ESC CONGRESS HIGHLIGHTS

PREVENTION AND HYPERTENSION

R. Ferrari

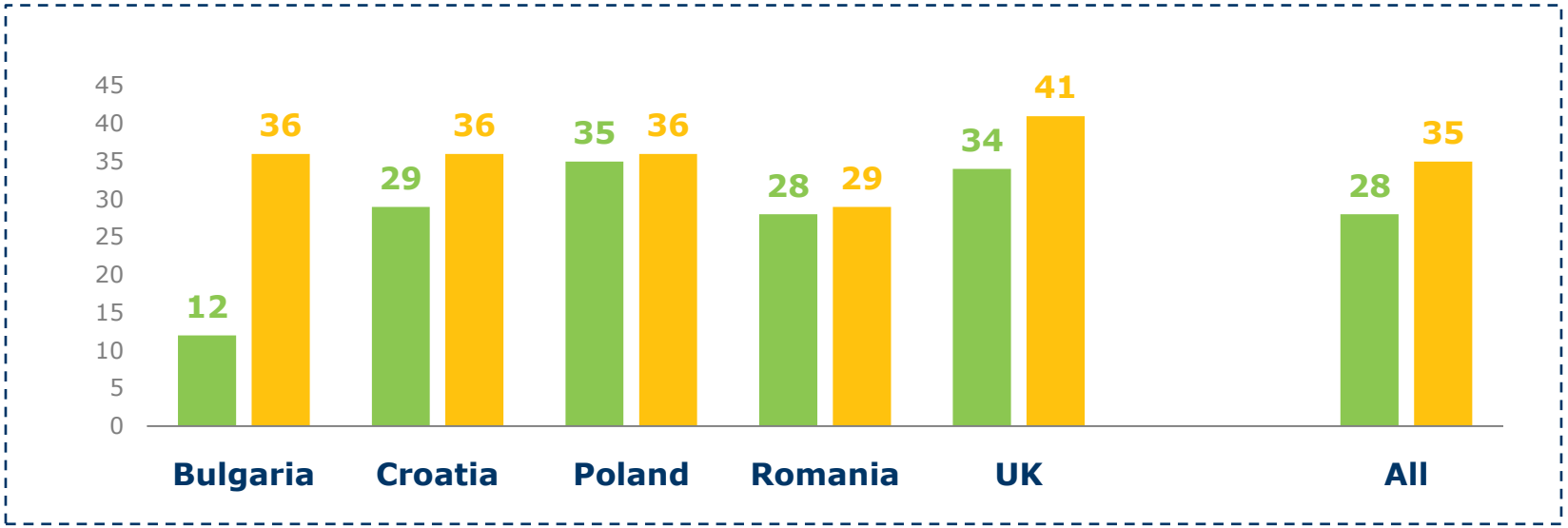
HYPERTENSION HIGHLIGHTS

BLOOD PRESSURE CONTROL IN EUROPE

Comparing EUROASPIRE II and IV

THERAPEUTIC CONTROL OF BLOOD PRESSURE* (%) EUROASPIRE III VS. IV

Bulgaria	Croatia	Poland	Romania	UK	Overall	P
+23.5%	+6.3%	+0.9%	+0.7%	+7.0%	+8.5%	P=0.12



* SBP/DBP <140/90 mmHg in patients using blood pressure lowering drugs 140/80 mmHg in diabetes

K. Koteseva (London, UK), FP 5069

HYPERTENSION HIGHLIGHTS

DRUG TREATMENT OF RESISTANT HYPERTENSION

PATHWAY-2

BACKGROUND

PATHWAY 2
Clinical Trials in Hypertension

- Resistant hypertension has been defined as uncontrolled blood pressure (BP) despite treatment with maximal tolerated doses of 3 BP-lowering medications, usually; an ACE-inhibitor or ARB + CCB + Thiazide-like Diuretic,
- The optimal drug treatment of resistant hypertension remains undefined
- There have been no RCTs directly comparing spironolactone with other BP-lowering drugs to determine whether spironolactone is the most effective treatment for resistant hypertension
- HYPOTHESIS: Further diuretic therapy with spironolactone will be more effective at lowering BP than alternative BP-lowering treatments, targeting different mechanisms

PATHWAY-2 STUDY DESIGN

PATHWAY-2 Clinical Trials in Hypertension

- **Double blind, Randomised, Placebo-Controlled, Cross-over Study**

314 Patients with Resistant Hypertension

- → Rx A + C + D
- → DOT* to exclude non-compliance
- → Home BP to exclude white coat hypertension
- → Secondary hypertension excluded

4 week Single blind placebo run in Treated with A+C+D

Randomisation

R

Plasma Renin

Doxazosin MR 4 – 8mg o.d.

Spironolactone 25 – 50mg o.d.

Home Systolic BP measured at 6 and 12 weeks

Placebo

Bisoprolol 5 – 10mg o.d.

Basline Clinic BP (mmHg)	**157/90**
Baseline Home BP (mmHg)	**148/84**

- → **12 weeks per treatment cycle**
- → **Forced titration; lower to higher dose at 6 weeks**
- → **No washout period between cycles**

*DOT = Directly Observed Therapy

PRIMARY OUTCOME

PATHWAY 2
Clinical Trials in Hypertension

Comparators (N=314)	Home Systolic BP difference (mmHg)	p value
Spironolactone vs placebo	-8.70 (-9.72,-7.69)	<0.001
Spironolactone vs mean Bisoprolol/Doxazosin	-4.26 (-5.13,-3.38)	<0.001
Spironolactone vs Doxazosin	-4.03 (-5.04,-3.02)	<0.001
Spironolactone vs Bisoprolol	-4.48 (-5.50,3.46)	<0.001

SERIOUS ADVERSE EVENTS AND WITHDRAWALS

	Bisoprolol	Spironolactone	Doxazosin	Placebo	p value
Serious adverse events	8 (2.6%)	7 (2.3%)	5 (1.7%)	5 (1.7%)	0.831
Any adverse event	68 (11.3%)	67 (10.4%)	58 (10.1%)	42 (9.1%)	0.711
Withdrawals for adverse events	2 (2.9%)	3 (3.4%)	8 (10.0%)	2 (2.6%)	0.084

p values for Fisher's exact test

IMPLICATIONS OF FINDINGS

PATHWAY Clinical Trials in Hypertension

- **PATHWAY-2 is the first RCT to directly compare spironolactone with other active BP-lowering treatments in patients with well characterised resistant hypertension**
- **The result in favor of spironolactone was unequivocal – Spironolactone is the most effective treatment for resistant hypertension, and these results should influence treatment guidelines globally**
- **Patients should not be defined as resistant hypertension unless their BP remains uncontrolled on spironolactone**

HYPERTENSION HIGHLIGHTS

RE-EVALUATING DIURETICS FOR HYPERTENSION

PATHWAY-3

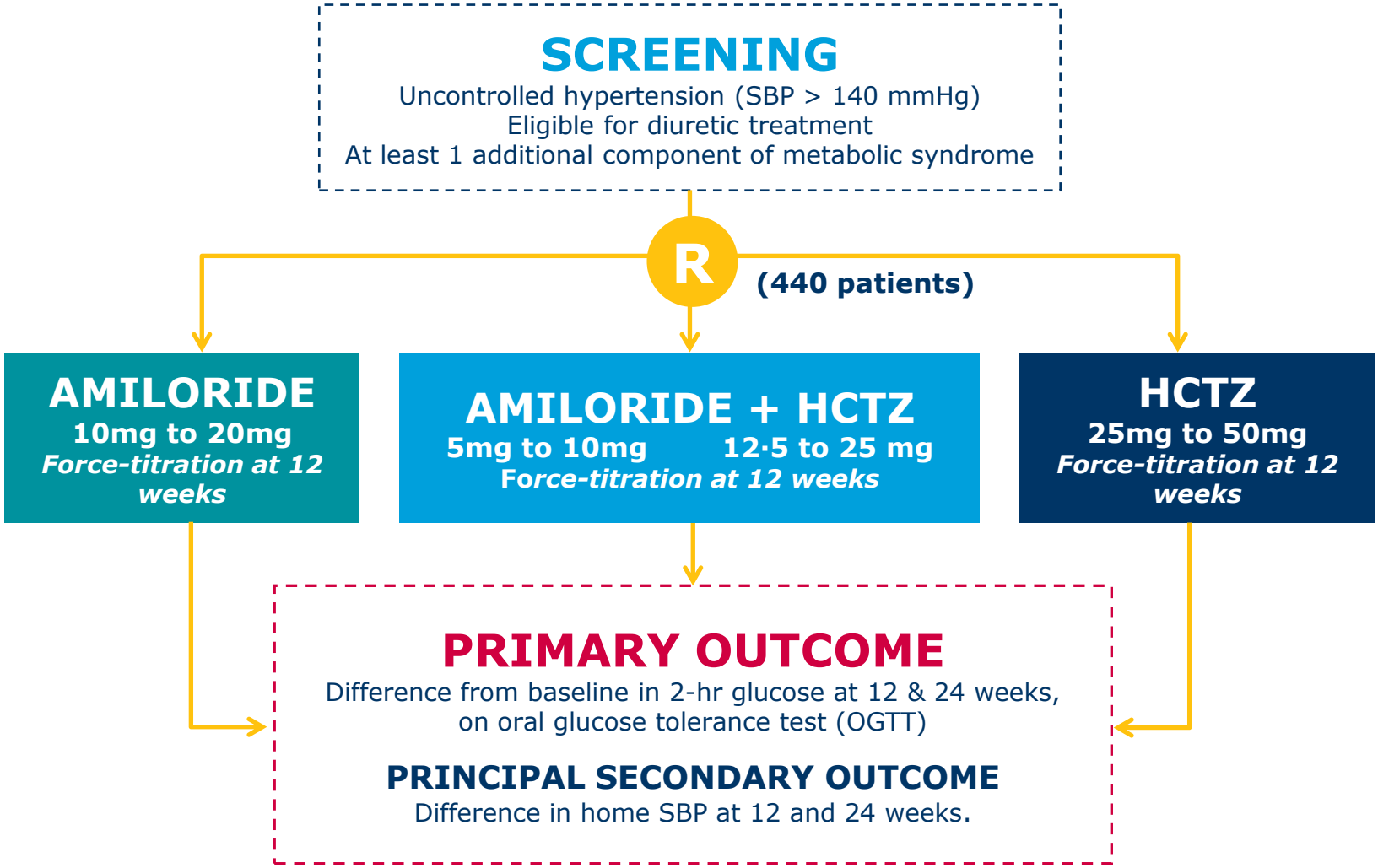
BACKGROUND

PATHWAY 3
Clinical Trials in Hypertension

- **Use of thiazide diuretics for hypertension has been complicated by glucose intolerance and hypokalemia, which has resulted in them being used in lower doses**
- **Potassium-sparing diuretics such as amiloride have been avoided because of a perceived lack of BP-lowering efficacy and increased risk of hyperkalemia on a background of increasing use of RAS blockers**
- **Increased risk of diabetes with thiazides appears linked to potassium-depletion – could this be avoided by using potassium-sparing diuretics, alone or in combination?**

STUDY METHODS AND DESIGN

PATHWAY 3
Clinical Trials in Hypertension

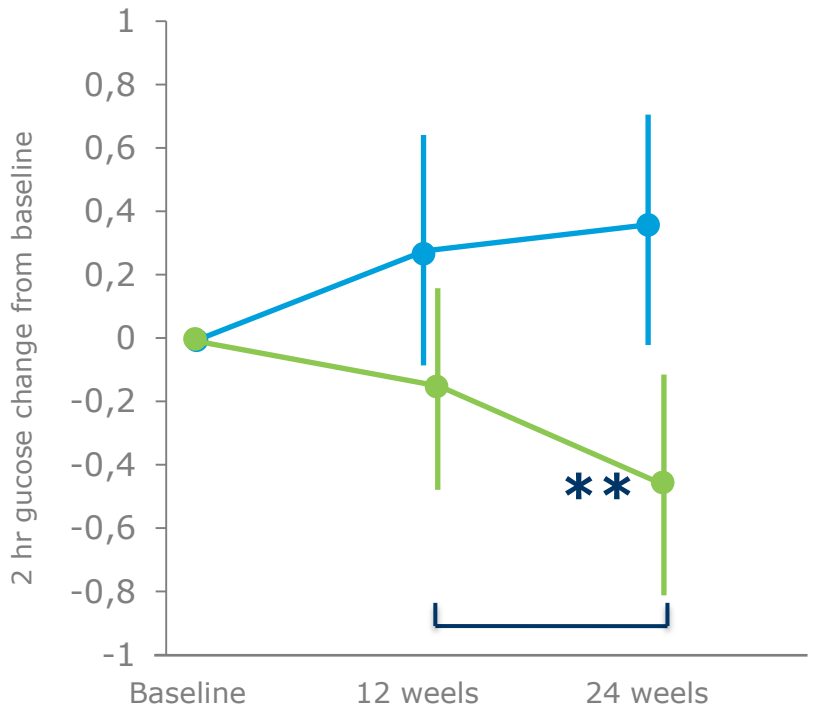


M. J. Brown (Cambridge, UK) FP 4140

HIERARCHICAL PRIMARY ENDPOINTS

PATHWAY 3
Clinical Trials in Hypertension

- **Difference in change from baseline in OGTT 2 hr glucose for [i] amiloride vs HCTZ**



Hydrochlorothiazide (HTCZ) 15-50 mg

Amiloride 10-20 mg

Average difference from HCTZ
(mmol/L) (12 & 24 weeks)

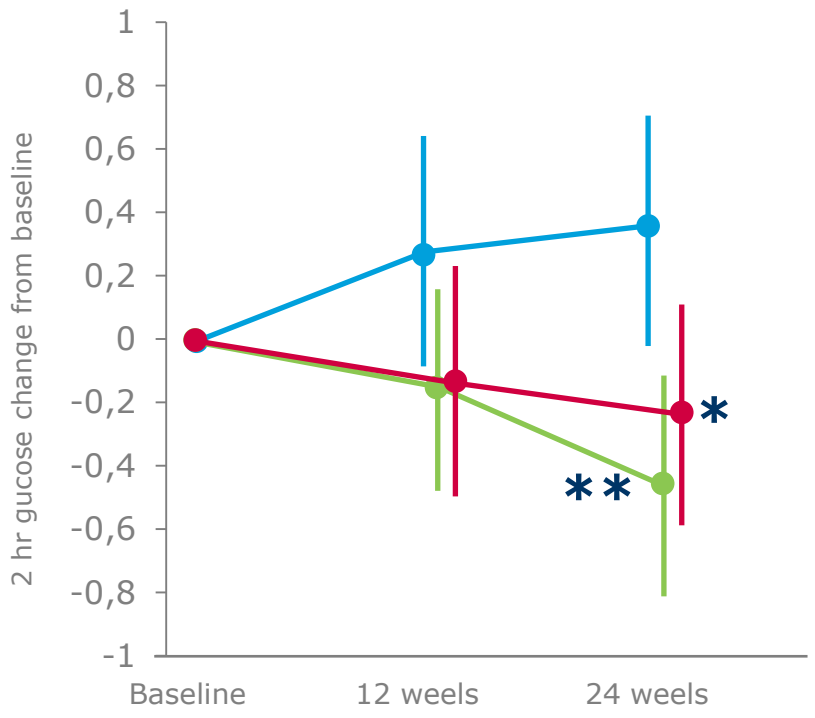
Amiloride n=132
-0.55 (-0.14,-0.96)
P=0.009

M. J. Brown (Cambridge, UK) FP 4140

HIERARCHICAL PRIMARY ENDPOINTS

PATHWAY 3
Clinical Trials in Hypertension

- **Difference in change from baseline in OGTT 2 hr glucose for [i] amiloride vs HCTZ, [ii] combination vs HCTZ**



Hydrochlorothiazide (HTCZ) 15-50 mg
Amiloride 10-20 mg
Amiloride / HTCZ combination 5/12.5 -10/25mg

High-dose difference from HCTZ
(mmol/L) (24 weeks)

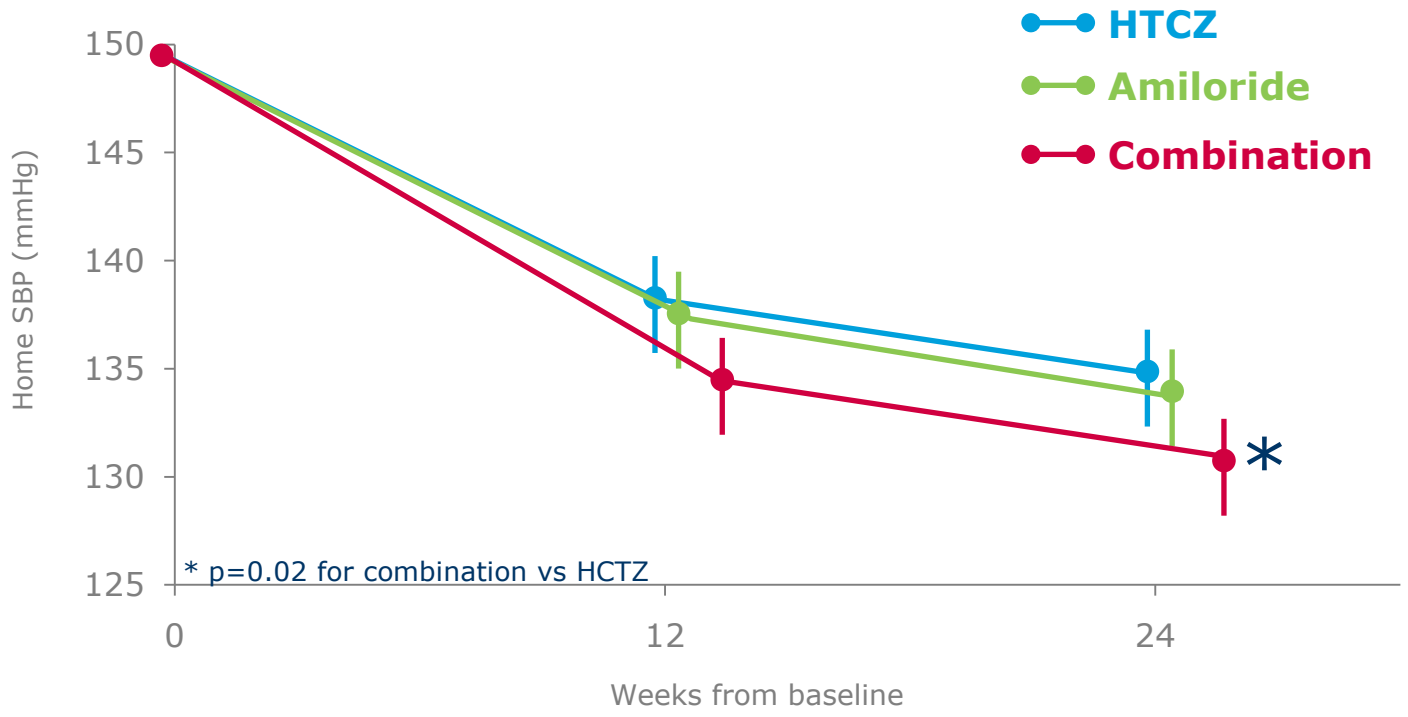
Amiloride n=132	Amiloride/HCTZ n=133
0.71 (0.21,1.21)	0.58 (0.08,1.06)
P=0.005	P=0.024

M. J. Brown (Cambridge, UK) FP 4140

SECONDARY ENDPOINTS
BLOOD PRESSURE REDUCTION

PATHWAY 3
Clinical Trials in Hypertension

Home SBP (mean, 95% CI) adjusting for baseline covariates



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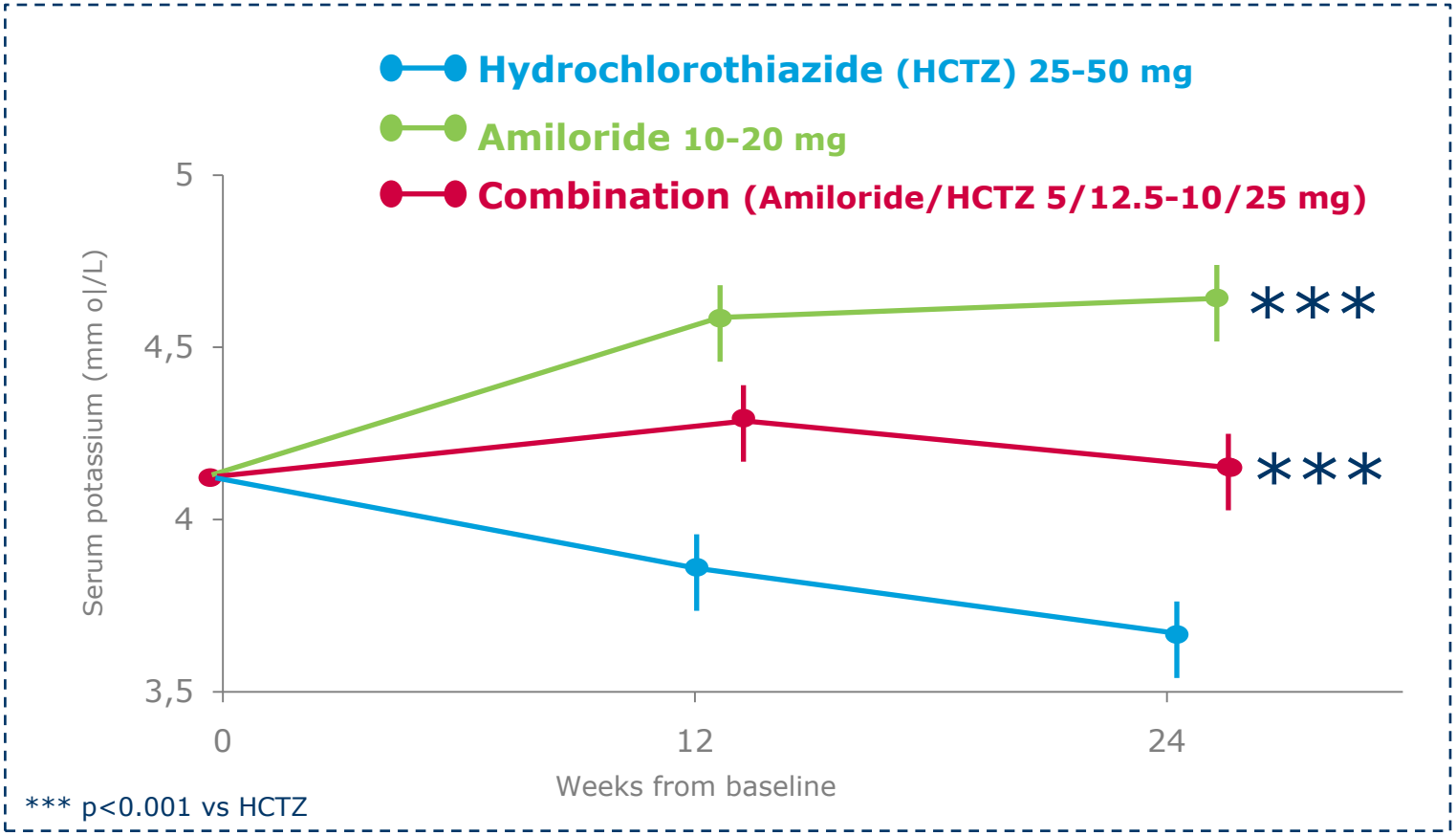
SECONDARY OUTCOMES
POTASSIUM

PATHWAY 3
Clinical Trials in Hypertension



Mean (95% CI) serum potassium, on a model adjusting for baseline covariaties

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IMPLICATIONS OF FINDINGS

PATHWAY
Clinical Trials in Hypertension

- **The combination of amiloride and HCTZ is a 'win-win' which at equipotent doses**
  - ➔ amplifies the desirable effects of each drug on BP,
  - ➔ neutralizes the undesirable changes in blood glucose and potassium
- **Amiloride-HCTZ is the only diuretic with superiority in outcome trials (vs CCB[1] and beta-blockade[2])**

PATHWAY-2 and PATHWAY-3 show that K^+-sparing diuretics are effective and safe for the treatment of hypertension

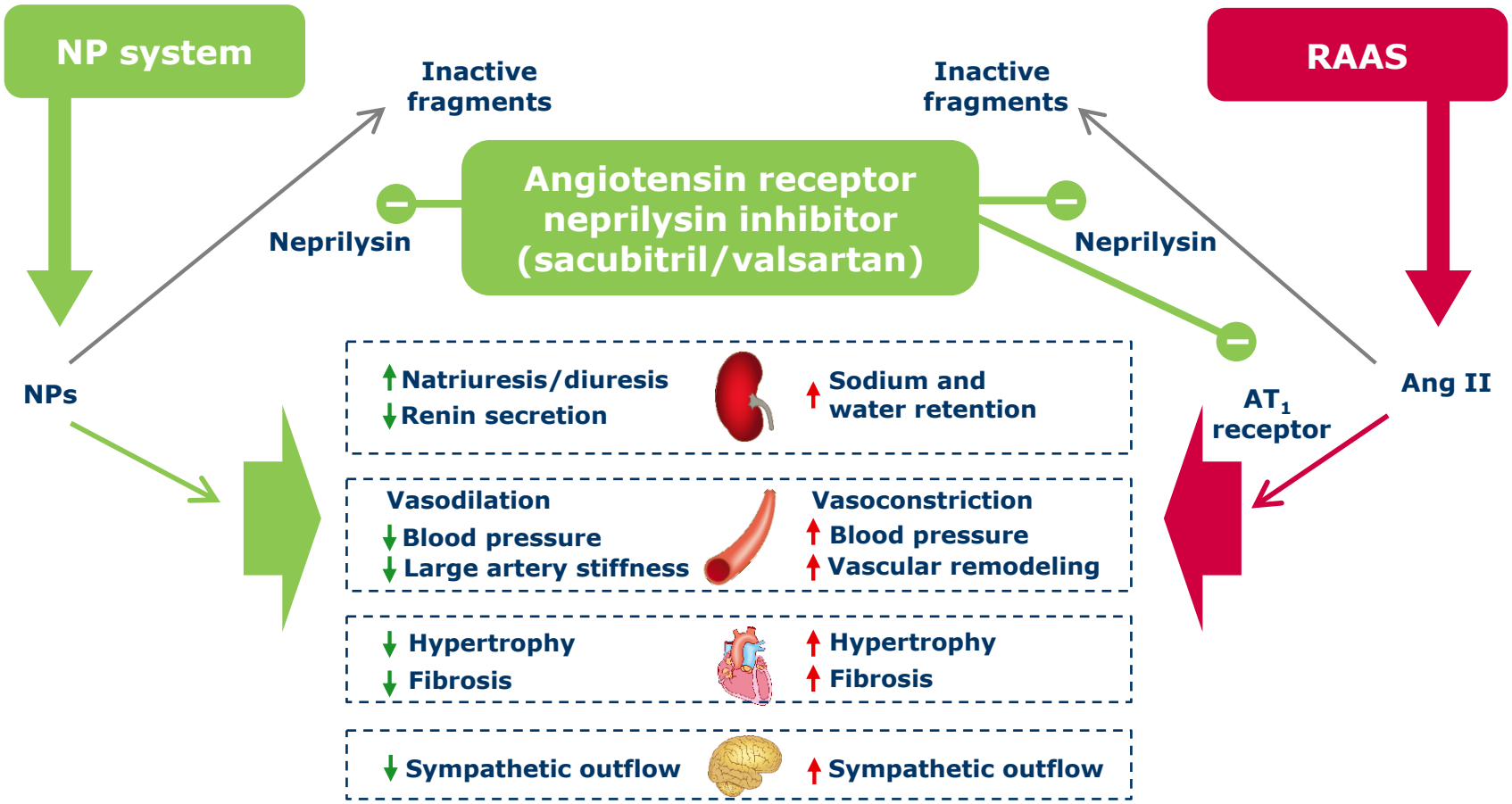
M. J. Brown (Cambridge, UK) FP 4140

HYPERTENSION HIGHLIGHTS

ARB/NEPRILYSIN INHIBITOR (ARNI) IN PATIENTS WITH SYSTOLIC HYPERTENSION

PARAMETER Study

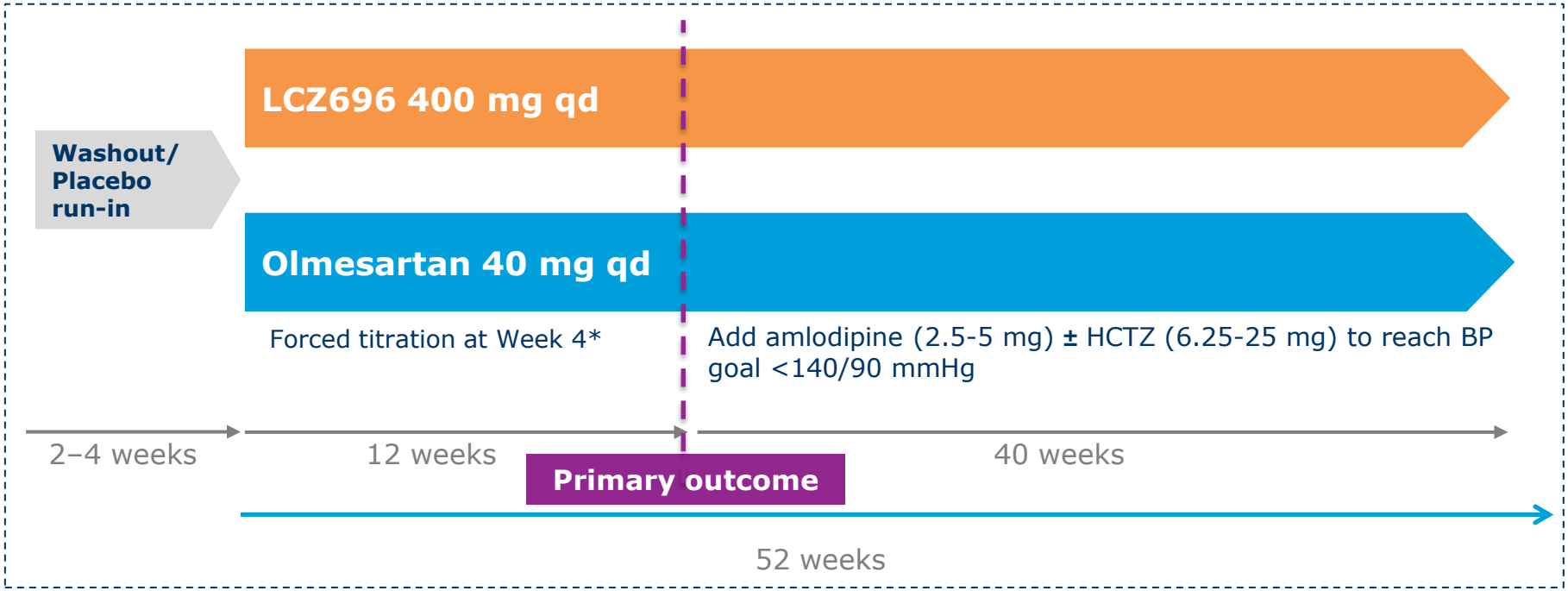
NOVEL MECHANISM OF ACTION OF LCZ696, A FIRST-IN-CLASS ANGIOTENSIN RECEPTOR NEPRILYSIN INHIBITOR (ARNI)



NP, natriuretic peptides;
RAAS, renin-angiotensin-aldosterone system

PARAMETER: STUDY DESIGN

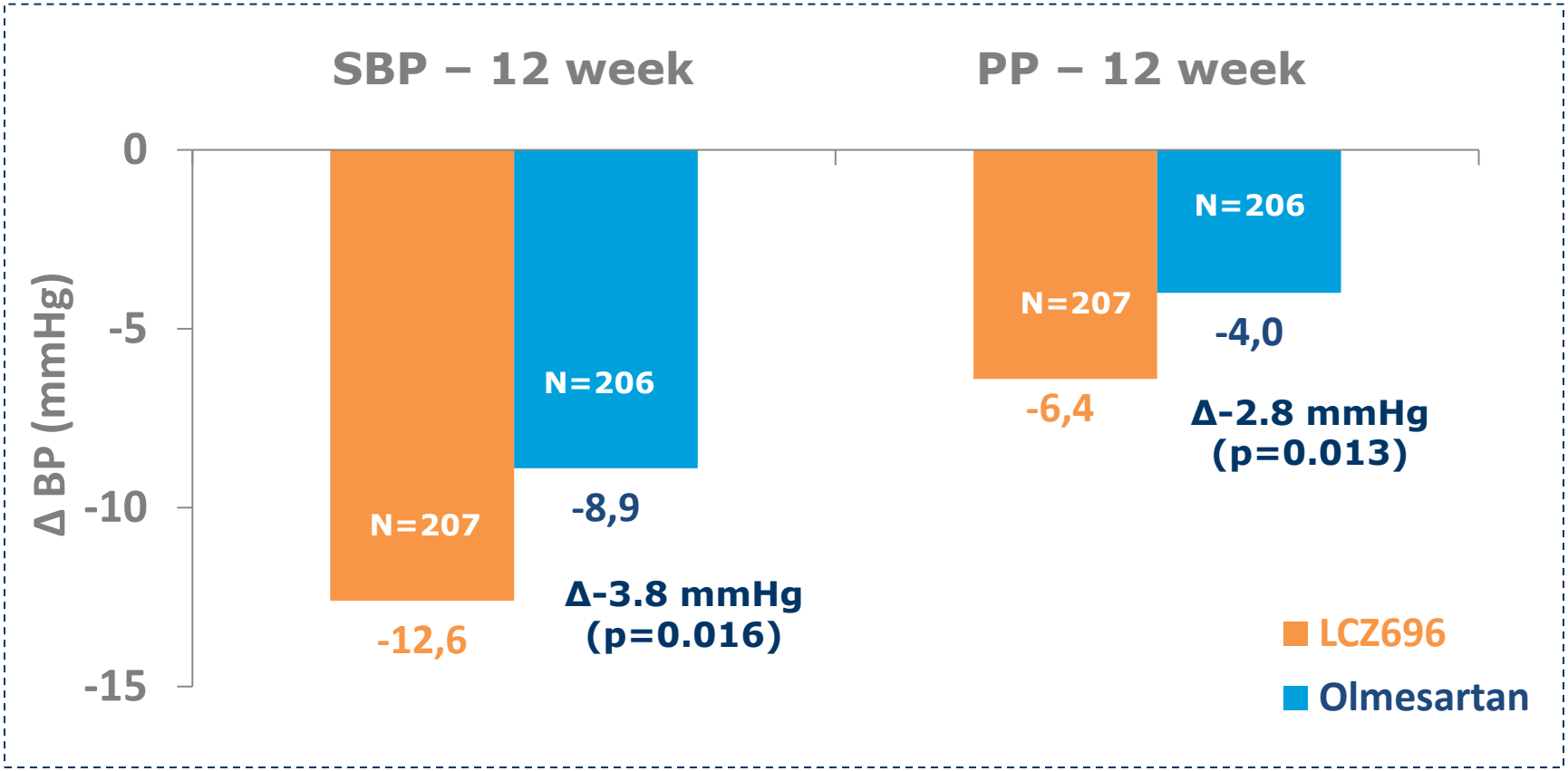
Multicenter, randomized, double-blind, active-controlled, 52-week study to evaluate the safety and efficacy of an LCZ696 regimen on central aortic pressures and arterial stiffness in elderly hypertensive patients



Patient population: Isolated Systolic Hypertension with Stiff Arteries

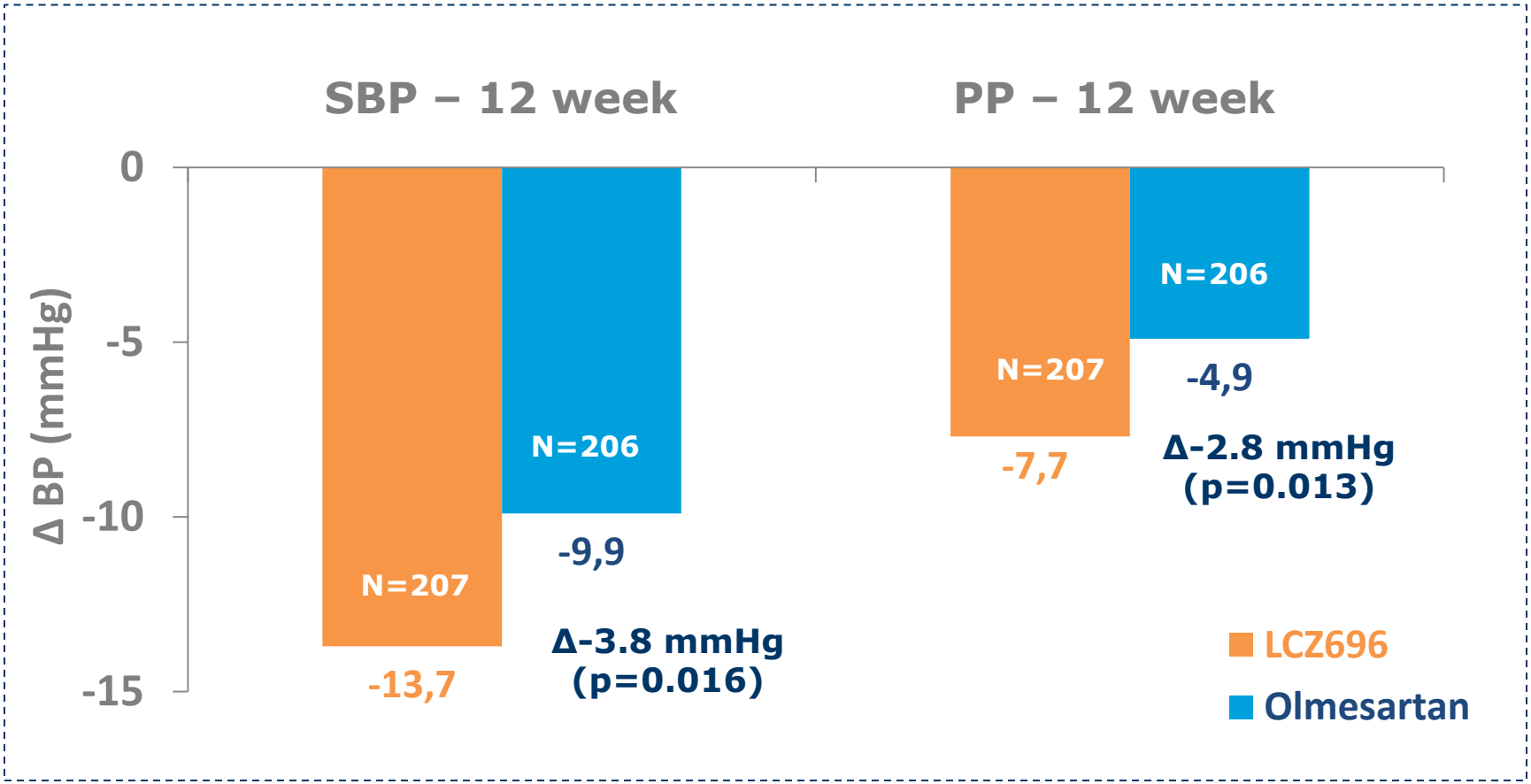
- 454 patients aged ≥60 years
- Elevated SBP (≥150 mmHg) & wide pulse pressure (>60 mmHg)

PARAMETER Study:
PRIMARY AND KEY SECONDARY OUTCOMES:
CHANGE FROM BASELINE IN MEAN CASP AND CPP AT WEEK 12



BP, blood pressure; PP, pulse pressure; SBP, systolic blood pressure

CHANGE IN BRACHIAL SBP AND PP AT WEEK 12

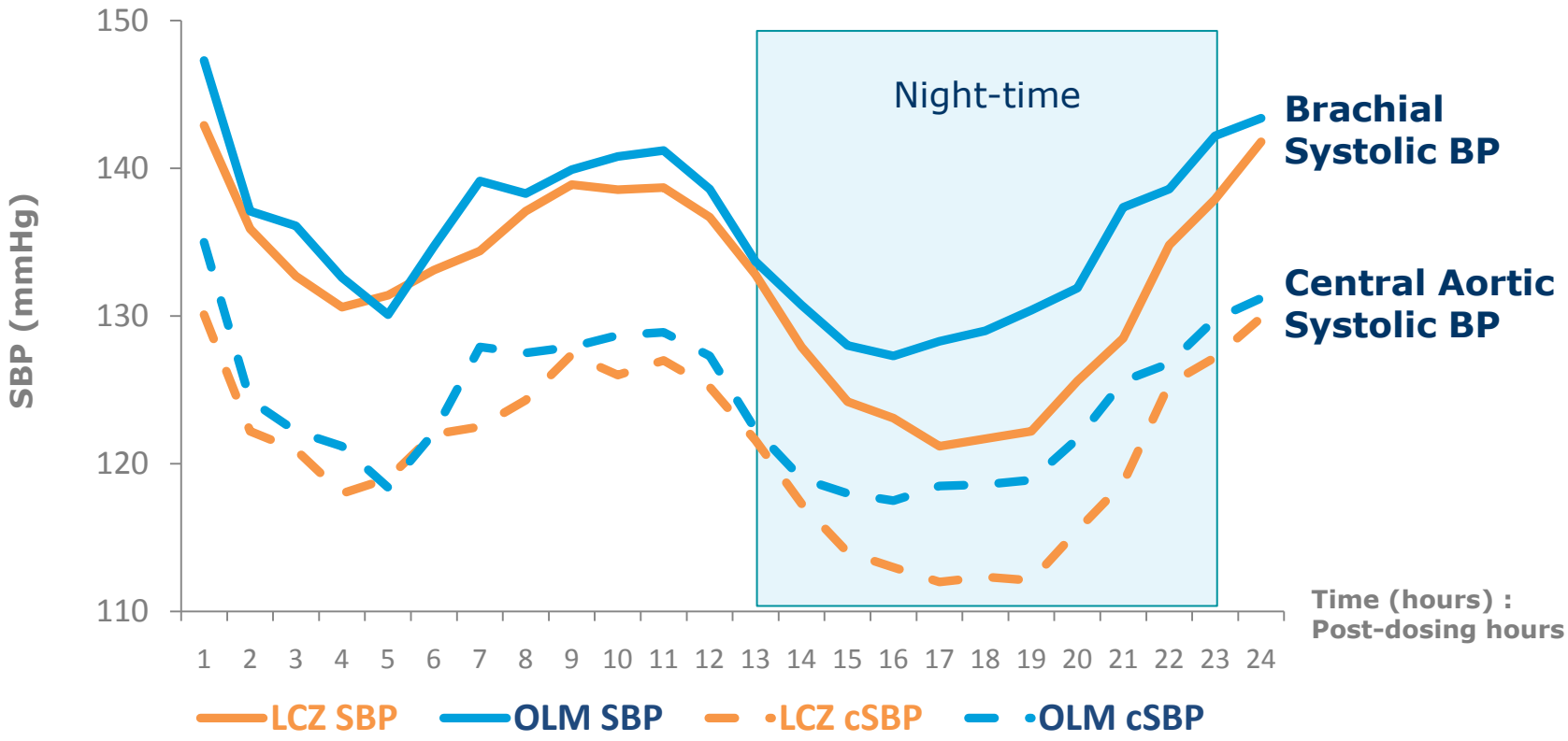


BP, blood pressure; PP, pulse pressure; SBP, systolic blood pressure

24-HOUR BRACHIAL AND CENTRAL AORTIC SBP AT WEEK 12

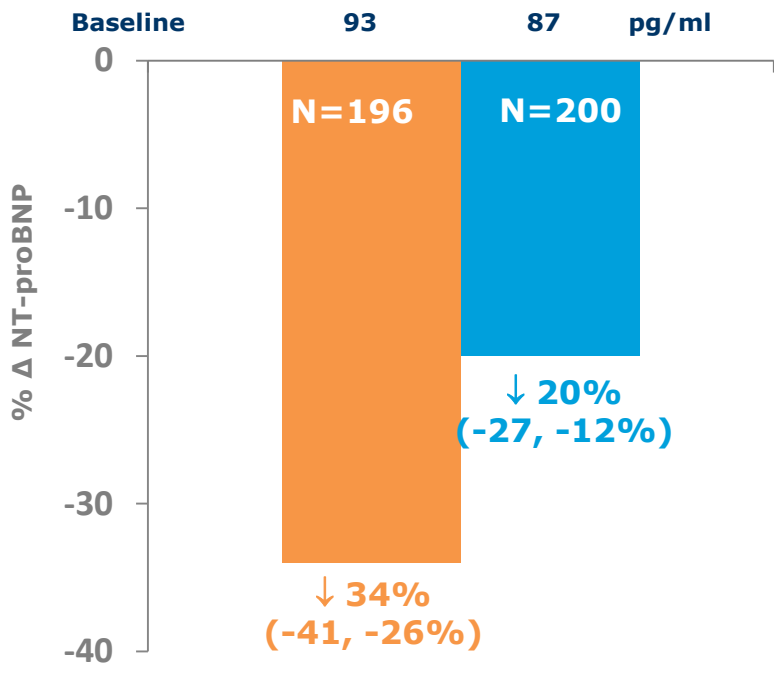
Mean Δ SBP: -4.1 mmHg, p<0.001 (-13.2 (LCZ696) *vs*. -9.1 (OLM) mmHg)

Mean Δ cSBP: -3.35 mmHg, p<0.001 (-12.1 (LCZ696) *vs*. -8.7 (OLM) mmHg)



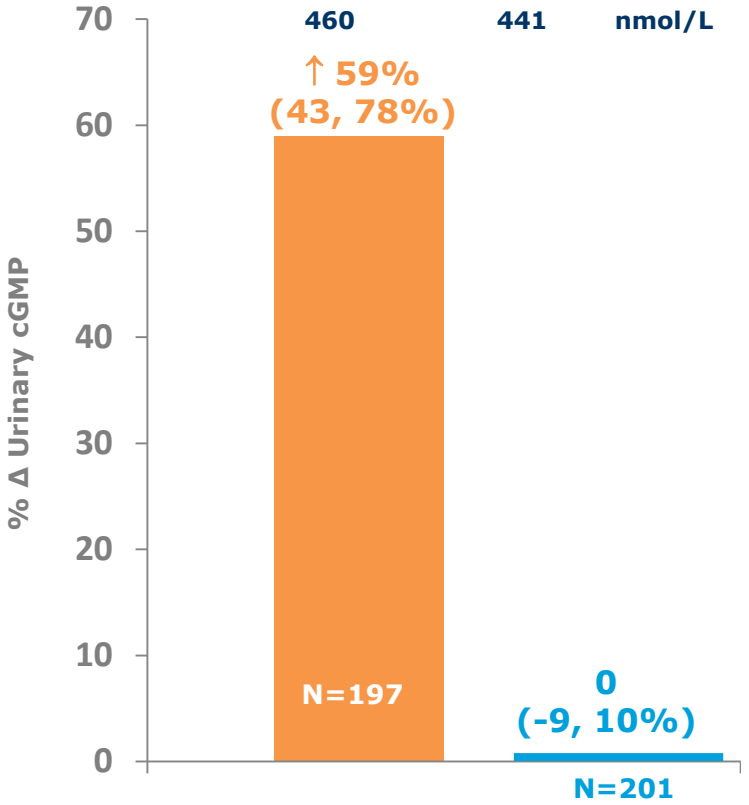
CHANGE FROM BASELINE IN NT-proBNP AND URINARY cGMP AT WEEK 12

NT-proBNP



% change in geometric means from baseline, 95% CI
NT-proBNP, N-terminal pro brain natriuretic peptide;
cGMP, cyclic guanosine monophosphate

Urinary cGMP



LCZ696 Olmesartan

PARAMETER study - Conclusions

- **PARAMETER is the first randomized study demonstrating the ability of LCZ696 to reduce central BP and PP, more effectively than an ARB, in high-risk older patients with systolic hypertension and an increased pulse pressure**

- **These results suggest that LCZ696 provides beneficial effects on central aortic haemodynamics and function, that could provide a therapeutic advantage beyond those observed with RAS blockade alone**

- BP control rates in Europe have improved but are still inadequate
- Hypertension Treatments 'Old and New'
- The 'Old' – A potassium-sparing diuretic 'renaissance'
- Spironolactone very effective and safe in resistant hypertension
- Higher dose amiloride as effective as a thiazide at lowering BP and the potential to reduce risk of diabetes and hypokalemia associated with thiazides
- The 'New' – Angiotensin receptor neprilysin inhibitor (ARNI) – reduces aortic and brachial BP and NT-proBNP in systolic hypertension – where next?

PREVENTIVE CARDIOLOGY

CLINICAL REALITY OF PRIMARY PREVENTION IN PEOPLE AT HIGH CARDIOVASCULAR RISK IN EUROPE

A comparison of EUROASPIRE III and IV surveys in general practice

Kornelia Kotseva

National Heart and Lung Institute, Imperial College London, UK on behalf of EUROASPIRE IV Investigators

STUDY POPULATION

- **EUROASPIRE III & IV Countries**
  - ➔ Bulgaria, Croatia, Poland, Romania, UK

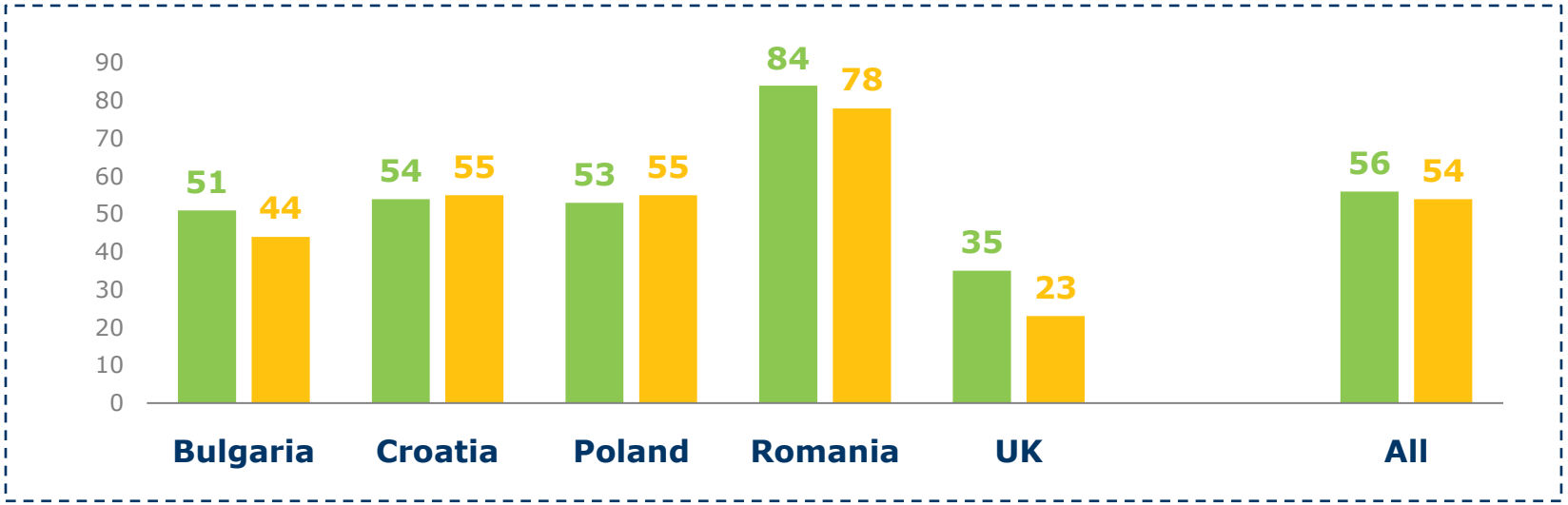
Survey	Time period	Patients	Women n (%)	Age (years) mean±SD
EUROASPIRE III	2007-2008	1985	1194 (60)	58±10
EUROASPIRE IV	2014-2015	1842	1002 (54)	59±12

  - ➔ 8 year time trend in the management of patients at high risk of cardiovascular disease

K. Koteseva (London, GB), FP 5069

OBESE PATIENTS EVER BEEN TOLD BY A HEALTH CARE PROFESSIONAL THAT THEIR DIET IS UNHEALTHY (%)

Bulgaria	Croatia	Poland	Romania	UK	Overall	P
-7.6%	+0.9%	+1.5%	-6.0%	-11.3%	-3.7%	P=0.24



** Body mass index ≥30 kg/m²*

➔ **Over 80% of high CVD risk patients were overweight or obese**

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EUROASPIRE IV: PRIMARY CARE

- **Proportions at goal for CVD prevention**

Lifestyles (%)	Men	Women	All
No smoking	78	87	83
Not obese	60	54	56
Physically active	34	30	32
Risk factor management			
BP <140/90 mm Hg (<140/80 if diabetes)	37	51	45
LDL-C <2.5 mmol/L (100 mg/dL)	23	15	18

- **Risk factors are not adequately managed in patients at high risk of cardiovascular disease.**

- **More concerted efforts are required to promote a healthy life style and achieve therapeutic goals.**

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PREVENTION AND HYPERTENSION

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