

Systematic Review: Antihypertensive Drug Therapy in Black Patients

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Background: Hypertension occurs more frequently and is generally more severe in black persons than in white persons, leading to excess morbidity and mortality.

Purpose: To systematically review the efficacy of different antihypertensive drugs in reducing blood pressure, morbidity, and mortality in hypertensive black adults.

Data Sources: The following databases were searched from their inception through November 2003: MEDLINE, EMBASE, LILACS (Literatura Latino-Americana y del Caribe en Ciencias de la Salud), African Index Medicus, and the Cochrane Library. PubMed was also searched from September 2003 through March 2004. Searches were conducted without language restriction.

Study Selection: Randomized, controlled trials of drugs versus placebo (blood pressure outcomes) or drugs versus placebo or other drugs (morbidity and mortality outcomes).

Data Extraction: 2 reviewers independently extracted data.

Data Synthesis: The efficacy of β -blockers in reducing systolic blood pressure and the efficacy of angiotensin-converting enzyme inhibitors in achieving diastolic blood pressure goals did not significantly differ from that of placebo (weighted mean difference

for β -blockers, -3.53 mm Hg [95% CI, -7.51 to 0.45 mm Hg]; relative risk for angiotensin-converting enzyme inhibitors, 1.35 [CI, 0.81 to 2.26]). In the pooled analyses, other reviewed drugs (calcium-channel blockers, diuretics, central sympatholytics, α -blockers, and angiotensin II receptor blockers) were more effective than placebo in reducing blood pressure, but only calcium-channel blockers remained effective in all prespecified subgroups, including patients with a baseline diastolic blood pressure of 110 mm Hg or greater. Main morbidity and mortality outcomes did not differ significantly between treatment groups when drugs were combined to reach blood pressure goals. However, trial results indicated a greater occurrence of diabetes with diuretics and a higher risk for cardiovascular events with drug regimens that included angiotensin-converting enzyme inhibitors.

Limitations: This meta-analysis evaluated the blood pressure lowering–efficacy of monotherapy only.

Conclusions: Drugs differ in their efficacy for reducing blood pressure in black patients, but there is no solid evidence that efficacy for reducing morbidity and mortality outcomes differs once patients achieve the blood pressure goal.

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Black persons of sub-Saharan African descent differ from white persons and other populations in cultural, social, and psychological roots, as well as in biological characteristics (1, 2). Although the black population is heterogeneous, hypertension investigators have considered black persons a distinct biological entity when studying environmental and genetic factors that might explain the observed group differences in risk for hypertension and response to treatment (1, 3–5). Not only are black persons more likely to develop hypertension, but compared with hypertension in other ethnic groups, the disorder in black patients is often more severe, more resistant to treatment, and more likely to be fatal at an earlier age (1, 3). Thus, hypertension seems to be a more aggressive disease in black patients; this has important implications for the choice of an antihypertensive agent (1).

However, there is no consensus on the optimum drug treatment strategy for hypertension in black patients (1, 6–11). Current guidelines offer different opinions (1, 7–11) and either contain no specific treatment strategies for black patients (7), describe strategies without a specific drug of choice for first-line treatment (8), or advise the use of a specific drug, usually a diuretic, as first-line treatment (1, 9–11). We conducted this systematic review to critically assess the existing evidence on the efficacy of all commonly used antihypertensive drugs in reducing blood pressure and morbidity and mortality outcomes in this population.

METHODS

Literature Search

We sought to identify all trials, published or unpublished, that considered the effect of different classes of antihypertensive drugs in hypertensive black adults. To identify relevant trials, we searched MEDLINE, EMBASE, LILACS (Literatura Latino-Americana y del Caribe en Ciencias de la Salud), African Index Medicus, and the Cochrane Library from their inception through November 2003 and searched PubMed from September 2003 through March 2004. We also searched the Database of Abstracts of Reviews of Effects, Best Evidence, and Reviews in Progress (all from the United Kingdom) and hand searched Index Medicus from 1953 backward. Finally, we searched for trials by using references from textbooks, narrative reviews, and systematic reviews; by contacting experts and pharmaceutical companies; and by searching the Internet. We did not restrict the searches to any specific languages. Detailed search and retrieval strategies have been published elsewhere (12, 13).

Selection Criteria

To assess the blood pressure–lowering efficacy of the drugs, we included randomized, placebo-controlled trials of at least 2 weeks' duration that compared single drugs with concurrent placebo treatment and provided quantitative data on effects on systemic arterial blood pressure (as a continuous or dichotomous measure) in black adults. We

also determined whether an increase in drug dose was needed for adequate blood pressure control.

To assess the effects of drugs on morbidity and mortality, we included randomized, controlled trials that lasted at least 1 year, that used single drug treatment or compared single drug–based combinations of antihypertensive drugs with other combinations or with concurrent placebo treatment, and provided separate quantitative data on morbidity or mortality in black adults. We further assessed whether drug dose was increased or other drugs were added to reach the blood pressure goal. In addition, we evaluated adverse effects; discontinuation of drug therapy; and dropouts due to lack of effect, adverse effects, or other reasons, as defined by the authors.

Trials that considered oral treatment with diuretics, calcium-channel blockers, centrally acting agents, peripheral adrenergic neuron antagonists, β -blockers, α -blockers, single agents with combined α - and β -blocking activity, direct vasodilators, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers were eligible for inclusion. We included only trials that reported the number of black patients treated (per protocol or intention-to-treat analysis).

Data Assessment

At least 2 reviewers independently assessed each eligible study. Disagreement was resolved through final discussion. Investigators of each study were contacted twice to obtain missing information.

We assigned a Jadad score ranging from 0 to 5 points to the included trials according to whether the investigators described the study as randomized and double-blind, reported the methods used to randomly assign patients and blind the intervention, and reported the number of withdrawals and dropouts and the reason (14). The score was calculated on the basis of separate descriptions of withdrawals and dropouts for black persons. Other quality aspects addressed were as follows: whether the study assessed the minimum drug dose needed to reach a maximum antihypertensive effect (15), whether outcome assessment was blinded, and whether the report described adverse effects.

Statistical Analysis

We performed the statistical analysis using Cochrane Review Manager (RevMan) software, version 4.2 (Cochrane Collaboration, Oxford, United Kingdom). When studies did not provide SDs, we imputed them per drug type by using the available SDs for each drug class (16). Quantitative analysis of outcomes was based on intention-to-treat results (primary) and per protocol analysis (secondary). Our measure of effect for each study was difference in means (in mm Hg) for systemic arterial blood pressure (continuous measure) and relative risk for dichotomous data. When a study provided only the differences between the drug and placebo groups, we entered data in RevMan as drug results, with a “nil” for placebo results. We included data from the first part of crossover studies when

such data were available; if not, we included the data these studies provided.

Before applying approximate chi-square tests for heterogeneity, we clinically assessed studies for heterogeneity in patient characteristics, interventions, and outcomes. We used I^2 statistics to quantify the proportion of total variation in the estimates of treatment effect that was due to heterogeneity (17). We then explored the sources of the heterogeneity and decided whether we should aggregate the studies. When we aggregated studies, we used the random-effects model. We did not aggregate results with a high variation across studies because of heterogeneity ($I^2 \geq 75\%$) (17).

We performed sensitivity analyses by reanalyzing data using fixed-effects models and by reanalyzing data after excluding studies with imputed SDs, crossover studies, and studies that used per protocol analysis.

We predefined the following subgroup analyses (13): patients with differential severity of hypertension before treatment allocation (18); studies conducted in Africa compared with U.S. and Caribbean studies (since European admixture of up to 25% has occurred in the black population in the Americas [19], possible genetic influences on drug responses might be stronger in African patients); and outcomes based on sex.

DATA SYNTHESIS

Trial Retrieval

Full reports or abstracts from more than 2900 references of papers yielded 30 trials that involved 53 interventions, 8 classes of antihypertensive drugs, and 20 006 black patients. Blood pressure was the main outcome measure in 26 of these trials (20–47) (Table 1). Figure 1 shows the trial flow and reasons for exclusion of trials.

Methodologic Quality of Included Studies

Jadad scores ranged from 2 to 4 (median, 3) in studies with blood pressure outcomes (Table 1) and from 3 to 5 in studies with morbidity and mortality outcomes. The Systolic Hypertension in the Elderly Program (SHEP) study lost 2 points—1 for method of randomization (which we could not retrieve) and 1 for withdrawals and dropouts; the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study and the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) both lost 1 point because of withdrawals and dropouts; the African-American Study of Kidney Disease and Hypertension (AASK) achieved the maximum score of 5 (48–61).

Studies with blood pressure outcomes used preset doses and did not report whether they assessed the minimum dose needed to reach a maximum antihypertensive effect in black people (15). No trial reported subgroup analyses based on baseline blood pressure. Three trials reported blinding of assessment of outcome (49, 53, 57).

Table 1. Characteristics of Included Studies with Blood Pressure Outcomes*

Study, Year (Reference)	Black Patients Randomly Assigned, n	Trial Location	Age, y	BP, mm Hg	Total Daily Dose of Drug Intervention, mg
ABC trial, 2000 (20)	304	USA	Mean, 52	DBP, 91–105	Candesartan cilexetil, 16–32
Conlin et al., 2003 (21)	18†	USA	Mean, 52	DBP, 90–109	Losartan, 50‡§
Dean et al., 1971 (22)	60	RSA	Adults	DBP, 100–116	Hydrochlorothiazide, 50, vs. mefruside, 25
Drayer and Weber, 1983 (23)	58†	USA	Mean, 53	DBP, 95–115	Captopril, 200§
Fadayomi et al., 1986 (24)	32	Nigeria	Mean, 48	DBP >100	Nifedipine, 40
Fiddes et al., 1994 (25)	46	USA	≥55	DBP, 95–114	Diltiazem extended-release, 240–480
Flack et al., 2001 (26)	381	USA	Mean, 50	DBP, 95–109	Losartan, 50–150§
Flack et al., 2003 (27)	233†	USA/RSA	Mean, 52	DBP, 95–109	Losartan, 50–100§
Frishman et al., 1995 (28)	62†	USA	≥21	DBP, 95–115	Hydrochlorothiazide, 25, vs. bisoprolol, 5§
Humphreys and Delvin, 1968 (29)	18	Jamaica	46–63	DBP, 100–155	Propranolol, 20–360‡
Materson et al., 1993, 1995 (6, 30)	621	USA	Mean, 58	DBP, 95–109	Diltiazem, 120–360, vs. hydrochlorothiazide, 12.5–50, vs. clonidine, 0.2–0.6, vs. captopril, 25–100, vs. prazosin, 4–20, vs. atenolol, 25–100
Moser and Lunn, 1982 (31)	20	The Bahamas	32–60	DBP, 101–119	Captopril, up to 450
Moser et al., 1984 (32)	77	USA	26–70	DBP, 90–114	Nitrendipine, 10–40
Opie et al., 1997 (33)	31†	RSA	18–75	DBP, 95–114	Nisoldipine coat-core, 30§
Salako et al., 1979 (34)	20	Nigeria	37–60	DBP, 95–120	Alprenolol sustained-release, 400‡
Seedat, 1980 (35)	24	RSA	Adults	DBP, 100–115	Chlorthalidone, 100, vs. atenolol, 25‡
Seedat, 1980 (36)	9	RSA	Mean, 44	DBP ≥ 110	Mefruside, 12.5–25, vs. debrisoquine, 10–20‡
Stein et al., 1992 (37)	25	Zimbabwe	<70	DPB, 96–114	Hydrochlorothiazide, 50‡§
TAIM, 1989, 1991 (38, 39)	98†	USA	Mean, 46	DBP, 90–100	Chlorthalidone, 25, vs. atenolol, 50¶
TOMHS, 1993, 1997 (40, 41)	177	USA	Mean, 54	DBP, 90–99	Amlodipine, 5–10, vs. chlorthalidone, 15–30, vs. enalapril, 5–10, vs. doxazosin, 2–4, vs. acebutolol, 400–800**
TROPHY study, 1997 (42)	68 obese patients	USA	21–75	DBP, 90–109	Hydrochlorothiazide, 12.5–50, vs. lisinopril, 10–40
Venter et al., 1990 (43)	50	RSA	25–65	DBP, 95–115	Penbutolol, 40–80‡
Venter et al., 1991 (44)	15†	RSA	25–65	DBP, 95–115	Xipamide, 20§
Venter et al., 1991 (45)	29	RSA	21–65	DBP, 95–115	Enalapril, 5–40, vs. prazosin, 2–20
Weir et al., 1998 (46)	56 salt-sensitive patients†	USA	Mean, 52	DBP, 95–115	Isradipine, 10–20,§ vs. enalapril, 10–40§††
Weir and Saunders, 1998 (47)	96†	USA	Mean, 54	DBP, 95–114	Trandolapril, 16§

* All interventions were placebo-controlled. ABC = Association of Black Cardiologists; BP = blood pressure; DBP = diastolic blood pressure; ITT = intention-to-treat; ND = no data reported for black persons; RSA = Republic of South Africa; TAIM = Trial of Antihypertensive Interventions and Management; TOMHS = Treatment of Mild Hypertension Study; TROPHY = Treatment in Obese Patients with Hypertension; USA = United States of America.

† Black patients evaluated in this review.

‡ Crossover trial

§ Highest dose of parallel arms included.

|| Blood pressure as continuous/dichotomous outcome, respectively.

¶ Other drugs were added for 12.5% of participants.

** Second drug added for 9.2% of participants; plus lifestyle interventions.

†† Plus a high- or low-salt diet.

Adverse effects were reported in 12 of 26 studies that had blood pressure outcomes, and dropouts and withdrawals were described in 14 studies (total rates, 0% to 52%; median, 14%). Two of the 4 trials with morbidity and mor-

tality outcomes described adverse effects (57, 61), and 1 reported the dropout percentage for black patients (31%) (57). Seventeen trials used intention-to-treat analysis, including all trials that had morbidity and mortality out-

Table 1—Continued

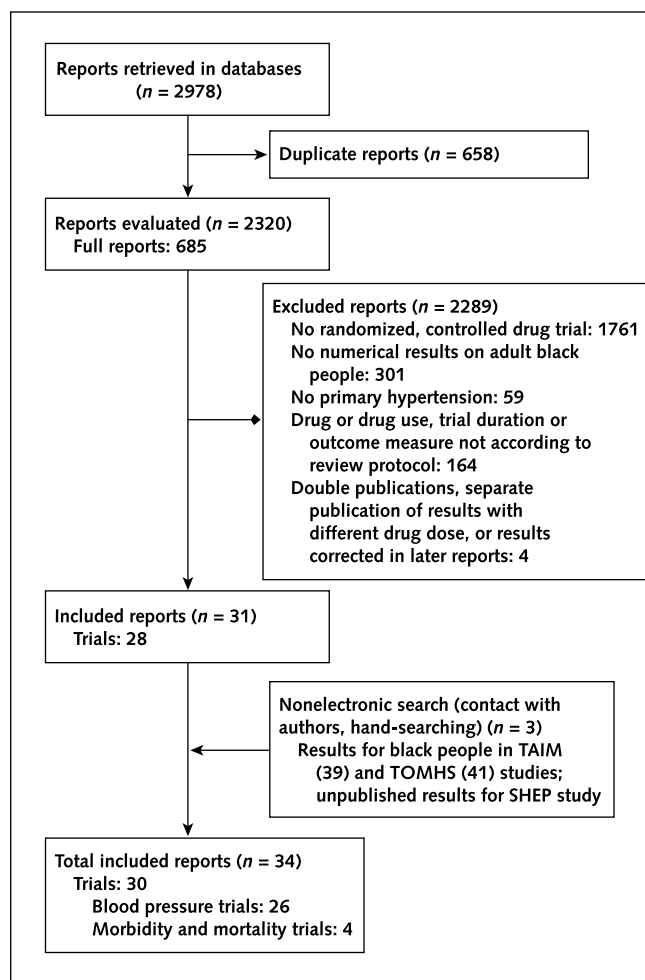
Treatment Duration	Outcome Measure: BP	Analysis of Results	Adverse Effects	Jadad Score					Total
				Study Described as Randomized	Method of Randomization	Study Described as Double-Blind	Method of Blinding	Descriptions of Withdrawals and Dropouts	
8 wk	Continuous/dichotomous	ITT	Reported	1	–	1	1	1	4
4 wk	Continuous	ITT	ND	1	–	1	1	1	4
2 wk	Continuous	Per protocol	ND	1	–	1	1	–	3
8 wk	Dichotomous	Per protocol	ND	1	–	1	–	1	3
6 wk	Continuous/dichotomous	Per protocol	Reported	1	–	1	1	–	3
8 wk	Continuous	ITT	ND	1	–	1	–	–	2
12 wk	Continuous/dichotomous	ITT	Reported	1	–	1	–	1	3
16 wk	Continuous	ITT	ND	1	–	1	1	–	3
4 wk	Continuous/dichotomous	ITT	ND	1	–	1	–	–	2
2 mo	Continuous/dichotomous	ITT	Reported	1	–	1	1	1	4
8 wk/1 y	Continuous/dichotomous	ITT	ND	1	–	1	–	1	3
4 wk	Continuous/dichotomous	Per protocol	Reported	1	–	1	–	–	2
5 wk	Continuous/dichotomous	Per protocol	ND	1	–	1	1	–	3
6 wk	Continuous	ITT	ND	1	–	1	1	–	3
8 wk	Continuous	Per protocol	Reported	1	–	1	1	1	4
4 wk	Continuous	ITT	Reported	1	–	1	–	1	3
4 wk	Continuous/dichotomous	ITT	ND	1	1	1	–	1	4
6 wk	Continuous/dichotomous	Per protocol	ND	1	–	1	–	1	3
6 mo	Continuous	ITT	ND	1	1	1	1	–	4
1 y	Continuous	Per protocol	Reported for women only	1	–	1	1	–	3
12 wk	Continuous	Per protocol	ND	1	–	1	1	–	3
12 wk	Continuous/dichotomous	Per protocol	Reported	1	–	1	1	1	4
12 wk	Continuous	Per protocol	Reported	1	–	–	–	1	2
10 wk	Continuous/dichotomous	Per protocol	Reported	1	–	1	1	1	4
4 wk	Continuous	Per protocol	ND	1	1	1	1	–	4
6 wk	Continuous	ITT	Reported	1	–	1	–	1	3

comes; 13 trials used per protocol analysis (Table 1). Seven studies were crossover studies (21, 29, 34–37, 43), and 1 provided separate data on the first part of the crossover study (43).

Trials with Blood Pressure Outcomes Blood Pressure–Lowering Efficacy

The trials with blood pressure outcomes included patients with baseline systolic blood pressure (SBP) up to 225

Figure 1. Trial flow.



With results for black patients in Materson and colleagues' study (6, 30), the Systolic Hypertension in the Elderly Program (*SHEP*) (49; unpublished report), the African American Study of Kidney Disease and Hypertension (56, 57), and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (60, 61) contained in 2 reports. TAIM = Trial of Antihypertensive Interventions and Management; TOMHS = Treatment of Mild Hypertension Study.

mm Hg and diastolic blood pressure (DBP) of up to 155 mm Hg. The median duration of active treatment was 8 weeks (range, 2 to 52 weeks). With the exception of β -blockers for SBP, all the reviewed antihypertensive drugs were more effective than placebo in reducing SBP and DBP as continuous measures, although the effect of α -blockers on diastolic blood pressure was of marginal significance (Figures 2 and 3). Four trials showed a tendency toward an increase in SBP with the use of β -blockers (29, 35, 39, 43), and trials that reported results of individual

patients (29, 34) found placebo-corrected increases in SBP (up to 30 mm Hg) in 38% of black participants and increases in DBP (up to 25 mm Hg) in 29% of black participants.

The DBP goal (DBP \leq 90 mm Hg or reduction in DBP of \geq 10 mm Hg [or 10% decrease], as defined by the author) was reached in 23% of the patients: 46% of those receiving calcium-channel blockers, 31% of those receiving diuretics, 23% of those receiving centrally acting agents, 19% of those receiving β -blockers, 19% of those receiving angiotensin II receptor blockers, 13% of those receiving α -blockers, 10% of those receiving ACE inhibitors, and 0% of those receiving postganglionic sympathetic neuron blockers (weighted means of placebo-corrected results). Table 2 reports the relative risks for reaching the DBP goal. The relative risk for postganglionic sympathetic neuron blockers could not be estimated, and we excluded this intervention (9 participants) from further analysis.

Adverse Effects

Adverse effects that occurred more frequently with drugs than with placebo were headache (20, 24, 26, 33), back pain (20), upper respiratory tract infections (20, 26), sinusitis (20, 26), polyuria and nocturia (24), dizziness (26), tinnitus (33), bronchospasms (with β -blockers) (34), tachycardia (with prazosin) (45), and cough (with enalapril) (45). Adverse laboratory effects included transitory leukopenia with the use of captopril (23) and well-known side effects of drugs, such as hypokalemia and hyperuricemia, with the use of diuretics (22, 35). Studies did not report greater frequency of adverse effects with higher drug dose.

Heterogeneity Analyses

With regard to clinical heterogeneity, most trials included patients with uncomplicated primary hypertension and no clinically significant end organ damage. Table 1 shows pretreatment DBP. Of the 8 classes of drugs reviewed, diuretics were used the most. The studies uniformly expressed blood pressure outcomes as change in mm Hg or as the percentage of patients reaching the DBP goal. We performed subgroup analyses to assess outcomes with differing baseline severity of hypertension (Table 2).

Calcium-channel blockers had high I^2 values on the test for heterogeneity for SBP and DBP reduction: 94% and 92%, respectively (Figures 2 and 3). The heterogeneity in size of the effect for this drug type resulted from the great reduction in blood pressure in Fadayomi and col-

(Legend for Figure 2, page 619). Random-effects model. Squares are weighted mean differences in reduction of SBP (mm Hg). The size of the squares represents study weight, and horizontal lines represent 95% CIs. Arrowheads depict data outside the scale. Results for Materson and colleagues' study (6) and Weir and colleagues' study (46) are weighted means of older and younger people and patients receiving a high- and a low-salt diet, respectively. Black diamonds are pooled estimates. Results for calcium-channel blockers are not pooled because the size of the effect is heterogeneous. ABC = Association of Black Cardiologists; TAIM = Trial of Antihypertensive Interventions and Management; TOMHS = Treatment of Mild Hypertension Study; TROPHY = Treatment in Obese Patients with Hypertension.

Figure 2. Systolic blood pressure (SBP)-lowering effect of different antihypertensive drugs in black patients.

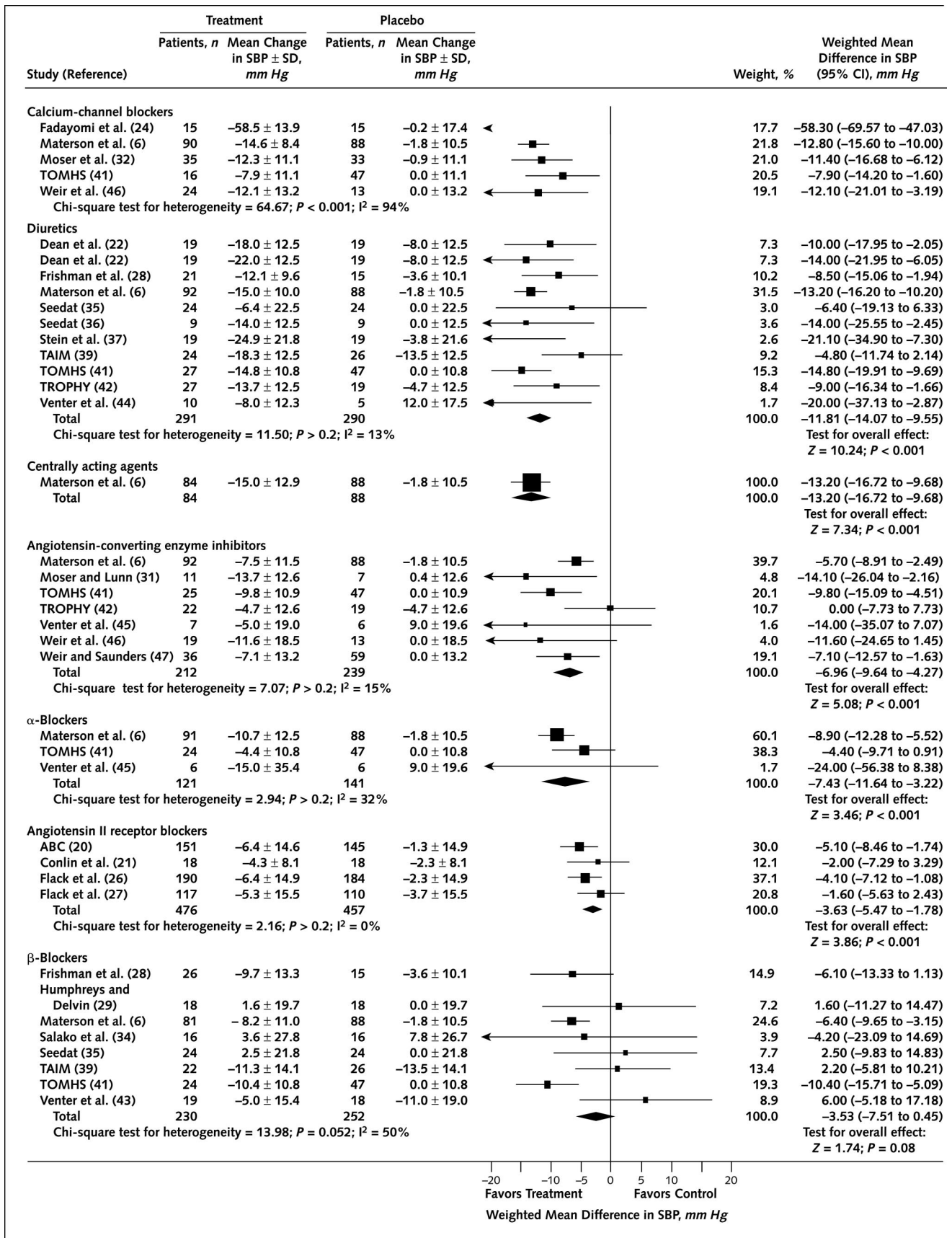


Figure 3. Diastolic blood pressure (DBP)-lowering effect of different antihypertensive drugs in black patients.

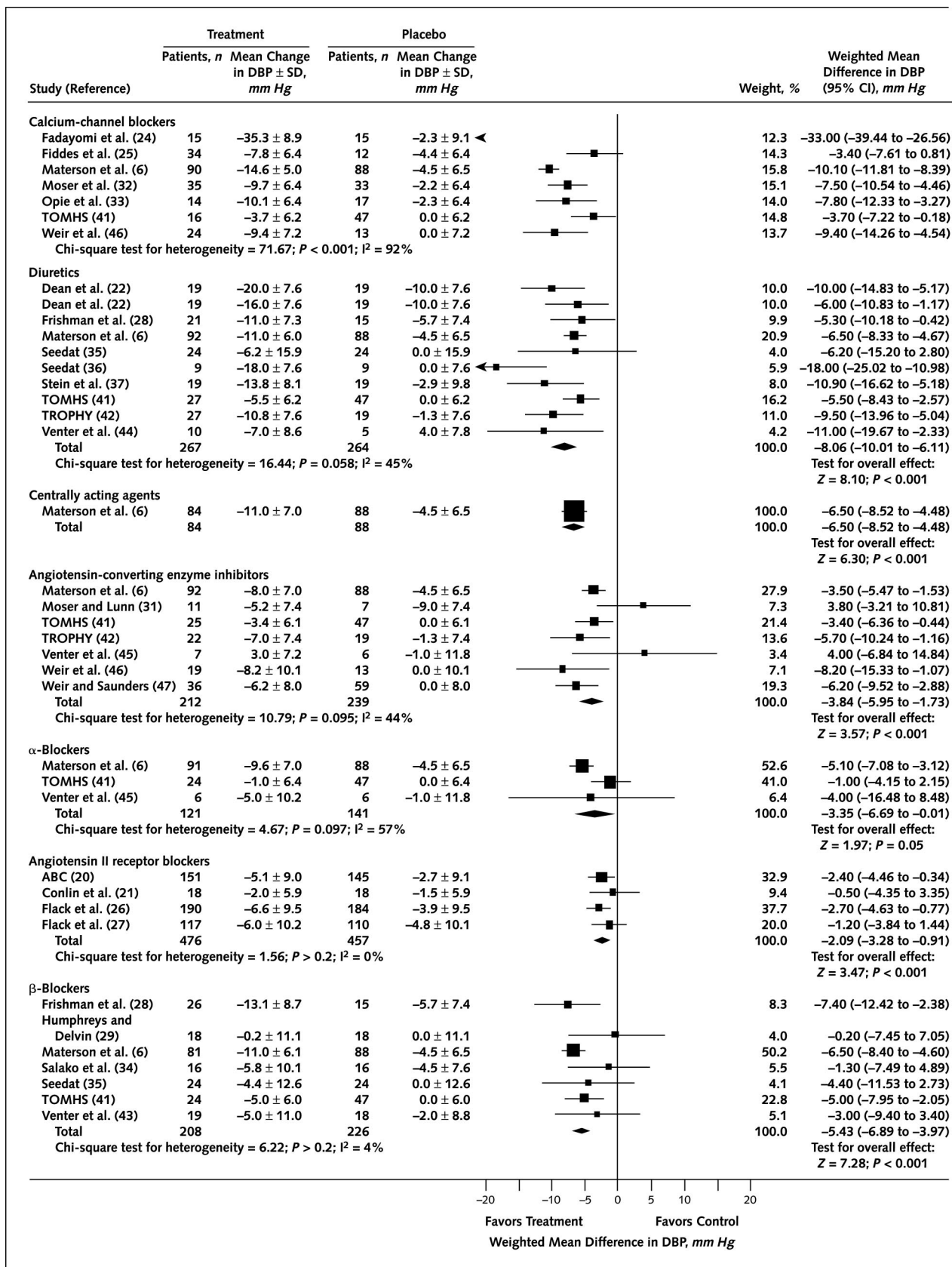


Table 2. Blood Pressure Reduction among Patients with Differing Baseline Blood Pressure*

Drug Type	Total Group		Baseline DBP, 90–99 mm Hg		Baseline DBP, 100–109 mm Hg		Baseline DBP ≥ 110 mm Hg	
	Trials, n	BP Reduction (95% CI), mm Hg†	Trials, n	BP Reduction (95% CI), mm Hg†	Trials, n	BP Reduction (95% CI), mm Hg†	Trials, n	BP Reduction (95% CI), mm Hg†
Calcium-channel blockers								
Change in SBP	5	Heterogeneity‡	1	-7.90 (-14.20 to -1.60)	1	-12.80 (-15.60 to -10.00)	3	Heterogeneity‡
Change in DBP	7	Heterogeneity‡	1	-3.70 (-7.22 to -0.18)	1	-10.10 (-11.81 to -8.39)	5	Heterogeneity‡
DBP goal§	3	3.39 (2.35 to 4.90)	ND	ND	1	3.51 (2.24 to 5.50)	2	3.23 (1.56 to 6.69)
Diuretics								
Change in SBP	11	-11.81 (-14.07 to -9.55)	1	-14.80 (-19.91 to -9.69)	3	-9.75 (-15.02 to -4.49)	7	-11.66 (-15.26 to -8.07)
Change in DBP	10	-8.06 (-10.01 to -6.11)	1	-5.50 (-8.43 to -2.57)	2	-7.28 (-9.86 to -4.70)	7	-9.31 (-12.43 to -6.18)
DBP goal§	4	2.49 (1.68 to 3.69)	ND	ND	1	2.64 (1.65 to 4.24)	3	2.43 (0.83 to 7.07)
Centrally acting agents								
Change in SBP	1	-13.20 (-16.72 to -9.68)	ND	ND	1	-13.20 (-16.72 to -9.68)	ND	ND
Change in DBP	1	-6.50 (-8.52 to -4.48)	ND	ND	1	-6.50 (-8.52 to -4.48)	ND	ND
DBP goal§	1	2.22 (1.35 to 3.63)	ND	ND	1	2.22 (1.35 to 3.63)	ND	ND
ACE inhibitors								
Change in SBP	7	-6.96 (-9.64 to -4.27)	1	-9.80 (-15.09 to -4.51)	2	-3.98 (-9.11 to 1.15)	4	-8.98 (-13.51 to -4.44)
Change in DBP	7	-3.84 (-5.95 to -1.73)	1	-3.40 (-6.36 to -0.44)	2	-3.85 (-5.66 to -2.04)	4	-2.51 (-8.42 to 3.40)
DBP goal§	3	1.35 (0.81 to 2.26)	ND	ND	1	1.74 (1.04 to 2.92)	2	1.01 (0.51 to 1.99)
α-Blockers								
Change in SBP	3	-7.43 (-11.64 to -3.22)	1	-4.40 (-9.71 to 0.91)	1	-8.90 (-12.28 to -5.52)	1	-24.00 (-56.38 to 8.38)
Change in DBP	3	-3.35 (-6.69 to -0.01)	1	-1.00 (-4.15 to 2.15)	1	-5.10 (-7.08 to -3.12)	1	-4.00 (-16.48 to 8.48)
DBP goal§	1	1.71 (1.02 to 2.86)	ND	ND	1	1.71 (1.02 to 2.86)	ND	ND
Angiotensin II receptor blockers								
Change in SBP	4	-3.63 (-5.47 to -1.78)	ND	ND	4	-3.63 (-5.47 to -1.78)	ND	ND
Change in DBP	4	-2.09 (-3.28 to -0.91)	ND	ND	4	-2.09 (-3.28 to -0.91)	ND	ND
DBP goal§	2	1.77 (1.41 to 2.21)	ND	ND	2	1.77 (1.41 to 2.21)	ND	ND
β-Blockers								
Change in SBP	8	-3.53 (-7.51 to 0.45)	1	-10.40 (-15.71 to -5.09)	2	-2.90 (-11.18 to 5.38)	5	-1.28 (-6.13 to 3.57)
Change in DBP	7	-5.43 (-6.89 to -3.97)	1	-5.00 (-7.95 to -2.05)	1	-6.50 (-8.50 to -4.40)	5	-3.81 (-6.60 to -1.03)
DBP goal§	3	1.87 (1.25 to 2.82)	ND	ND	1	1.98 (1.19 to 3.29)	2	1.70 (0.86 to 3.35)

* Placebo-corrected results. ACE = angiotensin-converting enzyme; BP = blood pressure; DBP = diastolic blood pressure; ND = no data reported; SBP = systolic blood pressure.

† For all values except for DBP goal, values are the weighted mean difference expressed in mm Hg.

‡ Heterogeneity in the size of the effect.

§ For DBP goal, values are the relative risk; a value >1.0 indicates a beneficial effect.

leagues' study (24), which included patients with a blood pressure as high as 210/130 mm Hg, versus the moderate reduction in the participants of the Treatment of Mild Hypertension Study (TOMHS) (41), in which pretreatment DBP was not higher than 99 mm Hg (Figures 2 and 3). Reanalyzing calcium-channel blocker studies without Fadayomi and colleagues' trial (for SBP and DBP reduction) and TOMHS (for DBP reduction) yielded I^2 values of 0% and 58%, respectively, with a change in SBP of -12.46 mm Hg (CI, -14.85 to -10.08 mm Hg) and a change in DBP of -7.93 mm Hg (CI, -10.27 to -5.59 mm Hg). After we omitted Fadayomi and colleagues'

study, 42% of patients receiving calcium-channel blockers reached the blood pressure goal.

Sensitivity Analyses

When we reanalyzed the data by using fixed-effects models or by excluding trials with imputed SDs, crossover studies, or trials using per protocol analysis, we found similar magnitudes of effect and conclusions about statistical heterogeneity. One exception was the effect of β -blockers on SBP: In a fixed-effect model, the change in SBP was -5.28 mm Hg (CI, -7.58 to -2.98 mm Hg); after ex-

(Legend for Figure 3, page 620). Random-effects model. Squares are weighted mean differences in reduction of DBP (mm Hg). The size of the squares represents study weight, and horizontal lines represent 95% CIs. Results for Materson and colleagues' study (6) and Weir and colleagues' study (46) are weighted means of older and younger people and patients receiving a high- and a low-salt diet, respectively. Black diamonds are pooled estimates. Results for calcium-channel blockers are not pooled because the size of the effect is heterogeneous. ABC = Association of Black Cardiologists; TAIM = Trial of Antihypertensive Interventions and Management; TOMHS = Treatment of Mild Hypertension Study; TROPHY = Treatment in Obese Patients with Hypertension.

clusion of trials that imputed SDs, the change was -4.69 mm Hg (CI, -8.62 to -0.76 mm Hg); and after exclusion of crossover studies, the change was -5.93 mm Hg (CI, -10.09 to -1.76 mm Hg). In addition, when we excluded trials that used per protocol analysis, the relative risk for reaching the blood pressure goal seen with ACE inhibitors became 1.74 (CI, 1.04 to 2.92).

Subgroup Analyses

Table 2 shows blood pressure reductions according to differing baseline blood pressures. Angiotensin-converting enzyme inhibitors and β -blockers performed relatively well in patients with a baseline DBP as high as 99 mm Hg, and diuretics did well in patients with a baseline DBP as high as 109 mm Hg. Calcium-channel blockers were the only drug type to remain effective for all blood pressure outcomes in all subgroups, including patients with a baseline DBP of 110 mm Hg or greater. The sizes of the effects for calcium-channel blockers in the subgroup of patients with a baseline DBP of 110 mm Hg or greater were heterogeneous ($I^2 = 94\%$ for SBP reduction and 92% for DBP reduction). When we reanalyzed the subgroup of patients with a DBP of 110 mm Hg or greater after excluding Fadayomi and colleagues' trial, the I^2 values for SBP and DBP became 0% and 24%; the change in SBP was -11.58 mm Hg (CI, -16.12 to -7.04 mm Hg), and the change in DBP was -6.96 mm Hg (CI, -9.28 to -4.63 mm Hg).

When we separately analyzed U.S./Caribbean studies (Table 1), calcium-channel blockers changed SBP by -11.89 mm Hg (CI, -14.12 to -9.67 mm Hg) and β -blockers led to a change of -5.32 mm Hg (CI, -9.35 to -1.28 mm Hg); the size of the effect of α -blockers on DBP became heterogeneous. When we separately analyzed data from African studies, however, only calcium-channel blockers remained more effective than placebo for all outcomes analyzed. Diuretics did not significantly differ from placebo in achieving the DBP goal (relative risk, 3.55 [CI, 0.41 to 31.05]), and ACE inhibitors, α -blockers, and β -blockers did not significantly differ from placebo in reduction of SBP and DBP. None of the African studies used a cutoff baseline DBP of less than 114 mm Hg, compared with 7 of the 15 U.S. and Caribbean studies (Table 1); thus, we could not determine whether the response of African black patients truly differed from that of U.S. and Caribbean black patients. We decided not to perform subgroup analyses based on sex since only 3 of the 43 studies reported data on the relative efficacy of drugs in men and women (24, 29, 47).

Trials with Morbidity and Mortality Outcomes

We did not pool the findings of the 4 trials (48–61) that reported morbidity and mortality outcomes in black patients because their patient characteristics, interventions, and end points differed. In the following section we discuss the results of these studies in more detail. Unless stated

otherwise, presented results are relative risks among black patients.

SHEP

The SHEP study included 657 (14%) black patients and studied the efficacy of chlorthalidone-based treatment versus placebo in reducing stroke occurrence as a primary outcome measure in patients older than 60 years who had an SBP of 160 to 219 mm Hg and a DBP less than 90 mm Hg (48–50). Secondary outcome measures included myocardial infarction, fatal coronary disease, and cardiovascular mortality. Active treatment (mean duration, 4.5 years) reduced stroke in black women (relative risk, 0.36 [CI, 0.16 to 0.83]) but not in black men (relative risk, 0.98 [CI, 0.39 to 2.44]) (49) and reduced cardiovascular events (hazard ratio for all cardiovascular events, 0.50 [CI, 0.32 to 0.78]) (unpublished results, SHEP trial investigators). This study did not report on blood pressure or the incidence of new-onset diabetes for black patients.

LIFE

The LIFE study included 533 (6%) black patients and compared the effect of losartan with that of atenolol on cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction as the primary composite end point (51–54). Study patients were 55 to 80 years of age and had an SBP of 160 to 200 mm Hg or a DBP of 95 to 115 mm Hg and left ventricular hypertrophy. The mean duration of treatment was 4.8 years.

Analysis of treatment effect by prespecified baseline characteristics showed a significant interaction for ethnicity ($P = 0.005$), indicating that the effect of losartan versus atenolol differed between black and nonblack patients (54). In contrast to the results calculated for the total group (relative risk, 0.86 [CI, 0.77 to 0.96], favoring losartan), there was a trend toward a greater risk with losartan in black patients (relative risk, 1.55 [CI, 1.00 to 2.38], obtained by using RevMan software; hazard ratio, 1.67 [CI, 1.04 to 2.66], according to the investigators). The investigators reported that blood pressure was similar in both treatment groups (54). We could not retrieve data on the incidence of new-onset diabetes in black patients in the different treatment groups.

AASK

The AASK trial included 1094 (100%) black patients age 18 to 70 years who had a DBP of 95 mm Hg or greater and a glomerular filtration rate (GFR) of 20 to 65 mL/min per 1.73 m² (55–57). The study compared the effects of 3 antihypertensive drugs (ramipril, amlodipine, and metoprolol) on the decline in GFR (GFR slope) over 3 to 6 years of follow-up. The primary outcome was a reduction in both the chronic GFR slope after 3 months and the mean total GFR slope from baseline to study end. The main secondary composite outcome included GFR decline,

end-stage renal disease, and death. The other secondary outcome was proteinuria.

In September 2000, the amlodipine arm was halted on the basis of prespecified and post hoc–defined stopping criteria for the secondary outcomes (56). The primary outcome did not significantly differ for the 3 drug comparisons (56, 57). Follow-up SBP was 2 mm Hg higher in the ramipril and metoprolol groups than in the amlodipine group, and DBP was 1 mm Hg higher in the ramipril group than in the other groups.

We calculated absolute and relative risk reductions for the main secondary composite outcome (56, 57). For ramipril versus metoprolol, the absolute risk reduction was 6% (CI, 0% to 12%) and the relative risk reduction was 18% (CI, 0% to 32%); for metoprolol versus amlodipine, the absolute risk reduction was –1% (CI, –8% to 6%) and the relative risk reduction was –3% (CI, –35% to 22%); and for ramipril versus amlodipine, the absolute risk reduction was 6% (CI, –1% to 13%) and the relative risk reduction was 23% (CI, –4% to 42%). After adjustment for covariates that included mean arterial pressure, relative risk reductions for these 3 comparisons were 22% (CI, 1% to 38%), 20% (CI, –10% to 41%), and 38% (CI, 13% to 56%), respectively (56, 57).

The difference in percentage change in geometric mean proteinuria from baseline to study end was significantly higher in the amlodipine group than in the other 2 groups ($P < 0.001$), but the investigators provided no absolute figures. The proportion of patients reporting angioedema and cough was highest in the ACE inhibitor group, whereas patients receiving calcium-channel blockers had more cases of peripheral edema. We could not retrieve data on the incidence of new-onset diabetes in the different treatment groups.

ALLHAT

The ALLHAT study included 15 094 (35%) black patients and compared the relative efficacy of chlorthalidone, amlodipine, lisinopril, and doxazosin in reducing morbidity and mortality among patients older than 55 years of age who had an SBP of 140 to 180 mm Hg or a DBP of 90 to 110 mm Hg and at least 1 other risk factor for coronary heart disease (58–61). The mean treatment duration was 4.9 years. The primary outcome measure was combined nonfatal myocardial infarction or fatal coronary heart disease (CHD). Major secondary outcomes included all-cause mortality, stroke, combined CHD, and combined cardiovascular disease (CVD); other secondary outcomes included heart failure. Black patients were younger, had a higher baseline DBP, higher baseline mean fasting serum glucose levels, and a higher incidence of diabetes mellitus at baseline (59).

The doxazosin arm was halted after an interim analysis in 2000. No significant differences were reported between the 3 drugs for the primary outcome (amlodipine vs.

chlorthalidone: relative risk, 1.01 [CI, 0.86 to 1.18]; lisinopril vs. chlorthalidone: relative risk, 1.10 [CI, 0.94 to 1.28]; doxazosin vs. chlorthalidone: no separate data for black patients; relative risk among the whole group, 1.03 [CI, 0.90 to 1.17]).

Although amlodipine and chlorthalidone did not significantly differ for the major secondary outcomes, the comparison between lisinopril and chlorthalidone favored the diuretic for stroke (relative risk, 1.40 [CI, 1.17 to 1.68]), combined CHD (relative risk, 1.15 [CI, 1.02 to 1.30]), and combined CVD (relative risk, 1.19 [CI, 1.09 to 1.30]). The comparison between doxazosin and chlorthalidone favored the diuretic for combined CVD (relative risk, 1.40 [CI, 1.25 to 1.57]). In addition, all comparisons for heart failure favored chlorthalidone (relative risks were as follows: compared with amlodipine, 1.47 [CI, 1.24 to 1.74]; compared with lisinopril, 1.32 [CI, 1.11 to 1.58]; compared with doxazosin, 2.18 [CI, 1.73 to 2.74]). According to the authors, adjustment for the higher follow-up blood pressure in the lisinopril group compared with the chlorthalidone group (mean difference in SBP, 4 mm Hg) did not alter the outcomes.

At 4 years, the incidence of type 2 diabetes in patients who did not have diabetes at baseline was as follows: chlorthalidone, 11.6%; amlodipine, 9.8% ($P = 0.04$ vs. chlorthalidone); and lisinopril, 8.1% ($P < 0.001$ vs. chlorthalidone). The investigators did not report separate results for black patients. The occurrence of angioedema in black patients was significantly greater in the ACE inhibitor group (0.7%) than in the chlorthalidone group (0.04%) ($P < 0.001$).

DISCUSSION

Most of the commonly used antihypertensive drugs were more effective than placebo in lowering SBP and DBP and in reaching DBP goals in black hypertensive patients. β -Blockers did not significantly differ from placebo in the reduction of systolic blood pressure, and ACE inhibitors did not significantly differ from placebo in reaching DBP goals. Moreover, trials that reported results for individual patients found that β_1 -selective-blockers or nonselective β -blockers increased blood pressure relative to placebo in up to 38% of the participants (29, 34).

Despite the blood pressure–lowering efficacy of most drugs, only 23% of the actively treated patients reached the DBP goal after adjustment for placebo effects. However, most investigators titrated doses moderately and did not report on whether they assessed the ability of the minimum dose to reach a maximum antihypertensive effect. With the possible exception of β -blockers (62, 63), higher doses might be needed for optimal effect in black people (15, 23, 47, 64), and more extended dose titration might increase the size of the blood pressure–lowering effect of drugs in this group.

We also found indications that drug class affected

blood pressure–lowering efficacy in patients with differing severities of hypertension. β -Blockers and ACE inhibitors were effective in patients with a pretreatment DBP as high as 99 mm Hg, but calcium-channel blockers were the only drug type effective for all blood pressure outcomes in all subgroups of black participants, including those with a baseline DBP of 110 mm Hg or greater. This observation might help explain conflicting results for the efficacy of blood pressure–lowering drugs in black patients (1, 6, 29, 41, 64).

We did not find sufficient evidence that efficacy of drugs differed in reducing morbidity and mortality outcomes in black patients independent of blood pressure. In particular, agents that reduce the genesis of or antagonize the effects of angiotensin II (which are increasingly presented as being able to reduce morbidity and mortality outcomes independent of blood pressure [53, 65, 66]) did not significantly differ from other drugs in the primary outcomes for black patients.

On the contrary, the LIFE study surprisingly showed a trend toward greater risk for the composite cardiovascular end point with the angiotensin II receptor blocker in black patients (54). Furthermore, although secondary (adjusted) outcomes in AASK indicated that the use of ACE inhibitors led to greater reduction of renal events in hypertensive black patients (56, 57), we need solid evidence that this practice will not increase the incidence of cardiovascular end points such as stroke (61) before clinicians advocate using these drugs in this population (8, 56, 57).

With regard to diuretics, data from the SHEP trial (48–50) indicated efficacy of diuretics in reducing stroke in black women and in reducing cardiovascular events. However, since not treating hypertension is no longer considered an option, comparisons with other drugs are needed. The ALLHAT investigators reported no significant differences in the primary outcome between chlorthalidone, amlodipine, and lisinopril in black patients (58–61), but chlorthalidone was more effective than the other drugs in reducing secondary outcomes such as stroke, cardiovascular disease, and heart failure. How should one interpret this evidence?

Many arguments have been raised against the ALLHAT conclusion that diuretics should be preferred for first-line antihypertensive therapy (67). From a methodologic point of view, secondary outcomes are, as stated in an early ALLHAT report, “soft data” to be used to “confirm or supplement the primary endpoint” (58). Since the drugs did not significantly differ for the primary outcome, there is no solid evidence of superiority of diuretics.

Moreover, in trials with such a large sample size as ALLHAT, very small differences between drugs that might not be clinically significant may become statistically significant. This is of particular concern with the multiple outcomes in ALLHAT (61). With 3 drug comparisons for 1 primary outcome, 16 secondary outcomes, and several intermediate and post hoc outcomes (many with interrelated

components studied in the total group as well as in 10 subgroups), this trial had at least 561 possible outcomes. This number sharply increases the likelihood that results become statistically significant only by chance.

Furthermore, the greater incidence of stroke in black patients in the ACE inhibitor group might merely have been the result of the combination of 2 drugs that are relatively ineffective in reducing blood pressure in this population—ACE inhibitors and β -blockers as first- and second-line treatment.

Finally, when one considers black patients, a point of concern with the use of diuretics is the greater occurrence of diabetes mellitus noted in the total group, which might have been even more pronounced in black participants if the higher mean fasting serum glucose levels at baseline in this group are considered (59). The follow-up period in ALLHAT might have been too short to show whether the greater incidence of diabetes seen in patients who used a diuretic significantly affected morbidity and mortality. Hence, although the ALLHAT results plausibly indicate that diuretics are useful in treating older black patients with hypertension and heart disease, there is insufficient evidence that diuretics are superior to other drugs.

One may wonder why the trials with morbidity and mortality outcomes did not reflect the differential blood pressure–lowering efficacy of drugs. One reason might be the different designs of these trials. Blood pressure trials assessed the effect of single drugs, while end-point reduction trials started with 1 type of drug in each treatment arm and added other drugs to achieve the blood pressure goal; this approach attenuates possible differences in blood pressure–lowering efficacy. Still, treatment arms based on ACE inhibitors and α -blockers (drugs with a marginal or nonsignificant placebo-corrected effect on the DBP goal) were associated with a greater relative risk for hard end points in the secondary outcomes than were diuretics, although the actual blood pressure in patients receiving doxazosin was not provided.

This review has several limitations. We assessed blood pressure–lowering efficacy of monotherapy only, mostly in participants without significant end organ damage. Furthermore, morbidity and mortality outcomes primarily concern specific subgroups of hypertensive patients who have or are at greater risk for concomitant cardiovascular and renal disease. We did not find indications of preferential publication of manuscripts with a certain direction or strength of study findings (68). RevMan funnel plots for diuretics showed no signs of asymmetry. Finally, although this review was based on the notion that the response of black patients to drug therapy differs from the response of other patient groups, we focused on which drug type improves outcomes in hypertensive black patients rather than assessing differences with other population groups.

A recent review on ethnic differences in blood pressure–lowering efficacy of drugs took this approach by using a MEDLINE search (69). The paper did not discuss 29 of

the 30 trials included in this review; among these were 14 trials in black patients only and 2 trials not indexed in MEDLINE. However, the author did conclude that despite overlap in responses, diuretics and calcium-channel blockers resulted in larger blood pressure decrements in black than in white patients, while ACE inhibitors and β -blockers had a smaller effect.

In conclusion, we found that commonly used antihypertensive drugs differ in their efficacy for lowering blood pressure in black patients. In particular, the efficacy of β -blockers for reducing SBP and the efficacy of ACE inhibitors for reaching the DBP goal were not significantly different from that of placebo. β -Blockers might even increase SBP (29, 34, 62, 63). Therefore, when β -blockers do not effectively reduce blood pressure, clinicians should consider discontinuing therapy with this drug rather than increasing the drug dose or adding a second drug (8). Calcium-channel blockers were the only drug type that effectively lowered blood pressure across all subgroups of black patients. However, there is no solid evidence that morbidity and mortality outcomes depend on the drug chosen for initial therapy when the addition of other drugs achieves the blood pressure goal.

Future trials should enroll enough black participants to perform primary analyses based on ethnicity and should report details on blood pressure reduction, adverse effects, and dropouts for this group. More research is needed to clarify the potential benefit of extended dose titration on the percentage of black patients achieving blood pressure goals. The research agenda should include trial designs that stratify patients by baseline severity of hypertension in order to assess blood pressure-lowering efficacy of drug regimens in different strata and to detect possible differences in pressor responses with the use of β -blockers.

Finally, future research should determine whether ACE inhibitors, α -blockers, and angiotensin-receptor blockers are indeed less effective than other drugs in reducing cardiovascular events such as stroke in black patients and whether the use of diuretics and β -blockers in younger black patients with uncomplicated hypertension leads to greater morbidity and mortality because of newly developed or worsening diabetes mellitus.

Until these issues are further clarified, drugs that ensure tight blood pressure control and have the lowest possible risk for side effects should be used in black patients with primary hypertension. For many black patients, calcium antagonists might seem appropriate for first-line treatment. For patients who cannot afford this drug (5), diuretics seem the best alternative.

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Note: Some analyses included in this paper are reported in a Cochrane Collaboration systematic review, which is to be published in the Coch-

rane Library. Cochrane Collaboration reviews are updated regularly to take account of new data from randomized, controlled trials.

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