Effects of Thiazide-Type and Thiazide-Like Diuretics on Cardiovascular Events and Mortality
Systematic Review and Meta-Analysis

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Abstract—Thiazide diuretics are recommended as first-line therapy for hypertension and are among the most commonly prescribed drugs worldwide. According to their molecular structure, thiazide diuretics can be divided in thiazide-type (TT) and thiazide-like (TL) diuretics. TL diuretics have a longer elimination half-life compared with TT diuretics and have been shown to exert additional pharmacological effects, which may differently affect cardiovascular risk. In this meta-analysis, we compared the effects of TT and TL diuretics on cardiovascular events and mortality. Randomized, controlled studies in adult hypertensive patients that compared TT or TL diuretics with placebo or antihypertensive drugs and had ≥1 year follow-up were included. Primary outcome was cardiovascular events; secondary outcomes included coronary events, heart failure, cerebrovascular events, and all-cause mortality. Meta-regression analysis was used to identify confounders and correct for the achieved blood pressure reductions. Twenty-one studies with >480,000 patient-years were included. Outcomes were not affected by heterogeneity in age, sex, and ethnicity among included studies, whereas larger blood pressure reductions were significantly associated with increased risk reductions for all outcomes (P<0.001). Corrected for differences in office blood pressure reductions among trials, TL diuretics resulted in a 12% additional risk reduction for cardiovascular events (P=0.049) and a 21% additional risk reduction for heart failure (P=0.023) when compared with TT diuretics. The incidence of adverse events was comparable among TT, TL diuretics, and other antihypertensive therapy. Our data suggest that the best available evidence seems to favor TL diuretics as the drug of choice when thiazide treatment is considered for hypertension. (Hypertension. 2015;65:00-00. DOI: 10.1161/HYPERTENSIONAHA.114.05122.) • Online Data Supplement

Key Words: blood pressure • cardiovascular diseases • diuretics • heart failure • hypertension • thiazides

Thiazide diuretics are widely recommended as first-line therapy for hypertension with >48 million prescriptions for hydrochlorothiazide in the United States in 2011. Clinical trials have demonstrated that thiazide diuretics reduce cardiovascular morbidity and mortality in hypertensive patients when given alone or in combination with β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and calcium antagonists. Thiazide diuretics can be separated according to their molecular structure in thiazide-type (TT) and thiazide-like (TL) diuretics with TT diuretics being to date the most commonly prescribed diuretic class in the United States. TT and TL diuretics differ with regard to their pharmacokinetic and pharmacodynamic properties, which may result in different blood pressure (BP)-dependent and BP-independent effects. TL diuretics such as chlorthalidone have a longer elimination half-life compared with TT diuretics resulting in better 24-hour BP reduction, especially during the night. In addition, experimental evidence suggests that TL diuretics exert additional effects on the vascular system by reducing platelet aggregation and vascular permeability. On the basis of the above, it is conceivable that TL diuretics may differentially affect cardiovascular disease compared with TT diuretics. Because prospective trials comparing TT and TL diuretics are lacking, the interchangeability of these 2 classes about cardiovascular risk reduction is subject of debate. Previous retrospective studies have concentrated on differences between hydrochlorothiazide and chlorthalidone and reported conflicting results. A meta-analysis of prospective studies indirectly comparing hydrochlorothiazide and chlorthalidone concluded that treatment with chlorthalidone resulted in less cardiovascular event (CVE) than treatment with hydrochlorothiazide. Because differences in pharmacological and pharmacokinetic properties may not be confined to hydrochlorothiazide and chlorthalidone, we compared the effects of TT and TL diuretics on cardiovascular outcome. To correct for...
nonequivalent doses, we additionally related the antihypertensive effect of TT and TL diuretics to the achieved cardiovascular risk reduction.

Methods

The primary objective of this systematic review and meta-analysis was to compare the effect of TT and TL diuretics on CVE; coronary events, heart failure, cerebrovascular events, and all-cause mortality in adult hypertensive (BP >140/90 mm Hg) patients.

Data Sources and Searches

In this meta-analysis, we adhered to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Medline, Embase, and Cochrane library were searched (until July 2014) for clinical trials, in which thiazide diuretics were given as first-line antihypertensive treatment (online-only Data Supplement). The electronic search strategy was designed by a medical librarian and reviewed by 2 authors (R.H.G.O.E., W.J.F.) who were trained in systematic review searches. Furthermore, bibliographies of previously published meta-analyses about thiazide diuretics were used to search for eligible clinical trials.14,15 Articles were first evaluated based on title and abstract. Case reports, guidelines, editorials, and reviews were excluded, as well as abstracts with a combination of title and abstract that indicated that there was no possibility that the article could fit the requirements of this review.

Study Selection

For this review, randomized, controlled studies that described the effect of either TT or TL diuretics in hypertensive patients aged ≥21 years on CVE or mortality, were considered. We included studies that used either placebo or other antihypertensive therapy as control treatment. Studies were included if patients had a mean systolic BP of ≥140 mm Hg, a mean diastolic BP of ≥90 mm Hg or received antihypertensive treatment at baseline. Treatment had to include TT or TL diuretics as first-line therapy with a standardized protocol for dose titration or add-on BP-lowering therapy. A minimum follow-up period of 1 year was considered to adequately study the effect of the different BP-lowering treatment regimens on cardiovascular end points and mortality. Two reviewers (W.J.F. and B.v.d.B.) independently assessed each eligible study. Disagreement was resolved through final discussion with a third author (B.J.H.v.d.B.).

Data Extraction and Quality Assessment

Data were extracted using a standardized data extraction form. Data extraction was done by 2 independent reviewers (W.J.F. and R.H.G.O.E.). We extracted data on key demographics, such as age, sex, body mass index, baseline BP, ethnicity, prevalence of cardiovascular disease and diabetes mellitus, and study characteristics such as study size, mean follow-up duration, treatment strategies, publication year, CVE definitions, and inclusion criteria. In addition, we collected data on BP changes and CVE. Because of differences in outcome definitions across trials, we calculated new predefined outcome measures using data that was reported by the authors of included studies. In this meta-analysis, CVE were defined as the aggregate of cerebrovascular events, coronary events, and heart failure. Cerebrovascular events were defined as a composite of stroke and transient ischemic attack, whereas coronary events included myocardial infarction and sudden death. We did not include cardiac angina, peripheral artery disease, coronary artery bypass grafting, coronary revascularization, other cardiovascular procedures, and accelerated hypertension because of differences in definitions and event reporting, or because they were only reported in few studies. Adverse events were defined as discontinuation of the drug because of side effects or serious adverse events. In individual studies, the risk of bias was assessed by R.H.G.O.E. and reviewed by B.v.d.B. according to the Cochrane Handbook Guidelines.13 The risk of bias was assessed for random sequence generation, allocation concealment, blinding of personnel and participants, blinding of outcome assessment, incomplete outcome data, and selective reporting (Table S1 in the online-only Data Supplement).

Data Analysis

Data were analyzed using Cochrane Review Manager Software (Review Manager 5.2) and SPSS (Version 20.0; SPSS, Inc, Chicago, IL). To compare demographics and follow-up duration of studies that investigated TT and TL diuretics, we calculated average values that were weighted by study size. Statistical heterogeneity was quantified by calculating I² that describes the percentage of total variation across studies that is caused by heterogeneity.14 Quantitative analyses of outcomes were based on intention-to-treat analysis whenever possible, using observational years to correct for differences in study duration. Risk ratios (RRs) and confidence intervals were calculated to combine outcomes across trials using a random effects model. We compared the effects of TT and TL diuretics with placebo and other antihypertensive drugs to test the effects of both diuretic classes on cardiovascular outcome.

Meta-regression analysis was performed to assess if the outcome measures were affected by patient characteristics, such as average patient age, proportion of male and female subjects, annual incidence of CVE, mean follow-up time, and the achieved mean BP reduction between randomized groups. The annual incidence of CVE was calculated for each study separately by dividing the number of CVE by the amount of patients-years of follow-up. For analysis of covariance, RRs were logarithmically transformed and plotted against the antihypertensive effect. This regression was weighted by the inverse variance of the natural logarithm of the RR. The slope and y-intercept of these regression lines were calculated and compared. Differences in y-intercept between TT and TL diuretics were considered to represent an additional effect, independent of BP reductions, whereas slope differences were considered to represent synergistic effects related to the size of BP reduction.

Sensitivity analyses were performed to test the robustness of the results and to detect factors that may induce heterogeneity. Because the group of other antihypertensive therapy consists of various antihypertensive classes, we performed separate, drug-adjusted analyses for those antihypertensive classes that were compared with both TT and TL diuretics. The analysis comparing calcium antagonists with thiazide diuretics was repeated with dihydropyridine compounds only. In other sensitivity analyses, we excluded studies that were not double-blinded, studies that included patients with a mean age >75 years, the preliminary discontinued arm in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and studies, in which additional drugs were used in combination with thiazide diuretics to assess the effect on the outcome measures.15 In addition, studies were weighted by the inverse variance and Mantel–Haenszel approach.

Results

Description of Studies

A total of 3712 records were found after searching in Medline, Embase, and the Cochrane database, and 350 full-text articles were reviewed (Figure S1). Twenty-one studies, containing 25 comparisons were included (Tables 1 and 2).15–36 Seventeen studies compared TT diuretics with either placebo (8 studies, totalling 105 053 person-years of observation) or other antihypertensive drugs (9 studies, totalling 167 181 patient-years of observation), whereas 8 studies compared TL diuretics with placebo (3 studies, totalling 30978 patient-years of observation) or other antihypertensive therapy (5 studies, totalling 201 205 patient-years of observation).

The weighted average value of mean ages across studies was lower in studies investigating TT diuretics (60 versus 68 years) when compared with studies involving TL diuretics. The average proportion of males across studies was higher in
TT diuretic studies (58% versus 50%). Ethnicity was reported in 12 of 21 studies accounting for 73% of all subjects. On the basis of these data, proportionally more white people were included in studies with TT diuretics (91%) than in studies with TL diuretics (63%). Studies with TT diuretics involved patients with a lower mean annual incidence of CVE (1.4%) when compared with studies investigating TL diuretics (3.3%). Treatment with TT diuretics resulted in larger BP reductions than TL diuretics when compared with placebo treatment. The average placebo-subtracted drop across all studies involving TT diuretics was 14.5/6.7 mm Hg (systolic BP/diastolic BP), whereas the average drop in BP in studies investigating TL diuretics was 13.0/4.6 mm Hg. The antihypertensive effect of TT and TL diuretics was comparable with the antihypertensive effect observed in corresponding control arms that received other antihypertensive drugs. Studies about TT diuretics were older (median, 1985; interquartile range, 1980–2000) when compared with studies involving TL diuretics (median, 2000; interquartile range 1991–2003). Mean follow-up time was comparable among studies with TT (4.3 years; SD, 0.9) and TL diuretics (4.2 years; SD, 1.0).

Table 1. Study Characteristics of Included Studies: Summary of Studies Comparing Thiazide-Type and Thiazide-Like Diuretics With Placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Medication (dose in mg)</th>
<th>n</th>
<th>FU, y</th>
<th>Age, y</th>
<th>Men, %</th>
<th>BMI</th>
<th>SBP/DBP, mm Hg</th>
<th>∆ SBP/DBP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide-type diuretics vs placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANBP-I 198016</td>
<td>Chlorothiazide 500–1000</td>
<td>1721</td>
<td>4.1</td>
<td>50</td>
<td>63</td>
<td>27</td>
<td>157.7/100.5</td>
<td>NA/−12.2</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>1706</td>
<td>4.0</td>
<td>51</td>
<td>64</td>
<td>27</td>
<td>157.1/100.4</td>
<td>NA/−6.6</td>
</tr>
<tr>
<td>EWPHBP 198517</td>
<td>HCTZ 25+Triamterene 50</td>
<td>416</td>
<td>4.7</td>
<td>72</td>
<td>31</td>
<td>26</td>
<td>183.0/101.0</td>
<td>−33.0/−16.0</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>424</td>
<td>4.6</td>
<td>72</td>
<td>30</td>
<td>27</td>
<td>182.0/101.0</td>
<td>−11.0/−6.0</td>
</tr>
<tr>
<td>Kuramoto 198118</td>
<td>Trichlormethiazide 1–4</td>
<td>38</td>
<td>4.0</td>
<td>75</td>
<td>52</td>
<td>NA</td>
<td>171.3/86.5</td>
<td>−19.3/−6.5</td>
</tr>
<tr>
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<td>Placebo</td>
<td>41</td>
<td>4.0</td>
<td>77</td>
<td>57</td>
<td>NA</td>
<td>166.1/85.5</td>
<td>−7.1/−5.5</td>
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<tr>
<td>MRC I 198519</td>
<td>Bendrofluazide 10</td>
<td>4297</td>
<td>5.0</td>
<td>52</td>
<td>52</td>
<td>NA</td>
<td>161.0/98.0</td>
<td>−25.0/−13.0</td>
</tr>
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<td></td>
<td>Placebo</td>
<td>8654</td>
<td>5.0</td>
<td>52</td>
<td>52</td>
<td>NA</td>
<td>161.0/98.0</td>
<td>−12.0/−7.0</td>
</tr>
<tr>
<td>MRC II 199220</td>
<td>HCTZ 25–50+Amiloride 2.5–5.0</td>
<td>1081</td>
<td>5.8</td>
<td>70</td>
<td>42</td>
<td>27</td>
<td>185.0/91.0</td>
<td>−34.0/−14.0</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>2213</td>
<td>5.8</td>
<td>70</td>
<td>42</td>
<td>27</td>
<td>185.0/90.0</td>
<td>−19.0/−6.0</td>
</tr>
<tr>
<td>USPHSH 197721</td>
<td>Chlorothiazide 500+RS 100</td>
<td>193</td>
<td>7.0</td>
<td>44</td>
<td>77</td>
<td>27</td>
<td>147.7/99.0</td>
<td>−16.5/−10.4</td>
</tr>
<tr>
<td></td>
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<td>7.0</td>
<td>45</td>
<td>83</td>
<td>27</td>
<td>146.2/99.0</td>
<td>1.5/−0.6</td>
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<tr>
<td>VA-I 196722</td>
<td>HCTZ 100+Reserpine 0.2+Hydralazine 150</td>
<td>73</td>
<td>1.7</td>
<td>50</td>
<td>100</td>
<td>28</td>
<td>185.6/121.2</td>
<td>−43.0/−29.7</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>70</td>
<td>1.3</td>
<td>51</td>
<td>100</td>
<td>27</td>
<td>186.8/121.0</td>
<td>NA/−1.3</td>
</tr>
<tr>
<td>VA-II 197023</td>
<td>HCTZ 50+Reserpine 0.2 + Hydralazine 75</td>
<td>186</td>
<td>3.2</td>
<td>51</td>
<td>100</td>
<td>27</td>
<td>162.1/103.8</td>
<td>−27.2/−17.4</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>194</td>
<td>3.3</td>
<td>52</td>
<td>100</td>
<td>27</td>
<td>165.1/104.7</td>
<td>4.2/1.2</td>
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<tr>
<td>Thiazide-like diuretics vs placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HYVET 200824</td>
<td>Indapamide 1.5</td>
<td>1933</td>
<td>1.8</td>
<td>84</td>
<td>39</td>
<td>25</td>
<td>173.0/90.8</td>
<td>−29.5/−12.9</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>1912</td>
<td>1.8</td>
<td>84</td>
<td>40</td>
<td>25</td>
<td>173.0/90.8</td>
<td>−14.5/−6.8</td>
</tr>
<tr>
<td>SHEP 199125</td>
<td>Chlorthalidone 12.5–25</td>
<td>2365</td>
<td>4.5</td>
<td>72</td>
<td>44</td>
<td>28</td>
<td>170.5/76.7</td>
<td>−26.5/−9.0</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2371</td>
<td>4.5</td>
<td>72</td>
<td>43</td>
<td>28</td>
<td>170.1/76.4</td>
<td>−15.0/−5.3</td>
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<tr>
<td>SHEP pilot 198926</td>
<td>Chlorthalidone 25</td>
<td>443</td>
<td>2.8</td>
<td>72</td>
<td>37</td>
<td>NA</td>
<td>172.0/75.0</td>
<td>−31.0/−7.0</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>108</td>
<td>2.8</td>
<td>72</td>
<td>37</td>
<td>NA</td>
<td>172.0/75.0</td>
<td>−15.0/−2.0</td>
</tr>
</tbody>
</table>

FU, age, BMI, and blood pressures are expressed as a mean. Hypertension was an inclusion criterion in all studies. ANBP indicates Australian National Blood Pressure study; BMI, body mass index; EWPHBP, European Working Party on High Blood Pressure; FU, follow-up; HCTZ, hydrochlorothiazide; HYVET, Hypertension in the Very Elderly Trial; MRC, Medical Research Council; NA, not available; RS, rauwolfia serpentina; SBP/DBP systolic/diastolic blood pressure; SHEP, Systolic Hypertension in the Elderly Program; USPHSH, United States Public Health Service Hospitals; and VA, Veterans Administration.

In comparison with placebo, TT (RR, 0.67 [0.56–0.81]; F=37%) and TL diuretics (RR, 0.67 [0.60–0.75]; F=0%) significantly reduced the number of CVE (Figure S2). In addition, TT and TL diuretics significantly reduced the number of cerebrovascular events (TT: RR, 0.52 [0.38–0.69]; F=25% and TL: RR, 0.68 [0.57–0.80]; F=0%) and heart failure (TT: RR, 0.36 [0.16–0.84]; F=14% and TL: RR, 0.47 [0.36–0.61]; F=0%) compared with placebo. In contrast to TT diuretics, treatment with TL diuretics also resulted in a significant reduction of coronary events (RR, 0.76 [0.61–0.96]; F=0%) and all-cause mortality (RR, 0.84 [0.74–0.96]; F=0%).

Primary Analysis

The antihypertensive effect of TT and TL diuretics was comparable with the antihypertensive effect observed in corresponding control arms that received other antihypertensive drugs. Studies about TT diuretics were older (median, 1985; interquartile range, 1980–2000) when compared with studies involving TL diuretics (median, 2000; interquartile range 1991–2003). Mean follow-up time was comparable among studies with TT (4.3 years; SD, 0.9) and TL diuretics (4.2 years; SD, 1.0).
Next, we compared thiazide diuretics with studies that used other antihypertensive therapy as control treatment. TT diuretics did not show a significant benefit on any of the outcomes. TL diuretics, however, more effectively reduced heart failure (RR, 0.71 [0.53–0.95]; \( I^2 = 91\% \)), and showed similar risk reductions for CVEs (RR, 0.86 [0.72–1.04]; \( I^2 = 88\% \)), cerebrovascular events (RR, 0.93 [0.86–1.01]; \( I^2 = 0\% \)), coronary events (RR, 1.01 [0.95–1.07]; \( I^2 = 0\% \)), and all-cause mortality (RR, 1.00 [0.95–1.05]; \( I^2 = 0\% \)) when compared with studies that used other antihypertensive therapy as control treatment.

We were not able to perform separate analyses stratified by ethnicity because of the lack of data. Sensitivity analyses did not result in any significant change in treatment effect.

**Meta-Regression**

Age, sex, ethnicity, follow-up duration, and annual incidence of CVE did not significantly affect the risk of all outcomes. The difference in MAP at the end of the study between treatment and control group significantly affected the risk of all outcomes. Larger BP differences between treated and control groups at the end of the study were significantly associated with a greater decrease of CVE (\( P<0.001 \)), coronary events

### Table 2. Study Characteristics of Included Studies: Summary of Studies Comparing Thiazide-Type and Thiazide-Like Diuretics With Other Antihypertensive Agents

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Baseline Medication</th>
<th>n</th>
<th>FU, y</th>
<th>Age, y</th>
<th>Men, %</th>
<th>BMI</th>
<th>Mean SBP/DBP, mm Hg</th>
<th>( Δ ) SBP/DBP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thiazide-type diuretics vs other antihypertensive agents</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCOMPLISH 2008[27]</td>
<td>Benazepril 40+HCTZ 12.5</td>
<td>5762</td>
<td>3.0</td>
<td>68</td>
<td>61</td>
<td>31</td>
<td>145.4/80.0*</td>
<td>−12.9/−5.6</td>
</tr>
<tr>
<td>ACCOMPLISH 2008[27]</td>
<td>Benazepril 40+Amlodipine 5</td>
<td>5744</td>
<td>3.0</td>
<td>69</td>
<td>60</td>
<td>31</td>
<td>145.3/80.1*</td>
<td>−13.7/−6.8</td>
</tr>
<tr>
<td>ANBP II 2003[28]</td>
<td>HCTZ</td>
<td>3039</td>
<td>4.1</td>
<td>72</td>
<td>48</td>
<td>27</td>
<td>168.0/91.0</td>
<td>−26.0/−12.0</td>
</tr>
<tr>
<td>ENBP II 2001[28]</td>
<td>Enalapril 30</td>
<td>3044</td>
<td>4.1</td>
<td>72</td>
<td>50</td>
<td>27</td>
<td>167.0/91.0</td>
<td>−26.0/−12.0</td>
</tr>
<tr>
<td>Berglund[29]</td>
<td>Bendroflumethiazide 2.5+KCl 570</td>
<td>53</td>
<td>6.0</td>
<td>NA</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Berglund[29]</td>
<td>Propranolol 80</td>
<td>53</td>
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<td>NA</td>
<td>100</td>
<td>NA</td>
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<td>NA</td>
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<tr>
<td>HAPPHY 1987[30]</td>
<td>Bendroflumethiazide 5 or HCTZ 25</td>
<td>3272</td>
<td>3.8</td>
<td>52</td>
<td>100</td>
<td>27</td>
<td>166.0/107.0</td>
<td>−26.0/−18.0</td>
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<tr>
<td>HAPPHY 1987[30]</td>
<td>Atenolol 100 or Metoprolol 200</td>
<td>3297</td>
<td>3.8</td>
<td>52</td>
<td>100</td>
<td>27</td>
<td>166.0/107.0</td>
<td>−26.0/−19.0</td>
</tr>
<tr>
<td>INSIGHT 2000[31]</td>
<td>HCTZ 25+Amlodipine 2.5</td>
<td>3164</td>
<td>3.5</td>
<td>65</td>
<td>47</td>
<td>28</td>
<td>173.0/99.0</td>
<td>−33.0/−17.0</td>
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<tr>
<td>MIDAS 1996[32]</td>
<td>Nifedipine 30</td>
<td>3157</td>
<td>3.5</td>
<td>65</td>
<td>46</td>
<td>28</td>
<td>173.0/99.0</td>
<td>−33.0/−17.0</td>
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<tr>
<td>INSIGHT 2000[31]</td>
<td>HCTZ 25–50</td>
<td>441</td>
<td>3.0</td>
<td>59</td>
<td>76</td>
<td>28</td>
<td>148.9/96.2</td>
<td>−19.5/−13.0</td>
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<tr>
<td>INSIGHT 2000[31]</td>
<td>Isradipine 5–10</td>
<td>442</td>
<td>3.0</td>
<td>58</td>
<td>80</td>
<td>28</td>
<td>150.6/96.7</td>
<td>−16.0/−13.0</td>
</tr>
<tr>
<td>MRC I 1985[33]</td>
<td>Bendroflumethiazide 10</td>
<td>4297</td>
<td>5.0</td>
<td>52</td>
<td>52</td>
<td>NA</td>
<td>161.0/98.0</td>
<td>−25.0/−13.0</td>
</tr>
<tr>
<td>MRC I 1985[33]</td>
<td>Propranolol 80–240</td>
<td>4403</td>
<td>5.0</td>
<td>51</td>
<td>52</td>
<td>NA</td>
<td>158.0/98.0</td>
<td>−20.5/−11.5</td>
</tr>
<tr>
<td>MRC II 1992[34]</td>
<td>HCTZ 25–50+Amlodipine 2.5–5.0</td>
<td>1081</td>
<td>5.8</td>
<td>70</td>
<td>42</td>
<td>27</td>
<td>185.0/91.0</td>
<td>−34.0/−14.0</td>
</tr>
<tr>
<td>MRC II 1992[34]</td>
<td>Atenolol 50</td>
<td>1102</td>
<td>5.8</td>
<td>70</td>
<td>41</td>
<td>27</td>
<td>185.0/91.0</td>
<td>−34.0/−14.0</td>
</tr>
<tr>
<td>NICS EH 2001[35]</td>
<td>Trichlormethiazide 2</td>
<td>210</td>
<td>5.0</td>
<td>70</td>
<td>26</td>
<td>24</td>
<td>172.6/93.4</td>
<td>−25.6/−14.4</td>
</tr>
<tr>
<td>NICS EH 2001[35]</td>
<td>Nicardipine 20</td>
<td>204</td>
<td>5.0</td>
<td>70</td>
<td>40</td>
<td>23</td>
<td>171.9/94.2</td>
<td>−24.9/−13.2</td>
</tr>
<tr>
<td><strong>Thiazide-like diuretics vs other antihypertensive agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALLHAT A 2002[36]</td>
<td>Chlorthalidone 12.5–25</td>
<td>15255</td>
<td>4.9</td>
<td>67</td>
<td>53</td>
<td>30</td>
<td>156.0/89.0</td>
<td>−22.1/−13.6</td>
</tr>
<tr>
<td>ALLHAT L 2002[36]</td>
<td>Amlodipine 2.5–10</td>
<td>9048</td>
<td>4.9</td>
<td>67</td>
<td>53</td>
<td>30</td>
<td>157.0/90.0</td>
<td>−22.3/−15.4</td>
</tr>
<tr>
<td>ALLHAT D 2000[37]</td>
<td>Lisinopril 10–40</td>
<td>9054</td>
<td>4.9</td>
<td>67</td>
<td>53</td>
<td>30</td>
<td>156.0/89.0</td>
<td>−22.1/−13.6</td>
</tr>
<tr>
<td>SHELL 2003[38]</td>
<td>Droxidopamine 2–8</td>
<td>9067</td>
<td>4.9</td>
<td>67</td>
<td>53</td>
<td>30</td>
<td>156.0/89.0</td>
<td>−20.1/−13.0</td>
</tr>
<tr>
<td>SHELL 2003[38]</td>
<td>Chlorthalidone 12.5</td>
<td>941</td>
<td>2.7</td>
<td>72</td>
<td>38</td>
<td>NA</td>
<td>178.2/86.8</td>
<td>−35.8/−7.8</td>
</tr>
<tr>
<td>SHELL 2003[38]</td>
<td>Lacidipine 4</td>
<td>942</td>
<td>2.7</td>
<td>72</td>
<td>40</td>
<td>NA</td>
<td>178.1/86.9</td>
<td>−35.1/−7.9</td>
</tr>
<tr>
<td>VHAS 1997[39]</td>
<td>Chlorthalidone 25</td>
<td>707</td>
<td>2.0</td>
<td>54</td>
<td>50</td>
<td>27</td>
<td>168.8/102.3</td>
<td>−28.6/−16.6</td>
</tr>
<tr>
<td>VHAS 1997[39]</td>
<td>Verapamil 240</td>
<td>707</td>
<td>2.0</td>
<td>55</td>
<td>48</td>
<td>27</td>
<td>169.1/102.2</td>
<td>−27.6/−17.0</td>
</tr>
</tbody>
</table>

FU, age, BMI, and blood pressures are expressed as a mean. Hypertension was an inclusion criterion in all studies. ACCOMPLISH indicates Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP, Australian National Blood Pressure study; BMI, body mass index; FU, Follow-up; HAPPHY, Heart Attack Primary Prevention in Hypertension; HCTZ, hydrochlorothiazide; INSIGHT, Intervention as a Goal in Hypertension Treatment; MIDAS, Multicenter Isradipine Diuretic Atherosclerosis Study; MRC, Medical Research Council; NA, not available; NICS EH, National Intervention Cooperative Study in Elderly Hypertensives; SBP/DBP systolic/diastolic blood pressure; SHELL, Systolic Hypertension in the Elderly: Lacidipine Long-Term; and VHAS, Verapamil in Hypertension and Atherosclerosis Study.

*During hypertension treatment.
†Median follow-up time.
(P=0.025), cerebrovascular events (P<0.001), heart failure (P=0.010), and all-cause mortality (P=0.001).

BP-Adjusted Analysis
Corrected for BP changes, TT diuretics did not result in an additional risk reduction for CVE (RR, 1.00 [0.91–1.09]) and heart failure (RR, 0.90 [0.68–1.21]), whereas treatment with TL diuretics resulted in a significant risk reduction for CVE (RR, 0.88 [0.79–0.98]) and heart failure (RR, 0.71 [0.57–0.89]) independent of BP. Consequently, the risk of CVE was 12% lower with TL diuretics (P=0.049) compared with TT diuretics, whereas the risk of heart failure was 21% lower (P=0.023; Figure) with TL diuretics. In addition, the regression line of TL diuretics had a significant steeper slope when compared with the regression line of TT diuretics for the outcome CVE (P=0.028). TT and TL diuretics did not show a BP-independent risk reduction for coronary events, cerebrovascular events, and all-cause mortality (Figure S4).

In sensitivity analyses, the significant beneficial effect of TL diuretics on CVE disappeared, whereas the beneficial effect about heart failure persisted. If the prematurely terminated doxazosin arm of ALLHAT was excluded (P=0.117) or only nonblack participants of the chlorthalidone, amlodipine, and lisinopril arm were analyzed (P=0.160), the significant benefit for CVE disappeared. However, TL diuretics remained significantly better in reducing heart failure when compared with TT diuretics when excluding the doxazosin arm of ALLHAT (P=0.012) or analyzing only nonblack participants of the chlorthalidone, amlodipine, and lisinopril arm of ALLHAT (P=0.039). When only analyzing double-blind trials, the beneficial effect of TL diuretics on heart failure (P=0.012) was still present, but not for CVE (P=0.182). Likewise after excluding studies that enrolled patients with a mean age >75 years, the beneficial effect of TL diuretics on heart failure (P=0.018) remained, whereas the benefit for CVE was no longer present (P=0.146).

Drug-Adjusted Analysis
In studies comparing thiazide diuretics with calcium antagonists, treatment with TL diuretics resulted in less CVE and heart failure, whereas studies comparing TT diuretics with calcium antagonists did not show a significant difference in treatment effect (Figure S3). Similar results were found when only dihydropyridine compounds were analyzed or when the analysis was restricted to hospitalized heart failure. In comparison with ACE inhibitors, treatment with TT diuretics was associated with a higher risk of CVE, whereas TL diuretics showed a similar risk reduction in CVE.

Adverse Events
Seventeen studies reported data on adverse events. For the comparison of TL diuretics with placebo, 2 studies reported adverse events. In the Hypertension in the Very Elderly Trial (HYVET), however, 99% of adverse events were considered not to be related to the trial medication. With only one trial left comparing TL diuretics and placebo on adverse events, we were not able to estimate the risk of adverse events for the comparison of TL diuretics and placebo. When compared with other antihypertensive therapy, TT (RR, 0.92 [0.74–1.15]) and TL diuretics (RR, 0.84 [0.68–1.03]) showed a similar amount of adverse events when comparable BP reductions were achieved.

Discussion
This meta-analysis suggests that TL diuretics result in a significantly larger risk reduction of CVE and heart failure when compared with TT diuretics. When similar BP reductions were achieved, treatment with TL diuretics was associated with 12% less CVE and 21% less heart failure than TT diuretics.

Randomized trials directly comparing TT and TL diuretics are lacking. We, therefore, pooled the results of studies comparing thiazide diuretics with placebo or other antihypertensive drugs totalling over 480,000 patient-years of observation.
Because subjects were not randomized to receive either TT or TL diuretics, populations differed in baseline characteristics. However, meta-regression analyses showed that differences in age, sex, ethnicity, and annual incidence of CVE among studies did not differently affect cardiovascular outcomes.

Our results are in line with a previous meta-analysis that reported a larger risk reduction of CVE with chlorthalidone compared with hydrochlorothiazide using a network meta-regression analysis. Because comparisons between chlorthalidone and hydrochlorothiazide were indirect in both the analyses, differences in outcome definitions among trials may lead to differences in event reporting. To ensure comparability of included studies in this analysis, we included only major CVE. Intervventional procedures and minor cardiovascular outcomes, such as cardiac angina, peripheral artery disease, or accelerated hypertension were excluded because of differences in definition and event reporting.

Although placebo groups are homogeneous among trials, various antihypertensive drugs, including β-blockers, calcium antagonists, ACE inhibitors, and α-blockers were used as active comparators. As a result, comparisons between placebo and TT or TL diuretics, showed low heterogeneity (F<50%), whereas some comparisons between TT or TL diuretics, and the group of other antihypertensive drugs showed significant heterogeneity. Among the studies that used other antihypertensive drugs as control treatment, antihypertensive classes were unequally distributed between comparisons with TT and TL diuretics. Beta-blockers, for example, were used 4× as control treatment in studies investigating TT diuretics, whereas there were no comparisons between TL diuretics and β-blockers. The significant heterogeneity disappeared in the drug-adjusted analysis, suggesting that the different groups of antihypertensive drugs that were included in these comparisons were the main cause of heterogeneity. In comparison with calcium antagonists, TL diuretics resulted in a greater reduction in CVE and heart failure, whereas TT diuretics had comparable efficacy. Because dihydropyridine calcium-channel blockers are known to induce peripheral edema, possible leading to false-positive event reporting for heart failure, hospitalized heart failure was analyzed separately. Despite these more stringent criteria, TL diuretics remained superior in reducing the risk of heart failure. Compared with ACE inhibitors, TT diuretics were less effective in reducing CVE, whereas the efficacy was comparable for TL diuretics.

The beneficial effects of TL diuretics on CVE and heart failure, that were independent of the achieved office BP reduction, may be best explained by the longer elimination half-life of TL diuretics that results in a better 24-hour BP reduction, compared with TT diuretics. Because dihydropyridine calcium-channel blockers are known to induce peripheral edema, possible leading to false-positive event reporting for heart failure, hospitalized heart failure was analyzed separately. Despite these more stringent criteria, TL diuretics remained superior in reducing the risk of heart failure. Compared with ACE inhibitors, TT diuretics were less effective in reducing CVE, whereas the efficacy was comparable for TL diuretics.

Because of the longer half-life of TL diuretics, an increase in adverse events may be anticipated, especially with regard to the occurrence of adverse events related to disturbances in sodium and potassium homeostasis. In this meta-analysis, we observed a similar incidence of adverse events for TT and TL diuretics with comparable reductions in office BP. This is in contrast with a previous retrospective study, which demonstrated a greater incidence of electrolyte abnormalities for chlorthalidone compared with hydrochlorothiazide. Because the mean starting dose of the more potent drug chlorthalidone (27.3 mg) exceeded that of hydrochlorothiazide (18.3 mg), it is conceivable that the higher incidence of adverse events was related to differences in dosing. This is supported by a meta-analysis of randomized controlled trials involving chlorthalidone and hydrochlorothiazide that concluded that the reduction of potassium levels by chlorthalidone, within the currently recommended doses, is equivalent to that of hydrochlorothiazide. In addition, a case-control study in hypovolemic patients showed that the risk of hypovolemia was similar when equally potent doses of hydrochlorothiazide and chlorthalidone were used.

A limitation in the interpretation of the results from this meta-analysis is the lack of randomized trials directly comparing the effect of TT and TL diuretics on CVE. Comparison of TT and TL diuretics is thus not randomized, which can introduce bias. Meta-regression analyses, however, did not identify a significant influence of demographic heterogeneity among studies. Finally, in sensitivity analyses, the beneficial effect of TL diuretics on CVE did not remain significant. This, however, may also be because of a significant reduction in power after excluding large number of patients. The beneficial effects of TL diuretics on heart failure, however, remained significant in all sensitivity analyses.

**Perspectives**

Currently, TL diuretics are far outnumbered by TT diuretics for the treatment of hypertension. This meta-analysis suggests that the millions of people who are treated with TT diuretics may receive suboptimal treatment. Future randomized controlled trials should compare TT and TL diuretics to determine the efficacy on cardiovascular outcome. In addition, these studies should investigate whether a different ability to improve 24-hour BP control and natriuresis, or additional effects of TL diuretics on platelet aggregation underlie the differences in cardiovascular risk reduction. Although awaiting further evidence, the available data seem to favor TL diuretics as the drug of choice when thiazide treatment is considered for hypertension—especially patients at risk for heart failure.

**Sources of Funding**

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Clinical Fellowship grants 90700408 and 90700310 of the Netherlands Organisation for Scientific research (NWO-ZonMW). Dr Brewster is a recipient of a Veni fellowship (grant number 916.10.156) awarded by NWO as part of its Innovational Research Incentives Scheme.

Disclosures
None.

References

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Thiazide Diuretics and Cardiovascular Risk


**Novelty and Significance**

**What Is New?**

- This meta-analysis provides evidence that thiazide-like (TL) diuretics are superior to thiazide-type (TT) diuretics in preventing heart failure and cardiovascular events when comparable blood pressure reductions are achieved.
- Our data suggest that TT and TL diuretics have a similar incidence of adverse events when comparable blood pressure reductions are achieved.

**What Is Relevant?**

- TT and TL diuretics are among the most commonly prescribed drugs for the treatment of hypertension. Although most guideline do not distinguish between these 2 classes, prescriptions for TL diuretics are far outnumbered by prescriptions for TT diuretics. As the available evidence from indirect comparisons suggest that TL diuretics are superior to TT diuretics, millions of patients may receive suboptimal treatment.

**Summary**

TL diuretics seem to be superior when compared with TT diuretics in preventing heart failure and cardiovascular events when comparable blood pressure reduction are achieved.
Effects of Thiazide-Type and Thiazide-Like Diuretics on Cardiovascular Events and Mortality: Systematic Review and Meta-Analysis

Rik H.G. Olde Engberink, Wijnanda J. Frenkel, Bas van den Bogaard, Lizzy M. Brewster, Liffert Vogt and Bert-Jan H. van den Born

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ONLINE DATA SUPPLEMENTS

Effects of thiazide-type and thiazide-like diuretics on cardiovascular events and mortality – a systematic review and meta-analysis

Rik H.G. Olde Engberink*, M.D., Wijnanda J. Frenkel†, M.D., Bas van den Bogaard†, M.D., Ph.D., Lizzy M. Brewster†, M.D., Ph.D., Liffert Vogt*, M.D., Ph.D., Bert-Jan H. van den Born†, M.D., Ph.D.

*Department of Nephrology, Academic Medical Centre, University of Amsterdam, the Netherlands
†Department of Vascular Medicine, Academic Medical Centre, University of Amsterdam, the Netherlands
**MEDLINE Search strategy**

Based on their pharmacological structure the following agents were supposed to be thiazide-type diuretics: hydrochlorothiazide, chlorothiazide, bendroflumethiazide, methyclothiazide, cyclopentiazid, hydroflumethiazid, polythiazid and trichlormethiazid. Thiazide-like diuretics included the following agents: chlorthalidone, indapamide and metolazone. Search strategies for EMBASE and the Cochrane Database were based on the search strategy mentioned below.

((("thiazides"[MeSH Terms] OR thiazid*[TIAB]) OR (benzothiadiazin*[TIAB]) OR (chlorothiazid*[TIAB]) OR (hydrochlorothiazid*[TIAB]) OR (trichlormethiazid*[TIAB]) OR (cyclopentiazid*[TIAB]) OR (hydroflumethiazid*[TIAB]) OR (methyclothiazid*[TIAB]) OR (polythiazid*[TIAB]) OR ("Chlorthalidone"[Mesh]) OR (chlorthalidon*[TIAB]) OR (Oxodoline[TIAB]) OR (Hygroton[TIAB]) OR (Indapamide[TIAB]) OR (Metolazone[TIAB])) AND ((ENDPOINT*[TIAB] OR OUTCOME*[TIAB]) OR ((("myocardial infarction"[MeSH Terms] OR myocardial infarct*[TIAB]) OR (heart attack*[TIAB]) OR ("myocardial ischaemia"[TIAB] OR "myocardial ischemia"[MeSH Terms] OR "myocardial ischemia"[TIAB]) OR ("ischemic heart disease"[TIAB]) OR ("ischaemic heart disease"[TIAB]) OR ("ischaemic heart diseases"[TIAB]) OR ("mortality"[Subheading] OR "mortality"[TIAB] OR "mortality"[MeSH Terms] OR ("brain infarction"[MeSH Terms] OR brain infarction*[TIAB]) OR (cerebral infarction*[TIAB]) OR (cerebrovascular accident*[TIAB]) OR ("renal insufficiency"[MeSH Terms] OR renal insufficiency*[TIAB]) OR (kidney insufficiency*[TIAB]) OR ("renal dialysis"[MeSH Terms] OR "renal dialysis"[TIAB]) OR (Heart Decompensation[TIAB]) OR (sudden death) OR (cardiac death[TIAB]) OR (Cardiac Arrest*[TIAB]))) NOT (animals[mesh] NOT human[mesh]))
References


Table S1 Study characteristics and the risk of bias table of included studies

**Accomplish**

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th>Multicenter, randomized, double-blind trial in the United States, Sweden, Norway, Denmark and Finland.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>11,506 patients with hypertension who were at high risk for cardiovascular events with mean age 68, male (61%). Baseline mean SBP/DBP was 145/80 mmHg. Patients were followed for 3 years.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Benazepril 40 mg and amlodipine 5 mg. Benazepril 40 mg and hydrochlorothiazide 12.5 mg. Amlodipine and hydrochlorothiazide were doubled if target of 140/90 mmHg or 130/80 mmHg was not reached.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Primary end point was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization.</td>
</tr>
</tbody>
</table>

**Risk of bias table**

<table>
<thead>
<tr>
<th><strong>Bias</strong></th>
<th><strong>Authors' judgement</strong></th>
<th><strong>Support for judgement</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>Randomized.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td>'patients were randomly assigned in a global one-to-one ratio to either of the two treatment groups, with assignments made centrally by telephone.'</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>Double blinded.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Low risk</td>
<td>'All prespecified study outcomes (as reported previously) were adjudicated according to standard criteria by a central committee whose members were unaware of study-group assignments.'</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>'For the primary efficacy endpoint, the primary analysis will be carried out using a log-rank test for the intent to-treat population, which consists of all randomized patients. Withdrawal of patients due to adverse events was similar.'</td>
</tr>
</tbody>
</table>
Selective reporting | Low risk | 'in subsequent prespecified analyses of the individual components of the primary and secondary end points, the event count was performed without censoring for previous end points.'

**ALLHAT**\(^2,3\)

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th>Randomized, double-blinded, active-controlled trial in North America</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>33,357 participants aged &gt; 55 years, mean age 67, with stage 1 or 2 hypertension and at least one other coronary heart disease risk factor. Male 53%. Patients with chlorthalidone, amlodipine and lisinopril were followed for a mean of 4.9 years. Patients with doxazosin were followed for a median of 3.3 years due to preliminary termination of the doxazosin arm.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Chlorthalidone vs doxazosin vs amlodipine vs lisinopril.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Primary outcomes: fatal CHD or non-fatal MI. Secondary outcomes: all-cause mortality, stroke, and combined CVD.</td>
</tr>
</tbody>
</table>

**Risk of bias table**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>The concealed randomization scheme was generated by computer, implemented at the clinical trials center, stratified by center and blocked in random block sizes of 5 to 9 to maintain balance.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>Double blind.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear risk</td>
<td>Blinding of the committee reviewing the endpoints is not stated.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>Intention to treat analysis.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Unclear risk</td>
<td></td>
</tr>
</tbody>
</table>
# Methods
Randomised, single-blind, placebo-controlled trial. Trial conducted in Australia.

## Participants
Ambulatory young patients, with mean age 50 years, range (30-59 years). Australian (White) or European born. Male (63%). Baseline mean SBP/DBP was 157/100 mmHg. The inclusion criteria were SBP < 200 mmHg and DBP 90-110 mmHg. Patients were followed for 4 years.

## Interventions
Chlorothiazide 500mg once or twice daily. Methyldopa, propranolol, or pindolol was added as second-order treatment, and hydralazine or clonidine added as third-order treatment. Control: placebo.

## Outcomes
Mortality, CHD, stroke, other CV events, systolic BP and diastolic BP.

### Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Unclear risk</td>
<td>At the clinic visit, eligible subjects who agreed to enter the study were randomly allocated, with stratification by age and sex, to one of the two trial regimens.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>High risk</td>
<td>Inadequate.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>Participants: Placebo tablets were identical in appearance to the active tablets. In an attempt to achieve comparable patterns of tablet taking in both groups, an estimate was made of the numbers of subjects in the active group likely to require one, two, or more drugs to obtain the desired reduction in blood-pressure. In accordance with this estimate, 2 in 3 of the placebo group were randomised to the first-order placebo tablet only, 2 in 9 to have a second-order tablet added, and the remaining 1 in 9 to have a third-order tablet added later. The study centre staff knew the trial regimen of each subject, and this information was available, on request, to a subject’s local doctor.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Low risk</td>
<td>A trial end-point committee, unaware of the subject’s treatment group and blood-pressure, made the final decision on acceptance of a trial end-point. An ECG committee, similarly &quot;blind&quot;, reported on all electrocardiographic tracings.</td>
</tr>
</tbody>
</table>
Incomplete outcome data | High risk | All components from the composite outcome were terminating events, without complementary mortality survey. All analyses regarding these separated components are subject to a censoring bias.

Selective reporting | Unclear risk | Not specified.

Other bias | High risk | The active group attended the clinic more frequently and took two or more types of tablet more frequently than those in the placebo group. Thus the attempt to achieve identical visiting patterns and tablet routines was only partly effective.

**ANBP II**

| Methods | Randomized, open-label study in family practices in Australia |
| Participants | 6,083 patients, with mean age 72 years, range (30-59 years), male (49%). Baseline mean SBP/DBP was 168/91 mmHg. The inclusion criteria were SBP > 160 mmHg or DBP > 90 mmHg and absence of recent (6 months) cardiovascular events. Mean follow-up was 4.1 years. |
| Interventions | The ACE inhibitor enalapril or the diuretic hydrochlorothiazide were recommended as initial therapy; however, the choice of the specific agent and dose was made by the family practitioner. To achieve the blood-pressure goals, the addition of beta-blockers, calcium-channel blockers, and alpha-blockers was recommended in both groups |
| Outcomes | Primary: Total cardiovascular events (fatal and non-fatal) Secondary: death and coronary heart disease events |

Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>Subjects were randomly assigned centrally by telephone to either ACE-inhibitor–based or diuretic-based treatment.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>High risk</td>
<td>Open label design.</td>
</tr>
</tbody>
</table>
Blinding of outcome assessment | Low risk | 'Study endpoint information is gained from a review of practice records every 3 months and these data are then assessed by an Endpoint Committee blinded for treatment randomization.'

Incomplete outcome data | Low risk | 'As the study will be analysed on an intention-to-treat basis, cessation of therapy will not invalidate outcome data.'

Selective reporting | Unclear risk |

---

**Berglund**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized, controlled trial.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>53 previously untreated patients, aged 47-54, male (100%). Baseline mean SBP/DBP was 168/91 mmHg. The inclusion criteria were SBP &gt; 170 or DBP &gt; 105 mmHg. Mean follow-up was 6 years.</td>
</tr>
<tr>
<td>Interventions</td>
<td>'Salures-K' (2.5 mg bendroflumethiazide + 0.57 g potassium chloride) 'Inderal' (80 mg propranolol). 'The dose was doubled to 5 mg bendroflumethiazide daily or 160 mg propranolol twice daily if blood pressure was not reduced to &lt; 160 systolic or &lt;95 mm Hg diastolic. If blood pressure still remained above these limits hydralazine 25-50 mg thrice daily was added.'</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Metabolic side effects, blood pressure, all-cause mortality.</td>
</tr>
</tbody>
</table>

### Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>Randomized.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>High risk</td>
<td>No reported blinding.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Low risk</td>
<td>Mortality as only relevant outcome parameter.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>High risk</td>
<td>No intention to treat analysis.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Unclear risk</td>
<td></td>
</tr>
</tbody>
</table>
**Methods**

Multicenter, double-blind, randomized, placebo-controlled trial in Europe.

**Participants**

840 patients, with mean age 72 years, male (31%). Baseline mean SBP/DBP was 183/101 mmHg. The inclusion criteria were, age > 60 years, SBP 160-239 mmHg and DBP 90-119 mmHg. Mean follow up was 4.63 years for the placebo group and 4.69 years for the treatment group.

**Interventions**

'All patients received daily one diuretic capsule containing either 25 mg hydrochlorothiazide and 50 mg triamterene or a placebo. The dosage could be increased, after at least two weeks, to two capsules per day. If the blood pressure remained high after one month, methyldopa tablets (500 mg) could be added to the active treatment group and placebo tablets in the placebo group, starting with half a tablet a day and increasing eventually to four tablets daily.'

**Outcomes**

Overall morbidity and mortality.

---

**Risk of bias table**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>Participants: Placebo capsules and tablets were identical in shape, taste, and colour to the active treatment medication. Personnel: These investigators were not aware of the treatment group to which the patients had been assigned.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear risk</td>
<td>'Data were sent to the coordinating office every three months on specially designed forms and deaths and other terminating events were classified independently by two investigators into previously agreed categories.'</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>High risk</td>
<td>Censoring attrition bias: Terminating non-fatal events: non-fatal cerebral or subarachnoid haemorrhage, development of hypertensive retinopathy grade III or IV, dissecting aneurysm, congestive heart failure not controllable without diuretics or antihypertensive drugs, hypertensive encephalopathy, severe increase in LVH, and a rise in BP exceeding the defined limits.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>--------------</td>
<td>----------------</td>
</tr>
</tbody>
</table>

**HAPPHY**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Multicenter, randomized controlled trial.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>6,569 patients aged 40-64 years, mean age 52, male (100%). Baseline mean SBP/DBP was 166/107 mmHg. The inclusion criteria were male, aged 40-64 and DBP 100-130 mmHg. Mean follow up was 3.8 years.</td>
</tr>
</tbody>
</table>
| Interventions | Diuretic (bendroflumethiazide 5 mg or hydrochlorothiazide 25 mg) or beta-blocker (atenolol 100 mg or metoprolol 200 mg) based therapy. Adjacent drugs were added if a DPB < 95 mmHg was not reached.  
Step 2: + hydralazine 75 mg.  
Step 3: + hydralazine 150 mg.  
Step 4: Step 3 + spironolactone 75 mg.  
Step 5: Step 3 + spironolactone 150 mg.  
Step 6: Step 5 + optional drug. |
| Outcomes | Primary: Coronary heart disease events and death. |

Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>Randomized to open treatment with a diuretic or beta-blocker after stratification into nine groups according to predicted CHD risk based upon, age, cholesterol, smoking habits and SBP.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>High risk</td>
<td>Open label study.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Low risk</td>
<td>'An independent end-point committee reviewed the diagnoses of the end-points without knowing to which treatment patients had been randomized.'</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>All analyses on intention to treat basis.</td>
</tr>
</tbody>
</table>
**Methods**
Randomized, double-blind, placebo-controlled trial performed in 195 centers in 13 countries in Western and Eastern Europe, China, Australasia, and North Africa.

**Participants**
3,845 patients, with mean age 84 years, male (61%). Baseline mean SBP/DBP was 173/91 mmHg. The inclusion criteria were, age > 80 years, SBP > 160 mmHg. Mean follow up was 1.8 years.

**Interventions**
'Indapamide (sustained release, 1.5 mg) or matching placebo. The angiotensin-converting–enzyme inhibitor perindopril (2 or 4 mg), or matching placebo, was added if necessary to achieve the target blood pressure of 150/80 mm Hg.'

**Outcomes**
Primary: Stroke (fatal or nonfatal). This end point did not include transient ischemic attacks. Secondary: Death from any cause, death from cardiovascular causes, death from cardiac causes, and death from stroke.

**Risk of bias table**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>'Patient randomisation will be initiated at the coordinating office at the Hammersmith campus of the Imperial College School of Medicine (ICSM) in London on receipt of the completed entry form.'</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td>'An interactive voice response system (IVRS) is employed to tell the investigator which 6-month drug pack to prescribe. The IVRS is a telephone system that allows investigators and the coordinating centre to interact in their native languages with a central patient database.'</td>
</tr>
</tbody>
</table>
| Blinding of participants and personnel | Low risk | **Participants:** 'After randomization, patients received either indapamide (sustained release, 1.5 mg) or matching placebo alone.'

**Personnel:** 'All end-points will be assessed by the End-Points Committee who will be blinded to the treatment that the patient received. Clinical and radiological evidence must be supplied by the investigator to support all diagnoses.'

| Blinding of outcome assessment | Low risk | All events that were possible end points were reviewed by an independent committee, unaware of the group assignment, using predefined definitions from the protocol. |
Incomplete outcome data | Low risk | The primary analysis was performed according to the intention-to-treat principle. Events that occurred during the open follow-up period were included in the intention-to-treat analysis.

Selective reporting | Unclear risk | Not specified.

**INSIGHT**

**Methods**
Prospective, randomised, controlled, double-blind trial in Europe and Israel.

**Participants**
6,321 patients aged 55–80 years, mean age 65, male (46%). Baseline mean SBP/DBP was 173/99 mmHg. The inclusion criteria were SBP > 150 mmHg and DPB > 95 mmHg, or SBP > 160 mmHg, and at least one additional cardiovascular risk factor. Mean follow up was 3.5 years.

**Interventions**
- Nifedipine 30 mg in a long-acting gastrointestinal-transport system (GITS) formulation.
- Co-amilozide (hydrochlorothiazide 25 g plus amiloride 2.5 mg).
- Dose titration was by dose doubling, and addition of atenolol 25–50 mg or enalapril 5–10 mg.

**Outcomes**
Primary outcomes: composite of death from any cardiovascular or cerebrovascular cause, together with non-fatal stroke, myocardial infarction, and heart failure.
Secondary outcomes: total mortality, death from a vascular cause, and non-fatal vascular events including transient ischaemic attacks, angina (new or worsening), and renal failure.

**Risk of bias table**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>'Randomisation was done after 4 weeks of placebo treatment, which could be shortened to 2 weeks in patients who had severe hypertension (blood pressure &gt;180 mm Hg systolic or 110 mm Hg diastolic).'</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td>'Dynamic randomisation (sometimes called minimisation).'</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>'All patients received one active and one placebo tablet taken at the same time of day.'</td>
</tr>
<tr>
<td>Bias</td>
<td>Authors' judgement</td>
<td>Support for judgement</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Random sequence generation</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
</tbody>
</table>

**Kuramoto**

**Methods**
Single site, double-blind, placebo controlled, randomized study in a home for the aged in Japan.

**Participants**
1283 patients in home for the aged, with mean age 76 years, (55% male). Baseline mean SBP/DBP was 169/86 mmHg. The inclusion criterion was age > 60 years and BP > 160/90 and less than 200/110 mmHg. Mean follow up was 4.4 years.

**Interventions**
Treatment: Step 1 - trichlormethiazide 1-4 mg/day (80% monotherapy); Step 2 - reserpine 0.3 mg/day or methyldopa 125-500mg/day or hydralazine 50-100mg/day. Placebo.

**Outcomes**
Cerebrovascular and cardiac complications
<table>
<thead>
<tr>
<th><strong>Allocation concealment</strong></th>
<th>Unclear risk</th>
<th>Not specified.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blinding of participants and personnel</strong></td>
<td>Low risk</td>
<td>Double blind.</td>
</tr>
<tr>
<td><strong>Blinding of outcome assessment</strong></td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
<tr>
<td><strong>Incomplete outcome data</strong></td>
<td>High risk</td>
<td>No intention to treat analysis. Censoring attrition bias. 'Patients were excluded from the trial when the blood pressure exceeded 200/110 and appearance of cerebrovascular or cardiac complications, other diseases which needed hospital admission, death, or moving out from the home'.</td>
</tr>
<tr>
<td><strong>Selective reporting</strong></td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
</tbody>
</table>

**MIDAS**

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th>Multicenter, randomized, double-blind, controlled trial.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>883 patients with mean age of 58.5 years, male (78%). Baseline mean SBP/DBP was 150/97 mmHg. The inclusion criteria was a sustained DBP 90 - 115 mmHg. Mean follow up was 3 years.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Hydrochlorothiazide 12.5-25 mg, twice a day. Isradipine, 2.5-5 mg, twice a day. 'The goal DPB was defined as a reduction of at least 10 mm Hg and a DBP of less than 90 mm Hg. However for patients with baseline DBPs between 105 and 115mm Hg, the goal DBP was set at less than 95 mm Hg. If the DBP had not reached this goal during treatment with the highest dose of study medication allowed by the protocol, open-label enalapril was added at dosages of 2.5, 5.0, 7.5, 10.0 mg twice per day to achieve the predetermined DBP goal.'</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Primary: rate of progression of mean maximum IMT</td>
</tr>
</tbody>
</table>
### Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>'The randomization process was stratified and blocked by clinic to provide equal probability of assignment to either treatment group throughout the study.'</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>Double blind.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Low risk</td>
<td>'All clinicians reviewing reported events were blinded to the randomizations assignments'.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>All randomized patients were followed up 36 months, intention to treat.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>High risk</td>
<td>'The Morbidity and Mortality Committee had decided that for the purpose of analysis at the end of the study, only 1 major vascular event was to be counted for each randomized participant, using the following hierarchy to determine which of the 'multiple' events in the same participant would be counted as the 'official' reportable event: (1) death, (2) stroke, (3) MI, (4) CHF, (5) angina pectoris'.</td>
</tr>
</tbody>
</table>

### MRC I13

<table>
<thead>
<tr>
<th>Methods</th>
<th>Single blind, randomized controlled trial in general practices comparing 2 treatments with placebo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Ambulatory patients, with mean age 52 years, range (35-64 years). Ethnicity not reported. Male 52%. Baseline mean SBP/DBP was 161.4/98.2 mmHg and pulse pressure was 63 mmHg. The inclusion criteria was SBP &lt; 200 mmHg and DBP 90-109 mmHg. Patients were followed for 5 years</td>
</tr>
<tr>
<td>Interventions</td>
<td>Bendrofluazide 10 mg daily (71% monotherapy), Propranolol 80-240 mg daily (78% monotherapy). Methyldopa was added if required. Control: placebo.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Main endpoints of the trial: stroke, coronary event, all cardiovascular events and all-cause mortality.</td>
</tr>
</tbody>
</table>
**Risk of bias table**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>'Randomisation was in stratified blocks of eight within each sex, 10 year age group, and clinic'.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>High risk</td>
<td>Participants: Patients were randomly allocated at entry to one of four treatments: the thiazide diuretic bendrofluazide; placebo tablets that looked like bendrofluazide; the 3 blocker propranolol; and placebo tablets that looked like propranolol. Personnel: Not blinded. Doctors were free to use their own judgment in managing obesity and advising on cigarette smoking, exercise, and salt intake, but they were asked to follow a consistent policy for treated and control patients.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>High risk</td>
<td>Censoring attrition bias. 'Events terminating a patient’s participation were: stroke, whether fatal or non-fatal; coronary events, including sudden death thought to be due to a coronary cause, death known to be due to myocardial infarction, and non-fatal myocardial infarction; other cardiovascular events, including deaths due to hypertension (ICD 400-404) and to rupture or dissection of an aortic aneurysm; and death from any other cause.'</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
</tbody>
</table>

**MRC II**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised, placebo controlled, single blind trial in 226 general practices in the MRC general practice research framework.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>4,396 patients with mean age 70 (range 65-74), male 42%. Baseline mean SBP/DBP was 185/91 mmHg. The inclusion criteria were, age 65-74 and SBP 160-209 mm Hg and DBP &lt;115 mm Hg during an eight week run in. Patients were not taking antihypertensive treatment. Mean follow up was 5.8 years.</td>
</tr>
</tbody>
</table>
### Interventions

**Diuretic Arm:**
- Step 1 - hydrochlorothiazide 25mg or 50mg + amiloride 2.5mg or 5 mg daily.
- Step 2 - atenolol 50mg daily.
- Step 3 - nifedipine up to 20mg daily.
- Step 4 – other drugs.

**Beta-blocker Arm:**
- Step 1 - atenolol 50mg daily.
- Step 2 - hydrochlorothiazide 25mg or 50mg + amiloride 2.5mg or 5 mg daily.
- Step 3 - nifedipine up to 20mg daily.
- Step 4 - other drugs.

**Placebo arm:** matching placebo.

### Outcomes

Main outcome measures: Strokes, coronary events, and deaths from all causes.

---

### Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>'All trial entrants were randomly allocated in equal proportions to one of four treatment categories. Randomisation was in stratified blocks of eight within each sex and clinic.'</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>High risk</td>
<td>'The trial was single blind: patients did not know which treatment group they were in, but the doctors and nurses did.'</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Low risk</td>
<td>'The diagnostic evidence for each terminating event was assessed by an arbitrator, blind to the treatment regimen. World Health Organisation criteria for classification of strokes and coronary events were used.'</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>High risk</td>
<td>Censoring attrition bias. 'A patient's participation in the trial ended with stroke, whether non-fatal or fatal; coronary events, defined as sudden death thought to be due to a coronary cause, death known to be due to a myocardial infarction, and non-fatal myocardial infarction; other cardiovascular events, including deaths due to hypertension and to rupture or dissection of an aortic aneurysm; and death from any other cause. The records of all patients were &quot;flagged&quot; at Southport NHS central register to ensure notification of death.'</td>
</tr>
</tbody>
</table>
Selective reporting | High risk
---|---

'If a patient had a non-fatal event followed by a fatal event in the same category, only the fatal event was included in the analyses. If a patient had two events in different categories, for example, a non-fatal stroke then a coronary event (fatal or non-fatal), then both were included.'

**NICS-EH**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized, double blind, controlled trial.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>429 ambulatory patients, with mean age 70, male 33%. Baseline mean SBP/DBP was 172/94 mmHg. The inclusion criteria were &gt; 60 years and SBP 160-220 mm Hg and DBP &lt;115 mm Hg during a four week run in, with no history of cardiovascular complications. Mean follow up was 5 years.</td>
</tr>
<tr>
<td>Interventions</td>
<td>20 mg sustained-release nicardipine hydrochloride twice daily (nicardipine group). 2 mg trichlormethiazide once daily (diuretic group).</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary: fatal and non-fatal major CV events.</td>
</tr>
</tbody>
</table>

Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>Double blind.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Low risk</td>
<td>For patients who had any end point, the attending physician’s judgment was assessed blindly by the Steering Committee and the diagnosis was confirmed.</td>
</tr>
</tbody>
</table>
Incomplete outcome data | High risk | Per-protocol analysis. 'Patients were randomly assigned to the nicardipine group (215) or the diuretic group (214). Eight and 4 patients did not attend the hospital after the observation period and were not treated; therefore they were withdrawn from the nicardipine and diuretic groups, respectively. Two patients were disqualified because of their age, and 1 patient in the nicardipine group was withdrawn on the basis of primary disease (primary aldosteronism).'

Selective reporting (reporting bias) | High risk | Censoring attrition bias. Patients were withdrawn because of both non-fatal cardiovascular end points and non-fatal non-cardiovascular end points.

**SHELL**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Multicenter, randomised, controlled trial in Italy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>1,882 outpatients with mean age of 72 years, male 39%. Baseline mean SBP/DBP was 178/87 mmHg. The inclusion criteria were &gt; 60 years and SBP &gt; 160mm Hg and DBP &lt; 95 mm Hg. Mean follow up was 2.7 years.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Lacidipine 4 mg/d. Chlorthalidone 12,5 mg/d. 'After 4 weeks, treatment was titrated upward first by increasing the dose of initial therapy (6mg, 25 mg) and by bringing back the monotherapy dose to the initial step and adding fosinopril 10 mg o.d. or any other ACE inhibitor.'</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary: Composite of cardiovascular and cerebrovascular events. Secondary: All-cause mortality, TIA.</td>
</tr>
</tbody>
</table>

Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>Randomized.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td>Randomization was made by BETA Trial Center using sequentially based criterion.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>High risk</td>
<td>Open design. 'Double blind setting in 12 centers for one year to evaluate objectively the efficacy and tolerability of the drugs employed.'</td>
</tr>
</tbody>
</table>
Blinding of outcome assessment | Low risk | 'Events were assessed according to predefined criteria by an independent committee unaware of the treatment group to which patients belonged'.

Incomplete outcome data | Low risk | 'Data were analysed on an intention-to-treat basis'.

Selective reporting | Unclear risk | Not specified.

**SHEP**

### Methods
Multicenter, randomized, double-blinded, placebo-controlled trial conducted in the USA.

### Participants
Ambulatory patients, with mean age 72 years, range (> 60 years). 13.9% of patients were African-Americans. Male (43%). Baseline mean SBP/DBP was 170/77 mmHg and pulse pressure was 93 mmHg. The inclusion criteria was SBP 160-219 mmHg and DBP <90 mmHg. Patients were followed for 4.5 years.

### Interventions
Chlorthalidone 12.5-25 mg (69%), Step 2. atenolol 25-50 mg (23%) or reserpine 0.05-0.1 mg.
Identical placebo.

### Outcomes
**Primary:** Nonfatal and fatal stroke.
**Secondary:** Cardiovascular and coronary morbidity and mortality, all-cause mortality, and quality of life measures.

### Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>'At the completion of the second baseline visit, after verification of eligibility, screenees were randomly allocated by the coordinating center to one of two treatment groups.'</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td>'Each randomization was carried out by telephone'</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>Matching placebos. Personnel was blinded.</td>
</tr>
</tbody>
</table>
Determination and diagnosis of outcomes are clearly described. Information related to study end points was collected by clinic staff. Occurrence of study events listed above was confirmed by a coding panel of three physicians blind to randomization allocation.

All analyses were by treatment assignment at randomization. Non-fatal events were not censored.

Not specified.

Methods
- Multicenter, randomized, double-blind, placebo-controlled study.

Participants
- 551 Ambulatory patients, with mean age 72 years, range (> 60 years). Male (37%). Baseline mean SBP/DBP was 172/75 mmHg. The inclusion criteria were SBP 160-219 mmHg and DBP <90 mmHg. Patients were followed for 2.8 years.

Interventions
- Treatment: Step 1 - chlorthalidone 25;
- Step 1 dose 2 - 50mg daily;
- Step 2 – randomized to either reserpine 0.05mg twice daily or metoprolol 50mg twice daily or hydralazine 25mg twice daily or matching placebo twice daily;
- Step 2 dose 2 - double dose of Step 2.
- Control: matching placebo.

Outcomes
- Primary outcome: stroke.

Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>Double blinded.</td>
</tr>
</tbody>
</table>
When the necessary documentation for a morbid event was assembled at the Coordinating Center, it was copied and mailed to the three members of the Morbidity and Mortality Committee (a neurologist and two internists). Working independently and without knowledge of the participant's treatment group assignment, each member made a diagnosis based on the criteria of Table 1.

Intention to treat analysis. ‘For any participant who had two or more events, one was designated the study event based on a hierarchical classification headed by death followed by four categories of nonfatal events in rank order of stroke, other hypertensive events, atherosclerotic events, and noncardiovascular events. When there were two events in one category, the event that occurred first was used.’

### Methods

**Participants**

389 patients, with mean age 44 years, male (80%). Baseline mean SBP/DBP was 148/99 mmHg. The inclusion criteria were <55 years, home DBP 90-114 mmHg and clinical DBP > 90 mmHg. Patients were followed for 7 years.

**Interventions**

Chlorothiazide 500 mg plus rauwolfia serpentina 100 mg in one tablet, two times daily.

Placebo.

**Outcomes**

Primary: cerebral haemorrhage or thrombosis, myocardial infarction, cardiovascular death and sudden death.

### Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>Randomized.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Not specified.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>Double blind.</td>
</tr>
<tr>
<td><strong>Blinding of outcome assessment</strong></td>
<td>Low risk</td>
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<td>----------------------------------</td>
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<tr>
<td>'All such events were reviewed by two consultants otherwise unassociated with the Trial, who were provided with all pertinent information except knowledge of treatment regimen.'</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Incomplete outcome data</strong></td>
<td>Unclear risk</td>
<td></td>
</tr>
<tr>
<td>Not specified.</td>
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</tr>
<tr>
<td><strong>Selective reporting</strong></td>
<td>Unclear risk</td>
<td></td>
</tr>
</tbody>
</table>

**VA-I20**

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th>Randomized, double blind, placebo-controlled trial in USA.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>Ambulatory patients, with mean age 51 years/ 53.8% patients were African-Americans. Male (100%). Baseline mean SBP/DBP was 186/121 mmHg and pulse pressure was 65 mmHg. The inclusion criterion was DBP &lt; 115-129 mmHg. Patients were followed for 1.5 years.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Hydrochlorothiazide 100 mg plus reserpine 0.2 mg plus hydralazine hydrochloride 150 mg. Placebo</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Mortality 'Class A events: funduscopic evidence of grade 3 or 4 hypertensive retinopathy (multiple striate hemorrhages or soft exudates in more than one quadrant, or bilateral papilledema), doubling of blood urea nitrogen (BUN) to levels above 60 mg/100 cc; dissecting aortic aneurysm; cerebrovascular hemorrhage as opposed to thrombosis; subarachnoid hemorrhage; congestive heart failure persisting despite digitalis and mercurial diuretics; and elevation of diastolic blood pressures to 140 mm Hg or higher on three repeated visits and average rehospitalization diastolic pressure to 130 mm Hg or higher.’ 'Nonterminating (Class B) Morbid Events: organic complications associated with atherosclerosis, such as cerebrovascular thrombosis (as constrained to hemorrhage which was considered a class A event) or myocardial infarction. Congestive heart failure which responded to routine therapy with digitalis or mercurials and did not require antihypertensive agents also was classified as a B event.'</td>
</tr>
</tbody>
</table>
### Risk of bias table

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<thead>
<tr>
<th>Bias</th>
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<th>Support for judgement</th>
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</thead>
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<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>'At the time of randomization, a sealed envelope was opened which assigned the patient to one of two possible regimens-active antihypertensive medications or their placebos.'</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td>'A table of random numbers was utilized by the statistician in determining the assignments.'</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>'The double-blind technique was employed by utilizing a series of complex code numbers to disguise the identity of the randomized treatments and by making active drugs and placebos identical in appearance. It is realized, however, that blood pressure levels and side effects made the maintenance of such a double-blind study difficult and imperfect.' 'Placebos were made up to correspond with each tablet of the active drugs.'</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear risk</td>
<td>No blinding for primary outcomes (mortality, MI, cerebrovascular event). Methods to determine MI and cerebrovascular events not described.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Unclear risk</td>
<td>The total number of dropouts was 12 or 8.4%. Nine occurred during the first two months following randomization. Seven had been randomized to placebos and five to active drugs. Thus, the dropout rate was small and was approximately equally divided between the active- and placebo-treated patients. No reported intention to treat analysis, missing outcome data balanced in numbers across groups. However no reason for drop out.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>High risk</td>
<td>Censoring attrition bias due to the terminating events.</td>
</tr>
</tbody>
</table>

### VA-II²¹

<table>
<thead>
<tr>
<th>Methods</th>
<th>Multicenter, randomized, double-blind, placebo-controlled trial.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>380 patients, with mean age 51 years, male (100%). Baseline mean SBP/DBP was 164/104 mmHg. The inclusion criteria were male and DBP 90-114 mmHg. Mean follow-up was 3.2 years.</td>
</tr>
</tbody>
</table>
Interventions
Treatment: Hydrochlorothiazide 50 mg, reserpine 0.2 mg, hydralazine hydrochloride 75 mg. Hydralazine hydrochloride was raised to 50 mg when DBP remained >90 mmHg. Control: Placebo.

Outcomes
Mortality, CHD, stroke, CHF, systolic BP and diastolic BP.

Risk of bias table

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
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</tr>
<tr>
<td>Allocation concealment</td>
<td>Low risk</td>
<td>'A table of random numbers was utilized by the statistician in determining the assignments.'</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>'Accepted patients were then randomly assigned double-blind to either active drugs or placebos. However personnel can be unblinded by high blood pressure during control visits.'</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear risk</td>
<td>'The records of the patients reported as having assessable morbid events. Such events were reviewed by two consulting physicians who had not participated in the trial.' Blinding of consulting physicians is not specified.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Unclear risk</td>
<td>'Fifty-six or 15% of the 330 randomized patients were classified as drop-outs during the course of the trial. Of this number 27 had been randomized to receive placebos and 29 to receive active drugs.' No reported intention to treat analysis, missing outcome data balanced in numbers across groups. However no reason for drop out.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>High risk</td>
<td>Censoring attrition bias due to the terminating events.</td>
</tr>
</tbody>
</table>
Methods

Multicentre, randomized, controlled study. Double blind for the first 6 months and open thereafter.

Participants

1,414 hypertensive patients, with mean age 53 years, male 49%. Baseline mean SBP/DBP was 169/102 mmHg. The inclusion criteria were SBP > 160 mmHg and DBP > 95 mmHg. Patients were followed for 2 years.

Interventions

240 mg sustained release verapamil.
25 mg chlorthalidone.
Captopril 25-50 mg was added if target was not reached (DBP < 90 or DBP < 95 with at least a 10% reduction). Patients not responding to combined therapy were switched to any chosen therapy by the treating doctors.

Outcomes

'The primary aim of the VHAS was to compare the efficacies and safeties of prolonged treatment (2 years) with slow-release verapamil and with chlorthalidone once a day of hypertensive patients. The secondary aims were: to determine, for a subgroup of these patients, the prevalence of carotid thickenings and atherosclerotic lesions; to compare the effects of the two study drugs on the progression of carotid wall lesions in these patients; and to obtain data on the incidence of cardiovascular events among hypertensive patients throughout the study.'

Risk of bias table

<table>
<thead>
<tr>
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<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Low risk</td>
<td>Randomized.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>Not reported.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>High risk</td>
<td>Double blind for the first 6 months and open thereafter.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>Unclear risk</td>
<td>No outcome assessment reported.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
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<td></td>
</tr>
<tr>
<td>Intention-to-treat analyses. In total 1099 patients completed the 2-year treatment period; 315 dropped out (21.6% of the verapamil group and 22.9% of the chlorthalidone group). Study discontinuation was due to poor compliance in 81.6% of cases and to adverse events related to treatment in 11.4% of cases (18 cases with verapamil and 18 cases with chlorthalidone).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Selective reporting | Unclear risk |
Table S2 Study characteristics of included studies  Summary of studies comparing thiazide-type and thiazide-like diuretics with placebo (A) and other antihypertensive agents (B). Follow-up, age and blood pressures are expressed as a mean. Hypertension was an inclusion criterion in all studies. * during hypertension treatment; † median follow up time.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study medication (dose in mg)</th>
<th>N</th>
<th>Entry criteria</th>
<th>FU (yrs)</th>
<th>Age (yrs)</th>
<th>Men (%)</th>
<th>BMI</th>
<th>Smoker (%)</th>
<th>White/Black (%)</th>
<th>SBP/DBP (mmHg)</th>
<th>Delta SBP/DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thiazide-type diuretics versus placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANBP-I 1980</td>
<td>Chlorothiazide 500-1000</td>
<td>1,721</td>
<td>No CV events</td>
<td>4.1</td>
<td>50</td>
<td>63</td>
<td>27</td>
<td>24</td>
<td>100/0</td>
<td>157.7/100.5</td>
<td>NA/-12.2</td>
</tr>
<tr>
<td>ANBP-I 1980</td>
<td>Placebo</td>
<td>1,706</td>
<td></td>
<td>4.0</td>
<td>51</td>
<td>64</td>
<td>27</td>
<td>26</td>
<td>100/0</td>
<td>157.1/100.4</td>
<td>NA/-6.6</td>
</tr>
<tr>
<td>EWPHBP 1985</td>
<td>HCTZ 25 + Triamterene 50</td>
<td>416</td>
<td>&gt;60 years</td>
<td>4.7</td>
<td>72</td>
<td>31</td>
<td>26</td>
<td>NA</td>
<td>NA</td>
<td>183.0/101.0</td>
<td>-33.0/-16.0</td>
</tr>
<tr>
<td>EWPHBP 1985</td>
<td>Placebo</td>
<td>424</td>
<td></td>
<td>4.6</td>
<td>72</td>
<td>30</td>
<td>27</td>
<td>NA</td>
<td>NA</td>
<td>182.0/101.0</td>
<td>-11.0/-6.0</td>
</tr>
<tr>
<td>Kuramoto 1981</td>
<td>Trichlormethiazide 1-4</td>
<td>38</td>
<td>&gt;60 years</td>
<td>4.0</td>
<td>75</td>
<td>52</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>171.3/86.5</td>
<td>-19.3/-6.5</td>
</tr>
<tr>
<td>Kuramoto 1981</td>
<td>Placebo</td>
<td>41</td>
<td></td>
<td>4.0</td>
<td>77</td>
<td>57</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>166.1/85.5</td>
<td>-7.1/-5.5</td>
</tr>
<tr>
<td>MRC I 1985</td>
<td>Bendroflauzide 10</td>
<td>4,297</td>
<td></td>
<td>5.0</td>
<td>52</td>
<td>52</td>
<td>NA</td>
<td>30</td>
<td>161.0/98.0</td>
<td>-25.0/-13.0</td>
<td></td>
</tr>
<tr>
<td>MRC I 1985</td>
<td>Placebo</td>
<td>8,654</td>
<td></td>
<td>5.0</td>
<td>52</td>
<td>52</td>
<td>NA</td>
<td>30</td>
<td>161.0/98.0</td>
<td>-12.0/-7.0</td>
<td></td>
</tr>
<tr>
<td>MRC II 1992</td>
<td>HCTZ 25-50 + Amiloride 2.5-5.0</td>
<td>1,081</td>
<td></td>
<td>5.8</td>
<td>70</td>
<td>42</td>
<td>27</td>
<td>17</td>
<td>NA</td>
<td>185.0/91.0</td>
<td>-34.0/-14.0</td>
</tr>
<tr>
<td>MRC II 1992</td>
<td>Placebo</td>
<td>2,213</td>
<td></td>
<td>5.8</td>
<td>70</td>
<td>42</td>
<td>27</td>
<td>18</td>
<td>NA</td>
<td>185.0/90.0</td>
<td>-19.0/-6.0</td>
</tr>
<tr>
<td>USPHSH 1977</td>
<td>Chlorothiazide 500 + RS 100</td>
<td>193</td>
<td>&lt;55 years</td>
<td>7.0</td>
<td>44</td>
<td>77</td>
<td>27</td>
<td>46</td>
<td>72/NA</td>
<td>147.7/99.0</td>
<td>-16.5/-10.4</td>
</tr>
<tr>
<td>USPHSH 1977</td>
<td>Placebo</td>
<td>196</td>
<td></td>
<td>7.0</td>
<td>45</td>
<td>83</td>
<td>27</td>
<td>47</td>
<td>72/NA</td>
<td>146.2/99.0</td>
<td>1.5/-0.6</td>
</tr>
<tr>
<td>VA-I 1967</td>
<td>HCTZ 100 + Reserpine 0.2 + Hydralazine 150</td>
<td>73</td>
<td>Male</td>
<td>1.7</td>
<td>50</td>
<td>100</td>
<td>28</td>
<td>NA</td>
<td>43/57</td>
<td>185.6/121.2</td>
<td>-43.0/-29.7</td>
</tr>
<tr>
<td>VA-I 1967</td>
<td>Placebo</td>
<td>70</td>
<td></td>
<td>1.3</td>
<td>51</td>
<td>100</td>
<td>27</td>
<td>NA</td>
<td>50/NA</td>
<td>186.8/121.0</td>
<td>NA/-1.3</td>
</tr>
<tr>
<td>VA-II 1970</td>
<td>HCTZ 50 + Reserpine 0.2 + Hydralazine 75</td>
<td>186</td>
<td>Male</td>
<td>3.2</td>
<td>51</td>
<td>100</td>
<td>27</td>
<td>NA</td>
<td>58/40</td>
<td>162.1/103.8</td>
<td>-27.2/-17.4</td>
</tr>
<tr>
<td>VA-II 1970</td>
<td>Placebo</td>
<td>194</td>
<td></td>
<td>3.3</td>
<td>52</td>
<td>100</td>
<td>27</td>
<td>NA</td>
<td>58/42</td>
<td>165.1/104.7</td>
<td>4.2/1.2</td>
</tr>
<tr>
<td><strong>Thiazide-like diuretics versus placebo</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HYVET 2008</td>
<td>Indapamide 1.5</td>
<td>1,933</td>
<td>&gt;80 years</td>
<td>1.8</td>
<td>84</td>
<td>39</td>
<td>25</td>
<td>6</td>
<td>NA</td>
<td>173.0/90.8</td>
<td>-29.5/-29.9</td>
</tr>
<tr>
<td>HYVET 2008</td>
<td>Placebo</td>
<td>1,912</td>
<td></td>
<td>1.8</td>
<td>84</td>
<td>40</td>
<td>25</td>
<td>7</td>
<td>NA</td>
<td>173.0/90.8</td>
<td>-14.5/-8.8</td>
</tr>
<tr>
<td>SHEP 1991</td>
<td>Chlorthalidone 12.5-25</td>
<td>2,365</td>
<td></td>
<td>4.5</td>
<td>72</td>
<td>44</td>
<td>28</td>
<td>13</td>
<td>86/14</td>
<td>170.5/76.7</td>
<td>-26.5/-9.0</td>
</tr>
<tr>
<td>SHEP 1991</td>
<td>Placebo</td>
<td>2,371</td>
<td></td>
<td>4.5</td>
<td>72</td>
<td>43</td>
<td>28</td>
<td>13</td>
<td>86/14</td>
<td>170.1/76.4</td>
<td>-15.0/-5.3</td>
</tr>
<tr>
<td>SHEP pilot 1989</td>
<td>Chlorthalidone 25</td>
<td>443</td>
<td>&gt;60 years</td>
<td>2.8</td>
<td>72</td>
<td>37</td>
<td>NA</td>
<td>11</td>
<td>82/NA</td>
<td>172.0/75.0</td>
<td>-31.0/-7.0</td>
</tr>
<tr>
<td>SHEP pilot 1989</td>
<td>Placebo</td>
<td>108</td>
<td></td>
<td>2.8</td>
<td>72</td>
<td>37</td>
<td>NA</td>
<td>11</td>
<td>82/NA</td>
<td>172.0/75.0</td>
<td>-15.0/-2.0</td>
</tr>
<tr>
<td>Study</td>
<td>Baseline medication</td>
<td>N</td>
<td>Entry criteria</td>
<td>FU (yrs)</td>
<td>Age (yrs)</td>
<td>Men (%)</td>
<td>BMI</td>
<td>Smoker (%)</td>
<td>White/Black (%)</td>
<td>Mean SBP/DBP (mmHg)</td>
<td>Delta SBP/DBP (mmHg)</td>
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</tr>
<tr>
<td><strong>Thiazide-type diuretics versus other antihypertensive agents</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>ACCOMPLISH</td>
<td>Benazepril 40 + HCTZ 12.5</td>
<td>5,762</td>
<td>High CV risk</td>
<td>3.0</td>
<td>68</td>
<td>61</td>
<td>31</td>
<td>11</td>
<td>83/13</td>
<td>145.4/80.1</td>
<td>-12.9/-5.6</td>
</tr>
<tr>
<td></td>
<td>Benazepril 40 + Amlodipine 5</td>
<td>5,744</td>
<td></td>
<td>3.0</td>
<td>69</td>
<td>60</td>
<td>31</td>
<td>11</td>
<td>84/12</td>
<td>145.3/80.1</td>
<td>-13.7/-6.8</td>
</tr>
<tr>
<td>ANBP II</td>
<td>HCTZ</td>
<td>3,039</td>
<td></td>
<td>4.1</td>
<td>72</td>
<td>48</td>
<td>27</td>
<td>7</td>
<td>95/NA</td>
<td>168.0/91.0</td>
<td>-26.0/-12.0</td>
</tr>
<tr>
<td>Berglund</td>
<td>Bendroflumethiazide 2.5 + KCl 570</td>
<td>53</td>
<td></td>
<td>6.0</td>
<td>NA</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td></td>
<td>Enalapril</td>
<td>3,044</td>
<td></td>
<td>4.1</td>
<td>72</td>
<td>50</td>
<td>27</td>
<td>7</td>
<td>95/NA</td>
<td>167.0/91.0</td>
<td>-26.0/-12.0</td>
</tr>
<tr>
<td>HAPPHY</td>
<td>Bendroflumethiazide 5 or HCTZ 25</td>
<td>3,272</td>
<td></td>
<td>3.8</td>
<td>52</td>
<td>100</td>
<td>27</td>
<td>34</td>
<td>&gt;99/NA</td>
<td>166.0/107.0</td>
<td>-26.0/-18.0</td>
</tr>
<tr>
<td></td>
<td>Atenolol 100 or Metoprolol 200</td>
<td>3,297</td>
<td></td>
<td>3.8</td>
<td>52</td>
<td>100</td>
<td>27</td>
<td>35</td>
<td>&gt;99/NA</td>
<td>166.0/107.0</td>
<td>-26.0/-19.0</td>
</tr>
<tr>
<td>INSIGHT</td>
<td>HCTZ 25 + Amiloride 2.5</td>
<td>3,164</td>
<td>≥ 1 CV RF</td>
<td>3.5</td>
<td>65</td>
<td>47</td>
<td>28</td>
<td>28</td>
<td>Mainly/NA</td>
<td>173.0/99.0</td>
<td>-33.0/-17.0</td>
</tr>
<tr>
<td></td>
<td>Nifedipine 30</td>
<td>3,157</td>
<td></td>
<td>3.5</td>
<td>65</td>
<td>46</td>
<td>28</td>
<td>28</td>
<td>Mainly/NA</td>
<td>173.0/99.0</td>
<td>-33.0/-17.0</td>
</tr>
<tr>
<td>MIDAS</td>
<td>HCTZ 25-50</td>
<td>441</td>
<td></td>
<td>3.0</td>
<td>59</td>
<td>76</td>
<td>28</td>
<td>21</td>
<td>74/21</td>
<td>148.9/96.2</td>
<td>-19.5/-13.0</td>
</tr>
<tr>
<td></td>
<td>Isradipine 5-10</td>
<td>442</td>
<td></td>
<td>3.0</td>
<td>58</td>
<td>80</td>
<td>28</td>
<td>19</td>
<td>71/22</td>
<td>150.6/96.7</td>
<td>-16.0/-13.0</td>
</tr>
<tr>
<td>MRC I</td>
<td>Bendroflumethiazide 10</td>
<td>4,297</td>
<td></td>
<td>5.0</td>
<td>52</td>
<td>52</td>
<td>NA</td>
<td>30</td>
<td>NA</td>
<td>161.0/98.0</td>
<td>-25.0/-13.0</td>
</tr>
<tr>
<td></td>
<td>Propranolol 80-240</td>
<td>4,403</td>
<td></td>
<td>5.0</td>
<td>51</td>
<td>52</td>
<td>NA</td>
<td>28</td>
<td>NA</td>
<td>158.0/98.0</td>
<td>-20.5/-11.5</td>
</tr>
<tr>
<td>MRC II</td>
<td>HCTZ 25-50 + Amiloride 2.5-5.0</td>
<td>1,081</td>
<td></td>
<td>5.8</td>
<td>70</td>
<td>42</td>
<td>27</td>
<td>17</td>
<td>NA</td>
<td>185.0/91.0</td>
<td>-34.0/-14.0</td>
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<tr>
<td></td>
<td>Atenolol 50</td>
<td>1,102</td>
<td></td>
<td>5.8</td>
<td>70</td>
<td>41</td>
<td>27</td>
<td>18</td>
<td>NA</td>
<td>185.0/91.0</td>
<td>-34.0/-14.0</td>
</tr>
<tr>
<td>NICS EH</td>
<td>Trichlormethiazide 2</td>
<td>210</td>
<td>&gt;60 years</td>
<td>5.0</td>
<td>70</td>
<td>26</td>
<td>24</td>
<td>9</td>
<td>NA</td>
<td>172.6/93.4</td>
<td>-25.6/-14.4</td>
</tr>
<tr>
<td></td>
<td>Nicardipine 20</td>
<td>204</td>
<td></td>
<td>5.0</td>
<td>70</td>
<td>40</td>
<td>23</td>
<td>11</td>
<td>NA</td>
<td>171.9/94.2</td>
<td>-24.9/-13.2</td>
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</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline medication</th>
<th>N</th>
<th>Entry criteria</th>
<th>FU (yrs)</th>
<th>Age (yrs)</th>
<th>Men (%)</th>
<th>BMI</th>
<th>Smoker (%)</th>
<th>White/Black (%)</th>
<th>Mean SBP/DBP (mmHg)</th>
<th>Delta SBP/DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thiazide-like diuretics versus other antihypertensive agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALLHAT A</td>
<td>Chlorthalidone 12.5-25</td>
<td>15,255</td>
<td>&gt;55 years</td>
<td>4.9</td>
<td>67</td>
<td>53</td>
<td>30</td>
<td>22</td>
<td>60/35</td>
<td>156.0/89.0</td>
<td>-22.1/-13.6</td>
</tr>
<tr>
<td></td>
<td>Amlodipine 2.5-10</td>
<td>9,048</td>
<td>≥ 1 CHD RF</td>
<td>4.9</td>
<td>67</td>
<td>53</td>
<td>30</td>
<td>22</td>
<td>60/35</td>
<td>157.0/90.0</td>
<td>-22.3/-15.4</td>
</tr>
<tr>
<td>ALLHAT L</td>
<td>Chlorthalidone 12.5-25</td>
<td>15,255</td>
<td>&gt;55 years</td>
<td>4.9</td>
<td>67</td>
<td>53</td>
<td>30</td>
<td>22</td>
<td>60/35</td>
<td>156.0/89.0</td>
<td>-22.1/-13.6</td>
</tr>
<tr>
<td></td>
<td>Lisinopril 10-40</td>
<td>9,054</td>
<td>≥ 1 CHD RF</td>
<td>4.9</td>
<td>67</td>
<td>54</td>
<td>30</td>
<td>22</td>
<td>59/36</td>
<td>156.0/89.0</td>
<td>-20.1/-13.6</td>
</tr>
<tr>
<td>ALLHAT D</td>
<td>Chlorthalidone 12.5-25</td>
<td>15,268</td>
<td>&gt;55 years</td>
<td>3.3</td>
<td>67</td>
<td>53</td>
<td>30</td>
<td>22</td>
<td>60/35</td>
<td>156.0/89.0</td>
<td>-21.0/-13.0</td>
</tr>
<tr>
<td></td>
<td>Doxazosin 2-8</td>
<td>9,067</td>
<td>≥ 1 CHD RF</td>
<td>3.3</td>
<td>67</td>
<td>54</td>
<td>30</td>
<td>22</td>
<td>59/36</td>
<td>145.0/84.0</td>
<td>-8.0/-8.0</td>
</tr>
<tr>
<td>SHELL</td>
<td>Chlorthalidone 12.5</td>
<td>940</td>
<td>&gt;60 years</td>
<td>2.7</td>
<td>72</td>
<td>38</td>
<td>NA</td>
<td>10</td>
<td>NA</td>
<td>178.2/86.8</td>
<td>-35.8/-7.8</td>
</tr>
<tr>
<td></td>
<td>Lacidipine 4</td>
<td>942</td>
<td></td>
<td>2.7</td>
<td>72</td>
<td>40</td>
<td>NA</td>
<td>15</td>
<td>NA</td>
<td>178.1/86.9</td>
<td>-35.1/-7.9</td>
</tr>
<tr>
<td>VHAS</td>
<td>Chlorthalidone 25</td>
<td>707</td>
<td>40-65 years</td>
<td>2.0</td>
<td>54</td>
<td>50</td>
<td>27</td>
<td>19</td>
<td>NA</td>
<td>168.8/102.3</td>
<td>-28.6/-16.6</td>
</tr>
<tr>
<td></td>
<td>Verapamil 240</td>
<td>707</td>
<td></td>
<td>2.0</td>
<td>55</td>
<td>48</td>
<td>27</td>
<td>17</td>
<td>NA</td>
<td>169.1/102.2</td>
<td>-27.6/-17.0</td>
</tr>
</tbody>
</table>
ANBP, Australian National Blood Pressure study; EWPHBP, European Working Party on High Blood Pressure; MRC, Medical Research Council; USPHSH, United States Public Health Service Hospitals; VA, Veterans Administration; HYVET, Hypertension in the Very Elderly Trial; SHEP, Systolic Hypertension in the Elderly Program; ACCOMPLISH, Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension; HAPPHY, Heart Attack Primary Prevention in Hypertension; INSIGHT, Intervention as a Goal in Hypertension Treatment; MIDAS, Multicenter Isradipine Diuretic Atherosclerosis Study; NICS-EH, National Intervention Cooperative Study in Elderly Hypertensives; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; SHELL, Systolic Hypertension in the Elderly: Lacidipine Long-Term; VHAS, Verapamil in Hypertension and Atherosclerosis Study; FU, follow-up; BMI, body mass index; HT, hypertension; SBP/DBP systolic/diastolic blood pressure; HCTZ, hydrochlorothiazide; RS, rauwolfia serpentina; CV cardiovascular; CHD, coronary heart disease; RF, risk factor; NA, not available.
Selection process for studies included in the meta-analysis according to the PRISMA 2009 flow diagram
Figure S2 Forest plot of the primary analysis.

<table>
<thead>
<tr>
<th>Placebo comparisons</th>
<th>Random effects model</th>
<th>RR (95% CI)</th>
<th>(\hat{d})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide-type</td>
<td>0.67 (0.56-0.81)</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>0.67 (0.60-0.75)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td><strong>Coronary events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide-type</td>
<td>0.81 (0.63-1.05)</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>0.76 (0.61-0.96)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td><strong>Cerebrovascular events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide-type</td>
<td>0.52 (0.38-0.69)</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>0.68 (0.57-0.80)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide-type</td>
<td>0.36 (0.16-0.84)</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>0.47 (0.36-0.61)</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide-type</td>
<td>0.86 (0.75-1.00)</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>0.84 (0.74-0.96)</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other drug comparisons</th>
<th>Cardiovascular events</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide-type</td>
<td>0.96 (0.84-1.09)</td>
<td>59%</td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>0.86 (0.72-1.04)</td>
<td>88%</td>
</tr>
<tr>
<td><strong>Coronary events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide-type</td>
<td>1.01 (0.83-1.24)</td>
<td>62%</td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>1.01 (0.95-1.07)</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Cerebrovascular events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide-type</td>
<td>0.94 (0.76-1.16)</td>
<td>56%</td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>0.93 (0.86-1.01)</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide-type</td>
<td>0.87 (0.61-1.23)</td>
<td>53%</td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>0.71 (0.53-0.95)</td>
<td>91%</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide-type</td>
<td>1.03 (0.94-1.12)</td>
<td>0%</td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>1.00 (0.95-1.05)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Pooled results of studies that compared thiazide-type and thiazide-like diuretics with placebo and other antihypertensive agents. CI, confidence interval; RR, risk ratio.
Figure S3 Forest plot of the drug-adjusted analysis.

<table>
<thead>
<tr>
<th>Calcium antagonists</th>
<th>Cardiovascular events</th>
<th>RR</th>
<th>(95% CI)</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide-type</td>
<td>0.97 (0.82-1.16)</td>
<td>37%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>0.93 (0.88-0.99)</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Coronary events     | Thiazide-type         | 1.08 (0.86-1.35) | 17%   |
|                     | Thiazide-like         | 1.01 (0.93-1.10) | 0%    |

| Cerebrovascular events | Thiazide-type      | 1.03 (0.81-1.31) | 20%   |
|                       | Thiazide-like       | 1.05 (0.93-1.18) | 0%    |

| Heart failure        | Thiazide-type       | 0.75 (0.37-1.51) | 54%   |
|                      | Thiazide-like       | 0.74 (0.67-0.83) | 0%    |

| All-cause mortality  | Thiazide-type       | 1.06 (0.93-1.22) | 0%    |
|                      | Thiazide-like       | 0.98 (0.84-1.14) | 33%   |

<table>
<thead>
<tr>
<th>ACE inhibitors</th>
<th>Cardiovascular events</th>
<th>RR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide-type</td>
<td>1.18 (1.01-1.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide-like</td>
<td>0.95 (0.90-1.01)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Coronary events      | Thiazide-type         | 1.40 (1.00-1.95) |
|                      | Thiazide-like         | 1.02 (0.93-1.11) |

| Cerebrovascular events | Thiazide-type      | 1.08 (0.87-1.34) |
|                        | Thiazide-like       | 0.88 (0.78-0.99) |

| Heart failure         | Thiazide-type       | 1.22 (0.89-1.68) |
|                      | Thiazide-like       | 0.91 (0.81-1.02) |

| All-cause mortality   | Thiazide-type       | 1.08 (0.89-1.32) |
|                      | Thiazide-like       | 1.00 (0.93-1.06) |

Pooled result of studies that compared thiazide-type and thiazide-like diuretics with calcium antagonists and ACE inhibitors. Seven studies compared thiazide diuretics with calcium antagonist of which 4 studies used thiazide-type diuretics and 3 studies used thiazide-like diuretics. The drug-adjusted analysis of ACE inhibitors is based on 2 studies. One study compared ACE inhibitors with thiazide-type diuretics and one study compared ACE inhibitors with thiazide-like diuretics. We were therefore not able to provide I² values for this analysis.

ACE, angiotensin-converting-enzyme; CI, confidence interval; RR, risk ratio.
Figure S4 C-E Association between the risk ratios of coronary events (C), cerebrovascular events (D) and all-cause mortality (E) and the difference in achieved mean arterial blood pressure (MAP) between treatment and control group.

![Graph showing association between risk ratios and MAP difference](image)

Circles and squares represent individual trials and have a size proportional to the calculated weight. Analysing Y-intercept, thiazide-like diuretics showed that thiazide-type and thiazide-like diuretics were comparable in reducing the risk of coronary events \( (p = 0.61) \) (C). No BP dependent effect (slopes) was seen for coronary events \( (p = 0.51) \) (C).
Circles and squares represent individual trials and have a size proportional to the calculated weight. Analysing Y-intercept, thiazide-like diuretics showed that thiazide-type and thiazide-like diuretics were comparable in reducing the risk of cerebrovascular events ($p = 0.36$) (D). No BP dependent effect (slopes) was seen for cerebrovascular events ($p = 0.47$) (D).
Circles and squares represent individual trials and have a size proportional to the calculated weight. Analysing Y-intercept, thiazide-like diuretics showed that thiazide-type and thiazide-like diuretics were comparable in reducing the risk of all-cause mortality (p = 0.35) (E). No BP dependent effect (slopes) was seen for all-cause mortality (p = 0.25) (E).
荟萃分析：利尿剂（摘要）

系统回顾和荟萃分析噻嗪型和噻嗪样利尿剂对心血管事件发生率和死亡率的影响

Effects of Thiazide-Type and Thiazide-Like Diuretics on Cardiovascular Events and Mortality Systematic Review and Meta-Analysis

Rik H.G. Olde Engberink, Wijnanda J. Frenkel, Bas van den Bogaard, Lizzy M. Brewster, Liffert Vogt, Bert-Jan H. van den Born

孙颖 译 程标 审校

噻嗪类利尿剂是高血压一线用药，也是世界范围内最常用的药物之一。根据分子结构的差异，噻嗪类利尿剂可以分为噻嗪型（thiazide-type，TT）和噻嗪样（thiazide-like，TL）利尿剂两种。其中TL利尿剂的保钠利水比TT利尿剂长，且有额外的药理作用，他们可能以不同方式影响心血管疾病的发生风险。在这项荟萃分析中，作者比较了TT和TL利尿剂对心血管事件和死亡率的影响。纳入标准：比较TT或TL利尿剂与安慰剂或降压药治疗成人高血压患者，且随访超过1年的随机对照研究。主要终点为心血管事件，次要终点包括心脏事件、心力衰竭、脑血管事件和全因死亡。通过meta回归分析鉴别混杂因素并校正达标血压值。纳入21项研究涵盖480,000例患者1年。临床终点不受年龄、性别和种族等异质性的影响，而血压降幅越大，终点事件发生率越低（P<0.001）。校正不同试验中诊室血压降值差异后，与TT利尿剂相比，TL利尿剂可导致心血管事件和心衰风险额外分别减少12%（P=0.049）和21%（P=0.023）。TT、TL利尿剂和其他降压药的不良事件发生率相当。研究结果表明，当考虑用利尿剂治疗高血压时，现有的最佳证据更倾向于支持选择噻嗪样利尿剂。

（Hypertension. 2015;65:1033-1040.）

动态血压监测（摘要）

基于诊室血压、家庭血压及动态血压对患者进行诊断分类的策略

Strategies for Classifying Patients Based on Office, Home, and Ambulatory Blood Pressure Measurement

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现有的高血压指南推荐：在诊室血压测量之后，进行家庭血压或动态血压监测是必不可少的。然而，应优先考虑家庭血压监测还是动态血压监测尚不明确。在831例未治疗的门诊患者中（平均年龄50.6岁，女性49.8%），我们进行了诊室血压（3次）、家庭血压（7天）以及24 h动态血压测量，并根据血压指南推荐的标准将患者分为正常血压、白大衣高血压、隐匿性高血压或持续性高血压。根据诊室血压和家庭血压测量结果，白大衣性、隐匿性及持续性高血压的患病率（患病率）分别为61（10.3%）、166（20.0%）和162（19.5%）。用白天（从8AM到6PM）血压替代家庭血压，证实了575例患者（69.2%）的分类诊断，下调到风险较低类别，即从隐匿性高血压重分类为正常血压（n=24）或从持续性高血压变为白大衣性高血压（n=9）的患者共有33人（4.0%），而上调到风险较高类别的，则从正常血压重分类为隐匿性高血压（n=179）或从白大衣高血压变为持续性高血压（n=44）的患者共有223人（26.8%）。用24 h动态血压代替白天血压来进行分类比较，结果是一致的。医分类到风险较高类别的患者，校正其他影响因素后，尿白蛋白/肌酐比值[+20.6%，可信区间（CI）：4.4-39.3]和主动脉内膜中层厚度（+0.30mm/s，CI：0.09-0.51）均高于依据家庭和白天动态血压分类都是正常血压或白大衣高血压即分类一致的患者。尿白蛋白/肌酐比值和主动脉内膜中层厚度这两个靶器官损伤指标及中心动脉脉搏波速度与年轻分类的几率呈正相关（P<0.048）。因此，为了准确地诊断高血压和决定是否启动降压治疗，诊室血压测量后应优先选择进行动态血压监测。应用家庭血压替代动态血压监测，将会有25%以上属于高风险的隐匿性高血压或持续性高血压的患者被漏诊。

（Hypertension. 2015;65:1258-1265.）