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Ohio Cardiovascular and Diabetes Health Collaborative



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Long-Acting, Low-Cost Medications to Achieve Blood Pressure Targets: Evidence for Chlorthalidone, Amlodipine, and Spironolactone

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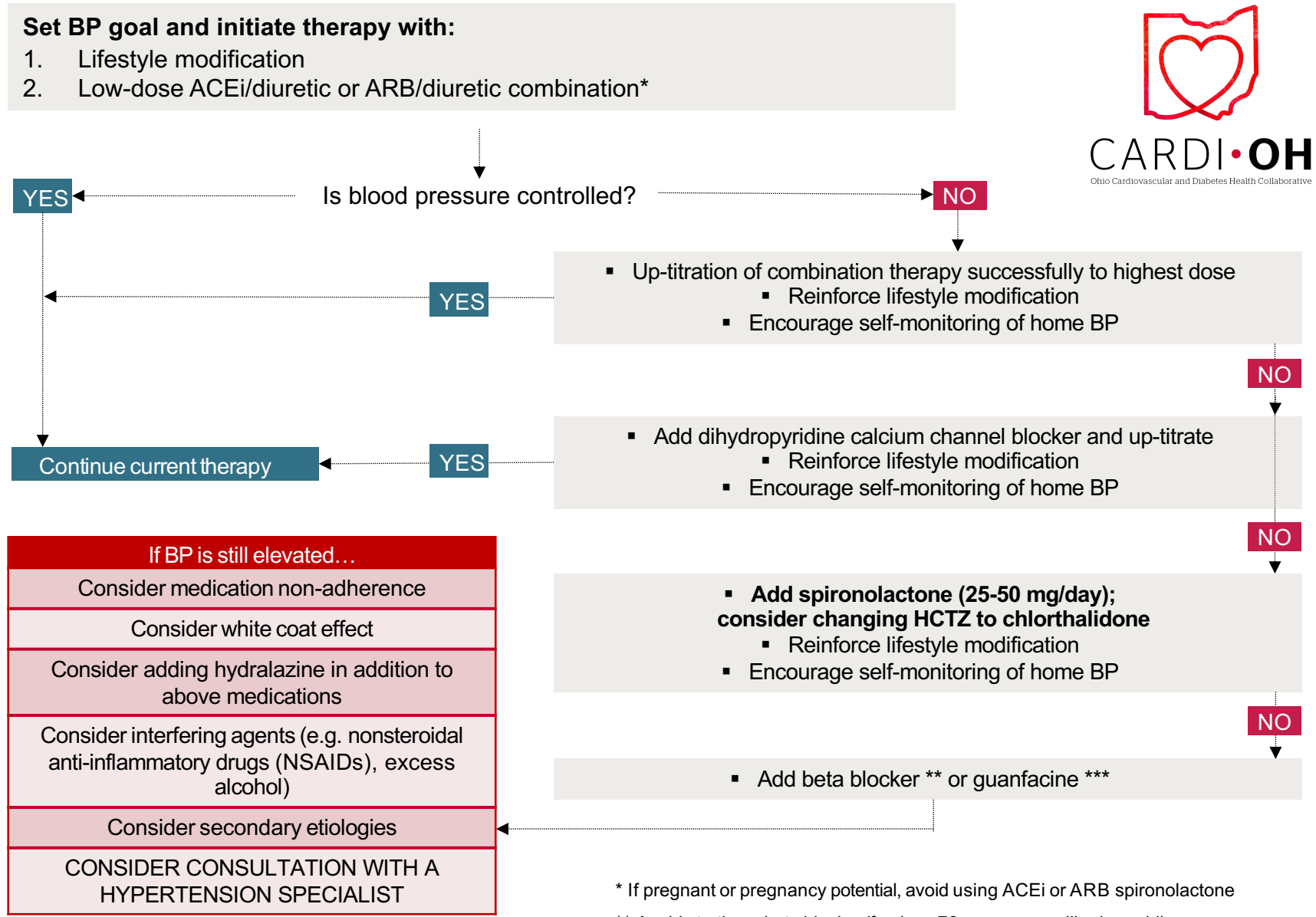
Topics Covered



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

Hypertension Change Package Algorithm

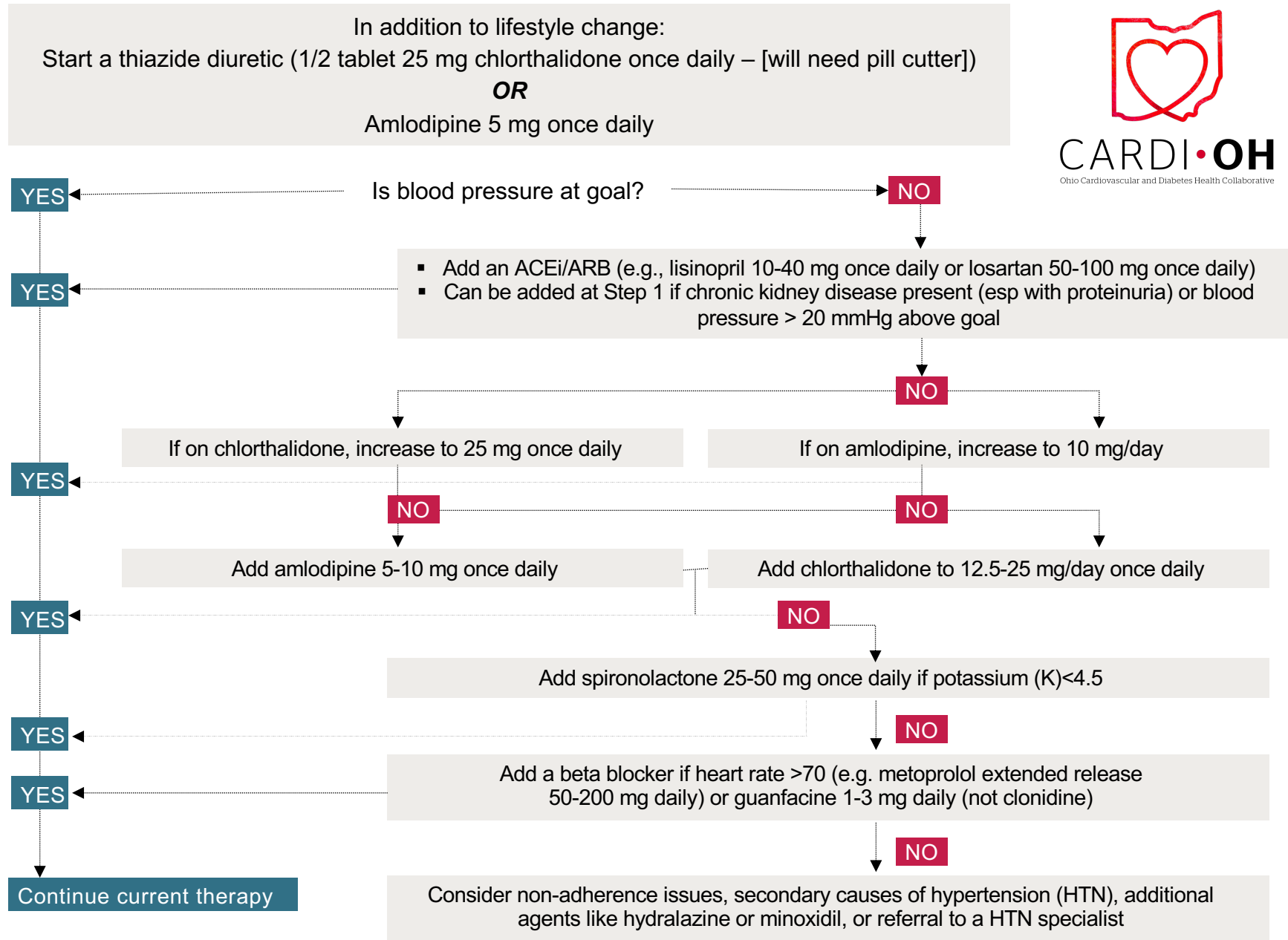
- Widely acceptable and effective algorithm using inexpensive combination therapy
- Nearly all guidelines recommend calcium channel blockers, renin-angiotensin system inhibitors (RASI) such as angiotensin-converting-enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), and thiazide (THZ) as initial agents prescribed for blood pressure (BP) control
- Doses of hydrochlorothiazide (HCTZ) shown to reduce BP and cardiovascular outcomes in clinical trials is 25-50 mg day, and not 12.5-25 mg/day commonly used in primary care settings**
- Fixed-dose combinations may lead to under-dosing of HCTZ - failure to intensify dose
- In addition, BP control gap between African American and non-African American hypertensives is reduced but not eliminated with use of this algorithm



* If pregnant or pregnancy potential, avoid using ACEi 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 Systolic Blood Pressure Intervention Trial (SPRINT), with chlorthalidone the preferred thiazide-like diuretic, especially for African American patients
- Non-African American patients could also start with either angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB)
- Very effective in achieving even systolic blood pressures < 120 mmHg
- No significant disparity in blood pressure 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 hydrochlorothiazide (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 calcium channel blockers 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)

*The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial

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/triamterene	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

Thiazide-type Diuretic Doses Used in Hypertension Clinical Outcome Trials



Trial	Drug	Dose of Thiazide (mg/d)
VA CSP M&M	HCTZ	100
EWPHE	HCTZ/triamterene	25-50
MRC Elderly	HCTZ/amiloride	25-50
ACCOMPLISH	HCTZ/ACEi vs calcium channel blocker/ACEi	12.5-25
HDFP	chlorthalidone	25-100
SHEP	chlorthalidone	12.5-25
ALLHAT	chlorthalidone	12.5-25
SPRINT	chlorthalidone	12.5-25
HAPPY	bendroflumethiazide HCTZ	5-10 50-100
PATS	indapamide	2.5
PROGRESS	indapamide (+ACEi)	2.5
HYVET	indapamide	1.5

Pharmacokinetics

A rationale for the selection of chlorthalidone over HCTZ

Compared to HCTZ, chlorthalidone has:

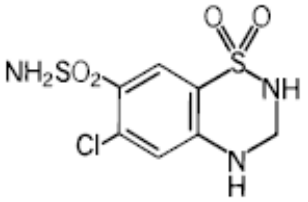
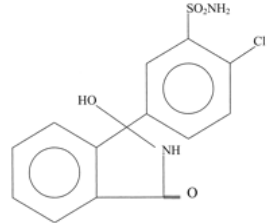
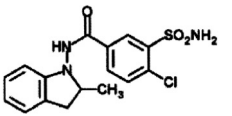
- ~ 2X potency in BP lowering
- Longer duration of BP lowering
- Larger evidence base documenting cardiovascular disease (CVD) reduction

The half-life of chlorthalidone is up to 60-72 hours, yielding:

- More potent and smoother BP control
- More gradual onset of diuretic action with less urinary urgency
- Greater tolerance to missed doses

Note: Amlodipine also has a long-half life



	Vd	Relative Potency*	Oral Bioavailability	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 red blood cells (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

Calcium Channel Blocker Half-Life

- Amlodipine, like chlorthalidone, has a very long half-life (40-60 hours) and consequently more tolerant of missed doses
- Amlodipine has an extensive evidence base demonstrating reduction of CVD events and can be prescribed as either an initial or add-on agent
- Amlodipine is effective regardless of age, race, or renal function
- In patients with kidney dysfunction, it should be combined with an ACEi or ARB

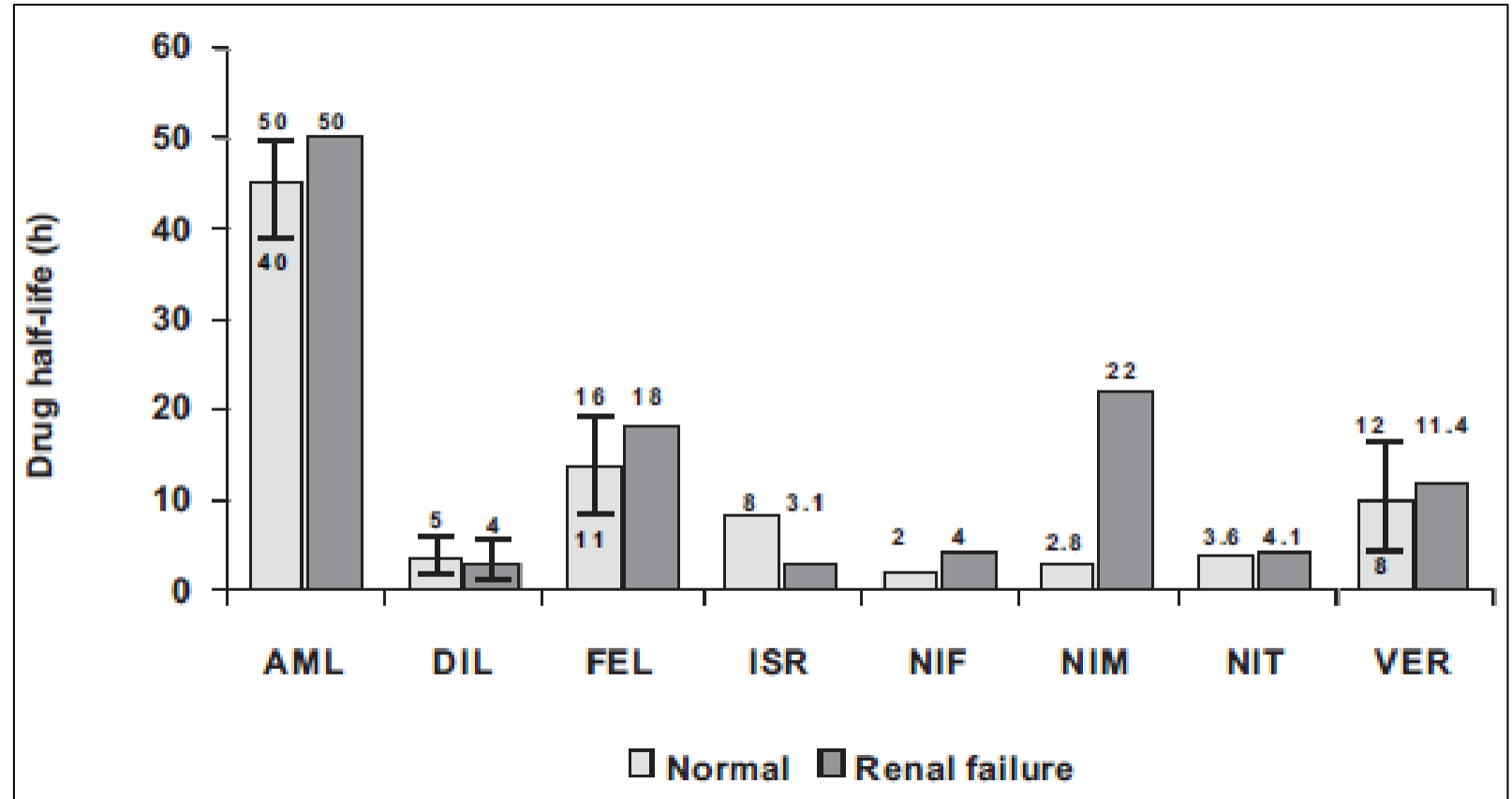


Figure 1. Drug Half-Life for Calcium Channel Blockers in the Presence of Renal Failure

AML = amlodipine; DIL = diliazem; FEL = felodipine; ISR = isradipine; NIF = nifedipine; NIM = nimodipine; VER = verapamil

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

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

- Spirolactone is effective in the treatment of resistant HTN, including in tolerable doses ≤ 50 mg/day

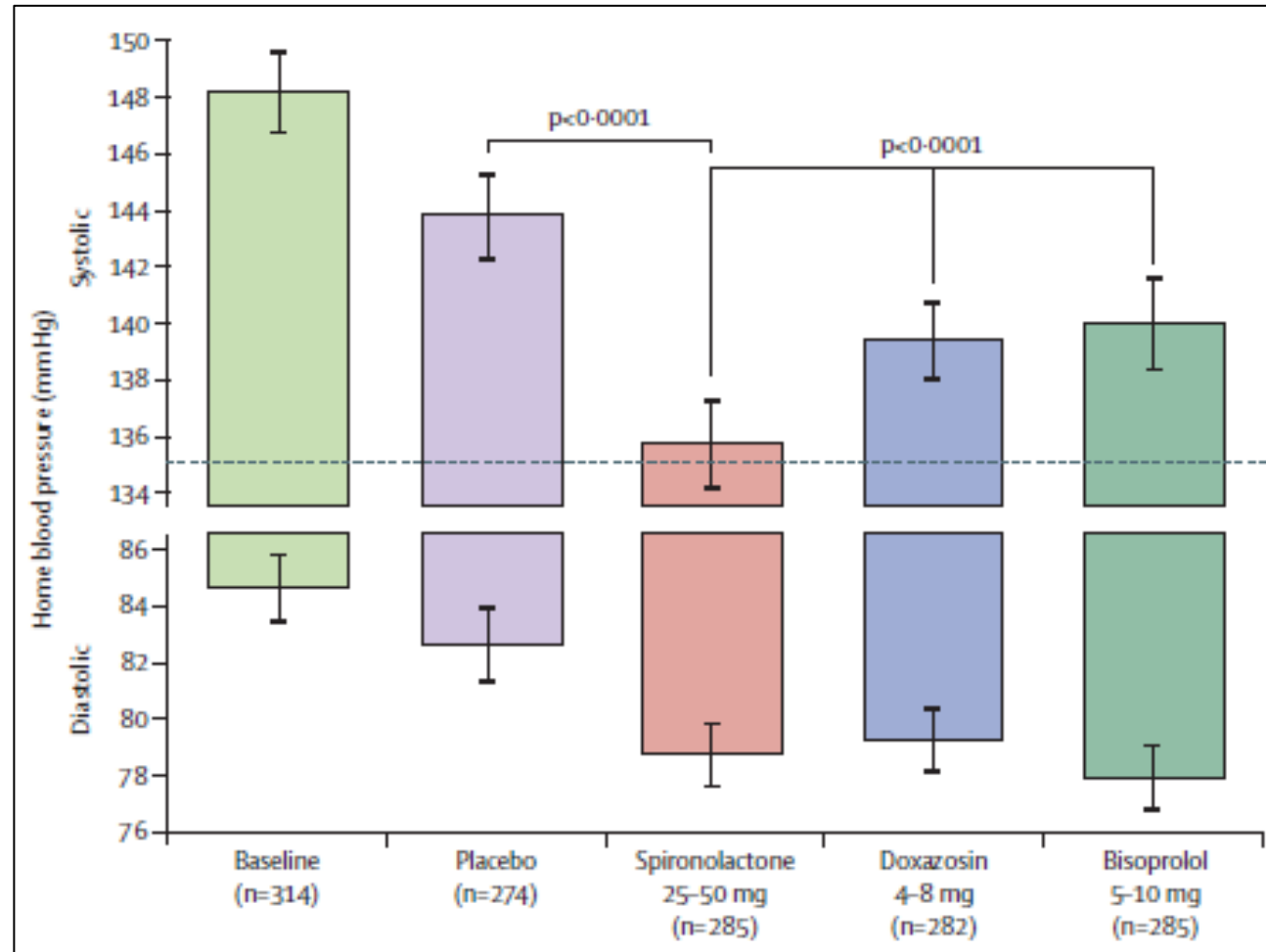


Figure 2. Home Systolic and Diastolic Blood Pressures Comparing Spirolactone with Each of the Other Cycles
 The top and bottom of each column represents the unadjusted home systolic and diastolic blood pressures, respectively, averaged across the mid-cycle (low-dose) and end-of-cycle (high dose) visits (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.

Bottom-Line

- Thiazide diuretics are very potent antihypertensives.
- Thiazide diuretics and calcium channel blockers are unsurpassed in reducing CVD outcomes in a wide range of clinical outcome trials, including the >42K participant ALLHAT trial and other trials.
- Due to thiazide diuretics' and calcium channel blockers' substantial evidence base demonstrating the reduction of CVD events, they are recommended as an initial or add-on agent by most national and international guidelines.
- Chlorthalidone and amlodipine have very long half-lives (60-72 hours) and thus more tolerant of missed doses.
- Thiazide diuretics and amlodipine are effective regardless of age or race.
- In patients with kidney dysfunction or heart failure, they should be combined with an ACEi or ARB.
- In patients with hypertension that is not controlled on a thiazide diuretic (including chlorthalidone), calcium channel blocker, and RASi or if needed for hypokalemia, the use of spironolactone (25-50 mg/day) should be considered.