Systematic review of antihypertensive therapies: Does the evidence assist in choosing a first-line drug?

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Abstract

Background: The available evidence about the effectiveness of specific first-line antihypertensive drugs in lowering blood pressure and preventing adverse outcomes has not been systematically quantified in a manner that would assist clinicians in choosing a first-line drug.

Methods: The following literature sources were searched: MEDLINE (1966–1997), the Cochrane Library (1998 CD-ROM, issue 2) and references from previous meta-analyses published from 1980 to 1997. Selected were randomized controlled trials of at least 1 year's duration that provided morbidity or mortality data and that compared 1 of 6 possible first-line antihypertensive therapies either with another 1 of the 6 drug therapies (drug–drug comparison) or with no treatment, including placebo (drug–no treatment comparison). The following outcomes were pooled according to trial design (drug–drug or drug–no treatment comparison) and the drug therapy: death, stroke, coronary artery disease, total cardiovascular events, withdrawal due to adverse effect, and decrease in systolic and diastolic blood pressure.

Results: Of 38 trials identified, 23 (representing 50 853 patients) met the inclusion criteria. Four drug classes were evaluated in the trials: thiazides (21 trials), β-adrenergic blockers (5), calcium-channel blockers (4) and angiotensin-converting-enzyme (ACE) inhibitors (1). In 5 drug–drug trials comparing thiazides with β-blockers, the former were associated with a significantly lower rate of withdrawal due to adverse effects (relative risk [RR] 0.69, 95% confidence interval [CI] 0.63–0.76). In the trials that had an untreated control group, low-dose thiazide therapy was associated with a significant reduction in the risk of death (RR 0.89, 95% CI 0.81–0.99), stroke (RR 0.66, 95% CI 0.56–0.79), coronary artery disease (RR 0.71, 95% CI 0.60–0.84) and cardiovascular events (RR 0.68, 95% CI 0.62–0.75). High-dose thiazide therapy, β-blocker therapy and calcium-channel blocker therapy did not significantly reduce the risk of death or coronary artery disease. When the results for total cardiovascular events were expressed in terms of absolute risk reduction, low-dose thiazide therapy reduced the risk by 5.7% (95% CI 4.2%–7.2%); the number needed to treat (NNT) for approximately 5 years to prevent one event was 18. In both the drug–drug and the drug–no treatment comparison trials, thiazides were significantly better at reducing systolic blood pressure than the other drug classes.

Interpretation: Low-dose thiazide therapy can be prescribed as the first-line treatment of hypertension with confidence that the risk of death, coronary artery disease and stroke will be reduced. The same cannot be said for high-dose thiazide therapy, β-blockers, calcium-channel blockers or ACE inhibitors.

One of the main components of managing a patient with hypertension is deciding which drug to prescribe for first-line therapy. This decision should be made primarily on the basis of the best available evidence of effectiveness — that is, the drug's ability to prevent adverse health outcomes that are important to the patient. The available evidence has not been organized in a way that helps clinicians make such decisions. There have been a number of systematic reviews of the effectiveness of antihypertensive therapy, but most have focused on overall effectiveness[1,2] or effectiveness in special groups such as elderly patients.[3–7]

Evidence

Études

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When all drug therapies are included in one review, there is an underlying assumption that the benefits of lowering blood pressure are independent of the mechanism by which this is achieved. This assumption has not been proven, and it is likely that the mechanism by which a drug lowers blood pressure will have effects that are independent of the blood-pressure-lowering effect. In addition, all antihypertensive drugs have actions other than lowering blood pressure. These other actions, both known and unknown, could enhance or negate the effectiveness associated with the decrease in blood pressure.

Only 2 reviews have attempted to distinguish between the effectiveness of antihypertensive therapies used as first-line agents.[1,8] Collins and associates[1] reviewed drug–drug comparison trials, but only 2 of the 3 trials included were appropriate to make that comparison. The review by Psaty and colleagues[8] had a number of deficiencies: drug–drug comparison trials were not included, trials were misclassified to drug therapy groups, and data on the effects of lowering blood pressure were not included.

The objectives for our systematic review were (a) to combine the evidence of effectiveness and efficacy from drug–drug comparison trials of first-line therapies; (b) to combine the evidence of effectiveness and efficacy from trials in which classes of drugs used as first-line therapy were compared with a placebo or an untreated control group; (c) to determine whether the dose of thiazide used affected outcomes; (d) to calculate from total cardiovascular events the best estimate of the overall absolute risk reduction and the number needed to treat for each drug class; and (e) to translate the evidence into clinical implications for first-line drug choices.

Methods

The following sources were searched: MEDLINE (1966–1997), the Cochrane Library (1998 CD-ROM, issue 2) and references from previous meta-analyses published from 1980 to 1997. In the case of incomplete reports, MEDLINE was searched for connected papers to retrieve missing information. Our search retrieved 9 trials not included in the review by Psaty and colleagues[8] and 6 trials that have not been included in previous reviews.

We included trials in which participants had hypertension defined as a systolic blood pressure of at least 160 mm Hg or a diastolic blood pressure of at least 90 mm Hg. We assumed that the effect on outcomes would be independent of whether the hypertension was defined in terms of systolic or diastolic pressure. All antihypertensive trials were included regardless of participants' comorbidities or baseline risk. We assumed that age and comorbidities would not affect the relative risk reduction associated with drug treatment. Trials using antihypertensive drugs for other indications (e.g., congestive heart failure) were excluded.

The drug classes of interest were thiazides, β-adrenergic blockers, angiotensin-converting-enzyme (ACE) inhibitors, calcium-channel blockers, α-adrenergic blockers and angiotensin II receptor antagonists. Supplemental drugs could be used as combination therapy or as stepped therapy. We assumed that these supplemental drugs would not systematically interact to affect the occurrences of the end points studied.

The following were the outcome measures of interest: death, including all-cause mortality; stroke, fatal and nonfatal; coronary artery disease, including fatal and nonfatal myocardial infarction and sudden or rapid cardiac death; and total cardiovascular events, including stroke and coronary artery disease plus congestive heart failure and other significant vascular events such as ruptured aneurysm (not included were surgical or other procedures, angina and transient ischemic attacks).

When primary trials reported outcomes that did not explicitly fit the above definitions, we made a decision based on maximizing the inclusion of data and maintaining concordance with how the data were classified in previous reviews.

We included trials that met the following criteria: random allocation of participants; comparison between a first-line drug therapy and another first-line drug therapy or no treatment (including placebo); recording of group baseline characteristics; clearly defined mortality and morbidity end points; at least 1 year of follow-up; clearly defined first-line treatment in 1 of 6 defined categories; and the majority (more than 70%) of patients in the treatment group taking the drug class of interest after 1 year. We included trials in which patients received concurrent therapy with drugs not in the classes of interest as well as trials in which supplemental drugs from other drug classes of interest were given as long as they were not taken by more than 50% of patients.

Because of the number of trials in which thiazides were compared with no treatment or placebo, we were able to evaluate whether the dose of the thiazide affected the outcomes. We divided the thiazide trials into high or low dose based on the starting dose used in the trial. We selected hydrochlorothiazide at a starting dose of 50 mg and above to define the high-dose therapy. The doses of the other thiazides equivalent to that dose were defined based on diuretic effect in human studies as much as possible (Appendix 1). We assumed that each thiazide would have a similar dose-response curve and that the usual range of prescription doses would represent a similar range on the dose-response curve. The average dose used in the predefined high- and low-dose groups was calculated as a weighted average from the trials in which the average dose was reported or could be estimated.

Data abstraction was done by 2 independent reviewers and compared when possible to data from previously published meta-analyses. The data represent only one morbid event per patient, because most studies usually recorded only the first morbid event. However, in some trials it was impossible to be certain, and so the category of total cardiovascular events could include a small proportion of patients counted more than once. This would occur similarly in both the treatment and the comparison groups.

Quantitative analyses of outcomes were based on intention-to-treat results. We used the relative risk (RR) ratio and a fixed-effects model to combine outcomes across trials. The weighting factor for each trial was the inverse of the within-study variance plus a between-study variance component (DerSimonian-Laird type random effects estimators[9]). The risk difference (RD), the absolute risk reduction (ARR = RD × 100) and the number needed to treat (NNT = 1/RD) were calculated only for the category of total cardiovascular events because this single value has the largest ARR and most meaningful NNT from a clinical standpoint.

Data for blood pressure reduction was combined using a weighted mean difference method, whereby the trials are weighted according to the number of subjects in the trial and the within-study variance. Some of the trials did not report a within-study variance for blood pressure decrease; in these studies an imputed standard deviation (SD) was assigned based on the highest SD for that group. In this way the weighting was based primarily on the numbers of subjects randomized to each group. Because of this

limitation, we report 99% confidence intervals (CIs) for this data instead of 95% CIs, which were the standard for the other data.

We performed sensitivity analyses to test for the robustness of the data and to determine whether the decision to include certain studies had a significant effect on the final estimates of effect size.

Results

We retrieved 38 studies of first-line therapy for hypertension published between 1966 and 1997. We excluded 15 reports[10–32] because they did not meet our inclusion criteria

Table 1: Summary of trials assessing effectiveness and efficacy of drugs as first-line therapy for hypertension

Trial	Total no. of patients	Duration, yr	Age range, yr	First-line treatment (and dose)	Other treatment
Drug–drug comparison					
Berglund et al[33,34]*	106	10	47–54	Bendrofluazide (2.5 mg) Propranolol (160 mg)	Hydralazine Hydralazine
HAPPHY[35]	6 569	3.8	40–64	Bendrofluazide (5 mg) or HCTZ (50 mg) Atenolol (100 mg) or metoprolol (200 mg)	Hydralazine, spironolactone Hydralazine, spironolactone
MRC-O[36]*	4 396	5.8	65–74	HCTZ (25 mg) or amiloride (2.5 mg) Atenolol (50 mg)	Atenolol, nifedipine HCTZ or amiloride, nifedipine
MRC-TMH[37]	17 354	5.5	35–64	Bendrofluazide (10 mg) Propranolol (80 mg)	Methyldopa Guanethidine, methyldopa
VACS[38]	394	1	30–69	HCTZ (50 mg) Propranolol (80 mg)	
MIDAS[39]	883	3	40–80	HCTZ (25 mg) Isradipine (5 mg)	Enalapril Enalapril
VHAS[40]	1 414	2	40–65	Chlorthalidone (25 mg) Verapamil (240 mg)	Captopril Captopril
GLANT[41]	1 936	1	40–80	Delapril (30–120 mg) CCB†	Beta-blocker, thiazide Beta-blocker, thiazide
Drug–no treatment comparison					
ATTMH[42]	3 427	4	30–69	Chlorothiazide (500 mg)	Methyldopa or propranolol or pindolol, hydralazine or clonidine
Barraclough[43]	116	1.5	45–69	Bendrofluazide‡	Methyldopa or debrisoquine
Carter[44]	97	4	40–80	Thiazide‡§	Methyldopa, bethanidine or debrisoquine
EWPHBPE[45]*	840	7	> 60	HCTZ (25 mg) or triamterene (50 mg)	Methyldopa
HSCS[46]	452	3	40–80	Methyclothiazide (10 mg)	Deserpidine
Kuramoto et al[47]*	91	2.7	> 60	Trichlormethiazide (1 mg)	Reserpine, methyldopa, hydralazine
Oslo study[48,49]	785	5–6	40–49	HCTZ‡	Propranolol or methyldopa
SHEP pilot study[50]*	551	2.8	> 60	Chlorthalidone (25 mg)	Hydralazine or reserpine or metoprolol
SHEP[51]*	4 736	4.5	> 60	Chlorthalidone (12.5 mg)	Atenolol or reserpine
SYST-EUR[52]	4 695	2.1	> 60	Nitrendipine (10 mg)	Enalapril, HCTZ
US PHSHCS[53]	389	7	21–55	Chlorothiazide (1 g)	Reserpine
VA-I[54]	143	1.5	35–70	HCTZ (100 mg)	Reserpine, hydralazine
VA-II[55]	380	3.7	48–52	HCTZ (100 mg)	Reserpine, hydralazine
VA-NHLBI[56,57]	1 012	2	21–50	Chlorthalidone (50 mg)	Reserpine
Wolff et al[58]	87	2	21–70	Chlorothiazide (1 g) or HCTZ (100 mg)	Reserpine, guanethidine

Note: HCTZ = hydrochlorothiazide, CCB = calcium-channel blocker.
*Considered in analysis as trial of low-dose thiazide therapy.
†Several dihydropyridine CCBs were used in the trial, at a range of doses.
‡Dose not specified.
§Type of drug not specified.

(Appendix 2). Table 1 summarizes the characteristics of the remaining 23 trials (representing 50 853 patients).[33–58] The first group of trials represents those that compared one first-line drug therapy with another. Two of the trials in this group[36,37] also included a placebo group, so we included them in our analysis of drug–no treatment comparison trials as well.

Drug–drug comparison trials

The outcomes of the drug–drug comparison trials are shown in Table 2. In the 5 trials that compared thiazides with β-blockers,[33–38] the thiazides were associated with a significantly lower rate of withdrawal due to adverse effects than the β-blockers; the lower incidence of total cardiovascular events with the thiazides was of borderline statistical significance. For this comparison total mortality data were available for the β-blockers atenolol, metoprolol and propranolol.[59] In this subgroup analysis, the total number of deaths was significantly lower with thiazides than with atenolol (thiazide 160/2680 v. atenolol 200/2706; RR 0.81, 95% CI 0.67–0.99), but not when thiazides were compared with the other 2 β-blockers.

In the 2 trials that compared a thiazide (hydrochlorothiazide) with a calcium-channel blocker (isradipine or verapamil),[39,40] there were no significant differences in any of the outcomes (Table 2). One trial compared an ACE inhibitor (delapril) with several dihydropyridine calcium-channel blockers;[41] outcomes tended to be better with the ACE inhibitor, except for withdrawals due to adverse effects (mostly dry cough), which were significantly higher with the ACE inhibitor (Table 2).

As for the efficacy of the drug therapies in lowering blood pressure in these trials, the reduction in systolic pressure was significantly greater with the thiazides than with the β-blockers or calcium-channel blockers (Table 3). The

Table 2: Adverse outcomes of first-line antihypertensive therapy in drug–drug comparison trials

Outcome	No. of events/ no. of patients		RR (and 95% CI)
Thiazide v. β-adrenergic blocker (5 trials)	*Thiazide*	*β-blocker*	
Death	367/8915	387/9037	0.97 (0.84–1.11)
Stroke	107/8862	130/8984	0.84 (0.65–1.08)
CAD	285/8862	317/8984	0.91 (0.78–1.07)
Total cardiovascular events*	431/8862	495/8984	0.88 (0.78–1.00)
Withdrawal due to adverse effects	624/8862	924/8984	0.69† (0.63–0.76)
Thiazide v. CCB (2 trials)	*Thiazide*	*CCB*	
Death	13/1148	13/1149	1.00 (0.47–2.15)
Stroke	7/1148	11/1149	0.64 (0.25–1.64)
CAD	16/1148	16/1149	1.00 (0.50–1.99)
Total cardiovascular events	24/1148	32/1149	0.75 (0.45–1.27)
Withdrawal due to adverse effects	54/1148	59/1149	0.91 (0.62–1.33)
ACE inhibitor v. CCB (1 trial)	*ACE inhibitor*	*CCB*	
Death	3/980	4/956	0.73 (0.16–3.26)
Stroke	4/980	10/956	0.39 (0.12–1.24)
CAD	2/980	0/956	4.90 (0.23–101)
Total cardiovasculuar events	6/980	12/956	0.49 (0.18–1.29)
Withdrawal due to adverse effects	95/980	28/956	3.31† (2.19–5.00)

Note: RR = relative risk, CI = confidence interval, CAD = coronary artery disease.
*Includes stroke, CAD, congestive heart failure and other significant vascular events (e.g., ruptured aneurysm).
†$p < 0.01$, as compared with 1.

Table 3: Efficacy of first-line antihypertensive therapy in lowering blood pressure, in drug–drug comparison trials

Drug; blood pressure	Mean decrease from baseline pressure, mm Hg		Weighted mean difference (and99%CI)
Thiazide v. β-blocker	*Thiazide*	*β-blocker*	
Systolic	–26.6	–24.3	–2.3* (–3.1 to –1.5)
Diastolic	–15.5	–15.2	–0.2 (–0.8 to 0.3)
Thiazide v. CCB	*Thiazide*	*CCB*	
Systolic	–25.1	–23.1	–2.0* (–3.6 to –0.3)
Diastolic	–15.2	–15.5	0.2 (–0.9 to 1.4)
ACE inhibitor v. CCB	*ACE inhibitor*	*CCB*	
Systolic	–23.0	–29.0	6.0* (3.7 to 8.3)
Diastolic	–13.0	–16.0	3.0* (1.2 to 4.8)

*$p < 0.01$, as compared with 0.

baseline blood pressures were similar in each group. The effect of these 3 classes of drugs on diastolic pressure was similar. In the one trial comparing an ACE inhibitor with a calcium-channel blocker, the latter had a greater effect on both the systolic and the diastolic pressures.[41]

Drug–no treatment comparison trials

In 16 of these trials a thiazide was the drug chosen for first-line therapy. We were therefore able to divide the trials into those in which the thiazide dose was considered low (5 trials) or high (11 trials) based on the starting dose (Appendix 1). Three of the trials did not specify the dose,[43,44,48] but we included them in the high-dose group because the prescribing of high-dose thiazide therapy was common when those trials were conducted. The weighted mean dose of thiazide, in hydrochlorothiazide equivalents, was about 90 mg for the high-dose trials and 26 mg for the low-dose trials.

Two of the drug–no treatment comparison trials assessed a β-blocker for first-line therapy,[36,37] and one assessed a calcium-channel blocker (nitrendipine).[52]

The combined outcome data for this group of trials are shown in Table 4. Low-dose thiazide therapy was similar to high-dose thiazide therapy in reducing the risk of stroke and total cardiovascular events; however, only the low-dose therapy was associated with a significantly lower incidence of coronary artery disease. For the β-blockers, none of the outcomes differed significantly between the treatment and control groups. The calcium-channel blocker, used in patients with isolated systolic hypertension, was associated with a significant reduction in stroke and cardiovascular events compared with the control group.[52]

The relative risk is the best way to compare effectiveness between drug classes and between categories. For the patient, however, it is more meaningful to have a measure of the absolute risk reduction (ARR) and the number needed to treat (NNT) for a specified period to prevent 1 event. We calculated this summary measure for total cardiovascular events for the 4 drug classes: for low-dose thiazide therapy the ARR was 5.7% (95% CI 4.2%–7.2%) and the NNT 18; for high-dose thiazide therapy the ARR was 1.5% (95% CI 0.9%–2.1%) and the NNT 67; for β-blockers the ARR was 0.7% (95% CI 0.1%–1.4%) and the NNT 142; and for calcium-channel blockers the ARR was 2.4% (95% CI 0.9%–3.8%) and the NNT 42. An estimate of the duration of treatment for the NNT can be derived from the duration of the trials in Table 1.

The combined data on the efficacy of the drugs in lowering blood pressure, expressed as the weighted mean difference in blood pressure between the treatment and control groups, are shown in Table 5. Data for systolic and diastolic pressure were missing for 4 of the 11 and 1 of the 11 high-dose thiazide trials respectively; however, these were small trials and thus would not have a significant effect on the overall estimate. The mean drop in systolic blood pressure was significantly greater (4–5 mm Hg) in the thiazide trials than in the other drug trials. The efficacy did not differ significantly between the high- and low-dose thiazide trials. The effect on diastolic blood pressure was similar for the 4 drug classes.

Table 4: Adverse outcomes of first-line antihypertensive therapy in drug–no treatment comparison trials

Drug; outcome	Group; no. of events: Active treatment	Group; no. of events: No treatment	RR (and 95% CI)
Thiazide, low dose (5 trials)	*n = 4 349*	*n = 5 163*	
Death	521	720	0.89* (0.81–0.99)
Stroke	197	355	0.66* (0.56–0.79)
CAD	221	374	0.71* (0.60–0.84)
Total cardiovascular events	527	899	0.68* (0.62–0.75)
Thiazide, high dose (11 trials)	*n = 7 769*	*n = 12 070*	
Death	221	377	0.90 (0.76–1.05)
Stroke	87	229	0.47* (0.37–0.61)
CAD	212	329	1.00 (0.84–1.19)
Total cardiovascular events	311	613	0.72* (0.63–0.82)
β-blocker (2 trials)	*n = 5 505*	*n = 10 867*	
Death	287	568	1.01 (0.88–1.15)
Stroke	98	243	0.80 (0.64–1.01)
CAD	183	393	0.92 (0.78–1.10)
Total cardiovascular events	297	661	0.89 (0.78–1.02)
CCB (1 trial)	*n = 2 398*	*n = 2 297*	
Death	123	137	0.86 (0.68–1.09)
Stroke	50	78	0.61* (0.43–0.87)
CAD	58	73	0.76 (0.54–1.07)
Total cardiovascular events	137	186	0.71* (0.57–0.87)

*$p < 0.05$, as compared with 1.

Interpretation

Randomized trials comparing one drug with another offer the best opportunity to detect differences between 2 classes of drugs. In the trials comparing thiazides with β-blockers[34–38] the number of patients who dropped out because of adverse effects was significantly lower in the thiazide group; the incidence of total cardiovascular events was lower in the thiazide group, although the difference was of borderline significance. This comparison also revealed a significant benefit in favour of thiazides for decreasing systolic blood pressure. These trials included 2 in which low-dose thiazide therapy was used[34,36] and 3 in which high-dose thiazide therapy was used.[35,37,38]

One of the drug–drug comparisons we excluded deserves mention here. The Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) study purported to show a benefit of metoprolol over thiazides.[20,21] It started as part of the Heart Attack Primary Prevention in Hypertension

(HAPPHY) trial,[35] and at the end of that trial it split off, and half the patients, those randomly assigned to receive metoprolol or thiazides, were followed for a further 14 months. The MAPHY trial has been criticized,[59,60] and since these patients were already included in the HAPPHY trial data, it is clearly inappropriate to include them twice. The controversy over the MAPHY trial calls attention to the unexplained higher mortality in the atenolol group than in the thiazide group, which was seen in one of the Medical Research Council (MRC) trials[36] and in our combined analysis of the mortality results from the HAPPHY trial and this MRC trial. The relatively poor outcomes seen with the β-blockers in our review are predominantly explained by the trials using atenolol.

In the only previous meta-analysis that included drug–drug comparison trials, Collins and associates[1] did not include the MAPHY trial either; however, they incorrectly included the International Prospective Primary Prevention Study in Hypertension (IPPPSH) trial.[19] In the IPPPSH trial thiazides were prescribed to 67% of patients in the β-blocker group and to 82% of those in the non-β-blocker group. The results of this trial cannot, therefore, be used to compare the effectiveness of β-blockers and thiazides.

In the trials that compared a first-line therapy with no treatment or placebo, it was more difficult to make clear inferences about differences in effectiveness of the different drug classes. Only a few trials evaluated β-blockers and calcium-channel blockers in this regard, and no trials evaluated ACE inhibitors or α-adrenergic blockers. It is important in this type of analysis not to include trials in which there was significant contamination by drugs from other classes. In our opinion, Psaty and colleagues[8] incorrectly included the trial by Coope and Warrender[12] and the STOP-Hypertension trial[27] in their β-blocker group. In the trial by Coope and Warrender 67% of patients in the active treatment group received bendrofluazide and 70% atenolol; in the STOP-Hypertension trial more than 70% in the active treatment group received thiazides and more than 70% received β-blockers.

Table 5: Efficacy of first-line antihypertensive therapy in lowering blood pressure, in drug–no treatment comparison trials

Drug; blood pressure	Mean difference from untreated control (and 99% CI), mm Hg
Thiazide, low dose	
Systolic	–15.6* (–16.7 to –14.5)
Diastolic	–6.0 (–6.8 to –5.2)
Thiazide, high dose	
Systolic	–14.9* (–15.8 to –14.1)
Diastolic	–7.3 (–7.8 to –6.7)
β-blocker	
Systolic	–10.3 (–11.2 to –9.5)
Diastolic	–5.7 (–6.4 to –5.1)
CCB	
Systolic	–10.0 (–11.2 to –8.8)
Diastolic	–5.0 (–5.6 to –4.4)

*$p < 0.01$, as compared with same parameter for β-blockers and CCB.

Our findings demonstrating a significant decrease in the incidence of coronary artery disease with high- and low-dose thiazide therapy are similar to those of Psaty and colleagues.[8] There were only minor differences in the trials reviewed by us and them. We classified the trial by Kuramoto and associates[47] as a low-dose thiazide trial, and they classified it as a high-dose trial. It fit into our low-dose category based on the starting dose of 1 mg of trichlormethiazide, although the article did not mention how many patients were maintained on the starting dose. Moving the trial from the low- to high-dose group did not change our findings. Unlike Psaty and colleagues, we excluded the Hypertension Detection and Follow-up Program trial[14–18] because it did not have an untreated control group and it studied the effect of lifestyle changes in addition to drug therapy, and we included one small trial, by Wolff and Lindeman,[58] which was also included in the meta-analyses by Collins and associates[1] and Gueyffier and colleagues.[2]

A potential limitation of attributing the benefit predominantly to thiazides in our review is the fact that in almost all of the trials supplemental drugs were added to various proportions of patients. We were able to do a sensitivity analysis of the impact of second-line central-nervous-system–active drugs, β-blockers and potassium-sparing diuretics on the outcomes with thiazides. In all cases removing these trials had little or no effect on the final risk ratio, which demonstrated that the data for thiazides are robust and that the benefits achieved were most likely attributable to the thiazides. (The details of these sensitivity analyses are available upon request from the authors.)

Our systematic review demonstrates the importance of analysing efficacy as well as effectiveness, and of analysing the effect on systolic as well as diastolic blood pressure.[1] Thiazides were consistently better at lowering systolic blood pressure than the other drug classes. This may be somewhat surprising; however, in all trials other than those of therapy for isolated systolic hypertension,[50–52] titration was based on diastolic blood pressure. This explains why the drop in diastolic pressure was similar for the different drug classes. Since systolic pressure is a better indicator of risk than diastolic pressure,[7] this observation could be one reason for better outcome data with thiazides.

The ARR for low-dose thiazide therapy (5.5%, 95% CI 4.1%–7.0% over about 5 years) most likely underestimates the benefits seen in practice for a number of reasons: (a) patients in the trials were at lower risk of cardiovascular events than other patients of the same age;[7] (b) many of the trials did not report all morbidity outcomes; (c) one of the largest benefits in these trials (not included as an outcome) was the decrease in the number of patients withdrawn because of excessively elevated blood pressure (these patients in the control group received appropriate antihypertensive treatment and decreased the difference in outcomes between the groups).

We feel confident in concluding that the benefits seen in the thiazide trials are predominantly the result of the thiazide being used as first-line therapy. The evidence shows

that starting with a low dose of thiazide and titrating up only if necessary significantly reduces the risk of coronary artery disease. In contrast, starting with a high dose (50 mg of hydrochlorothiazide or the equivalent) does not. Since the high-dose therapy was no more efficacious than the low-dose therapy in lowering blood pressure, we feel that there is no justification for using high doses or for comparing low- and high-dose thiazide therapies in a trial. The current standard recommendation for the use of thiazides in the management of hypertension is therefore justifiable based on the evidence presented here: start with a low dose (12.5 mg of hydrochlorothiazide or the equivalent), increase the dose only if necessary, and do not exceed a dose of 50 mg of hydrochlorothiazide or the equivalent.

There is growing evidence that the surrogate marker — the lowering of blood pressure — is inadequate in predicting health outcomes with antihypertensive therapy. The difference in the impact of low- and high-dose thiazide therapy on the incidence of coronary artery disease is one example. The results of a number of drug–drug comparison trials[11,36,39,41] also suggest this conclusion.

More trials comparing drug therapy with a placebo or no treatment are unlikely to be forthcoming. Therefore, the data in Table 4 are unlikely to change. Further drug–drug comparison trials are under way.[61–64] Their results, when available, can be added to the data in Table 2. In the mean time, clinicians must choose a first-line drug therapy using the available evidence. At present low-dose thiazide therapy can be prescribed with confidence that the risk of death, coronary artery disease and stroke will be reduced. The same cannot be said for high-dose thiazide therapy or for any of the other classes of antihypertensive drugs.

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Appendix 1: Starting doses of thiazide used by authors to divide trials into high-dose and low-dose categories

	Dose group; starting dose	
Drug	High-dose therapy	Low-dose therapy
Hydrochlorothiazide	≥ 50 mg/d	< 50 mg/d
Chlorothiazide	≥ 0.5 g/d	< 0.5 g/d
Chlorthalidone	≥ 50 mg/d	< 50 mg/d
Bendrofluazide	≥ 5 mg/d	< 5 mg/d
Methyclothiazide	≥ 5 mg/d	< 5 mg/d
Trichlormethiazide	≥ 2 mg/d	< 2 mg/d

Appendix 2: Studies excluded from systematic review, and reasons for exclusion

Study	Reasons for exclusion
CASTEL[10,11]	No untreated control group. Drug–drug comparison not possible because only 1 of the 3 treatments fit criteria of first-line drug class of interest
Coope et al[12]	Active treatment group given both β-blocker (70% of patients) and thiazide (67%)
HANE[13]	Morbidity and mortality outcomes not reported
HDFP[14–18]	No untreated control group. Treated group received risk-factor management as well as drug therapy
IPPPSH[19]	β-blocker therapy compared with non-β-blocker therapy, but both groups also received thiazides
MAPHY[20,21]	Study population represented subgroup of HAPPHY study population
Materson et al[22,23]	Morbidity and mortality outcomes not reported
Morgan et al[24]	No untreated control group. Not randomized; allocation to treatment based on time of presentation to clinic
PATS[25]	Patients without hypertension included
STONE[26]	Not randomized; large numbers lost to follow-up
STOP-Hypertension[27]	Active treatment group given both β-blocker (> 70% of patients) and thiazide (> 70%)
SYST-China[28,29]	Not randomized; employed alternate allocation
Sprackling et al[30]	Active treatment did not fit criteria of first-line drug class of interest
Strandberg et al[31]	No untreated control group. Treated group received lifestyle management as well as drug therapy
TOMHS[32]	Morbidity and mortality outcomes not reported separately for different drug treatments