Meta-Analysis: Diuretics

Head-to-Head Comparisons of Hydrochlorothiazide With Indapamide and Chlorthalidone

Antihypertensive and Metabolic Effects

George C. Roush, Michael E. Ernst, John B. Kostis, Suraj Tandon, Domenic A. Sica

See Editorial Commentary, pp 983–984

Abstract—Hydrochlorothiazide (HCTZ) has often been contrasted with chlorthalidone, but relatively little is known about HCTZ versus indapamide (INDAP). This systematic review retrieved 9765 publications, and from these, it identified 14 randomized trials with 883 patients comparing HCTZ with INDAP and chlorthalidone on antihypertensive potency or metabolic effects. To make fair comparisons, the dose of the diuretic in each arm was assigned 1 of 3 dose levels. In random effects meta-analysis, INDAP and chlorthalidone lowered systolic blood pressure more than HCTZ: −5.1 mm Hg (95% confidence interval, −8.7 to −1.6); P=0.004 and −3.6 mm Hg (95% confidence interval, −7.3 to 0.0); P=0.052, respectively. For both comparisons, there was minimal heterogeneity in effect across trials and no evidence for publication bias. The HCTZ–INDAP contrast was biased in favor of greater HCTZ potency because of a much greater contribution to the overall effect from trials in which the HCTZ arm had a higher dose level than the INDAP arm. For the HCTZ–INDAP comparison, no single trial was responsible for the overall result nor was it possible to detect significant modifications of this comparison by duration of follow-up, high- versus low-bias trials, or the presence or absence of background medications. There were no detectable differences between HCTZ and INDAP in metabolic adverse effects, including effects on serum potassium. In conclusion, these head-to-head comparisons demonstrate that, like chlorthalidone, INDAP is more potent than HCTZ at commonly prescribed doses without evidence for greater adverse metabolic effects. (Hypertension. 2015;65:1041-1046. DOI: 10.1161/HYPERTENSIONAHA.114.05021.)

Online Data Supplement

Key Words: blood pressure ■ chlorthalidone ■ hydrochlorothiazide ■ hypokalemia ■ indapamide

Recommended as first line agents in most hypertension guidelines, chlorthalidone and hydrochlorothiazide (HCTZ), and the thiazide-like diuretic, chlorthalidone (CTDN), with respect to duration of action, antihypertensive potency, nonblood pressure–related pleiotropic features, reduction of left ventricular hypertrophy, and reduction of cardiovascular events. These studies have been accompanied by many helpful commentaries contrasting the 2 medications. However, relatively little is known as to how HCTZ compares with another thiazide-like medication, indapamide (INDAP), even though both INDAP and CTDN have been recommended in place of HCTZ. Therefore, we conducted a systematic review and meta-analysis of head-to-head randomized controlled trials to address this question. In addition, head-to-head trials contrasting HCTZ with CTDN were analyzed to further quantify the relative potency of those 2 drugs and to place the HCTZ–INDAP comparisons in context.

Methods

This review and analysis followed recommended guidelines. Using each of the 3 diuretics as keywords, we searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials with both narrow and broad searches (Figure S1 in the online-only Data Supplement for further details). General inclusion criteria were randomized trials of hypertensives reported in English with systolic blood pressure (SBP), metabolic parameters, or cardiovascular events as outcomes and contrasting 2 or 3 of the diuretics (HCTZ, CTDN, and INDAP) with one another. For trials limited to antihypertensive and metabolic effects as outcomes, exclusion criteria were BP limited...
to standing BP only, drug dose titrated to effect on the outcome; follow-up <2 weeks; and follow-up >6 months (because such trials are likely to be focused on other outcomes and therefore might measure blood pressure less rigorously). Sitting BP was chosen over supine BP where both were given. Trials were limited to diuretics at commonly prescribed doses (online-only Data Supplement).

To make fair comparisons between drugs, the diuretic dose in milligrams in each arm was classified according to 3 dose levels (or steps) using 10 different sources (Section 1 and Table S1 in the online-only Data Supplement): HCTZ: 12.5, 25, and 50; CTDN: 6.25, 12.5, and 25; INDAP immediate-release: 1.25, 2.5, and 5; INDAP sustained release: 1.5, 2.0, and 2.5. Each trial was then classified by relative dose level: HCTZ higher (HCTZ dose higher than INDAP or CTDN dose), INDAP higher (INDAP dose higher than HCTZ dose), CTDN higher (CTDN dose higher than HCTZ dose), and dose equivalent (drugs given at the same dose in the 2 arms).

Data analyzed were mean effect, SD, and number of patients, n, in each arm. Where necessary, the SD was computed as SE times n1/2. Ninety-five percent confidence intervals (95% CI) were obtained by pooling the variances of each arm. For the overall effect, variances of confidence limits for all trials were pooled. Random effects meta-analysis was used throughout. The DerSimonian–Laird model was used initially, supplemented by the more conservative Knapp–Hartung model where appropriate.

Sensitivity analyses were (1) a leave-one-trial-out analysis, (2) analysis of low- versus high-bias trials, (3) analysis of trials with background versus no background drug, (4) analysis with follow-up >4 weeks versus ≤4 weeks, (5) use of a 2-level classification for INDAP (1.25/2.5) rather than the 3-level classification (1.25/2.5/5), (6) use of the single most precise study, a (7) use of the 3 largest studies, and (8) analyses for publication bias using funnel plots and testing by the Duval–Tweedie method. All analyses used Comprehensive Meta-Analysis software, version 3.2.00089 (March 24, 2014).

Results

The search yielded 9765 references (Figure S1) of which were 14 eligible trials: 10 with HCTZ–INDAP comparisons of SBP, 3 with HCTZ–CTDN comparisons of SBP, and 9 with HCTZ–INDAP comparisons of metabolic parameters (Table 1). No trials compared CTDN with INDAP, and all trials lacked cardiovascular events as outcomes. Contrasting CTDN with HCTZ on metabolic effects was lacking. Table 1 shows baseline characteristics. One HCTZ–INDAP comparison lacked information on SDs and attempts to reach its authors were unsuccessful; including this trial would have favored INDAP compared with HCTZ with respect to antihypertensive effect. Seven trials were double blind. Table S2 gives the 4 other data quality characteristics.

### Table 1. Characteristics of Trials Comparing HCTZ With INDAP and HCTZ With CTDN

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number, Baseline SBP</th>
<th>Baseline Comorbidities When Specified</th>
<th>HCTZ and INDAP Dose or HCTZ and CTDN Dose</th>
<th>Relative Dosage</th>
<th>Weeks of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhigjee et al* (black patients)*</td>
<td>19, NR†‡, No CVD, no DM</td>
<td>25 and 2.5</td>
<td>HCTZ and INDAP</td>
<td>Equivalent</td>
<td>4</td>
</tr>
<tr>
<td>Bhigjee et al* (Indian patients)*</td>
<td>18, NR†‡, No CVD, no DM</td>
<td>25 and 2.5</td>
<td>Equivalent</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Elliott et al**</td>
<td>11, 168‡ Serum uric acid &gt;8 mg/dL, no CKD</td>
<td>25 and 2.5</td>
<td>Equivalent</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Emeriau et al†¹</td>
<td>524, 175 (Age 65+) No CAD, no symptomatic CHF, no CKD</td>
<td>25 and 1.5 SR</td>
<td>HCTZ&gt;INDAP</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Kreft et al†²</td>
<td>17, 151‡ No CVD or DM</td>
<td>50 and 2.5</td>
<td>HCTZ&gt;INDAP</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Krum et al†³</td>
<td>18, 141 All with DM</td>
<td>12.5 and 2.5§</td>
<td>INDAP&gt;HCTZ</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Madden et al†⁴</td>
<td>28, 167 All had CKD</td>
<td>50 and 2.5</td>
<td>HCTZ&gt;INDAP</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Malini et al†⁵</td>
<td>31, 165 Uncomplicated hypertension (all on enalapril at baseline)</td>
<td>25 and 2.5¶</td>
<td>Equivalent</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Plante et al⁶</td>
<td>24, 137 Not reported</td>
<td>50 and 2.5</td>
<td>HCTZ&gt;INDAP</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Plante et al⁷</td>
<td>42, 183 Age 65+</td>
<td>50 and 2.5</td>
<td>HCTZ&gt;INDAP</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Radevski et al**</td>
<td>42, 149‡ Excludes insulin-dependent DM</td>
<td>12.5 and 2.5</td>
<td>INDAP&gt;HCTZ</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Spence et al**</td>
<td>39, 150 No angina, CHF, aortic stenosis, or DM</td>
<td>25 and 2.5</td>
<td>Equivalent</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

HCTZ versus CTDN

| Ernst et al* | 24, 142 No MI or stroke in the previous 6 mo | 50 and 25 | Equivalent | 8 |
| Pareek et al² | 18, 154‡ No CVD, no DM | 12.5 and 6.25 | Equivalent | 4 |
| Kwon et al³ | 28, 152 No CHF | 25 and 12.5 | Equivalent | 8 |

CAD indicates coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CTDN, chlorthalidone; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HCTZ, hydrochlorothiazide; INDAP, indapamide; MI, myocardial infarction; NA, not available; SBP, systolic blood pressure, and SR, sustained release.

*Includes data on metabolic measurements.
†Not relevant. Trial used only for metabolic outcomes.
‡Crossover trial.
§Both medications added to 20 mg of fosinopril.
¶Both medications added to 20 mg of enalapril.
Relative to HCTZ, INDAP produced a greater reduction in SBP: −5.1 mm Hg (95% CI, −8.7 to −1.6), P=0.004 (Figure 1). There was minimal heterogeneity across the 10 trials. Because of substantial differences in dose levels for the 2 drugs, the result was biased in favor of HCTZ having a greater potency than INDAP (description in Figure 1 and Table S3). INDAP and HCTZ were not detectably different in their effects on serum potassium (Figure 2). Relative differences in other metabolic effects are shown in Table 2. As with potassium, there were no detectable differences between HCTZ and INDAP for these metabolic effects.

Results for sensitivity analyses are as follows: (1) the overall results were not dependent on any 1 trial (Figure S2a). (2) For SBP reduction, there was no statistically significant interaction between the INDAP–HCTZ effect and the following: (a) trials with low versus high bias (Figure S2b), (b) trials with nondiuretic background medications versus trials without such drugs (SBP reductions were −2.6 [−10.0 to 4.8] and −5.5 [−9.1 to −1.9], respectively, P=0.500 for interaction; there were only 2 trials with background medications, so statistical power was limited.), and (c) trials with short (<4 weeks) versus long (>4 weeks) follow-up (SBP reductions were −8.8 [−17.2 to −0.4] and −4.2 [−7.1 to −1.3], respectively, P value=0.315 for interaction). (3) Using a 2-level classification for INDAP dose (1.25/2.5) rather than the 3-level classification (1.25/2.5/5) led to a weight of 84% from trials with the HCTZ dose being lower than the INDAP dose and 16% from trials with the HCTZ dose being higher than the INDAP dose. (4) There was no detectable publication bias with identical observed and adjusted differences in BP potency between the 2 drugs (Figure S3a). (5) The trial with the smallest SE gave a reduction in SBP by INDAP versus HCTZ of −3.3 (−6.5 to −0.1) (Figure 1).11 (6) The 3 largest trials showed a mean SBP reduction of −6.4 (−11.1 to −1.7).11,13,18

Contrasting HCTZ with CTDN also showed a greater reduction in SBP from CTDN compared with HCTZ: −3.6 (95% CI, −7.3 to 0.0), P=0.052 (Figure 3). The trial with the narrowest SE (and also the largest number) showed a difference of −2.5 (−6.9 to 1.89). The trial with the highest quality had the greatest reduction in SBP by CTDN relative to HCTZ: −6.3 (−16.3 to 3.7). There was again no evidence for publication bias for this comparison (Figure S3b).

**Discussion**

These head-to-head comparisons demonstrate that, at commonly used doses, INDAP lowers SBP more than HCTZ without evidence for greater adverse effects. There was also evidence (although limited to fewer patients) that CTDN was more potent than HCTZ. Compared with an estimated 9.5-mm Hg reduction in SBP from HCTZ relative to placebo from Peterzan et al., INAP and CTDN lowered SBP by 54% and 38% more than HCTZ, respectively. The advantage in anti-hypertensive potency of INDAP compared with HCTZ was probably underestimated because of the much greater weight on the overall effect from trials in which HCTZ was given at a higher dose level than INDAP. This HCTZ–CTDN head-to-head synthesis is consistent with the masterful but indirect comparisons of previous meta-analyses. The present...
In spite of greater antihypertensive potency, INDAP did not have a detectably greater effect than HCTZ on metabolic adverse effects. Findings regarding serum potassium are consistent with previous studies showing declines in serum potassium from INDAP immediate-release 2.5 mg of −0.30 to −0.42 mEq/L, similar to the decline found with HCTZ 25 mg. Unlike HCTZ, INDAP has no effect on serum lipids.

Initially, thiazide-related diuretics lower BP via diuretic effects, but ultimately, their antihypertensive effects stem from decreased peripheral arterial resistance through unknown mechanisms. In contrast, INDAP is known to also operate via a direct vasodilator effect from inhibitory activity against vasopressors and decreased inward flow of calcium ions in vascular smooth muscle. Consistent with this mechanism, INDAP reduces BP in end-stage renal disease, unlike HCTZ.

At 2.5 mg per day, INDAP has been described as a weak diuretic. However, its natriuretic and aquaretic effects are dose related. Doubling the dose to 5 milligrams daily promotes volume loss, similar to the effect of 40 mg of furosemide. Thus, at the 5-mg dose, INDAP would address the salt and volume excess of resistant hypertension (as well as provide optimal antihypertensive potency) and would also be a useful diuretic for salt-sensitive hypertension.

Limitations of this study include the wide CIs reflecting some limitations in statistical power, the absence of 24-hour blood pressure measurements (which are better predictors of cardiovascular events), and the absence of cardiovascular events as outcomes. Also, half of the weight for the HCTZ–INDAP comparison came from 1 trial. In addition, these results must be properly interpreted: this analysis does not demonstrate that INDAP is more efficacious than HCTZ for reducing SBP (ie, that INDAP’s superiority is maintained at the 5-mg dose). INDAP would address the salt and volume excess of resistant hypertension (as well as provide optimal antihypertensive potency) and would also be a useful diuretic for salt-sensitive hypertension.

Table 2. Trends for Adverse Metabolic Effects From HCTZ Compared With INDAP With Change (95% Confidence Intervals)

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Change From INDAP Minus Change From HCTZ</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low potassium</td>
<td>−0.1 (−0.3 to 0.2)</td>
<td>mEq/L</td>
</tr>
<tr>
<td>Low sodium</td>
<td>1 (−1 to 3)</td>
<td>mEq/L</td>
</tr>
<tr>
<td>High creatinine</td>
<td>0.1 (−0.1 to 0.2)</td>
<td>mg/dL</td>
</tr>
<tr>
<td>High glucose</td>
<td>4 (3 to 11)</td>
<td>mg/dL</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>−5 (−17 to 7)</td>
<td>mg/dL</td>
</tr>
<tr>
<td>High uric acid</td>
<td>−0.2 (−0.7 to 0.4)</td>
<td>mg/dL</td>
</tr>
</tbody>
</table>

HCTZ indicates hydrochlorothiazide; and INDAP indapamide.

Figure 3. Meta-analysis for systolic blood pressure reduction comparing hydrochlorothiazide (HCTZ) and chlorthalidone (CTDN). τ=0 and F=0%, indicating no detectable heterogeneity across trials and no need for the Knapp-Hartung model. CI indicates confidence interval.
Perspectives
In 2013 in the United States, there were 50 million prescriptions for HCTZ making this the 12th most commonly prescribed drug. However, HCTZ has lesser antihypertensive potency as shown here and has several other types of deficiencies. CTBN is generally offered as the alternative, and the present results, based on head-to-head trials, confirm CTBN’s superiority reported from indirect HCTZ–CTBN comparisons. However, in countries such as the United States, clinicians may avoid CTBN because it has only 1 unscored dose preparation, which is at the maximum recommended dose, making it an impractical choice for many patients. In contrast, INDAP has low and intermediate dose formulations and, in Europe, is also available in slow release, thus giving it much greater flexibility than CTBN. Like CTBN ($19 per month), INDAP immediate-release is relatively inexpensive and, in Europe, is also available in slow-release, thus giving it much greater flexibility than CTBN. CTDN ($19 per month), INDAP immediate-release is relatively inexpensive and it much greater flexibility than CTDN. Like CTDN ($19 per month), INDAP immediate-release is relatively inexpensive and, in Europe, is also available in slow release, thus giving it much greater flexibility than CTDN. Although US guidelines for the management of resistant hypertension advocate CTDN, this analysis implies that INDAP should also be preferred compared with HCTZ for this condition. In addition, these results support the view that CTBN and INDAP are preferable to HCTZ for managing hypertension in general.

Disclosures
None.

References
30. Vegely C, Walker MK, Zeller M, Radermakers JR, Maupoil V, Schiavi P, Guez D, Rochette L. Antioxidant properties of indapamide, 5-OH indapamide and...


42. Aubert I, Djian F, Rouffy J. Beneficial effects of indapamide on lipoproteins and apoproteins in ambulatory hypertensive patients. *Am J Cardiol.* 1990;65:77H–80H.


Head-to-Head Comparisons of Hydrochlorothiazide With Indapamide and Chlorthalidone: Antihypertensive and Metabolic Effects
George C. Roush, Michael E. Ernst, John B. Kostis, Suraj Tandon and Domenic A. Sica

Hypertension. 2015;65:1041-1046; originally published online March 2, 2015; doi: 10.1161/HYPERTENSIONAHA.114.05021

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/65/5/1041

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2015/03/02/HYPERTENSIONAHA.114.05021.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/
Clinics, Head-to-Head Comparisons of Hydrochlorothiazide with Indapamide and Chlorthalidone: Antihypertensive and Metabolic Effects

George C. Roush,1,2 Michael E. Ernst,3 John B. Kostis,4 Suraj Tandon,2 and Domenic A. Sica5
January 23, 2015

1Corresponding author
2UCONN School of Medicine and St. Vincent’s Medical Center, Bridgeport, CT, USA
3University of Iowa Hospital and Iowa City, IA, USA
4Cardiovascular Institute, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ, USA
5Department of Medicine and Pharmacology, Virginia Commonwealth University, Richmond, VA, USA

Running title: Potency of HCTZ, Indapamide and Chlorthalidone

Corresponding author: George C. Roush

Telephone 203-622-3033. Fax 203-625-9556. groush@gcr0.com
Section 1. Classification of dose levels: Text and Table S1.

The dose levels are based on the following 10 sources: randomized trials (7 in number); the hypertension guidelines from JNC 8, the American Society of Hypertension, and the International Society of Hypertension; 2 textbooks (one published by the American Heart Association and another authored by 2 hypertension specialists); a popular evidence based reference for physicians; a widely used mobile application for physicians; review articles (8 in number), and dosage forms identified by 3 different sources.

**HCTZ:** 12.5 / 25/ 50. All sources support this 3 level classification.

**INDAP IR:** 1.25/ 2.5/ 5. This was supported by 4 out of the 9 sources, 2 of which were commonly used physician references (UpToDate and Epocrates mobile), as well as by 4 studies of dosage,\(^1\)\(^3\),\(^1\)\(^4\) including the fact that INDAP has a substantially stronger diuretic effect at 5 mg than at 2.5 mg.\(^1\)\(^5\) The alternative would be a 2 level classification (1.25/2.5). This issue was examined and reported in the RESULTS section as a sensitivity analysis.

**INDAP SR:** 1.5/ 2/ 2.5. This was consistent with the 3 dosage forms and with the following: (1) The mean systolic BP lowering for indapamide IR 2.5 and indapamide SR 2 are virtually identical being within 0.1 mmHg of each other.\(^4\) (2) Combining data from two reports shows that indapamide IR 2.5 is about 20% more potent than indapamide SR 1.5 although confidence limits were wide.\(^1\)\(^6\),\(^1\)\(^7\) This implies that indapamide SR 1.5 is at a lower dose level than indapamide IR 2.5, particularly if one considers that doubling the dose of an antihypertensive produces only a 22% increase in potency.\(^1\)\(^8\)

**CTDN:** 6.25/ 12.5/ 25. One might replace the 1\(^{\text{st}}\) and 3\(^{\text{rd}}\) level assignments of 6.25 and 25, respectively, with, for example, 12.5 and 50, or possibly just 2 dosage levels, 12.5 and 25. At the low end, our assignment of 6.25 is warranted by the recognition among many physicians that a starting dose of 12.5 might be too high for frail or elderly patients, and this viewpoint is reflected in the presence of 6.25 mg formulations stand alone and in fixed dose preparations in India and a 12.5 mg tablet that is scored in Venezuela. At the high dose end of the spectrum, CTDN at 12.5-25 mg in ALLHAT reduced cardiovascular events equal to or greater than the reductions from each of the 3 comparator drugs (lisinopril, amlodipine, and doxazosin) while producing a worrisome 8% prevalence of hypokalemia (ALLHAT 2002) and suggesting to many clinicians that CTDN doses above 25 mg are unnecessarily risky. These classifications are also consistent with a prior meta-analysis of HCTZ and CTDN (Peterzan 2012).

FILE SUPPLEMENT REFERENCES


Table S1. Dose range in milligrams for hydrochlorothiazide, chlorthalidone, and indapamide from randomized trials, hypertension guidelines, textbooks, physician references, and dosage forms used for the 3 level classifications in this analysis.

<table>
<thead>
<tr>
<th>Antihypertensive</th>
<th>HCTZ</th>
<th>INDAP IR</th>
<th>INDAP SR</th>
<th>CTDN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACCOMPLISH 2008</td>
<td>2.5: PATS 1995</td>
<td></td>
<td>25-100: HDFP 1979*</td>
</tr>
<tr>
<td>Doses used in research or review articles with blood pressure as the outcome (see text)</td>
<td>5 mg as the maximum dose</td>
<td>1.25/ 2/ 2.5</td>
<td>6.25 / 12.5/ 25 for CTDN roughly equipotent with 12.5/ 25/ 50 for HCTZ^12</td>
<td></td>
</tr>
<tr>
<td>JNC8 2014^1</td>
<td>12.5-50</td>
<td>1.25-2.5</td>
<td></td>
<td>12.5-25</td>
</tr>
<tr>
<td>American Society of Hypertension^2</td>
<td>12.5-50</td>
<td>1.25-2.5</td>
<td></td>
<td>12.5-25</td>
</tr>
<tr>
<td>International Society of Hypertension^2</td>
<td>12.5-50</td>
<td>1.25-2.5</td>
<td></td>
<td>12.5-25</td>
</tr>
<tr>
<td>Hypertension Primer 2008 (AHA)^3</td>
<td>12.5-50</td>
<td>1.25-5</td>
<td></td>
<td>12.5-50</td>
</tr>
<tr>
<td>Clinical Hypertension 2010^9</td>
<td>12.5-50</td>
<td>1.25-5</td>
<td></td>
<td>12.5-50</td>
</tr>
<tr>
<td>UpToDate (Lexicomp) 2014</td>
<td>12.5-50</td>
<td>1.25-5</td>
<td></td>
<td>12.5-100</td>
</tr>
<tr>
<td>Epocrates Mobile 2014</td>
<td>12.5-50</td>
<td>1.25-5</td>
<td></td>
<td>12.5-100</td>
</tr>
<tr>
<td>Dosage forms^6</td>
<td>12.5/ 25/ 50</td>
<td>1.25, 1.5, 2.5, 3</td>
<td>1.25/ 2/ 2.5</td>
<td>6.25, 12.5 (scored),^8 15, 25, 50, 100</td>
</tr>
<tr>
<td>3 level classification for this paper^17</td>
<td>12.5/ 25/ 50</td>
<td>1.25/ 2.5/ 5</td>
<td>1.25/ 2/ 2.5</td>
<td>6.25/ 12.5/ 25</td>
</tr>
</tbody>
</table>

*Trials using the diuretic as a combination tablet with another anti-hypertensive were excluded.

^8 Knowledge that the 12.5 mg CTDN tablet is scored is based on a communication from the manufacturer of this tablet to the first author.
Table S2. Gender distribution, mean age, and features of data quality in trials comparing HCTZ with INDAP and HCTZ with CTDN

<table>
<thead>
<tr>
<th>Author</th>
<th>% men</th>
<th>mean age</th>
<th>BP measurement</th>
<th>Blinding</th>
<th>Losses to follow up</th>
<th>Drop outs</th>
<th>Intention-to-treat analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhigjee (Black patients)</td>
<td>37, 44</td>
<td>Not relevant (study used only for metabolic outcomes)</td>
<td>double</td>
<td>none</td>
<td>none</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Bhigjee (Indian patients)</td>
<td>37, 44</td>
<td>Not relevant (study used only for metabolic outcomes)</td>
<td>double</td>
<td>none</td>
<td>none</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Elliott</td>
<td>46, 56</td>
<td>Sphygmomanometer, right arm, in triplicate, after 5+ minutes supine.</td>
<td>double</td>
<td>none</td>
<td>none</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Emeriau</td>
<td>39, 72</td>
<td>Sphygmomanometer, same arm each visit, triplicate, after 10+ minutes supine.</td>
<td>double</td>
<td>none</td>
<td>none</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Kreeft</td>
<td>65, 34-66³</td>
<td>Sphygmomanometer, 3 measures averaged, after 15 minutes supine.</td>
<td>double</td>
<td>none</td>
<td>2³</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Krum</td>
<td>50, 56</td>
<td>Sphygmomanometer, 3 measures averaged, seated</td>
<td>open</td>
<td>none</td>
<td>2²</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Maffoul</td>
<td>43, 55</td>
<td>Supine</td>
<td>open</td>
<td>none</td>
<td>none</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Malini</td>
<td>55, 54</td>
<td>Triplicate, after 5+ minutes supine.</td>
<td>open</td>
<td>none</td>
<td>none</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Plante a</td>
<td>37, 52</td>
<td>Supine position.</td>
<td>double</td>
<td>none</td>
<td>none</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Plante b</td>
<td>53, 77</td>
<td>Sphygmomanometer, right arm, triplicate with last 2 averaged, after 5+ minutes supine</td>
<td>open</td>
<td>none</td>
<td>none</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Radevski</td>
<td>33, 57</td>
<td>Per The American Heart Association.</td>
<td>open</td>
<td>none</td>
<td>None</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>Spence²</td>
<td>67, 55</td>
<td>Sphygmomanometer, triplicate, after 10+ minutes supine.</td>
<td>double</td>
<td>none</td>
<td>none</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Ernst</td>
<td>53, 48</td>
<td>Taken according to standard guidelines (Pickering 2005) by a study nurse blinded as to diuretic.</td>
<td>Patients only</td>
<td>none</td>
<td>none</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Pareek</td>
<td>37, 44</td>
<td>Not described</td>
<td>Open</td>
<td>none</td>
<td>none</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>Kwon</td>
<td>46, 50</td>
<td>Oscillometric. 10 minute rest. Supine position</td>
<td>open</td>
<td>none</td>
<td>none</td>
<td>yes</td>
<td></td>
</tr>
</tbody>
</table>

BP: blood pressure

¹2 of 19 patients were withdrawn for poor adherence.

²2 of 20 patients were withdrawn by their personal physicians for “various reasons”

³With the exception of Kreeft et al and Krum et al, none of the authors commented explicitly on losses to follow up and drop outs.

⁴Considered a low bias trial.
<table>
<thead>
<tr>
<th>Study</th>
<th>Dosage of HCTZ/INDAP</th>
<th>Relative Dose Levels</th>
<th>Weight In percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elliott</td>
<td>25/2.5</td>
<td>Equivalent</td>
<td>3.2</td>
</tr>
<tr>
<td>Emeriau</td>
<td>25/1.5 SR</td>
<td>HCTZ level greater</td>
<td>50.0</td>
</tr>
<tr>
<td>Kreeft</td>
<td>50/2.5</td>
<td>HCTZ level greater</td>
<td>3.4</td>
</tr>
<tr>
<td>Krum</td>
<td>12.5/2.5</td>
<td>INDAP level greater</td>
<td>4.2</td>
</tr>
<tr>
<td>Madkour</td>
<td>50/2.5</td>
<td>HCTZ level greater</td>
<td>3.6</td>
</tr>
<tr>
<td>Malini</td>
<td>25/2.5</td>
<td>Equivalent</td>
<td>12.0</td>
</tr>
<tr>
<td>Plante a</td>
<td>50/2.5</td>
<td>HCTZ level greater</td>
<td>4.0</td>
</tr>
<tr>
<td>Plante b</td>
<td>50/2.5</td>
<td>HCTZ level greater</td>
<td>8.0</td>
</tr>
<tr>
<td>Radevski</td>
<td>12.5/2.5</td>
<td>INDAP level greater</td>
<td>3.5</td>
</tr>
<tr>
<td>Spence</td>
<td>25/2.5</td>
<td>Equivalent</td>
<td>8.1</td>
</tr>
<tr>
<td>All Trials</td>
<td></td>
<td></td>
<td>100.0</td>
</tr>
</tbody>
</table>

*Summary results:
Weight from trials with HCTZ level greater than INDAP level = 68.95%
Weight from trials with INDAP level greater than HCTZ level = 7.74%
Weight from trials with HCTZ and INDAP given at the same levels = 23.31%
Narrow Search Algorithm
Within each database the search used the diuretic keywords as follows:

\[
[(\text{HCTZ and CTDN}) \\
\text{OR} \\
(\text{HCTZ and INDAP}) \\
\text{OR} \\
(\text{CTDN and INDAP})]
\]

- 365 articles
- Remove duplicates and articles not meeting criteria based on review of titles, abstracts, and entire articles.
- 14 articles

Broad Search Algorithm
Within each database for each diuretic the search used its diuretic keyword to retrieve the articles.

- 9,400 articles
- Remove duplicates and articles not meeting criteria based on review of titles, abstracts, and entire articles.
- 14 articles

Figure S1. Search algorithms for systematic review. The 3 databases --- PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials --- were searched for randomized trials with systolic BP, metabolic parameters, or cardiovascular events as outcomes and comparing 2 or 3 of the diuretics with one another. For the broad search algorithm, after the keyword for one of the diuretics (e.g., HCTZ) was used to retrieve a set of articles, the search function in Microsoft Word was used to scan titles and abstracts for the other 2 diuretics (e.g., INDAP and CTDN). See text for further inclusion and exclusion criteria. The two search algorithms, narrow and broad, yielded the same 14 articles for review and analysis.
Figure S2a. Removing 1 trial and analyzing the remaining trials for the effect on systolic blood pressure showed that no particular trial accounted for the overall difference between HCTZ and INDAP arms.

Figure S2b. High and low bias trials did not differ significantly in the effect on systolic blood pressure from HCTZ versus INDAP, P = 0.262.
Figures S3a and S3b. Funnel plots for mean systolic blood pressure reduction by INDAP and CTDN compared to HCTZ for observed differences (clear diamonds) and differences adjusted for small studies (solid diamonds). There was no evidence for publication bias for either analysis.