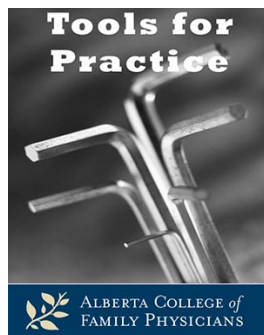


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**Reviewed: June 29, 2015**  
**Evidence Updated: 4 network meta-analyses and cohort study added**  
**Bottom line: Unchanged**  
**First Published: February 6, 2012**



## **Is Hydrochlorothiazide the Best Thiazide Diuretic for Hypertension?**

**Clinical Question: When choosing a thiazide diuretic for hypertension, is hydrochlorothiazide (HCTZ) the best choice?**

**Bottom-line: The available data suggest that hydrochlorothiazide is at best equal to and very likely inferior to chlorthalidone for improving blood pressure (BP) and clinical outcomes. Consider chlorthalidone when initiating thiazide diuretic therapy for hypertension.**

### **Evidence:**

- No trials specifically compare HCTZ to other thiazide diuretics on cardiovascular or mortality outcomes. We must rely on less rigorous study designs and other outcomes:
  - Chlorthalidone reduces systolic BP better than HCTZ at equivalent doses with similar effects on potassium:<sup>1,2</sup>
    - Chlorthalidone 25 mg, compared to HCTZ 50 mg, provided superior BP reduction overall (12 versus 7 mmHg on 24-hr monitor) and at nighttime (13 versus 6 mmHg).<sup>3</sup>
  - Retrospective (and thus not considered definitive) analysis of the MRFIT trial: Chlorthalidone-based regimen reduced mortality versus HCTZ-based regimen (HR: 0.79 [95% CI: 0.68 to 0.92];  $P=0.0016$ ).<sup>4</sup>
  - Retrospective cohort study of 29,873 patients from Ontario found no difference in cardiovascular outcomes but increased risk of electrolyte abnormalities with chlorthalidone.<sup>5</sup>
  - Large trials using chlorthalidone (like ALLHAT<sup>6</sup> and SHEP<sup>7</sup>) have demonstrated reductions in cardiovascular endpoints whereas HCTZ evidence is less robust.
  - Network meta-analysis of nine randomized controlled trials found chlorthalidone associated with fewer cardiovascular events than hydrochlorothiazide (Relative risk ~0.8).<sup>8</sup> However, these were indirect comparisons.
    - Other indirect comparisons with thiazide diuretics (not just hydrochlorothiazide) have found either no difference in cardiovascular

outcomes<sup>9</sup> or, in more recent studies, reduced cardiovascular events with chlorthalidone/indapamide.<sup>10,11</sup>

**Context:**

- Thiazide diuretics are first-line for hypertensive patients without compelling indications for an alternate drug.<sup>12-14</sup>
- Meta-analysis<sup>15</sup> (19 trials): found 24-hour BP with 12.5-25 mg doses of HCTZ compared to other antihypertensive drugs:
  - Systolic 4.5-6.2 mmHg and diastolic 2.9-6.7mmHg higher.
- Chlorthalidone has a longer half-life than HCTZ (50-60 versus 9-10 hours), which may explain the superior BP control, especially at nighttime.<sup>16</sup>
- HCTZ's advantage is availability in many combination preparations which may improve adherence.<sup>17</sup>
- Indapamide is another thiazide-like diuretic with good evidence for reduction in cardiovascular endpoints as first<sup>18</sup> or second-line antihypertensive.<sup>19</sup>

**Original Authors:**

G. Michael Allan MD CCFP, Raj S. Padwal MD MSc FRCP(C)

**Updated:**

Adrienne J Lindblad BSP ACPR PharmD

**Reviewed:**

G. Michael Allan MD CCFP

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