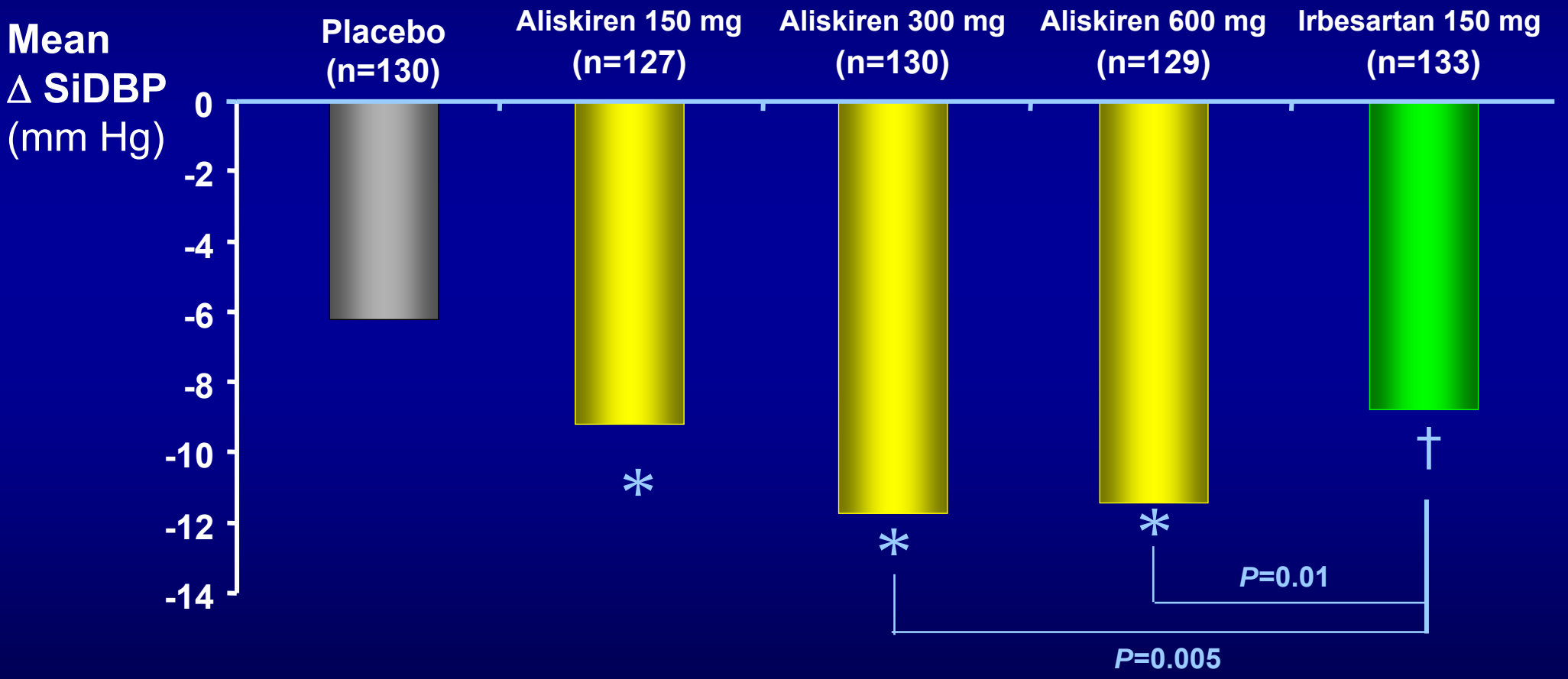
Aliskiren vs Irbesartan

Study Design



Gradman AH et al. Circulation 2005;111:1012

Clinic SiDBP Reduction at trough: ITT analysis



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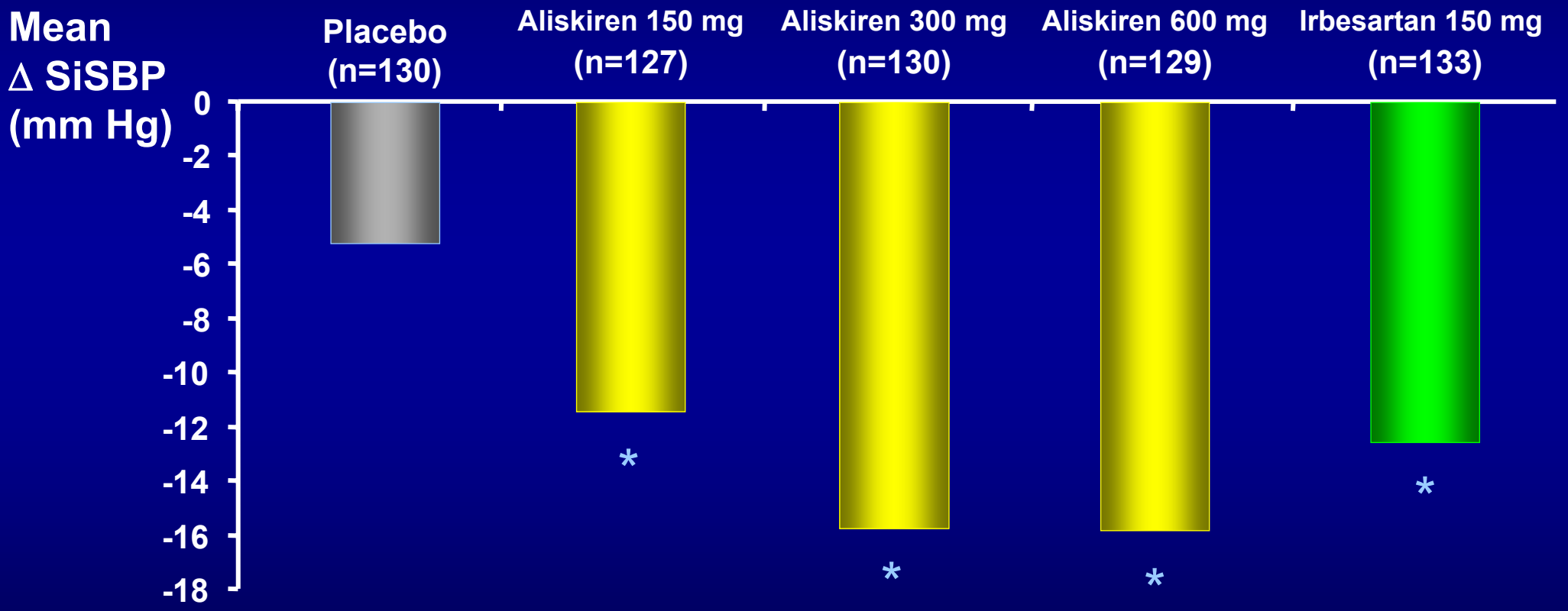
Clinic SiSBP Reduction at trough: ITT analysis



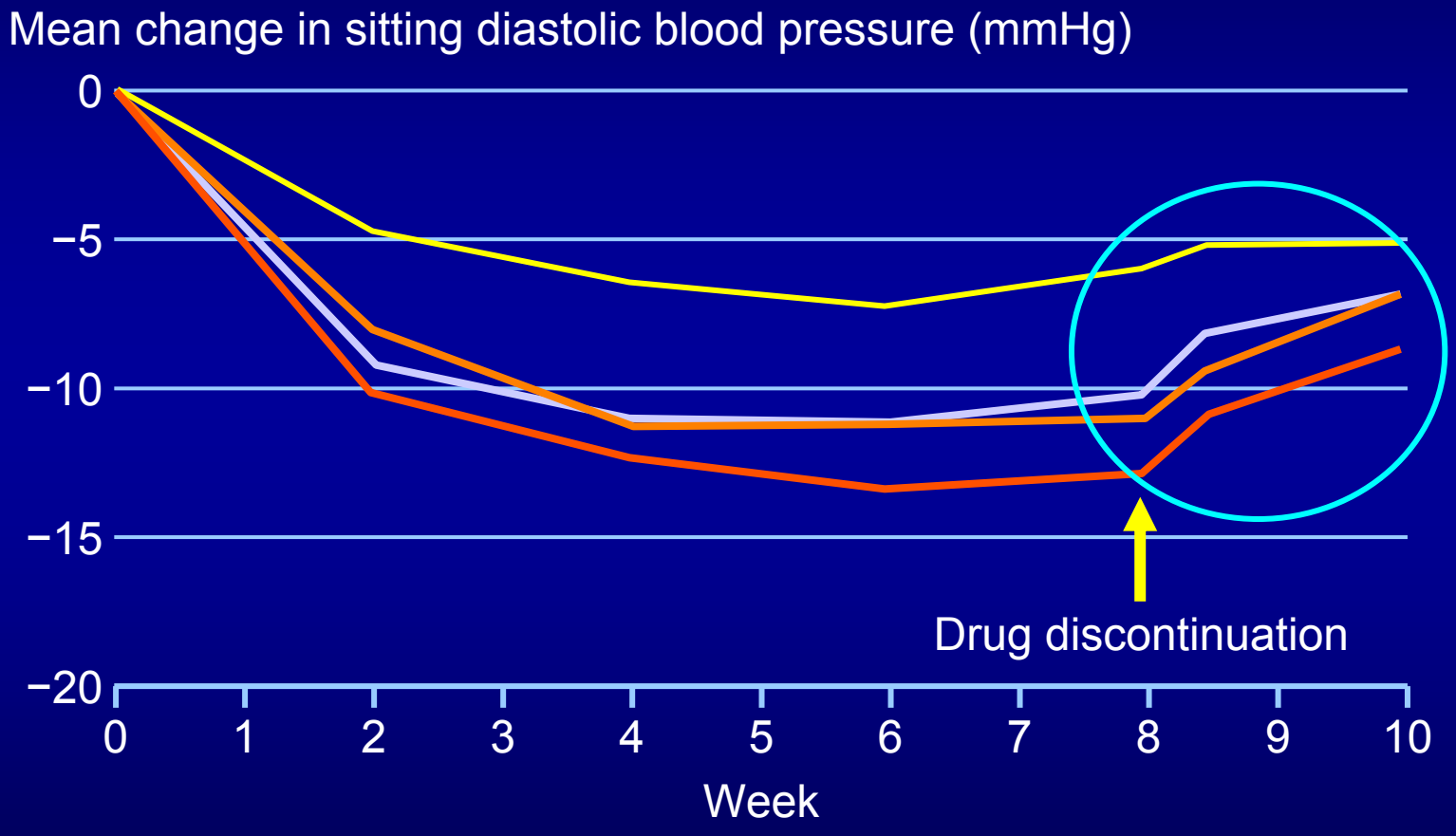
Gradman AH et al. Circulation 2005;111:1012

Safety and Tolerability

Patients with AE (%)	Placebo (n=131)	Aliskiren 150 mg (n=127)	Aliskiren 300 mg (n=130)	Aliskiren 600 mg (n=130)	Irbesartan 150 mg (n=134)
Any AE	32.1	26.8	36.2	33.1	36.6
D/C due to AE	2.3	3.9	3.1	2.3	2.2
Serious AE	0.8	–	–	–	0.7
Most Frequent AEs (≥2%)					
Headache	5.3	2.4	6.2	4.6	3.0
Diarrhea	1.5	1.6	0.8	6.9	1.1
Dizziness	3.8	1.6	3.1	2.3	3.7
Fatigue	3.1	0.8	3.8	1.5	1.5
Back pain	–	1.6	2.3	1.5	4.5

Gradman AH et al. Circulation 2005;111:1012

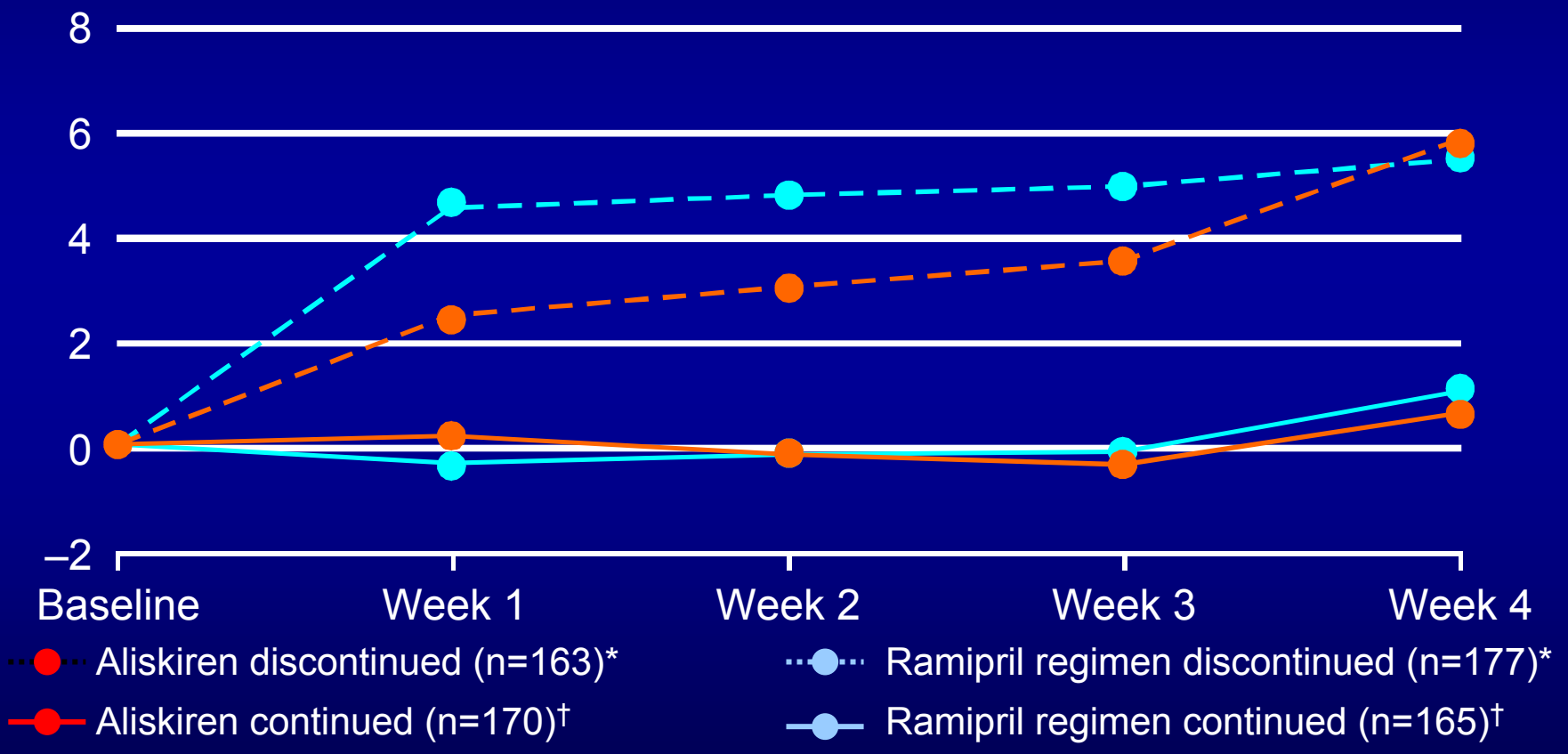
Aliskiren demonstrates persistence of effect after discontinuation



Herron J, *et al*. 2006

DBP returns to baseline levels more rapidly after discontinuation of ramipril compared with aliskiren

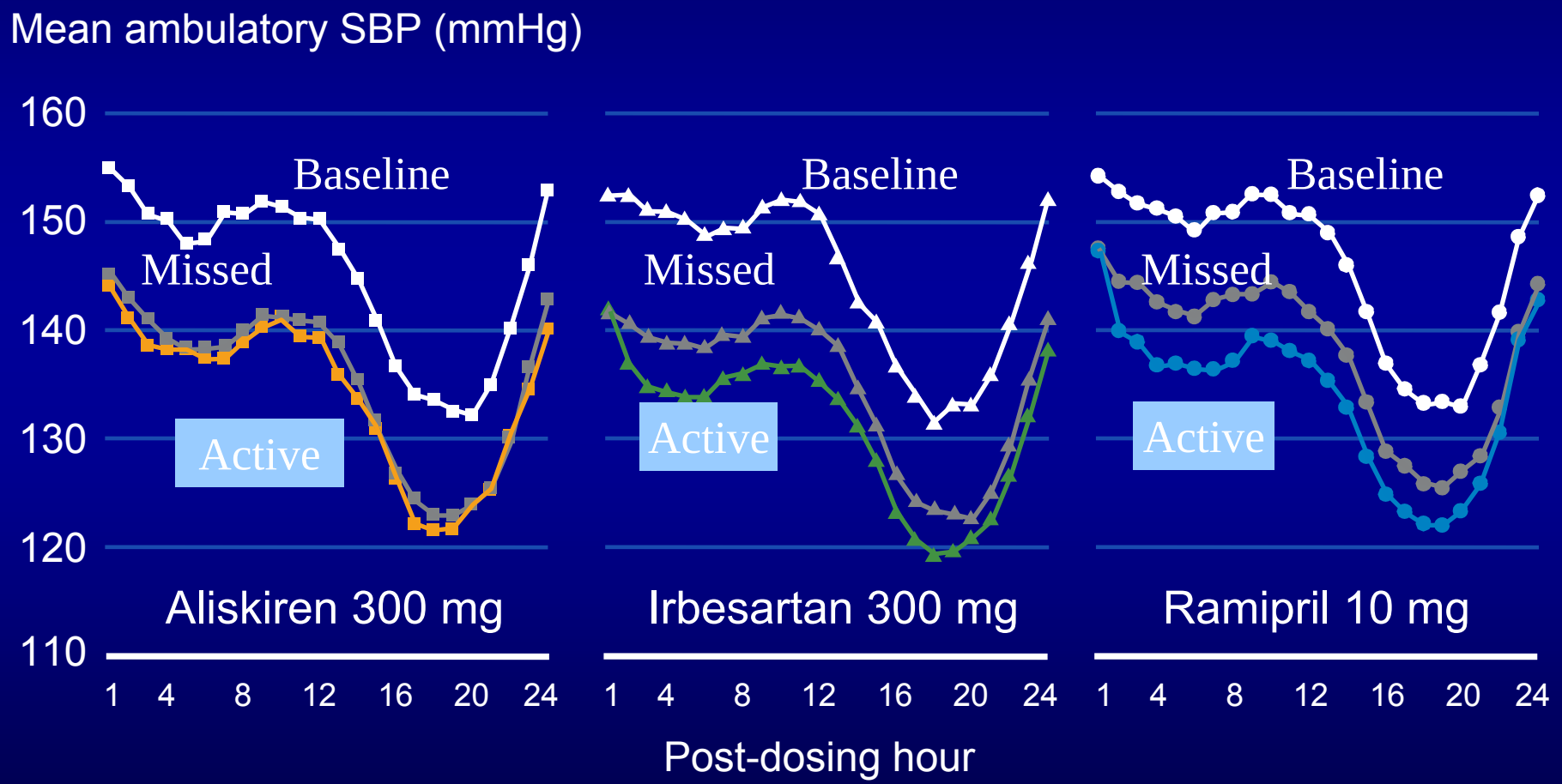
Mean change in mean sitting DBP during the 4-week withdrawal period (mmHg)



*Following 26-weeks' treatment, patients randomized to discontinuation received placebo for 4 weeks;
†Patients continuing active treatment could be receiving aliskiren 150 or 300 mg, or ramipril 5 or 10 mg, with or without optional HCTZ (12.5 mg or 25 mg).

Andersen K, *et al*. 2008

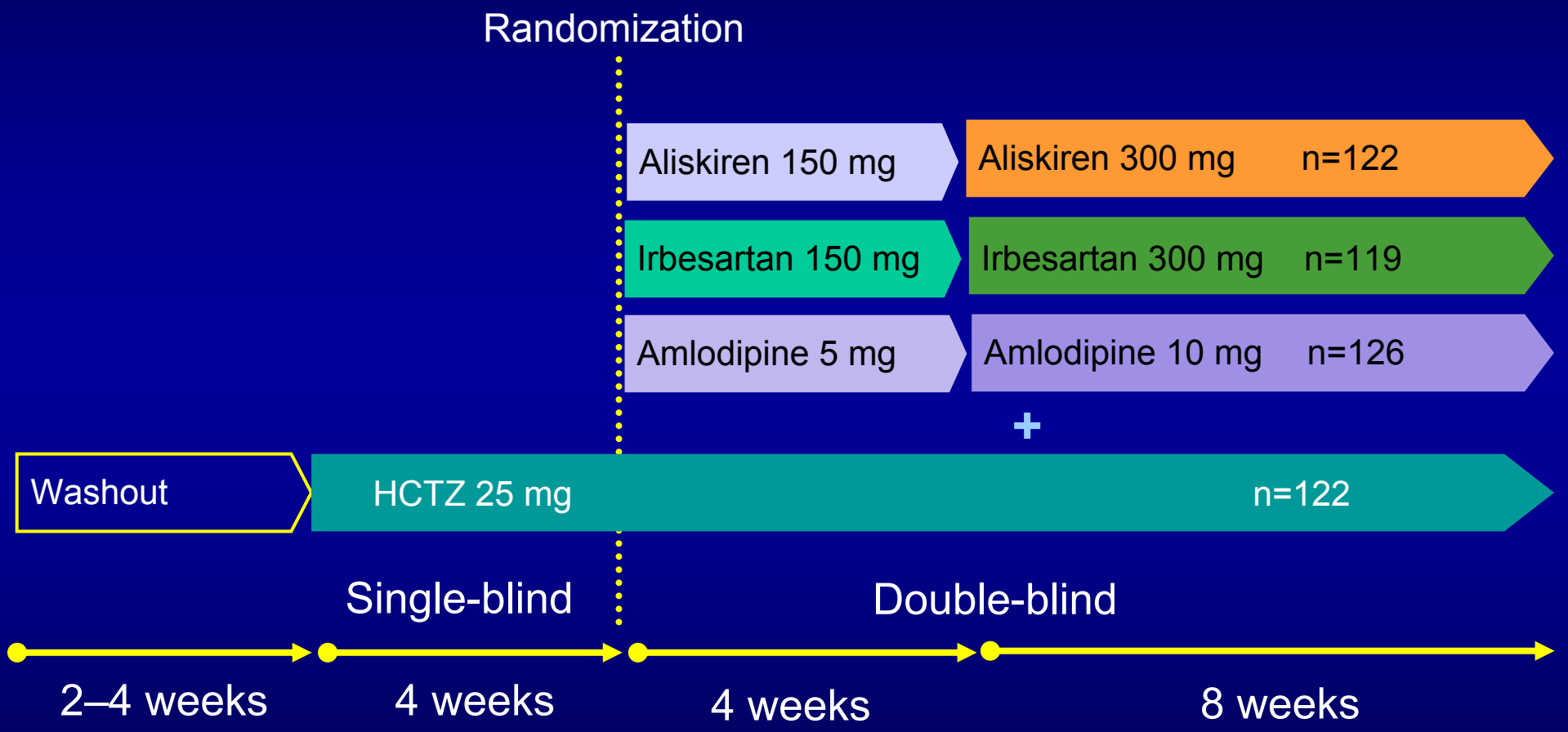
Change in ambulatory SBP from active dose to missed dose is numerically smaller with aliskiren than irbesartan or ramipril



Data are shown as hourly mean values for the ABPM completer population

Palatini P, *et al*. 2008

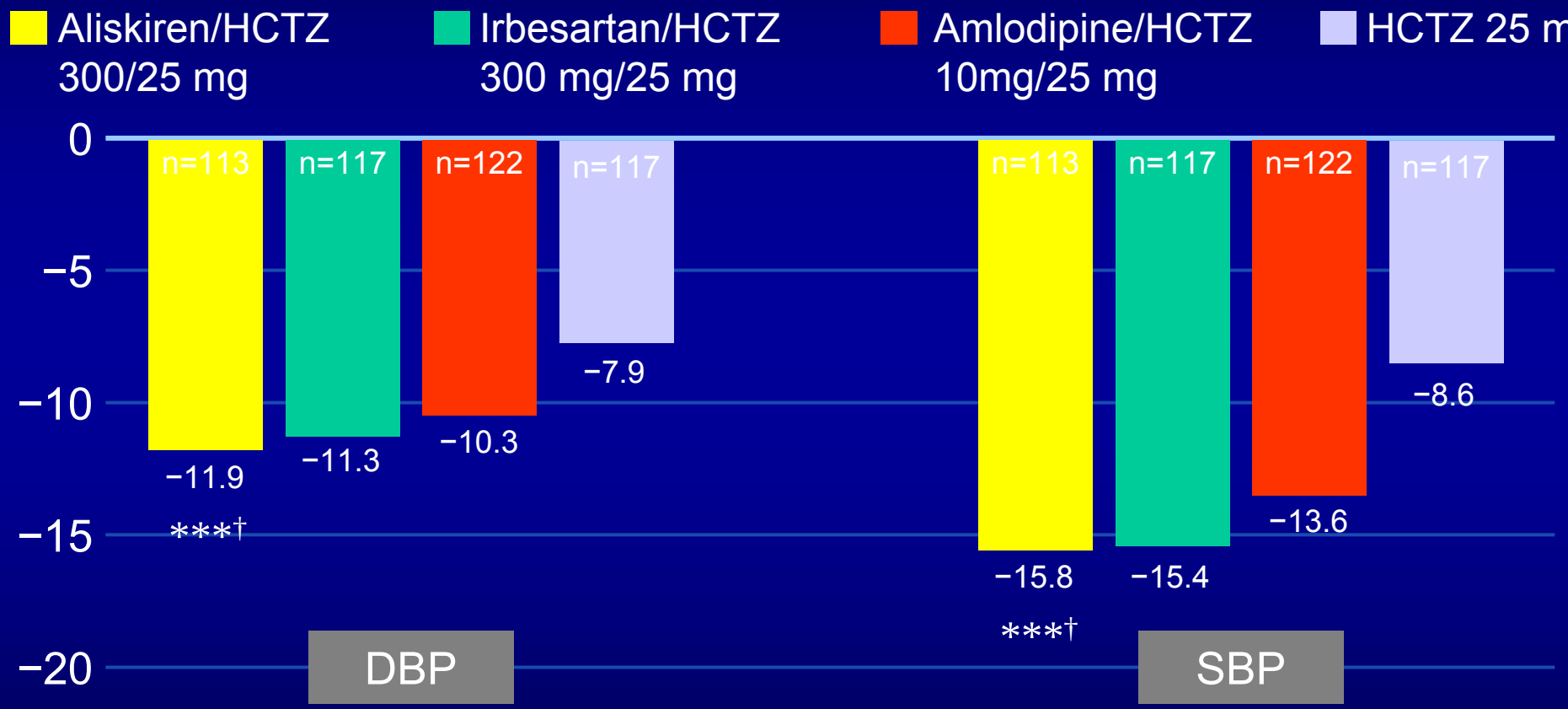
Aliskiren combined with HCTZ in patients with hypertension and obesity



Non-response to HCTZ defined as DBP ≥90 mmHg after 4 weeks of treatment with HCTZ 25 mg od. Obesity was defined as a BMI ≥30kg/m^2.

Jordan J, *et al.*, 2007

Aliskiren provides additional BP-lowering when added to HCTZ

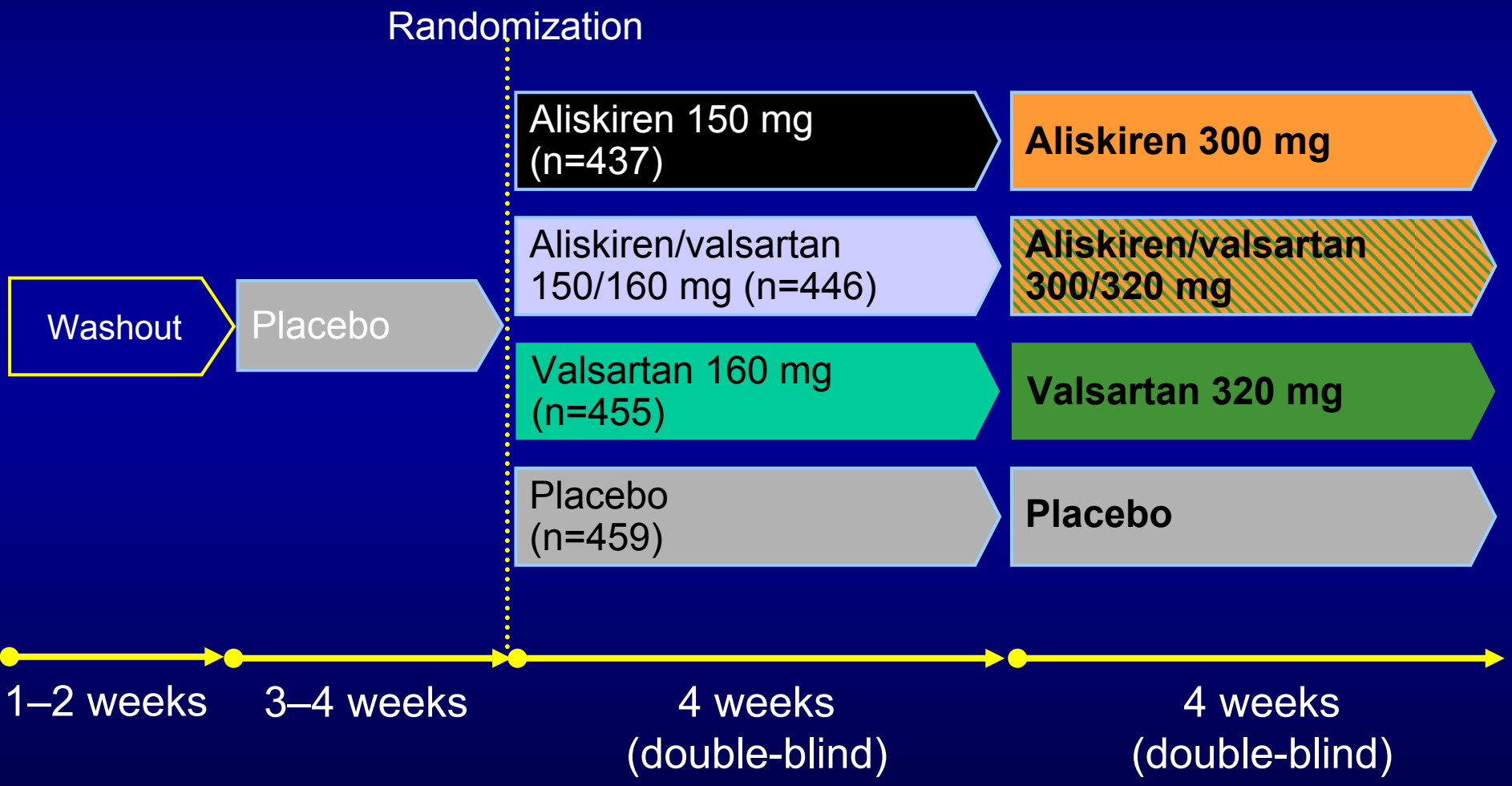


Mean change from baseline in mean sitting BP at Week 8 (mmHg)

***p<0.0001 vs HCTZ; †p=non-significant vs irbesartan/HCTZ and amlodipine/HCTZ. Comparisons for irbesartan/HCTZ and amlodipine/HCTZ vs HCTZ monotherapy were not conducted.

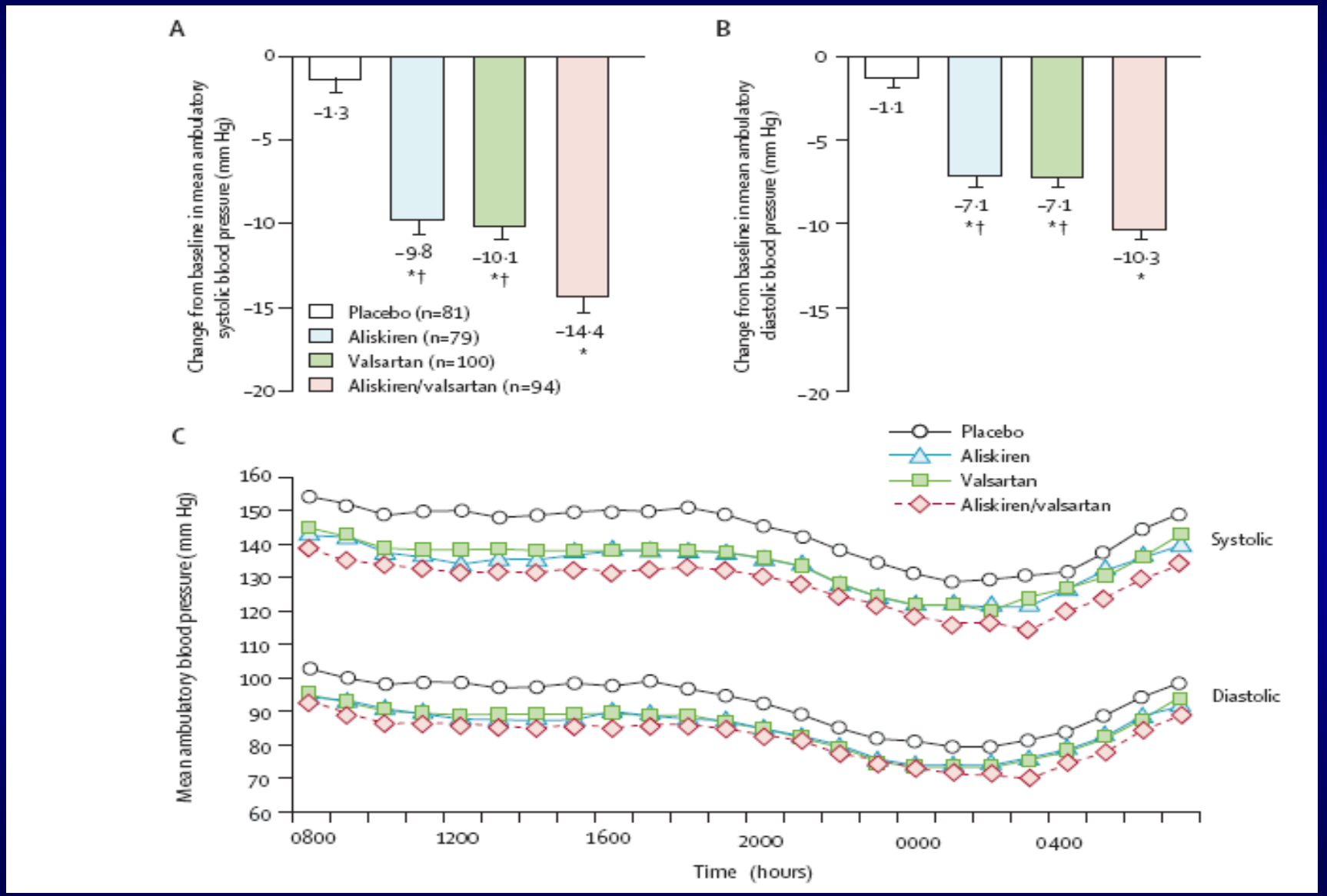
Jordan J, *et al.* 2007

Aliskiren and valsartan combination therapy



Oparil S, *et al*. Lancet, 2007

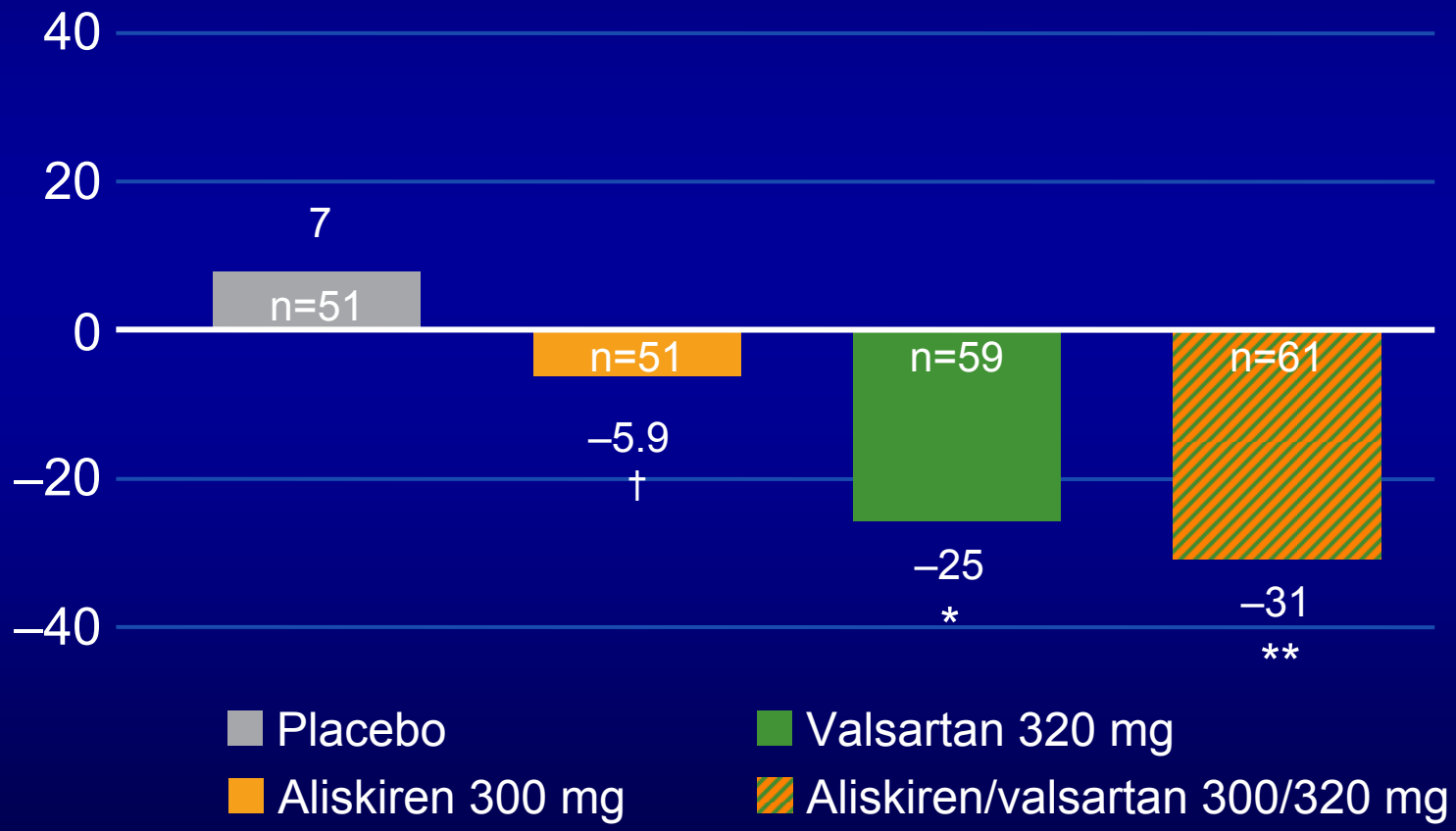
Effect of aliskiren alone/combined with valsartan on ambulatory BP



Oparil S, Lancet, 2007, 370:221

Aliskiren/valsartan combination therapy provides additional reductions in aldosterone

Geometric mean change from baseline in plasma aldosterone concentration at Week 8 (%)



*p<0.001, **p<0.0001 vs placebo
†p<0.01 vs aliskiren/valsartan combination

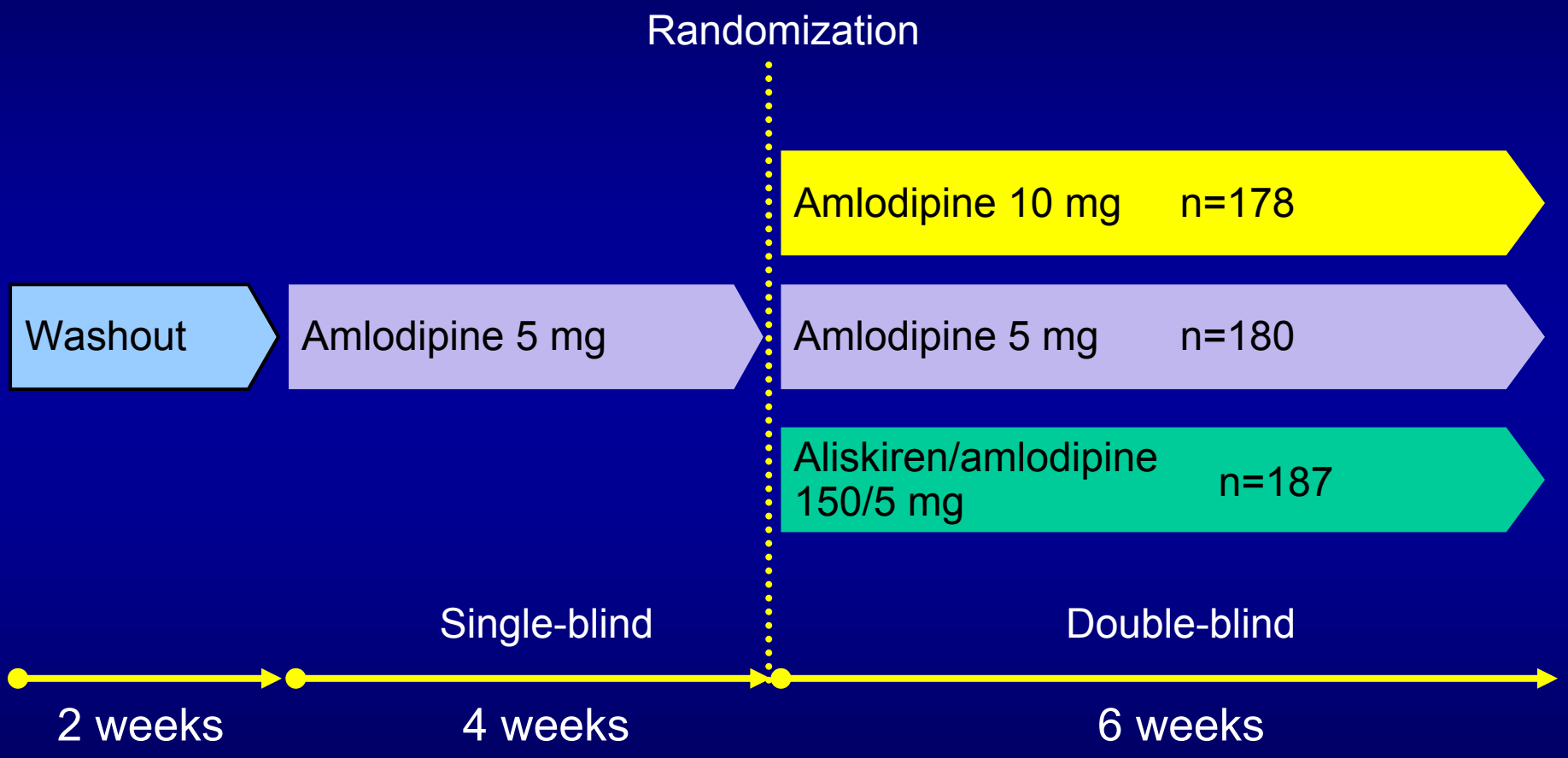
Oparil S, *et al.* 2007

Tolerability profile of aliskiren alone or combined with valsartan.

	Placebo (n=458*)	Aliskiren (n=437)	Valsartan (n=455)	Aliskiren/valsartan (n=446)
Adverse events				
Any adverse event	168 (37%)	149 (34%)	167 (37%)	156 (35%)
Any serious adverse event	5 (1%)	8 (2%)	6 (1%)	3 (0·7%)
Discontinuations due to adverse events	10 (2%)	11 (3%)	11 (2%)	7 (2%)
Most frequent adverse events (≥2% in any treatment group)				
Headache	41 (9%)	14 (3%)	25 (5%)	19 (4%)
Nasopharyngitis	9 (2%)	16 (4%)	20 (4%)	12 (3%)
Dizziness	9 (2%)	8 (2%)	11 (2%)	8 (2%)
Fatigue	5 (1%)	4 (1%)	10 (2%)	8 (2%)
Nausea	11 (2%)	6 (1%)	7 (2%)	7 (2%)
Laboratory abnormalities				
Serum potassium†				
<3·5 mmol/L	17 (4%)	11 (3%)	20 (4%)	12 (3%)
>5·5 mmol/L‡	12 (3%)	7 (2%)	7 (2%)	18 (4%)
≥6·0 mmol/L	6 (1%)	4 (1%)	5 (1%)	2 (0·5%)
Creatinine§				
>176·8 µmol/L	0	1 (0·2%)	2 (0·4%)	4 (0·9%)
Blood urea nitrogen§				
>14·3 mmol/L	0	1 (0·2%)	1 (0·2%)	0

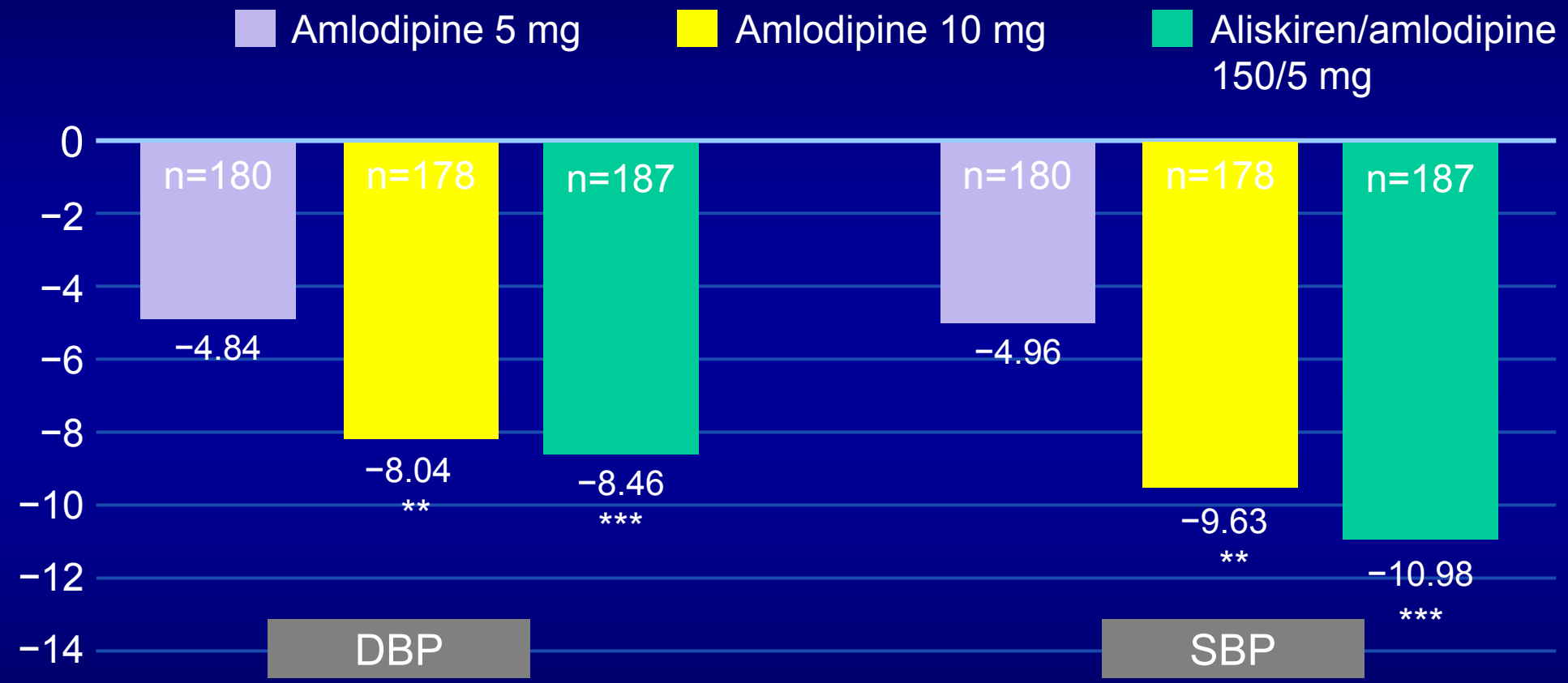
Oparil S, Lancet, 2007, 370:221

Aliskiren in non-responders to amlodipine



Munger M, *et al.* 2006

Aliskiren improves BP control when added to amlodipine 5 mg



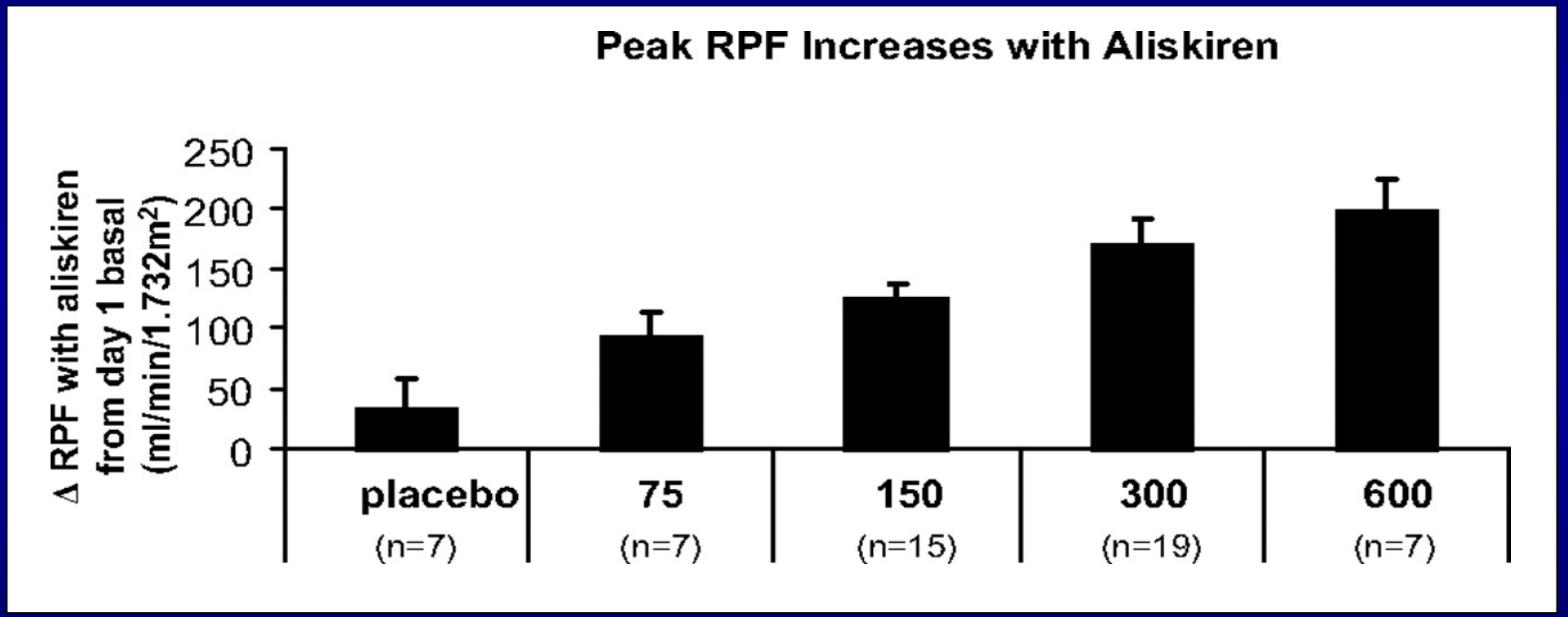
Mean change from baseline in mean sitting BP (mmHg)

**p=0.002, ***p<0.0001 vs amlodipine 5 mg

Munger M, *et al.* 2006

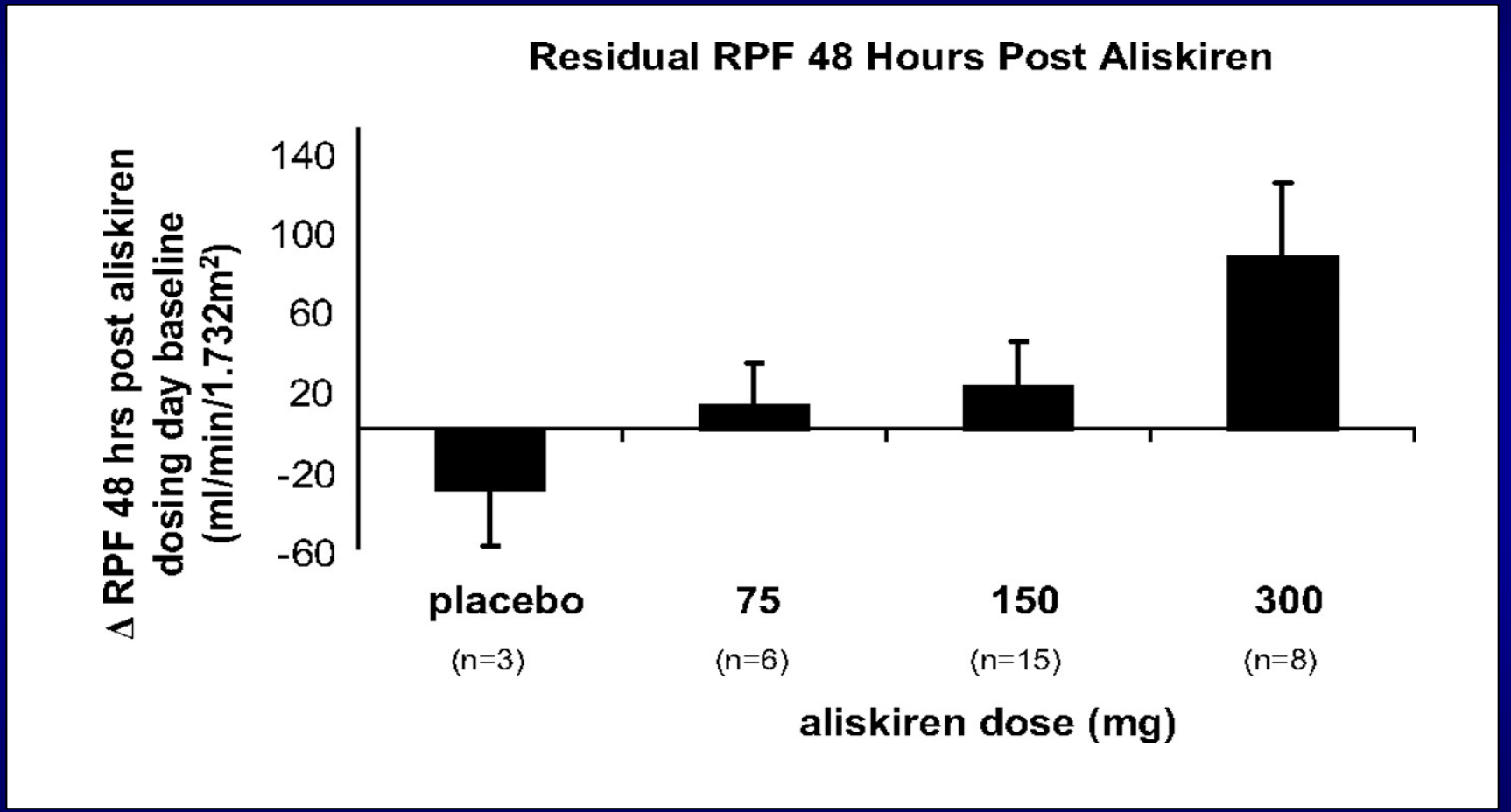
Aliskiren and the kidney

Dose-response of the direct renin inhibitor aliskiren and the peak rise in RPF on a low-sodium diet



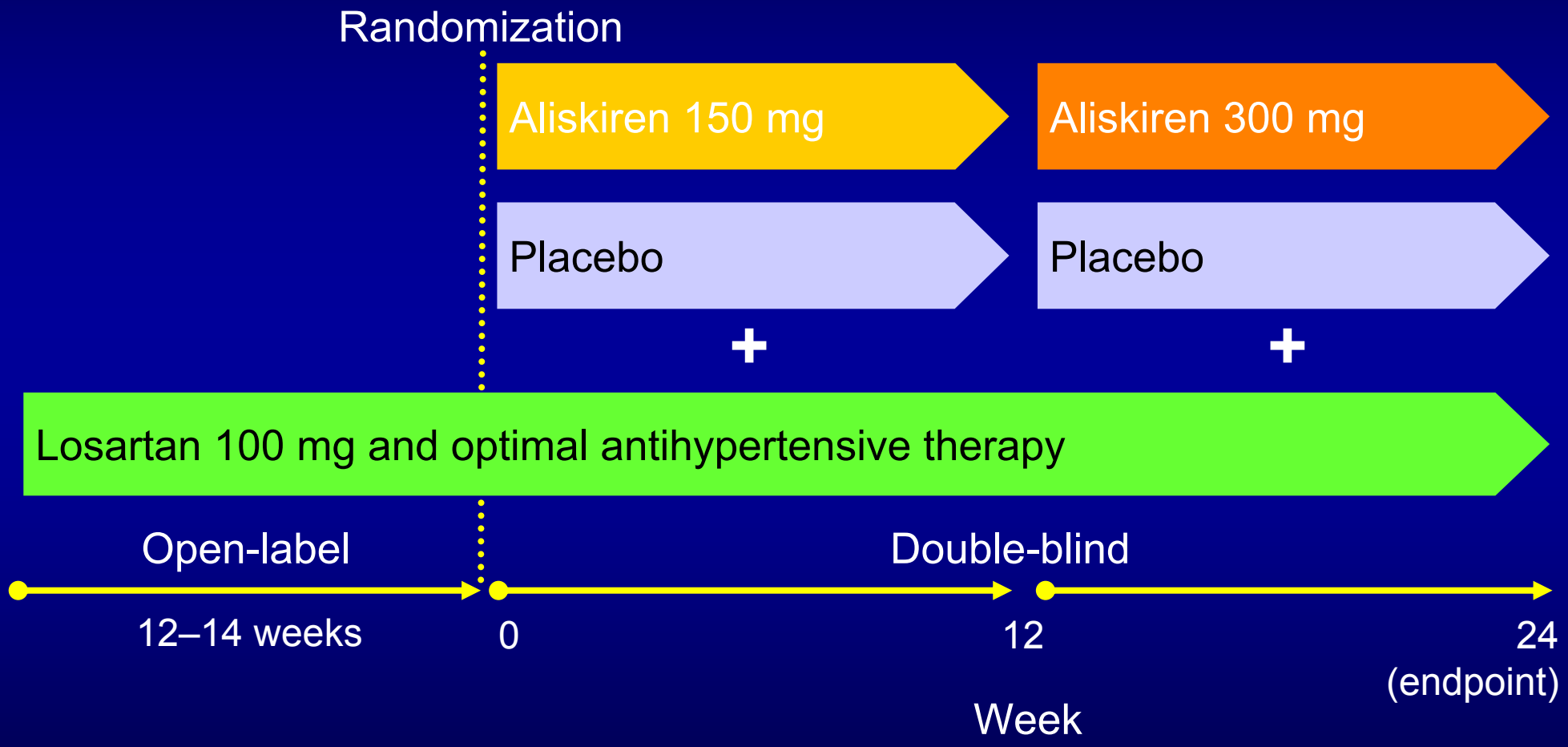
Fisher, N. D.L. et al. Circulation 2008;117:3199-3205

Residual RPF changes 48 hours after each dose of aliskiren



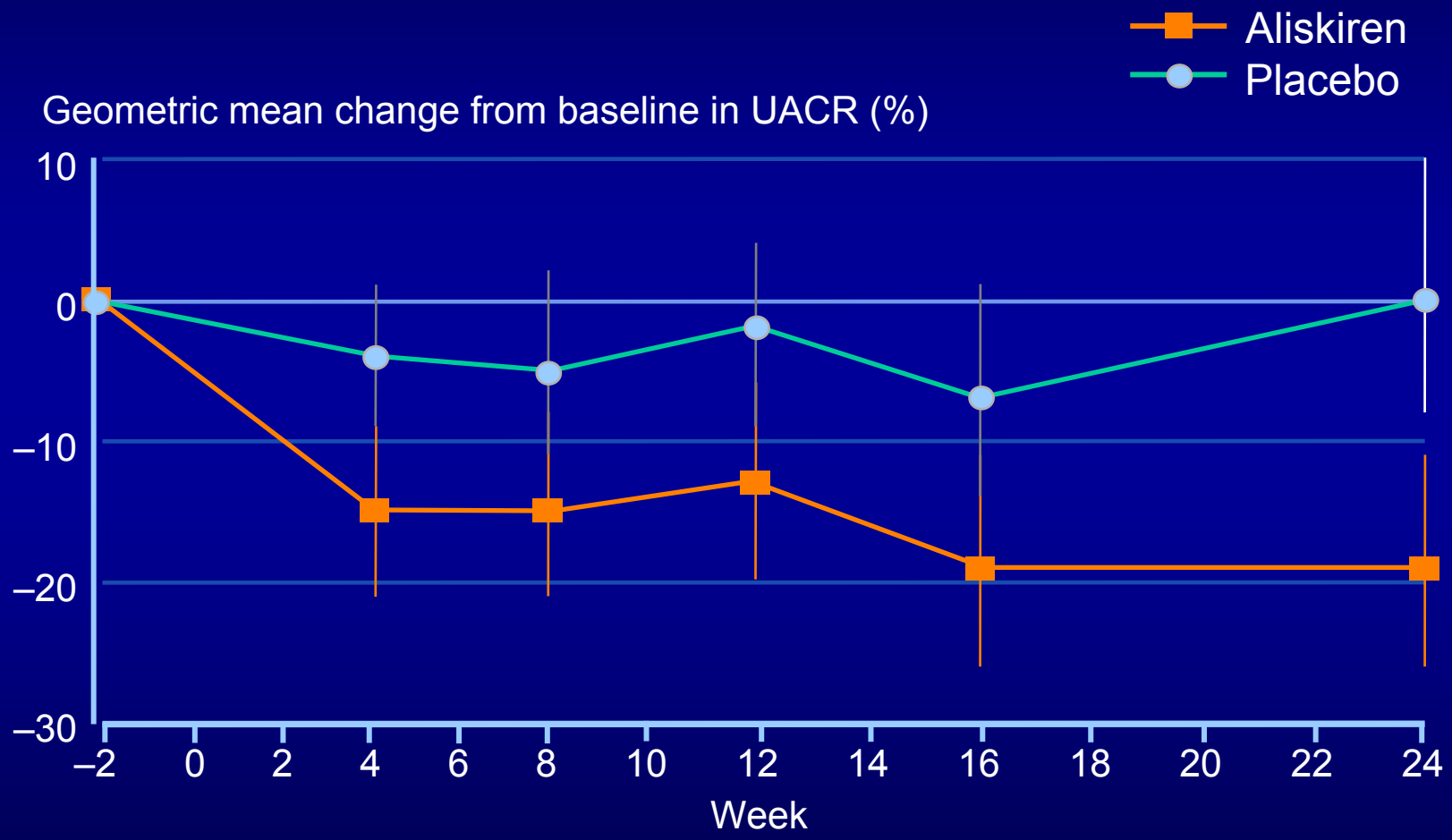
Fisher, N. D.L. et al. Circulation 2008;117:3199-3205

A double-blind, randomized, placebo-controlled study in hypertensive patients with type 2 diabetes and nephropathy



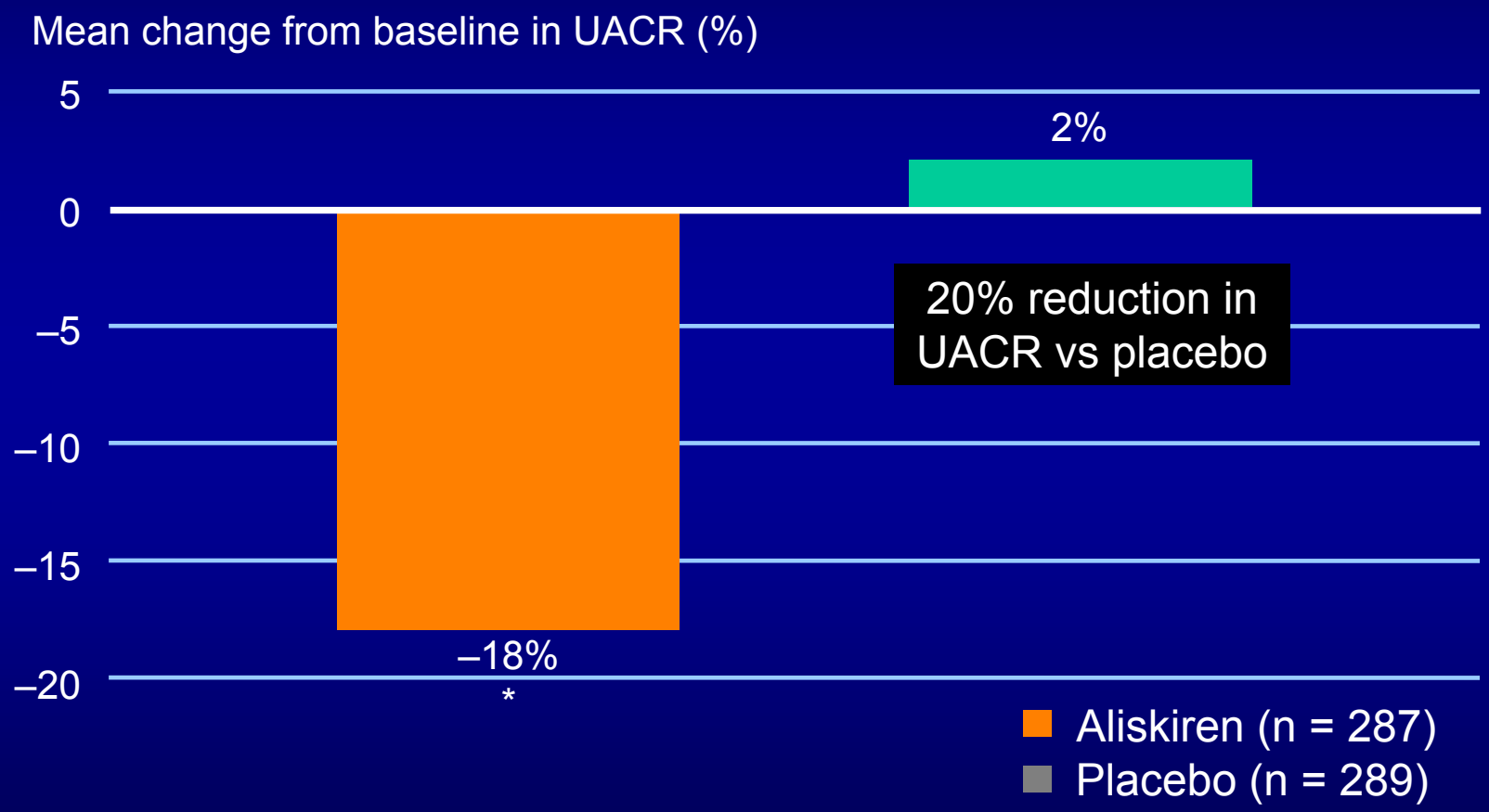
Forced titration at week 12
All doses were administered once daily

Changes in UACR with aliskiren and placebo throughout the course of the study



Data are shown as change from baseline in geometric mean (95% CI)
Baseline was the week –2 value
UACR, urinary albumin:creatinine ratio

Aliskiren significantly reduced UACR from baseline to week 24 endpoint compared with placebo



*p = 0.0009
Data are shown as percentage change in geometric mean
Baseline was week −2 value
UACR, urinary albumin:creatinine ratio

Effect of study treatments on laboratory values

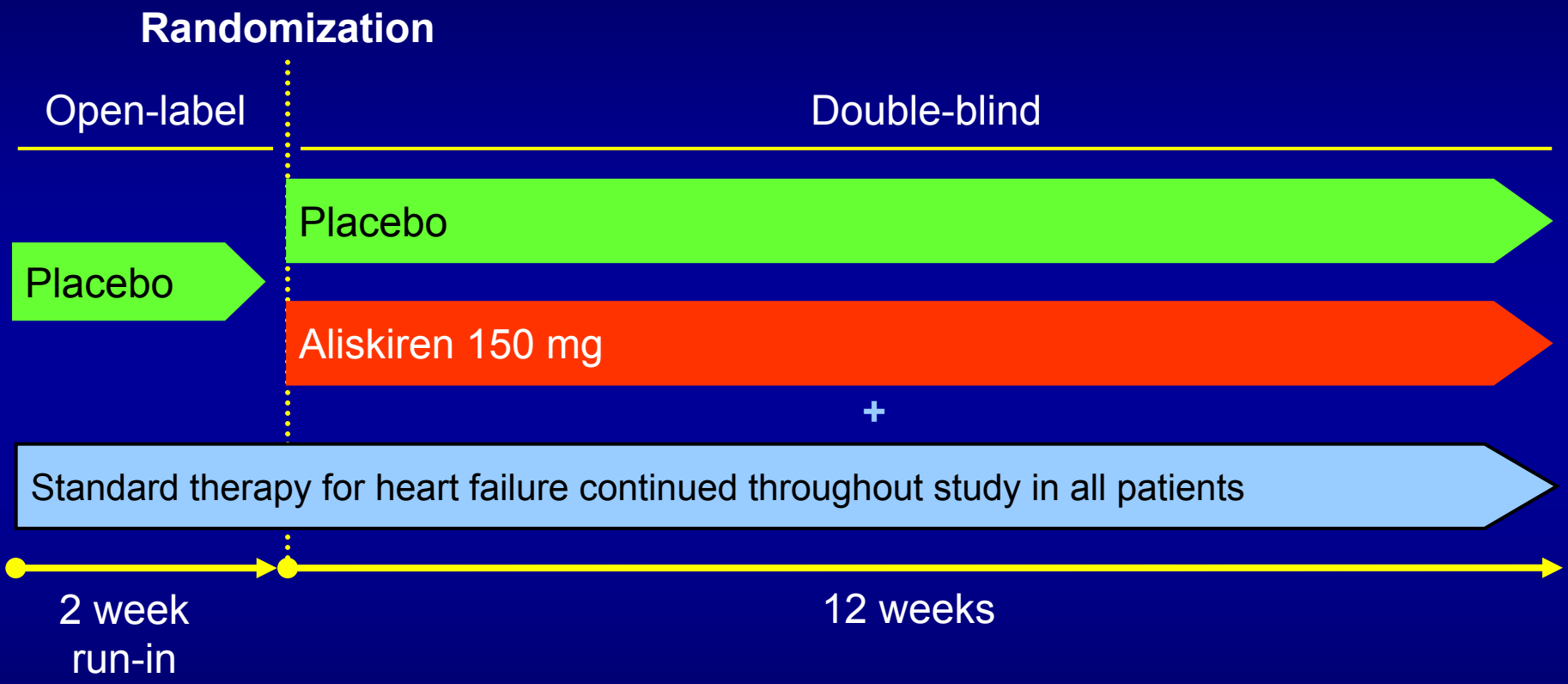
	Aliskiren (n = 299)	Placebo (n = 297)
Serum potassium, n (%)		
< 3.5 mEq/L	15 (5.0)	11 (3.7)
> 5.5 mEq/L	41 (13.7)	32 (10.8)
≥ 6.0 mEq/L	14 (4.7)	5 (1.7)
Creatinine > 2.0 mg/dL, n (%)	37 (12.4)*	54 (18.2)
BUN > 40.0 mg/dL, n (%)	65 (21.7)	66 (22.2)

- The proportion of patients with serum creatinine levels > 2.0 mg/dL was significantly higher with placebo than aliskiren (p = 0.049).
- The incidence of serum potassium > 6.0 mEq/L was greater with aliskiren than placebo, although this was not statistically significant (p = 0.059).

*p = 0.049 based on Chi-squared test
Data are presented as number (%) of patients with pre-specified abnormal laboratory values at any time during the double-blind period
BUN, blood urea nitrogen

Aliskiren and the heart

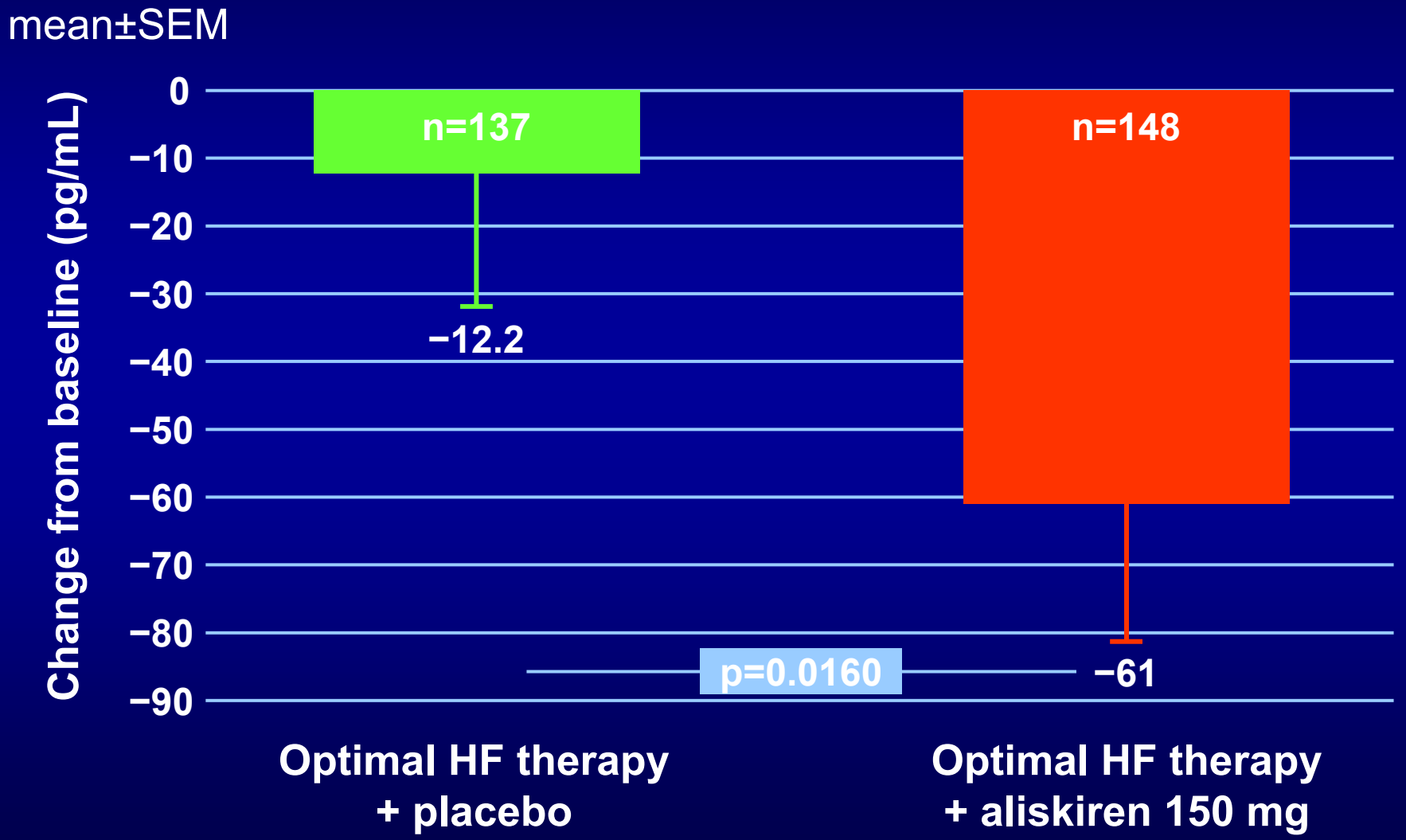
ALOFT: study design



n=302 patients with stable HF, history of hypertension, BNP >100 pg/mL
Patients stratified at randomization for LVEF of >40% or ≤40%

McMurray J, et al.

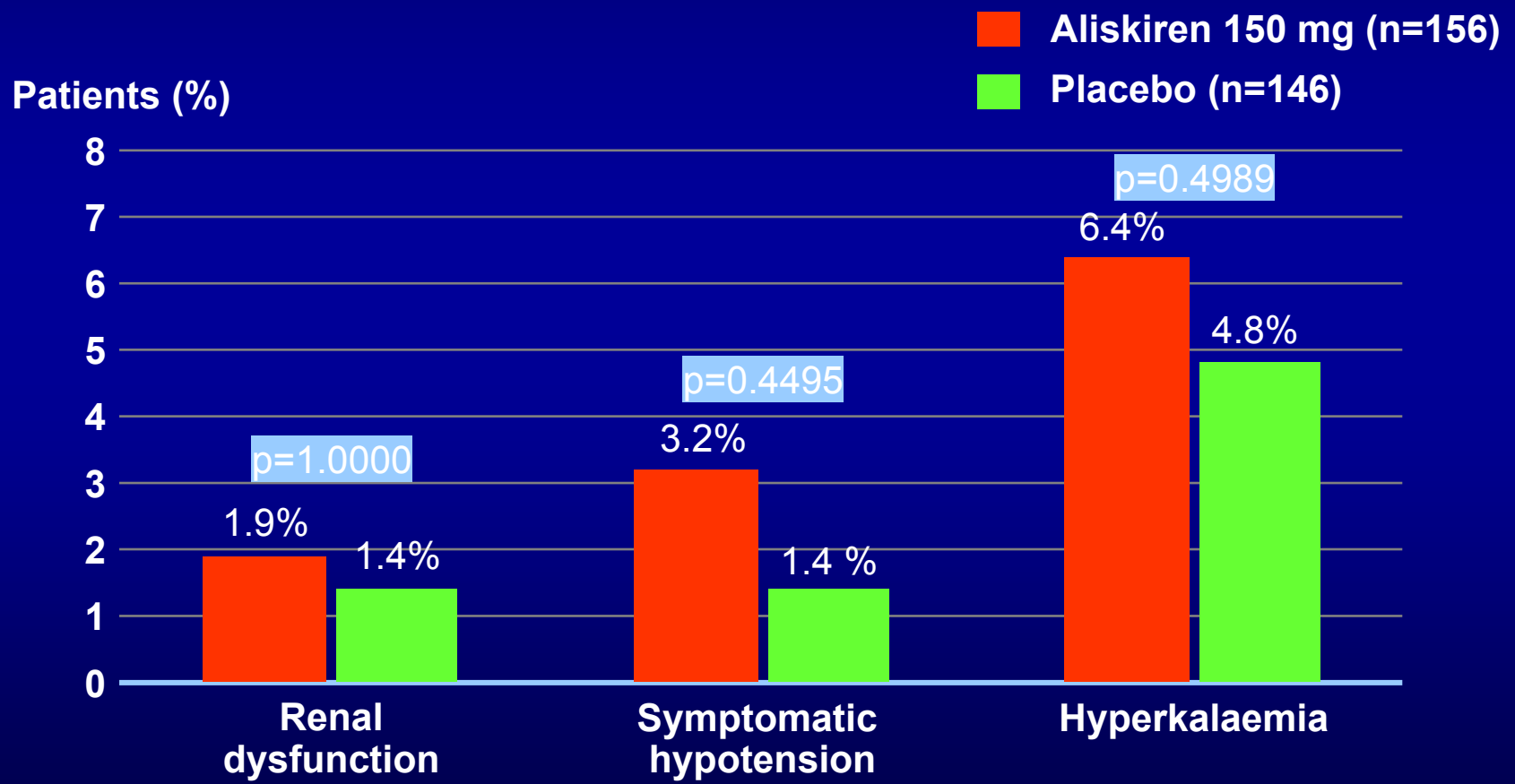
ALOFT findings: significant reduction in BNP levels



McMurray J, et al.

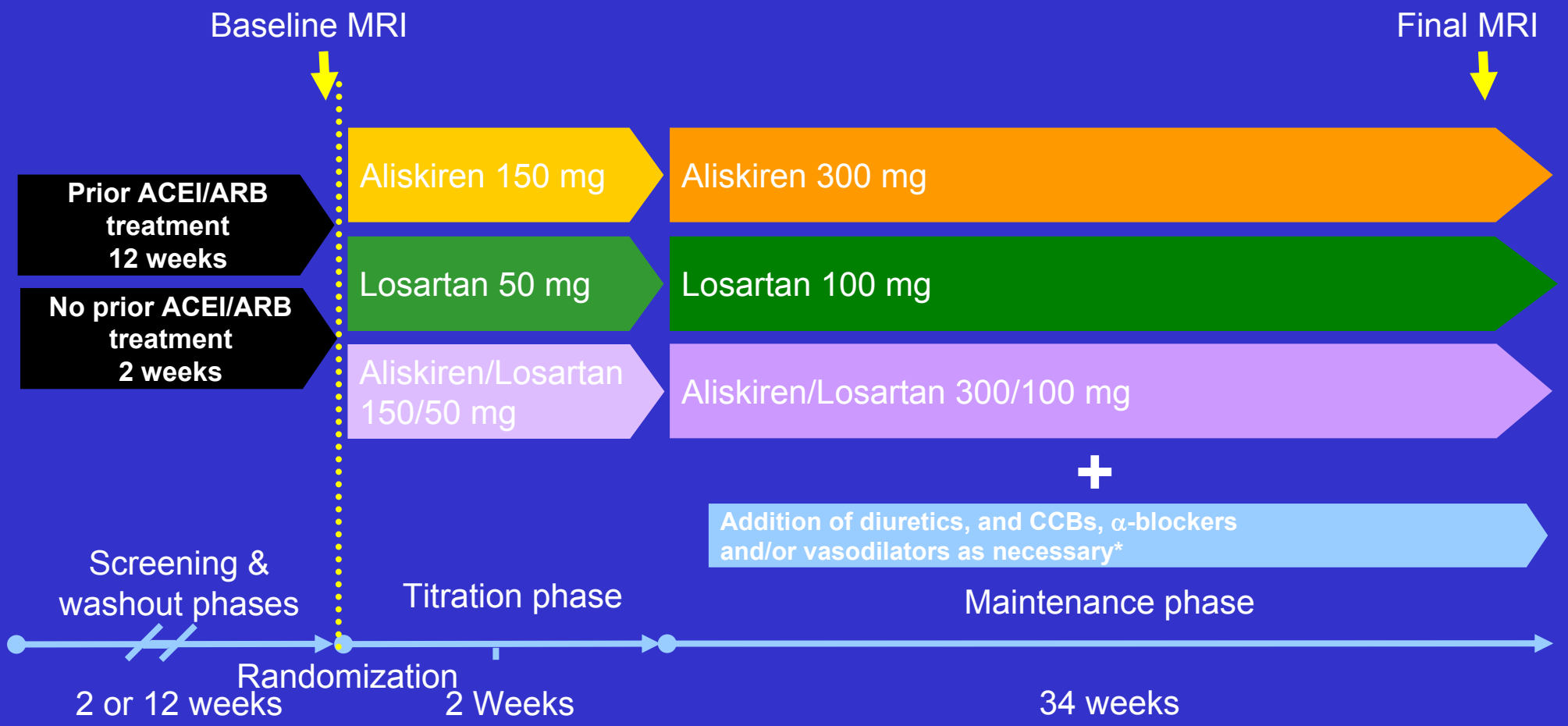
ALOFT: pre-specified safety assessments

No significant increase in renal dysfunction, symptomatic hypotension or hyperkalaemia compared to placebo



McMurray J, et al.

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

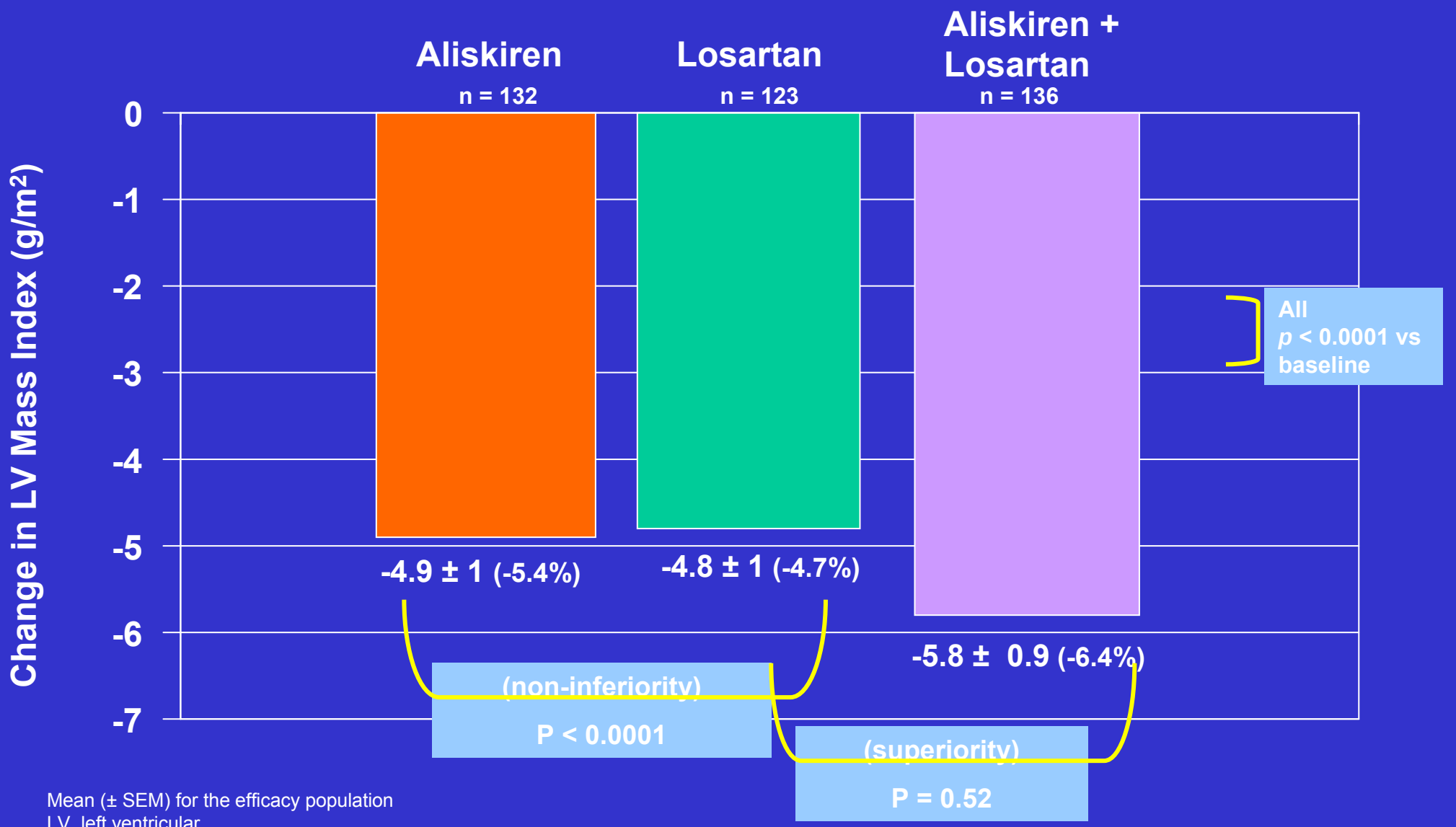


*To achieve BP target of < 140/90 mmHg (< 130/80 mmHg for patients with diabetes)

77 centers in 9 countries

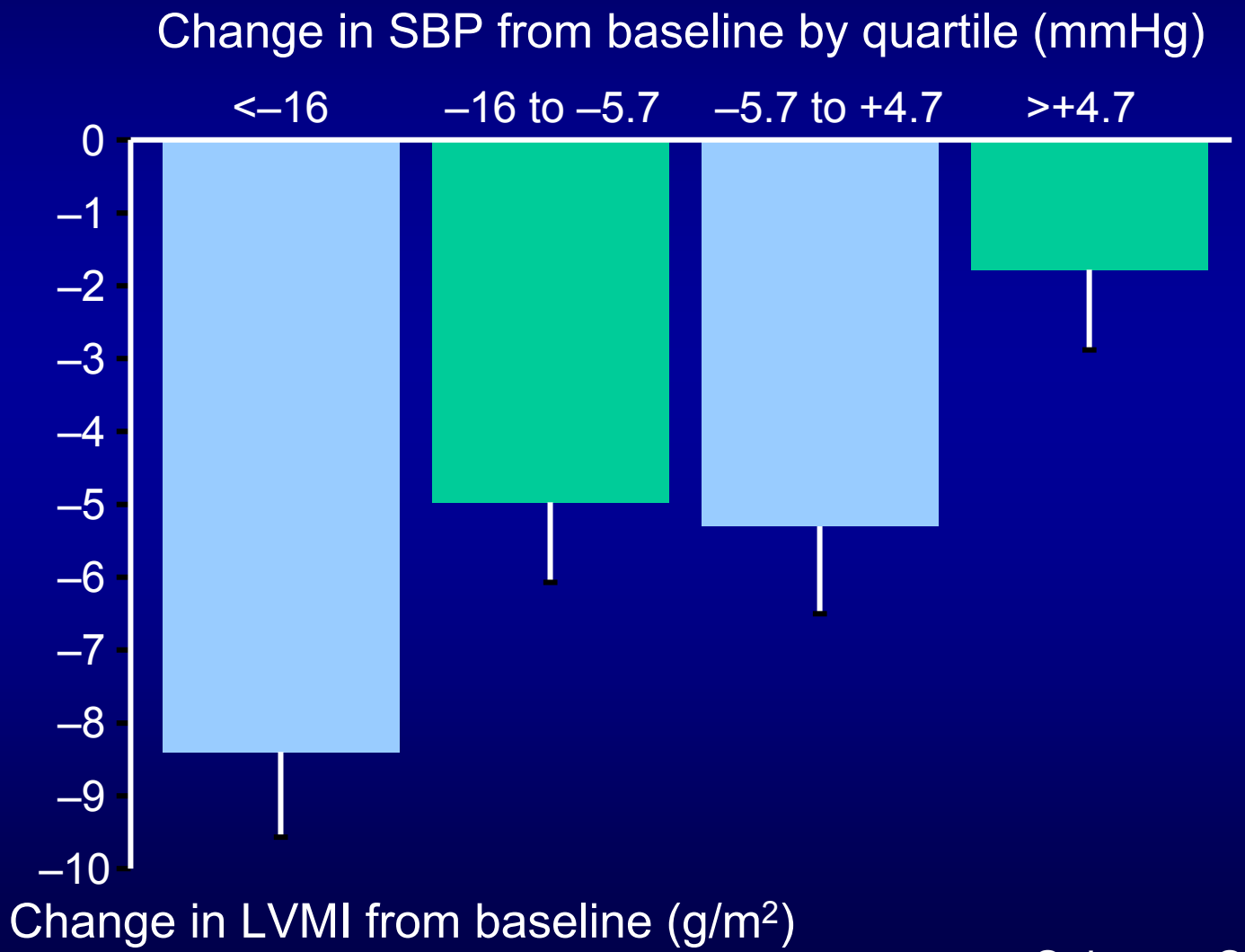
CCBs, calcium channel blocker; LV, left ventricular

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



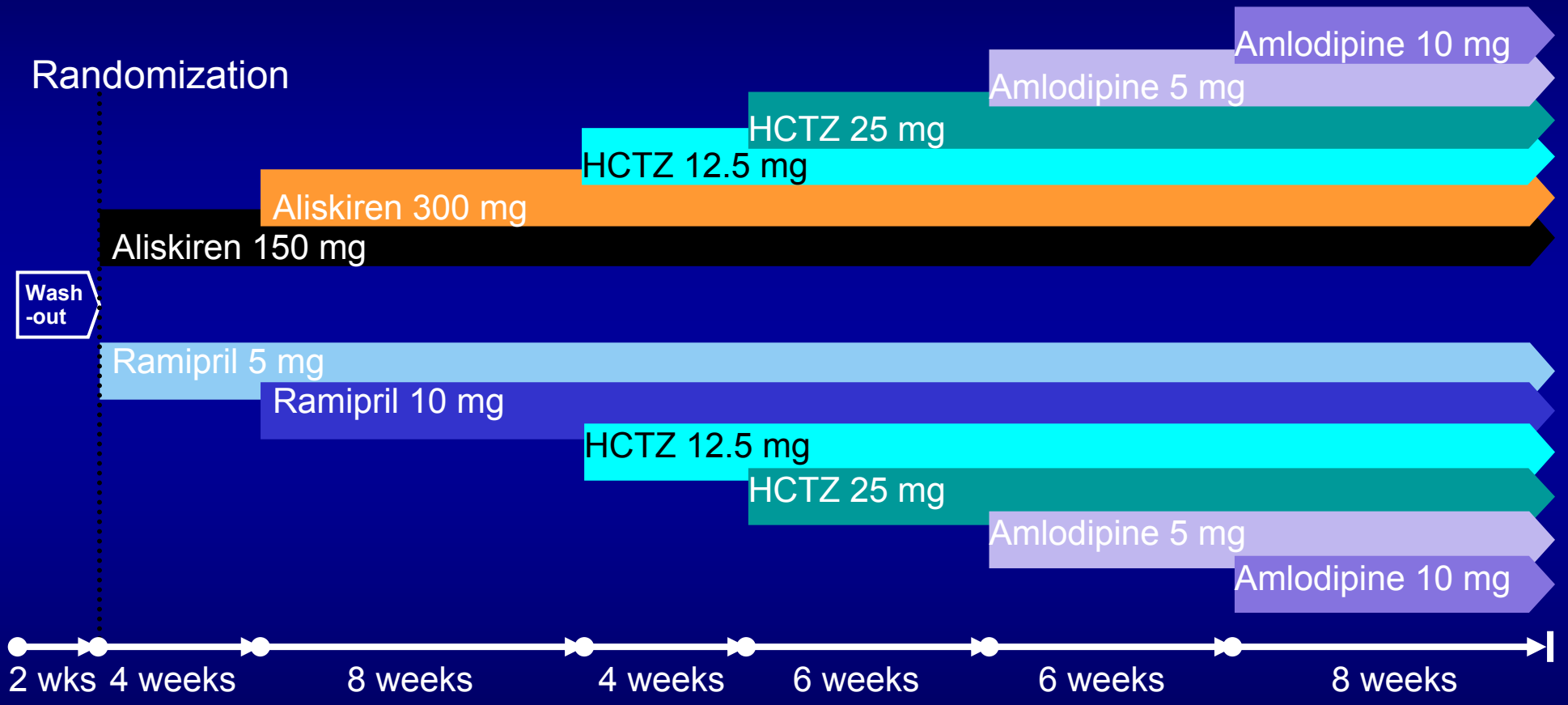
Mean (± SEM) for the efficacy population
LV, left ventricular

Greater reductions in SBP are associated with greater reductions in LVMI



Solomon SD, et al. 2008

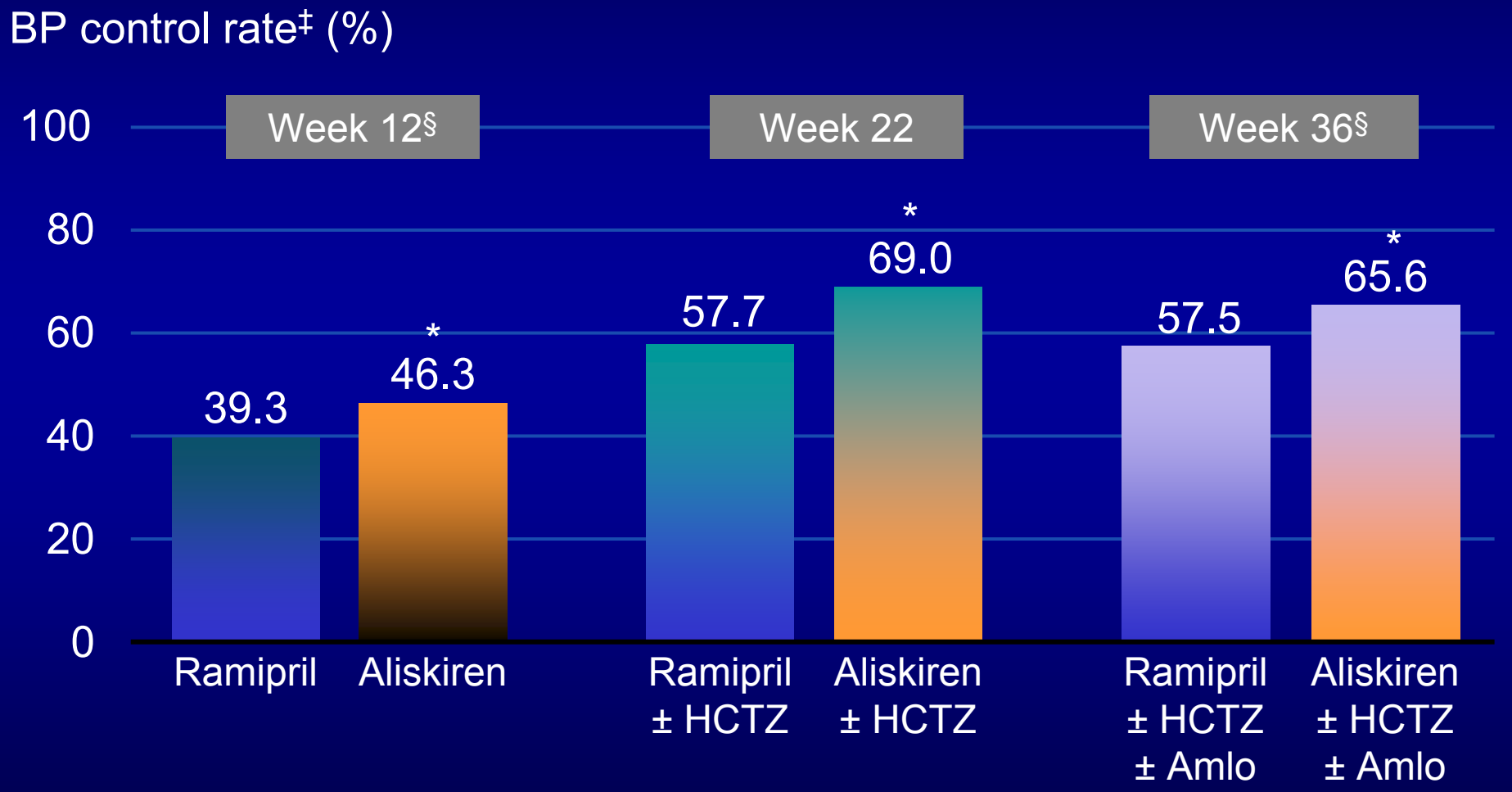
AGELESS study
Design overview



Patients with SBP ≥140 mmHg after 4 weeks' treatment with aliskiren 150 mg or ramipril 5 mg receive up-titration of aliskiren or ramipril, and then sequential addition and up-titration of HCTZ and amlodipine as required

Duprez D, *et al*. 2008

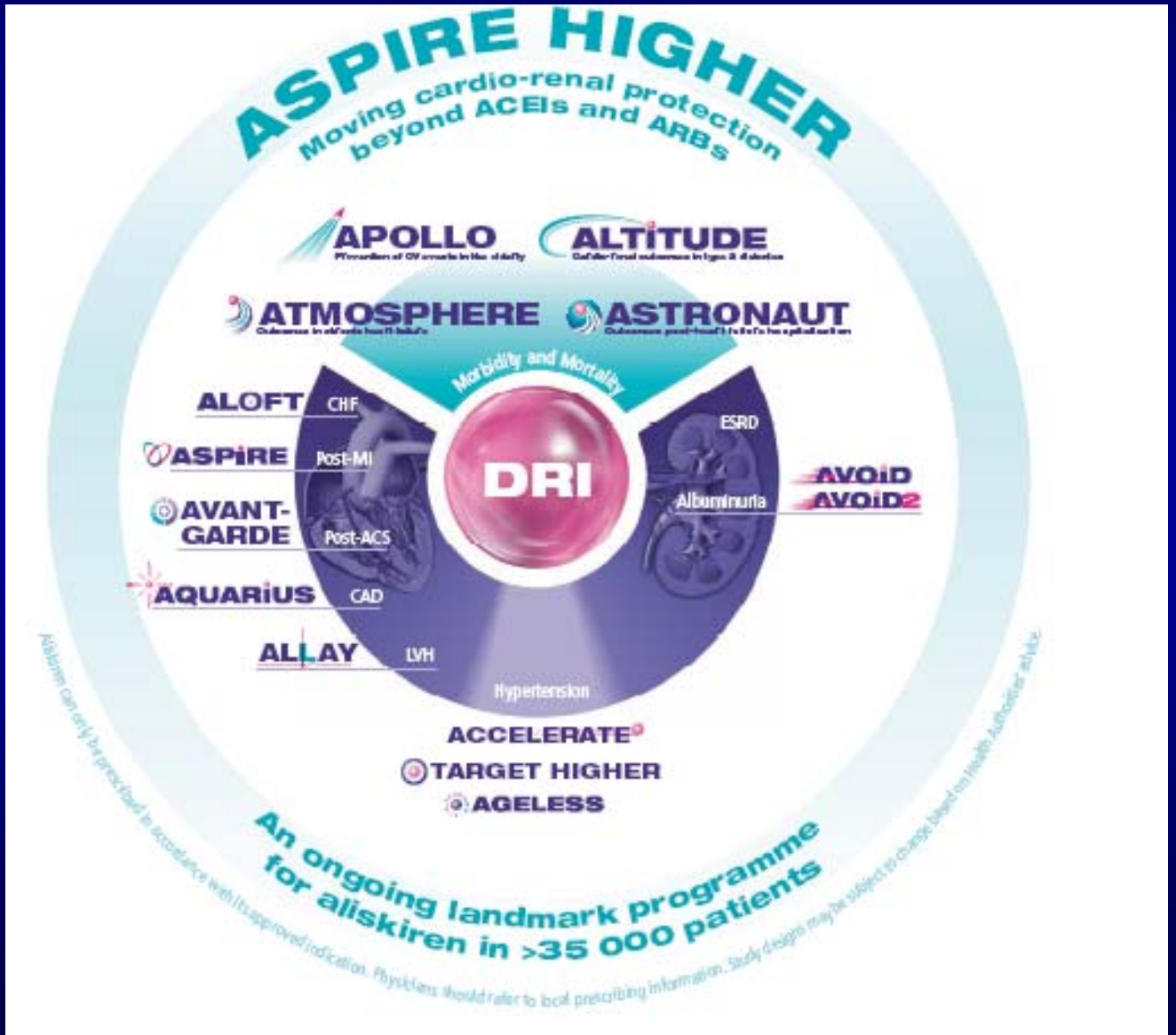
Aliskiren-based therapy vs ramipril-based therapy in elderly patients



‡Control defined as BP<140/90 mmHg. *p<0.05 vs ramipril-based therapy (superiority)
§Data calculated using last observation carried forward. Dosages: ramipril = 5 or 10 mg; aliskiren = 150 or 300 mg; HCTZ = 12.5 or 25 mg; amlo (amlodipine) = 5 or 10 mg.

Duprez D, *et al*. 2008

Future studies with Aliskiren: The ASPIRE HIGHER clinical trial programme

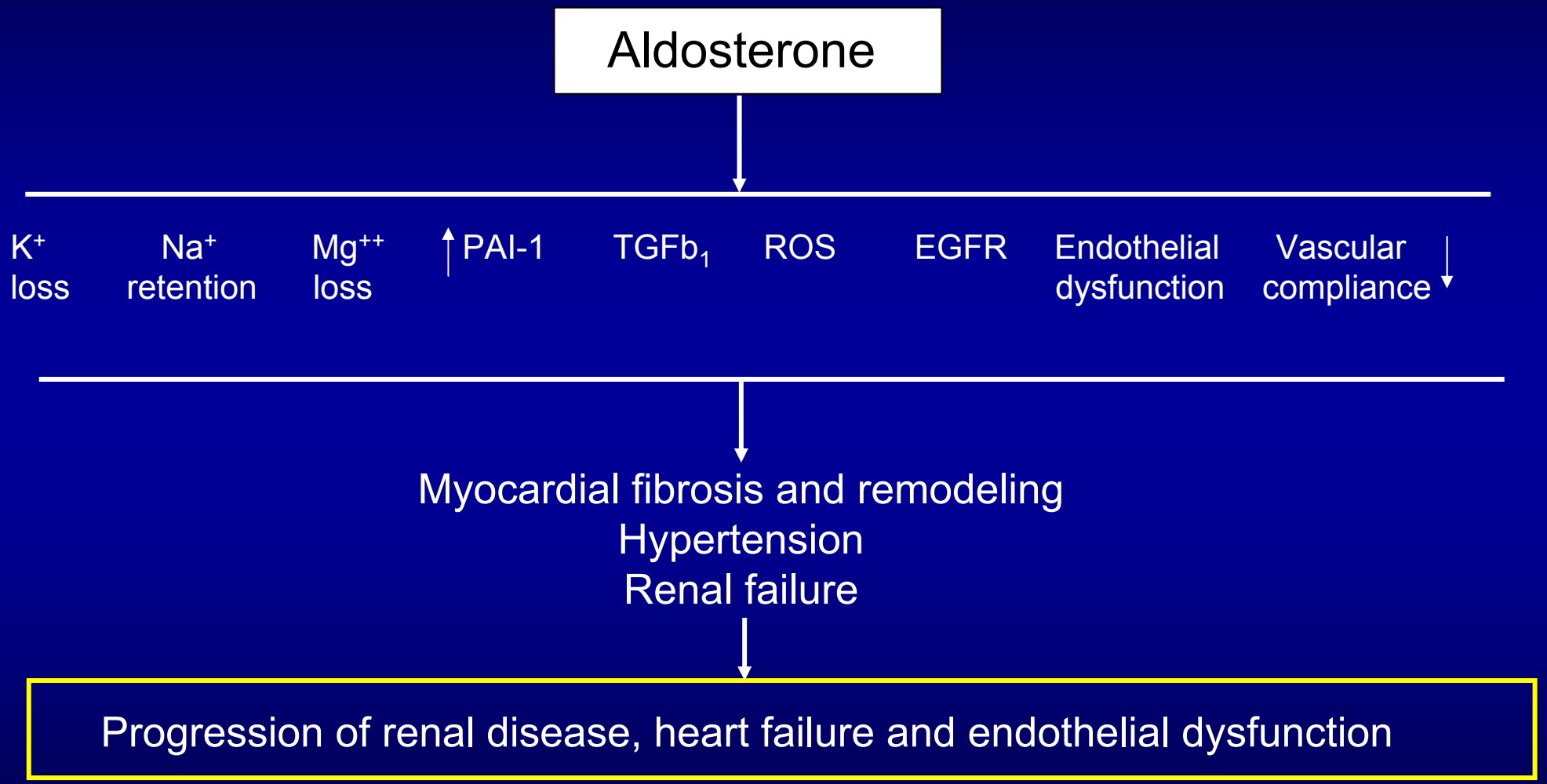


Dzau VJ, *et al*. 2006
Kopyt NP. 2005

Theoretical potential advantages of renin inhibitors

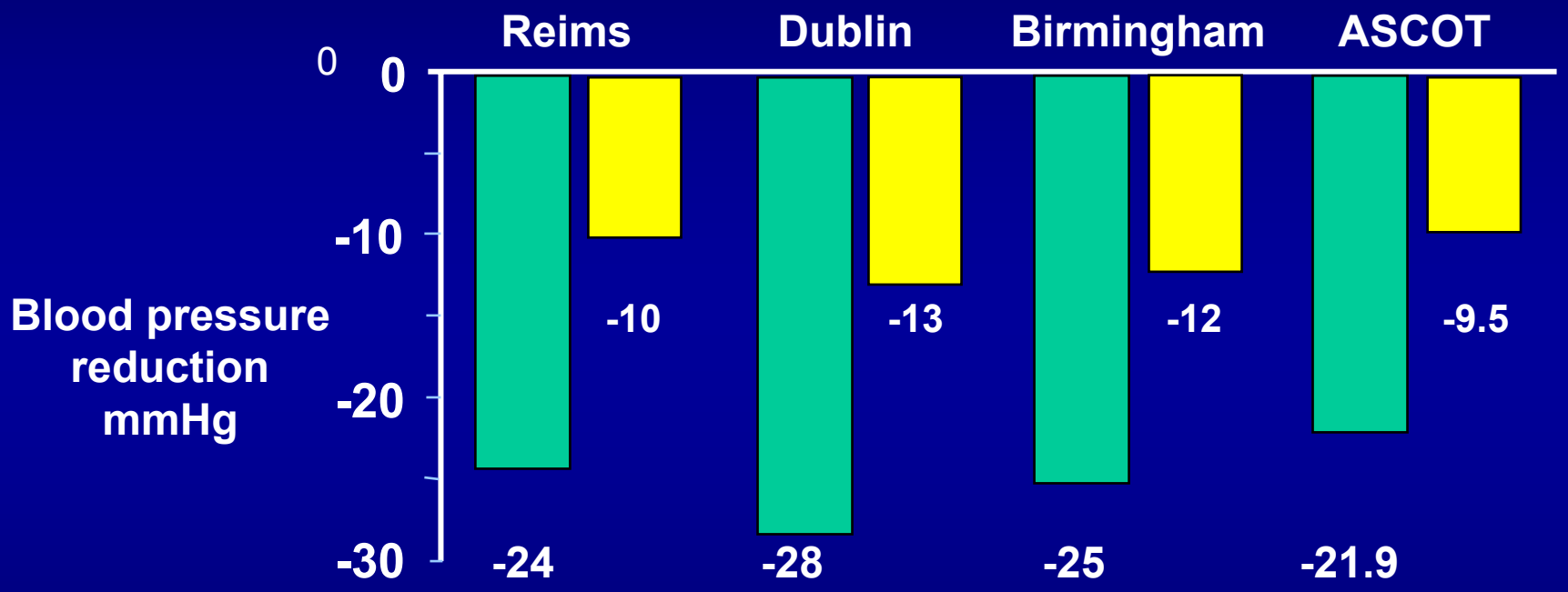
1. Species specificity: Highly specific for human renin
2. Inhibition of the rate-limiting step of Ang II formation
3. Substrate specificity: Angiotensinogen
4. Render the RAS quiescent
    - Suppression of all Ang I-derived peptides
    - Inhibition of ACE-independent pathways of Ang II generation
    - No stimulation of AT_2 or other AT_n receptors
    - Neutralization of consequences of the counter-regulatory renin release triggered by RAS blockade
    - Potential interaction with the (pro)renin receptor?
5. Compete well with established RAS blockers in hypertension
6. Well tolerated
7. Potential advantages
    - in patients with chronic nephropathies
    - In patients with diabetes (nephropathy, retinopathy)

Deleterious effects of aldosterone



Adapted from Epstein M, Am J Med, 2006; 119:912

Blood pressure reduction with spironolactone in resistant hypertension: results of several studies



On top of ACE, CCB and diuretics
The response is independent of the aldosterone/renin ratio

Adapted from Pimenta et al, 2007

Conclusions

Today we have several possibilities to block the renin-angiotensin aldosterone system in our patients.

ACEI, ARBs are well tolerated and effective not only to lower BP but also to protect organs such as the heart and the kidney.

Renin inhibition with aliskiren is as effective as ARBs and ACEIs In their ability to lower BP with a very long duration of action.

Today's challenges are to define how to integrate these different strategies acting on the RAA system in our patients and to define which patient will benefit the most of each therapy.