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Ohio Cardiovascular Health Collaborative

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Cardi-OH ECHO - Hypertension

Thursday, March 7, 2019

Advances in Hypertension Pharmacotherapy

Michael B. Holliday, MD

Associate Professor

Department of Family and Community Medicine

University of Cincinnati

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.

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Objectives

- Identify BP targets for hypertension pharmacologic treatment
- Use a patient-centered approach to arrive at more effective anti-hypertensive regimens
- Prescribe potentially underutilized medications to achieve blood pressure treatment goals

Determinants of Patient-centered Pharmacotherapy

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- Diagnosis threshold and treatment targets
- Effective drug combinations
- Interventions that increase adherence to therapy

Accurate Diagnosis of Hypertension

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Corresponding Values of SBP/DBP for Clinic, HBPM, Daytime, Nighttime and 24-Hour ABPM Measurements

Clinic	HBPM	Daytime ABPM	Nighttime ABPM	24-Hour ABPM
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/80	120/70	130/80
160/100	145/90	145/90	140/85	145/90

ABPM = ambulatory blood pressure monitoring.; **BP** = blood pressure; **DBP** = diastolic blood pressure; **SBP** = systolic blood pressure; **HBPM** = home blood pressure monitoring

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Accurate Diagnosis of Hypertension

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Out-of-Office Blood Pressure Measurement

Rationale:

- Provides a better risk prediction than office-based monitoring
- cardiac (LVH) and renal (albuminuria) consequences of hypertension than office readings

Uses and Advantages

- Helps identify WCH and masked hypertension
- Multiple readings throughout the day may reveal patterns in blood pressure and periods when control is inadequate.
- Improves patient adherence
- Reduces costs
- Take readings 1 week per month, 2 readings in the AM and PM, throw out the first day and get 24 values for a week q month.

Pickering TG, White W. *J Clin Hypertens.* 2008; 10:850-855; Izzo JL, Sica DA, Black HR, eds, and the Council for High Blood Pressure Research (American Heart Association). *Hypertension Primer: The Essentials of High Blood Pressure,* 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2008: 339-342

Accurate Diagnosis of Hypertension

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Categories of BP in Adults*

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	*or*	80–89 mm Hg
Stage 2	≥140 mm Hg	*or*	≥90 mm Hg

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.

Table 6

Estimating CVD Risk

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Clinical Condition (s)	BP Threshold mm Hg	BP Goal mm Hg
General		
Clinical CVD or 10 year ASCVD risk ≥ 10%	≥130/80	<130/80
No clinical CVD and 10 year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; non-institutionalized, ambulatory, community-living adults)	≥130 (SBP)	<130 (SBP)
Specific Comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease post-renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/90	<130/80
Peripheral arterial disease	≥130/80	<130/80

Adherence

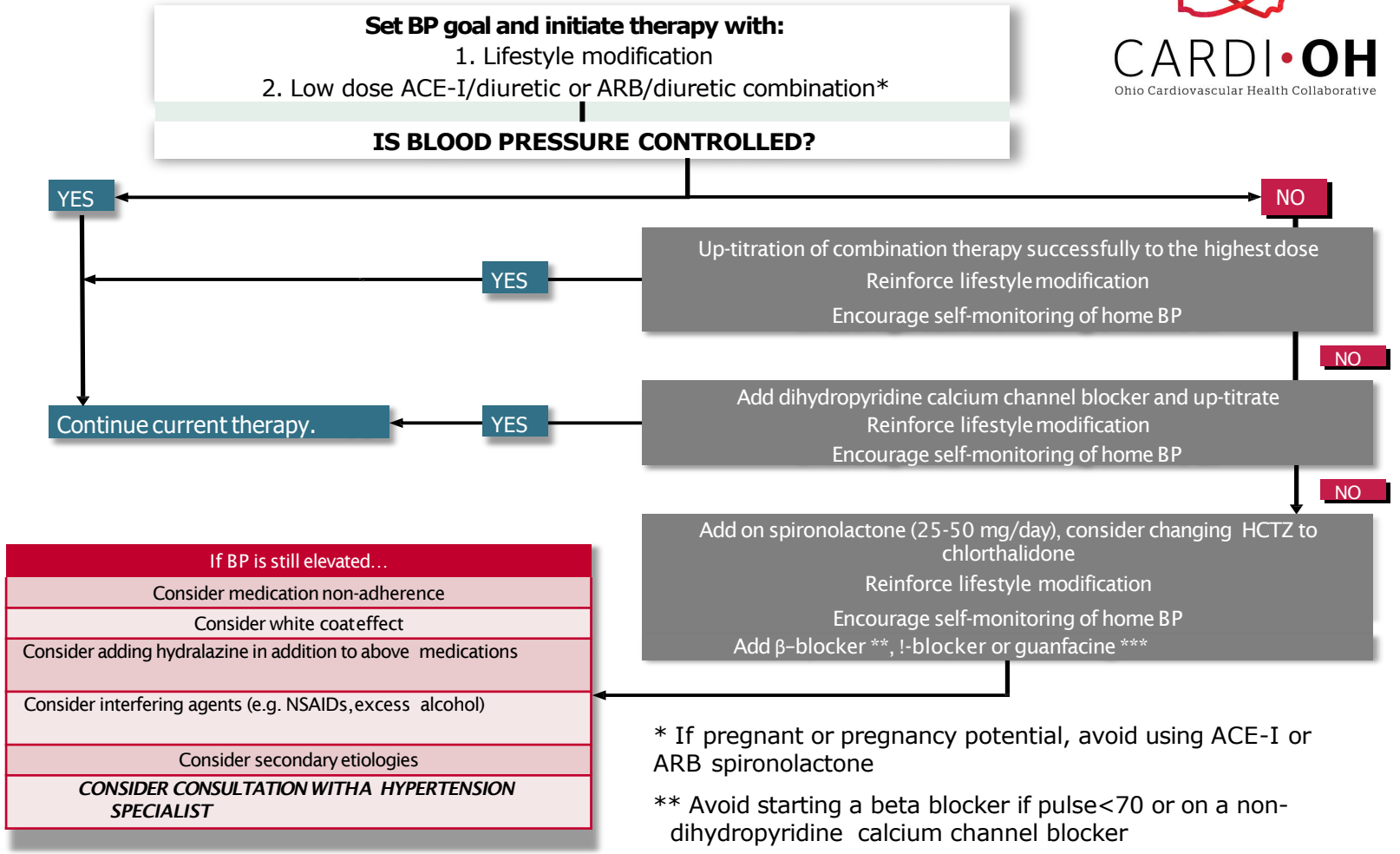
- Urine studies show partial nonadherence in over 1/2 of patients and no drug in 1/3
- Promising interventions
  - Regimen simplification
  - Reduction of out-of-pocket costs
  - Team-based collaborative care
  - Self-monitoring of BP




Hypertension. 2017;70:5-9

Hypertension Change Package Algorithm

- Widely acceptable and effective algorithm using inexpensive combination therapy.
- May lead to under-dosing of HCTZ (failure to intensify dose).
- Effective dose for BP reduction and CV outcome for HCTZ is 25-50 mg day, not 12.5-25 mg/day commonly used in primary care settings.
- Evidence of increased BP control rates and reduction in BP control
- However, BP gap exists between African Americans and non-African American hypertensives with use of this algorithm.



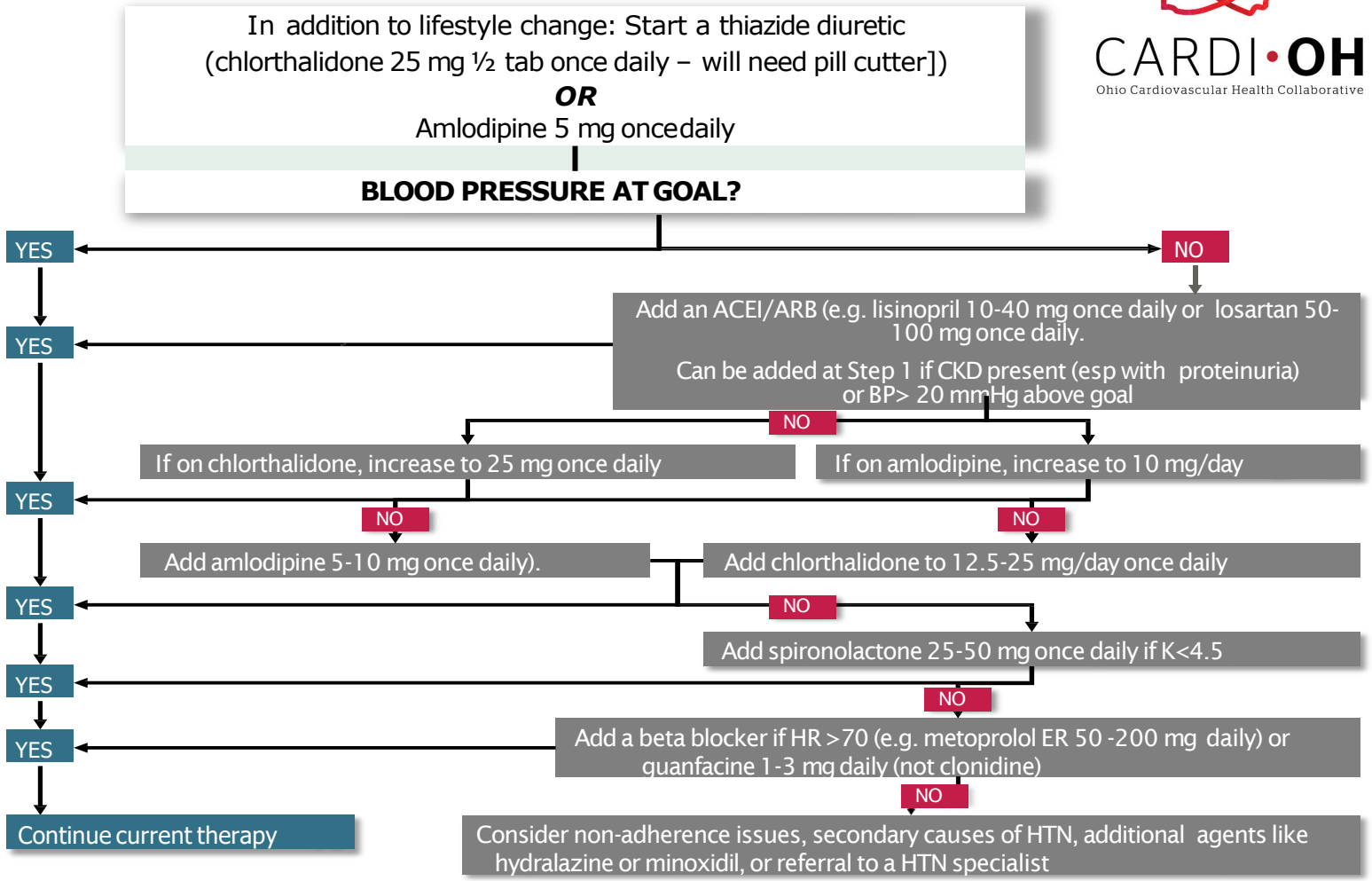
* If pregnant or pregnancy potential, avoid using ACE-I or ARB spironolactone

** Avoid starting a beta blocker if pulse<70 or on a non-dihydropyridine calcium channel blocker

*** Guanfacine has similar mechanism of action as clonidine and is once daily instead of 3 times per day

Hypertension Drug Treatment Algorithm

- This algorithm was recommended in SPRINT trial, with chlorthalidone the preferred thiazide-like diuretic – especially for African-American patients.
- Non-African-American patients could also start with ACEI or ARB.
- Very effective in achieving even SBPs < 120 mmHg.
- No significant disparity in BP lowering or outcome benefit similar across race/ethnicity was seen in the SPRINT trial.
- May be better option in practices with large numbers of African-American hypertensives since uses chlorthalidone rather than HCTZ as initial therapy.



Thiazide-type Diuretic Doses in Hypertension Morbidity Trials

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- Doses used in outcome trials using thiazide type diuretics.
- ACCOMPLISH trial is the one trial that used doses equivalent to 12.5-25 HCTZ. It is also the only trial showing inferior benefit of thiazide-type diuretics compared to CCBs or any other class of antihypertensives.
- There is a tendency to under-dose diuretics, and doing so sacrifices both BP lowering and clinical benefit.
- Summary: 25mg or less of HCTZ may compromise the benefits of thiazide diuretics (as well as its BP-lowering potency).

Trial	Drug	Dose of Thiazide (mg/d)
VA CSP M&M	HCTZ	100
HDFP	chlorthalidone	25-100
MRC I	bendroflumethiazide	10
HAPPHY	bendroflumethiazide HCTZ	5-10 50-100
EWPHE	HCTZ/triamterine	25-50
MRC Elderly	HCTZ/amiloride	25-50
SHEP	chlorthalidone	12.5-25
ALLHAT	chlorthalidone	12.5-25
ACCOMPLISH	**HCTZ**	**12.5-25**
SPRINT	chlorthalidone	12.5-25

Pharmacokinetics

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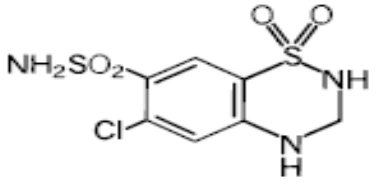
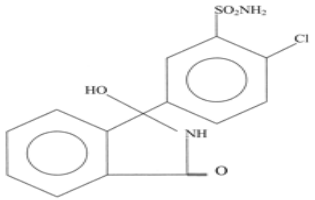
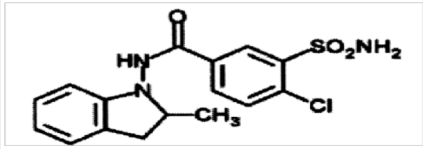
A rationale for the selection of chlorthalidone over HCTZ:

- Among the differences between the two include chlorthalidone's longer half-life and duration of action.
- The half-life of chlorthalidone is 60-72 hours, yielding more potent and smoother BP control, more gradual onset of diuretic action with less urinary urgency, and patients are more tolerant to missed doses.
- Note: amlodipine also has a very long half-life

	Vd	Relative Potentcy*	Oral Bioavail	Onset (h)	Peak (h)		Half-life (h)	Duration (h)
HCTZ 	3-4 L/kg 40% protein bound	1	~70%	2	4-6		6-9 (single dose) **8-15** (long-term dosing)	12 (single dose) **16-24** (long-term dosing)
Chlorthalidone 	3-13 L/kg 75% protein bound ***98% distribution into RBC***	1	~65%	2-3	2-6		40 (single dose) **45-60** (long-term dosing)	24-48 (single dose) **48-72** (long-term dosing)
Indapamide 		20	~93%	1-2	<2		**14**	**Up to 36**
Amlodipine					4-6		40-60	**24-72**

* Per most pharmacology texts; research suggests otherwise.

Carter BL, Ernst ME, Cohen JD. Hypertension 2004;43:4-9

Abernathy DR, Cardiol 1992; 80:31-36

Calcium Channel Blocker Half-Life

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- Amlodipine, like chlorthalidone, has a very long half-life (40-60 hrs) and consequently more tolerant of missed doses.
- It has a significant evidence base demonstrating reduction of CVD events, and thus can be prescribed as an initial or add-on agent.
- It is effective regardless of age, race, or renal function.
- In patients with kidney dysfunction, it should be combined with either an ACEI or ARB (but not both)

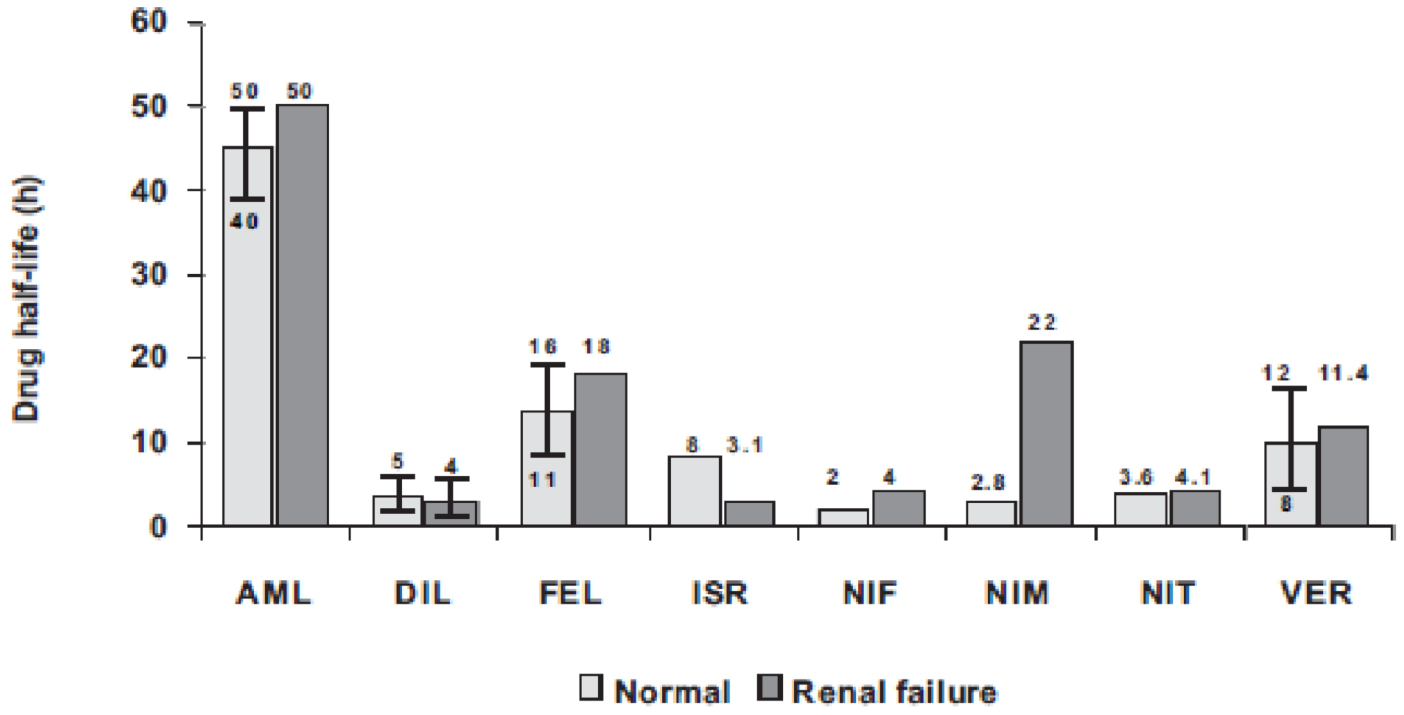

Figure 1. Drug half-life for calcium channel blockers in the presence of renal failure. AML = amlodiphine; DIL = dilatiazem; FEL = felodipine; ISR = isradipine; NIF = nifedipine; NIM = nimodipine; VER = verapamil

Sica DA. J Clin Hypertens 2005; 7(4) Supp 1: 21-26

Use of Spironolactone

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- It is a potassium sparing/mineralocorticoid receptor inhibitor diuretic.
- Is a preferred agent for treatment of primary aldosteronism.
- Shown effective as add-on in patients with resistant hypertension, obesity, and sleep apnea.
- Great complement in treatment of hypokalemia associated with chlorthalidone.
- Risk of gynecomastia and impotence, but usually at doses greater than 50 mg/day.

Spironolactone Compared to Doxazosin and Bisoprolol in the Treatment of Resistant HTN – Pathway 2 Trial

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- Spironolactone is effective in the treatment of resistant hypertension, including in tolerable doses ≤ 50 mg/day.

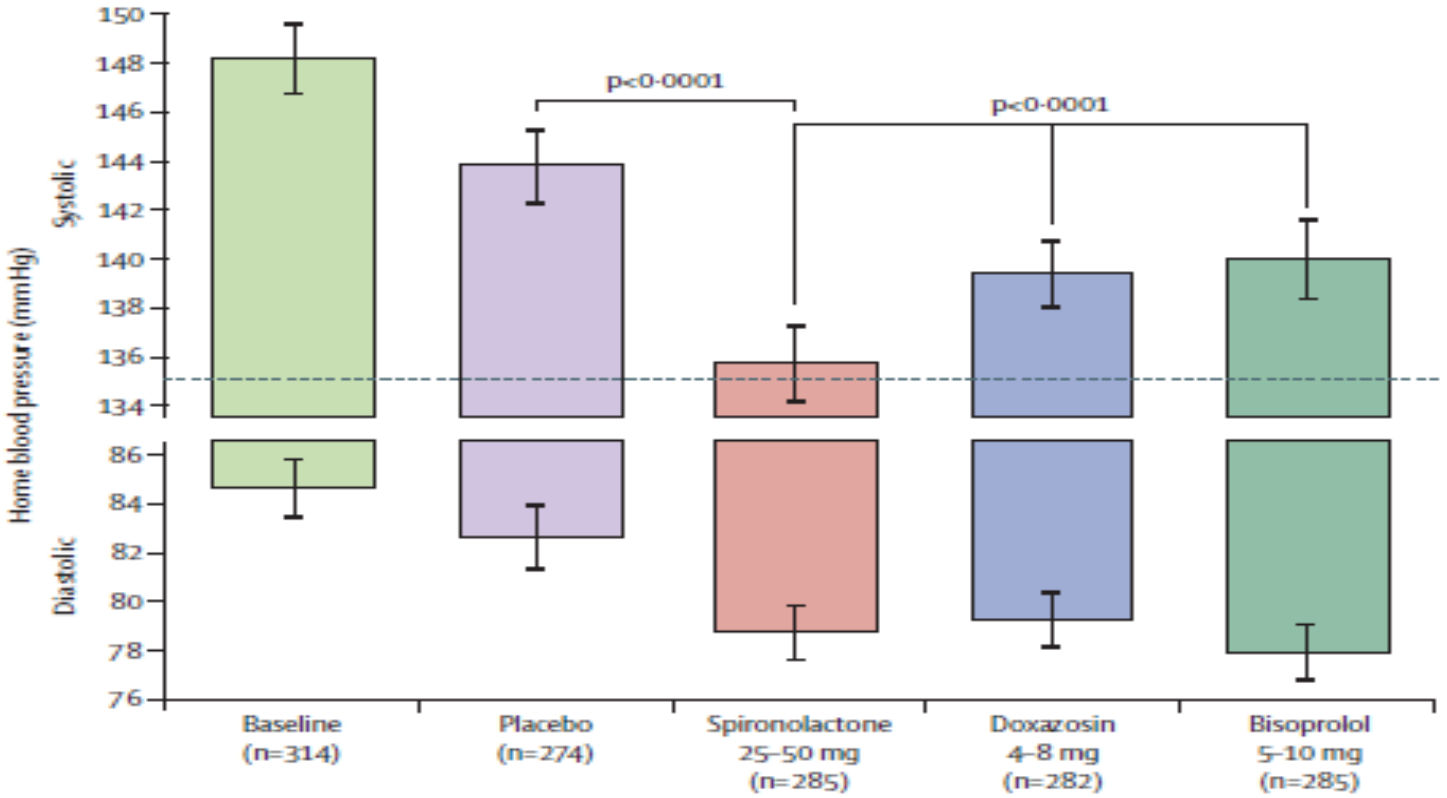

Figure 2: **Home systolic and diastolic blood pressures comparing spironolactone with each of the other cycles**
The top and bottom of each column represents the unadjusted home systolic and diastolic blood pressures, respectively, averaged across the mid-cycle (low-dose) and end-of-cycle (high-dose) visits (6 weeks and 12 weeks) in which patients received the drug. Error bars represent 95% CI. Comparisons are as described under methods for the primary endpoint.

Williams B et al. Lancet 2015; 386: 2059-68

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Thank you!

Questions/Discussion