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

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

**IS BLOOD PRESSURE CONTROLLED?**

- YES
  - Up-titration of combination therapy successfully to the highest dose
  - Reinforce lifestyle modification
  - Encourage self-monitoring of home BP

- NO
  - Add dihydropyridine calcium channel blocker and up-titrate
  - Reinforce lifestyle modification
  - Encourage self-monitoring of home BP

- NO
  - Add on spironolactone (25-50 mg/day), consider changing HCTZ to chlorthalidone
  - Reinforce lifestyle modification
  - Encourage self-monitoring of home BP
  - Add β-blocker **, α-blocker or guanfacine ***

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**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

**CONSIDER CONSULTATION WITH A HYPERTENSION SPECIALIST**

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* 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

March 2019
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

In addition to lifestyle change: Start a thiazide diuretic (chlorthalidone 25 mg ½ tab once daily – [will need pill cutter])

OR

Amlodipine 5 mg once daily

BLOOD PRESSURE AT GOAL?

YES

Add an ACEI/ARB (e.g. lisinopril 10-40 mg once daily or losartan 50-100 mg once daily)
Can be added at Step 1 if CKD present (esp with proteinuria) or BP> 20 mmHg above goal

NO

If on chlorthalidone, increase to 25 mg once daily
If on amlodipine, increase to 10 mg/day

YES

Add amlodipine 5-10 mg once daily
Add chlorthalidone to 12.5-25 mg/day once daily

NO

Add spironolactone 25-50 mg once daily if K<4.5

YES

Add a beta blocker if HR >70 (e.g. metoprolol ER 50-200 mg daily) or guanfacine 1-3 mg daily (not clonidine)

NO

Continue current therapy

Consider non-adherence issues, secondary causes of HTN, additional agents like hydralazine or minoxidil, or referral to a HTN specialist

March 2019
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)

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

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### 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.

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Vd</th>
<th>Relative Potency</th>
<th>Oral Bioavail</th>
<th>Onset (h)</th>
<th>Peak (h)</th>
<th>Half-life (h)</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCTZ</td>
<td>3-4 L/kg</td>
<td>1</td>
<td>~70%</td>
<td>2</td>
<td>4-6</td>
<td>6-9 (single dose)</td>
<td>12 (single dose)</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>3-13 L/kg</td>
<td>1</td>
<td>~65%</td>
<td>2-3</td>
<td>2-6</td>
<td>40 (single dose)</td>
<td>24-48 (long-term dosing)</td>
</tr>
<tr>
<td>Indapamide</td>
<td>20</td>
<td>1</td>
<td>~93%</td>
<td>1-2</td>
<td>&lt;2</td>
<td>14 (Up to 36)</td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>4-6</td>
<td>1</td>
<td>40-60</td>
<td>24-72</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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 = dilatiazem; 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
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 ≤ 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