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Ohio Cardiovascular Health Collaborative

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Cardi-OH ECHO - Hypertension

Thursday, March 28, 2019

Disclosure Statements

The following planners, speakers, moderators, and/or panelists of the CME activity have financial relationships with commercial interests to disclose:

- Adam T. Perzynski, PhD reports being co-founder of Global Health Metrics LLC, a Cleveland-based software company and royalty agreements for forthcoming books with Springer publishing and Taylor Francis publishing.
- Siran M. Koroukian, PhD reports ownership interests in American Renal Associates, and Research Investigator subcontract support from Celgene Corporation.
- George L. Bakris, MD reports partial salary from Bayer as FIDELIO PI, partial salary from Janssen as CREDENCE Steering Committee, partial salary from Vascular Dynamics as Calm-2 Steering Committee, and receiving honorarium as a consultant to Merck, NovoNordisk.
- These financial relationships are outside the presented work.

All other planners, speakers, moderators, and/or panelists of the CME activity have no financial relationships with commercial interests to disclose.

Update on Resistant Hypertension

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University of Chicago Medicine

Chicago, Illinois

High Points of Discussion

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- New Definitions of Resistant Hypertension
- What is the appropriate work up and evaluation
- Trials of different medication combinations, and focus on Lifestyle Modification as base therapy for all
- When to refer? Who to refer to?
- How to get appropriate medications.

Updated Definition of Resistant Hypertension

- Failure to reach goal BP (<130/80 mm Hg for the overall population)
- Despite adhering to full doses of an appropriate *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 B et.al. Hypertension 2018;72:e53-e90)

Not All Refractory Hypertension is True Treatment-Resistant Hypertension

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- Not all patients who fail to respond to antihypertensive therapy have true treatment-resistant hypertension
- Long-term outcomes vary substantially among the various subtypes of refractory hypertension
- Optimal treatment modalities and approach to management vary among subtypes

Secondary Hypertension[1]	Pseudoresistance[1,2]	Masked Hypertension[2]	White coat hypertension[2]	True treatment-resistant hypertension*[3]
Hypertension elicited or exacerbated by other drugs or diseases	**Apparent hypertension due to lack of adherence, poor BP measurement technique**	Clinic BP <140/90 mm Hg; daytime BP >135 or >85 mm Hg	Clinic BP ≥140 or ≥90 mm Hg; daytime BP <135/85 mm Hg	BP ≥140/90 mm Hg despite adequate doses of ≥3 drugs (including diuretic) after exclusion of spurious hypertension

*European Society of Hypertension definition
BP=blood pressure.
1. Calhoun DA et al. *Circulation.* 2008;117:e510-526; 2. Pierdomenico SD et al. *Am J Hypertens.* 2005;18:1422-1428; 3. Mancia G et al. *J Hypertens*. 2007;25:1751-1762.

Specific Clinical Issues Associated with Treatment Resistance

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Issue Associated with Treatment Resistance	Management Consideration(s)
Volume control – edema resolution	Thiazide → Chlorthalidone → Loop diuretic
Heart rate control inadequate	β-, α,β-blocker, verapamil, diltiazem
Renin and aldosterone levels low	Low salt diet, avoid nighttime shift work, amiloride
Renin low, aldosterone normal-high normal	Mineralocorticoid receptor antagonist
Might split-dosing of medications improve control?	Evaluate BP pattern according to home and ambulatory BP monitoring.
Medication adherence questionable	Initiate indirect and/or direct methods to detect nonadherence; if nonadherence documented (partial or complete), discuss frankly, nonjudgmentally with patient and family.
Pattern of BP response to medications outside clinician visit times unknown	Identify meal effects on BP, duration of medication effect, relationship of BP to side-effects using out-of-office BP monitoring.
Sleep disordered breathing; significant anxiety associated with highly variable hypertension	Initiate non-drug strategies concurrently with or separate from antihypertensive drug therapy.

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

Best Proven Nonpharmacologic Interventions for Prevention and Treatment of Hypertension*

	Nonpharmacologic Intervention	Dose	Approximate Impact on SBP	
			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 intake	Alcohol consumption	In individuals who drink alcohol, reduce alcohol to: ● Men: <2 drinks daily ● Women: <1 drink daily	-4 mm Hg	-3 mm Hg

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

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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)

Similar Dose Conversation HCTZ to Chlorthalidone on Office BP Response in Patients Not at Goal BP

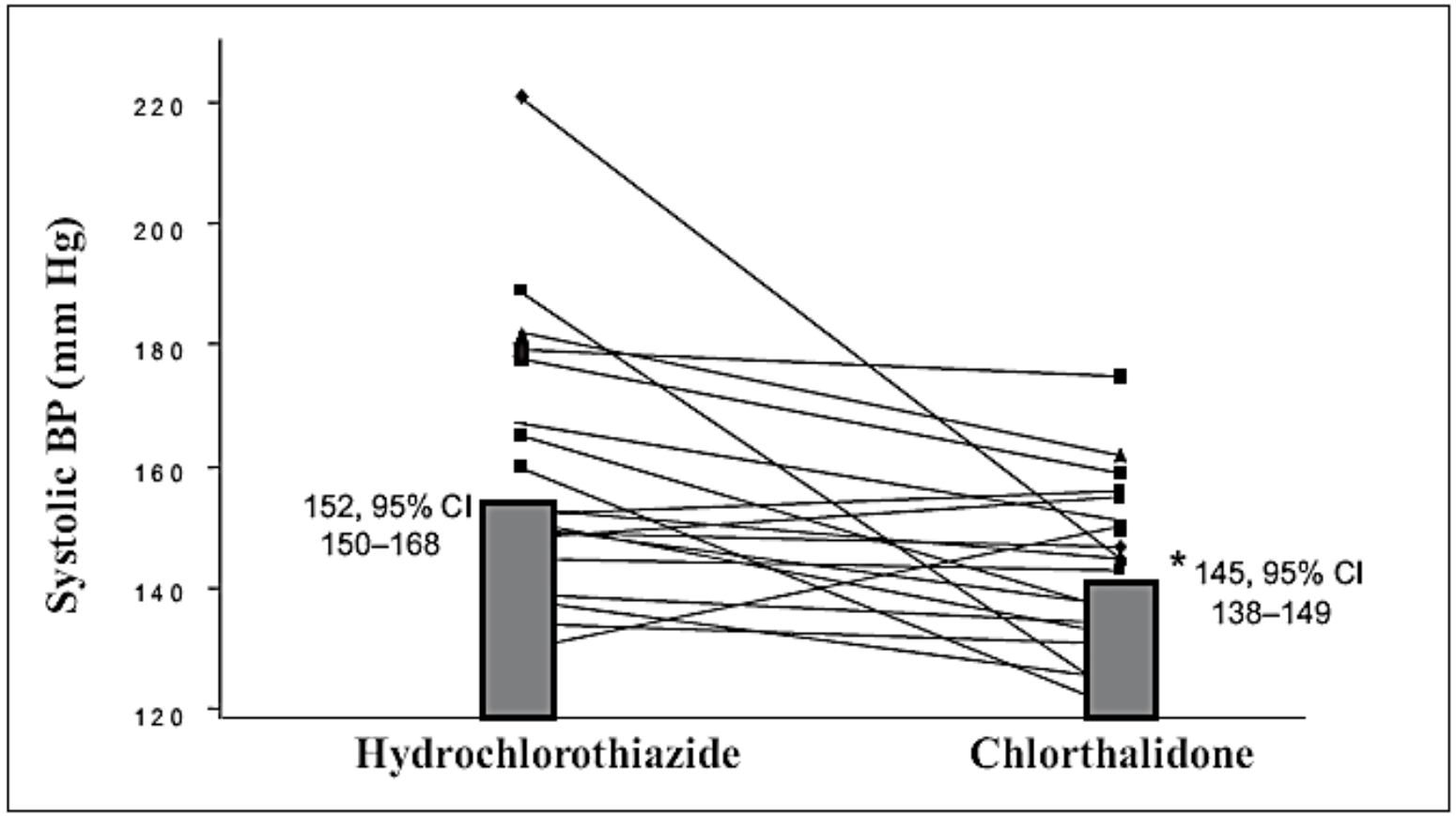

*Figure. Changes in median systolic blood pressure (BP) after 6–8 weeks in each of 19 patients on stable doses of hydrochlorothiazide who were changed to the same dose of chlorthalidone. CI=confidence interval; *p=0.035. Shaded boxes represent median value for each group.*

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

Guidelines Mandate Use of Combination Treatment Under Two Circumstances

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- **European Guidelines:** everyone with diagnosis of hypertension >140/90 mmHg
- **US Guidelines:** anyone with a BP >20/10 above the goal (i.e. >150/90 mmHg)

Whelton P et.al. Hypertension 2018; Williams B et.al. Eur Heart J 2018

American Society of Hypertension Evidenced Based Fixed Dose Antihypertensive Combinations

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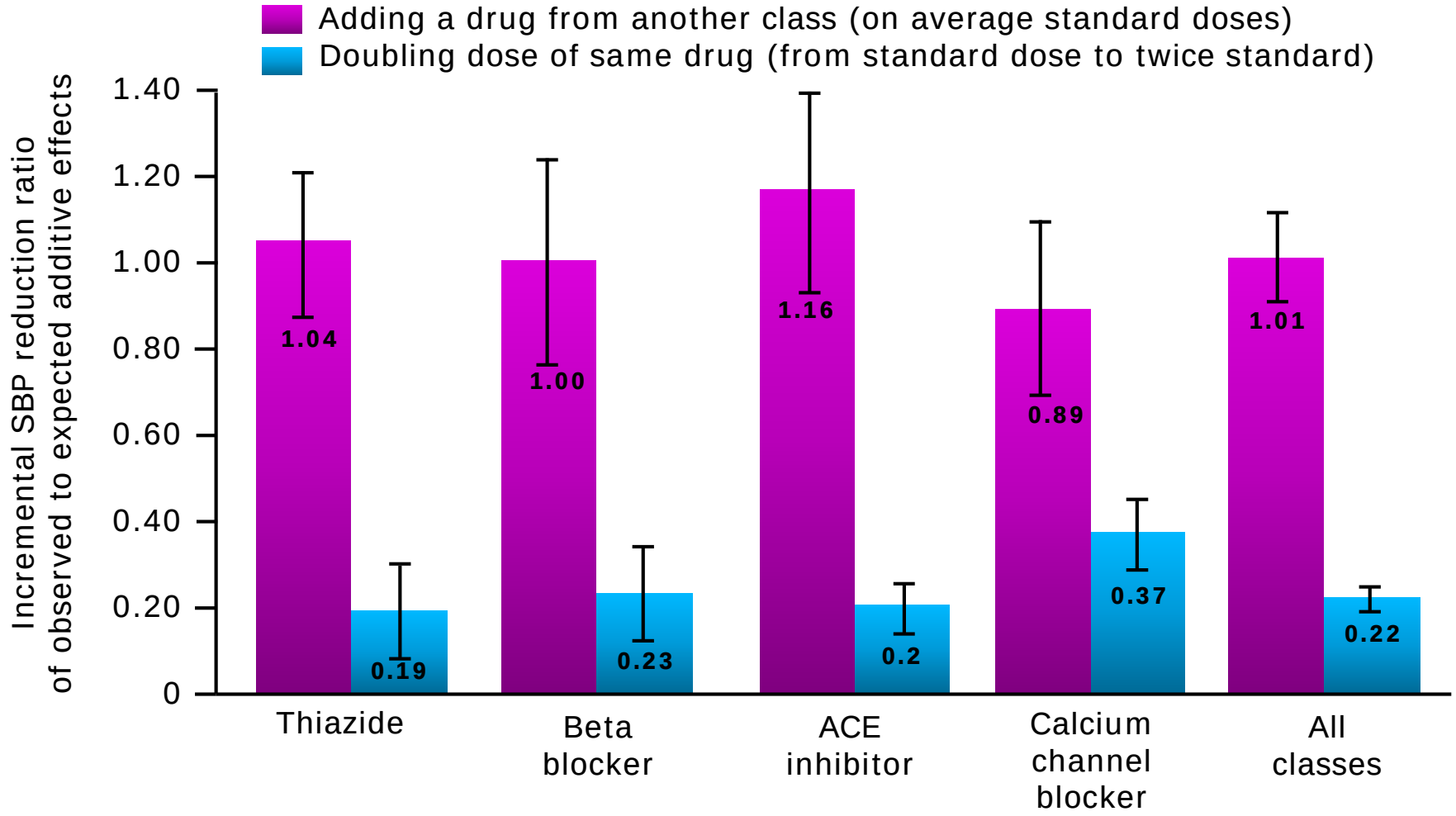
Preferred
• ACE inhibitor/diuretic* • ARB/diuretic* • ACE inhibitor/CCB* • ARB/CCB*
Acceptable
• Beta blocker/diuretic* • CCB (dihydropyridine)/β-blocker • CCB/diuretic • Renin inhibitor/diuretic* • Renin inhibitor/ARB* • Thiazide diuretics/K+ sparing diuretics*
Less Effective
• ACE inhibitor/ARB • ACE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

*SPC available in US

Gradman A et.al. J Am Soc Hypertens 2010;4:42-50

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.

TABLE 1 Demographic and baseline characteristics

Demographic variable	AZL-M/CLD (n = 77)	OLM/HCTZ (n = 76)
Age, y (mean [SD])	67.9 (8.24)	68.9 (9.10)
Sex, n, male/female	32/45	45/31
Race, n, Caucasian/Black/ Asian	57/18/2	62/12/2
Region, n, US/Europe	39/38	37/39
Weight, kg (mean [SD])	83.5 (17.90)	90.1 (21.59)
BMI, kg/m^2 (mean [SD])	30.4 (6.23)	31.6 (6.52)
Diabetes, n (%)	33 (42.9)	32 (42.1)
eGFR, mL/min/1.73 m^2 (mean [SD])	48.3 (10.21)	47.7 (8.76)
Baseline eGFR category, n (%)		
CKD stage 3a (eGFR ≥ 45 and < 60 mL/ min/1.73 m^2)	40 (51.9)	39 (51.3)
CKD stage 3b (eGFR ≥ 30 and < 45 mL/ min/1.73 m^2)	31 (40.3)	33 (43.4)
≥ 60 mL/min/1.73 m^2	6 (7.8)	4 (5.3)
SBP, mm Hg (mean [SD])	151.1 (10.30)	149.0 (7.80)
DBP, mm Hg (mean [SD])	84.8 (10.31)	84.7 (9.68)
SBP categories, n (%)		
< 140 mm Hg	11 (14.3)	10 (13.2)
≥ 140 to < 160 mm Hg	60 (77.9)	64 (84.2)
≥ 160 to < 180 mm Hg[a]	5 (6.5)	2 (2.6)
DBP categories, n (%)		
< 90 mm Hg	52 (67.5)	50 (65.8)
≥ 90 mm Hg	25 (32.5)	26 (34.2)

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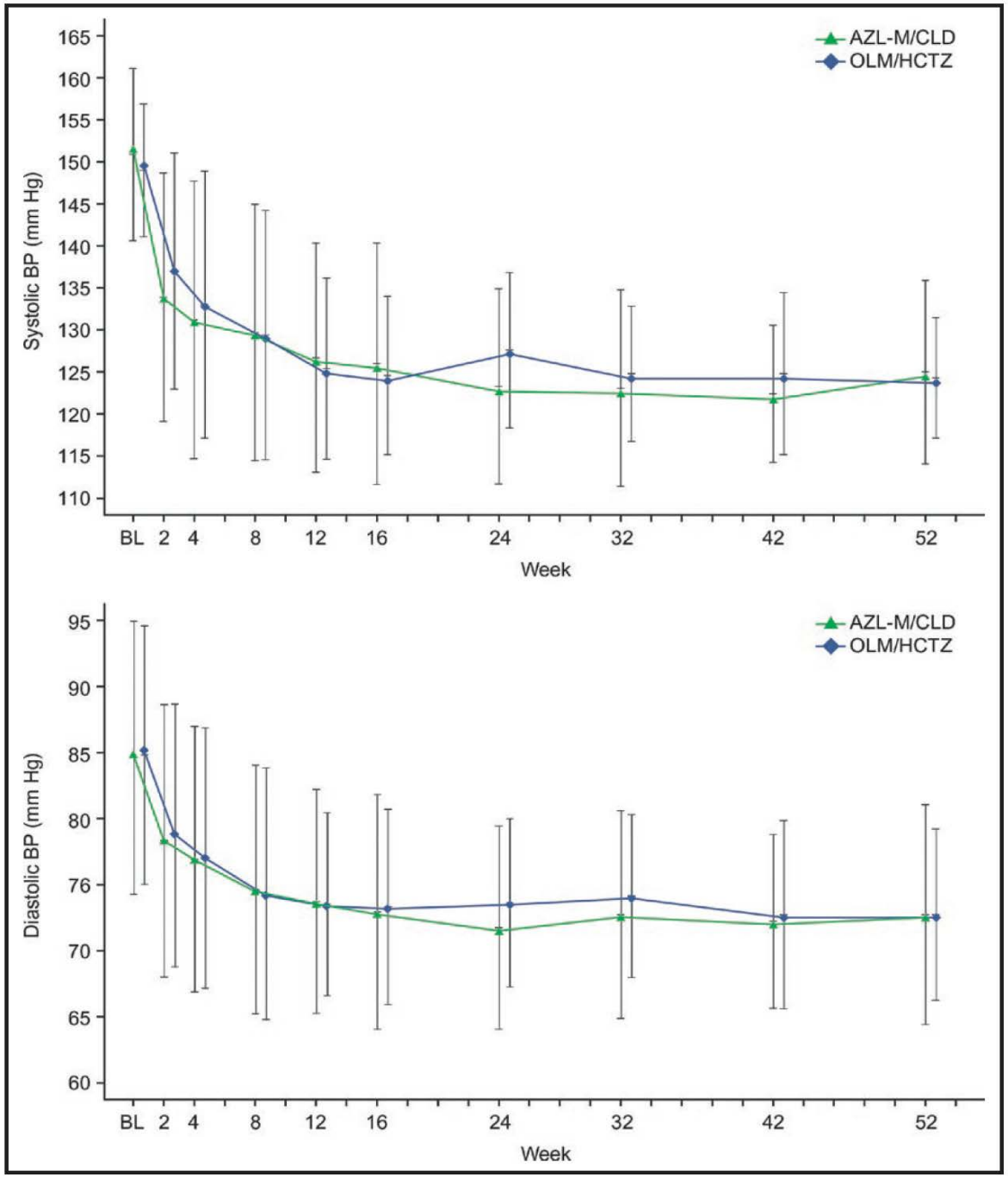
Bakris GL, et.al. J Clin Hypertens (Greenwich). 2018;20:694-702.



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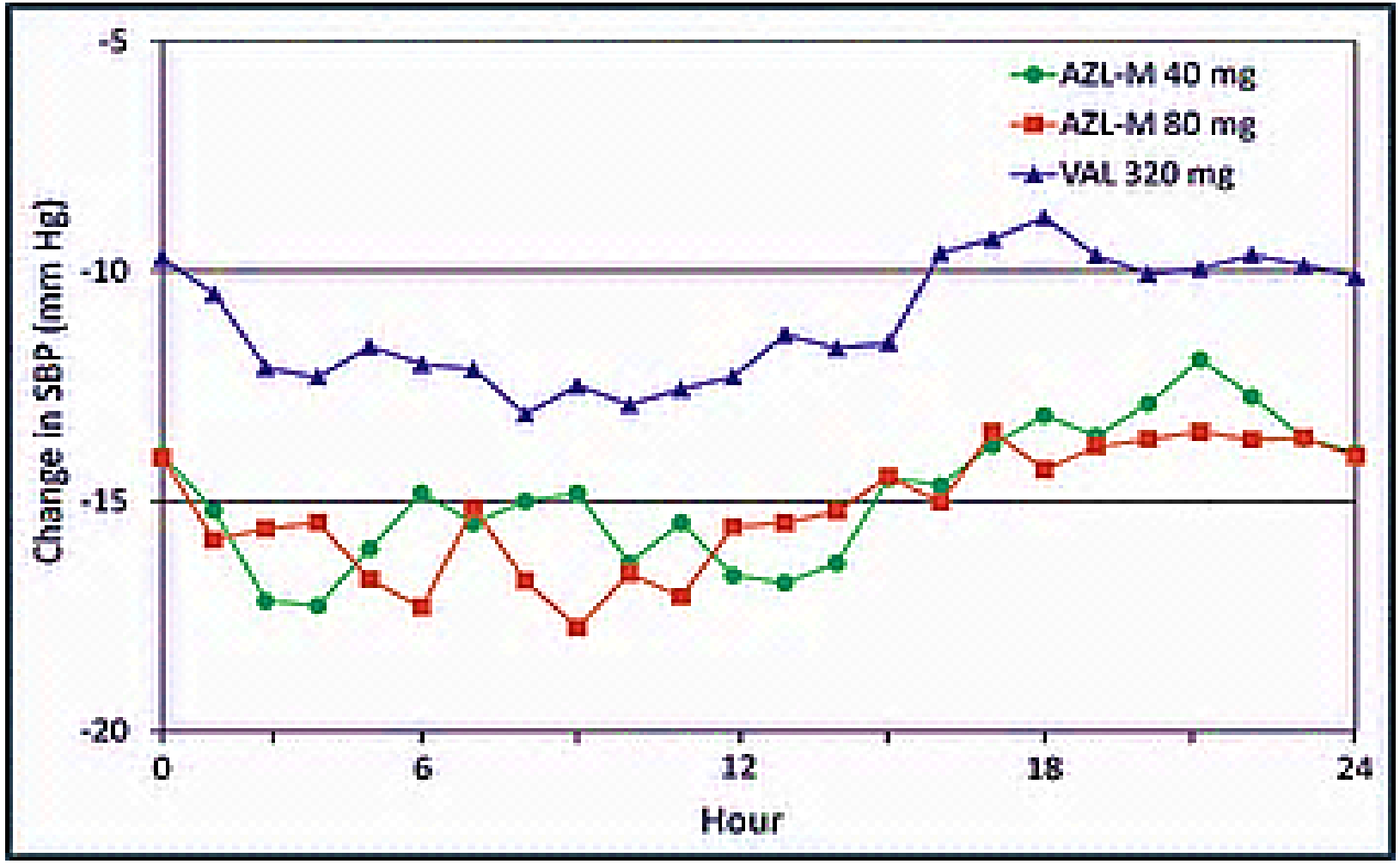
Mean BP Changes over One Year between Two Combinations

Bakris GL, et.al. J Clin Hypertens (Greenwich). 2018;20:694-702.

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



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.

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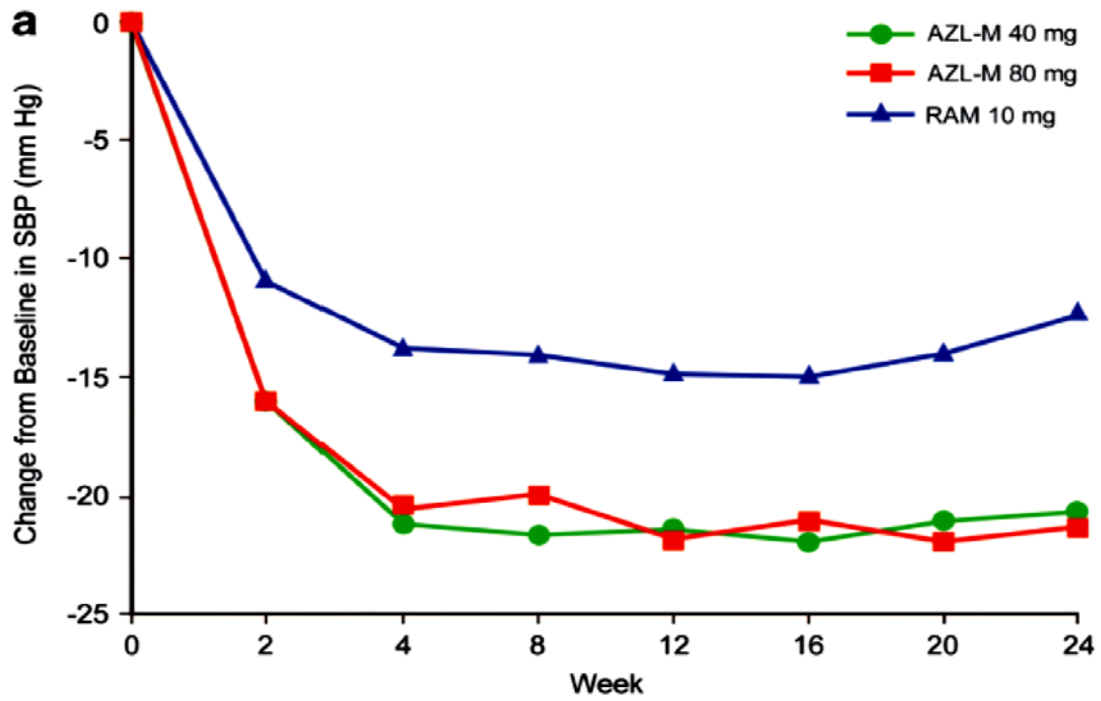
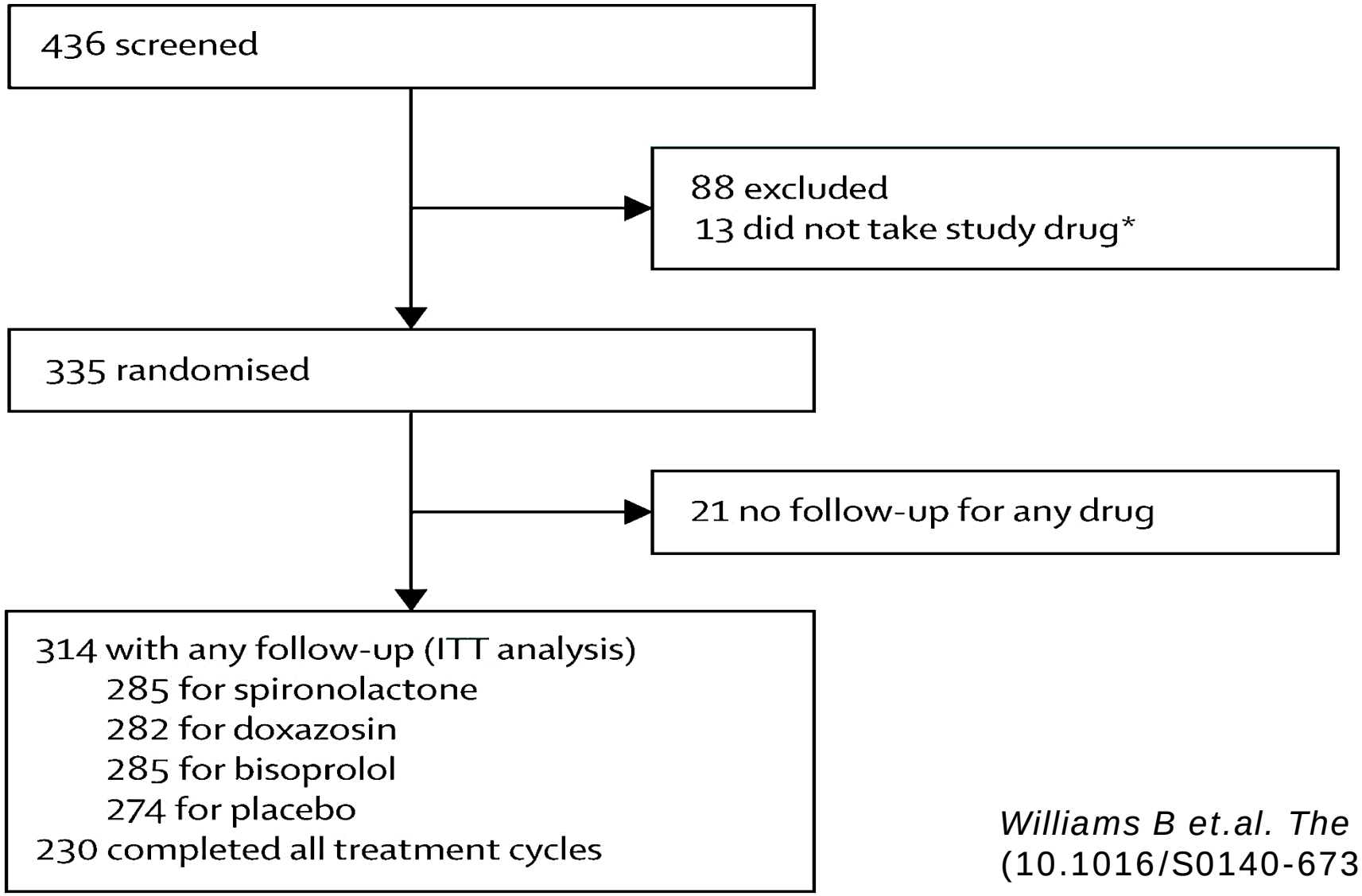
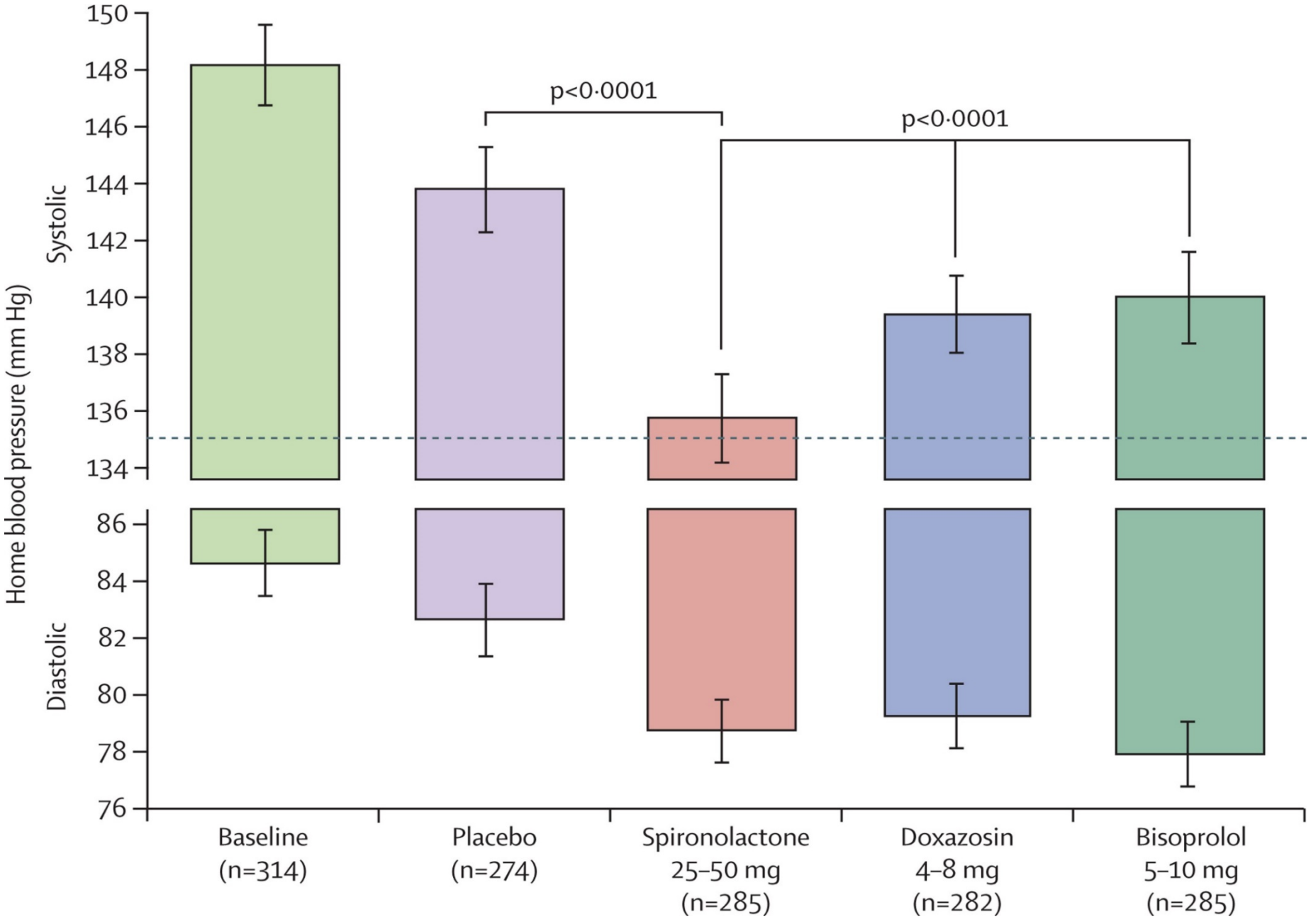


Bonner G, Bakris GL… et.al. and Kupfer S J Hum Hypertens 2013;27:479-486

Spironolactone Versus Placebo, Bisoprolol, and Doxazosin to Determine the Optimal Treatment for Drug-resistant Hypertension (PATHWAY-2): A Randomised, Double-blind, Crossover trial



Williams B et.al. The Lancet DOI: (10.1016/S0140-6736(15)00257-3)



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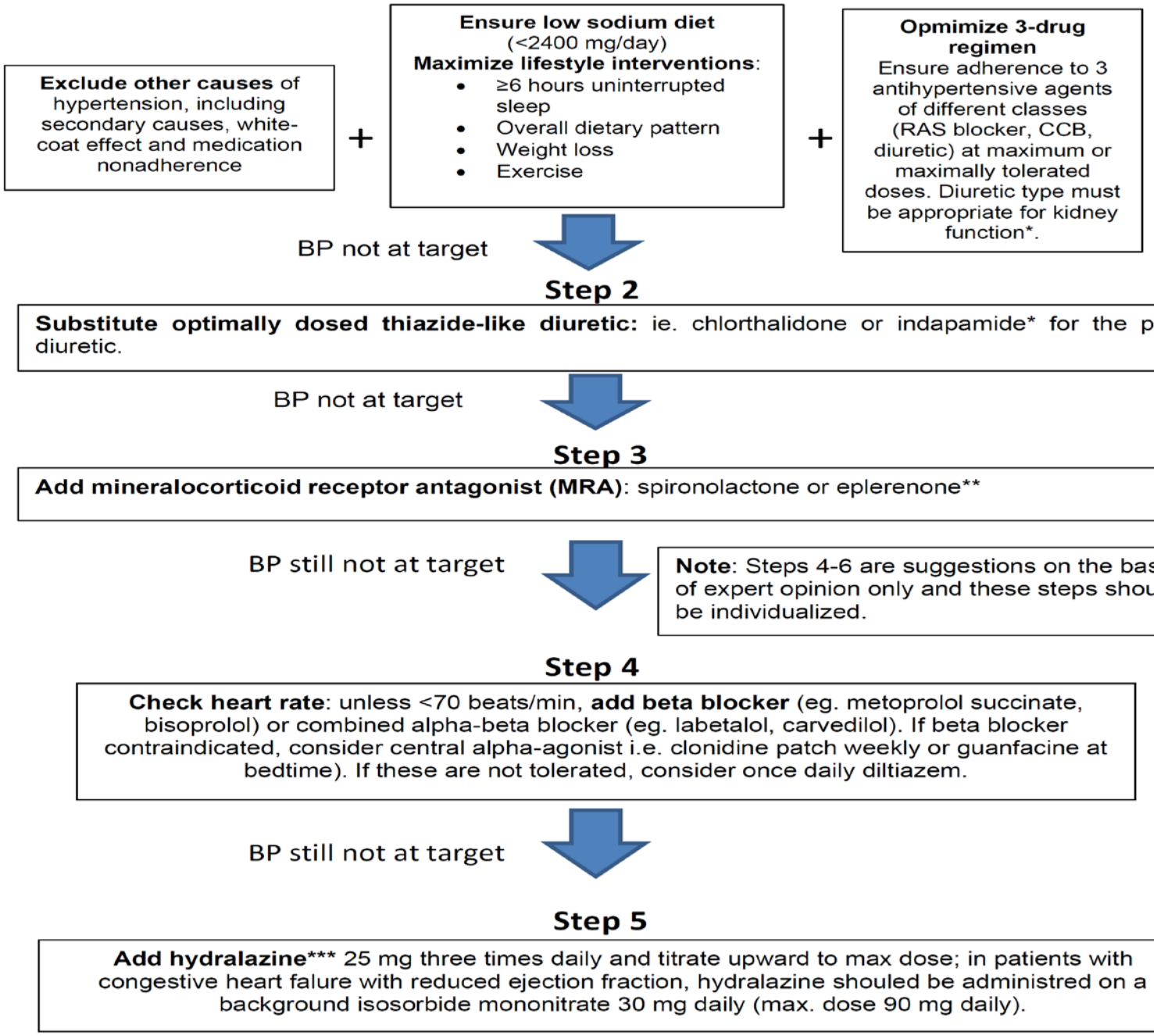
Williams B et.al. The Lancet DOI: (10.1016/S0140-6736(15)00257-3)

Predictors of Hyperkalemia before Starting Therapy Derived from Trials

- eGFR <45 mL/min/1.73m^2
- Serum potassium of >4.5 mEq/L
- eGFR <45 mL/min/1.73m^2 **+** serum K+ >4.5 mEq/L (*HIGHEST PREDICTOR*)

Lazich I, et al. *Semin Nephrol.* 2014; Khosla N, et al. *Am J Nephrol.* 2009.

Figure 3 **Management of Resistant Hypertension**



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BP still not at target

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Step 6

Substitute minoxidil** 2.5 mg 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 a beta blocker and a diuretic

**** Require the concomitant use of a beta blocker and a loop diuretic

When to Defer to a Hypertension Specialist

- How to find a Hypertension Specialist:
  - http://www.ahscp.org/specialist-and-clinician-directory/
- Issues generating referral
  - Any patient who you have been unable to control with 3 or more meds
  - Any patient who has an eGFR below 30 ml/min or has a >30% sustained increase in serum creatinine even of BP is controlled –sign of kidney disease)
  - Any patient who claims side effects from all meds-even though no clear evidence

Summary

- Resistant Hypertension is defined as BP >130/80 mmHg while taking maximally tolerated doses of a CCB, thiazide type-diuretic, and RAS blocker.
- Assuming patient adherence is not an issue spironolactone should be the fourth drug added if CKD is not present (ie eGFR <45 ml/min).
- Start with single pill combination therapy if BP >20/10 mmHg (150/90 mmHg) above the goal with either RAS+CCB or RAS+ diuretic
- Beta blockers should not be used unless compelling indications such CAD or heart failure

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Thank you!

Questions/Discussion