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Effective Health Care

Bulletin on the effectiveness of health service interventions for decision makers

This bulletin summarises the research evidence on the effects of antihypertensive drugs on blood pressure reduction and morbidity and mortality outcomes in black people.

Effectiveness of antihypertensive drugs in black people

- Black people of African or Afro-Caribbean origin have higher blood pressure levels and a higher prevalence of hypertension compared to the general UK population. This is associated with higher rates of stroke morbidity and mortality.
- There is insufficient evidence to conclude that any antihypertensive drug or drug combination is superior in reducing morbidity and mortality outcomes in hypertensive black people.
- The commonly used antihypertensive drugs differ in their efficacy to lower blood pressure levels in black people. In particular, the blood pressure lowering effects of ACE inhibitors for diastolic and beta-blockers for systolic blood pressure were not significantly different from placebo. Beta-blockers might even increase systolic blood pressure.
- Less than a quarter of the black participants in randomised controlled trials (RCTs) reduced blood pressure to predefined levels with limited or no dose titration. Higher doses might increase the efficacy of drugs, with the possible exception of beta-blockers.
- The stepped approach advocated by the British Hypertension Society, involving first-line therapy with either a calcium channel blocker or a thiazide-type diuretic appears justified.
- Future trials should enrol enough black participants to perform primary analyses based on ethnicity, and should report details on systolic and diastolic blood pressure reduction, goal blood pressures, adverse effects and dropouts.

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CENTRE FOR REVIEWS AND DISSEMINATION

A. Introduction

Hypertension is particularly common in black people. In this bulletin, the term 'black people' refers to black people of sub-Saharan African ancestral origin.[1]

A recent review of UK-based surveys found that black people of African or Afro-Caribbean origin had higher blood pressure levels and a higher prevalence of hypertension compared to the general white population.[2] In the UK, this is associated with higher rates of stroke morbidity and mortality.[3]

Premature death from stroke for people of West African origin is nearly three times higher for men and 81% higher for women than in the general population. For people of Afro-Caribbean origin it is 68% higher for men and 57% higher for women.[3] However, premature death from coronary heart disease (CHD) for people of Afro-Caribbean or West African origin is much lower than average at around half the rate found in the general population for men and two-thirds of the rate found in women.

The higher prevalence of hypertension among black populations compared to the general white population has led some to suggest that there may be a genetic explanation for the difference.[4] However, the extent to which genetics plays a role is as yet undetermined.

Antihypertensive drugs work in different ways to lower blood pressure. Some drugs lower blood pressure by removing extra fluid and salt from the body (e.g. diuretics) Others lower blood pressure by slowing down the heartbeat (e.g. beta-blockers), or by relaxing, widening or preventing the narrowing of blood vessels (e.g. angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers).

There is some evidence suggesting that the rates of detection, treatment and control may be higher among black populations in the UK than the general population.[2] Higher rates of use of antihypertensive drugs among black people may indicate awareness on the part of health professionals about the prevalence of hypertension and associated risk of stroke in this population group.

There is currently no consensus on the optimum drug treatment strategy for hypertension in black people.[5-10] This lack of consensus is reflected in current guidelines, which contain either no specific treatment strategies for black people,[7,9] strategies without a specific drug of choice for first-line treatment,[5] or the advice to use a specific drug,[6,8] or choice of drugs,[10] as a first-line therapy. In addition, none of the guideline recommendations are informed by all of the available evidence relating to this population subgroup.

This issue of *Effective Health Care* summarises the available research evidence on the effects of commonly used antihypertensive drugs on blood pressure reduction and morbidity and mortality outcomes in black people.

B. Nature of the evidence

This bulletin is based on a systematic review of randomised controlled trials (RCTs) carried out by researchers based at the Department of Internal Medicine, Academic Medical Center, Amsterdam and at the Centre for Reviews and Dissemination.[11] The review will be made available on the Cochrane Library.[12,13] Further details of review methods are available in the Appendix.

This bulletin focuses on the question of which drug type is effective in improving outcomes in hypertensive black people, rather than whether their response is different from other population subgroups. The latter question was addressed in a recent review on ethnic differences in the blood pressure-lowering efficacy of drugs.[14] Twenty-nine of the 30 RCTs reviewed in this bulletin were not assessed in the Sehgal review, including 14 trials that involved black participants only.

C. Trials with morbidity and mortality outcomes

The most important outcome with regard to treatment of black people with hypertension is the reduction of mortality and morbidity. Four RCTs with morbidity and mortality outcomes in black people were included.[15-28] All the RCTs were of at least one year in duration and provided separate morbidity and/or mortality data in black adults. The four RCTs compared a single drug treatment with concurrent placebo treatment or other single or combination drug treatments. In each study, if blood pressure goals were not achieved and/or the study drug was contraindicated, secondary drug(s) could be added.

Differences between the RCTs in patient characteristics, interventions and outcome measures meant that meta-analysis (a statistical method used to combine the results of independent studies) was not undertaken. The main findings from each of the studies are described below.

The Systolic Hypertension in the Elderly Program study (SHEP)[15-17]

SHEP included 4736 men and women aged 60 years and older with systolic blood pressures (SBP) of 160 mmHg or above and

diastolic blood pressures (DBP) of under 90 mmHg. Of the 657 (14%) trial participants that were black, 217 were men and 440 were women.

SHEP studied the efficacy of chlorthalidone (a thiazide-type diuretic) versus placebo in reducing stroke occurrence. Secondary outcome measures included myocardial infarction, fatal coronary heart disease (CHD) and cardiovascular mortality. Patients were randomly assigned to receive either a placebo or a low-dose of chlorthalidone and, if needed, a secondary drug. The secondary drug was a low-dose of atenolol (a beta-blocker) or where atenolol was contraindicated, reserpine (an adrenergic antagonist) was used. Participants were followed for an average of 4.5 years.

Data from the study indicated that treatment with chlorthalidone reduced stroke in black women (RR=0.36; 95% CI: 0.16;0.83), but not in black men (RR 0.98; 95% CI: 0.39;2.44) Chlorthalidone was also found to reduce cardiovascular events (hazard ratio for all cardiovascular events 0.50 95% CI: 0.32;0.78, unpublished results, SHEP trial investigators). Blood pressure levels were not reported for black participants.

The Losartan Intervention For Endpoint reduction in hypertension study (LIFE)[18-21]

LIFE included 9193 participants aged 55–80 years with essential hypertension (sitting blood pressure 160–200/95–115 mm Hg) and left ventricular hypertrophy. Participants were randomly assigned to either losartan (an angiotensin II receptor blocker) or atenolol (a beta-blocker) for at least four years and until 1040 patients had a primary cardiovascular event (death, heart attack, or stroke). Of the 533 (6%) trial participants who were black, 270 were assigned to losartan and 263 to atenolol.

Analysis of treatment effect by prespecified baseline characteristics showed a significant interaction for ethnicity (p=0.005), indicating that the effect of losartan vs atenolol differed between black and non-black patients.[21] In contrast to the results calculated for the total group which favoured losartan (RR 0.86; 95% CI: 0.77;0.96), there was a trend towards a greater risk with losartan in black people (RR 1.55; 95% CI: 1.00;2.38) obtained by using Revman software. The investigators reported that blood pressure was similar in both treatment groups.[21]

The African-American Study of Kidney disease and hypertension (AASK)[22-24]

All of the 1094 participants in AASK were black men and women aged 18–70 years with hypertension, a glomerular filtration rate (GFR) of 20–65 mL/min and no other identified causes of renal insufficiency. GFR is a measure of the kidneys' ability to filter and remove waste products. The study compared the effects of ramipril (an ACE inhibitor), amlodipine (a calcium channel blocker) and metoprolol (a beta-blocker) on the progression of kidney disease. The primary outcome was the rate of change in renal function as measured by GFR (the GFR slope). The main secondary composite outcome included reduction in GFR by 50% or more, end-stage renal disease and death. The other secondary outcome was proteinuria.

In September 2000, the amlodipine group was halted on the advice of a data and safety monitoring board based on mainly post-hoc defined stopping criteria regarding the secondary outcomes.[23,24] Interim analyses had shown a slower rate of deterioration of renal function in the ramipril and metoprolol groups relative to the amlodipine group.[23]

Data from the study indicated that no significant differences were reported in the primary outcome for the three drug comparisons.[23,24] For the secondary composite outcome, ramipril reduced the risk of experiencing a 50% (or more) GFR decline, end-stage renal disease and or death by 22% (95% CI: 1%;38%; p=0.04) when compared to metoprolol, and by 38% (95% CI: 14%;56%; p=0.004) when compared to amlodipine.

The Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT)[25-28]

The ALLHAT study included 42,418 participants aged over 55 years with at least one other risk factor for coronary heart disease. Of these, 15094 (35%) were black participants. The study compared the effects of chlorthalidone (a thiazide-type diuretic), amlodipine (a calcium channel blocker), lisinopril (an ACE inhibitor) and doxazosin (an alpha-blocker) on morbidity and mortality from coronary heart disease. The primary outcome measure was combined non-fatal myocardial infarction or fatal CHD. Major secondary outcomes included: all-cause mortality, stroke, combined CHD and combined cardiovascular disease (CVD) and other secondary outcomes included heart failure. Black patients were younger, had higher DBP levels, higher mean fasting serum glucose levels and greater incidence of diabetes mellitus at baseline.[26] The doxazosin group was halted in March 2000 after an interim analysis showed that participants on the drug had 25% more CVD events and were twice as likely to be hospitalized for heart failure compared to participants in the chlorthalidone group.

The ALLHAT study group reported no significant difference in the primary outcome of non-fatal myocardial infarction or fatal CHD between chlorthalidone, amlodipine and lisinopril in black participants. For the major

Table 1 Characteristics of included studies with blood pressure outcomes

Study, Year (Reference)	Black Patients Randomly Assigned, n	Country/ Region	Age, y	BP, mm Hg	Total Daily Dose of Drug Intervention, mg	Treatment Duration	Outcome Measure: BP	Analysis of Results	Adverse Effects	Jadad Score					
										Randomization	Method of Randomization	Double-Blind	Method of Blinding	Drop outs	Total
ABC trial, 2000[29]	304	USA	Mean, 52	DBP, 91–105	Candesartan cilexetil, 16–32	8 wk	Continuous/ Dichotomous	ITT	Reported	1		1	1	1	4
Conlin et al., 2003[30]	18†	USA	Mean, 52	DBP, 90–109	Losartan, 50†§	4 wk	Continuous	ITT	ND	1	–	1	1	1	4
Dean et al., 1971[31]	60	Africa	Adults	DBP, 100–116	Hydrochlorothiazide, 50, vs. mefruside, 25	2 wk	Continuous	Per protocol	ND	1	–	1	1	–	3
Drayer et al., 1983[32]	58†	USA	Mean, 53	DBP, 95–115	Captopril, 200§	8 wk	Dichotomous	Per protocol	ND	1	–	1	–	1	3
Fadayomi et al., 1986[33]	32	Africa	Mean, 48	DBP > 100	Nifedipine, 40	6 wk	Continuous/ Dichotomous	Per protocol	Reported	1	–	1	1	–	3
Fiddes et al., 1994[34]	46	USA	≥55	DBP, 95–114	Diltiazem extended-release, 240–480	8 wk	Continuous	ITT	ND	1	–	1	–	–	2
Flack et al., 2001[35]	381	USA	Mean, 50	DBP, 95–109	Losartan, 50–150§	12 wk	Continuous/ Dichotomous	ITT	Reported	1	–	1	–	1	3
Flack et al., 2003[36]	233†	USA/Africa	Mean, 52	DBP, 95–109	Losartan, 50–100§	16 wk	Continuous	ITT	ND	1	–	1	1	–	3
Frishman et al., 1995[37]	62†	USA	≥21	DBP, 95–115	Hydrochlorothiazide, 25, vs. bisoprolol, 5§	4 wk	Continuous/ Dichotomous	ITT	ND	1	–	1	–	–	2
Humphreys et al., 1968[38]	18	Caribbean	46–63	DBP, 100–155	Propranolol, 20–360†	2 mo	Continuous/ Dichotomous	ITT	Reported	1	–	1	1	1	4
Materson et al., 1993, 1995[39,62]	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	8 wk/1 y_	Continuous/ Dichotomous	ITT	ND	1	–	1	–	1	3
Moser et al., 1982[40]	20	Caribbean	32–60	DBP, 101–119	Captopril, up to 450	4 wk	Continuous/ Dichotomous	Per protocol	Reported	1	–	1	–	–	2
Moser et al., 1984[41]	77	USA	26–70	DBP, 90–114	Nitrendipine, 10–40	5 wk	Continuous/ Dichotomous	Per protocol	ND	1	–	1	1	–	3
Opie et al., 1997[42]	31†	Africa	18–75	DBP, 95–114	Nisoldipine coat-core, 30§	6 wk	Continuous	ITT	ND	1	–	1	1	–	3
Salako et al., 1979[43]	20	Africa	37–60	DBP, 95–120	Alprenolol sustained-release, 400†	8 wk	Continuous	Per protocol	Reported	1	–	1	1	1	4
Seedat, 1980[44]	24	USA	Adults	DBP, 100–115	Chlorthalidone, 100, vs. atenolol, 25†	4 wk	Continuous	ITT	Reported	1	–	1	–	1	3
Seedat, 1980[45]	9	USA	Mean, 44	DBP≥ 110	Mefruside, 12.5–25, vs. debrisoquine, 10–20†	4 wk	Continuous/ Dichotomous	ITT	ND	1	1	1	–	1	4
Stein et al., 1992[46]	25	Africa	<70	DPB, 96–114	Hydrochlorothiazide, 50†§	6 wk	Continuous/ Dichotomous	Per protocol	ND	1	–	1	–	1	3
TAIM, 1991[47,48]	98†	USA	Mean, 46	DBP 90–100	Chlorthalidone, 25, vs. atenolol, 50¶	6 mo	Continuous	ITT	ND	1	1	1	1	–	4
TOMHS, 1993, 1997[49,50]	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** Hydrochlorothiazide, 12.5–50,	1 y	Continuous	Per protocol	Reported for women only	1	–	1	1	–	3
TROPHY, 1997[51]	68 obese patients	USA	21–75	DBP, 90–109	vs. lisinopril, 10–40 Penbutolol, 40–80†	12 wk	Continuous	Per protocol	ND	1	–	1	1	–	3
Venter et al., 1990[52]	50	Africa	25–65	DBP, 95–115	Xipamide, 20§	12 wk	Continuous/ Dichotomous	Per protocol	Reported	1	–	1	1	1	4
Venter et al., 1991[53]	15†	Africa	25–65	DBP, 95–115	Enalapril, 5–40,	12 wk	Continuous	Per protocol	Reported	1	–	–	–	1	2
Venter et al., 1991[54]	29	Africa	21–65	DBP, 95–115	vs. prazosin, 2–20 Isradipine, 10–20,§	10 wk	Continuous/ Dichotomous	Per protocol	Reported	1	–	1	1	1	4
Weir et al., 1998[55]	56 salt-sensitive patients†	USA	Mean, 52	DBP, 95–115	vs. enalapril, 10–40§†† Trandolapril, 16§	4 wk	Continuous	Per protocol	ND	1	1	1	1	–	4
Weir et al., 1998[56]	96†	USA	Mean, 54	DBP, 95–114		6 wk	Continuous	ITT	Reported	1	–	1	–	1	3

N=number of black patients randomized; DBP= diastolic blood pressure; SBP=systolic blood pressure; Mg=milligram; Jadad score: RA=randomization, MR=method of randomization, DB=double blind, MB=method of blinding, DO=dropouts; †=Black patients evaluated in this review; ‡=Crossover trial; §=Highest dose of parallel arms included; _=blood pressure as continuous/dichotomous outcome; ¶=other drugs were added in 12.5% of participants; **=Second drug added in 9.2% of participants, plus lifestyle interventions; ††=Plus a high- or low-salt diet, ITT = intention to treat; ND = no data reported.

Table 2 Blood pressure reduction among patients with differing baseline blood pressure*

	Total Group		Baseline DBP, 90–99 mm Hg		Baseline DBP, 100–109 mm Hg		Baseline DBP ≥ 110 mm Hg	
Drug Type	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)
Alpha-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
Beta-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; SBP=systolic blood pressure; †=Weighted mean difference; ‡=Heterogeneity in the effect size; §=For DBP goal, values are the relative risk and a value >1.0 indicates a beneficial effect, ND = no data reported.

secondary outcomes, there were no significant differences between amlodipine and chlorthalidone. Comparisons between lisinopril and chlorthalidone favoured the diuretic for stroke (RR: 1.40; 95% CI: 1.17;1.68) combined CHD (RR: 1.15; 95% CI: 1.02;1.30) and combined CVD (RR: 1.19; 95% CI: 1.09;1.30) There was also a significant difference in favour of chlorthalidone when compared to doxazosin for combined CVD (RR: 1.40; 95% CI: 1.25;1.57). For the secondary outcome of heart failure, chlorthalidone was favoured over amlodipine (RR: 1.47; 95% CI: 1.24;1.74), lisinopril (RR: 1.32; 95% CI: 1.11;1.58), and doxazosin (RR: 2.18; 95% CI: 1.73;2.74). Adjusting for the higher follow up blood pressure levels reported for lisinopril compared to chlorthalidone did not alter the outcomes.

The incidence of type 2 diabetes at four years (for non-diabetics at baseline) was 11.6% for chlorthalidone, 9.8% for amlodipine and 8.1% for lisinopril. No separate results were reported for black people.

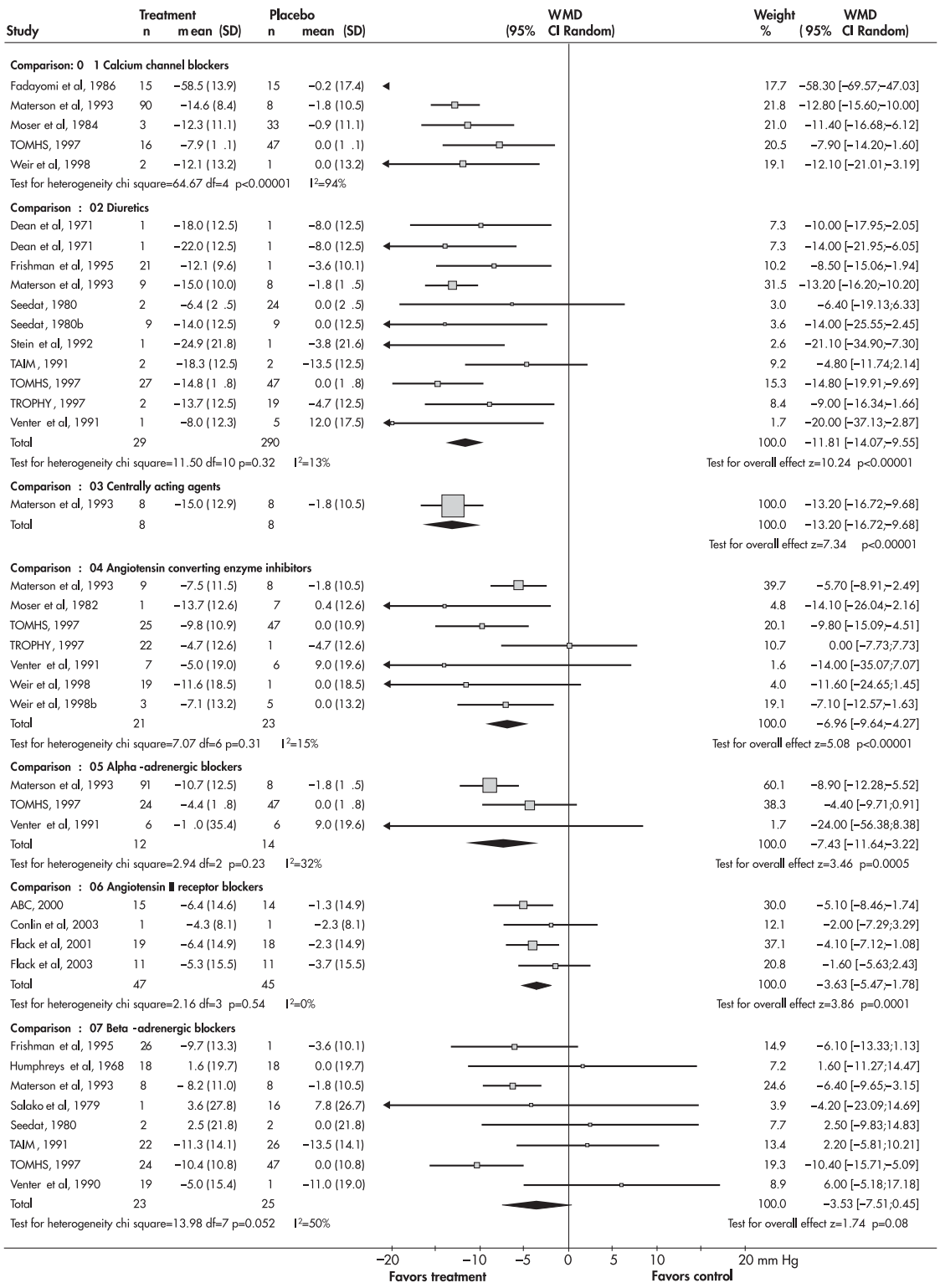
D. RCTs with blood pressure outcomes

Twenty-six RCTs that assessed the blood pressure lowering efficacy of antihypertensive drugs were included (see Table 1).[29-56] All the RCTs were of at least two weeks in duration, had compared single drugs against placebo treatment and provided data in black adults on the effects on systemic arterial blood pressure.

Most trials included participants with uncomplicated primary hypertension without clinically significant end organ damage. Pre-treatment DBP levels varied from 90 mm Hg to more than 150 mm Hg (see Table 2). Of the eight classes of drugs studied, diuretics were the most frequently assessed (11 RCTs). Blood pressure outcomes were expressed in mmHg or as the percentage of participants reaching goal blood pressure.

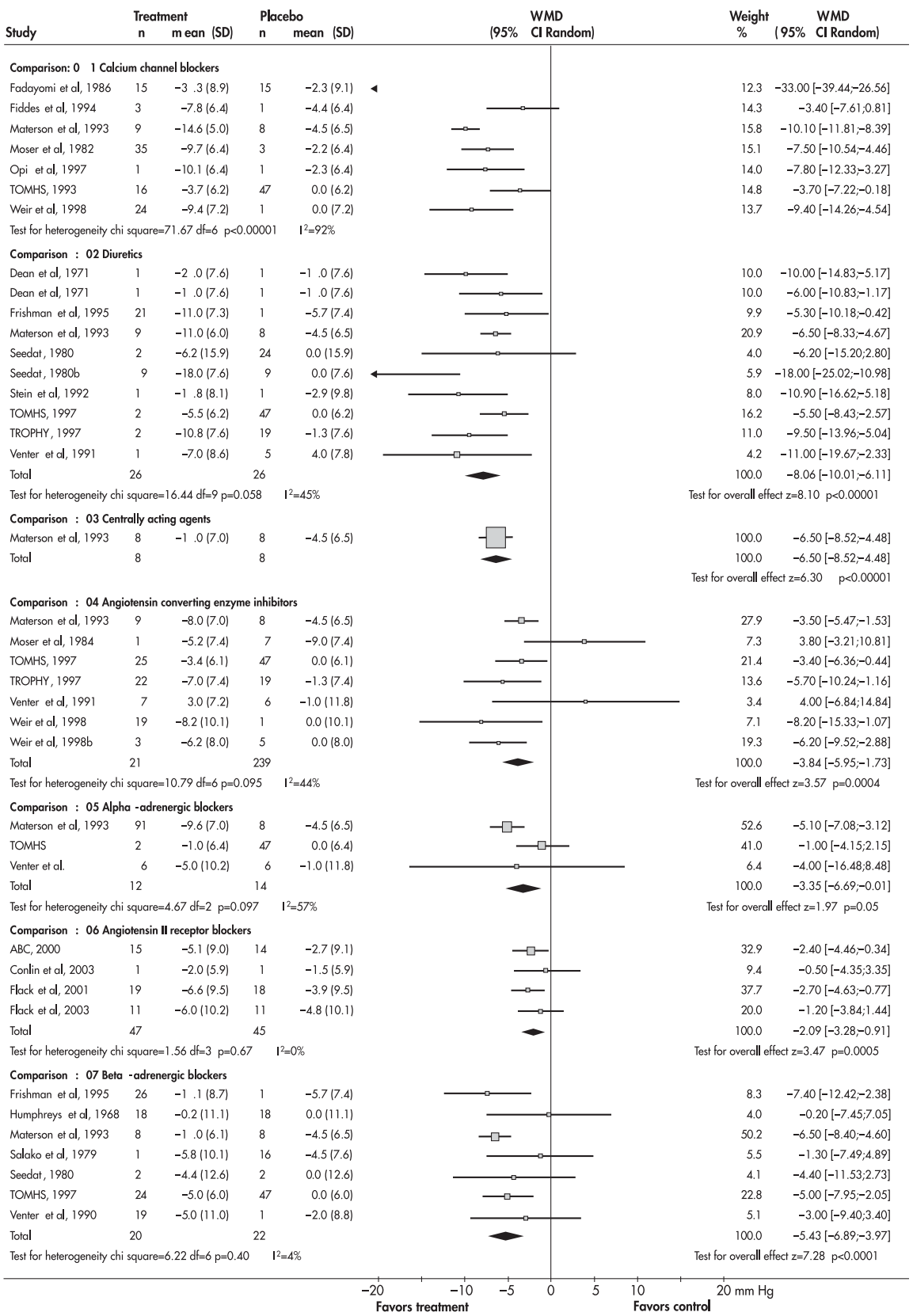
With the exception of beta-blockers for SBP, all the reviewed antihypertensive drugs were more effective than placebo in reducing SBP and DBP. Figure 1 shows the SBP-lowering effects of different antihypertensive drugs. Figure 2 shows the DBP-lowering effects of different antihypertensive drugs.

The percentage of all participants reaching goal DBP (as defined by



Random=random effects model. Grey squares are weighted mean differences (WMD) in reduction of systolic or diastolic blood pressure (mm Hg), with horizontal lines representing 95% confidence intervals (CI) and the size of the squares representing study weight. Results for Materson[39] and Weir[55] are weighted means of older and younger people and high and low salt diet respectively. Black diamonds are pooled estimates. Results for calcium blockers are not pooled because of heterogeneity in the size of the effect.

Fig.1 Systolic blood pressure lowering effects of different antihypertensive drugs.



Random=random effects model. Grey squares are weighted mean differences (WMD) in reduction of systolic or diastolic blood pressure (mm Hg), with horizontal lines representing 95% confidence intervals (CI) and the size of the squares representing study weight. Results for Materson[39] and Weir[55] are weighted means of older and younger people and high and low salt diet respectively. Black diamonds are pooled estimates. Results for calcium blockers are not pooled because of heterogeneity in the size of the effect.

Fig.2 Diastolic blood pressure lowering effects of different antihypertensive drugs

each trial) was 23%. The percentage of all participants reaching goal DBP for each drug type was 46% for calcium channel blockers, 31% for diuretics, 23% for centrally acting agents, 19% for beta-blockers, 19% for angiotensin II receptor blockers, 13% for alpha-blockers, 10% for ACE inhibitors and 0% for postganglionic sympathetic neuron blockers. Blood pressure reduction from differing baseline blood pressure levels is shown in Table 2.

In the seven studies that assessed calcium channel blockers,[33,34,39,41,42,50,55] there were significant differences in the size of the reported effects (statistical heterogeneity) for both SBP and DBP (see Figures 1 and 2). The source of the heterogeneity was the large reduction in blood pressure observed in the Fadayomi study[33] which included people with high SBP/DBP of up to 210/130 mmHg. Additionally, the TOMHS study[50] included people with much lower DBP (up to 99 mmHg). Participants in other studies had comparable blood pressure levels. After reanalysing the remaining trials without the Fadayomi study (and TOMHS study for DBP), heterogeneity was no longer present, resulting in a revised blood pressure lowering effect of calcium channel blockers for SBP (WMD: −12.46; 95% CI: −14.85;−10.08) and DBP (WMD: −7.93; 95% CI: −10.27;−5.59). In addition, after a similar reanalysis of blood pressure reduction from differing baseline blood pressure levels (see Table 2), calcium channel blockers were found to reduce BP from all differing baseline blood pressure levels. Goal DBP was reached in 42% of the patients with the Fadayomi trial omitted.

In a separate analysis of North American/Caribbean studies (see Table 1), it could not be assessed whether true differences existed in the response of African black people versus American and Caribbean black people.

Adverse effects occurred more frequently with drugs than placebo. Reported adverse effects were headache,[29,33,35,42] back pain,[29] upper respiratory infections,[29,35] sinusitis,[29,35] polyuria, nocturia,[33] dizziness,[35] tinnitus,[42] bronchospasms with the use of beta-blockers,[43] tachycardia with prazosin,[54] cough and transitory leucopenia with ACE inhibitors,[32,54] and hypokalaemia and hyperuricaemia with diuretics.[31,44] Studies did not report greater occurrence of adverse effects with higher drug dose.

E. Implications

- In this bulletin only the blood pressure lowering efficacy of monotherapy has been assessed, mostly in participants without significant end-organ damage. The blood pressure lowering efficacy of combination therapy was not evaluated.
- There is insufficient evidence to conclude that any antihypertensive drug or drug combination is superior in reducing morbidity and mortality outcomes in hypertensive black people.
- In four studies assessing antihypertensive drug effects on morbidity and mortality, none reported any significant differences between drugs in the primary outcomes. Study results for secondary outcomes indicated higher rates of diabetes with diuretics and an increased risk of cardiovascular events such as stroke with ACE inhibitors, alpha-blockers and angiotensin receptor blockers.
- The commonly used antihypertensive drugs differ in their efficacy to lower blood pressure levels in black people. In particular, the blood pressure lowering effects of ACE inhibitors for DBP and beta-blockers for SBP was not significantly different from placebo. Beta-blockers might even increase SBP.
- Less than a quarter of the black participants in RCTs reached goal blood pressure with limited or no dose titration. Higher doses might increase efficacy of drugs, with the possible exception of beta-blockers.
- Regarding blood pressure lowering efficacy, the stepped approach advocated by the British Hypertension Society, involving first-line therapy with either a calcium channel blocker or a diuretic, appears justified.
- Future trials should enrol a sufficient number of black participants to perform primary analyses based on ethnicity, with stratification for baseline risk and extended dose titration incorporated in the study design. Reports on black people should include details on systolic and diastolic blood pressure reduction, goal blood pressures, adverse effects and dropouts.

F. Appendix on Methods

Literature searches were undertaken to identify all RCTs, published or otherwise, that considered the effect of different classes of antihypertensive drugs in hypertensive black adults. To identify relevant RCTs, the following databases were searched Medline; Embase; Literatura Latino-Americana y del Caribe en Ciencias de la Salud (LILACS), African Index Medicus (AIM) and the Cochrane Library till November 2003; and Pubmed September 2003–March 2004. The Database of Abstracts of Reviews of Effects; Best Evidence (UK),

Reviews in Progress (UK) were searched and a hand search of Index Medicus back from 1953 was undertaken.

Additional RCTs were identified from references from textbooks, narrative and systematic reviews; through contacting experts and pharmaceutical companies and by searching the internet. Searches were conducted without language restriction. Detailed search and retrieval strategies are published elsewhere.[12,13]

To assess blood pressure lowering efficacy of drugs, randomized, placebo-controlled trials of at least two weeks duration that considered single drugs against concurrent placebo treatment and provided quantitative data in black adults on effects on systemic arterial blood pressure (as a continuous or dichotomous measure) were included. Whether increase in drug dose was needed for adequate blood pressure control was also assessed

To assess drug effects on morbidity and mortality, randomized controlled trials of at least one year duration were included, that used single drug treatment or compare single drug-based combinations of antihypertensive drugs against other combinations or against concurrent placebo treatment and provided separate quantitative morbidity and/or mortality data in black adults. Only trials reporting the number of black patients treated were included (per protocol or intention to treat analysis). Retrospective pooled analyses of several trials were excluded.

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

A Jadad score ranging from 0–5 points was assigned to the included trials, based on whether the study was described as randomised and double blind, reported the methods of randomisation and blinding of intervention and described dropouts with reason.[57] The score was calculated based on separate description of dropouts for black people. Other quality aspects addressed were whether the minimum drug dose to reach a maximum antihypertensive effect was assessed, [58] whether outcome assessment was blinded and whether papers reported adverse effects.

Statistical analysis was performed using Cochrane Review Manager (RevMan) software, version 4.2. When not provided, standard deviations (SD) were imputed per drug type, using the available SDs for each class of drug.[59] Quantitative analysis of outcomes was based on intention to treat results (primary) and per protocol analysis (secondary). The measure of effect for each study was difference in means for systemic arterial blood pressure as a continuous measure and relative risk for dichotomous data. When only drug-placebo differences were provided, we entered data in RevMan as drug results with a 'nil' for placebo results. When available, we included data from the first part of crossover studies.

Studies were assessed for clinical heterogeneity in patient characteristics, interventions, and outcomes, before applying approximate chi square tests for statistical heterogeneity. I^2 statistics were used to quantify the proportion of total variation in the estimates of treatment effect that was due to heterogeneity.[60] When statistical heterogeneity was found across studies, we explored the sources of the heterogeneity and decided if we should aggregate the studies. If so, the random effects model was used.

Sensitivity analysis was performed by reanalysing data using fixed and random effects models and by reanalysing data excluding studies with imputed standard deviations, crossover studies and studies using per protocol analysis.

The following subgroup analyses were predefined:[12] patients with differential severity of hypertension prior to treatment allocation;[61] studies conducted in Africa versus American and Caribbean studies (since an admixture of white European ancestry of up to 25% has occurred in the black population in the Americas,[4] possible genetic influences on drug responses might be stronger in African patients); and outcomes based on gender.

References

1. Myers HF, McClure H. Psychosocial factors in hypertension in blacks: the case for an interactional perspective. In: Fray JCS, Douglas JG, editors. *Pathophysiology of hypertension in blacks*. Oxford: Oxford University Press, 1993:90-106.

2. Agyemang C, Bhopal R. Is the blood pressure of people from African origin adults in the UK higher or lower than that in European origin white people? A review of cross-sectional data. *J Hum Hypertens* 2003;17:523-34.

3. British Heart Foundation. *British Heart Foundation Statistics Database*. British Heart Foundation; 2004. [cited 27 April 2004]. Available from: http://www.heartstats.org

4. Cooper R, Rotimi C. Hypertension in populations of West-African origin: is there a genetic predisposition? *J Hypertens* 1994;12:215-27.

5. Douglas JG, Bakris GL, Epstein M, et al. Management of high blood pressure in African Americans: Consensus Statement of the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. *Arch Intern Med* 2003;163:525-41.

6. Lemogoum D, Seedat YK, Mabadeje AF, et al. Recommendations for prevention,

diagnosis and management of hypertension and cardiovascular risk factors in sub-Saharan Africa. *J Hypertens* 2003;21:1993-2000.

7. World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organisation (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 2003;21:1983-92.

8. Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure*, 2003. Available from: http://www.nhlbi.nih.gov/guidelines/hypertension/jncintro.htm

9. Guidelines Committee ESH-ESoC. 2003 European Society Hypertension - European Society of Cardiology Guidelines for the management of arterial hypertension. *J Hypertens* 2003;21:1011-53.

10. Williams B, Poulter NR, Brown MJ, et al. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens* 2004;18:139-85.

11. Brewster LM, van Montfrans GA, Kleijnen J. A systematic review of antihypertensive drug therapy in black people. *Ann Intern Med* 2004;141:

12. Brewster LM, Kleijnen J, van Montfrans GA. Pharmacotherapy for hypertension in people of sub-Saharan Africa or of sub-Saharan African descent. (Protocol for a Cochrane review). *The Cochrane Library, Issue 3, 2001*. Chichester: John Wiley & Son, 2001.

13. Brewster LM, Kleijnen J, van Montfrans GA. Pharmacotherapy for hypertension in black people. (Cochrane Review). *The Cochrane Library*. Chichester: John Wiley & Son, In press.

14. Sehgal AR. Overlap between whites and blacks in response to antihypertensive drugs. *Hypertension* 2004;43:566-72.

15. The Systolic Hypertension in the Elderly Program (SHEP) Cooperative Research Group. Rationale and design of a randomized clinical trial on prevention of stroke in isolated systolic hypertension. *J Clin Epidemiol* 1988;41:1197-208.

16. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systeolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991;265:3255-64.

17. The Systolic Hypertension in the Elderly Program (SHEP) Cooperative Research Group. Implications of the systolic hypertension in the elderly program. *Hypertension* 1993;21:335-43.

18. Dahlof B, Devereux R, de Faire U, et al. The Losartan Intervention for Endpoint reduction (LIFE) in hypertension study: rationale, design, and methods. *Am J Hypertens* 1997;10:705-13.

19. Okin PM, Devereux RB, Jern S, et al. Baseline characteristics in relation to electrocardiographic left ventricular hypertrophy in hypertensive patients: the Losartan Intervention for Endpoint reduction (LIFE) in hypertension study. *Hypertension* 2000;36:766-73.

20. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;359:995-1003.

21. Julius S, Alderman MH, Beevers G, et al. Cardiovascular risk reduction in hypertensive black patients with left ventricular hypertrophy:the LIFE study. *J Am Coll Cardiol* 2004; 43(6):1047-55.

22. Gassman JJ, Greene T, Wright JT, et al. Design and statistical aspects of the African American Study of Kidney Disease and Hypertension (AASK). *J Am Soc Nephrol* 2003;14:S154-65.

23. Agodoa LY, Appel L, Bakris GL, et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA* 2001;285:2719-28.

24. Wright JTJ, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002;288:2421-31.

25. Davis BR, Cutler JA, Gordon DJ, et al. Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Am J Hypertens* 1996;9:342-60.

26. Grimm RHJ, Margolis KL, Papademetriou VV, et al. Baseline characteristics of participants in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Hypertension* 2001;37:19-27.

27. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2000;283:1967-75.

28. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment ot Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288.

29. Association of Black Cardiologists (ABC) Candersartan Study Group. The Association of Black Cardiologists (ABC) Candersartan Study Group. Evaluation of candesartan cilexetil in black patients with systematic hypertension: the ABC trial. *Heart Dis* 2000;2:392-9.

30. Conlin PR, Erlinger TP, Bohannon A, et al. The DASH diet enhances the blood pressure response to losartan in hypertensive patients. *Am J Hypertens* 2003;16:337-42.

31. Dean G, Louw S, Hersch C, et al. A double-blind trial in hypertension comparing Baycaron (FBA 1500), hydrochlorothiazide and placebo. *S Afr Med J* 1971;45:323.

32. Drayer JI, Weber MA. Monotherapy of essential hypertension with a converting-enzyme inhibitor. *Hypertension* 1983;5:108-13.

33. Fadayomi MO, Akinroye KK, Ajao RO, et al. Monotherapy with nifedipine for essential

hypertension in adult blacks. *J Cardiovasc Pharmacol* 1986;8:466-9.

34. Fiddes R, Heym H, Hilty W, et al. Blood pressure control with diltiazem XR, a novel extended-release formulation of diltiazem HCI, in mature and elderly hypertensive patients. *Clin Ther* 1994;16:209-21.

35. Flack JM, Saunders E, Gradman A, et al. Antihypertensive efficacy and safety of losartan alone and in combination wiht hydrochlorothiazide in adult African Americans with mild to moderate hypertension. *Clin Ther* 2001;23:1193-208.

36. Flack JM, Oparil S, Pratt JH, et al. Efficacy and tolerability of eplerenone and Iosartan in hypertensive black and white patients. *J Am Coll Cardiol* 2003;41:1148-55.

37. Frishman WH, Burris JF, Mroczek WJ, et al. First-line therapy option with low-dose bisoprolol fumarate and low-dose hydrochlorothiazide in patients with stage I and stage II systemic hypertension. *J Clin Pharmacol* 1995;35:182-88.

38. Humphreys GS, Delvin DG. Ineffectiveness of propranolol in hypertensive Jamaicans. *BMJ* 1968;2:601-3.

39. Materson BJ, Reda DJ, Cushman WC, et al. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. *N Engl J Med* 1993;328:914-21.

40. Moser M, Lunn J. Responses to captopril and hydrochlorothiazide in black patients with hypertension. *Clin Pharmacol Ther* 1982;32:307-12.

41. Moser M, Lunn J, Nash DT, et al. Nitrendipine in the treatment of mild to moderate hypertension. *J Cardiovasc Pharm* 1984;6:S1085-9.

42. Opie LH, Muller FO, Myburgh DP, et al. Efficacy and tolerability of nisoldipine coat-core formulation in the treatment of essential hypertension: The South African Multicenter ANCHOR Study. *Am J Hypertens* 1997;10:250-60.

43. Salako LA, Falase AO, Aderounmu AF. Placebo-controlled, double-blind clinical trial of alprenolol in African hypertensive patients. *Curr Med Res Opin* 1979;6:358-63.

44. Seedat YK. Trial of atenolol and chlorthalidone for hypertension in black South Africans. *BMJ* 1980;281:1241-43.

45. Seedat YK. An evaluation of debrisoquine and mefruside in the treatment of hypertension in African and Indian patients. *Curr Med Res Opin* 1980;7:68-72.

46. Stein CM, Neill P, Kusemamuriwo T. Antihypertensive effects of low doses of hydrochlorothiazide in hypertensive black Zimbabweans. *Int J Cardiol* 1992;37:231-5.

47. Davis BR, Blaufox MD, Hawkins CM, et al. Trial of antihypertensive interventions and management. Design, methods, and selected baseline results. *Control Clin Trials* 1989;10:11-30.

48. Wassertheil-Smoller S, Davis BR, Oberman AS, et al. The Taim Study: sex-race differences in effects of diet and drugs on cardiovascular risk. *Cardiovascular Risk Factors* 1991;1:3-11.

49. Neaton JD, Grimm RHJ, Prineas RJ, et al. Treatment of mild hypertension study. Final results. *JAMA* 1993;270:713-24.

50. Grimm RH, Grandits GA, Flack JM. Are black and white hypertensives really different? *ABC digest of Urban Cardiology* 1997:10-6.

51. Reisin E, Weir MR, Falkner B, et al. Lisinopril versus hydrochlorothiazide in obese hypertensive patients: a multicenter placebo-controlled trials. Treatment in Obese Patients with Hypertension (TROPHY) Study Group. *Hypertension* 1997;30:140-5.

52. Venter CP, Joubert PH, Venter HL, et al. Penbutolol in the treatment of mild to moderate essential hypertension in black South Africans. *J Clin Pharmacol* 1990;30:533-7.

53. Venter CP, Muntingh GL, Venter HL, et al. The effect of xipamide on mild-moderate hypertension in black South Africans - results of a clinical trial. *Med Sci Res* 1991;19:217-8.

54. Venter CP, Venter HL, Muntingh GL. Die effekte van enalapril en prasosien op geringe tot matige hipertensie in swart Suid-Afrikaners. Resultate van 'n kliniese proef. *S Afr Med J* 1991:324-6.

55. Weir MR, Chrysant SG, McCarron DA, et al. Influence of race and dietary salt on the antihypertensive efficacy of an angiotensin-converting enzyme inhibitor or a calcium channel antagonist in salt-sensitive hypertensives. *Hypertension* 1998;31:1088-96.

56. Weir MR, Saunders E. Renin status does not predict the anti-hypertensive response to angiotensin converting enzyme inhibition in African-Americans. *J Hum Hypertens* 1998;12:189-94.

57. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.

58. Rose M, McMahon FG. Some problems with antihypertensive drug studies in the context of the new guidelines. *Am J Hypertens* 1990;3:151-5.

59. Altman DG, editor. *Practical statistics for medical research.* 1st ed. London: Chapman & Hall, 1991.

60. Higgins J, Thompson S, Deeks J, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.

61. Schmid CH, Lau J, McInosh MW, et al. An empirical study of the effect of the control rate as a predictor of treatment efficacy in meta-analysis of clinical trials. *Stat Med* 1998;17:1923-42.

62. Materson BJ, Reda DJ, Cushman WC. Department of Veterans Affairs single-drug therapy of hypertension study. Revised figures and new data. *Am J Hypertens* 1995;8:189-92.

Effective Health Care

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