Advance-HTN

Lorundrostat Efficacy and Safety in Patients with Uncontrolled Hypertension

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Disclosures: Dr. Laffin serves/served as a consultant or on steering committees for Arrowhead, AstraZeneca, Crispr Therapeutics, Eli Lilly, Idorsia, Medtronic, Mineralys, Novo Nordisk, Novartis, Recor, and Ripple Medical. He has received research funding from AstraZeneca for studies of rosuvastatin. He receives royalties from Belvoir Media Group, Elsevier, and Springer Nature.

Background

Lorundrostat is an aldosterone synthase inhibitor which is a novel class of blood pressure lowering medication

Rather than blocking the mineralocorticoid receptor, aldosterone synthase inhibitors disrupt aldosterone biosynthesis

Data from a lorundrostat dose-finding trial suggested safe and effective blood pressure control

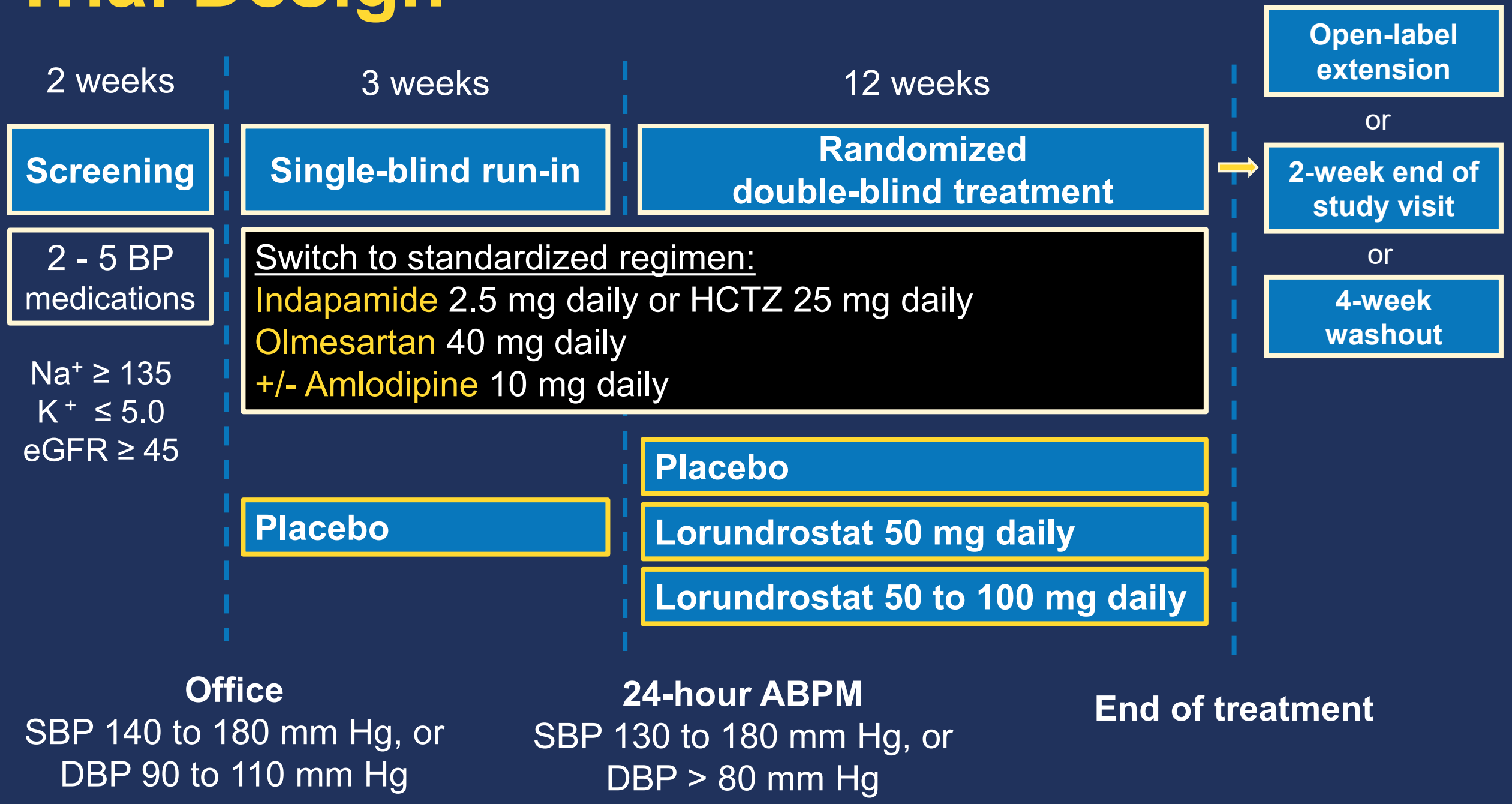
Objective

Assess the 24-hour blood pressure lowering effect of lorundrostat taken once daily in participants with uncontrolled and treatment-resistant hypertension on a standardized antihypertensive regimen

Trial Design

- Multicenter (103 sites in the United States)
- Prospective
- Randomized
- Double-blind
- Placebo-controlled
- Parallel group
- Phase 2b trial

Trial Design



Primary End Point

Change in 24-hour average systolic blood pressure from baseline (randomization) to week 12 compared with placebo

Key Secondary End Points*

Change in 24-hour average systolic blood pressure from baseline to week 4

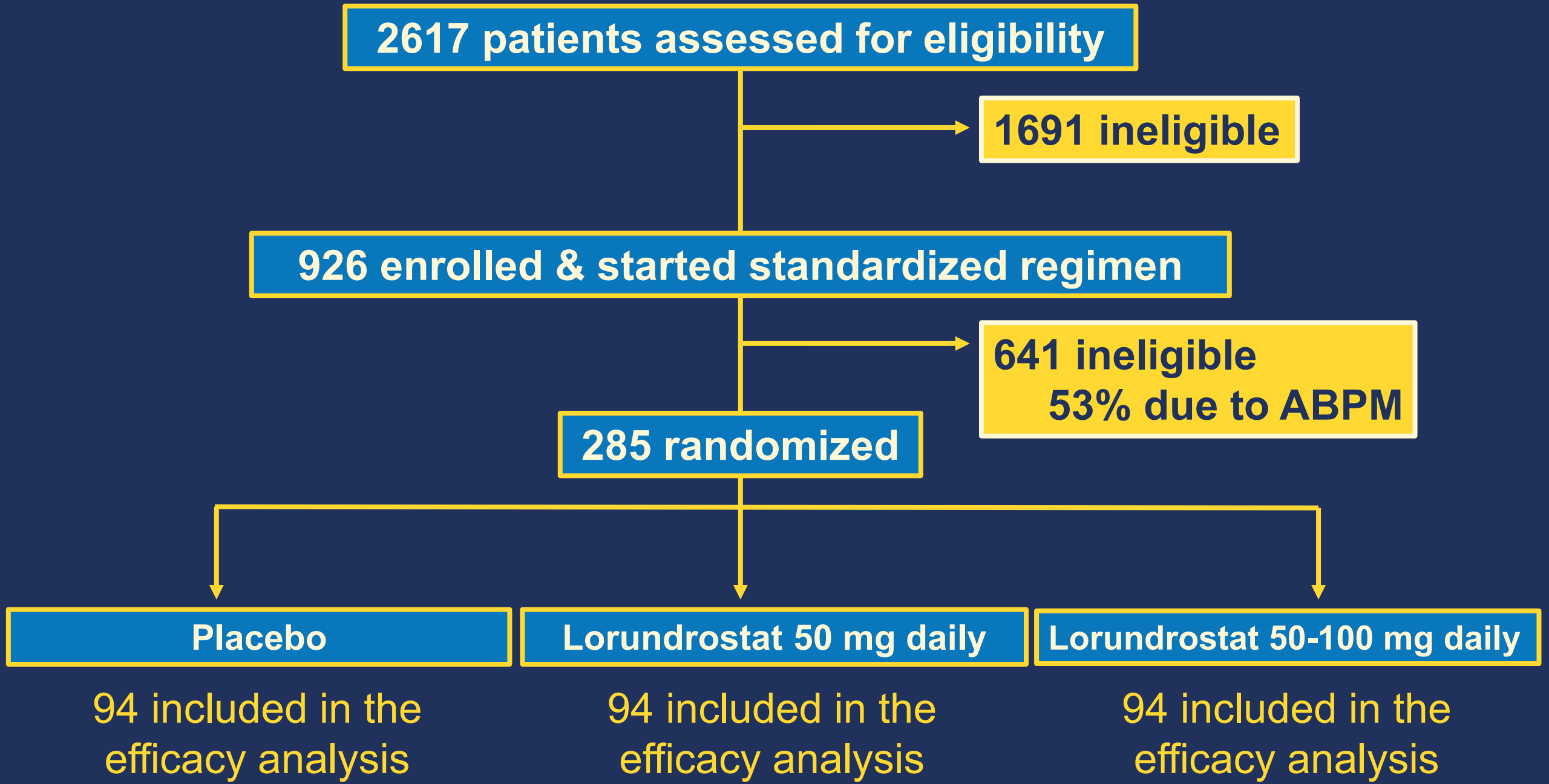
Change in office systolic blood pressure from baseline to week 12 among participants escalated to 100 mg daily

Proportion of participants with 24-hour average systolic blood pressure <125 mm Hg at week 4

Change in 24-hour average systolic blood pressure from baseline to week 4 by obesity status

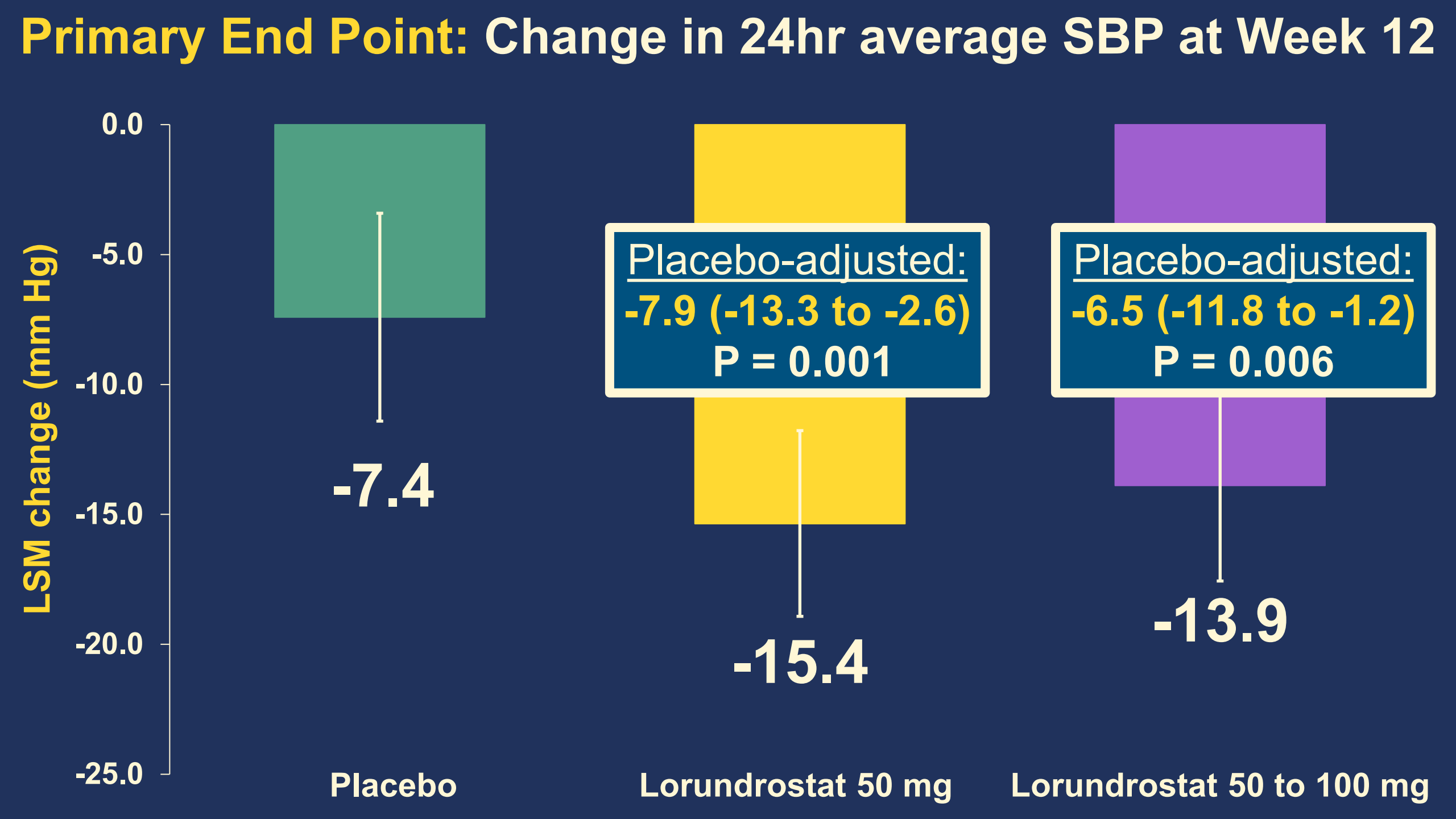
Change in 24-hour average systolic blood pressure from baseline to week 4 by number of BP medications in standardized regimen

*Controlled for multiplicity with a graphical testing approach

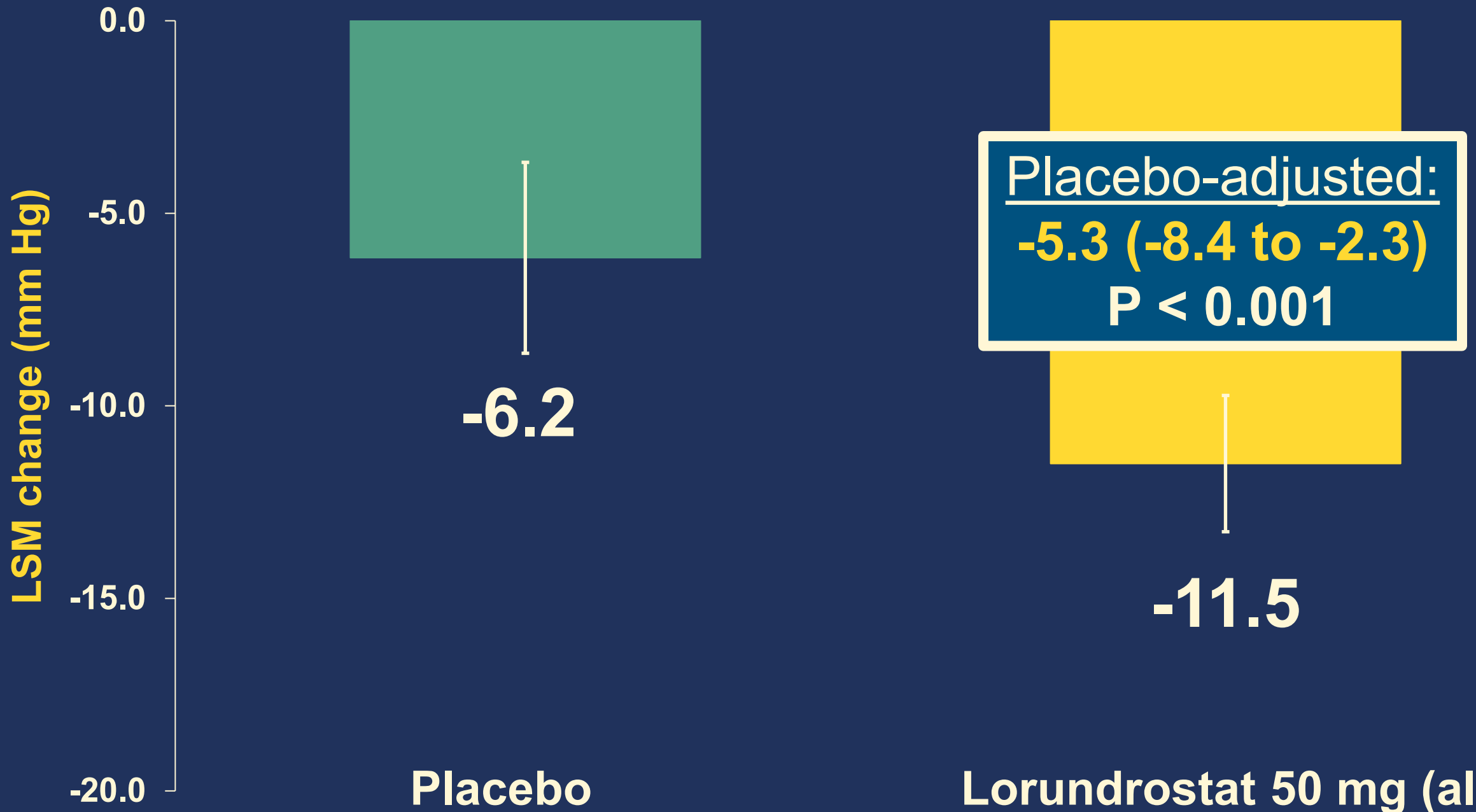

2617 patients assessed for eligibility
1691 ineligible
926 enrolled & started standardized regimen
641 ineligible
53% due to ABPM
285 randomized
Placebo
Lorundrostat 50 mg daily
Lorundrostat 50-100 mg daily
94 included in the efficacy analysis
94 included in the efficacy analysis
94 included in the efficacy analysis

Participant Characteristics	Placebo	Lorundrostat 50 mg	Lorundrostat 50 to 100 mg
Age (years)	59	61	61
Women (%)	35%	40%	44%
Black or African-American (%)	46%	53%	58%
BMI (kg/m^2)	32	31	32
eGFR (Randomization)	74	77	76
Office BP (Screening)	155/91	153/88	152/89
24h ABPM (Randomization)	141/87	141/86	141/87

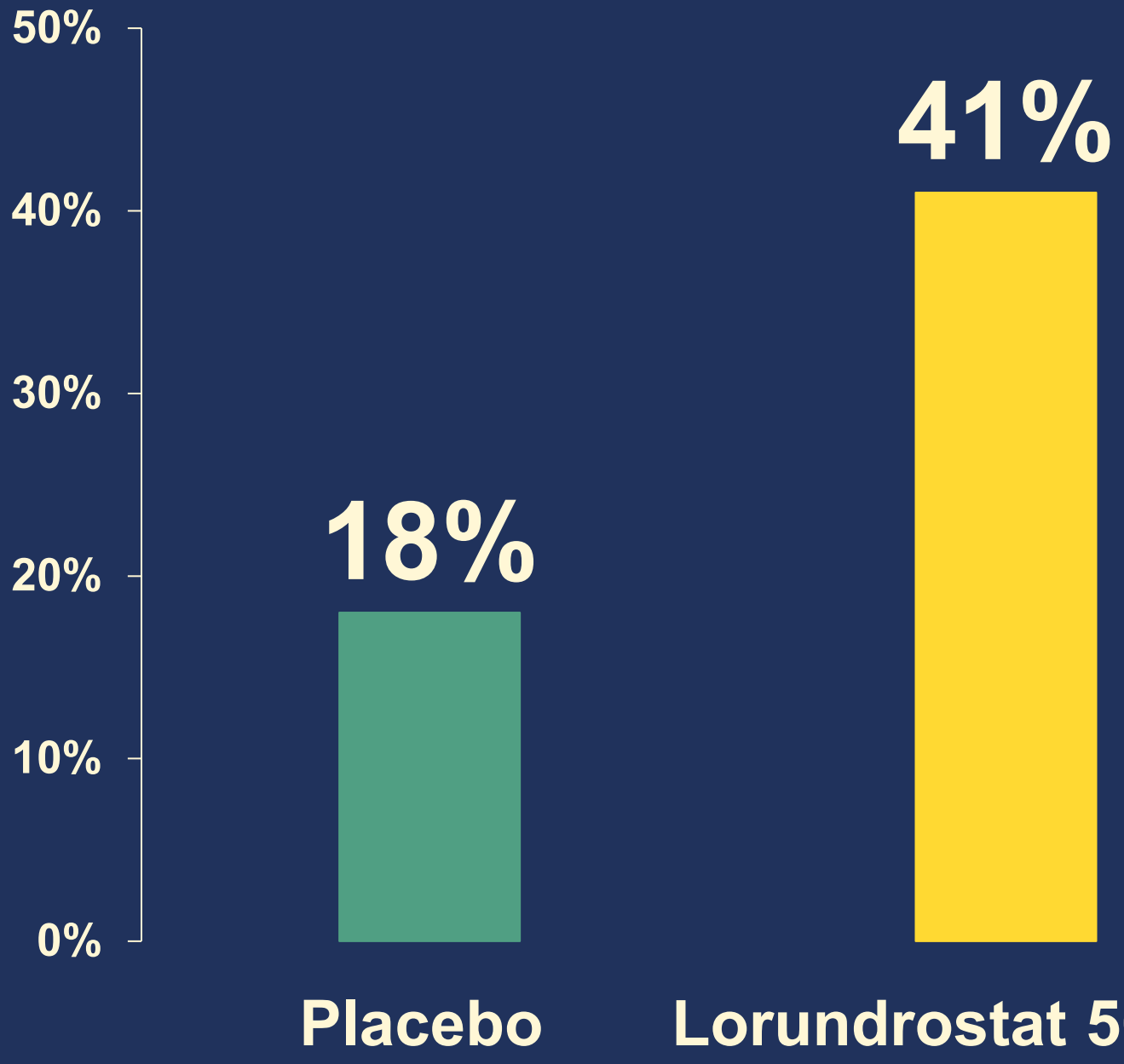
Primary End Point: Change in 24hr average SBP at Week 12



Secondary End Point: Change in 24h average SBP at Week 4



Secondary Endpoint: Proportion with 24h average SBP < 125 mm Hg at Week 4

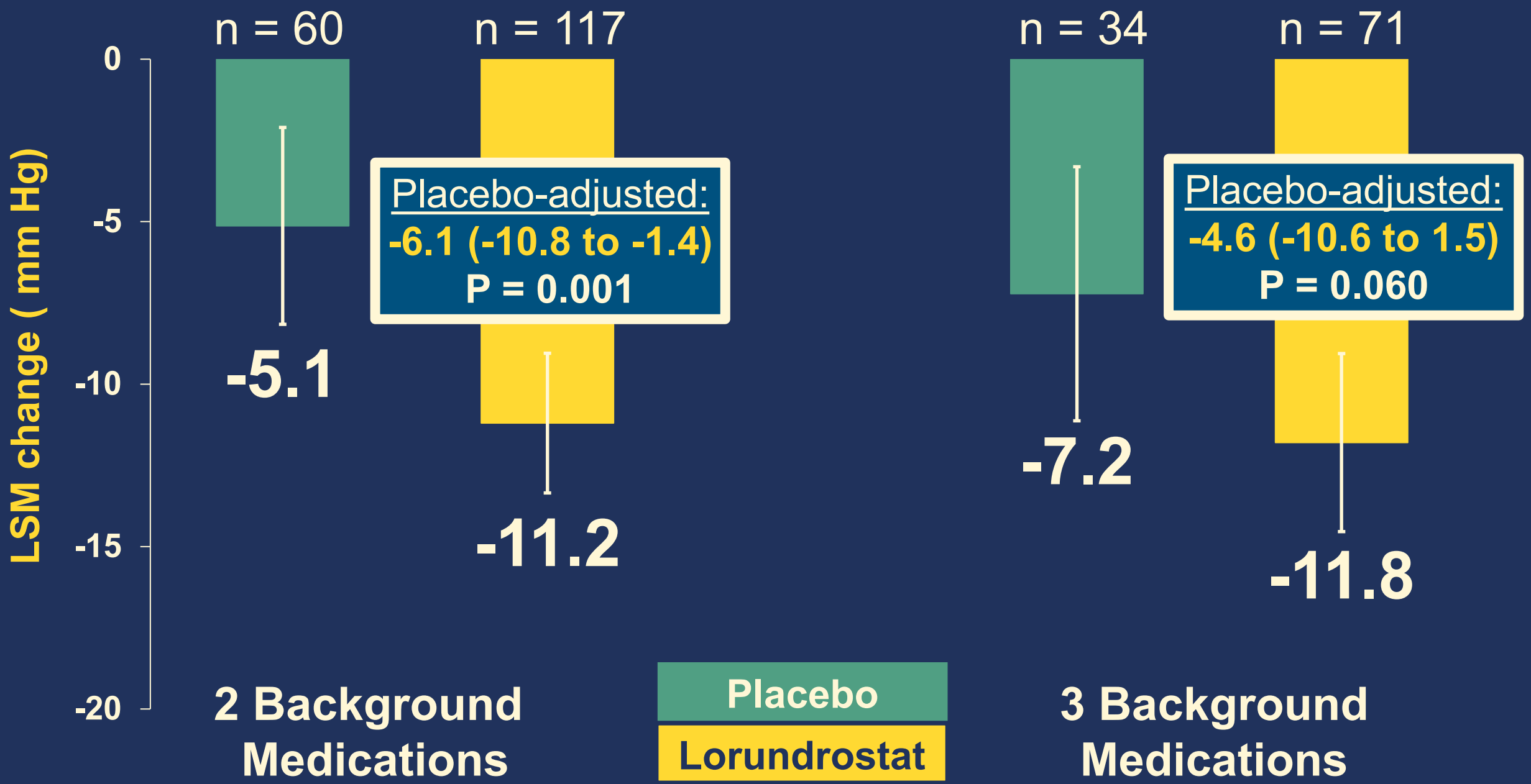


Odds ratio (95% CI)

3.3 (1.4 to 7.8)

P < 0.001

Secondary End Point: Change in 24h average SBP at Week 4



Additional Key Secondary End Points

Change in **office** systolic blood pressure from baseline to week 12 in participants escalated to 100 mg (n=19)	**-17.5 mm Hg (-30.3 to -4.7)** **P < 0.001**
Relationship of BMI to blood pressure reduction at 4 weeks	No clear relationship

Adverse Events	Placebo	Lorundrostat 50 mg	Lorundrostat 50 to 100 mg
Any serious AE	2%	6%	8%
Any study-drug related serious AE	0	2%	1%
Hypotension	3%	9%	8%
Hyponatremia	6%	9%	11%
Hyperkalemia (>6.0 mmol / L) - Single value	0	5%	7%
Hyperkalemia (>6.0 mmol / L) - Confirmed via per protocol repeat testing - Spurious values (including suspected hemolysis) and values obtained following double-blind treatment period are excluded	0	2%	3%

Limitations

Phase 2b trial, additional data using office blood pressure on top of usual care is anticipated from phase 3 trial (Launch-HTN)

Not head-to-head with other classes of antihypertensive medications

Not a cardiovascular or kidney outcome trial

Conclusions

Lorundrostat effectively lowered 24-hour blood pressure among patients with well-treated uncontrolled and true resistant hypertension

A dose escalation strategy from 50 to 100 mg did not lower blood pressure more than 50 mg and was associated with numerically more adverse events

Acknowledgements

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Additional Manuscript Co-Authors	Branko Kopjar, Kathy Wolski, Shivani Bhikam, Matt Luther, Debbie Cohen, Ashish Sarraju, Mike Wilkinson, John Flack

Final Thoughts

New therapies for hypertension treatment are needed

Drugs that target aldosterone production have great potential for blood pressure reduction and reduction of cardiovascular risk

Clinical trials need to test new therapies in the populations that are at highest risk and will derive the most benefit