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Cardiometabolic Health Congress

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Foundations of Cardiometabolic Health Certification Course

Certified Cardiometabolic Health Professional (CCHP)

Approach to True Resistant Hypertension

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Duality of Interest

CONSULTANT FOR: MERCK, BAYER, VIFOR, IONIS, ALNYLAM, ASTRA ZENECA, HORIZON, BAYER

GRANT/ CLINICAL TRIALS RESEARCH SUPPORT FROM: BAYER, VASCULAR DYNAMICS, NOVO NORDISK,

Updated Definition of Apparent Resistant Hypertension

- Failure to reach goal BP <130/80 mm Hg

The MAJOR DIFFERENCE in Apparent RHTN you are trusting them taking the meds. In True RHTN you documented they are taking the drugs

True Resistant Hypertension

- Failure to reach goal BP <130/80 mm Hg while documenting ingestion of *three-drug* antihypertensive regimen including an *appropriate diuretic for kidney function, a* CCB and a RAS blocker maximally dosed

(JNC 7, Chobanian AV et.al. Hypertension, 2003; AHA Position Paper-Hypertension 2008; White WB et.al. J Am Soc Hypertens 2014; Carey RM, et.al. Hypertension 2018;72:e53-e90.*)*

Two Most Common Non-Disease Causes for Apparent Resistant Hypertension

- White Coat Hypertension (Anxiety)
- Poor Medication Adherence

ALL the Following Need to be Present Before Diagnosing Someone as Having TRUE Resistant Hypertension

1. Adherence with: Low Sodium Diet Intake and Medication
2. Good Sleep Quality (i.e., minimum of 6-7 hours of uninterrupted sleep a night)
3. Substitutions of drugs with greater effect within the Same Class i.e. ARBs and diuretics
4. Rule out all Secondary Causes of Hypertension

Before saying anyone is resistant must rule out the most common secondary cause of hypertension:

PRIMARY ALDOSTERONISM

Best Proven Nonpharmacologic Interventions for Prevention and Treatment of Hypertension

	Nonpharmacologic Intervention	Dose	Hypertension	Normotension
Physical activity	**Aerobic**	● 90-150 min/wk ● 65%-75% heart rate reserve	-5/8 mm Hg	-2/4 mm Hg
	Dynamic Resistance	● 90-150 min/wk ● 50%-80% 1 rep maximum ● 6 exercises, 3 sets/exercise, 10 repetitions/set	-4 mm Hg	-2 mm Hg
	Isometric Resistance	● 4 x 2 min (hand grip), 1 min rest between exercises, 30%-40% maximum voluntary contraction, 3 sessions/wk ● 8-10 wk	-5 mm Hg	-4 mm Hg
Healthy diet	DASH dietary pattern	Diet rich in fruits, vegetables, whole grains, and low-fat dairy products with reduced content of saturated and total fat	-11 mm Hg	-3 mm Hg
Weight loss	**Weight/body fat**	Ideal body weight is best goal but at least 1 kg reduction in body weight for most adults who are overweight	-5 mm Hg	-2/3 mm Hg
Reduced intake of dietary sodium	**Dietary sodium**	<1,500 mg/d is optimal goal but at least 1,000 mg/d reduction in most adults	-5/6 mm Hg	-2/3 mm Hg
Enhanced intake of dietary potassium	Dietary potassium	3,500-5,000 mg/d, preferably by consumption of a diet rich in potassium	-4/5 mm Hg	-2 mm Hg
Moderation in alcohol	Alcohol consumption	In individuals who drink alcohol, reduce alcohol to: ● Men: <2 drinks daily	-4 mm Hg	-3 mm Hg

Journal of the American Society of Hypertension 11(2) (2017) 122–129

Review Article

Sleep, insomnia, and hypertension: current findings and future directions

S. Justin Thomas, PhD[a,*] and David Calhoun, MD[b]

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[b]*Department of Medicine, Division of Cardiovascular Disease, University of Alabama at Birmingham, Birmingham, AL, USA*

Manuscript received October 10, 2016 and accepted November 26, 2016

Reported associations between insomnia and hypertension have been inconsistent.

Insomnia combined with a short sleep duration (<5 hours, but not > 5 hours) is associated with a significantly increased risk of hypertension.

Nurses Health Study

71,617 women 45-65 years

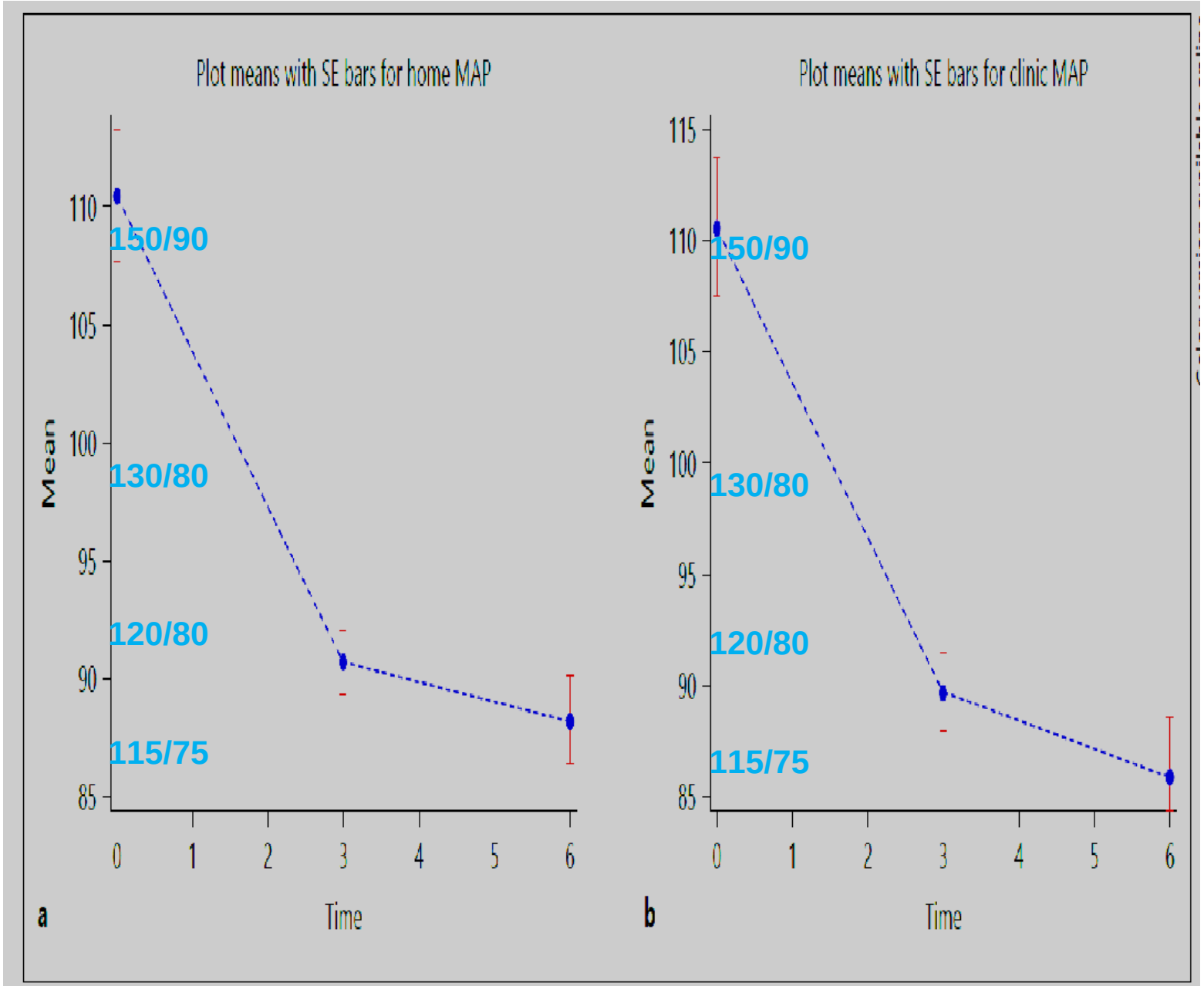
10-year follow-up of Incident CHD

Sleep Duration	Relative Risk	Confidence Interval
5 hours	1.82	1.34 – 2.41
6 hours	1.30	1.08 – 1.57
7 hours	1.06	0.89 – 1.26
8 hours	1	1

(Ayas et al 2003)

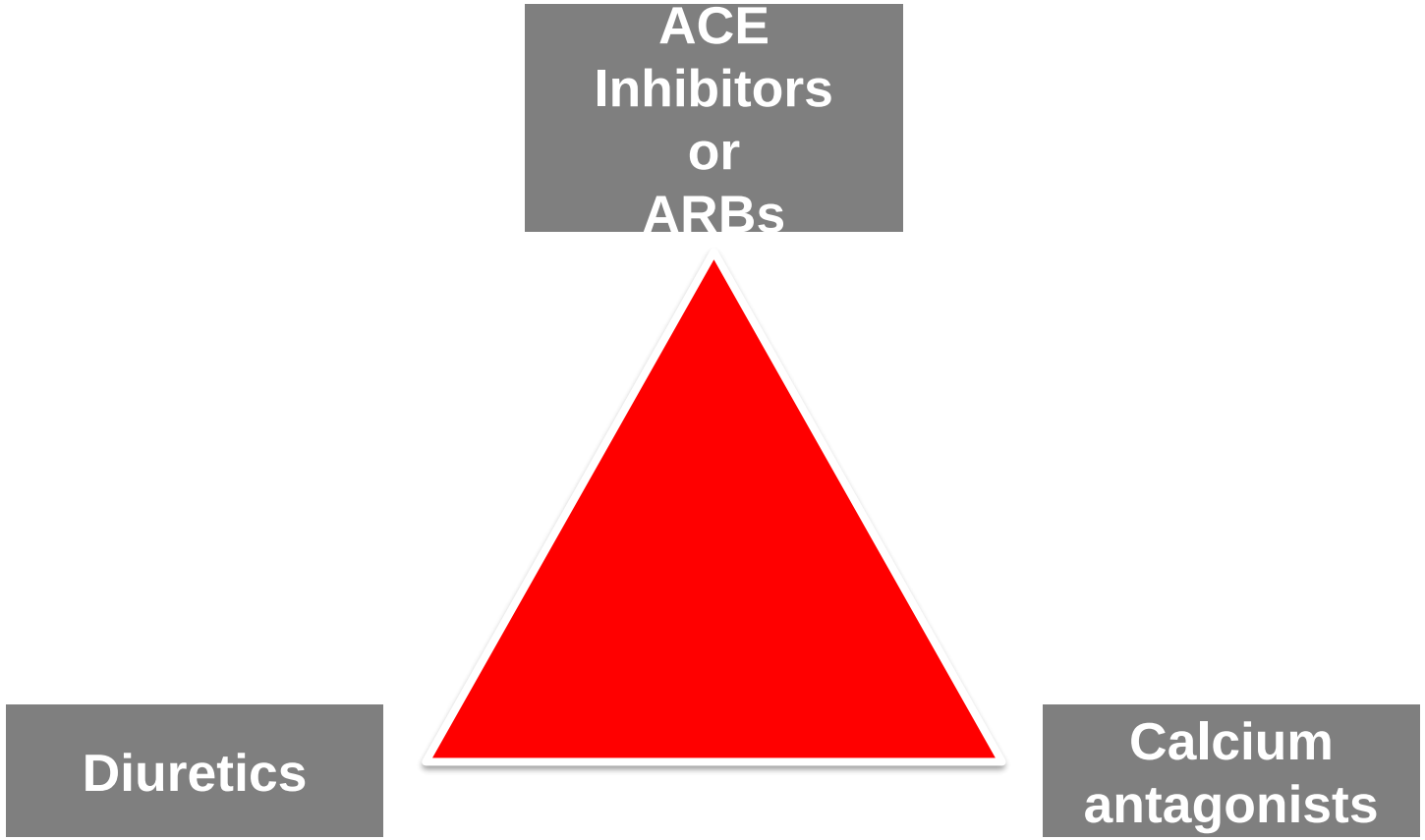
BP Change after Months of Restored Sleep Duration

Variables	Total (n = 30)
Gender n (%)	
Male	13 (43)
Female	17 (57)
Age, years, n (%)	
30–49	4 (13)
50–70	11 (37)
>70	15 (50)
Race, n (%)	
African American	17 (57)
White	13 (43)
Diabetes mellitus, n (%)	12 (40)
Hyperlipidemia, n (%)	17 (57)
BMI, kg/m^2, mean ± SD	32±8
OSA, n (%)*	16 (53)
Baseline BP, mm Hg, mean ± SD**	
Clinic	156±21.27/88±17
Home	159±17.3/86±16.6
eGFR, mL/min, mean ± SD	43±16
Baseline eGFR, mL/min, n (%)	
15–60	27 (90)
<15	3 (10)
Sleep duration, h, n (%)	
>6	0
4–6	15 (50)
<4	15 (50)
Sleep variables, n (%)	
Inability to initiate sleep	18 (60)
Inability to stay asleep	23 (77)



Ali W et.al. Am J Nephrology 2020;51:249-254

Initial Combinations of Medications*



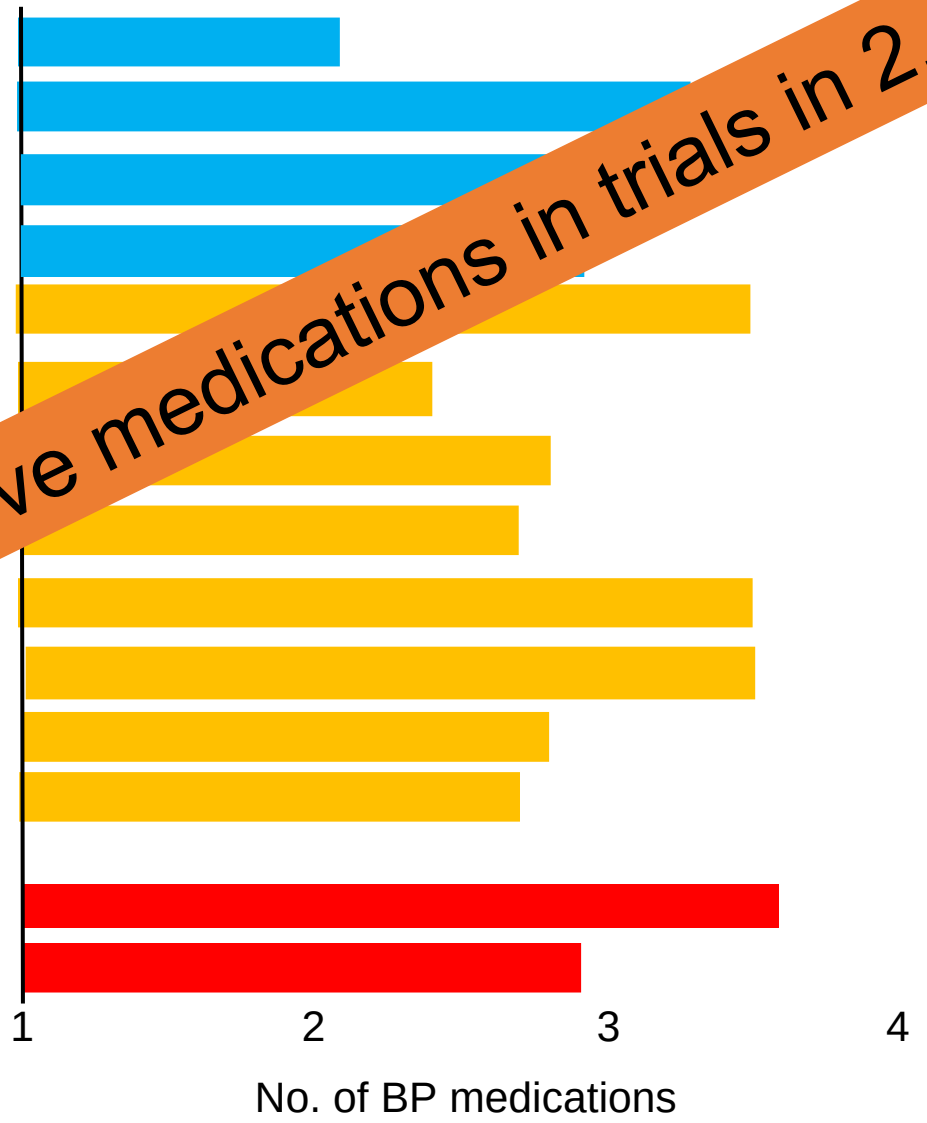
*** Compelling indications may modify this.**

Trials of Urine Metabolites Assessing Adherence in Hypertension

- Jung O et.al. Journal of Hypertension. 201 (4):766-774
- Tomaszewski, M et.al. Heart 20 00:855–861

Both studies show about a 45% adherence with BP lowering meds

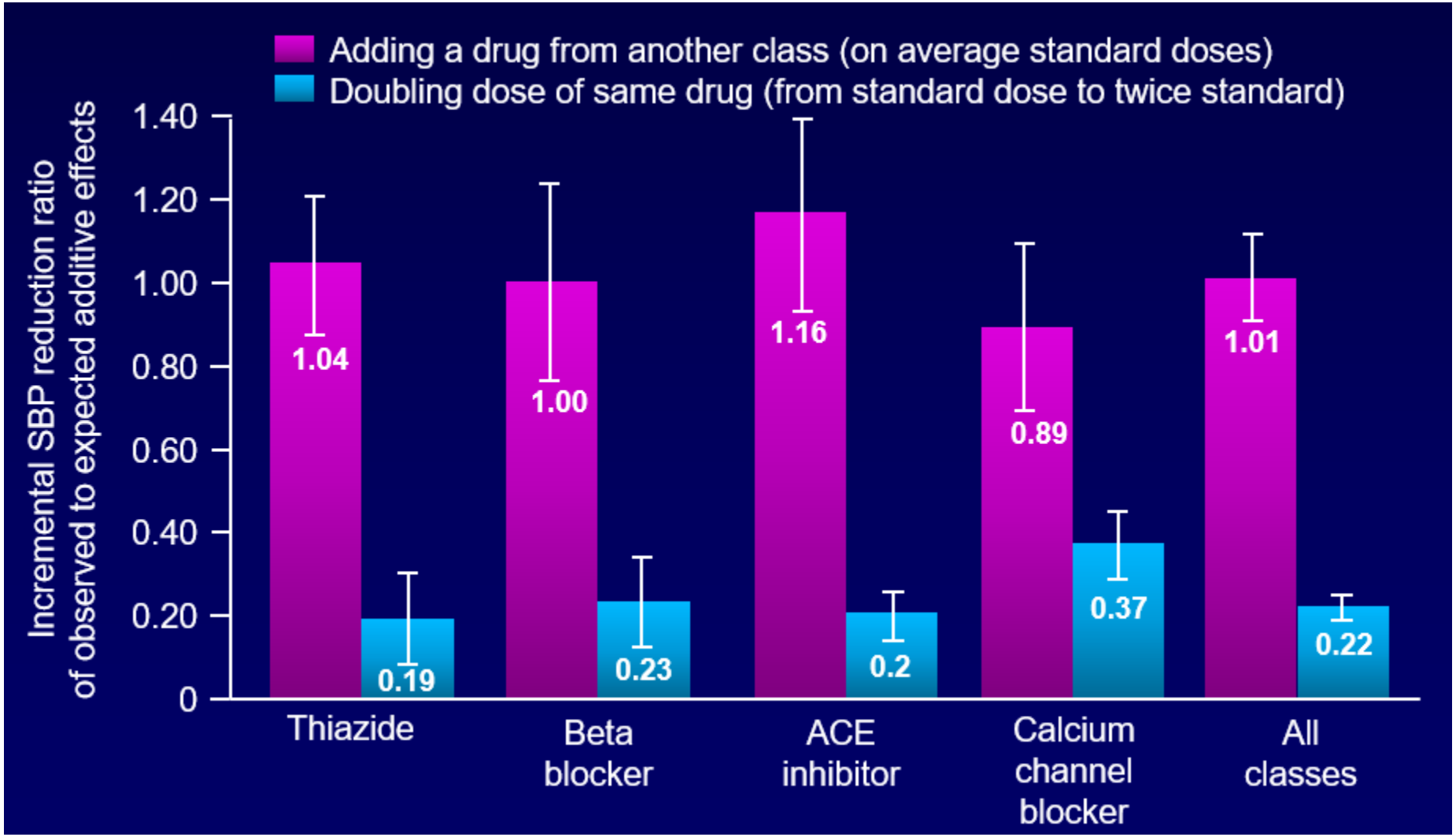
	Trial	SBP achieved (mm Hg)
Hypertension	ALLHAT	138
	HOT	138
	ACCOMPLISH	132
	SPRINT (intensive)	121
Diabetes	ACCORD (intensive)*	119
	ACCORD (standard)*	133
	INVEST	133
	IDNT	
	REN	
	…on D	127
	…CD	132
…ease	UKPDS	144
	MDRD	132
	AASK	128



Average number of antihypertensive medications in trials in 2.6 meds

Bold italic studies-both diabetes and kidney disease outcomes

Ratio of Observed to Expected Incremental BP-Lowering Effects of Adding a Drug or Doubling the Dose According to Drug Class



Wald DS et al. Am J Med. 2009;122:290-300.

American Society of Hypertension Evidenced Based Fixed Dose Antihypertensive Combinations

Preferred
· **ACE inhibitor/diuretic***
· **ARB/diuretic***
· **ACE inhibitor/CCB***
· **ARB/CCB***
Acceptable
· Beta blocker/diuretic*
· CCB (dihydropyridine)/β-blocker
· CCB/diuretic
· Renin inhibitor/diuretic*
· Renin inhibitor/ARB*
· Thiazide diuretics/K+ sparing diuretics*
Less Effective
· ACE inhibitor/ARB
· ACE inhibitor/β-blocker
· ARB/β-blocker
· CCB (nondihydropyridine)/β-blocker
· Centrally acting agent/β-blocker

* SPC avaialble in US

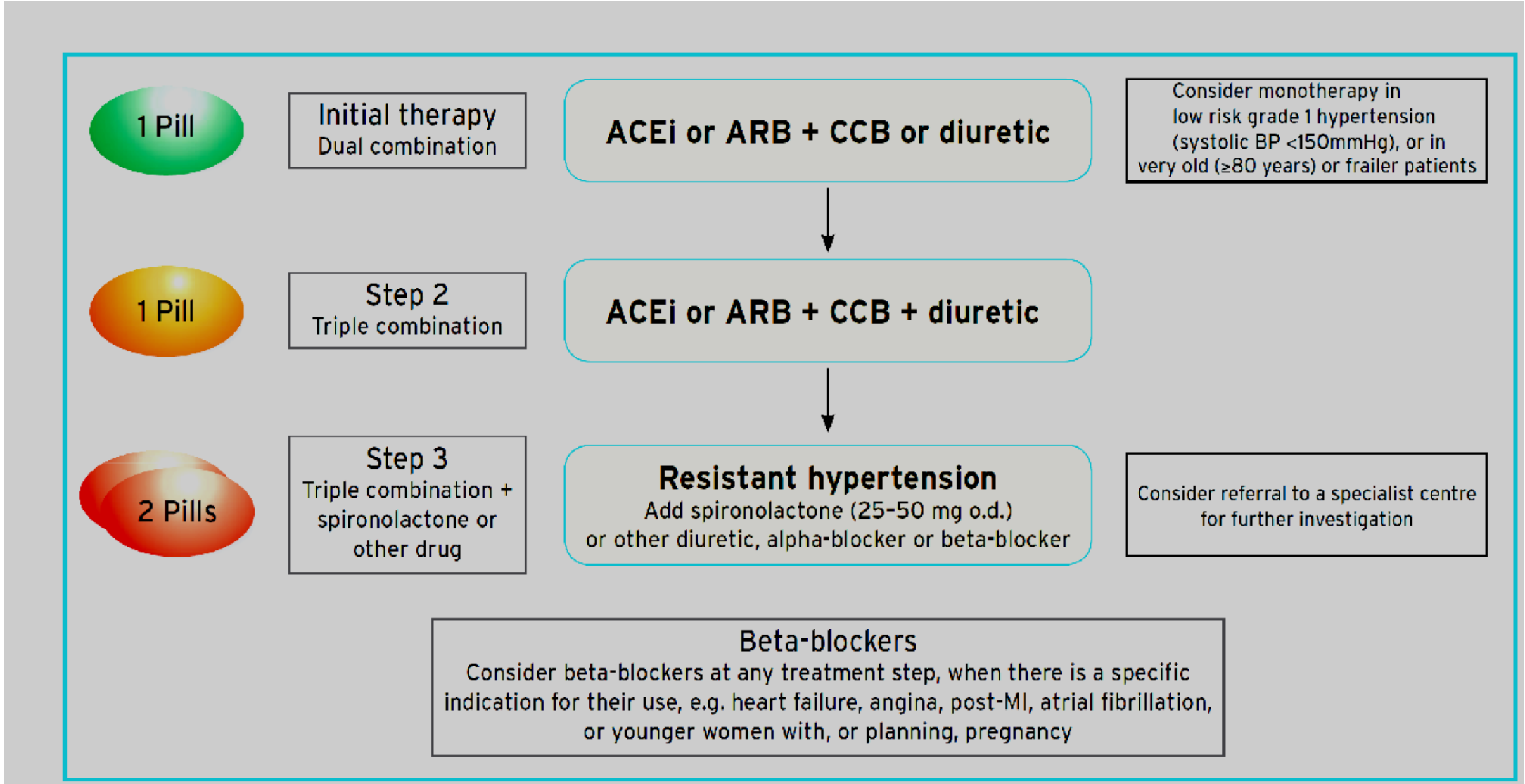
Gradman AH, et.al… and Bakris GL J Clin Hypertens (Greenwich) 2011;13:146-54.

AHA/ACC 2017

COR	LOE	Recommendations for Choice of Initial Medication
I	A^{SR}	For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or
COR	**LOE**	**Recommendations for Choice of Initial Monotherapy vs Initial Combination Drug Therapy**
I	C-EO	Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target
IIa	C-EO	Initiation of antihypertensive drug therapy with a single antihypertensive drug is reasonable in adults with stage 1 hypertension and BP goal <130/80 mm Hg with dosage titration and sequential addition of other agents to achieve the BP target

J Am Coll Cardiol. Sep 2017, 23976

ESC/ESH 2018

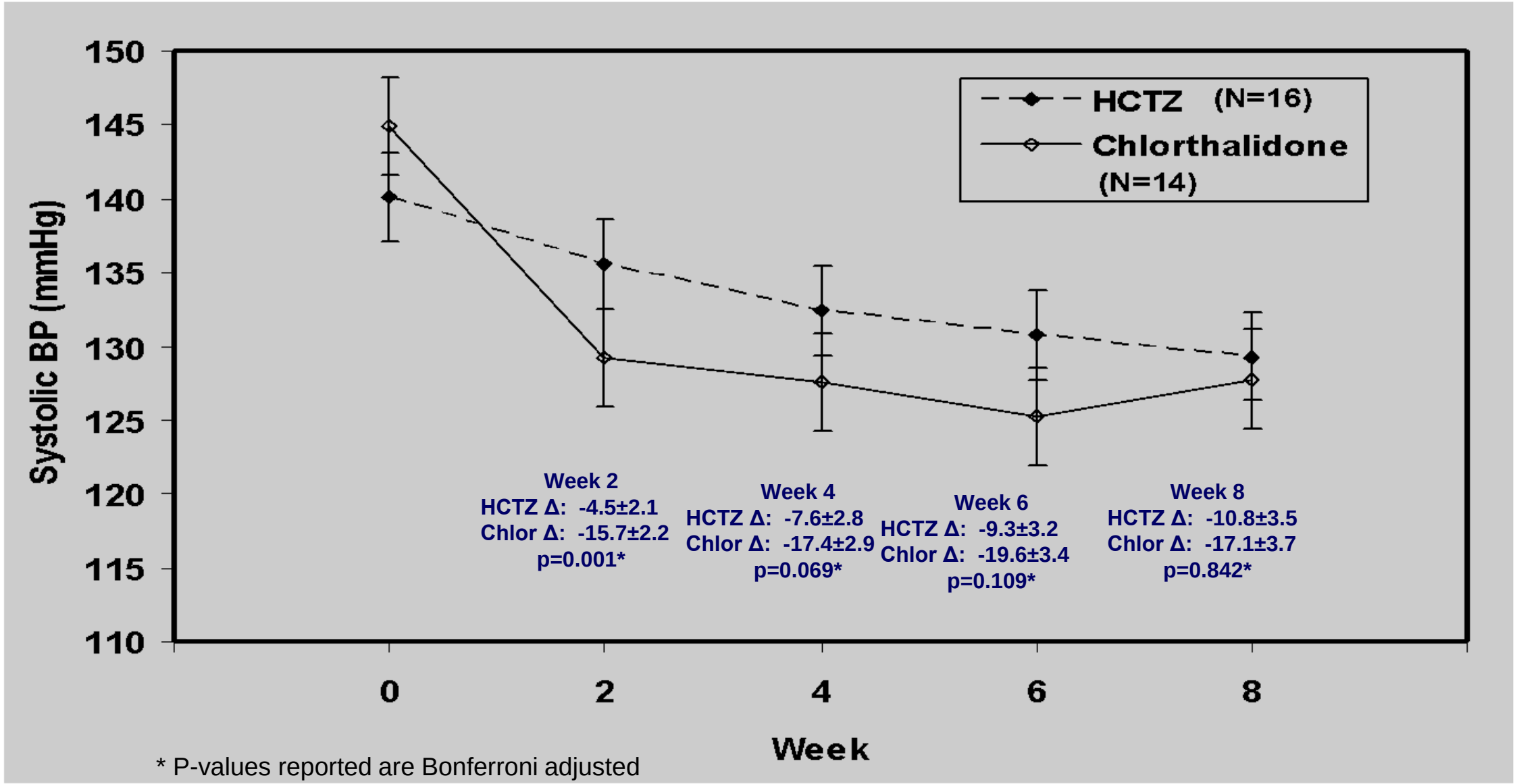


Williams B et.al Eur Heart J 2018

Type/classes of agents and agents within the class selected as base therapy to establish resistance

- Not all thiazide or thiazide-type diuretics are the same
- Not all ARBs are the same

Mean Office SBP Change



* P-values reported are Bonferroni adjusted

Ernst ME, et al. Hypertension 2006; 47:352-358

Similar Dose Conversation (HCTZ and Chlorthalidone on Office BP Response in Patients Not at Goal BP)

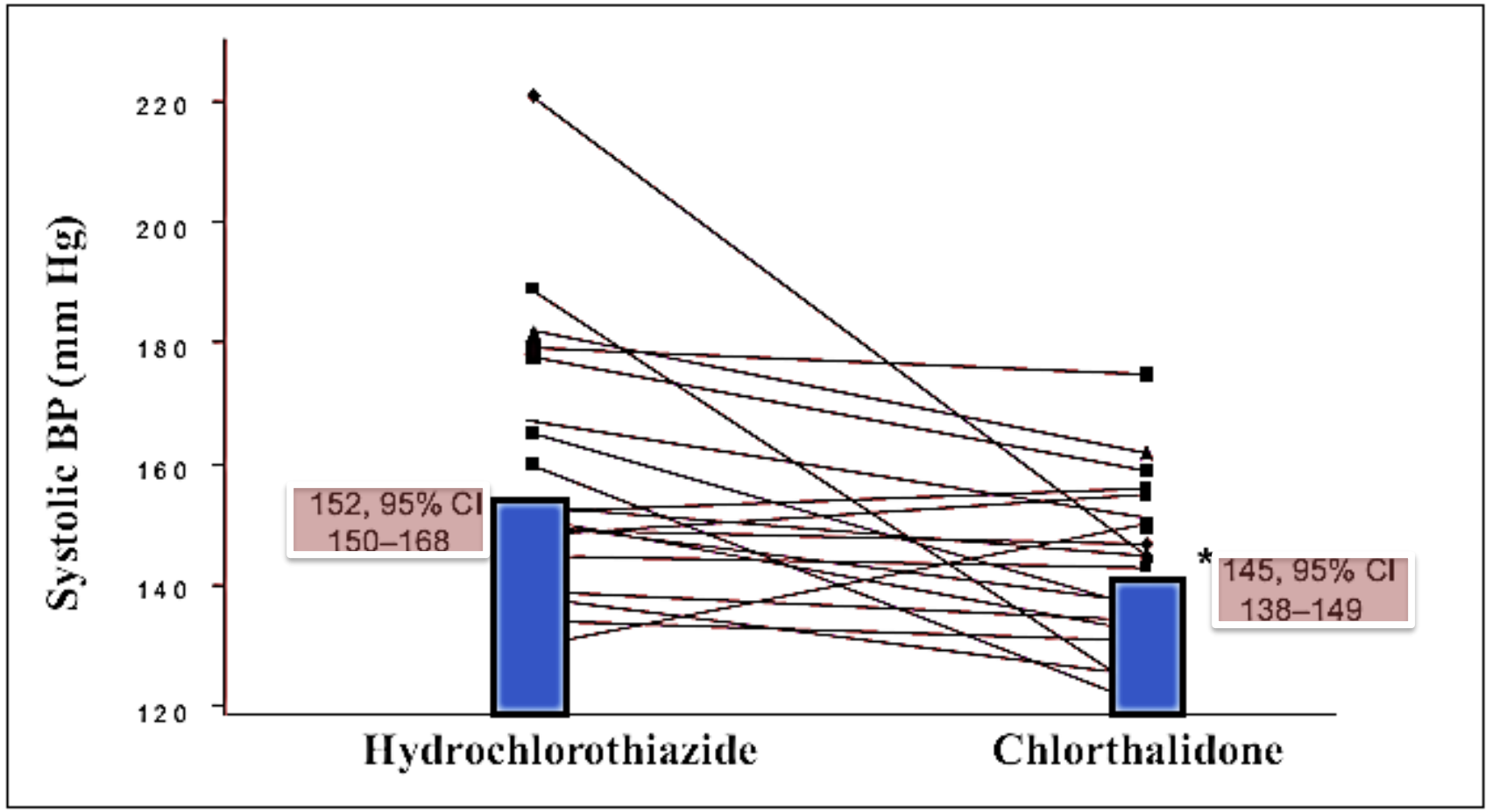


*Figure. Changes in median systolic blood pressure (BP) after 6–8 weeks in each of 19 patients on stable doses of hydrochlorothiazide who were changed to the same dose of chlorthalidone. CI=confidence interval; *p=0.035. Shaded boxes represent median value for each group.*

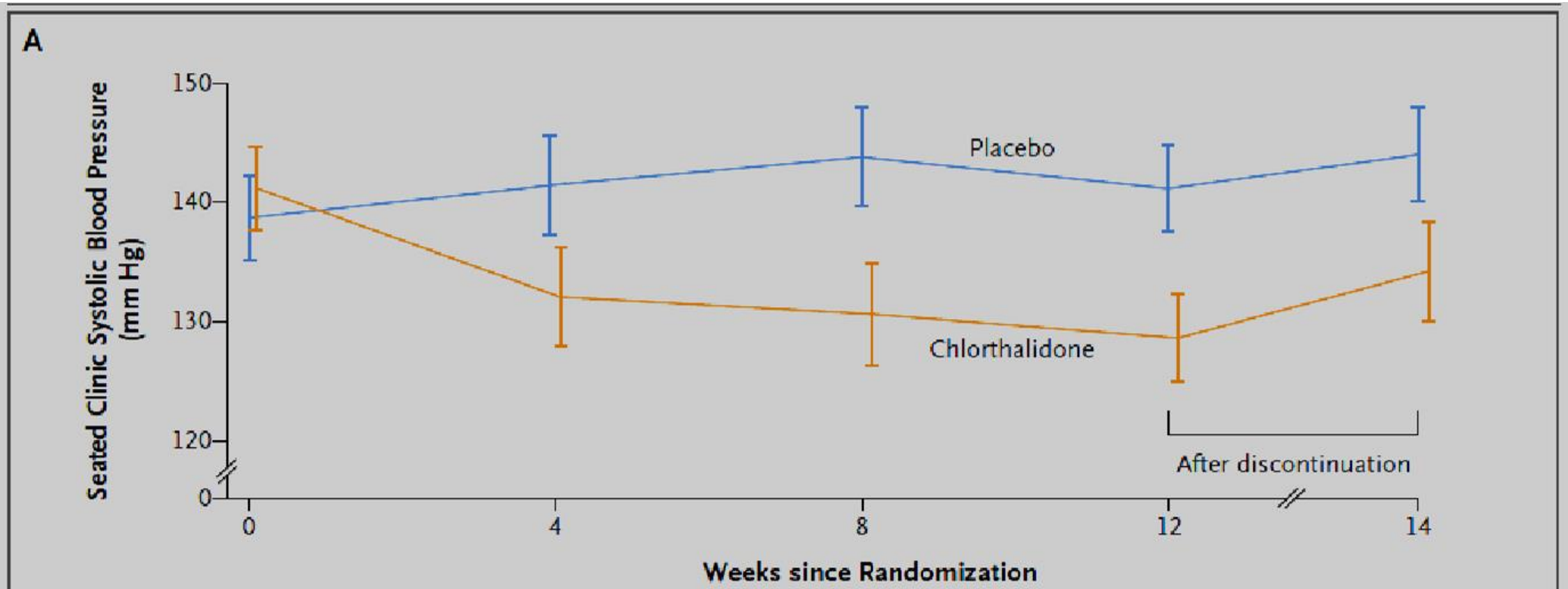
Khosla N et.al.J Clin Hypertens 2005;7:354-6.

Demographic Characteristics of The Chlorthalidone in Chronic Kidney Disease (CLICK) Trial: a Double-Blind Trial to Assess Chlorthalidone in Stage 4 CKD

Characteristic	Chlorthalidone (N=81)	Placebo (N=79)
Age — yr	66.2±10.8	66.7±10.8
Male sex — no. (%)	62 (77)	62 (78)
Race or ethnic group — no. (%)†		
White	46 (57)	47 (59)
Black	32 (40)	32 (41)
Asian	2 (2)	0
Hispanic	1 (1)	0
Medical history — no. (%)		
Diabetes mellitus	60 (74)	61 (77)
Systolic blood pressure — mm Hg	141.2±15.1	138.7±16.0
Diastolic blood pressure — mm Hg	69.2±12.3	67.9±13.9
Pulse rate — beats/min	66.5±11.7	64.3±11.1
Median spot urinary albumin-to-creatinine ratio (IQR)§	862 (187–2274)	812 (128–2022)
Urinary albumin-to-creatinine ratio category — no. (%)§		
<30	5 (6)	9 (11)
30 to <300	19 (23)	19 (24)
≥300	56 (69)	51 (65)
Estimated GFR — ml/min/1.73 m²	23.5±4.2	22.8±4.2
Median NT-proBNP (IQR) — pg/ml	545 (189–1342)	636 (274–1601)

Agarwal R, et.al. N Engl J Med 2021-online.

Systolic BP in Trial Groups Over Time



Mean Change from Baseline (95% CI) — mm Hg				
Placebo	2.7 (–0.9 to 6.3)	5.1 (1.4 to 8.8)	2.4 (–0.6 to 5.5)	5.3 (1.8 to 8.8)
Chlorthalidone	–9.2 (–12.9 to –5.5)	–10.6 (–14.5 to –6.8)	–12.6 (–15.8 to –9.5)	–7.0 (–10.7 to –3.3)
Difference	–11.9 (–17.1 to –6.7)	–15.7 (–21.0 to –10.5)	–15.1 (–19.4 to –10.7)	–12.3 (–17.5 to –7.2)

Agarwal R, et.al. N Engl J Med 2021-online.

ARBs – Are They All Created Equal?

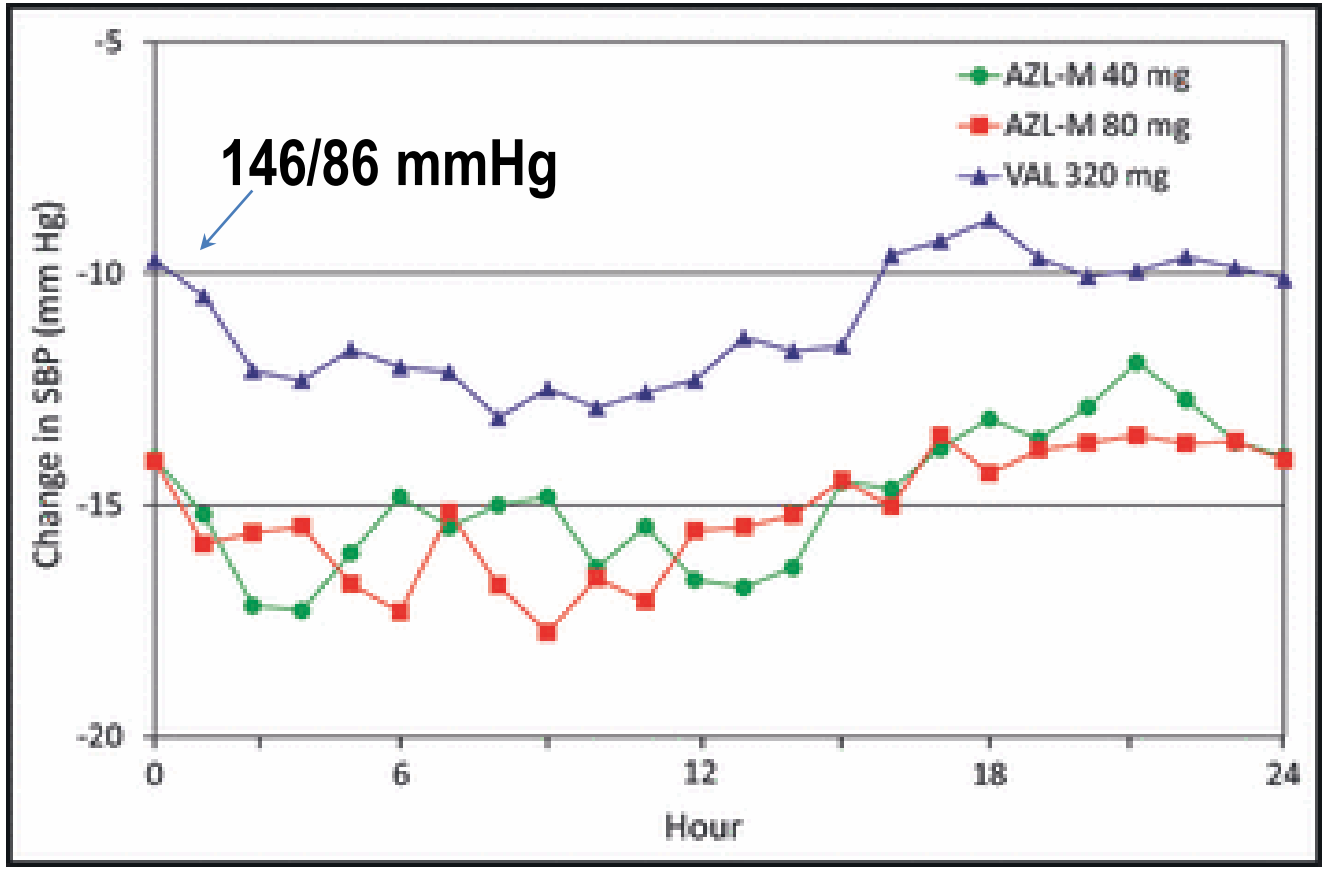
- Losartan#
- Valsartan#
- Irbesartan#
- Telmisartan^
- Olmesartan
- Candesartan
- Azilsartan**

FDA Indications

#Renal indication, CV risk reduction in heart failure, ^ alternative to ACE inhibitor for CV risk reduction

Comparison of the Novel Angiotensin II Receptor Blocker Azilsartan Medoxomil vs Valsartan by Ambulatory Blood Pressure Monitoring

N=984

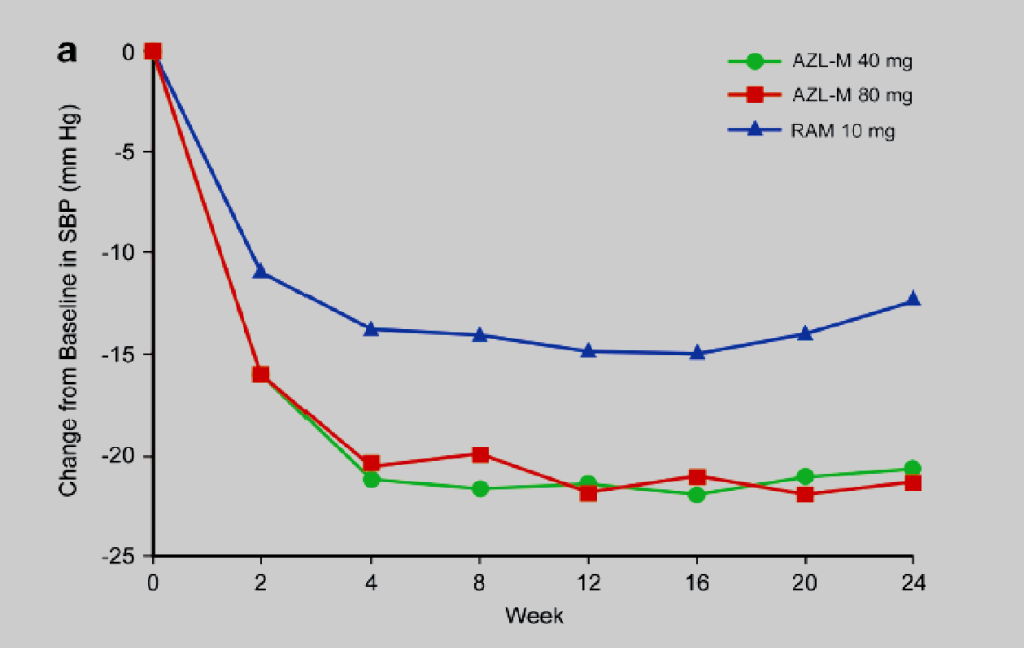


Sica D et.al. The Journal of Clinical Hypertension 2011;13, Issue 7, pages 467-472

Table 2. Baseline blood pressure and changes in clinic and ABPM of SBP/DBP after 24 weeks of treatment

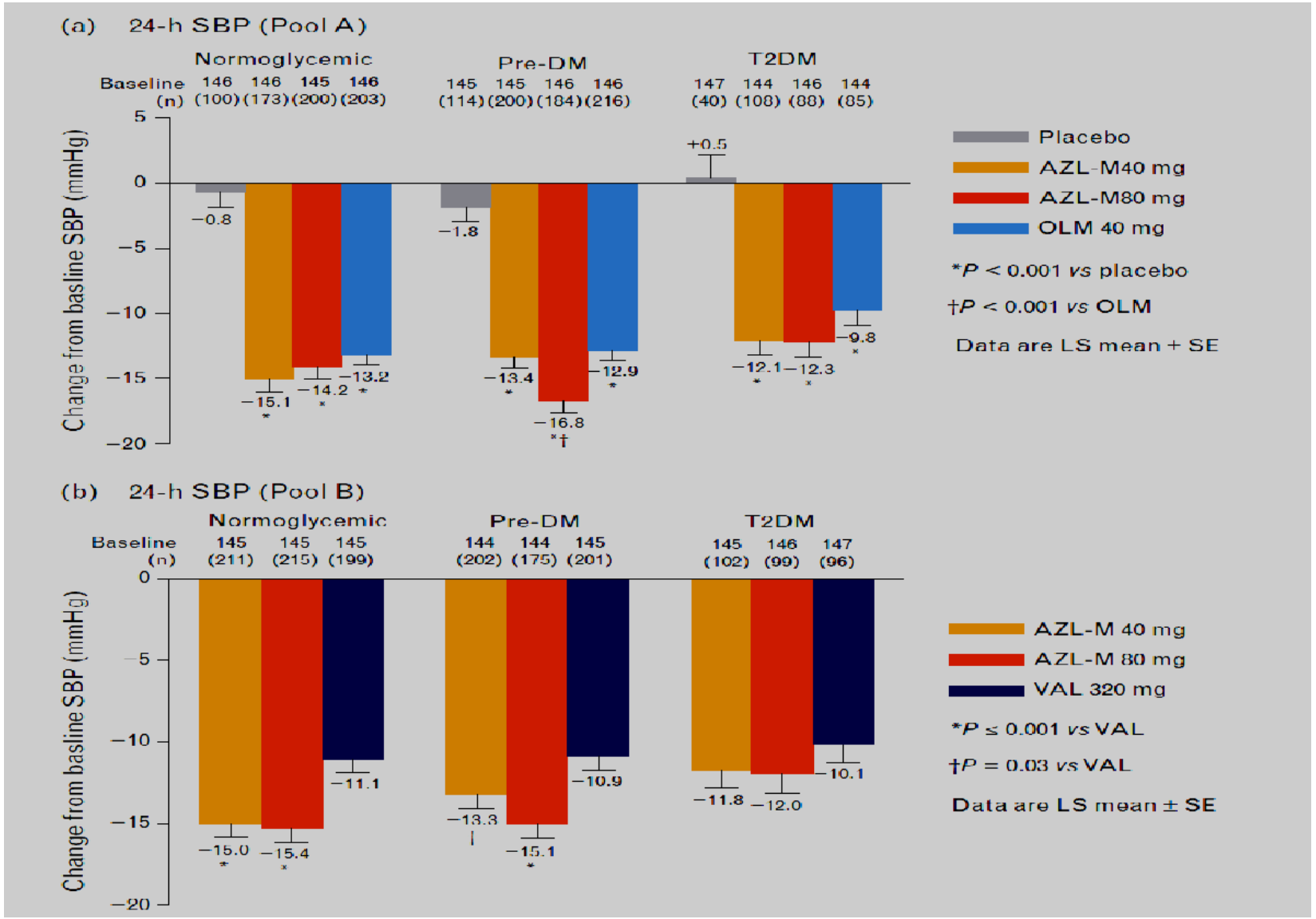
LS mean (s.e.)	*AZL-M 40*		*AZL-M 80*		*RAM 10*	
	SBP	*DBP*	*SBP*	*DBP*	*SBP*	*DBP*
Baseline clinic BP	160.9 ± 0.5	94.8 ± 0.5	161.5 ± 0.5	95.7 ± 0.5	161.4 ± 0.5	94.6 ± 0.5
Change from BL to week 24	− 20.6 ± 0.9	− 10.2 ± 0.6	− 21.2 ± 0.9	− 10.5 ± 0.6	− 12.2 ± 0.9	− 4.9 ± 0.6
Baseline 24-h mean ABPM	140.7 ± 1.0	86.4 ± 0.8	139.5 ± 1.0	86.0 ± 0.7	141.0 ± 1.0	86.7 ± 0.8
Change from BL to week 24						
24-h mean	− 12.7 ± 1.0	− 8.0 ± 0.7	− 12.3 ± 1.0	− 8.3 ± 0.6	− 7.8 ± 1.0	− 5.3 ± 0.7
Mean daytime (0600–2200 hours)	− 12.6 ± 1.0	− 8.2 ± 0.7	− 12.4 ± 1.0	− 8.5 ± 0.7	− 8.1 ± 1.1	− 5.6 ± 0.7
Mean nighttime (0000–0600 hours)	− 12.8 ± 1.1	− 7.4 ± 0.8	− 12.7 ± 1.1	− 8.2 ± 0.8	− 6.9 ± 1.1	− 4.4 ± 0.8
Mean trough (22–24 h)	− 15.6 ± 1.2	− 10.2 ± 0.9	− 14.9 ± 1.2	− 9.9 ± 0.9	− 6.7 ± 1.2	− 4.5 ± 0.9

Abbreviations: ABPM, ambulatory blood pressure monitoring; AZL-M, azilsartan medoxomil; BL, baseline; DBP, diastolic blood pressure; LS, least square; RAM, ramipril; SBP, systolic blood pressure. AZL-M vs RAM: $P<0.05$ for all comparisons.



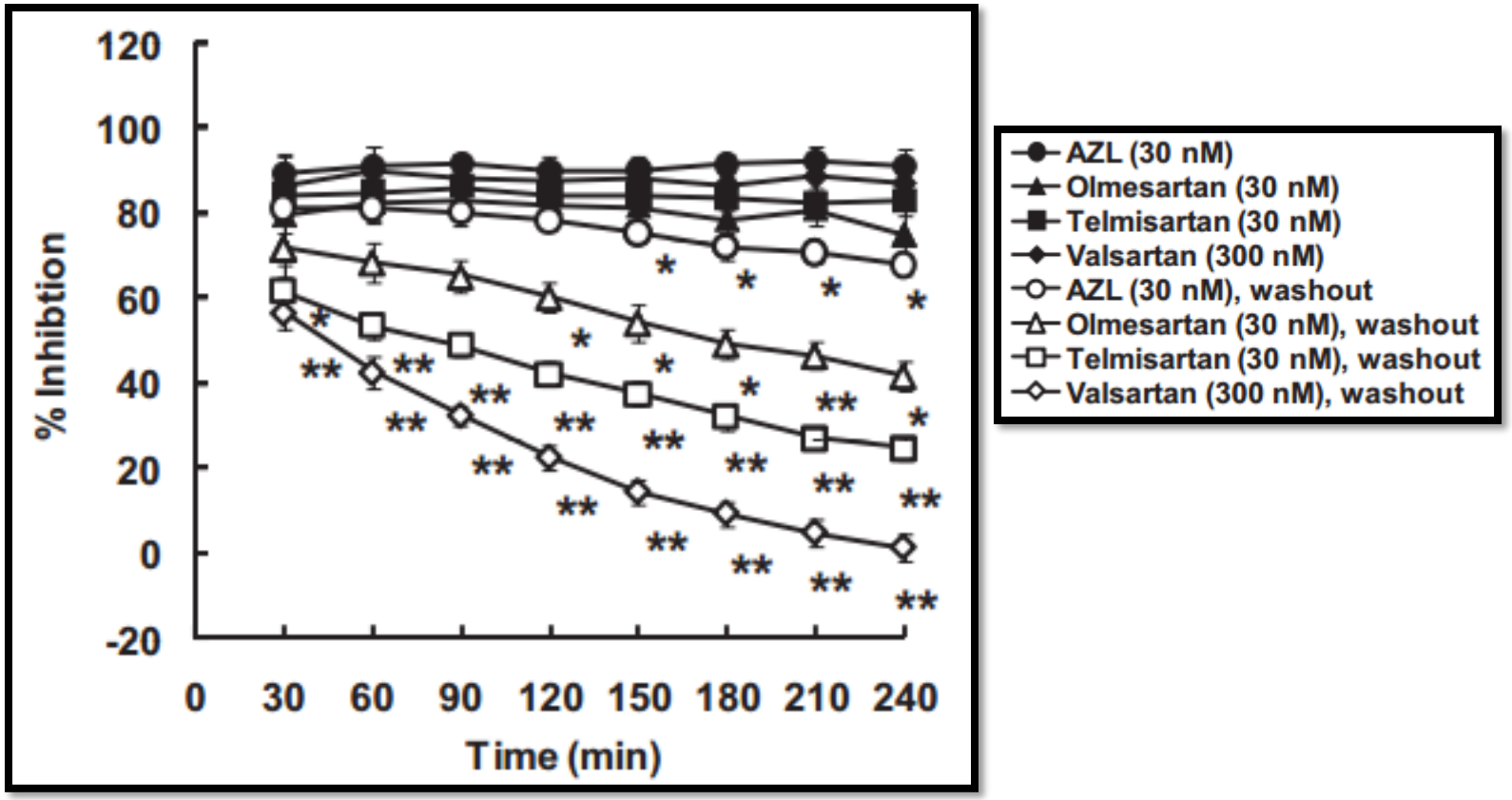
Bonner G, Bakris GL… et.al. and Kupfer S J Hum Hypertens 2013;27:479-486

Changes from Baseline in ABPM



White WB,et.al J Hypertens., 2016-online

Time Course of Dissociation of Azilsartan from AT1 Receptors



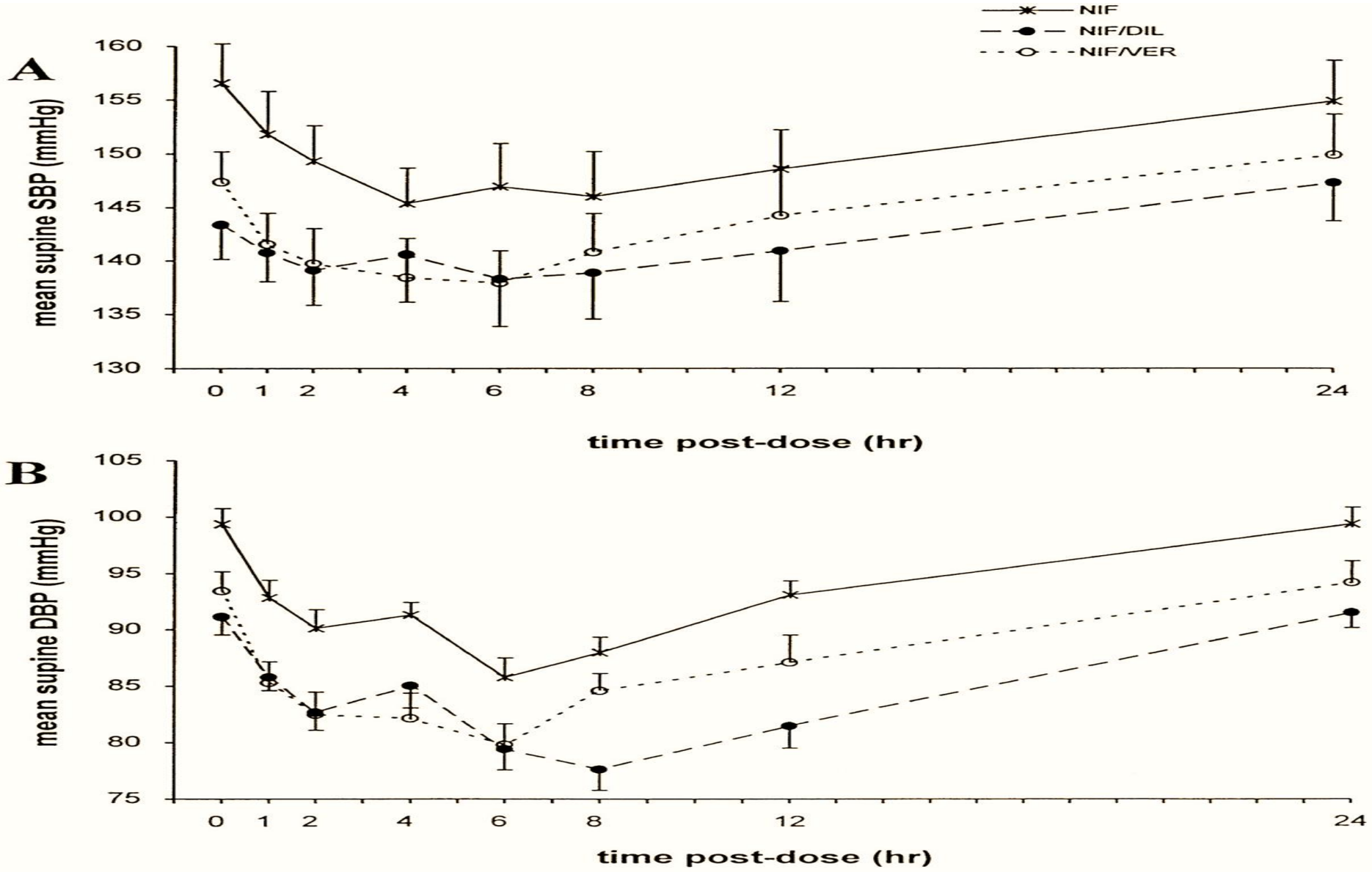
Time course of dissociation of AZL, olmesartan, telmisartan, and Valsartan from human AT_1 receptors in radioligand binding studies on human AT_1 Receptors

Slow dissociation of Azilsartan from AT_1 receptors than other ARBs including olmesartan, telmisartan, and Valsartan

Ojima M et.al. JPET 2011;336:801–808

Combining DHP and Non DHP CCBs: Effect on BP

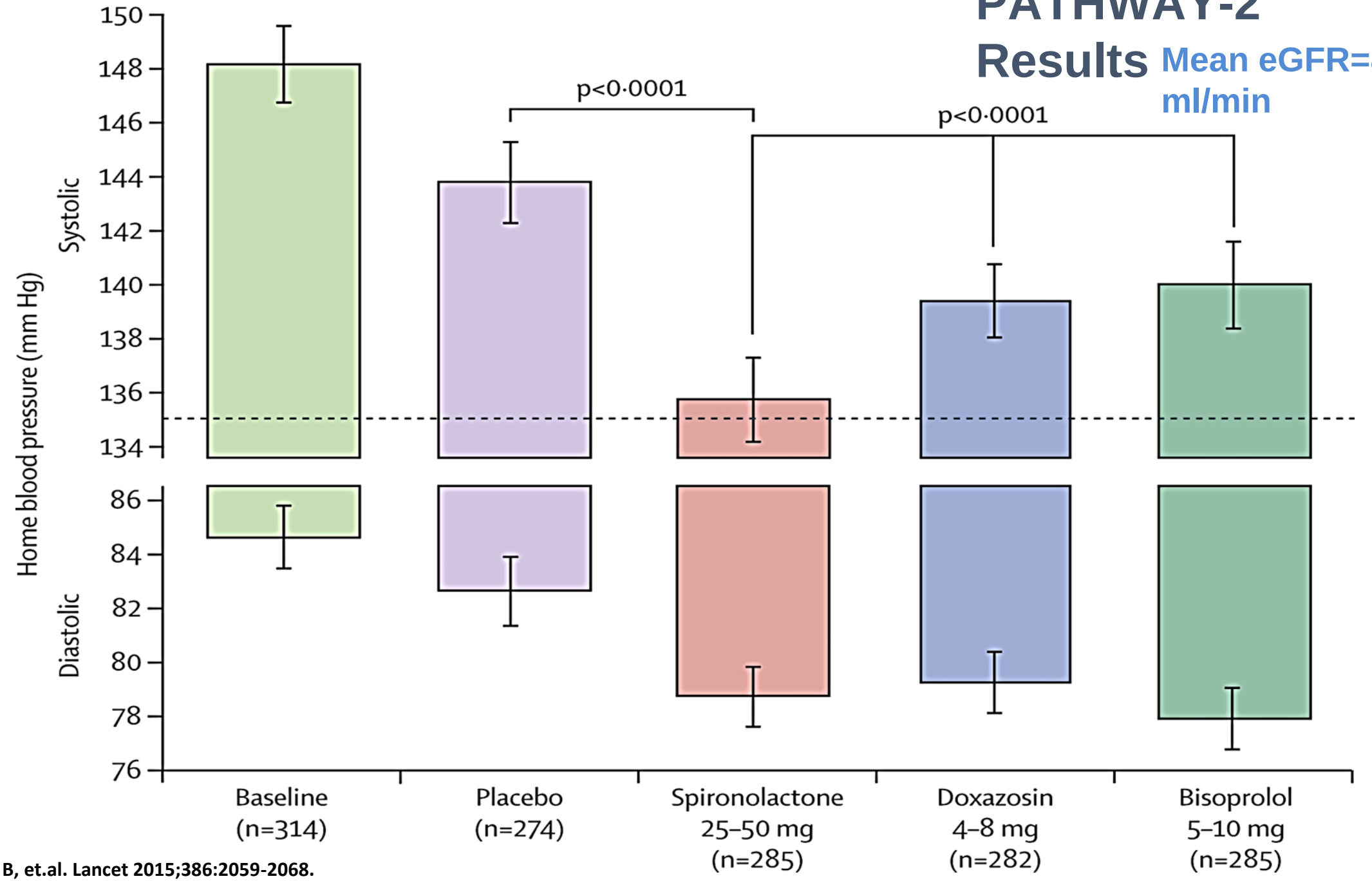
Mean SBP (A) and mean DBP (B) versus time after steady-state oral dosing with nifedipine (NIF) alone, NIF/DIL, and NIF/VER.



Saseen J et.al. Hypertension 1996;28:109-114

PATHWAY-2 Results

Mean eGFR=82 ml/min



Williams B, et.al. Lancet 2015;386:2059-2068.

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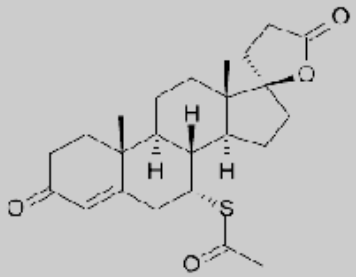
Future Drug Development in Resistant Hypertension

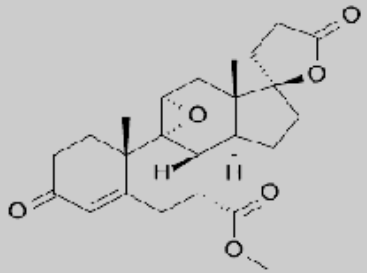
George L. Bakris, MD, FAHA, FASN
Professor of Medicine
Director, Am Heart Assoc. Comprehensive Hypertension Center
The University of Chicago Medicine
Chicago, Illinois USA

Two different classes of agents that inhibit the MR

Steroidal MRAs (Aldosterone Antagonists)

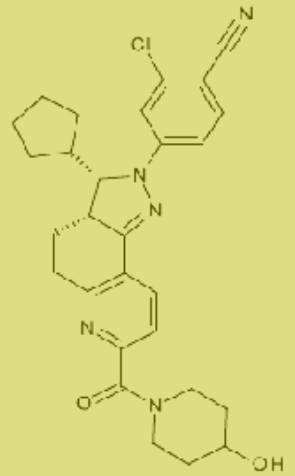


Spironolactone

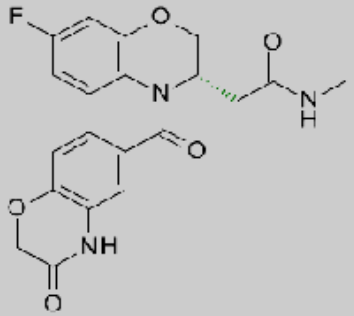


Eplerenone

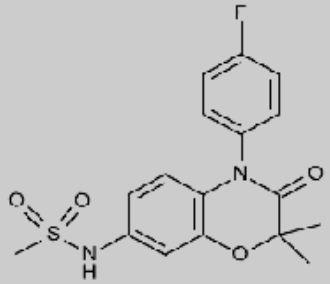
Nonsteroidal MRAs



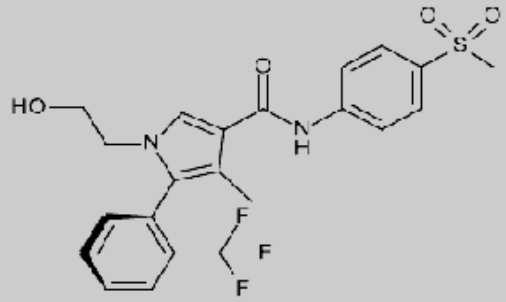
KBP-5074
(Phase II)



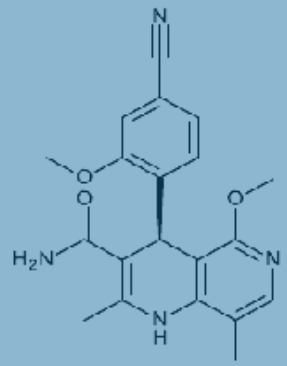
AZD9977
(Phase II)



Apararenone
MT-3995
(Phase II)



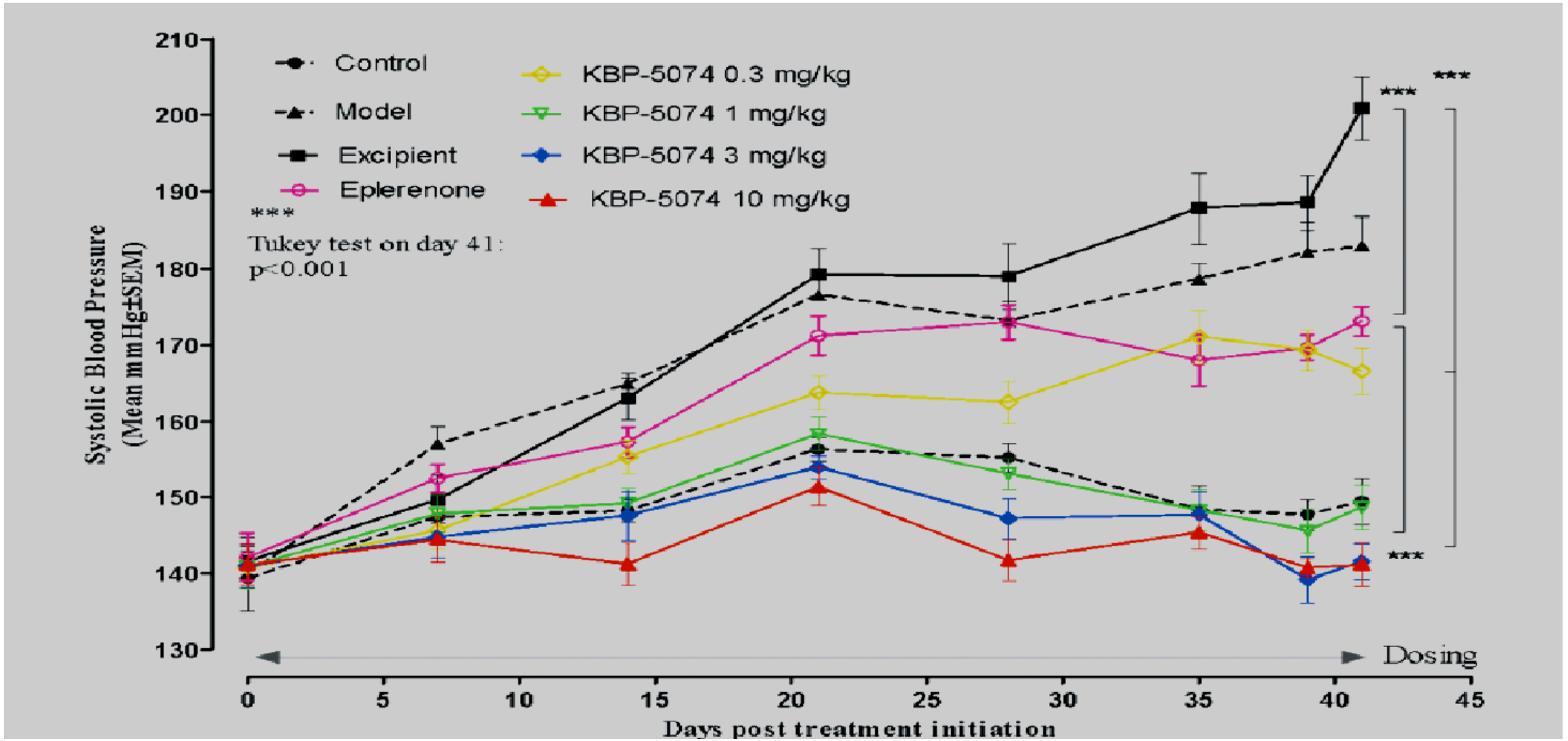
Esaxerenone
CS-3150
(launched in Japan)



Finerenone
BAY 94-8862
(launched in the U.S.)

Kintscher U, Bakris GL, and Kolkhof P. Br J Pharmacol 2021, in press

KBP-5074 Effect on Systolic Blood Pressure in a Pre-clinical Rodent Model



Pitt B et.al. EXPERT OPINION ON INVESTIGATIONAL DRUGS 2021, VOL. 30, NO. 10, 1017–1023

BLOCK-CKD Eligibility Criteria

			Albuminuria categories (mg albumin/g creatinine)		
			A1 Normal to mildly elevated	**A2** Moderately elevated	**A3** Severely elevated
			0-29	**30-299**	**≥300-4999**
GFR categories (mL/min/1.73 m²)	**G1**	**>90**			
	G2	**60–89**			
	G3a	**45–59**			
	G3b	**30–44**			
	G4	**15–29**			
	G5	**<15**			

Key inclusion criteria*

- Stage 3b/4 CKD: eGFR 15-44
- Aged 18-85 and uncontrolled HTN
- SBP 140-179 mm Hg despite on 2+ anti-HTN medication
- Serum potassium ≤4.8 mmol/L

Key exclusion criteria

- Current MRA therapy
- Resting trough-cuff seated SBP ≥ 180 or < 140 mmHg
- Serum potassium > 4.8 mmol/L
- Chronic or intermittent potassium binders

* This study population cannot receive spironolactone or eplerenone due to contra-indications in the package insert

Bakris G et.al. Hypertension 2020, 76.1: 144-149

BLOCK-CKD Study Design

465 patients screened

Screen (4 weeks)

Run-in (2 weeks)

162 patients randomized

R

- Placebo daily (12 weeks N=57)
- KBP-5074 0.25 mg daily (12 weeks N=51)
- KBP-5074 0.5 mg daily (12 weeks N=54)

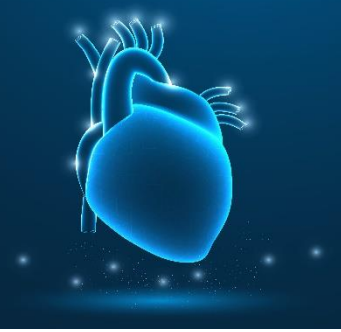
138 patients completed

Follow up (4 weeks)

Endpoints

Primary SBP

Reduction of SBP from baseline



Secondary: DBP /UACR

Reduction of DBP
Reduction of UACR

Safety

- AE/SAE
- eGFR/Potassium

Bakris G et.al. Hypertension 2020, 76.1: 144-149

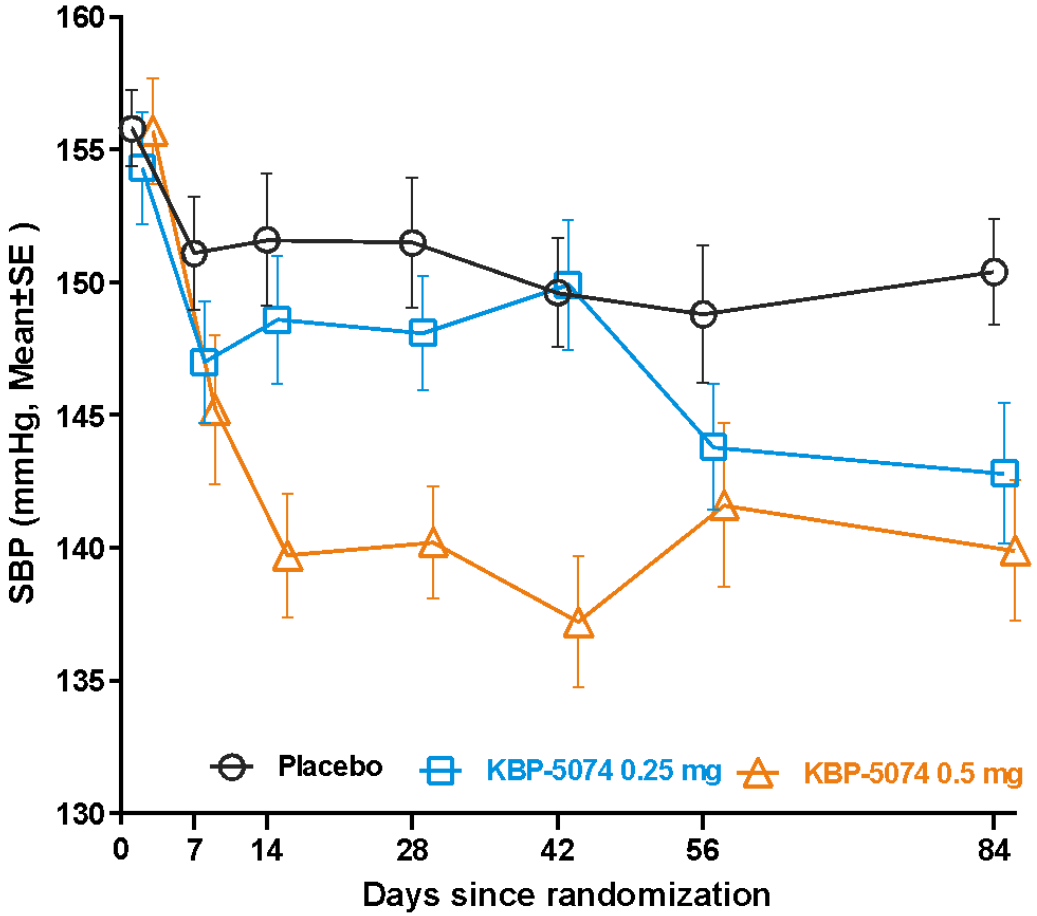
Baseline Characteristics

	Placebo N=57	KBP 5074 0.25 mg N=51	KBP 5074 0.5 mg N=54	Overall N=162
Age: mean (SD)	65.9 (10.64)	65.4 (10.76)	64.8 (13.04)	65.4 (11.47)
Gender: n (%) • Female • Male	 23 (40.4) 34 (59.6)	 27 (52.9) 24 (47.1)	 23 (42.6) 31 (57.4)	 73 (45.1) 89 (54.9)
SBP (mmHg): mean (SD)	155.8 (10.84)	154.3 (15.07)	155.7 (14.75)	155.3 (13.55)
DBP (mmHg): mean (SD)	85.9 (11.46)	89.0 (12.17)	88.4 (13.06)	87.7 (12.23)
UACR (mg/g): n (%) • Macroalbuminuria (>300) • Microalbuminuria (30-300) • Other (<30)	 29 (50.9) 15 (26.3) 11 (19.3)	 27 (52.9) 9 (17.6) 15 (29.4)	 28 (51.9) 17 (31.5) 9 (16.7)	 84 (51.9) 41 (25.3) 35 (21.6)
eGFR at randomization (mL/min/1.73 m^2) mean (SD)	31.6 (9.60)	31.9 (10.47)	32.2 (9.84)	**31.9 (9.90)**
• Stage 3b (30-44) • **Stage 4 (15-29)**	32 (56.1) **25 (43.9)**	31 (60.8) **20 (39.2)**	36 (66.7) **18 (33.3)**	99 (61.1) **63 (38.9)**
Potassium, central (mmol/L): mean (SD)	4.43 (0.359)	4.33 (0.384)	4.37 (0.443)	4.38 (0.396)
Background HTN medication: n (%) • Less than 3	 6 (10.5)	 7 (13.7)	 5 (9.3)	 18 (11.1)
• **3 or more**	**51 (89.5)**	**44 (86.3)**	**49 (90.7)**	**144 (88.9)**

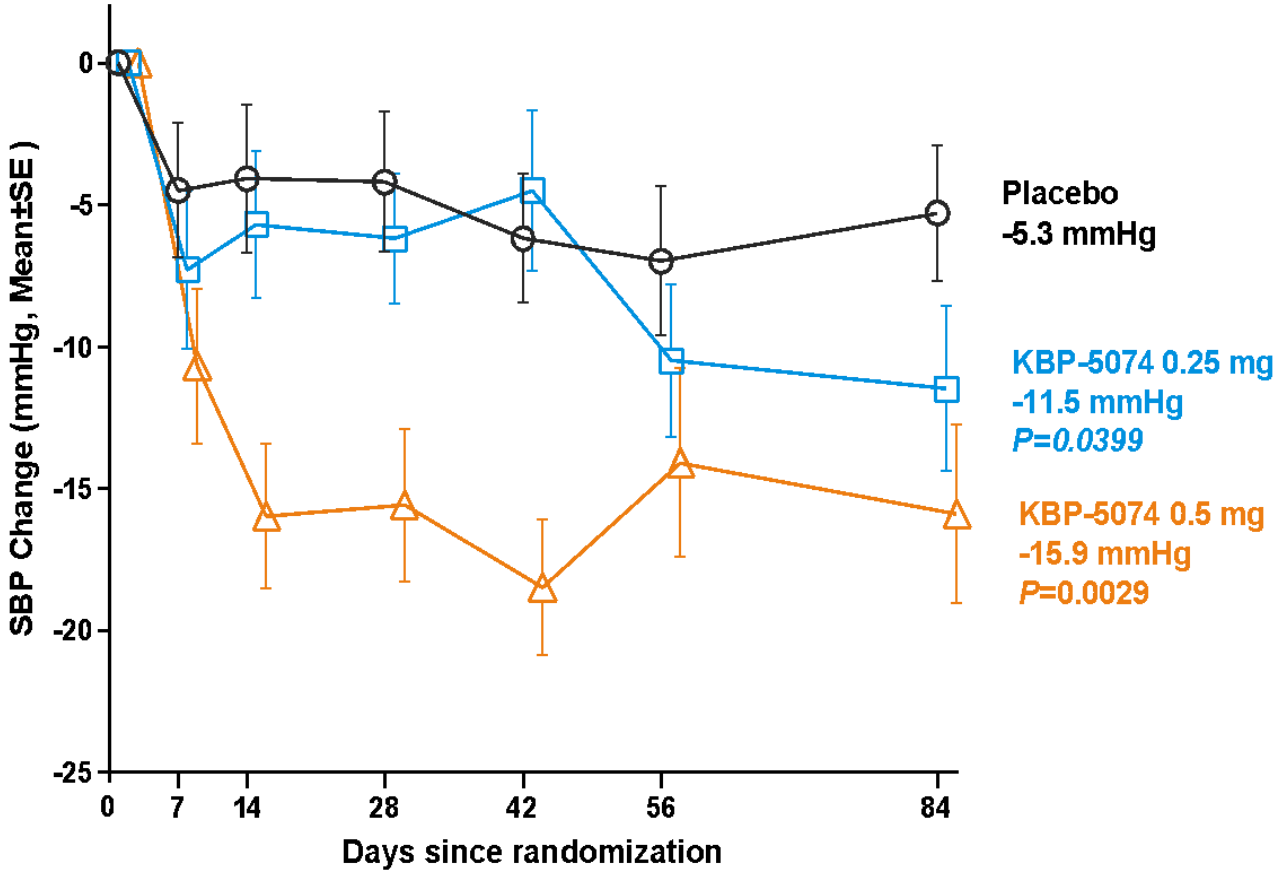
Bakris G et.al. Hypertension 2020, 76.1: 144-149

Primary Endpoint: SBP Change From Baseline: ITT/LOCF

SBP value over time by treatment



SBP Change from baseline over time by treatment



Bakris GL et.al. Hypertension. 2020;76: 144 –149

Investigator-Reported Treatment-Emergent Adverse Events

Safety outcome, n (%)	Placebo N=57	KBP 5074 0.25 mg N=51	KBP 5074 0.5 mg N=54	Overall N=162
Completed Study	47 *(82.5%)*	47 *(92.5%)*	44 *(81.5%)*	138 *(85.2%)*
Early Termination	10 *(17.5%)*	4 *(7.8%)*	10 *(18.5%)*	24 *(14.8%)*
• Serious AE* related to study drug	0	0	0	0
• Hospitalizations due to Hyperkalemia	0	0	0	0
• Acute Kidney Injury (AKI)	0	0	0	0
Reasons leading to treatment discontinuation				
Hyperkalemia	2 *(3.5%)*	0 *(0%)*	2 *(3.7%)*	4 *(2.5%)*
Other (Withdrawal by Subject, Other Adverse Events)	8 *(14.0%)*	4 *(7.8%)*	8 *(14.8%)*	20 *(12.3%)*

* AE, adverse event

Bakris GL et.al. Hypertension. 2020;76: 144 –149

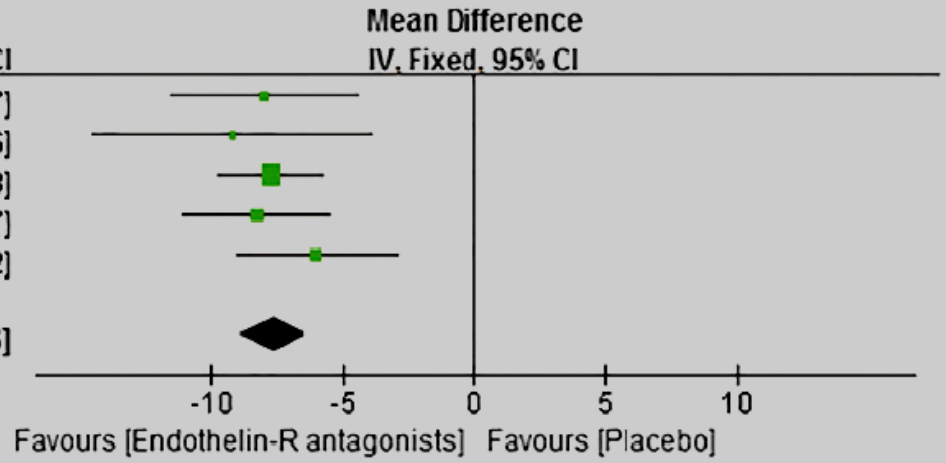
Effects of endothelin receptor antagonists on systolic and diastolic ambulatory blood pressure versus placebo

24-hours SBP

Study or Subgroup	Endothelin-R antagonists Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bakris 2010	-10	19.08	364	-2	16.43	120	13.4%	-8.00 [-11.53, -4.47]
Black 2007	-9.2	13.82	76	0	13.82	39	5.9%	-9.20 [-14.54, -3.86]
Krum 1998	-8.44	6.85	194	-0.7	6.3	49	41.4%	-7.74 [-9.75, -5.73]
Weber 2009	-9.37	13.39	247	-1.1	13.21	132	21.3%	-8.27 [-11.07, -5.47]
Zeeuw 2014	-6.97	9.38	161	-1	9.67	50	18.0%	-5.97 [-9.02, -2.92]
Total (95% CI)			**1042**			**390**	**100.0%**	**-7.65 [-8.95, -6.36]**

Heterogeneity: $Chi^2 = 1.73$, $df = 4$ ($P = 0.79$); $I^2 = 0\%$

Test for overall effect: $Z = 11.60$ ($P < 0.00001$)

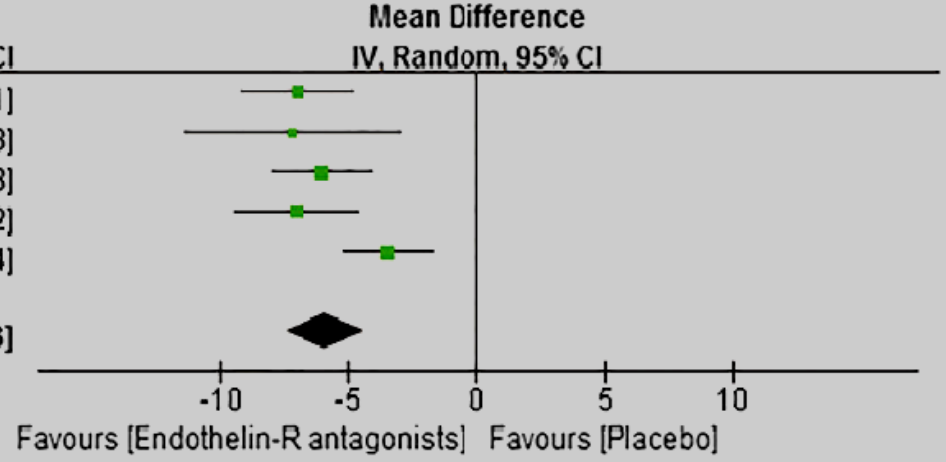


24-hours DBP

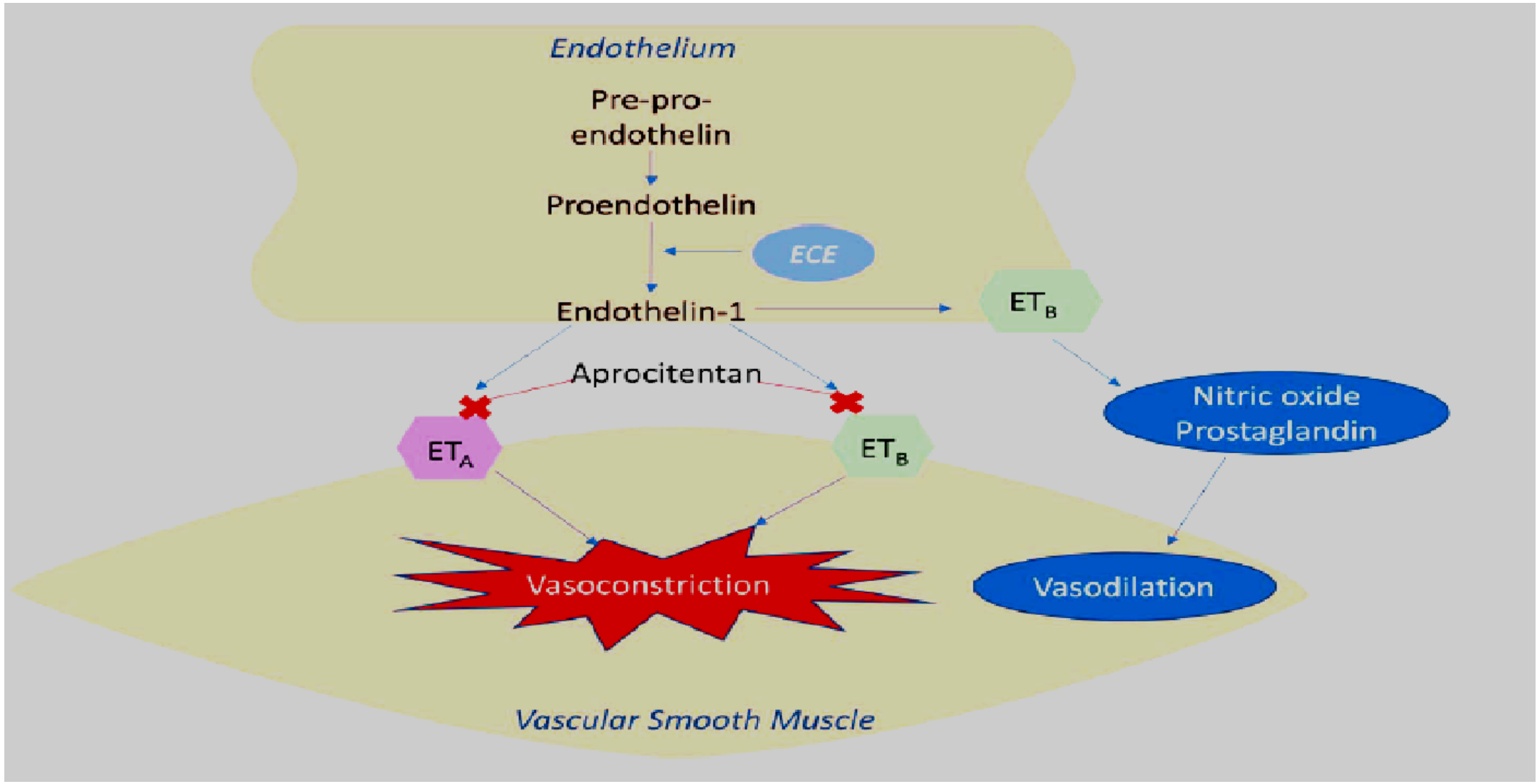
Study or Subgroup	Endothelin-R antagonists Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bakris 2010	-8	19.08	364	-1	5.48	120	21.4%	-7.00 [-9.19, -4.81]
Black 2007	-7.2	10.81	76	0	10.81	39	10.3%	-7.20 [-11.37, -3.03]
Krum 1998	-6.65	6.19	194	-0.6	6.3	49	23.3%	-6.05 [-8.02, -4.08]
Weber 2009	-7.63	11.21	247	-0.6	11.48	132	19.8%	-7.03 [-9.44, -4.62]
Zeeuw 2014	-4.48	5.58	161	-1	5.46	50	25.2%	-3.48 [-5.22, -1.74]
Total (95% CI)			**1042**			**390**	**100.0%**	**-5.92 [-7.50, -4.33]**

Heterogeneity: $Tau^2 = 1.79$; $Chi^2 = 9.37$, $df = 4$ ($P = 0.05$); $I^2 = 57\%$

Test for overall effect: $Z = 7.33$ ($P < 0.00001$)

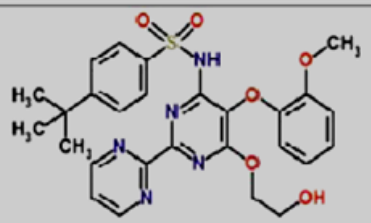
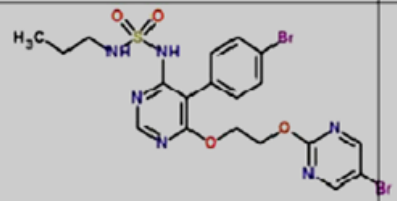
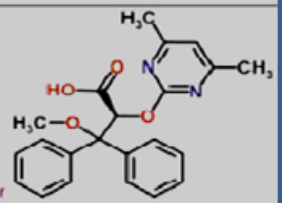
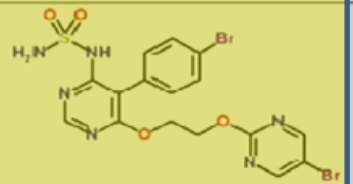
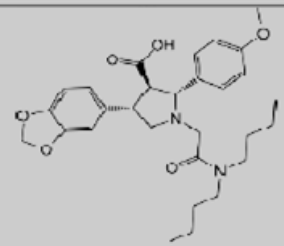
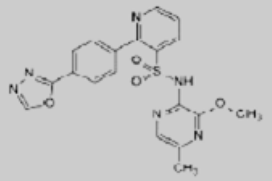


Aprocitentan is a dual endothelin-receptor antagonist (ERA), with a 1:16 inhibitory ratio of ETA:ETB



McCoy EK et.al. J Cardiovasc Pharmacol 2021;77:699–706

Pharmacological characteristics of endothelin receptor antagonists on the market or still under investigations.

	Bosentan	Macitentan	Ambrisentan	Aprocitentan (ACT-132577)	Atrasentan	Zibotentan
Structure						
Official or target indication	PAH	PAH	PAH	Resistant hypertension	Diabetic nephropathy	Sclerodermia
Time to max concentration (hours)	3-5	4-12	1.7-3.3	30	0.8	1
Terminal half life (hours)	5.4	16	15	40.2-65.6	26.4	8.17
Excretion in urine (%)	<3%	50%	low	Not detected	<10%	93
ET_A selectivity	20	782	616	61	>1000	>1000

Burnier M Current Hypertension Reports (2018) 20: 51

PRECISION trial (ClinicalTrials.gov Identifier: NCT03541174)

Purpose: Evaluate blood pressure-lowering effect of ***aprocitentan*** (dual ETA/ETB) blockers when added to other antihypertensive drugs of patients with resistant hypertension

Design Multicenter, blinded, placebo run in, randomized, parallel-group, phase 3 study

Allocation: It has 3 parts: **Part 1**: double-blind, randomized to aprocitentan 12.5 mg, aprocitentan 25 mg or placebo **Part 2**: single blind aprocitentan 25 mg **Part 3:** double-blind re-randomized to aprocitentan 25 mg or placebo Masking: triple (participant, care provider, investigator)

Estimated enrollment 600 participants treated with at least 3 antihypertensive therapies of different pharmacological classes for at least 4 weeks before the screening visit

Primary outcome -***Change from baseline to week 4 of double-blind treatment in trough sitting systolic blood pressure***

https://clinicaltrials.gov/ct2/show/NCT03541174

MANAGEMENT OF RESISTANT HYPERTENSION

Exclude other causes of hypertension, including secondary causes, white-coat effect and medication nonadherence

+

Ensure low sodium diet (<2400 mg/day)
Maximize lifestyle interventions
- ≥ 6 hrs uninterrupted sleep
- Overall dietary pattern
-Weight loss
-Exercise

+

Optimize 3-drug regimen
Ensure adherence to 3 of different classes (RAS blocker, CCB, diuretic) at maximum or maximally tolerated doses. Diuretic type must be appropriate for kidney function*

BP not at target

Step 2

Substitute optimally dosed thiazide-like diuretic: i.e. chlorthalidone or indapamide* for the prior diuretic

BP not at target

Step 3

Add mineralocorticoid receptor antagonist (MRA): spironolactone or eplerenone**

BP still not at target

Step 4

Note: Steps 4-6 are suggestions on the basis of expert opinion only and these steps should be individualized.

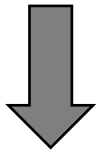
Check Heart Rate: Unless <70 beats/ min, **add beta blocker** (eg. metoprolol succinate, bisoprolol) or combined alpha-beta blocker (eg. labetalol, carvedilol). If beta blocker contradicted, consider central alpha-agonist i.e. clonidine patch weekly or guanfacine at bedtime). If these are not tolerated, consider once daily diltiazem.

BP still not at target

Step 5

Add hydralazine* ** 25mg three times daily and titrate upward to max dose; in patients with congestive heart failure with reduced ejection fraction, hydralazine should be administered on a background isosorbide mononitrate 30 mg daily (max. dose 90 mg daily)

BP still not at target



Step 6

Substitute minoxidil**** 2.5mg two to three times daily for hydralazine and titrate upward. If BP still not at target, consider referral to a hypertension specialist and/or for ongoing experimental studies- www.clinicaltrials.gov

- * These diuretics maintain efficacy down to estimated glomerular filtrations rates of 30ml/min/1/73m^2
- ** Use caution if eGFR<30 ml/min/1.73m2
- *** Require concomitant use of beta blocker and a diuretic
- **** Require the concomitant use of a beta blocker and a loop diuretic

Carey RM, et.al. Hypertension 2018;72:e53-e90.

Alternative Nonpharmacologic Therapies

- Renal Denervation

Approved in parts of Europe

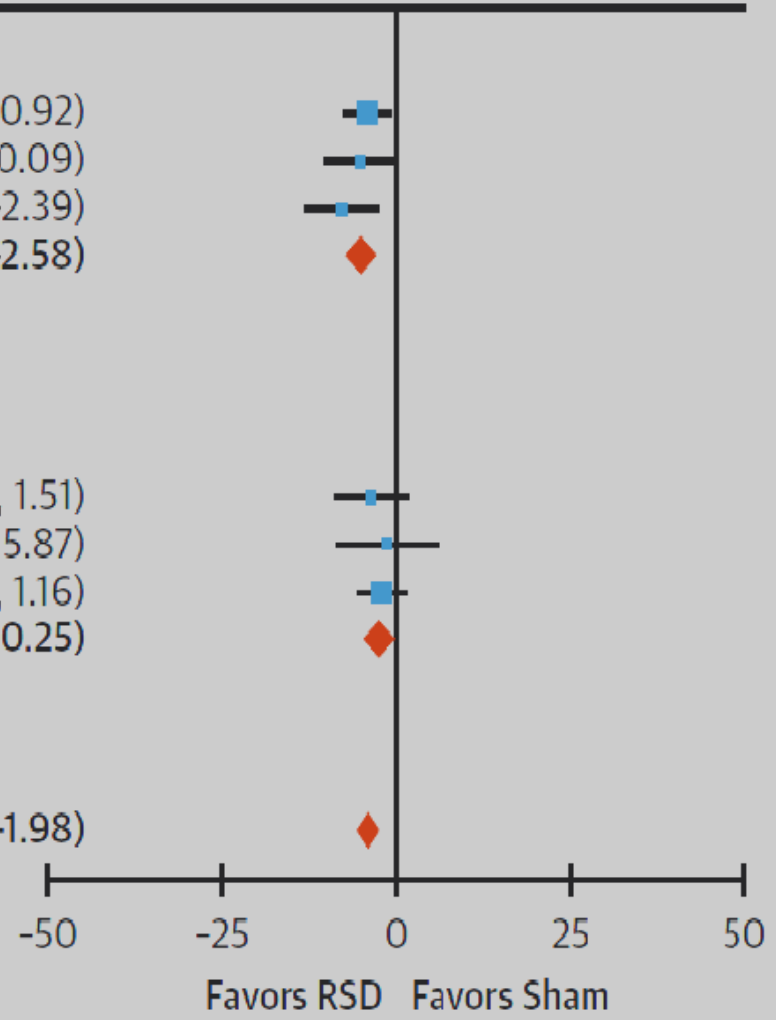
- Baroreceptor Activation

Approved for Heart Failure in parts of Europe

24-h Ambulatory Systolic Blood Pressure Changes With RSD Versus Sham-Controlled Group

A

Study or Subgroup	RSD Mean	RSD SD	RSD Total	Sham Mean	Sham SD	Sham Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 Second Generation Trials								
RADIANCE-HTN SOLO	-7	8.6	74	-3.1	9.7	72	31.6%	-3.90 (-6.88, -0.92)
SPYRAL HTN-OFF MED	-5.5	10.7	35	-0.5	10.4	36	11.6%	-5.00 (-9.91, -0.09)
SPYRAL HTN-ON MED	-9	11	36	-1.6	10.7	36	11.1%	-7.40 (-12.41, -2.39)
Subtotal (95% CI)			**145**			**144**	**54.3%**	**-4.85 (-7.12, -2.58)**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.39$, df = 2 (P = 0.50); $I^2 = 0\%$								
Test for overall effect: Z = 4.19 (P < 0.0001)								
1.1.2 First Generation Trials								
Desch et al	-7	11	32	-3.5	9.8	35	11.2%	-3.50 (-8.51, 1.51)
ReSET	-3.7	16.4	35	-2.6	12.8	33	5.8%	-1.10 (-8.07, 5.87)
SYMPLICITY HTN-3	-6.75	15.11	329	-4.79	17.25	162	28.8%	-1.96 (-5.08, 1.16)
Subtotal (95% CI)			**396**			**230**	**45.7%**	**-2.23 (-4.70, 0.25)**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.38$, df = 2 (P = 0.83); $I^2 = 0\%$								
Test for overall effect: Z = 1.76 (P = 0.08)								
Total (95% CI)			**541**			**374**	**100.0%**	**-3.65 (-5.33, -1.98)**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.11$, df = 5 (P = 0.53); $I^2 = 0\%$								
Test for overall effect: Z = 4.28 (P < 0.0001)								
Test for subgroup differences: $Chi^2 = 2.35$, df = 1 (P = 0.13); $I^2 = 57.4\%$								



Sarder et.al. JACC 2019;73:1633 – 42

Summary

- Updated Hypertension Guidelines continue to emphasize **combination therapy** and **adherence with drugs and lifestyle**.

- For now, Think of spironolactone as 4th drug after diuretics, CCB and RAS blocker in people with eGFR above 45 ml/min /1.73m^2 who are at lower risk of hyperkalemia.

- Remember there is a range of efficacy **within certain drug classes**