



# CARDI•OH

Ohio Cardiovascular Health Collaborative



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## Evidence for Use of Chlorthalidone-Amlodipine-Spironolactone

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## Topics Covered

- Effective treatment algorithms
- Evidence-based thiazide diuretic dosing
- Amlodipine and spironolactone use in challenging patients

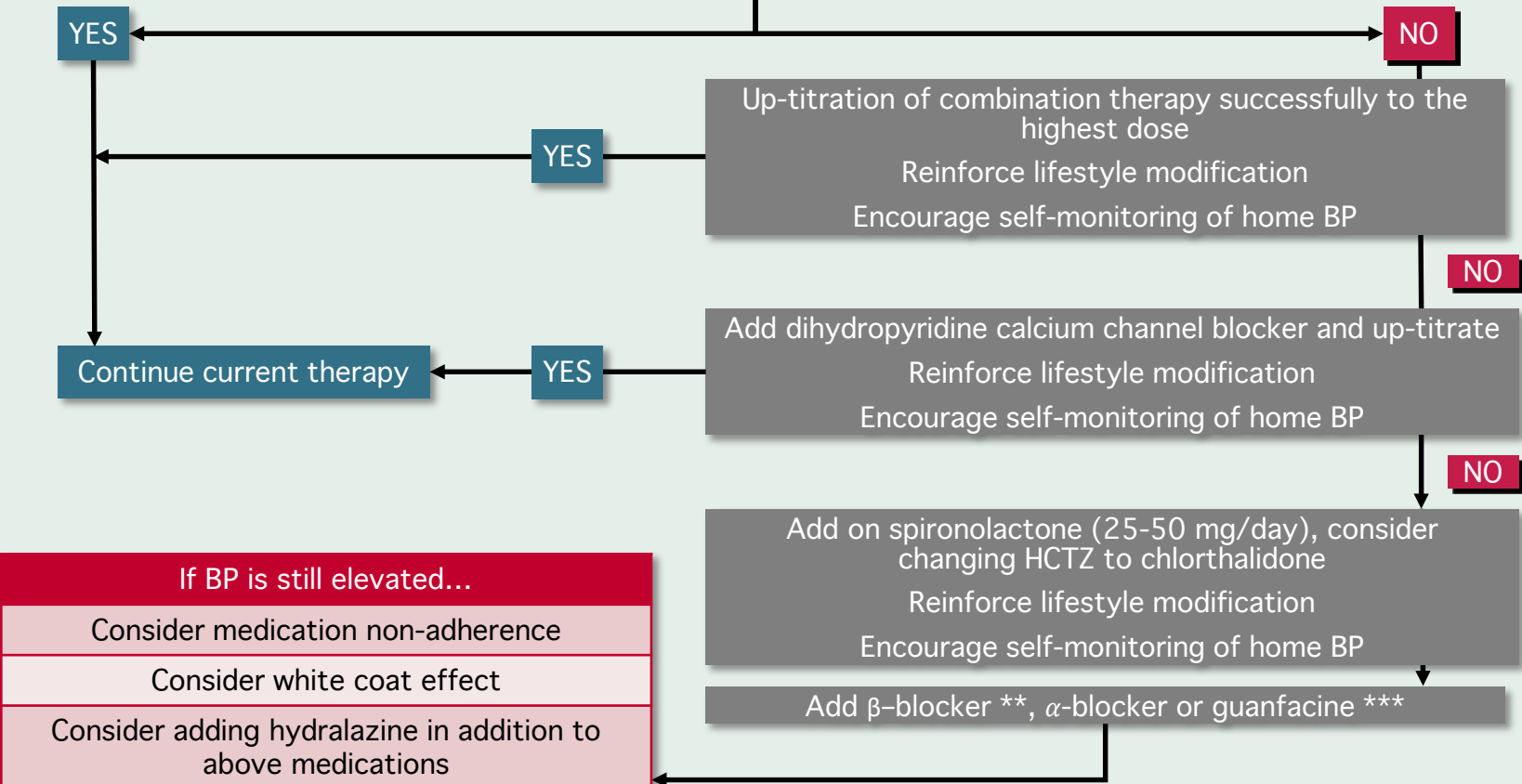
# Hypertension Change Package Algorithm

- 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 control gap exists between African American and non-African American hypertensives with use of this algorithm



Set BP goal and initiate therapy with:  
 1. Lifestyle modification  
 2. Low dose ACE-I/diuretic or ARB/diuretic combination\*

IS BLOOD PRESSURE CONTROLLED?



If BP is still elevated...
Consider medication non-adherence
Consider white coat effect
Consider adding hydralazine in addition to above medications
Consider interfering agents (e.g. NSAIDs, excess alcohol)
Consider secondary etiologies
<b>CONSIDER CONSULTATION WITH A HYPERTENSION SPECIALIST</b>

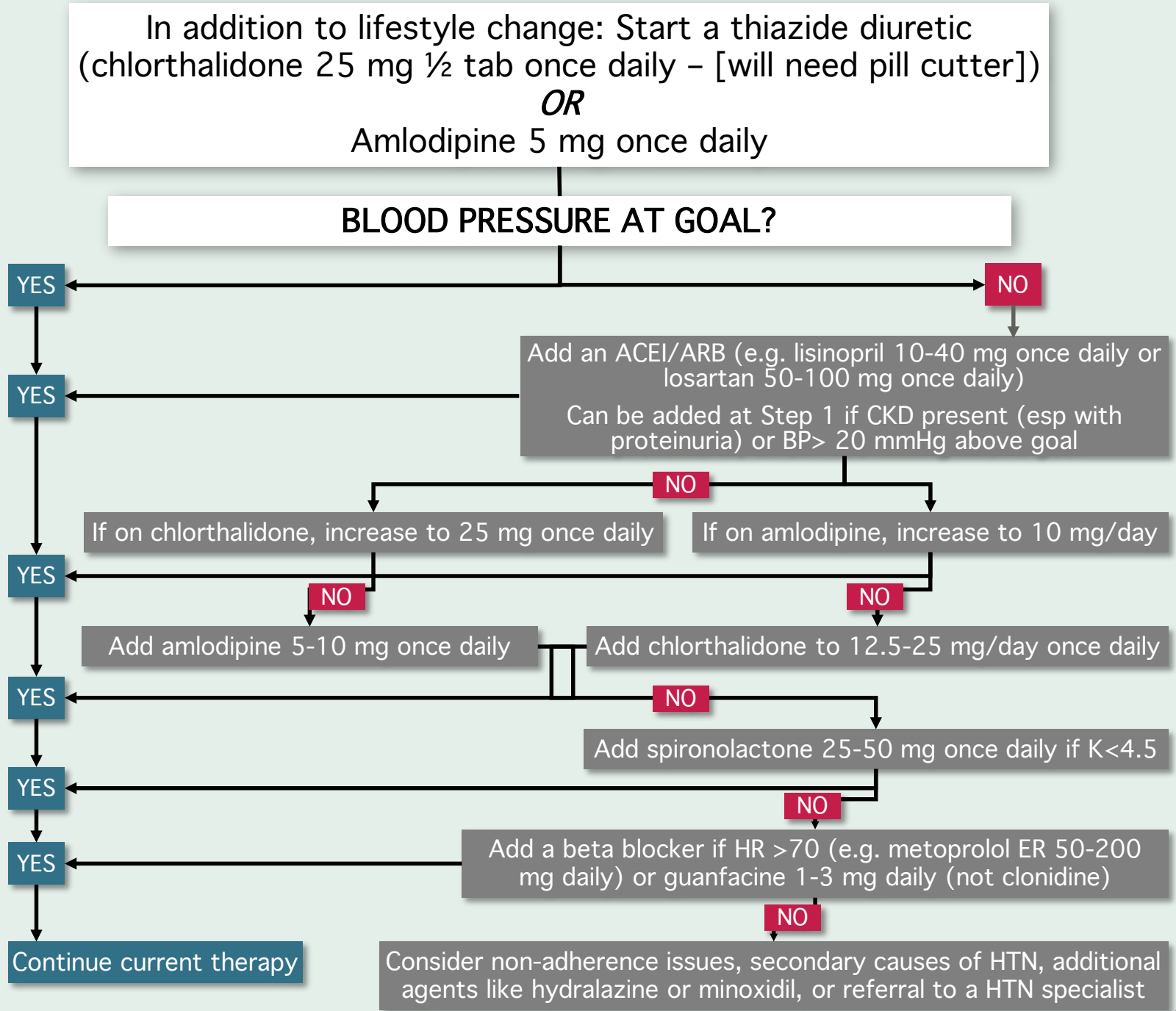
\* If pregnant or pregnancy potential, avoid using ACE-I or ARB  
 spironolactone

\*\* 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 either 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

- 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 less of HCTZ may compromise the benefits of thiazide diuretics (as well as its BP-lowering potency)

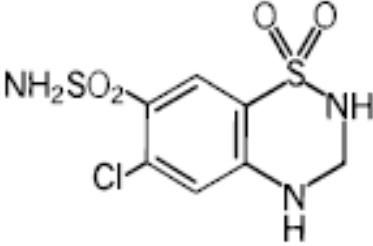
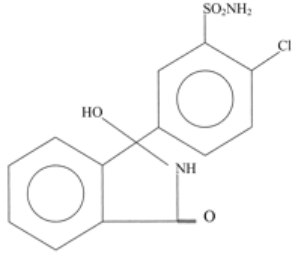
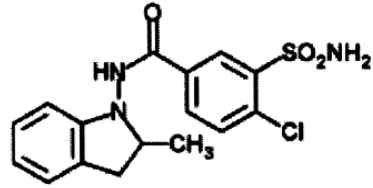



Trial	Drug	Dose of Thiazide (mg/d)
VA CSP M&M	HCTZ	100
HDFP	chlorthalidone	25-100
MRC I	bendroflumethiazide	10
HAPPHY	bendroflumethiazide	5-10
	HCTZ	50-100
EWPHE	HCTZ/triamterine	25-50
MRC Elderly	HCTZ/amiloride	25-50
SHEP	chlorthalidone	12.5-25
ALLHAT	chlorthalidone	12.5-25
<b>ACCOMPLISH</b>	<b>HCTZ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

# Pharmacokinetics

## *A rationale for the selection of chlorthalidone over HCTZ*

- Compared to HCTZ, chlorthalidone is ~ twice as potent in BP lowering, more gradual onset of diuretic action, longer duration of action of BP lowering, and has larger evidence base documenting CVD reduction
- 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 long-half life

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

\* 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

- 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 an ACEI or ARB

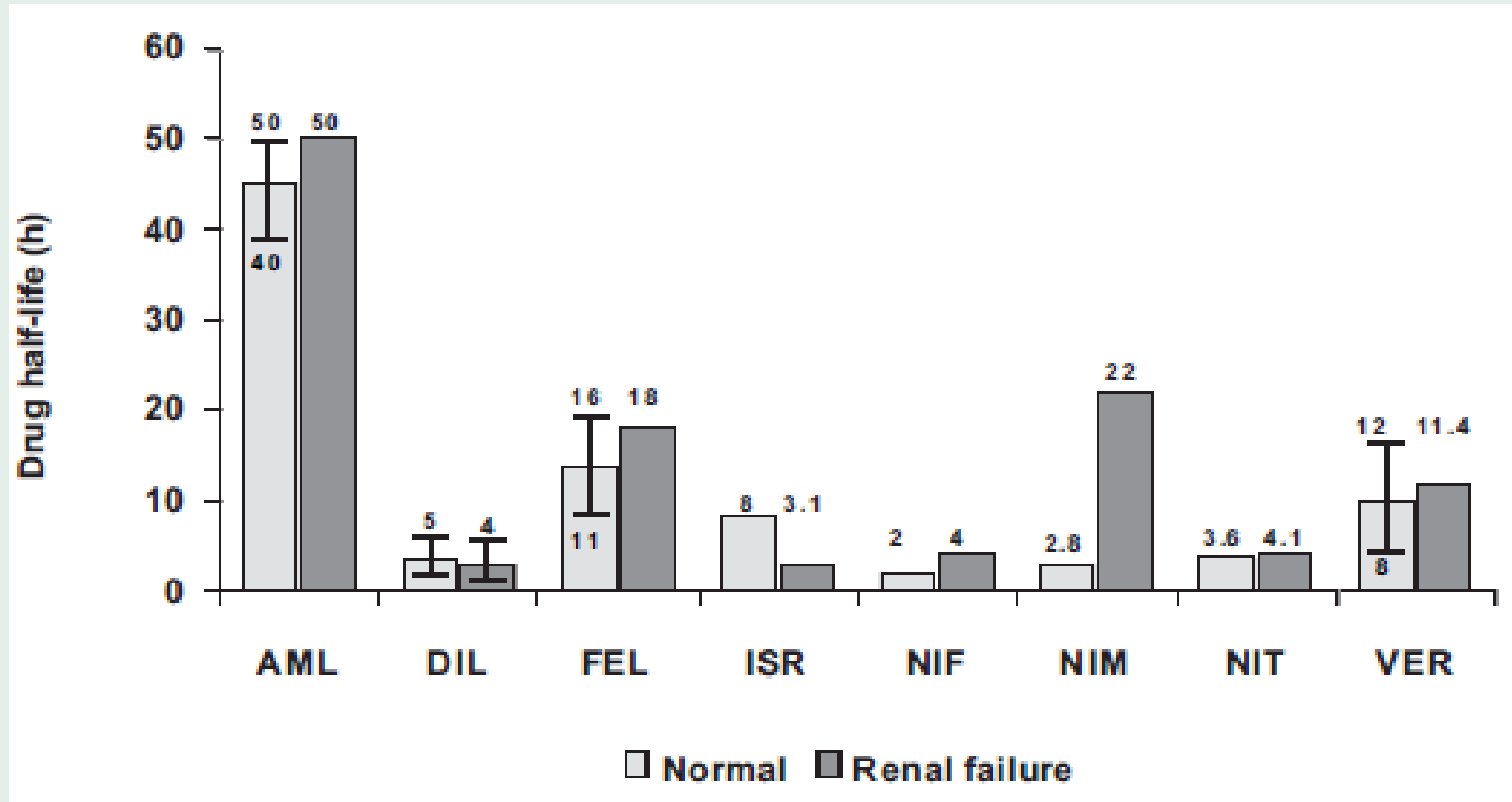


Figure 1. Drug half-life for calcium channel blockers in the presence of renal failure. AML = amlodipine; DIL = diliazem; FEL = felodipine; ISR = isradipine; NIF = nifedipine; NIM = nimodipine; VER = verapamil

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

# Use of Spironolactone

- 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

- Spironolactone is effective in the treatment of resistant hypertension, including in tolerable doses  $\leq 50$  mg/day

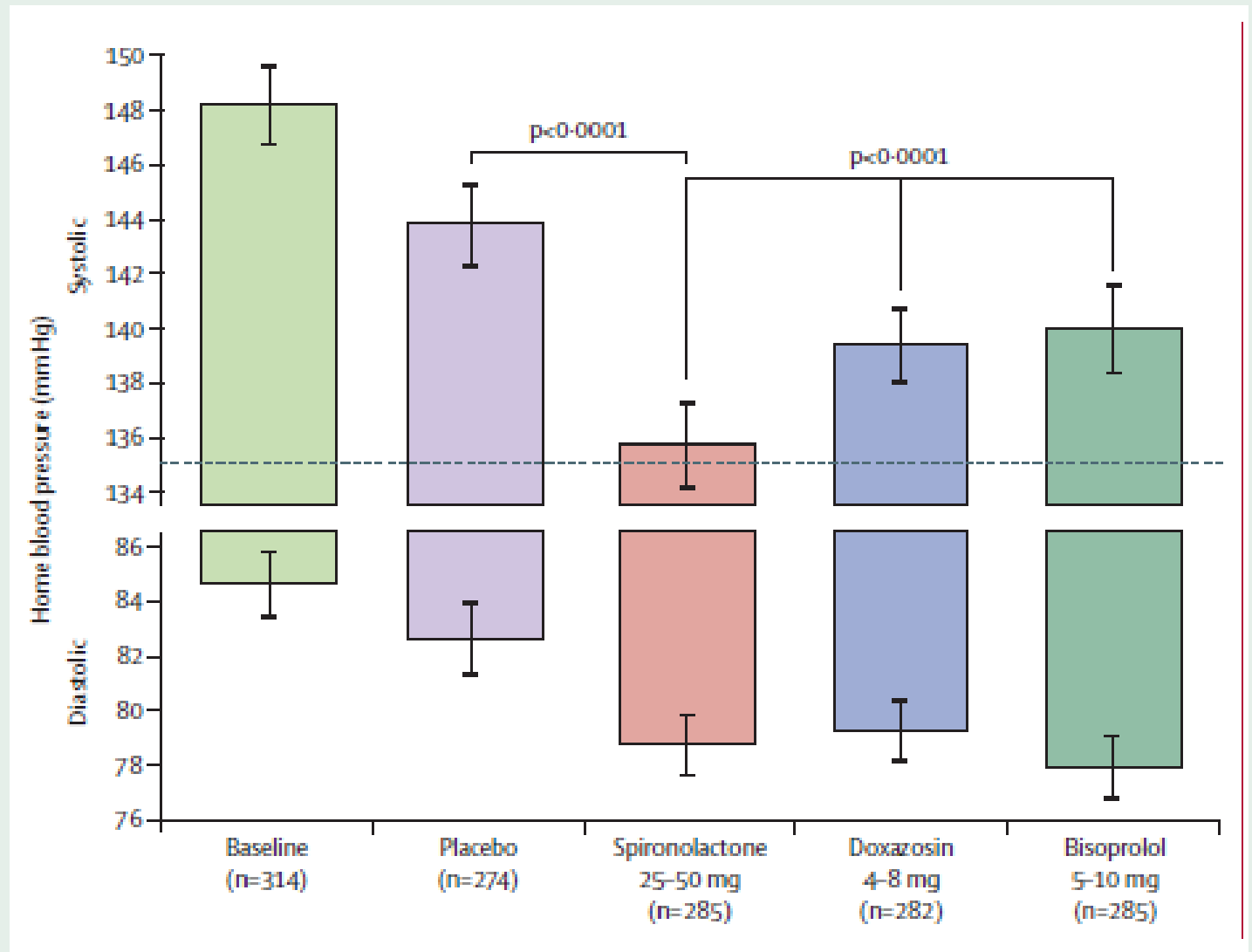


Figure 2. Home systolic and diastolic blood pressures comparing spironolactone with each of the other cycles

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