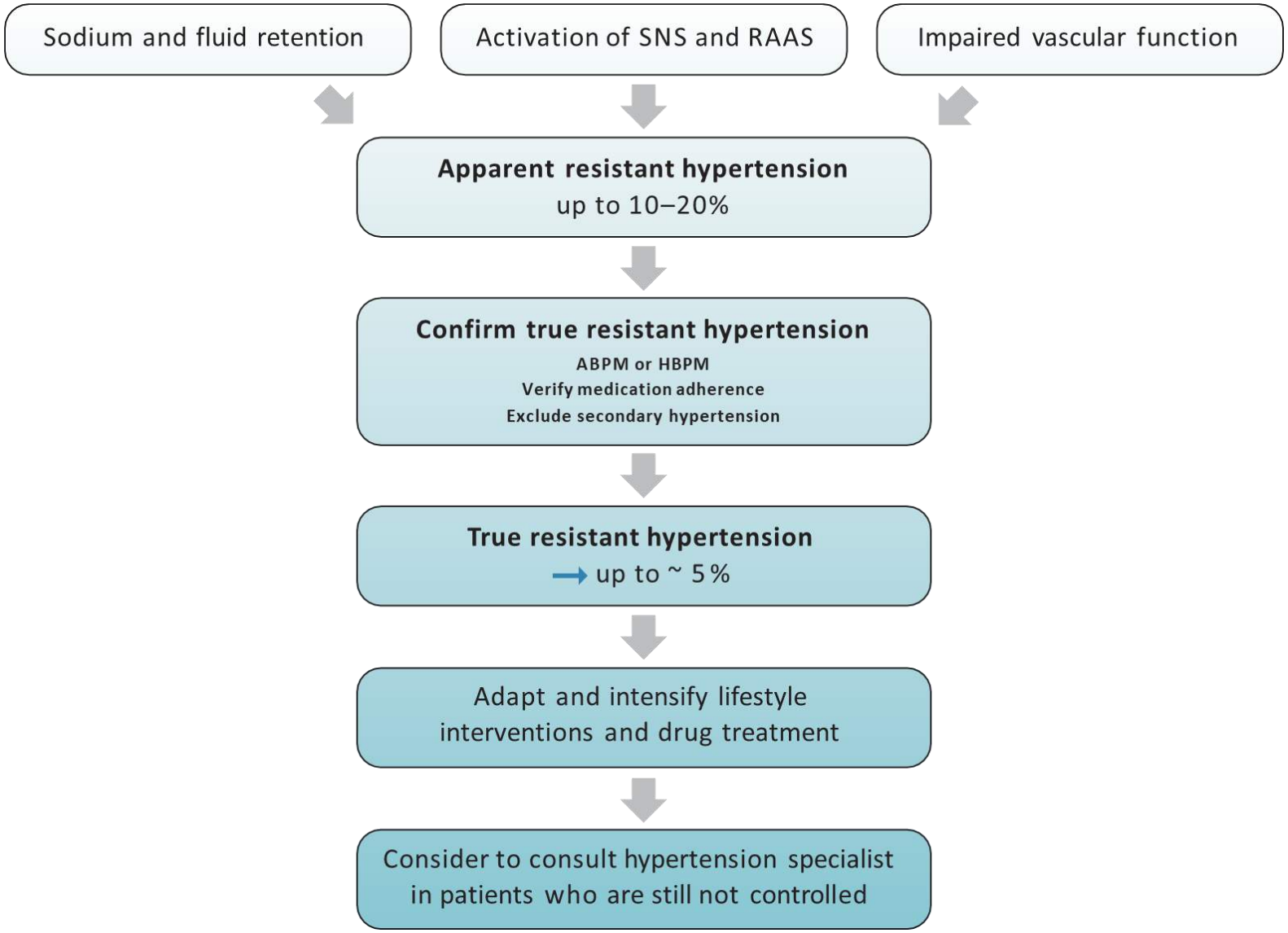
Resistant HT: OMT or RDN ?

P. van de Borne (Brussels, Belgium)

2023 ESH Guidelines
for the management
of arterial hypertension

Characteristics of true resistant hypertension



Mancia, Kreutz et al. J Hypertens. 2023;41:1874-2071

TABLE 1

Proper blood pressure measurement

Patients should sit, relaxed, for at least 5 minutes, with an empty bladder, without talking; they should not have consumed caffeine, smoked, or exercised in the last 30 minutes.
Use a device that has been properly calibrated, and a proper-sized cuff: the bladder should wrap around 80% of the patient's arm; a small cuff will result in higher blood pressure readings.
Take measurements in both arms, on bare skin, with the patient's arm supported; use the arm with the higher reading for subsequent readings, and repeat measurements 1 to 2 minutes apart.
Use the average of at least 2 readings obtained on at least 2 occasions to estimate blood pressure.

Overestimation up to 7.1 / 4.7 mm Hg (normal cuff on large arm)

M Aylett et al. Evaluation of normal and large sphygmomanometer cuffs using the Omron 705CP J Hum Hypertens. 2001 Feb;15(2):131-4. doi: 10.1038/sj.jhh.1001133.

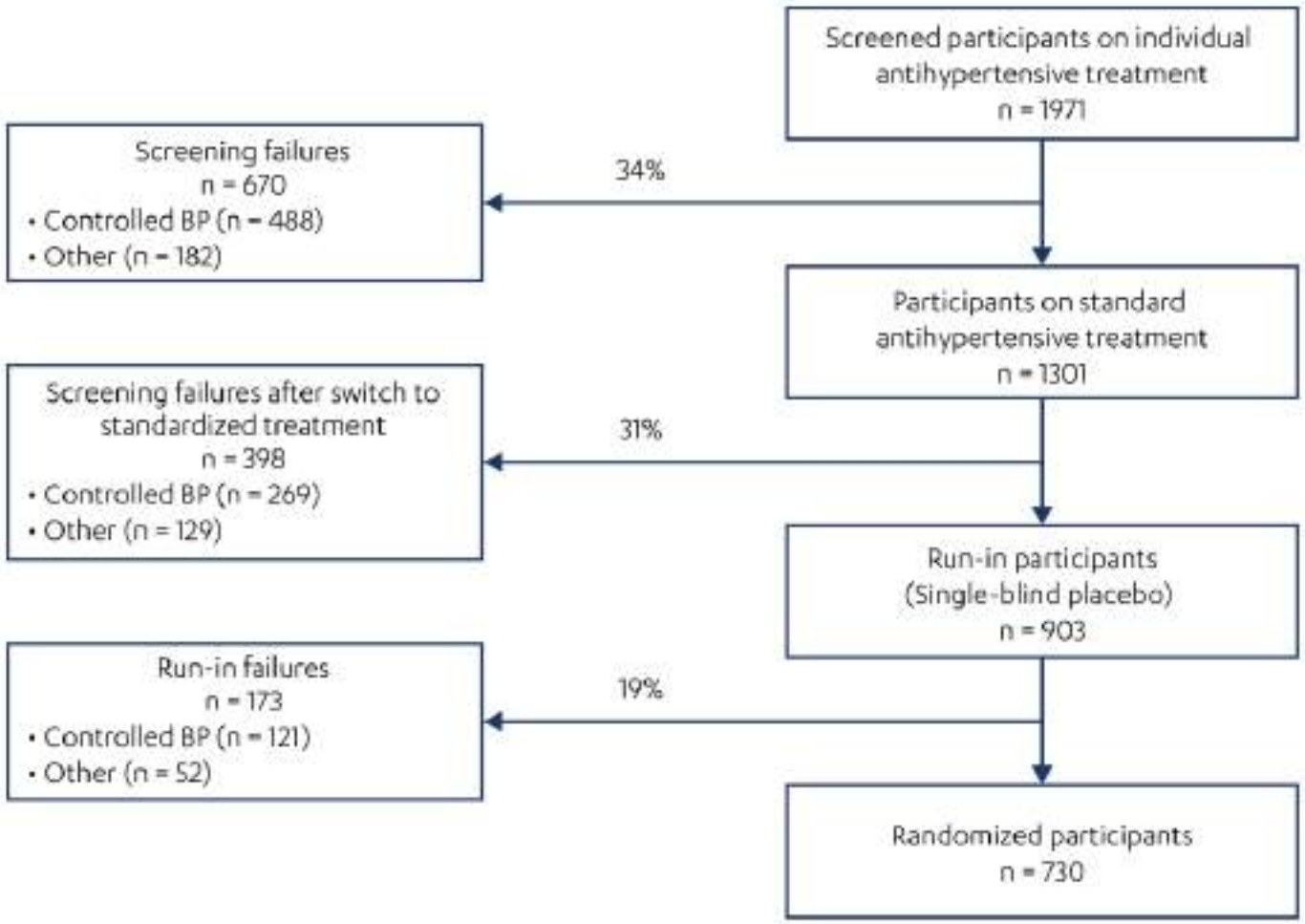
Resistant hypertension: A stepwise approach J. Yahr et al. CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 90 NUMBER 2 FEBRUARY 2023doi:10.3949/ccjm.90a.22046

Investigating the Endothelin Receptor Antagonist Aprocitentan in Resistant Hypertension: Design and Baseline Characteristics of the PRECISION Study

Objectives

To demonstrate the BP-lowering effect of 2 dose strengths of aprocitentan after 4 weeks of treatment and the sustained effect of 1 dose strength of aprocitentan after 9 months of treatment at Week 40

Figure 3. Participant disposition and the main reasons for screening and run-in failures.



Key inclusion criteria at randomization include:
mean trough SiSBP ≥140 mmHg (unattended automated office BP measurement, uAOBPM)
≥80% compliance with the **standardized background antihypertensive treatment** during the run-in period
≥**80% compliance** with the study treatment **(placebo)**

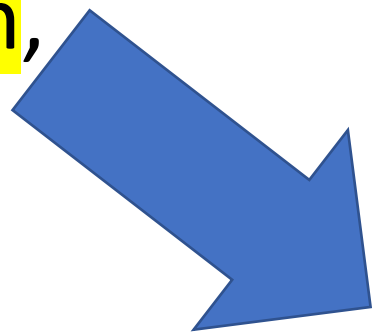
+/-50%
screen failure due to:
accurate **BP measurement**,
prerecruitment **medical inertia**,
and **adherence improvement**
during the run-in period

Poster presented at the European Society of Cardiology (ESC) Congress; August 27-30, 2021; Poster 6350

Undiagnosed secondary hypertension

Endocrinological disorders

- primary hyperaldosteronism,
- hypo/hyperthyroidism,
- hyperparathyroidism,
- pheochromocytoma,
- acromegaly,
- congenital adrenal hyperplasia,
- carcinoid tumor,



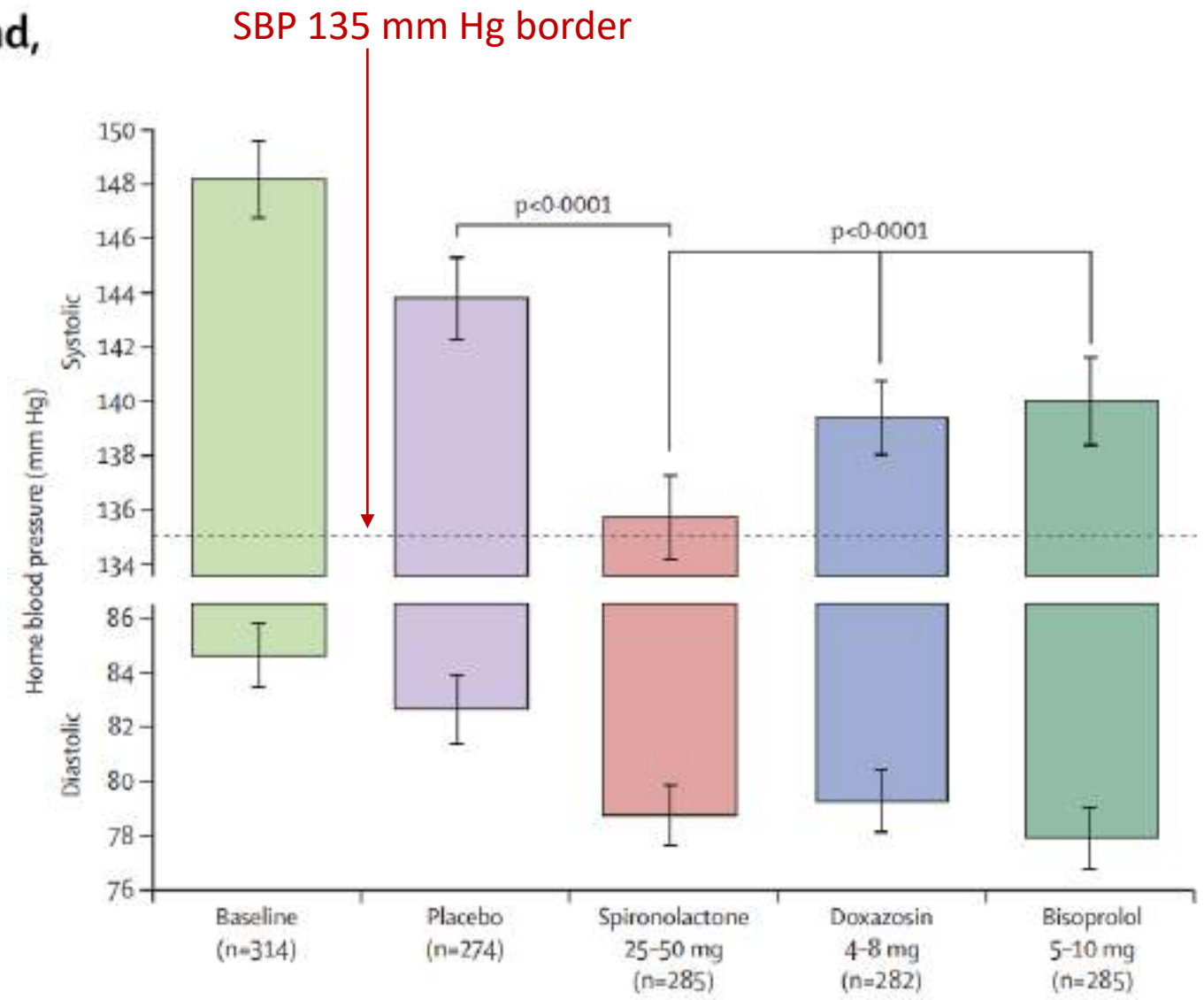
NOT SO EASY TO DIAGNOSE …

Adapted from A. Doroszko et al., Resistant Hypertension, Adv Clin Exp Med 2016, 25, 1, 173–183. DOI: 10.17219/acem/58998

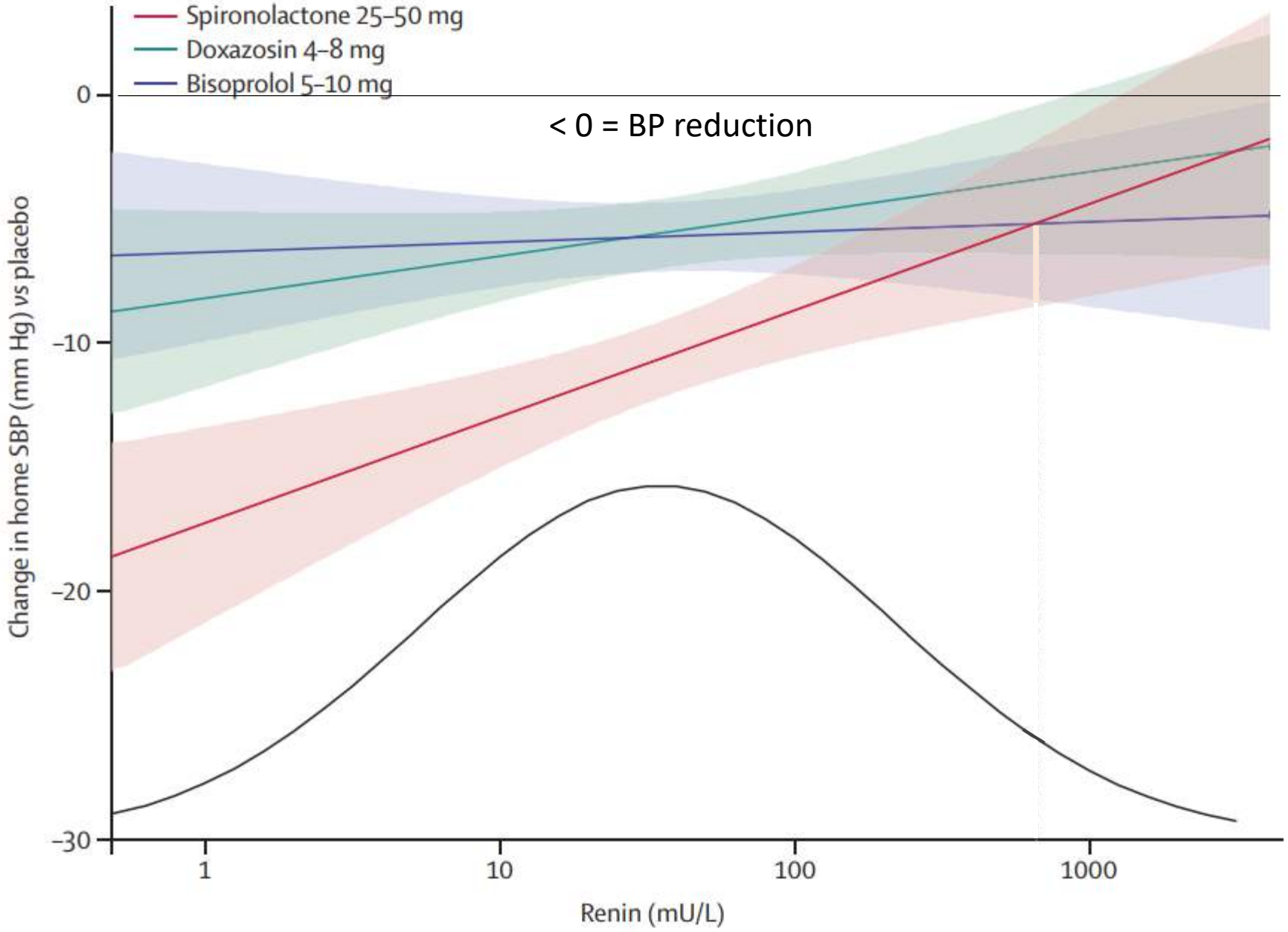
Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

Bryan Williams, Thomas M MacDonald, Steve Morant, David J Webb, Peter Sever, Gordon McInnes, Ian Ford, J Kennedy Cruickshank, Mark J Caulfield, Jackie Salsbury, Isla Mackenzie, Sandosh Padmanabhan, Morris J Brown, for The British Hypertension Society's PATHWAY Studies Group*

- Double-blind, placebo-controlled, crossover trial, aged 18–79 yrs
- **Seated clinic SBP ≥ 140 mm Hg** (or ≥135 mm Hg for patients with diabetes) and **home SBP ≥ 130 mm Hg**,
- Despite treatment for at least 3 months with **maximally tolerated doses of three drugs** which had to be **an ACE inhibitor or an ARB; a CCB and a diuretic.**
- 6 weeks cycles at lowest dose (**Spironolactone, Doxazosin, Bisoprolol, Placebo**), followed by 6 weeks forced titration to twice this dose.

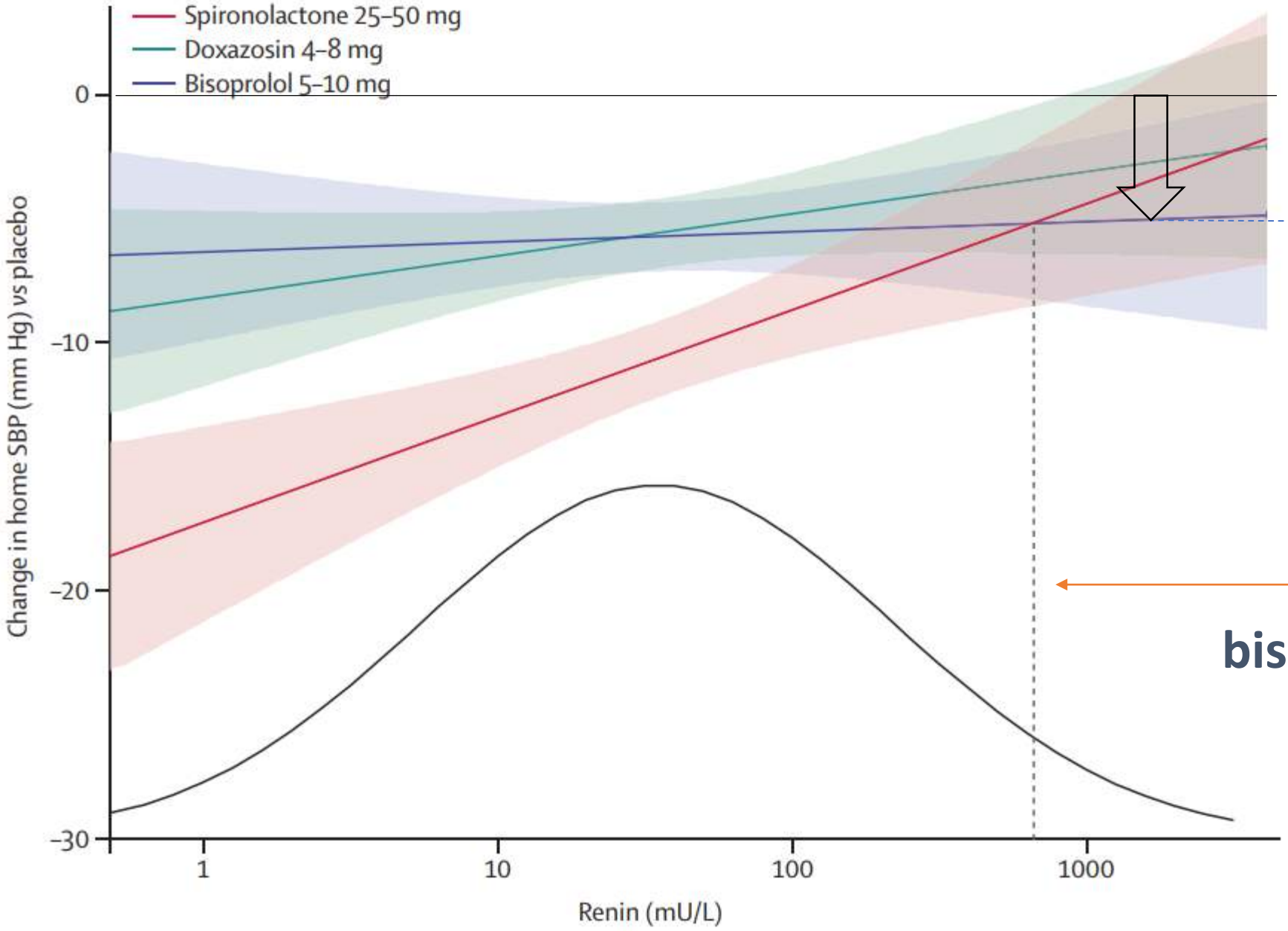


Lancet 2015; 386: 2059–68



One would expect elevated plasma renin levels in patients receiving **ACE inhibitor or an ARB, a CCB and a diuretic**, all of **which usually increase plasma renin levels.**

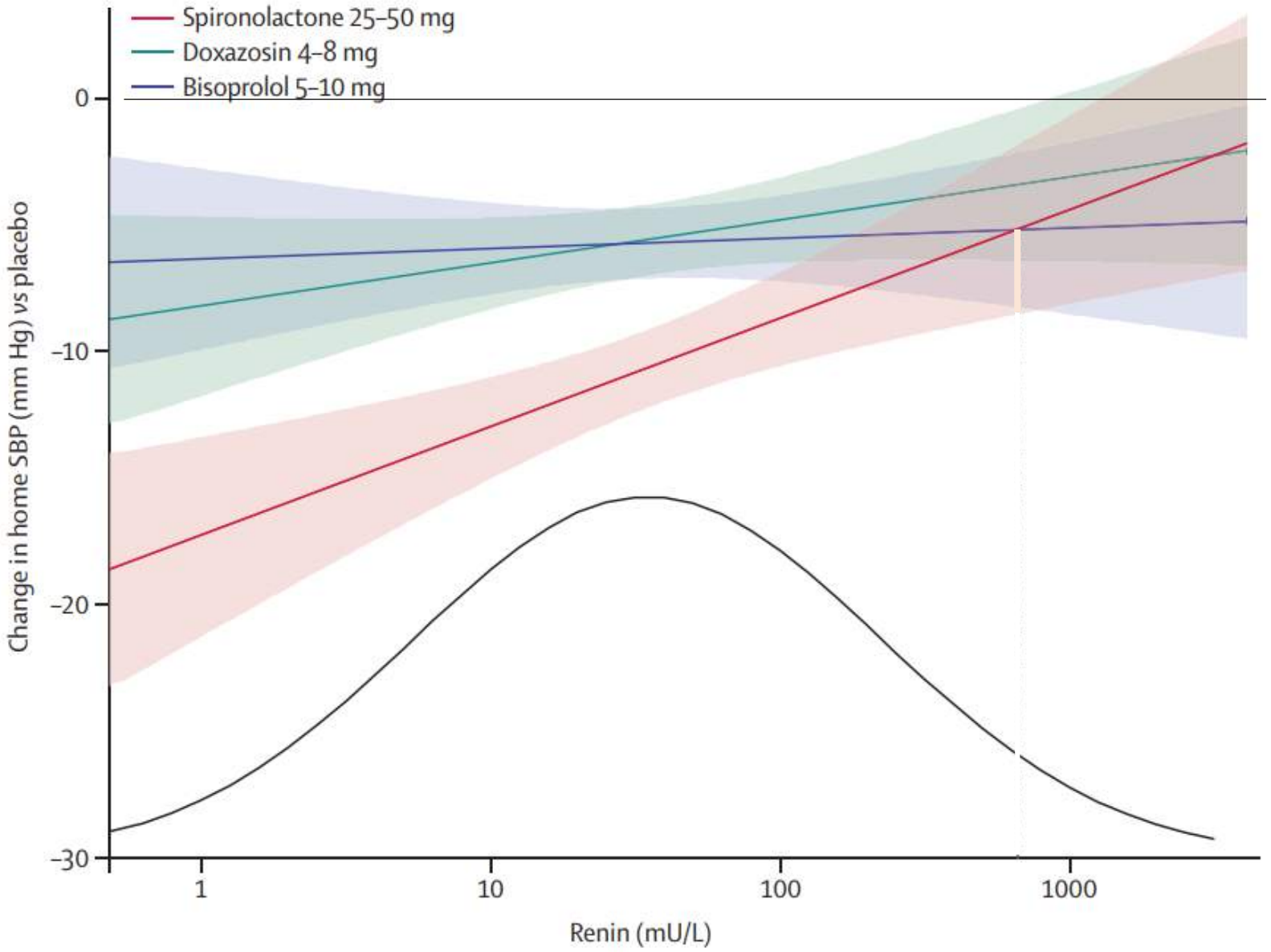
Lancet 2015; 386: 2059–68



BP reduction with
bisoprolol
>
spironolactone

shows BP fall on
bisoprolol > **spironolactone**
only in the top 3%
of the renin distribution.

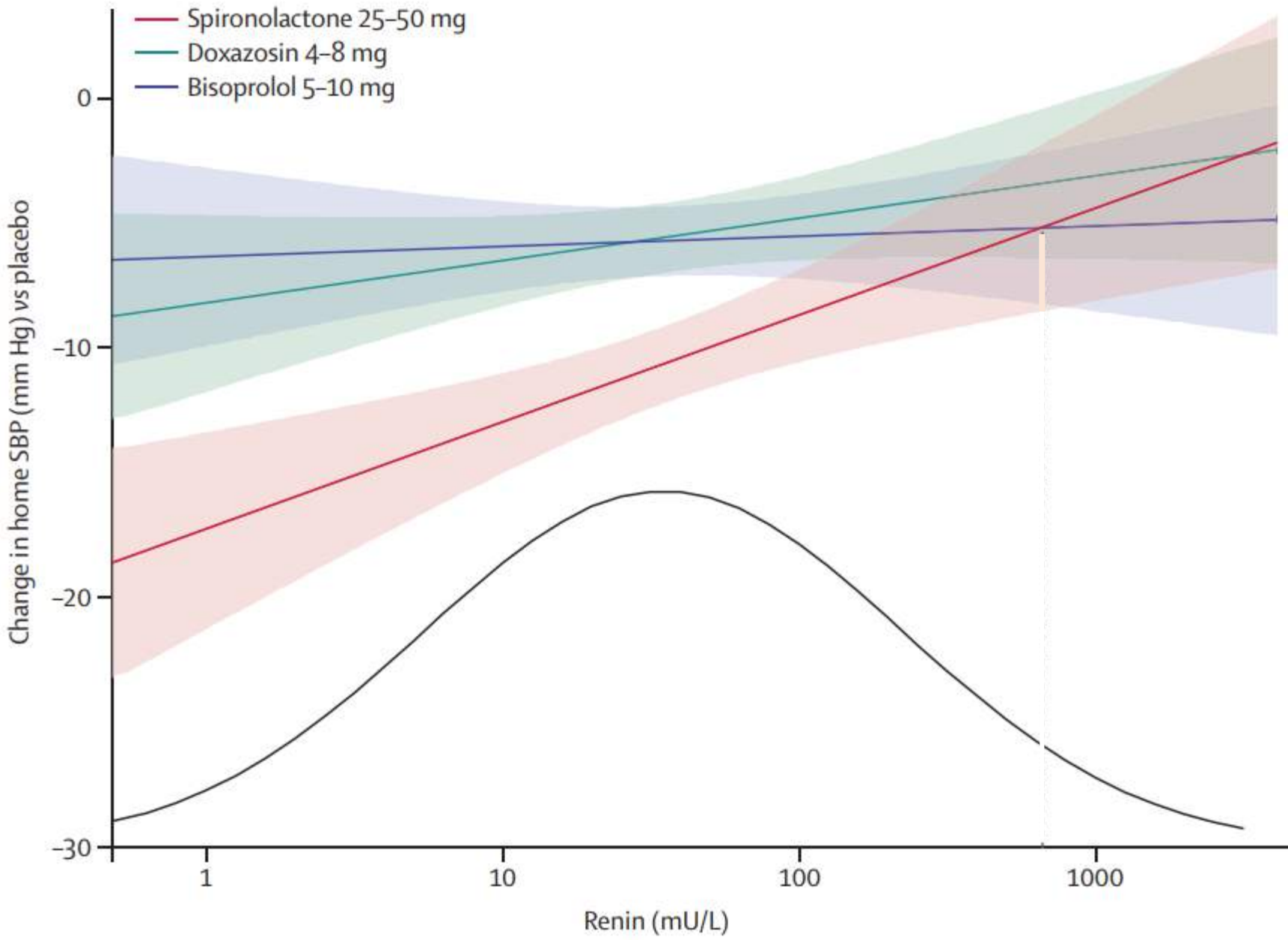
Lancet 2015; 386: 2059–68



Clear inverse relation between **home SBP fall with spironolactone** and **plasma renin**, not seen with bisoprolol or doxazosin.

Resistant hypertension is most often caused by excessive sodium retention, despite existing anti HT (including a diuretic) therapy

Lancet 2015; 386: 2059–68



+/-70% patients achieved home SBP < 135 mm Hg with spironolactone

(specific somatic mutations in adrenal gland can result in micro-aldosterone producing adenomas, which are difficult to detect by conventional imaging)

The average reduction in home systolic blood pressure by spironolactone was > to placebo (-9 mm Hg [95% CI –9,72 to –7,69])

Lancet 2015; 386: 2059–68

The Unrecognized Prevalence of Primary Aldosteronism:

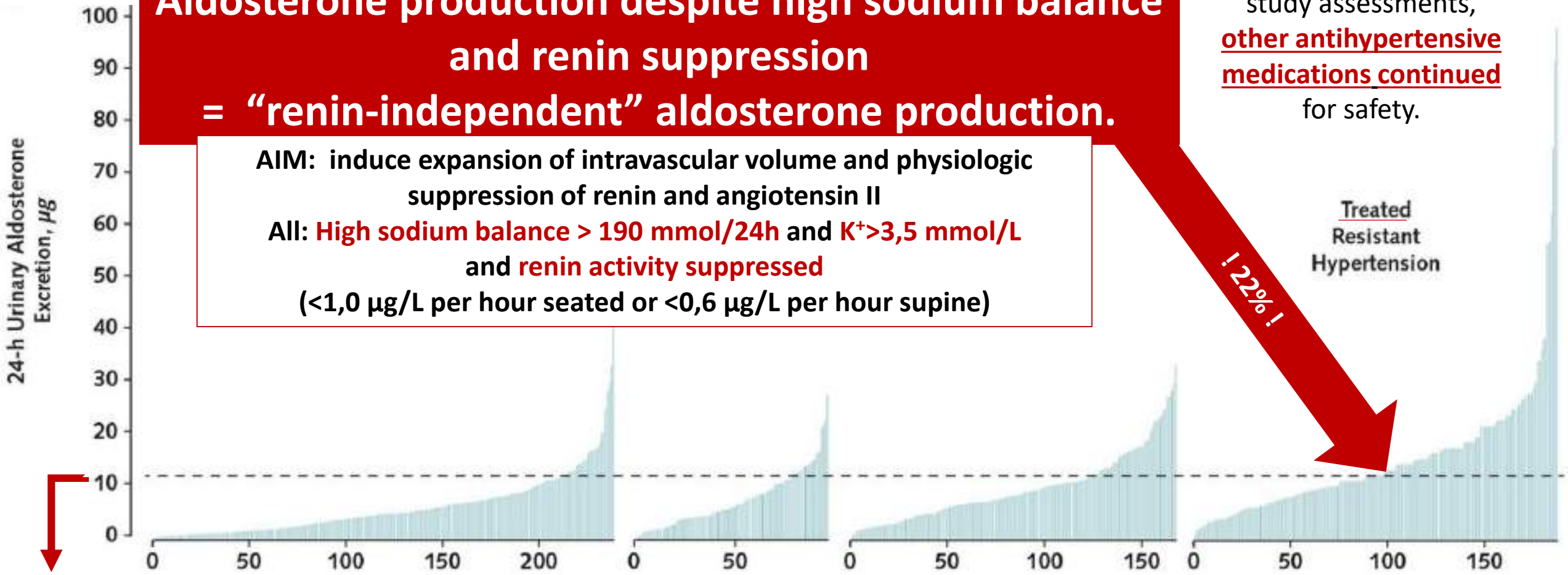
A Cross-sectional Study

Jenifer M. Brown, MD, Mohammad Siddiqui, MD, David A. Calhoun, MD, Robert M. Carey, MD, Paul N. Hopkins, MD, MSPH, Gordon H. Williams, MD, Anand Vaidya, MD, MMSc
Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (J.M.B., G.H.W., A.V.); University of Alabama at Birmingham, Birmingham, Alabama (M.S., D.A.C.); University of Virginia Health System, Charlottesville, Virginia (R.M.C.); and University of Utah School of Medicine, Salt Lake City, Utah (P.N.H.).

In **resistant hypertensive patient** subgroup,
stop mineralocorticoid receptor antagonists or amiloride
6 weeks before
study assessments,
other antihypertensive medications continued
for safety.

Aldosterone production despite high sodium balance and renin suppression
= "renin-independent" aldosterone production.

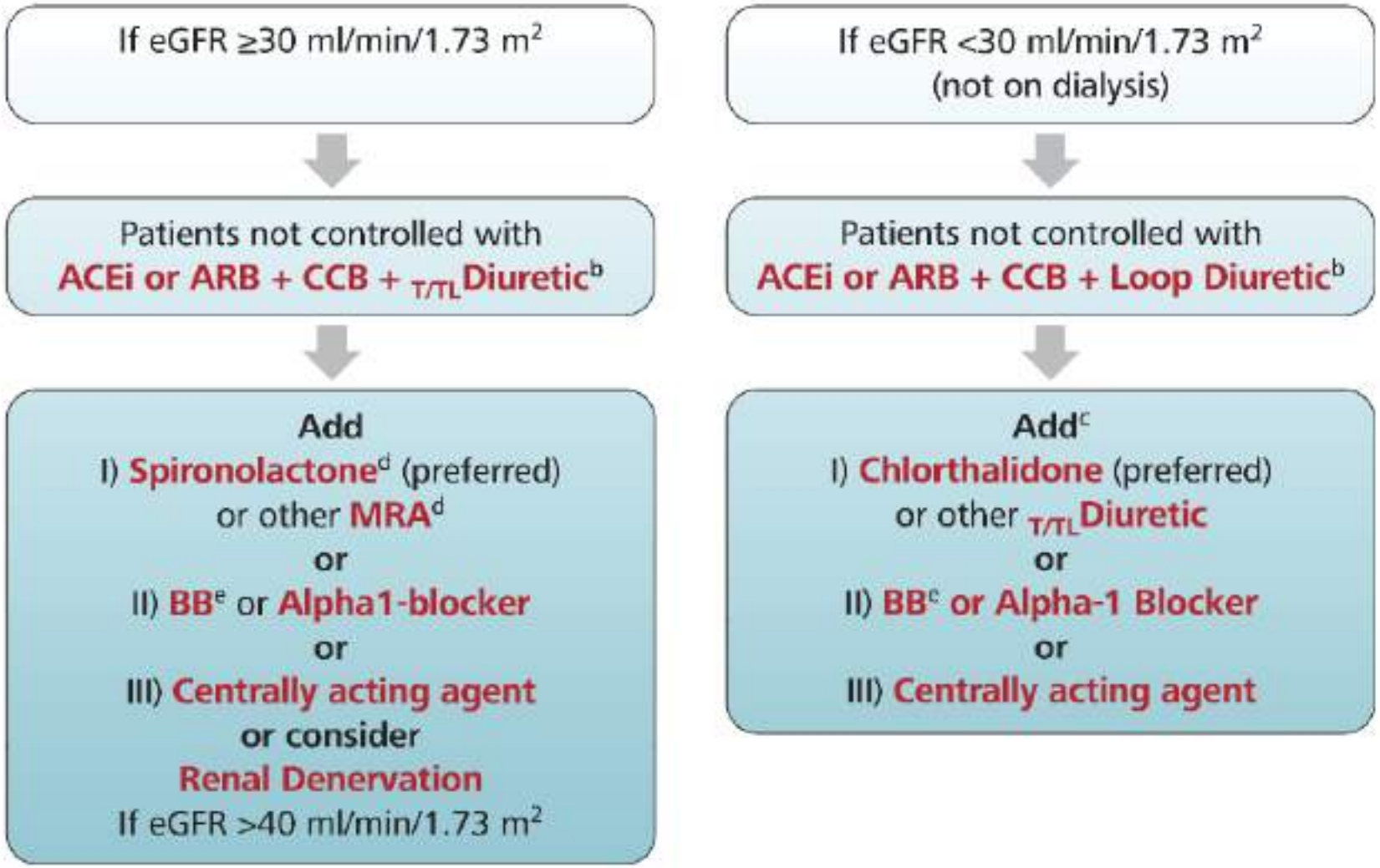
AIM: induce expansion of intravascular volume and physiologic suppression of renin and angiotensin II
All: High sodium balance > 190 mmol/24h and K^+>3,5 mmol/L and renin activity suppressed
(<1,0 µg/L per hour seated or <0,6 µg/L per hour supine)



Biochemically overt primary aldosteronism diagnosed when urinary aldosterone levels > 12 µg/24 h.

Ann Intern Med. 2020 July 07; 173(1): 10–20.

BP-lowering strategy in true resistant hypertension



Mancia, Kreutz et al. J Hypertens. 2023;41:1874-2071

Aldosterone and Treatment-Resistar

Jane A. Leopold, M.D., and Julie R. Ingelfi

Spironolactone competes with aldosterone to bind to the mineralocorticoid receptor (aldosterone receptor) in the distal convoluted tubule cells of the kidney.

Spironolactone is nonselective — it binds androgen and progesterone receptors, leading to off-target effects such as gynecomastia.

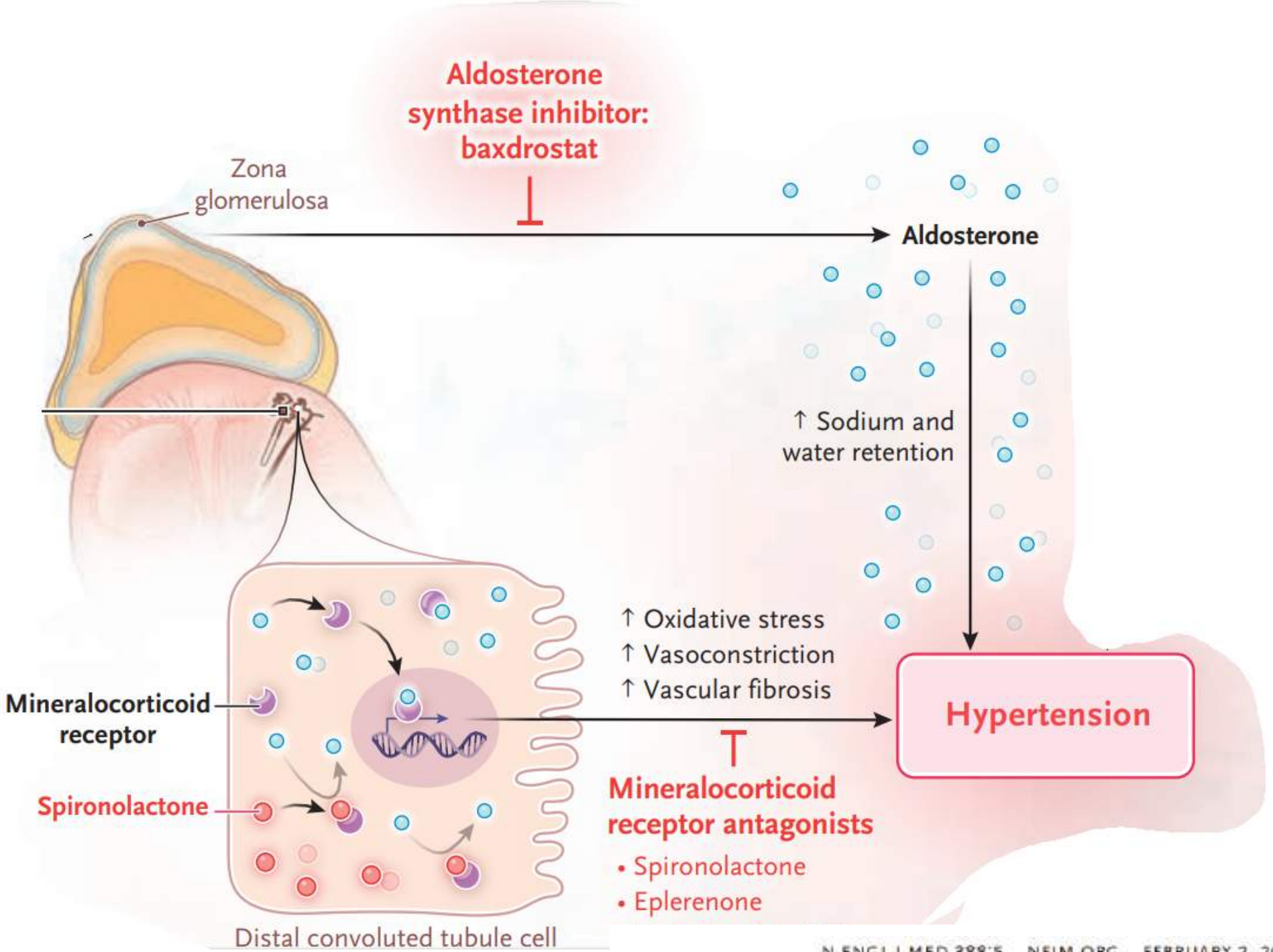


Table 1. Similarities and Differences between Aldosterone Synthase Inhibition with Baxdrostat and Mineralocorticoid Receptor Antagonism.

Variable	Aldosterone Synthase Inhibition with Baxdrostat BARDOXSTAT	Mineralocorticoid Receptor Antagonism SPIRONOLACTONE
Enzyme activities		
Aldosterone synthase activity (CYP11B2)	Decreased	Increased
11β-hydroxylase activity (CYP11B1)	Unchanged	Unchanged
Hormone levels		
Aldosterone pathway		
Plasma aldosterone level	Decreased	Increased
Plasma 11-deoxycorticosterone level	Increased	Increased
Cortisol pathway		
Plasma cortisol level	Unchanged	Unchanged
Plasma 11-deoxycortisol level	Unchanged	Unchanged
Plasma corticotropin level	Unchanged	Unchanged
Receptor status		
Mineralocorticoid receptor	Unblocked and not stimulated	Blocked
Mineralocorticoid receptor–independent nongenomic pathway	Not stimulated	Stimulated
Pharmacodynamic effects		
Serum potassium level*	Increased	Increased
Blood pressure	Decreased	Decreased
Plasma renin activity	Increased	Increased

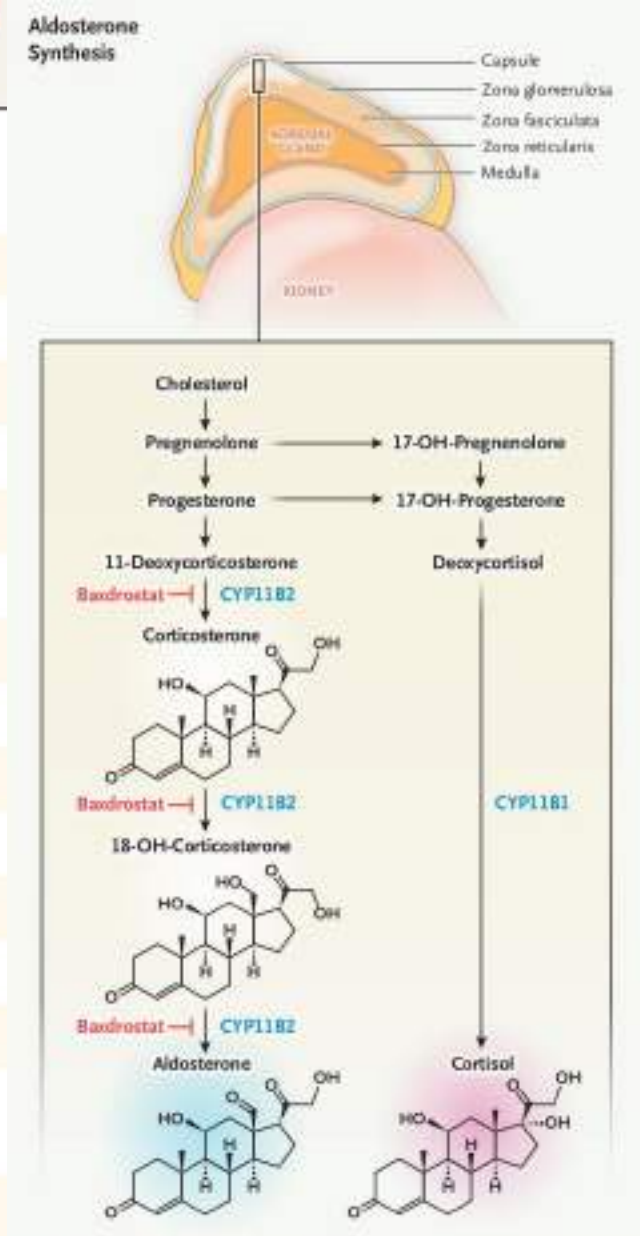
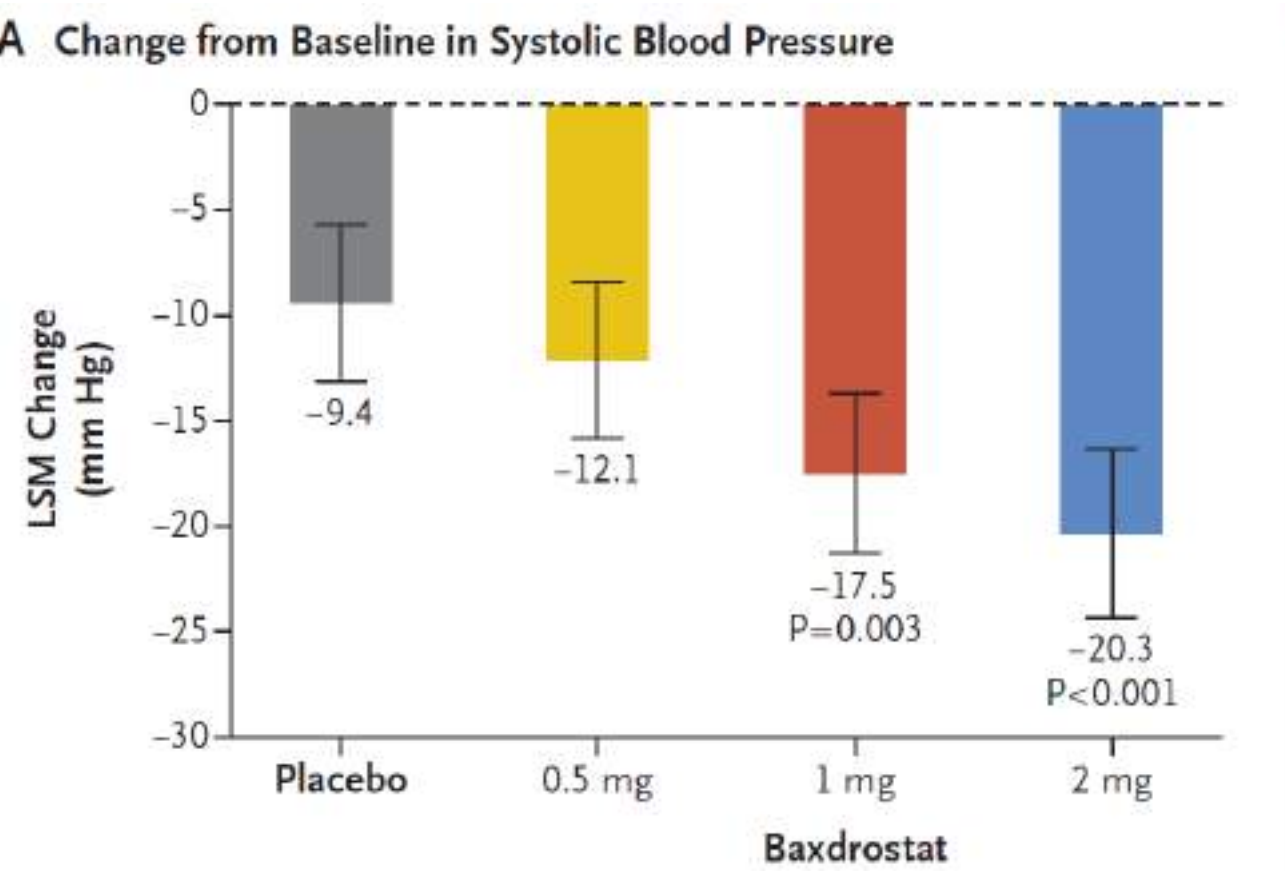
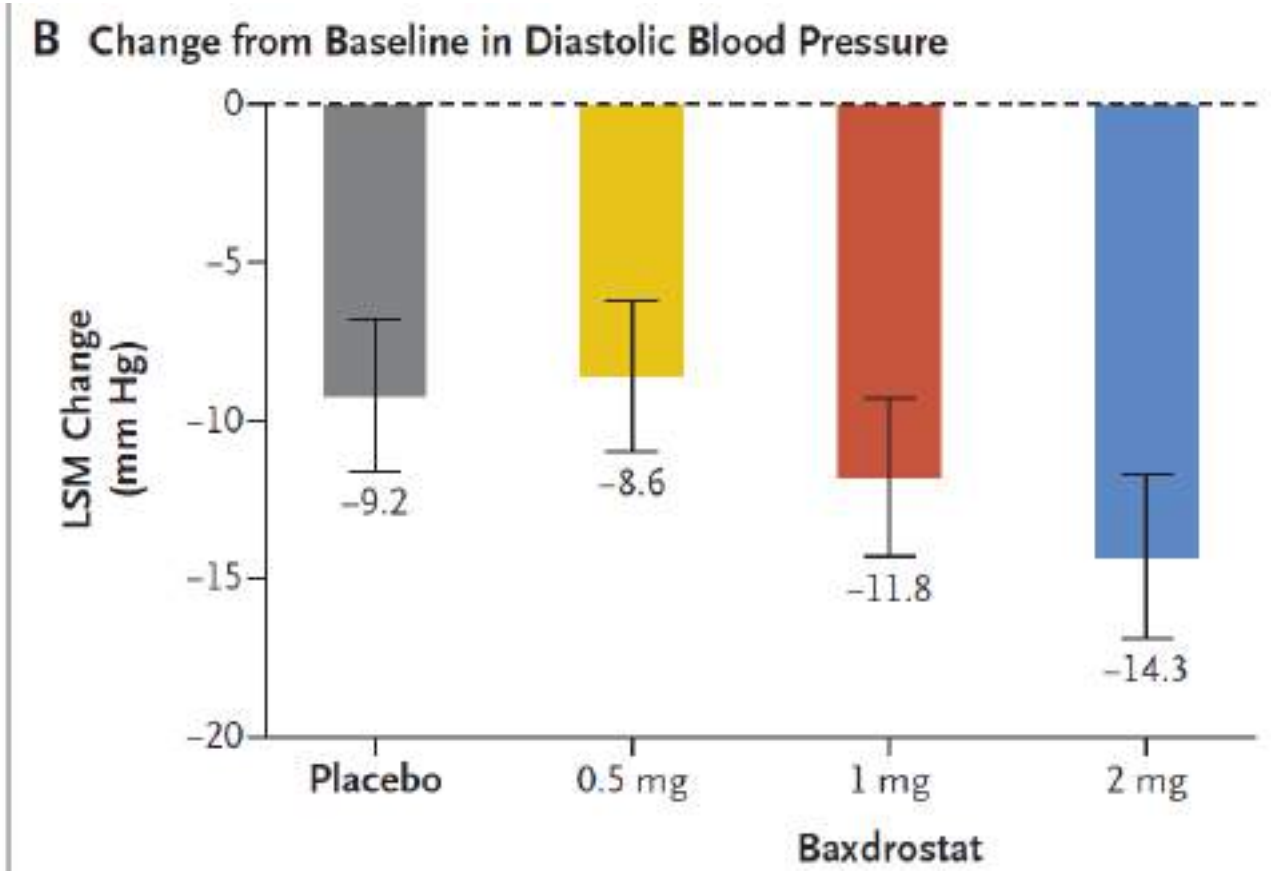


Figure 2. Aldosterone Synthesis in the Zona Glomerulosa.
In the zona glomerulosa of the adrenal gland, the CYP11B2 enzyme (also known as aldosterone synthase) catalyzes the synthesis of aldosterone. CYP11B2 and CYP11B1 (also known as 11β-hydroxylase, which synthesizes cortisol and is the final enzyme in the cortisol-synthesis pathway) share 93% sequence similarity, and drugs that block CYP11B2 have the potential to block CYP11B1.

Baxdrostat for Resistant Hypertension (phase 2)

Baxdrostat ↓ plasma aldosterone levels but not cortisol levels:
selectivity ratio 100:1 for aldosterone synthase vs. 11β-hydroxylase for cortisol synthesis (shares 93% sequence similarity with aldosterone synthase)





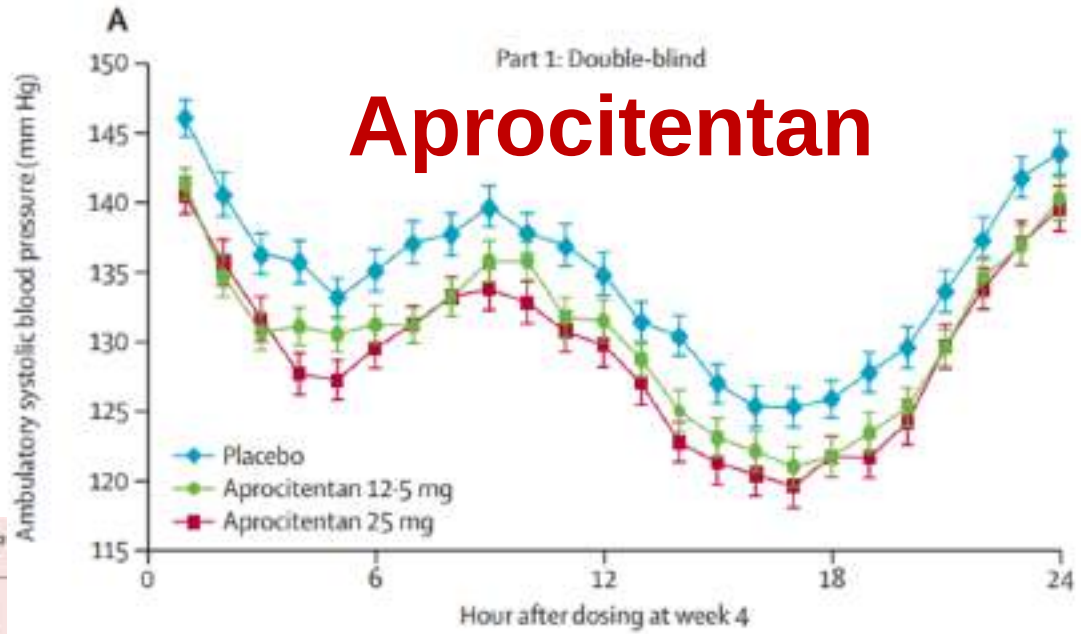
MW. Freeman et al. N Engl J Med 2023;388:395-405. DOI: 10.1056/NEJMoa2213169

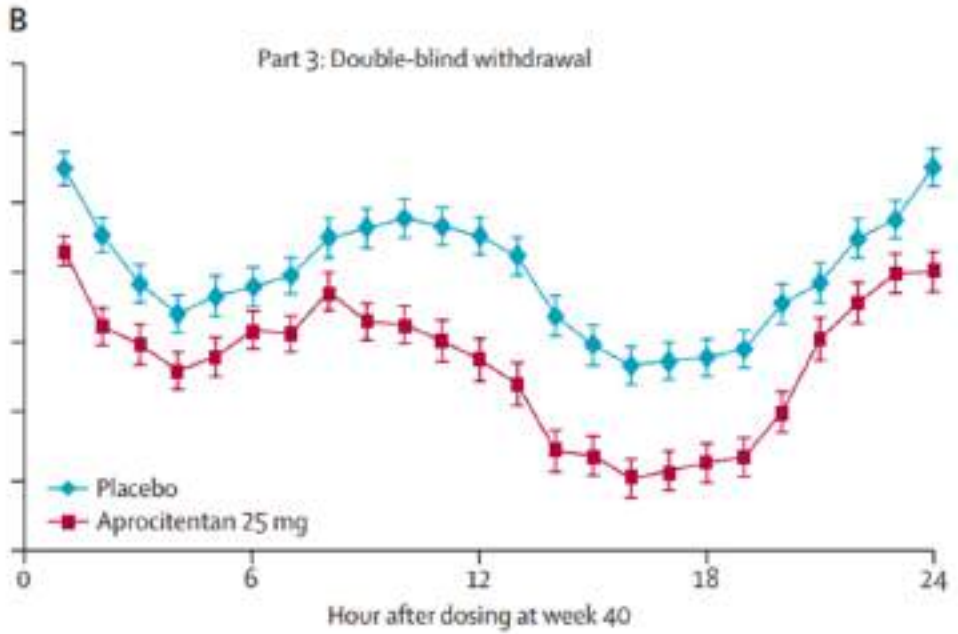
NB: only 12 weeks, no ABPM and GFR > 45 ml/min and adherence >70% and very large Placebo effect

Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial

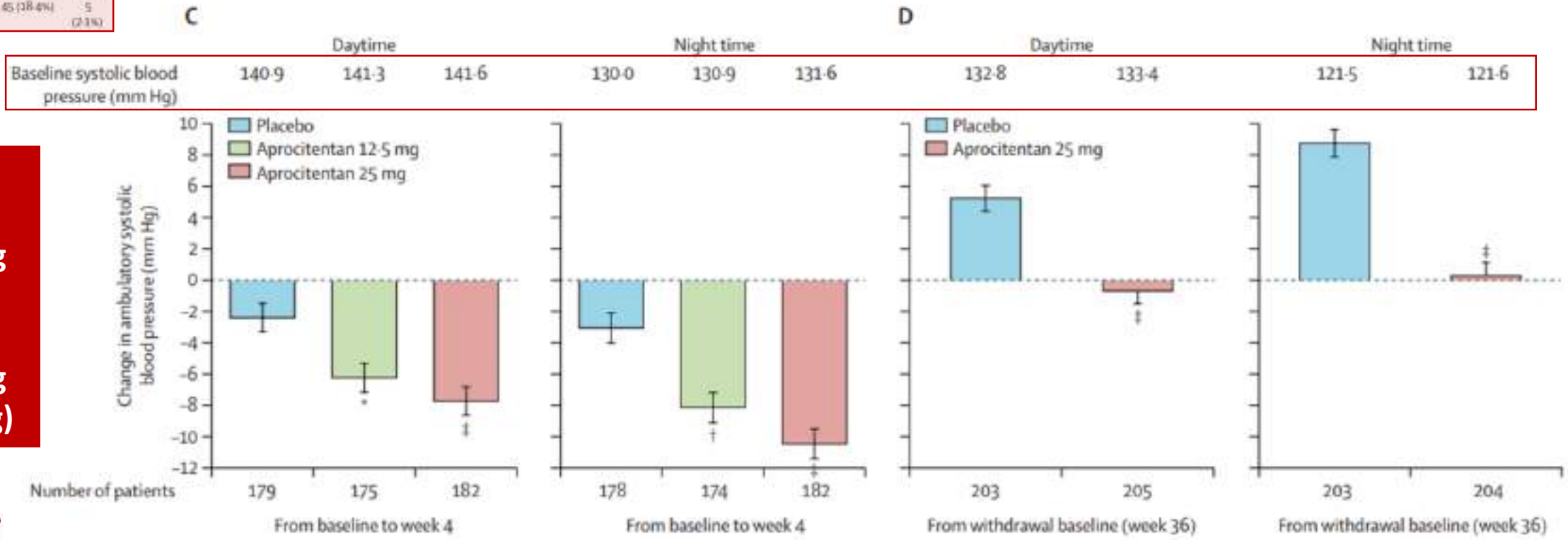
Aprocitentan

	Aprocitentan 12·5 mg	Aprocitentan 25 mg	Placebo
Part 1: Double-blind	243	245	142
Patients with at least one event	30 (12·3%)	47 (19·2%)	7 (2·9%)
Oedema or fluid retention	22 (9·1%)	45 (18·4%)	5 (2·1%)





24 h SBP ABPM:
–4·2 mm Hg (Apro 12,5 mg)
–5·9 mm Hg (Apro 25 mg)



Lancet 2022; 400: 1927–37

TABLE 1. Comparisons of the main characteristics (approximate average for the patients who were randomized to renal denervation and to SHAM control) and the net results of five new studies of intravascular renal denervation (Lancet 2017–2021).

Variable	RADIANCE-HTN SOLO	SPYRAL HTN-OFF	SPYRAL HTN-ON	SPYRAL OFF PIVOTAL	RADIANCE-HTN TRIO
No. randomized	146	80	80	331	136
Age (years)	54	54	53	53	53
% men	60	70	84	66	80
BMI (kg/m^2)	30	30	32	31	33
Office SBP (mmHg)	154	162	164	163	163
Office DBP (mmHg)	100	101	101	102	104
24-h SBP (mmHg)	143	152	152	151	145
24-h DBP (mmHg)	88	99	98	99	89
Net results (mmHg) expressed as difference in reductions between renal denervation and control (SHAM)					
Change Office-SBP	−6.5	**−7.7**	−6.8	−6.7	−5.0
Change Office-DBP	−4.1	−4.9	−3.5	−4.1	−4.0
Change 24h-SBP	−4.1	−5.0	−7.4	−4.1	−5.6
Change 24h-DBP	−1.8	−4.4	−4.1	−2.9	−3.0
Change daytime SBP	−6.3	−6.1	−4.0	−5.0	
Change daytime DBP	−2.6	−4.1	−4.0	−2.9	

BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

EFFECTS ON 24H AMBULATORY BLOOD PRESSURE CORRECTED FOR SHAM

−4.1 24h SBP	−5.0 24h SBP	−7.4 24h SBP	24h SBP −4.1
−1.8 24h DBP	−4.4 24h DBP	−4.1 24h DBP	24h DBP −2.9

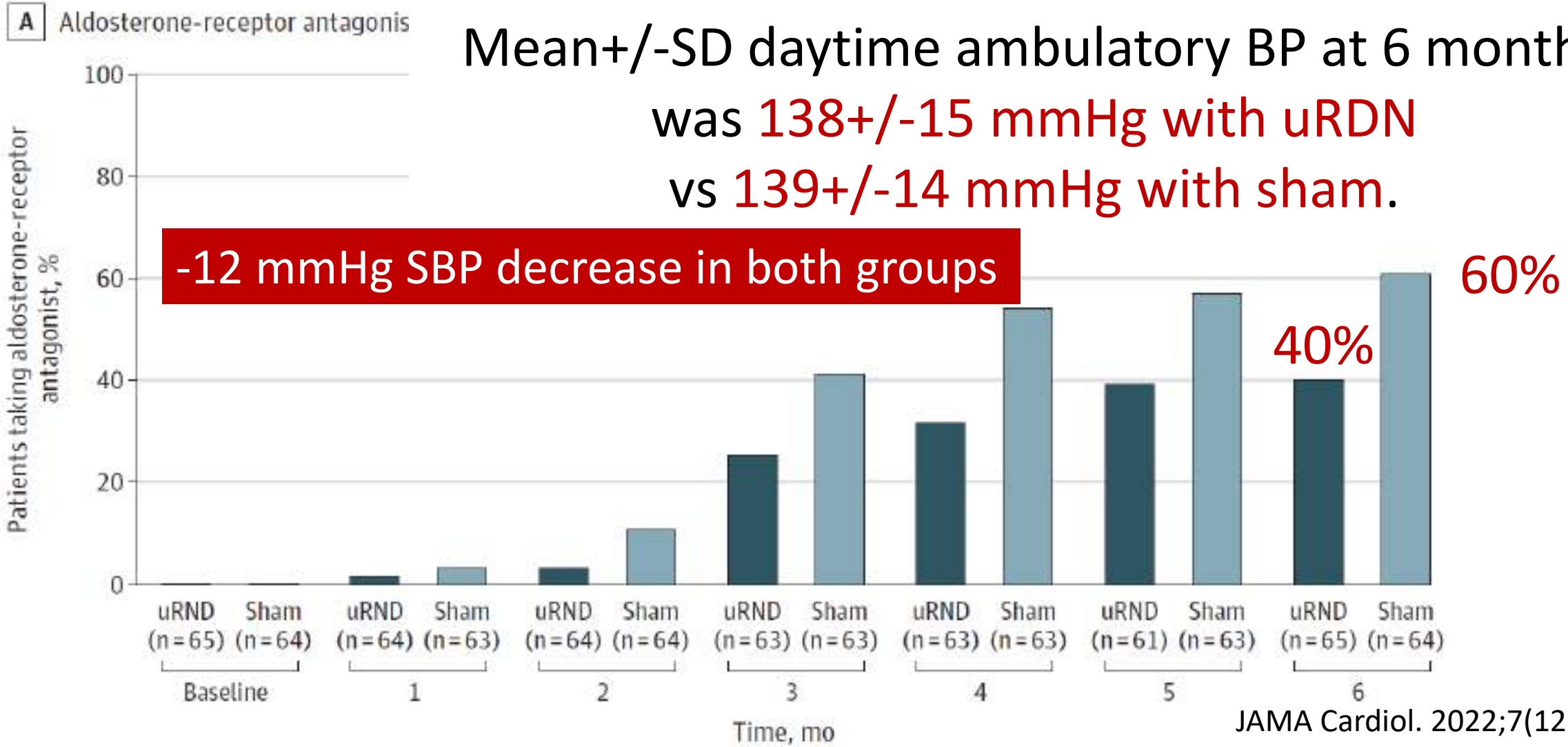
FH. Messerli et al. Renal denervation in the antihypertensive arsenal. Journal of Hypertension 2022, 40:1859–

Effects of Renal Denervation vs Sham in Resistant Hypertension After Medication Escalation
Prespecified Analysis at 6 Months of the RADIANCE-HTN TRIO Randomized Clinical Trial

Findings In this randomized, sham-controlled, clinical trial including 136 patients with RHTN, the BP-lowering effect of uRDN was sustained at 6 months with similar daytime systolic ambulatory BP compared with sham despite fewer medications, especially aldosterone antagonists.

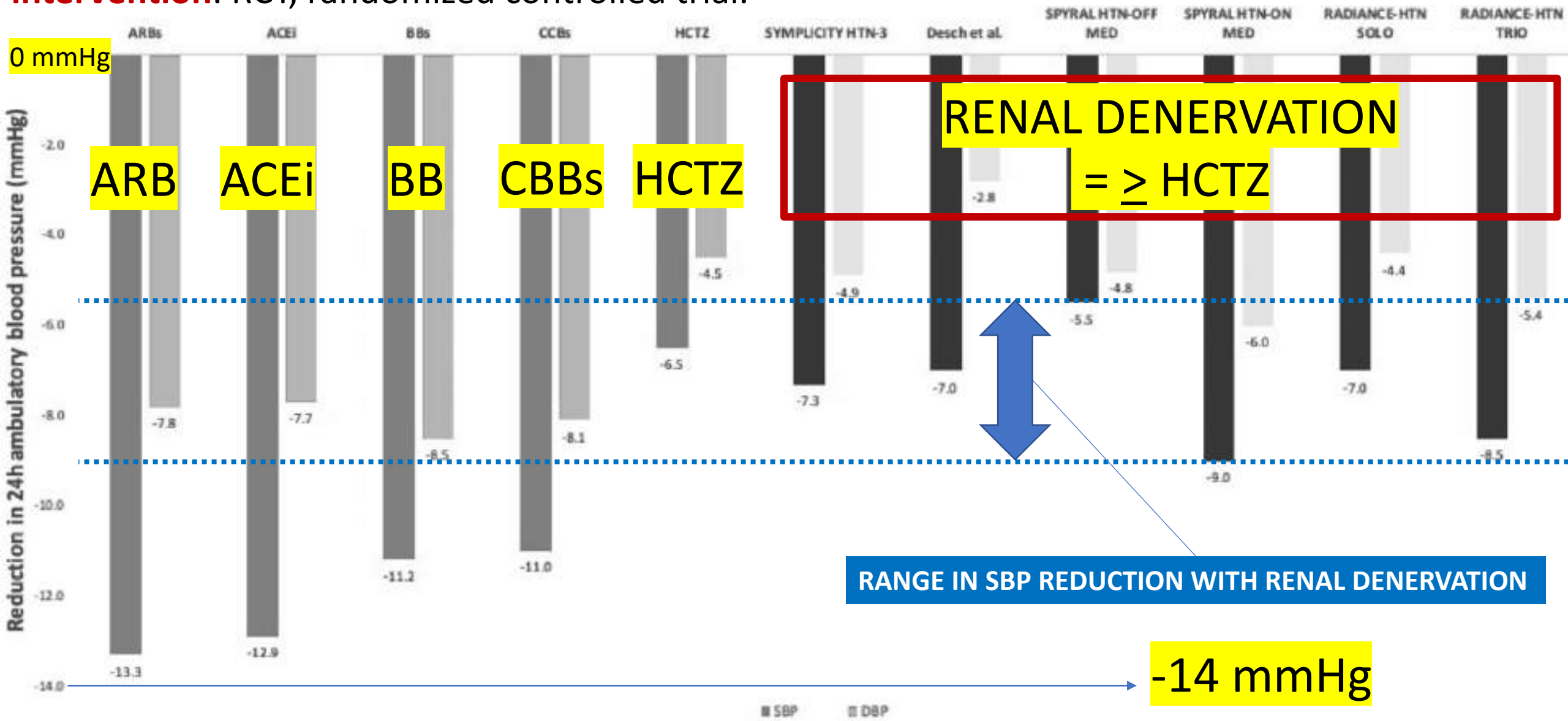
Mean+/-SD daytime ambulatory BP at 6 months was 138+/-15 mmHg with uRDN vs 139+/-14 mmHg with sham.

-12 mmHg SBP decrease in both groups



JAMA Cardiol. 2022;7(12):1244-1252.

Reduction in systolic and diastolic 24 h ambulatory blood pressure (mmHg) achieved by individual antihypertensive drugs and in sham-RCTs comparing renal denervation to sham intervention. RCT, randomized controlled trial.



FH. Messerli et al. Renal denervation in the antihypertensive arsenal. Journal of Hypertension 2022, 40:1859–

- RDN lowers BP to an extent *at best* corresponding to 1 antihypertensive drug
- Clinically impossible to predict who responds to RDN and who does not.
- Complete lack of outcome data with RDN.
- No reversibility of antihypertensive effect if hypotension (in contrast to standard antihypertensive therapy)
- Safety data on RDN available for up to 3 years and in CKD, but long-term BP reduction unconvincing.
- Can RDN be repeated? If so, how often? Does repeated RDN lead to scarring of renal arteries?

FH. Messerli et al. Renal denervation in the antihypertensive arsenal. Journal of Hypertension 2022, 40:1859–

RESISTANT HYPERTENSION - CHECK LIST !

Diagnostic criteria for resistant hypertension	ESH/ESC 2018
BP control not achieved despite the concurrent use of three antihypertensive drugs	✓
Concurrent use of 4 antihypertensive agents irrespective of BP control	-
Preferential combination of an ACE inhibitor or an ARB, a CCB, and a diuretic	✓
Mandatory use of a diuretic	✓
All drugs up-titrated to maximal or maximally-tolerated doses	✓
BP level confirmed by ABPM or HBPM	✓
Adherence to therapy assessed and confirmed	✓
Adherence to life style recommendation assessed and confirmed	✓
Secondary hypertension excluded	✓

G. Lamirault et al. Resistant hypertension: Novel insights. Curr Hypertens Rev. 2020;16(1):61-72. doi: 10.2174/1573402115666191011111402.

Resistant HT: OMT or RDN ?

P. van de Borne (Brussels, Belgium)

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THANK YOU FOR YOUR KIND ATTENTION