REVIEW

Health Outcomes Associated With Various Antihypertensive Therapies Used as First-Line Agents

A Network Meta-analysis

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Context Establishing relative benefit or harm from specific antihypertensive agents is limited by the complex array of studies that compare treatments. Network meta-analysis combines direct and indirect evidence to better define risk or benefit.

Objective To summarize the available clinical trial evidence concerning the safety and efficacy of various antihypertensive therapies used as first-line agents and evaluated in terms of major cardiovascular disease end points and all-cause mortality.

Data Sources and Study Selection We used previous meta-analyses, MEDLINE searches, and journal reviews from January 1995 through December 2002. We identified long-term randomized controlled trials that assessed major cardiovascular disease end points as an outcome. Eligible studies included both those with placebo-treated or untreated controls and those with actively treated controls.

Data Extraction Network meta-analysis was used to combine direct within-trial between-drug comparisons with indirect evidence from the other trials. The indirect comparisons, which preserve the within-trial randomized findings, were constructed from trials that had one treatment in common.

Data Synthesis Data were combined from 42 clinical trials that included 192 478 patients randomized to 7 major treatment strategies, including placebo. For all outcomes, low-dose diuretics were superior to placebo: coronary heart disease (CHD; RR, 0.79; 95% confidence interval [CI], 0.69-0.92); congestive heart failure (CHF; RR, 0.51; 95% CI, 0.42-0.62); stroke (RR, 0.71; 0.63-0.81); cardiovascular disease events (RR, 0.76; 95% CI, 0.69-0.83); cardiovascular disease mortality (RR, 0.81; 95% CI, 0.73-0.92); and total mortality (RR, 0.90; 95% CI, 0.84-0.96). None of the first-line treatment strategies–β-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCBs), α-blockers, and angiotensin receptor blockers–was significantly better than low-dose diuretics for any outcome. Compared with CCBs, low-dose diuretics were associated with reduced risks of cardiovascular disease events (RR, 0.94; 95% CI, 0.89-1.00) and CHF (RR, 0.74; 95% CI, 0.67-0.81). Compared with ACE inhibitors, low-dose diuretics were associated with reduced risks of CHF (RR, 0.88; 95% CI, 0.80-0.96), cardiovascular disease events (RR, 0.94; 95% CI, 0.89-1.00), and stroke (RR, 0.86; 0.77-0.97). Compared with β-blockers, low-dose diuretics were associated with a reduced risk of cardiovascular disease events (RR, 0.89; 95% CI, 0.80-0.98). Compared with α-blockers, low-dose diuretics were associated with reduced risks of CHF (RR, 0.51; 95% CI, 0.43-0.60) and cardiovascular disease events (RR, 0.84; 95% CI, 0.75-0.93). Blood pressure changes were similar between comparison treatments.

Conclusions Low-dose diuretics are the most effective first-line treatment for preventing the occurrence of cardiovascular disease morbidity and mortality. Clinical practice and treatment guidelines should reflect this evidence, and future trials should use low-dose diuretics as the standard for clinically useful comparisons.

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In 1993 and again in 1997, the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure recommended low-dose diuretics and β-blockers as first-line treatment for patients with uncomplicated hypertension.[1,2] This recommendation reflected the wealth of clinical trial evidence about the health benefits associated with low-dose diuretics and β-blockers.[3-8] The early trials of diuretics and β-blockers had generally randomized patients with high blood pressure to active therapy or to placebo. Early answers were clearest for patients with the highest level of blood pressure.[4,5] These studies answered the question of whether several specific antihypertensive treatments improved health outcomes.

Clear evidence of health benefits associated with diuretics and β-blockers precluded further long-term placebo-controlled trials. Thus, the recent large long-term trials have evaluated one active treatment against another active treatment in terms of their ability to prevent cardiovascular events.[9-15] In these

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active-treatment comparison trials, participants in each treatment group have been randomized to receive one of a variety of first-line agents, including not only diuretics and β-blockers, but also α-blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs). These comparative trials address the question of which first-line treatment regimen is optimal.

As this history suggests, the clinical trials in hypertension have provided a patchwork of evidence about the health benefits of antihypertensive agents. Some trials used placebo or untreated controls, and others used active-treatment comparison groups. Among the latter, the choice of the treatment and comparison therapies has varied from one trial to the next. Several approaches to the synthesis of these complex data are possible.[3,16,17] The Blood Pressure Trialists, for instance, conducted a prospective series of mini–meta-analyses, but this method left many "unresolved issues"[17(p1963)] due to multiple comparisons and low power.[18] In this study, we used a new technique, called network meta-analysis,[19] to synthesize the available evidence from placebo-controlled and comparative trials in a single meta-analysis. In addition to updating our previous meta-analysis of low-dose diuretics,[3] the primary aim was to compare low-dose diuretics with each of the other 5 active first-line therapies evaluated in large long-term trials in terms of major health outcomes.

METHODS

Using MEDLINE searches, previous meta-analyses,[3,16,17,20-24] and journal reviews from January 1995 through December 2002, we identified studies designed to evaluate the effects of antihypertensive therapies on the occurrence of myocardial infarction and stroke. For randomized trials, a MEDLINE search was used to identify randomized clinical trials designed to evaluate the effects of antihypertensive therapies on the occurrence of cardiovascular morbidity and mortality. To update the literature search conducted for a previous meta-analysis,[3] the search strategy for 1995 to 2002 was based on the search terms *cerebrovascular disorders* or *cerebrovascular disorder* or *heart diseases* or *heart disease* and *antihypertensive agents* (therapeutic use) or *hypertension* (drug therapy). All available English and non-English abstracts were reviewed (n = 1097), and the full text was consulted as necessary to clarify eligibility status. We limited attention to the 6 most commonly used antihypertensive classes (diuretics, β-blockers, CCBs, ACE inhibitors, ARBs, and α-blockers).

To be eligible for inclusion, studies had to be randomized controlled trials that evaluated major cardiovascular disease end points in hypertensive patients over the course of at least 1 year. Trials that recruited patients who had congestive heart failure (CHF) or who had a myocardial infarction were not eligible. The treatment had to be unconfounded by other therapies, such as smoking cessation or lipid-lowering, but factorial design trials such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[12,15] were eligible. Trials published since 1995 had to have a minimum of 400 person-years of observation. Open randomized trials that used an untreated control group were included,[25,26] but we excluded nonrandomized studies,[27] nonfactorial multiple risk factor intervention trials,[28,29] trials using first-line agents other than the 6 noted above,[30,31] and trials that used a placebo group plus other antihypertensive therapies to reduce blood pressure to the same target level as the active treatment.[32-34]

All eligible trials[4-15,25,26,35-71] are listed in TABLE 1 with data on number of events by randomized group. Data for one trial[69] were finalized after the search was completed.[68] Data were abstracted independently by 2 of the authors (B.M.P. and G.S.), and differences were resolved by consensus.

Coronary heart disease (CHD) included fatal and nonfatal myocardial infarction and CHD death; stroke, fatal and nonfatal stroke; and CHF, fatal and nonfatal CHF. Cardiovascular disease events included CHD, stroke, CHF, and other cardiovascular disease mortality. While the definition of end points varied slightly among the trials, the end point definitions and methods of classification were identical across treatment groups within each trial. For all comparisons, this meta-analysis aggregates these in-trial comparisons across studies.

Each arm of the trials was classified according to its primary treatment strategy. While most studies used more than 1 drug in a treated group, the agents were usually applied in a stepped-care approach so that the first-line therapy was clearly identified. The primary treatment strategies of interest in this meta-analysis were (1) placebo, untreated, or usual care; (2) low-dose diuretic therapy, which generally started with the equivalent of 12.5 to 25 mg per day of chlorthalidone or hydrochlorothiazide; (3) β-blocker therapy; (4) ACE inhibitors; (5) ARBs; (6) CCBs; and (7) α-blockers. High-dose diuretic therapy was defined as starting doses greater than or equal to the equivalent of 50 mg of chlorthalidone or hydrochlorothiazide and titrating upward[72]; diuretic dosages were unstated in 2 studies,[25,35] but were assigned to the high-dose diuretic group. While high-dose diuretics were included in the standard meta-analysis[73] that compared any therapy with no therapy, this treatment strategy is not presented as part of the network meta-analysis since high-dose diuretic therapy is no longer used or recommended for the treatment of high blood pressure. None of the CCBs was a short-acting drug or formulation.

For the main analysis, the logarithm of the relative risk (RR) for each trial and its SE were calculated and used in a network meta-analysis.[19] Network meta-analysis preserves the within-trial randomized comparison of each study and, at the same time, combines all available comparisons between treatments. These comparisons included both the direct within-trial comparisons between 2 treatment strategies and the indirect comparisons constructed from 2 trials that have 1 treatment in common. By way of illustration, the Intervention as a Goal in Hypertension Treatment

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Table 1. Cardiovascular Events and Outcomes by Randomized Treatment

Source	No. of Subjects	Mean Follow-up, y	Intervention	No. of Subjects					
				CHD*	Stroke*	CHF*	Major Cardiovascular Events	Total Mortality	Cardiovascular Disease Mortality†
VA I,[4] 1967	73	1.5	High-dose diuretics	0	1	0	1	0	0
	70		Placebo	2	3	2	12	4	4
VA II,[5] 1970	186	3.3	High-dose diuretics	8	5	0	16	10	8
	194		Placebo	8	20	11	44	21	19
Carter,[25] 1970	50	4.0	High-dose diuretics	2	10	3	15	13	10
	49		Not treated	2	21	4	27	22	16
Barraclough et al,[35] 1973	58	2.0	High-dose diuretics	1	0	0	1	1	0
	58		Placebo	2	0	1	3	3	1
HSCSG,[36] 1974	233	3.0	High-dose diuretics	5	37	0	44	26	15
	219		Placebo	7	42	6	57	24	19
USPHS,[37] 1977	193	7.0	High-dose diuretics	15	1	0	16	2	2
	196		Placebo	17	6	2	25	4	4
VA-NHLBI,[38] 1978	508	1.5	High-dose diuretics	6	0	0	8	2	2
	504		Placebo	5	0	0	5	0	0
HDFP,[7,8] 1982	5485	5.0	High-dose diuretics	171	102	NA	273	349	195
	5455		Usual care	189	158	NA	347	419	240
Hegeland,[26] 1980	406	5.5	High-dose diuretics	14	0	0	14	10	7
	379		Not treated	10	5	1	18	9	6
ANBPS,[39] 1980	1721	4.0	High-dose diuretics	33	13	3	49	25	8
	1706		Placebo	33	22	3	58	35	18
Kuramoto et al,[40] 1981	44	4.0	High-dose diuretics	0	3	0	4	7	3
	47		Placebo	2	4	3	9	7	3
EWPHE,[41] 1985	416	4.7	Diuretics	29	21	NA	67	135	67
	424		Placebo	47	31	NA	93	149	93
MRC,[6] 1985	4297	4.9	High-dose diuretics	119	18	NA	140	128	69
	4403		ß-Blockers	103	42	NA	146	120	65
	8654		Placebo	234	109	NA	352	253	139
Coope and Warrender,[42] 1986	419	4.4	ß-Blockers	35	20	22	NA	60	35
	465		Not treated	38	39	36	NA	69	50
HAPPHY,[43] 1987	3272	3.8	High-dose diuretics	116	41	22	192	101	60
	3297		ß-Blockers	132	32	32	197	96	57
SHEP pilot,[44] 1989	443	2.8	Diuretics	8	11	6	32	32	14
	108		Placebo	2	6	2	12	7	5
SHEP,[45,46] 1991 and 1997	2365	4.5	Diuretics	104	103	55	289	213	90
	2371		Placebo	141	159	105	414	242	112
STOP,[47] 1991	812	2.1	ß-Blockers or diuretics	25	29	19	58	36	17
	815		Placebo	28	53	39	94	63	41
MRC,[48] 1992	1081	5.8	Diuretics	48	45	NA	107	134	66
	1102		ß-Blockers	80	56	NA	151	167	95
	2213		Placebo	159	134	NA	309	315	180
Dutch TIA,[49] 1993	732	2.6	ß-Blockers	45	52	NA	97	64	41
	741		Placebo	40	62	NA	95	58	33
PATS,[50] 1995	2841	2.0	Diuretics	25	159	NA	194	146	87
	2824		Placebo	21	217	NA	247	158	101
TEST,[51] 1995	372	2.6	ß-Blockers	29	81	NA	97	51	34
	348		Placebo	36	75	NA	92	60	39
MIDAS,[52] 1996	442	3.0	Dihydropyridine CCB	6	6	2	25	8	NA
	441		Diuretics	5	3	0	14	9	NA
SYST-EUR,[53,54] 1997 and 1999	2398	2.5	Dihydropyridine CCB	36	49	40	145	135	64
	2297		Placebo	47	80	51	194	147	82
VHAS,[55] 1997	707	2.0	Nondihydropyridine CCB	8	5	2	15	5	5
	707		Diuretics	9	4	0	13	4	4
ABCD,[56,57] 1998 and 2000	235	5.0	Dihydropyridine CCB	27	11	8	47	18	11
	235		ACE inhibitor	9	7	10	29	14	6

(continued)

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Table 1. Cardiovascular Events and Outcomes by Randomized Treatment (cont)

Source	No. of Subjects	Mean Follow-up, y	Intervention	No. of Subjects					
				CHD*	Stroke*	CHF*	Major Cardiovascular Events	Total Mortality	Cardiovascular Disease Mortality†
FACET,[58] 1998	191	2.5	Dihydropyridine CCB	13	10	0	23	5	NA
	189		ACE inhibitor	10	4	0	14	4	NA
UKPDS,[59,60] 1998	400	8.4	ACE inhibitor	61	21	12	94	75	48
	358		ß-Blocker	46	17	9	72	59	34
CAPPP,[13] 1999	5492	6.1	ACE inhibitor	162	189	75	363	0.93 (0.76-1.14)‡	76
	5493		ß-Blockers or diuretics	161	148	66	335	1.00	95
NICSEH,[61] 1999	204	4.2	Dihydropyridine CCB	2	8	0	11	2	2
	210		Diuretics	2	8	3	12	2	0
STOP-2,[14] 1999	2196	5.0	Dihydropyridine CCB	179	207	186	450	362	212
	2213		ß-Blockers or diuretics	154	237	177	460	369	221
	2205		ACE inhibitor	139	215	149	437	380	226
INSIGHT,[9] 2000	3157	3.5	Dihydropyridine CCB	77	67	26	200	153	60
	3164		Diuretics	61	74	12	182	152	52
NORDIL,[10] 2000	5410	4.5	Nondihydropyridine CCB	183	159	63	466	231	131
	5471		ß-Blockers or diuretics	157	196	53	453	228	115
ALLHAT,[12] 2000	9067	3.3	α-Blockers	365	244	491	1592	514	130
	15 268		Diuretics	608	351	420	2245	851	218
AASK,[62-64] 2001 and 2002	436	3.0	ACE inhibitor	NA	NA	NA	0.59 (0.40-0.83)‡	18	NA
	217		Dihydropyridine CCB	NA	NA	NA	1.00	13	NA
	441		ß-Blocker	NA	NA	NA	0.52 (0.35-0.74)‡	NA	NA
PROGRESS,[65] 2001	1281	3.9	ACE inhibitor	48	157	NA	227	NA	93
	1280		Placebo	52	165	NA	237	NA	77
	1770		ACE inhibitor and diuretics	67	150	NA	231	NA	88
	1774		Placebo	102	255	NA	367	NA	121
IDM,[66] 2001	194	2.0	High-dose ARB	NA	NA	NA	9	3	NA
	195		Low-dose ARB	NA	NA	NA	NA	0	NA
	201		Placebo	NA	NA	NA	17	1	NA
Lewis et al,[67] 2001	579	2.6	ARB	NA	NA	NA	138	87	NA
	567		Dihydropyridine CCB	NA	NA	NA	128	83	NA
	569		Placebo	NA	NA	NA	144	93	NA
LIFE,[11] 2002	4605	4.7	ARB	198	232	153	508	383	204
	4588		ß-Blocker	188	309	161	588	431	234
CONVINCE,[70] 2002§	8179	3.0	Nondihydropyridine CCB	133	133	126	364	NA	152
	8297		ß-Blockers or diuretics	166	118	100	365	NA	143
ELSA,[71] 2002	1157	3.8	ß-Blocker	17	14	NA	33	17	8
	1177		Dihydropyridine CCB	18	9	NA	27	13	4
ALLHAT,[15] 2002	15 255	4.9	Diuretics	1362	675	870	3941	2203	992
	9048		Dihydropyridine CCB	798	377	706	2432	1256	592
	9054		ACE inhibitor	796	457	612	2514	1314	609
ANBP2,[68,69] 2002 and 2003	3044	4.1	ACE inhibitor	173	112	69	490	195	84
	3039		Diuretics	195	107	78	529	210	82

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; ABCD, Appropriate Blood Pressure Control in Diabetes; ACE, angiotensin-converting enzyme; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBPS, Australian National Blood Pressure Study; ANBP2, Australian National Blood Pressure 2 Trial; ARB, angiotensin II type 1 receptor blockers; CAPPP, Captopril Prevention Project; CCB, calcium channel blockers; CHD, coronary heart disease; CHF, congestive heart failure; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular Endpoints; Dutch TIA, Dutch Transient Ischemic Attack Trial Study Group; ELSA, European Lacidipine Study on Atherosclerosis; EWPHE, European Working Party on High Blood Pressure in the Elderly; FACET, Fosinopril versus Amlodipine Cardiovascular Events Trial; HAPPHY, Heart Attack Primary Prevention in Hypertension Trial Research Group; HDFP, Hypertension Detection and Follow-up Program Cooperative Group; HSCSG, Hypertension Stroke Cooperative Study Group; IDM, Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria study; INSIGHT, Intervention as a Goal in Hypertension Treatment; LIFE, Losartan Intervention For Endpoint Reduction in Hypertension Study; MIDAS, Multicenter Isradipine Diuretic Atherosclerosis Study; MRC, Medical Research Council Working Party; NA, not available; NICSEH, National Intervention Cooperative Study in Elderly Hypertensives; NORDIL, Nordic Diltiazem Study; PATS, Post-Stroke Antihypertensive Treatment Study; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trial in Old Patients with Hypertension; SYST-EUR, Systolic Hypertension in Europe Trial; TEST, Tenormin After Stroke and Transient Ischemic Attack; UKPDS, UK Prospective Diabetes Study; USPHS, US Public Health Service Hospitals Cooperative Study; VA-NHLBI, Veterans Administration National Heart, Lung, and Blood Institute Feasibility Study; VA I and II, Veterans Administration Cooperative Study I and II; VHAS, Verapamil in Hypertension and Atherosclerosis Study.

*Includes fatal and nonfatal events.

†Includes CHD, stroke, CHF, and other cardiovascular disease death.

‡Indicates relative risk (95% confidence interval).

§Data were available separately for diuretics and ß-blockers for major cardiovascular events.

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(INSIGHT)[9] trial provided a direct within-trial comparison of diuretics and CCBs for stroke (RR of 1.11 in favor of CCBs) and for CHF (RR of 0.46 in favor of diuretics). Systolic Hypertension in the Elderly Program (SHEP)[45] and Systolic Hypertension in Europe Trial (SYST-EUR),[53] both placebo-controlled trials, used diuretics and CCBs as active treatment. Therefore, the RRs from these 2 placebo-controlled trials can be used to provide estimates of the RR for the indirect comparison between diuretic and CCBs. For the outcome of stroke, multiplying the RR for diuretics vs placebo in SHEP times the RR for placebo vs CCBs in SYST-EUR yielded an indirect comparison of $0.65 \times 1.69 = 1.10$ in favor of the CCB, which was almost identical to the direct estimate of 1.11 from INSIGHT. For the outcome of CHF, the indirect comparison produced an RR of 0.70 (in favor of diuretics; from 0.53×1.33) compared with the direct estimate of 0.46 from INSIGHT. Other indirect comparisons can be computed with 2 or more intermediate treatments rather than the placebo-treatment arm used in this example. Network meta-analysis combines all available direct and indirect comparisons.

As Bucher et al[74] have shown, indirect estimates can be combined in large samples if there is no interaction between the treatment effects and the populations or major subgroups in a trial. This requirement for combining similar effect estimates across trials also holds for standard meta-analyses. Indirect estimates cannot simply be assumed to be reliable. The reliability of treatment effects is assessed by computing the differences between various comparisons of the same 2 treatments. The variance of these differences over and above what would be expected from sampling error within each trial is expressed as a variance estimate called the "incoherence" of the network of trials. In the example used in the previous paragraph, the direct and indirect RRs for CHF (0.46 vs 0.71) were more incoherent or heterogeneous than the direct and indirect RRs for stroke (1.11 vs 1.10). Incoherence is a property of the fitted model, and it is incorporated in inferences in a similar way to the heterogeneity estimate in a standard random-effects meta-analysis.[73] When the incoherence is small or moderate, it is used to increase the SE of the estimated treatment differences and to reduce the weight given to indirect comparisons. When the incoherence is sufficiently large, combining the trials may not be appropriate.

These computations were performed by fitting a linear mixed model to the log RRs from each trial with a random effect specific to each pair of treatments. Weights were used to avoid double counting of trials, such as ALLHAT,[15] that had 3 or more arms. The single line of *R* source code required to estimate each model appears in Figure 4 of the network meta-analysis methods article by Lumley.[19] Each of the 6 main analyses modeled a single outcome as a function of the various first-line treatment strategies. A similar random-effects linear mixed model was used to evaluate blood pressure differences between treatments, and the inverse of the sample size was used for the weights. Because the estimated incoherence for each meta-analysis was small, the incoherence had only a small effect on the width of the confidence intervals (CIs).

Our primary hypothesis involved low-dose diuretics, which are currently recommended as the first-line therapy.[1] The RRs that are less than 1.0 indicate that low-dose diuretic therapy is superior to the comparison treatment strategy. We evaluated 2 alternative approaches to handling trials that included both diuretics and β-blockers in a single treatment group.[10,13,14,47] In one approach, the 2-drug category was included as a separate treatment, and in the other, the trials were weighted according to the allocation of 68% to β-blockers and 32% to diuretics.[75] Since the 2 approaches yielded almost identical estimates of the associations for placebo and β-blockers, we decided to present the simpler model in this article. We also evaluated alternative models that included separate categories for the dihydropyridine CCBs and the nondihydropyridine CCBs. With RRs of less than 1.0 indicating that nondihydropyridines were superior to dihydropyridines, the RRs were 1.12 (95% CI, 0.86-1.46) for CHD; 0.96 (95% CI, 0.76-1.21) for stroke; 0.96 (95% CI, 0.75-1.21) for heart failure; 0.94 (95% CI, 0.81-1.09) for cardiovascular disease events; 0.87 (95% CI, 0.71-1.06) for cardiovascular disease mortality; and 0.93 (95% CI, 0.74-1.09) for total mortality. Since there were no significant differences between the 2 subclasses, the CCBs were presented as a single treatment strategy.

RESULTS

The 42 trials from the United States, Europe, Scandinavia, Australia, Japan, and China included a total of 192 478 patients followed up for an average of 3 to 4 years. The high-dose diuretic trials, generally completed in the 1970s and 1980s, were followed by trials that used low-dose diuretics. Trials completed in the last decade were usually larger than the early trials, and some of them recruited special populations, including individuals with diabetes,[56,58,60,66,67] older adults,[41,42,45,53] those with a history of cerebrovascular disease,[25,50,65] and blacks with renal disease.[62,63] Some details about individual trials are provided in Table 1 and in previous meta-analyses.[3,16,17,20-24] ALLHAT,[15] which has not been part of a previous meta-analysis, included 33 357 participants aged 55 years or older with at least 1 other CHD risk factor (mean follow-up was 4.9 years).

The standard meta-analysis of any drug treatment vs no treatment, which omits all active-control trials, appears in TABLE 2. Compared with placebo, an untreated control group, or usual care, any active treatment was associated with important reductions in the risk of all major outcomes. Combining all types of active treatments in this analysis involved the unevaluated assumption that all treatments had a similar effect. For the outcomes of stroke and major cardiovascular events, there was significant heterogeneity, which may be the result of important differences between drug classes.

For the network meta-analysis, we first conducted an analysis that ex-

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cluded ALLHAT,[15] the largest comparative trial and the mixed β-blocker diuretic trials.[10,13,14,47,70] TABLE 3 summarizes 3 independent sets of RRs that compare low-dose diuretics with CCBs or ACE inhibitors: the ALLHAT results; the direct comparisons between trials[9,52,55,61,69] other than ALLHAT; and indirect comparisons between the trials other than ALLHAT. For the comparison between diuretic and ACE inhibitor, the 1 remaining direct comparison trial was the Second Australian National Blood Pressure study.[69] Depending on the outcome, the indirect comparisons used information from 14 to 24 trials or pairs of trial arms (FIGURE 1); and the indirect comparisons included paths that passed through placebo, low-dose diuretics, β-blockers, and CCBs. For 5 of the 6 outcomes, the point estimates for the indirect meta-analysis of diuretics and ACE inhibitors were closer to those of ALLHAT than the direct estimates from the Second Australian National Blood Pressure Study. For all outcomes and for both drug comparisons, the point estimates from the 3 sources of data were generally similar. Neither the direct nor the indirect estimates differed from ALLHAT in a systematic way across outcomes. The similarity among estimates suggests that combining data from the 3 sources is reasonable and appropriate.

FIGURE 2 was constructed from the network meta-analyses to highlight treatment comparisons for all major end points. In Figure 2A, low-dose diuretic therapy was compared with placebo. The RRs were significantly less than 1.0 for all 6 outcomes: CHD (RR, 0.79; 95% CI, 0.69-0.92); CHF (RR, 0.51; 95% CI, 0.42-0.62); stroke (RR, 0.71; 0.63 -0.81); cardiovascular disease events (RR, 0.76; 95% CI, 0.69-0.83); cardiovascular disease mortality (RR, 0.81; 95% CI, 0.73-0.92); and total mortality (RR, 0.90; 95% CI, 0.84-0.96).

Figure 2B compares the performance of β-blockers with low-dose diuretics. For all outcomes, low-dose diuretics were associated with a lower point estimate for events than β-blockers, but the findings were significant only for the incidence of cardiovascular disease events (RR, 0.89; 95% CI, 0.80-0.98). For some outcomes, (marked by asterisks), β-blockers were significantly better than placebo. For cardiovascular disease events, specifically, the RR was 0.85 (95% CI, 0.78-0.94). The product (0.76) of these 2 RRs (0.85 × 0.89) represents the RR for low-dose diuretics vs placebo (Figure 2A).

In Figure 2C, low-dose diuretics were associated with a significantly

Table 2. Fixed and Random Effects Meta-analysis Comparing any Antihypertensive Drug Treatment vs No Treatment for Each Outcome*

Outcome	No. of Trials	Effects Model	RR (95% CI)	*P* Value for Heterogeneity
Coronary heart disease	24	Fixed	0.86 (0.80-0.93)	.55
		Random	0.87 (0.80-0.94)	.55
Stroke	23	Fixed	0.69 (0.64-0.74)	.004
		Random	0.68 (0.61-0.76)	.004
CHF	7	Fixed	0.54 (0.45-0.66)	.66
		Random	0.60 (0.49-0.74)	.80
Major CVD events	28	Fixed	0.78 (0.74-0.81)	<.001
		Random	0.73 (0.62-0.87)	<.001
CVD mortality	23	Fixed	0.84 (0.78-0.90)	.10
		Random	0.84 (0.78-0.90)	.10
Total mortality	25	Fixed	0.90 (0.85-0.95)	.58
		Random	0.90 (0.85-0.95)	.59

Abbreviations: CHF, congestive heart failure; CI, confidence interval; CVD, cardiovascular disease; RR, relative risk.
*The no treatment comparison group includes placebo-treated controls, participants not treated in open trials, and participants receiving usual care.

Table 3. ALLHAT vs Meta-analysis* of the Other Direct and Indirect Evidence Comparisons of Calcium Channel Blockers and Angiotensin-Converting Enzyme Inhibitors With Low-Dose Diuretics

		Calcium Channel Blockers†		Angiotensin-Converting Enzyme Inhibitors‡	
Outcome	Evidence	No. of Trials	RR (95% CI)	No. of Trials	RR (95% CI)
Coronary heart disease	Direct	4	0.83 (0.61-1.11)	1	1.13 (0.93-1.38)
	Indirect	25	0.81 (0.66-0.99)	24	0.94 (0.76-1.16)
	ALLHAT	1	1.02 (0.93-1.11)	1	1.01 (0.93-1.10)
Stroke	Direct	4	1.03 (0.77-1.38)	1	0.96 (0.73-1.24)
	Indirect	25	0.96 (0.78-1.17)	24	0.83 (0.67-1.02)
	ALLHAT	1	1.09 (0.94-1.22)	1	0.87 (0.77-0.98)
CHF	Direct	4	0.50 (0.27-0.92)	1	1.13 (0.82-1.56)
	Indirect	15	0.85 (0.68-1.06)	14	0.86 (0.63-1.19)
	ALLHAT	1	0.72 (0.66-0.80)	1	0.84 (0.76-0.93)
Major CVD events	Direct	4	0.89 (0.78-1.01)	1	1.08 (0.97-1.21)
	Indirect	29	0.90 (0.78-1.03)	28	0.88 (0.77-1.01)
	ALLHAT	1	0.96 (0.92-1.01)	1	0.91 (0.86-0.95)
CVD mortality	Direct	3	0.83 (0.59-1.26)	1	0.98 (0.72-1.33)
	Indirect	26	0.91 (0.72-1.15)	25	0.85 (0.69-1.04)
	ALLHAT	1	0.99 (0.90-1.10)	1	0.97 (0.88-1.06)
Total mortality	Direct	4	0.99 (0.80-1.22)	1	1.08 (0.89-1.30)
	Indirect	23	0.99 (0.88-1.13)	22	0.96 (0.84-1.09)
	ALLHAT	1	1.04 (0.98-1.12)	1	1.00 (0.93-1.06)

Abbreviations: ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Present Heart Attack Trial; CHF, congestive heart failure; CVD, cardiovascular disease; CI, confidence interval; RR, relative risk.
*Excludes ALLHAT,[15] which is listed separately, as well as the mixed ß-blocker and diuretic trials.[10,13,14,47,70] An RR that is less than 1.0 indicates that diuretics are superior.
†The direct comparison included 4 trials,[9,52,55,61] and the indirect comparison excluded these 4 trials.
‡The only direct comparison came from the Australian Study[69]; and the indirect comparison excluded this trial.

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lower risk of CHF (RR, 0.88; 95% CI, 0.80-0.96), stroke (RR, 0.86; 95% CI, 0.77-0.97), and cardiovascular disease events (RR, 0.94; 95% CI, 0.89-1.00) than ACE inhibitors. In Figure 2D, low-dose diuretics were associated with significantly lower risks of CHF (RR, 0.74; 95% CI, 0.67-0.81) and cardiovascular disease events (RR, 0.94; 95% CI, 0.89-1.00) than CCBs. For the other outcomes in Figure 2C and Figure 2D, the differences did not achieve conventional levels of significance ($P<.05$). Again, asterisks in these figures indicate that the drug class differs significantly from placebo for that outcome.

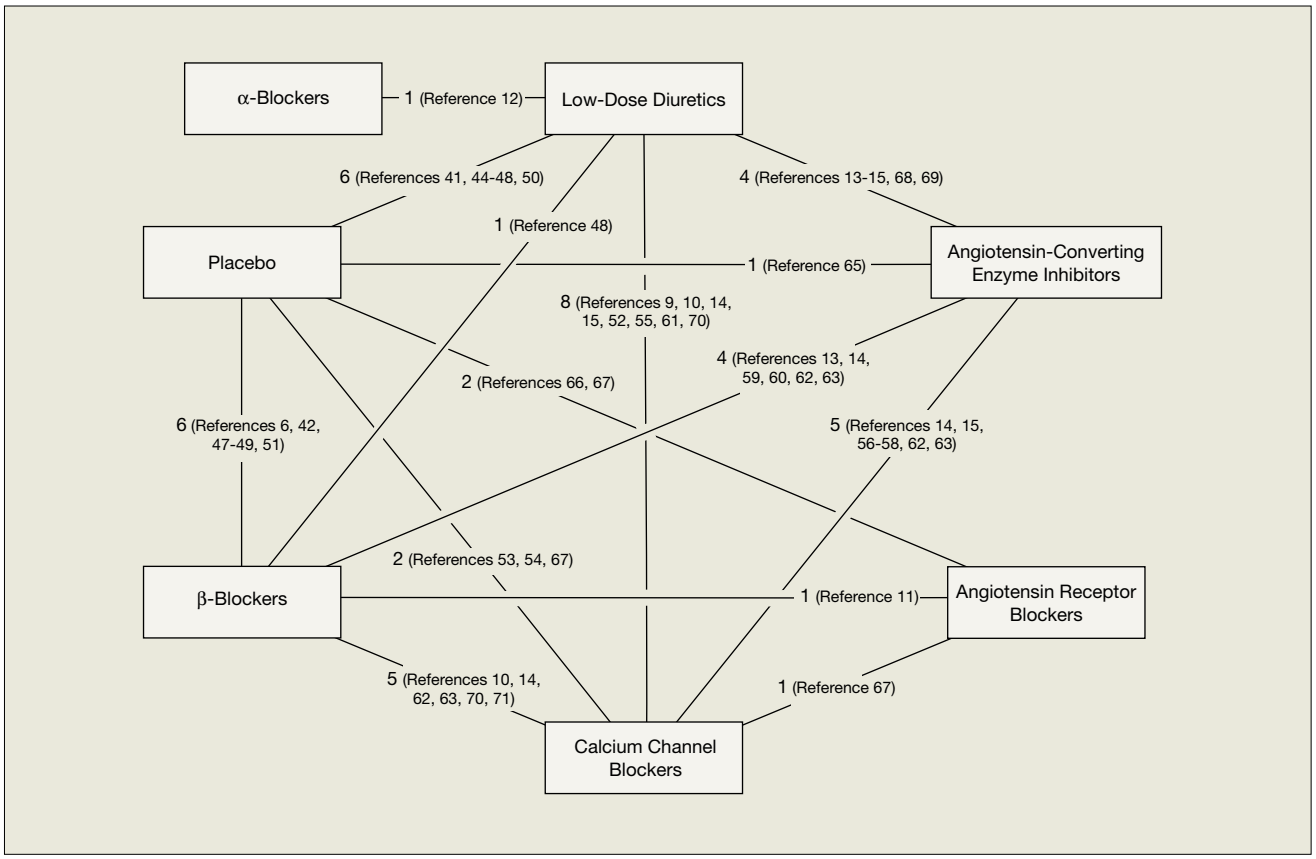
Only 3 trials evaluated ARBs, and in Figure 2E, all the CIs for RRs comparing ARBs and low-dose diuretics included the null. The comparison of α-blockers and low-dose diuretics (Figure 2F) was based on data from ALLHAT.[12]

The estimates of incoherence for each outcome in this network meta-analysis were small (TABLE 4). For instance, the differences between the direct and the indirect comparisons of drugs in this meta-analysis inflated the width of the 95% CI by about 0.5% for CHD and by about 5% for cardiovascular disease mortality. While low-dose diuretics were often associated with slightly lower mean levels of blood pressure than other classes of antihypertensive drugs (TABLE 5), none of the differences was significant.

COMMENT

In this network meta-analysis, we combined clinical trial data from 42 studies that included 192 478 patients randomized to 7 major treatment strategies. For all outcomes, the network meta-analysis confirmed that low-dose diuretics were superior to placebo. While several other treatment strategies were significantly better than placebo for some end points, none of the other first-line treatment strategies–β-blockers, ACE inhibitors, CCBs, α-blockers, and ARBs–was significantly better than low-dose diuretics for any major cardiovascular disease outcome. In 8 of the 30 between-drug comparisons, however, low-dose diuretics were significantly better than other treatments for the pre-

Figure 1. Network Meta-analysis of First-Line Antihypertensive Drug Treatments



Each first-line drug treatment is a node in the network. The links between the nodes are trials or pairs of trial arms. The numbers along the link lines indicate the number of trials or pairs of trial arms for that link in the network. Reference numbers indicate the trials contributing to each link. A trial such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial[12,15] (ALLHAT) with multiple arms appears along several links (diuretics-angiotensin-converting enzyme (ACE) inhibitors, diuretics-calcium channel blockers (CCBs), ACE inhibitors-CCBs, and diuretics-α-blockers). High-dose diuretic trials were excluded.

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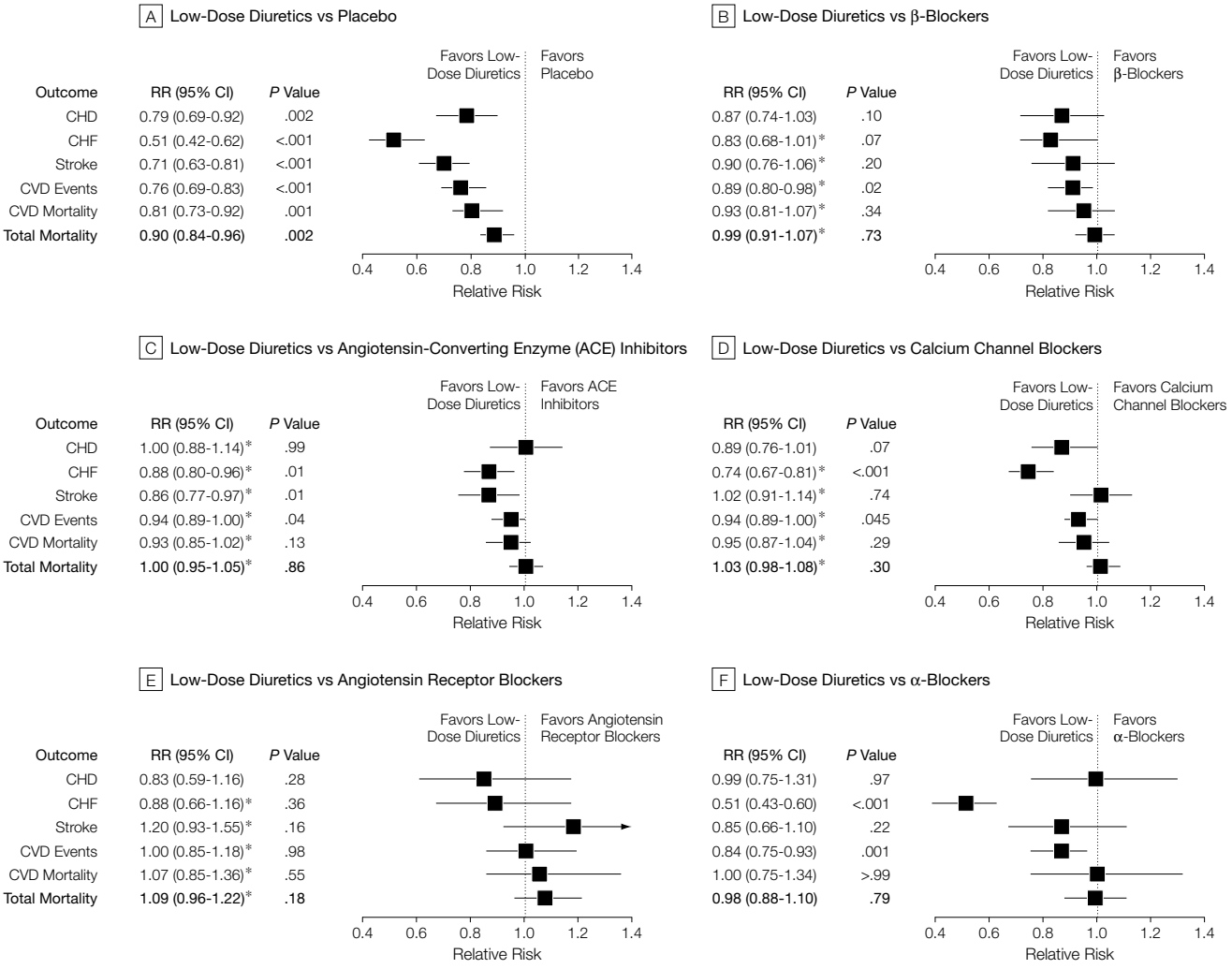
vention of cardiovascular disease health outcomes. Among nonsignificant between-drug comparisons, 13 favored low-dose diuretics, 5 favored other therapies, and 4 were indifferent. This network meta-analysis provides compelling evidence that low-dose diuretics are the most effective first-line treatment for preventing the occurrence of cardiovascular disease morbidity and mortality.

β-blockers have long been identified as another preferred first-line treatment for hypertension. In this network meta-analysis, similar to our previous article,[3] β-blockers were superior to placebo for the prevention of stroke, CHF, cardiovascular disease events, and total mortality. At the same time, β-blockers were inferior to low-dose diuretics for all outcomes, significantly so for cardiovascular disease events. For uncomplicated hypertension, β-blockers should be considered a second-line antihypertensive agent.

There are no large long-term trials evaluating the optimal second-line antihypertensive therapy, which could include ACE inhibitors, CCBs, and ARBs, as well as β-blockers. In addition to information about the health outcomes in hypertension trials, many investigators use the findings about major cardiovascular benefits from other large long-terms trials to recommend the use of specific drugs for compelling indications.[1,76] β-blockers have been particularly effective in patients with coronary disease[77-79] or heart failure,[80,81] and many guidelines recommend them over CCBs as first-line therapy for improving health outcomes in secondary-

Figure 2. Network Meta-analysis of First-Line Treatment Strategies in Randomized Controlled Clinical Trials in Hypertension



Asterisks, placed after the closed parentheses of the 95% CI, indicate that β-blockers ($P<.05$), angiotensin-converting enzyme inhibitors ($P<.05$), calcium channel blockers ($P<.05$), and angiotensin-receptor blockers ($P<.05$) were significantly better than placebo for that outcome. α-Blockers were not significantly better than placebo for any outcome ($P>.05$). CHD indicates coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CVD, cardiovascular disease; and RR, relative risk.

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prevention settings.[82-86] Like β-blockers, ACE inhibitors have also proven to be a robust therapy, effective in a number of secondary-prevention settings, including coronary disease[87,88] and heart failure.[89] ACE inhibitors, which may be preferred in special populations such as those with diabetes,[90] are also superior to amlodipine in blacks with renal disease.[62]

Based exclusively on indirect comparisons, there were no significant differences between low-dose diuretics and ARBs. However, the number of ARB trials was small, and this analysis lacked power. The uncertainty occasioned by the small number of ARB trials is reflected in the wide CIs in Figure 2E.

In this meta-analysis (Table 5) and in several of the comparative trials, including ALLHAT,[15] the various treatment strategies were associated with slightly different amounts of blood-pressure lowering. The RRs estimated for the outcomes in this meta-analysis preserved the within-trial comparisons of the treatment strategies just as they were implemented and without adjustment for any in-trial blood pressure differences that may have occurred. In ALLHAT,[15] adjustment for in-trial blood pressure had minor effects on the estimated RRs. While differences in outcomes in this network meta-analysis may reflect differences in achieved levels of blood pressure, the blood pressure differences were generally small (Table 5). Epidemiological evidence from the Framingham Heart Study[91] suggests that adjustment for the 2.4-mm Hg difference in systolic blood pressure between low-dose diuretics and CCBs (Table 5) would have increased the RR for heart failure in Figure 2D only slightly–from 0.74 to about 0.77.

Previous traditional meta-analyses have been constrained by the evolving configuration of the trial designs. With standard techniques of meta-analysis, comparisons of diuretics or β-blockers with placebo were possible.[3] Comparisons of CCBs to all other active therapies were also possible.[16] Alternatively, it was possible to use various subsets of the trials to evaluate each major type of within-trial comparisons as the Blood Pressure Lowering Treatment Trialists did in their prospective series of mini–meta-analyses.[17] All these traditional approaches to meta-analysis ignore part of the available data.

Network meta-analysis incorporates both the direct and indirect comparisons between treatments. In this study, the direct and indirect comparisons were similar (Table 3). Recent empirical evidence suggests the validity of indirect comparisons for a number of conditions and interventions.[92] In a series of 44 meta-analyses that permitted comparisons between direct and indirect results, the number of significant differences (n=3) was only slightly higher than the number expected by chance alone (n=2.2). Song et al[92] conclude that the validity of indirect comparisons depends on the internal validity and the similarity of the evaluated trials, including similarity in dose.

Like heterogeneity in traditional random-effects models of meta-analysis, incoherence is used to quantify variation among estimates and is incorporated into the estimation of the CI. Although the estimated incoherence of the final models in this network meta-analysis was low (Table 4), additional methodological and empirical work needs to be done to evaluate the direct and indirect comparisons across a number of types of interventions. Traditional limitations of meta-analyses due to variations in the treatment regimens, in populations or major subgroups within trials, and in the conduct of the trials also apply to this network meta-analysis.

As investigators gain experience with the use of indirect comparisons[74,92] and with the technique of network meta-analysis,[19] it may be possible to forego some placebo-controlled trials in selected therapeutic areas. In the presence of compelling evidence of the effect of one drug against placebo, comparative trials with a second agent can provide indirect estimates of its effect against placebo.[74,92] This principle is the same as the requirement for good anchoring trials before launching equivalence trials.[93,94]

While an occasional hypertensive patient cannot take diuretics because of an allergy or an intolerable adverse effect,[95] low-dose diuretics were significantly better than other therapies in reducing the occurrence of cardiovascular disease health outcomes for 8 of the 30 between-drug comparisons. In this network meta-analysis, the most effective drug was also the least expensive. Thus, cost-effectiveness analyses are not required.

Based on extensive clinical trial evidence, meta-analysis, and network meta-analysis, low-dose diuretics are the treatment of first choice for patients with uncomplicated hypertension who need pharmacological therapy. Moreover, low-dose diuretics should serve as the

Table 4. Estimates of Incoherence

Outcome	Incoherence*
Coronary heart disease	0.000927
Stroke	0.000685
CHF	0.003856
Major CVD events	0.000217
CVD mortality	0.005752
Total mortality	0.000408

Abbreviation: CHF, congestive heart failure; CVD, cardiovascular disease.
*Estimates are SDs; estimates as variances can be obtained by squaring the SDs.

Table 5. Change in Systolic and Diastolic Blood Pressures for Each Drug Class Compared With Low-Dose Diuretics*

	Systolic Blood Presure		Diastolic Blood Pressure	
	Difference (95% CI)	*P* Value	Difference (95% CI)	*P* Value
Angiotensin receptor blocker	−4.9 (−10.2 to 0.5)	.08	0 (−2.4 to 2.4)	.96
α-Blocker	−2.0 (−11.3 to 7.3)	.67	1.0 (−1.0 to 3.0)	.33
ACE inhibitor	−3.0 (−6.4 to 0.4)	.09	−0.5 (−1.7 to 0.6)	.36
β-Blocker	−1.8 (−5.4 to 1.9)	.34	0.9 (−0.6 to 2.3)	.26
Calcium channel blocker	−2.4 (−5.3 to 0.5)	.11	−0.1 (−1.1 to 0.9)	.82
Placebo	−13.2 (−16.3 to −10.1)	<.001	−4.9 (−6.1 to −3.6)	<.001

Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval.
*Negative numbers mean that low-dose diuretics reduced blood pressure more than the comparison therapy. The incoherence estimates were 0.00000006 for systolic blood pressure and 0.00042926 for diastolic blood pressure.

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active-treatment control arm of future superiority or equivalence trials in patients with hypertension. Trials evaluating the optimal second-line treatment strategy may be appropriate. Until then, recommendations about the best second-line therapies should be based, when possible, on evidence from large long-term outcome trials mounted for other compelling indications such as coronary disease and heart failure.[76]

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