Thiazide or Thiazide–Like?

Choosing Wisely Academic Detailing Conference
Digby Pines October 12-14
Disclosures

- Pam McLean-Veysey, Team Leader Drug Evaluation Unit
  - DEU funded by the Drug Evaluation Alliance of NS. (DEANS).
  - DEU prepares Drug Evaluation Reports for the Atlantic Common Drug Review (ACDR)
  - Has no conflicts of interest
Faculty/Presenter Disclosure

Faculty: Dr. Brian Moses

Relationships with commercial interests:

- Grants/Research Support: None
- Speakers Bureau/Honoraria: AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Eli Lilly, Janssen, Novartis, NovoNordisk, Pfizer, Sanofi Aventis, and Servier.
- Consulting Fees: AstraZeneca, Bayer, BMS/Pfizer, NovoNordisk, Eli Lilly, Novartis.
- Other: None
Objectives

- To present and critique evidence behind the Canadian Hypertension Guideline recommendation for the preferential use of chlorthalidone versus hydrochlorothiazide.
- To discuss a case and application of this evidence to practice, including safety considerations.
- To present costs of various diuretic products.
CASE HT

- 45 yo male, Caucasian, 200 pounds (91 Kg) 5'11" (1.8 m)
- Hypertension diagnosed after several measurements and using automated office BP 148/93; p 85 BPM.
- Family history of hypertension (Mother and Father). Mother died of stroke.
- No diabetes, coronary artery or kidney disease. Non-smoker
- Self employed in IT
- Patient wants to start treatment.
- You generally start Hydrochlorothiazide 12.5 mg daily but…
  What was it you read in latest Canadian guidelines about diuretics?
  Check website
Professional Resources

Hypertension Canada Guidelines

- 2018 Hypertension Canada Guidelines for Adults and Children (PDF)
- 2018 Hypertension Canada Guidelines for Pregnancy (PDF)
- Hypertension 2020 Highlights Booklet (PDF)
- Hypertension 2020: Putting the Guidelines into Practice Slide Deck EN (PPT)
- Hypertension 2020: Putting the Guidelines into Practice Slide Deck FR (PPT)


Resources
- Guidelines
- HT in Pregnancy
- Booklet

Bingo - Slide set found!

http://guidelines.hypertension.ca/chep-resources/
Longer-acting Diuretics Should be Preferred
(i.e., thiazide-like are preferred to thiazides)

**Longer-acting (thiazide-like):** chlorthalidone, indapamide

**Shorter-acting (thiazides):** hydrochlorothiazide
First Line Treatment of Adults with Systolic/Diastolic Hypertension Without Other Compelling Indications

TARGET <140/90 mmHg (non-automated measurement method)
Initial Treatment

Health Behaviour Management

- Thiazide/thiazide-like diuretic
- ACE-I
- ARB
- Long-acting CCB
- β-blocker
- Single pill combination

† Long-acting diuretics like indapamide and chlorthalidone are preferred over shorter acting diuretics like hydrochlorothiazide.

* β-blockers are not indicated as first-line therapy for age 60 and above.

** Recommended SPC choices are those in which an ACE-I is combined with a CCB, an ARB with a CCB, or a CE-I or ARB with a diuretic
Need some details

What does the main publication say?

Guidelines

Hypertension Canada’s 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children

http://guidelines.hypertension.ca/chep-resources
Indications for drug therapy for adults with diastolic hypertension with or without systolic hypertension

- Initial therapy should be with either monotherapy or single pill combination (SPC).

- Recommended monotherapy choices are:
  - Thiazide/thiazide-like diuretic (Grade A), with longer-acting diuretics preferred (Grade B) (No references in publication)
    - β-blocker (in patients younger than 60 years; Grade B),
    - ACE inhibitor (in non-black patients; Grade B),
    - ARB (Grade B), or
    - Long-acting calcium channel blocker (CCB) (Grade B).

http://guidelines.hypertension.ca/chep-resources
Indications for drug therapy for adults with isolated systolic hypertension

Initial therapy should be

- single-agent therapy with a thiazide/thiazide-like diuretic (Grade A),
- a long-acting dihydropyridine CCB (Grade A),
- ARB (Grade B)

If there are adverse effects, another drug from this group should be substituted.

- Hypokalemia should be avoided in patients treated with thiazide/thiazide-like diuretic monotherapy (Grade C).
- No mention to long-acting diuretic being preferred

http://guidelines.hypertension.ca/chep-resources
GRADE recommendations

Grade A

- based on randomized trials (or systematic reviews of trials) with
  - high levels of internal validity and statistical precision, and for which the study results can be directly applied to patients because of similar clinical characteristics and the clinical relevance of the study outcomes.

Grade B

- based on randomized trials, systematic reviews or pre-specified subgroup analyses of randomized trials that
  - have lower precision, or
  - there is a need to extrapolate from studies because of differing populations or
  - reporting of validated intermediate/surrogate outcomes rather than clinically important outcomes.

http://guidelines.hypertension.ca/chep-resources
**Back to slide deck:**

Olde Engberink Meta analysis of 21 RCTs
> 1 year Follow-up;
> 480,000 patient-years
Mean age 60-68

- **TT** = 17 studies vs. placebo or other antihypertensive
  - 9 of 17 studies included HCTZ
    - 1 studied 12.5 mg dose; remaining 25, 50, 100 mg doses
    - 1 HCTZ monotherapy; remaining combination therapy
- **TL** = 8 studies vs. placebo or other antihypertensive
  - 7 studies chlorthalidone 12.5-25 mg; 1 indapamide 1.5 mg

**OUTCOMES:** CVE defined as the aggregate of cerebrovascular events, coronary events, and heart failure

- Greater BP lowering effect with TT

**NO head to head TT vs TL studies**

TT = Thiazide Type; TL= Thiazide like
Olde Engberink et al *Hypertension* 2015;65(5):1033-40
2nd reference from slide deck


Chlorthalidone More Effective Than Hydrochlorothiazide in BP Reduction

Kruskal-Wallis test used with Dunn's test for multiple comparisons; comparison between baseline and Wilcoxon signed rank test results. Mean 24h SBP was significantly lower for the chlorthalidone group than for the HCTZ group at week 4 (125.52 vs. 139.71 mmHg, respectively, P=0.019) and week 12 (121.87 vs. 136.64 mmHg, respectively, P=0.013). Intent-to-treat population.

http://guidelines.hypertension.ca/chep-resources
Pareek AK, 2016

- 12 week, DB, DD, PG **N=54**, conducted in India

- **Patients:** Stage 1 hypertension (BP 140-159/90-99); mean age 45, mostly non-smokers. Excluded those with comorbid conditions.

- **Interventions/Comparisons**
  - Chlorthalidone 6.25 mg daily **N=16**
  - HCTZ 12.5 mg daily **N=18**
  - Controlled Release HCTZ **N=20** (not available in Canada)

- **Outcome**
  - Change in BP 24-h ambulatory blood pressure (ABP) monitoring and office based BP.

Office BP
*No difference in proportion < 140/90

Office DBP

Office SBP

**p < 0.001; *p < 0.01; Wilcoxon signed rank test was used for comparisons. DBP = diastolic blood pressure; other abbreviations as in Figures 2 and 3.

A significant decrease of both 24-h and nighttime ambulatory BP with chlorthalidone, 6.25 mg/day, was observed. There was no significant decrease with HCTZ, 12.5 mg/day.

**p < 0.001; *p < 0.01; Wilcoxon signed rank tests were used for comparison. CTD = chlorthalidone; HCTZ — hydrochlorothiazide; SBP — systolic blood pressure."

2017 HC Guidelines included 3 references to support chlorthalidone over HCTZ


ADDITIONAL REFERENCE

Roush 2015 Meta Analysis
Head-to-Head Comparisons of Hydrochlorothiazide With Indapamide and Chlorthalidone: Antihypertensive and Metabolic Effects *Hypertension* 2015;65: 1041-6.

- N= 4 randomized trials; N=883 patients

- **Comparisons**: HCTZ vs. indapamide or chlorthalidone - effect on antihypertensive potency and metabolic effects

- **Outcome**: Difference in SBP
  - INDAP vs. HCTZ: −5.1 mm Hg (95% CI, −8.7 to −1.6); *P*=0.004
  - Chlorthalidone vs. HCTZ: −3.6 mm Hg (95% CI, −7.3 to 0.0); *P*=0.052

- HCTZ vs INDAP no difference in metabolic adverse effects, or K+.

- No trials chlorthalidone vs INDAP

- No studies of metabolic effects of chlorthalidone with HCTZ

- All trials lacked cardiovascular events as outcomes.
**Additional meta analyses**

  - First-line low-dose thiazides reduced all morbidity and mortality outcomes in adult patients with moderate to severe primary hypertension.
  - First-line ACE inhibitors and calcium channel blockers may be similarly effective, but the evidence was of lower quality.
  - First line high-dose thiazides and first-line beta-blockers were inferior to first-line low-dose thiazides.

  - the maximal blood pressure-lowering effect of different thiazides similar.
  - thiazides reduced average blood BP vs placebo by
    - 9 mmHg (95% CI 9 to 10)/4 mmHg (95% CI 3 to 4) high-quality evidence.

- **Liang meta analysis 2017- see next slide**
  - included direct comparative studies
N= 12 trials; 5 indapamide vs HCTZ; 7 chlorthalidone vs HCTZ

- Thiazide-like diuretics vs Thiazide type
  - Additional reduction in
    - Systolic BP 5.59 [5.69, 5.49]; P < 0.001
    - Diastolic BP 1.98 [3.29, 0.66]; P = 0.003

- No statistically significant difference in incidence of
  - hypokalemia 1.58 [0.80, 3.12]; P = 0.19 (4 studies)
  - hyponatremia 0.14 [0.57, 0.30], P = 0.54 (2 studies)
  - blood glucose 0.13 [0.16, 0.41], P = 0.39
  - total cholesterol 0.13 [0.16, 0.41], P = 0.39

- No hard clinical outcomes reported
Observational Studies

Retrospective Cohort Studies

  - Ontario N= 29,900
  - Chlorthalidone vs HCTZ
    - **no difference in CVE** (MI, Heart failure, stroke)↑ risk of low Na and K

  - CVE lower in both diuretic groups over 7 years
    - Chlorthalidone aHR : 0.51 (95% CI: 0.43 to 0.61); P= 0.0001
    - HCTZ: aHR 0.65 (95% CI: 0.55 to 0.75); P=0.0001
  - Chlorthalidone > HCTZ  HR 0.79 (95% CI 0.68-0.92)
  - Lower BP, cholesterol, LDL, **potassium** and higher uric acid.

Ongoing Point of Care prospective study Veterans Affairs Co-operative study #597
What are other guidelines saying?
No class of medications (i.e., angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers, or beta blockers) was significantly better than thiazides and thiazide-like diuretics as a first-line therapy for any outcome.
If diuretic treatment is to be initiated or changed,

- offer a thiazide-like diuretic, such as chlorthalidone (12.5–25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide.

- For people who are already having treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, continue treatment with the bendroflumethiazide or hydrochlorothiazide.
# Single entity thiazides

<table>
<thead>
<tr>
<th>THIAZIDES</th>
<th>UNIT COST (NS Pharmacare- Rounded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide</td>
<td></td>
</tr>
<tr>
<td>12.5 mg</td>
<td>0.03</td>
</tr>
<tr>
<td>25 mg</td>
<td>0.02</td>
</tr>
<tr>
<td>50 mg</td>
<td>0.03</td>
</tr>
<tr>
<td>100 mg</td>
<td>0.12</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td></td>
</tr>
<tr>
<td>50 mg</td>
<td>0.13 – (dose ¼ to ½ tablet)</td>
</tr>
<tr>
<td>Indapamide (e.g., Lozide and generics)</td>
<td></td>
</tr>
<tr>
<td>1.25 mg</td>
<td>0.07</td>
</tr>
<tr>
<td>2.5 mg</td>
<td>0.12</td>
</tr>
</tbody>
</table>
## Combination Products Thiazide-like Diuretics

<table>
<thead>
<tr>
<th>Thiazide like diuretic (strengths in mg)</th>
<th>Unit Cost (NS Pharmacare- Rounded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol+ Chlorthalidone (e.g. Tenoretic and generics)</td>
<td></td>
</tr>
<tr>
<td>50/25</td>
<td>0.32</td>
</tr>
<tr>
<td>100/25</td>
<td>0.52</td>
</tr>
<tr>
<td>Perindopril+ Indapamide (e.g. Coversyl Plus and generics)</td>
<td></td>
</tr>
<tr>
<td>Low dose 2/0.625</td>
<td>Non benefit on NS Pharmacare</td>
</tr>
<tr>
<td>4/1.25</td>
<td>0.51</td>
</tr>
<tr>
<td>8/2.5</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Note: many combinations with hydrochlorothiazide (e.g. +ACEI or ARB ranging from $0.20 to $0.69 per tablet depending on agent and strength
You have considered all the evidence on which the Guideline Statement was based ... and then some!

You decide to

A. Prescribe chlorthalidone 50 mg ¼ tablet once daily
B. Prescribe HCTZ 12.5 mg once daily
C. Prescribe HCTZ 25 mg daily
D. Prescribe Indapamide 1.25 mg daily
E. Other

Discussion