

Clinical Events in High-Risk Hypertensive Patients Randomly Assigned to Calcium Channel Blocker Versus Angiotensin-Converting Enzyme Inhibitor in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

Frans H.H. Leenen, Chuke E. Nwachuku, Henry R. Black, William C. Cushman, Barry R. Davis, Lara M. Simpson, Michael H. Alderman, Steven A. Atlas, Jan N. Basile, Aloysius B. Cuyjet, Richard Dart, James V. Felicetta, Richard H. Grimm, L. Julian Haywood, Syed Z.A. Jafri, Michael A. Proschan, Udho Thadani, Paul K. Whelton, Jackson T. Wright; for the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Collaborative Research Group

Abstract—The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) provides a unique opportunity to compare the long-term relative safety and efficacy of angiotensin-converting enzyme inhibitor and calcium channel blocker–initiated therapy in older hypertensive individuals. Patients were randomized to amlodipine (n=9048) or lisinopril (n=9054). The primary outcome was combined fatal coronary heart disease or nonfatal myocardial infarction, analyzed by intention-to-treat. Secondary outcomes included all-cause mortality, stroke, combined cardiovascular disease (CVD), end-stage renal disease (ESRD), cancer, and gastrointestinal bleeding. Mean follow-up was 4.9 years. Blood pressure control was similar in nonblacks, but not in blacks. No significant differences were found between treatment groups for the primary outcome, all-cause mortality, ESRD, or cancer. Stroke rates were higher on lisinopril in blacks (RR=1.51, 95% CI 1.22 to 1.86) but not in nonblacks (RR=1.07, 95% CI 0.89 to 1.28), and in women (RR=1.45, 95% CI 1.17 to 1.79), but not in men (RR=1.10, 95% CI 0.92 to 1.31). Rates of combined CVD were higher (RR=1.06, 95% CI 1.00 to 1.12) because of higher rates for strokes, peripheral arterial disease, and angina, which were partly offset by lower rates for heart failure (RR=0.87, 95% CI 0.78 to 0.96) on lisinopril compared with amlodipine. Gastrointestinal bleeds and angioedema were higher on lisinopril. Patients with and without baseline coronary heart disease showed similar outcome patterns. We conclude that in hypertensive patients, the risks for coronary events are similar, but for stroke, combined CVD, gastrointestinal bleeding, and angioedema are higher and for heart failure are lower for lisinopril-based compared with amlodipine-based therapy. Some, but not all, of these differences may be explained by less effective blood pressure control in the lisinopril arm. (*Hypertension*. 2006;48:374-384.)

Key Words: antihypertensive therapy ■ hypertension, detection and control ■ calcium channel blockers ■ angiotensin-converting enzyme ■ cardiovascular diseases ■ stroke ■ heart failure

The success in the management of hypertension and prevention of its sequelae is owed, in part, to the many antihypertensive drugs available to physicians and patients. By the early 1990s, all of the classes of antihyper-

tensive drugs were shown effective in lowering blood pressure (BP), but few morbidity and mortality efficacy data were available except for thiazide-type diuretics and β -blockers. Angiotensin-converting enzyme (ACE) inhib-

Received February 20, 2006; first decision March 13, 2006; revision accepted May 31, 2006.

From the University of Ottawa Heart Institute (F.H.H.L.), Ottawa, Ontario, Canada; National Heart, Lung, and Blood Institute (M.A.P., C.E.N.), Bethesda, Md; Rush-Presbyterian-St. Luke's Medical Center (H.R.B.), Chicago, Ill; Memphis Veterans Affairs Medical Center (W.C.C.), Tenn; University of Texas Health Science Center School of Public Health (B.R.D., L.M.S.), Houston; Albert Einstein College of Medicine (M.H.A.), Bronx, NY; Bronx Veterans Affairs Medical Center (S.A.A.), NY; Charleston Veterans Affairs Medical Center (J.N.B.), SC; New Jersey Medical School (A.B.C.), Newark; Marshfield Clinic (R.D.), Marshfield, Wis; Carl T. Hayden Veterans Affairs Medical Center (J.V.F.), Phoenix, Ariz; Berman Center for Outcomes and Clinical Research (R.H.G.), Minneapolis, Minn; Los Angeles County–University of Southern California Medical Center (L.J.H.); Fargo Veterans Affairs Medical Center (S.Z.A.J.), ND; University of Oklahoma Health Sciences Center and Veterans Affairs Medical Center (U.T.), Oklahoma City; Tulane University Health Sciences Center (P.K.W.), New Orleans, La; University Hospitals of Cleveland (J.T.W.), Ohio.

The first 2 authors contributed equally to this work.

A list of the ALLHAT Collaborative Research Group members has been published previously.²

Correspondence to Frans H.H. Leenen, Hypertension Unit, University of Ottawa Heart Institute, H-360, 40 Ruskin St, Ottawa, Ontario K1Y 4W7, Canada. E-mail fleenen@ottawaheart.ca

© 2006 American Heart Association, Inc.

Hypertension is available at <http://www.hypertensionaha.org>

DOI: 10.1161/01.HYP.0000231662.77359.de

itors and calcium channel blockers (CCBs), both widely prescribed,¹ were compared with diuretics in the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT).² The main results of ALLHAT showed that treatment regimens initiated with a diuretic (chlorthalidone), an ACE inhibitor (lisinopril), or a CCB (amlodipine) did not differ in the primary end point of combined fatal coronary heart disease (CHD) and nonfatal myocardial infarction (MI). However, there was a 38% higher risk of heart failure (HF), a component of the cardiovascular disease (CVD) composite end point, among patients assigned to CCB compared with diuretic. For the ACE inhibitor group there was a 10% greater risk of combined CVD events, with a 15% greater risk of stroke (40% in black participants) and 19% greater risk of HF.² Chlorthalidone was also more effective than the α_1 -blocker doxazosin in preventing several major cardiovascular outcomes.³ More effective BP control in the chlorthalidone arm likely contributed to some of the differences in outcomes.^{2,3}

Before and during active clinical follow-up in ALLHAT, reports emerged on beneficial effects of ACE inhibitors, such as improved survival and reduced morbidity in patients with HF, left ventricular dysfunction, or CHD, or those at high risk for CHD.⁴⁻⁶ On the other hand, in the early mid-1990s, several studies reported unfavorable cardiovascular outcomes with CCBs in patients with CHD or with hypertension and diabetes.^{7,8} In addition, concerns were raised regarding the overall safety of chronic use of CCBs, specifically, increased incidence of cancer^{9,10} and gastrointestinal (GI) bleeding.^{11,12}

The protocol of ALLHAT prespecified 3 comparisons: amlodipine, doxazosin, or lisinopril compared with chlorthalidone. The database from ALLHAT also provides a unique opportunity to compare the long-term relative safety and outcomes of ACE inhibitor- and CCB-based regimens in a randomized double-blind clinical trial setting, although this was not a prespecified comparison.

The purpose of this analysis, therefore, is to compare cardiovascular and other outcomes among 18 102 men and

women with high-risk hypertension randomly assigned to the ACE inhibitor lisinopril or the dihydropyridine (DHP) CCB amlodipine. Prespecified subgroups were examined with special emphasis on outcomes in blacks versus nonblacks because of previously reported interactions for several major outcomes with lisinopril.²

Methods

ALLHAT participants were men and women, age ≥ 55 years, with untreated systolic (140 to 180 mm Hg) and/or diastolic (90 to 110 mm Hg) hypertension, or treated hypertension ($\leq 160/100$ mm Hg on 1 to 2 antihypertensive drugs at visit 1) with ≥ 1 additional risk factor for CHD.^{13,14} All of the participants gave written informed consent, and all of the centers obtained institutional review board approval.

The BP goal for all participants was $<140/90$ mm Hg, to be achieved by titrating the dose of assigned study drug (step 1) and adding open-label step 2 (atenolol, clonidine, or reserpine) or step 3 (hydralazine) agents when necessary. Other drugs, including low doses of open-label step 1 drug classes, were permitted along with blinded drugs if clinically indicated. Step 1 drugs were encapsulated and identical in appearance. Dosages were 2.5, 5, and 10 mg per day for amlodipine and 10, 20, and 40 mg per day for lisinopril. After initial monthly titration visits, participants were seen every 3 months in year 1 and every 4 months thereafter. An ECG and blood samples for creatinine, glucose, potassium, and total cholesterol were analyzed centrally at baseline and at annual (potassium) or biennial (ECG, fasting glucose, creatinine, and total cholesterol) visits thereafter.

The primary outcome was a composite of fatal CHD or nonfatal MI.¹³ Four major prespecified secondary outcomes were: (1) all-cause mortality, (2) fatal and nonfatal stroke, (3) combined CHD (primary outcome+coronary revascularization+hospitalized angina), and (4) combined CVD (combined CHD+stroke+nonhospitalized treated angina+HF [fatal, hospitalized, or treated nonhospitalized]+peripheral arterial disease [PAD]). Individual components of the combined outcomes were also examined. Other prespecified secondary outcomes included end-stage renal disease ([ESRD] dialysis, renal transplant, or renal death), cancer, hospitalization for GI bleeding, angioedema, and ECG-left ventricular hypertrophy (LVH). Standardized procedures were used for reporting and validation of study end points.^{13,15} Prespecified subgroups included: (1) men versus women, (2) participants <65 versus ≥ 65 years, (3) black versus nonblack participants, and (4) diabetic versus nondiabetic patients. Post hoc subgroups included gender sub-

TABLE 1. Baseline Characteristics and Average Follow-Up BPs by Race, Gender, and Treatment Group

Variable	Blacks				Nonblacks			
	Men		Women		Men		Women	
	Amlodipine (n=1464)	Lisinopril (n=1464)	Amlodipine (n=1749)	Lisinopril (n=1746)	Amlodipine (n=3304)	Lisinopril (n=3403)	Amlodipine (n=2531)	Lisinopril (n=2441)
Baseline characteristics, n %								
Age, y mean (SD)	66.0 (7.6)	66.2 (7.2)	66.3 (8.2)	66.4 (8.3)	67.0 (7.1)	67.0 (7.4)	67.7 (8.1)	67.4 (8.1)
On antihypertensive medications	1323 (90)	1323 (90)	1610 (92)	1600 (92)	2938 (89)	3032 (89)	2300 (90)	2209 (91)
Type 2 diabetes	549 (38)	504 (34)	754 (43)	755 (43)	1125 (34)	1110 (33)	895 (35)	843 (35)
History of CHD	273 (19)	313 (22)	252 (15)	226 (13)	1129 (34)	1183 (35)	548 (22)	548 (23)
Cigarette smoker	463 (32)	468 (32)	315 (18)	336 (19)	690 (21)	719 (21)	512 (20)	458 (19)
On aspirin	422 (29)	446 (30)	361 (21)	351 (20)	1624 (49)	1668 (49)	861 (34)	793 (32)
Average follow-up BPs, mean \pm SE								
Average systolic BP	139.2 \pm 0.3	141.9 \pm 0.3	140.6 \pm 0.3	144.5 \pm 0.4	137.2 \pm 0.2	137.2 \pm 0.2	137.8 \pm 0.2	139.1 \pm 0.3
Average diastolic BP	80.9 \pm 0.2	82.4 \pm 0.2	79.9 \pm 0.2	82.0 \pm 0.2	77.8 \pm 0.1	78.4 \pm 0.1	77.2 \pm 0.1	78.1 \pm 0.1
Δ lisinopril vs amlodipine, mm Hg (systolic/diastolic)	2.7/1.6		3.9/2.1		0.0/0.5		1.3/0.9	

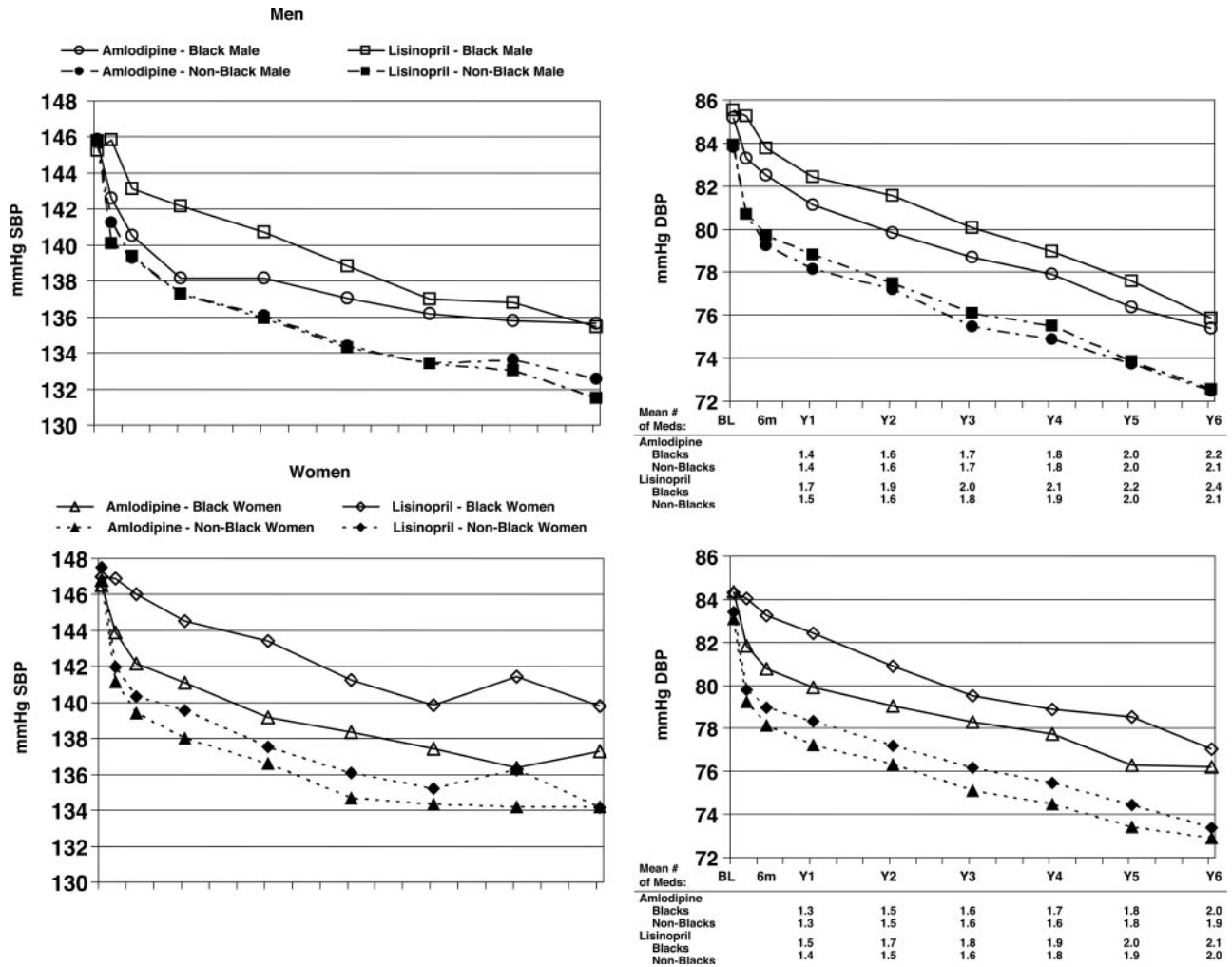


Figure 1. Baseline and follow-up BPs by race and gender.

groups by race and the presence or absence of CHD at baseline. The latter was ascertained at the randomization visit as “known prior MI, angina, primary cardiac arrest, coronary artery stenosis >50%, reversible perfusion defect, or major coronary revascularization procedure.”

Statistical Methods

Data were analyzed according to participants’ randomized treatment assignments (intent-to-treat analysis). Baseline characteristics and intermediate outcomes were compared across the 2 treatment groups using the z test for continuous covariates and contingency table analysis for categorical data. Cumulative event rates were calculated using the Kaplan–Meier method. Hazard ratios (relative risks [RRs]) and 95% confidence intervals (CIs) were obtained from the Cox proportional hazards regression model.¹⁶ The Cox proportional hazards regression model assumption was examined using log–log plots and testing a treatment–time (time-dependent) interaction term; if it was violated, the RR estimate from a 2-by-2 table was used.¹⁶ Heterogeneity of effects in the subgroups was examined by testing for treatment–covariate interaction with the Cox proportional hazards regression model by using $P < 0.05$. In this post hoc comparison of lisinopril versus amlodipine, it is noteworthy that with a CHD event rate combined across arms of $(796 + 798) / (9054 + 9048) = 0.08806$, the power to detect a 20% reduction for one arm relative to another is well over 99% if no multiple comparison adjustment is used, and it is $\approx 99\%$ if the same adjustment that was used for comparisons with chlorthalidone in the main trial analysis² is used for comparisons among active arms, as suggested by Proschan.¹⁷

Results

Detailed baseline characteristics were reported previously.^{2,14} Table 1 shows some of the major baseline characteristics by race and gender. For several characteristics, blacks and nonblacks are clearly different, but none differed significantly between the 2 treatment groups. Mean length of follow-up was 4.9 years for both treatment arms. At trial closeout, 258 (2.8%) of the amlodipine group and 276 (3.0%) of the lisinopril group had unknown vital status. Among these, the distribution of baseline factors was similar for the 2 groups. Of the expected follow-up visits, 84% to 87% were completed by years 4 and 5, 2% to 3% less in the lisinopril compared with the amlodipine arm.²

Intermediate Outcomes

BP

Mean seated BP at randomization was 146/84 mm Hg in both groups. Changes in BP during follow-up by race and gender are shown in Figure 1 and average follow-up BPs in Table 1. During follow-up, BP decreased progressively, but the average follow-up BP remained higher by 1.5/1.1 mm Hg in the lisinopril compared with the amlodipine arm. Among prespecified subgroups, in both male and female nonblacks, the 2 treatments rapidly decreased BP, remaining somewhat higher in the lisino-

pril arm (0.0/0.5 mm Hg in men and 1.3/0.9 mm Hg in women). In contrast, in blacks, the BP decreased less for both treatment arms than in nonblacks and remained higher in the lisinopril arm compared with the amlodipine arm: by 4.3/1.8 mm Hg at year 2 and 2.4/1.1 mm Hg at year 4 in the black women for an average follow-up BP difference of 3.9/2.1 mm Hg and 2.6/1.7 mm Hg at year 2 and 0.8/1.0 mm Hg at year 4 in the black men for an average follow-up BP difference of 2.7/1.6 mm Hg (Figure 1 and Table 1). The 2 treatments showed only minor differences (≤ 1 mm Hg higher in the lisinopril arm) in the 2 age subgroups, in nondiabetics, and in the patients with CHD at baseline. In diabetic subjects, the systolic BP remained higher by 1.4 to 2.0 mm Hg in the lisinopril arm.

In the amlodipine group, 87.6% of participants were taking amlodipine or another CCB at year 1 and 80.4% at year 5.² Persistence on allocated treatment was significantly lower in the lisinopril group (82.4% and 72.6% at years 1 and 5, respectively).² In the subgroups, women and blacks in the lisinopril arm showed the lowest (71% and 70%) persistence on allocated treatment. The diabetic participants showed similar persistence (78% and 77%) for the 2 treatments. The average number of antihypertensive medications (Figure 1, below diastolic BP plots) at years 2 and 4 were 1.5 and 1.7 in the amlodipine arm and 1.7 and 1.9 in the lisinopril arm ($P < 0.001$ lisinopril versus amlodipine).

Blood Glucose, LVH, and Glomerular Filtration Rate

Changes in fasting cholesterol and potassium showed only minor differences between the 2 treatment arms (Table 2). Among individuals classified as normoglycemic at baseline, 11.5% and 13% progressed into the impaired fasting glucose range (6.1 to 6.9 mmol/L), and another 9.4% and 10.4% progressed to new-onset diabetes by year 4, not significantly different by treatment. However, among those with impaired fasting glucose at baseline, during follow-up, more patients on amlodipine versus lisinopril stayed in this range, and more progressed to diabetes.

ECG-LVH at baseline was present in 5% of participants. Over 4 years of follow-up, ECG-LVH tended to decrease with no difference between the 2 treatment arms. Estimated glomerular filtration rate (GFR) decreased over 4 years of follow-up, significantly more so in the lisinopril versus amlodipine arm.

Primary and Secondary Outcomes

For the primary outcome of nonfatal MI and fatal CHD and the secondary outcomes of all-cause mortality and combined CHD, event rates were similar for the 2 treatment arms (Table 3 and Figure 2). The predefined subgroups also showed no significant differences for CHD (Figure 3). For cause-specific mortality (data not shown), rates also did not differ, with 6-year rates per 100 persons for cardiovascular death of 8.5 in both arms and for noncardiovascular death of 8.0 per 100 persons in the amlodipine arm compared with 8.6 per 100 persons in the lisinopril arm.

For 2 major secondary outcomes, stroke and combined CVD, the 2 treatment arms did differ. Stroke rates were significantly higher (RR=1.23; 95% CI, 1.08 to 1.41) in the

lisinopril arm. This treatment effect was consistent across subgroups by age and diabetic status but not by race and gender (Figures 3 and 4). Both male and female blacks showed increased stroke rates on lisinopril compared with amlodipine (Figure 4): +52% in male and +48% in female participants. Female nonblacks also suffered more strokes on lisinopril versus amlodipine (+41%) but not male nonblacks (−10%), and nonblacks showed a significant ($P=0.02$) interaction for treatment and gender (Figure 4). However, the 3-way interaction term included in the full model (treatment–gender–race) is nonsignificant ($P=0.112$). With only the 2-way interaction terms included in the full model, treatment–gender is not significant ($P=0.110$), whereas treatment–race remains significant ($P=0.025$). Combined CVD was modestly higher in the lisinopril arm (RR=1.06; 95% CI, 1.00 to 1.12; $P=0.047$). Across subgroups, no significant interactions were found (Figure 3). Individual components of the combined CVD outcome showed a variable pattern. Both all HF and hospitalized/fatal HF were significantly lower in the lisinopril arm across subgroups (Figure 3). This difference did not emerge until 3 years of follow-up when the rates started to diverge (Figure 2). In contrast, hospitalized angina rates and rates for PAD were marginally ($P < 0.05$) higher in the lisinopril arm. Coronary revascularization rates did not differ. These patterns were consistent across subgroups (data not shown).

Table 4 shows the major outcomes in patients with versus without CHD at baseline. In both subgroups, stroke rates were increased (by 31% [$P=0.05$] and 21% [$P=0.04$]) on lisinopril versus amlodipine. In the subgroup with CHD at baseline, the 2 treatment arms showed no significant differences in rates for the other outcomes. In the subgroup without CHD at baseline, the lisinopril arm showed significantly higher rates for angina and PAD, whereas the amlodipine arm showed higher rates for HF. However, there were no significant interactions between treatment (lisinopril versus amlodipine) and CHD history (yes versus no) for any of these outcomes.

To assess possible differences in the severity of the strokes, MIs and the HF between the 2 treatment arms, case fatality rates were evaluated. Cumulative mortality was high after all 3 events, reaching $\approx 40\%$ after 5 years, but did not differ for the 2 treatment arms (data not shown).

Other Secondary Outcomes

Six-year rates for all cancers were 10.0 ± 0.4 and 9.9 ± 0.4 in the amlodipine and lisinopril treatment groups, not significantly different for the whole group or any of the subgroups. Rates for ESRD were also similar (2.1 ± 0.2 versus 2.0 ± 0.2) with no obvious differences in the subgroups. In contrast, 6-year rates of hospitalization for GI bleeding were significantly higher on lisinopril versus amlodipine (9.6 ± 0.4 versus 8.0 ± 0.4 ; $P=0.004$), consistent across the subgroups (Figure 3). Use of aspirin at baseline did not influence the difference in nonblacks, but in blacks on aspirin, the impact of lisinopril tended ($P=0.187$ for interaction) to be more marked (10.3 versus 6.8% ; $P=0.03$) than in blacks not on aspirin (8.7% versus 7.6% ; $P=0.23$). Angioedema was reported in 38 patients in the lisinopril arm versus 3 in the amlodipine arm

TABLE 2. Fasting Glucose Among Nondiabetics (Baseline Fasting Glucose <6.1 mmol/L*) and Among Those With Baseline Impaired Fasting Glucose (6.1 to 6.9 mmol/L), LVH by ECG, and Estimated GFR at Baseline, 2, and 4 Years of Follow-Up

Variable	Amlodipine	Lisinopril	P Value L vs A
Nondiabetics at baseline			
Fasting glucose, mmol/L			
Baseline, mean (SE)	5.1 (0.01)	5.1 (0.01)	
N	4124	4196	
2 years, mean (SE)	5.5 (0.03)	5.5 (0.03)	0.98
N	1814	1763	
4 years, mean (SE)	5.7 (0.04)	5.7 (0.04)	0.46
N	1571	1474	
Impaired fasting glucose (6.1 to 6.9 mmol/L) if nondiabetic at baseline			
2 years, n (%)	166 (9.2)	136 (7.9)	0.12
4 years, n (%)	204 (13.0)	169 (9.4)	0.16
Diabetes (≥ 7.0 mmol/L) if nondiabetic at baseline			
2 years, n (%)	142 (7.8)	139 (7.9)	0.94
4 years, n (%)	163 (10.4)	139 (9.4)	0.30
Impaired fasting glucose at baseline			
Fasting glucose, mmol/L			
Baseline, mean (SE)	6.5 (0.01)	6.5 (0.01)	
N	666	695	
2 years, mean (SE)	7.3 (0.14)	7.0 (0.12)	0.17
N	308	284	
4 years, mean (SE)	7.6 (0.16)	7.1 (0.14)	0.01
N	270	240	
Impaired fasting glucose (6.1 to 6.9 mmol/L) if impaired fasting glucose at baseline			
2 years, n (%)	69 (22.4)	75 (26.4)	0.49
4 years, n (%)	70 (25.9)	53 (22.1)	0.05
Diabetes (≥ 7.0 mmol/L) if impaired fasting glucose at baseline			
2 years, n (%)	134 (43.5)	111 (39.1)	0.53
4 years, n (%)	127 (47.0)	98 (40.8)	0.03
LVH on ECG, ^{†‡} n (%)			
Baseline	400 (5.2)	416 (5.4)	0.53
2 years	260 (4.3)	264 (4.5)	0.53
4 years	267 (5.0)	264 (5.3)	0.61
Estimated GFR, mL/min per 1.73 m ² mean (SD)			
Baseline, mean (SD)	78.1 (19.7)	77.7 (19.9)	0.08
n	8640	8636	
2 years, mean (SD)	78.0 (20.5)	74.0 (20.0)	<0.001
n	5794	5516	
4 years, mean (SD)	75.1 (20.7)	70.7 (20.1)	<0.001
n	4924	4621	

*Conversion factor for glucose from mmol/L to mg/dL is 0.0555.

[†]Participants with ECG at baseline, 2 years, and 4 years, respectively, numbered for amlodipine: 7747, 6033 (66.7%), and 5294 (58.5%), and for lisinopril: 7716 (85.2%), 5803 (64.1%), and 5011 (55.3%).

[‡]Measured LVH differs from LVH by ECG as reported in the baseline characteristics table of the final article²; that LVH was an inclusion criteria question (LVH within 2 years) was not verified by the ALLHAT ECG Center.

($P < 0.001$). Of these, 23 versus 2 occurred in blacks and 15 versus 1 in nonblacks (both $P < 0.001$).

Discussion

In the high-risk hypertensive population in ALLHAT there is no apparent difference in the efficacy of treatments based on the ACE inhibitor lisinopril, and the DHP-CCB amlodipine,

for the primary outcome of fatal CHD plus nonfatal MI (RR = 1.01; 95% CI, 0.91 to 1.11). Across the major prespecified subgroups, the ratio showed only minor variations: in nonblacks with equivalent BP control, the RR was 0.97, whereas in blacks with higher BPs on lisinopril, the RR tended to be higher (1.09; 95% CI, 0.92 to 1.30). Our observations are consistent with the overview by the Blood Pressure Lowering

TABLE 3. Clinical Outcomes by Antihypertensive Treatment Group*

Outcome	Amlodipine		Lisinopril		Lisinopril vs Amlodipine		
	No. of Total Events	6-Year Rate per 100 Persons (SE)	No. of Total Events	6-Year Rate per 100 Persons (SE)	RR (95% CI)	z Score	P Value
Primary outcome							
CHD	798	11.3 (0.4)	796	11.4 (0.4)	1.01 (0.91–1.11)	0.18	0.854
Secondary outcome							
All-cause mortality	1256	16.8 (0.5)	1314	17.2 (0.5)	1.05 (0.97–1.13)	1.24	0.214
Combined CHD†	1466	19.9 (0.5)	1505	20.8 (0.5)	1.04 (0.97–1.12)	1.17	0.243
Stroke	377	5.4 (0.3)	457	6.3 (0.3)	1.23 (1.08–1.41)	3.01	0.003
Combined CVD‡	2432	32.0 (0.6)	2514	33.3 (0.6)	1.06 (1.00–1.12)	1.99	0.047
ESRD	129	2.1 (0.2)	126	2.0 (0.2)	0.99 (0.77–1.26)	−0.09	0.929
Cancer	707	10.0 (0.4)	703	9.9 (0.4)	1.01 (0.91–1.12)	0.11	0.913
Hospitalized for GI bleed§	449	8.0 (0.4)	526	9.6 (0.4)	1.20 (1.06–1.37)	2.89	0.004
Other components of combined CVD							
HF	706	10.2 (0.4)	612	8.7 (0.4)	0.87 (0.78–0.96)		0.007
Hospitalized/fatal HF	578	8.4 (0.4)	471	6.9 (0.4)	0.81 (0.72–0.92)		<0.001
Angina (hospitalized or treated)	950	12.6 (0.4)	1019	13.6 (0.4)	1.09 (1.00–1.19)	1.92	0.055
Angina (hospitalized)	630	8.4 (0.4)	693	9.6 (0.4)	1.12 (1.00–1.24)	2.01	0.045
Coronary revascularizations	725	10.0 (0.4)	718	10.2 (0.4)	1.00 (0.91–1.11)	0.07	0.943
Peripheral arterial disease (hospitalized or fatal)	265	3.7 (0.2)	311	4.7 (0.4)	1.19 (1.01–1.40)	2.09	0.036

*CHD, coronary heart disease, includes nonfatal MI and fatal CHD; ESRD includes kidney disease death, kidney transplant, or start of chronic renal dialysis; HF includes fatal, nonfatal hospitalized, or treated.

†Combined CHD indicates CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina.

‡Combined CVD indicates CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized HF, and peripheral arterial disease (hospitalized or outpatient revascularization).

§Denominators are 6757 amlodipine and 6665 lisinopril.

||2×2 table RR rather than Cox proportional hazards.

Treatment Trialists' Collaboration (BPLTTC) of 6 trials of ACE inhibitors versus CCBs mainly in nonblacks, showing no treatment differences in this outcome between these 2 classes of antihypertensive treatments.¹⁸

In contrast, the major prespecified secondary end point of stroke did show significant differences between the 2 treatment arms. Across the major prespecified subgroups, this difference in stroke rates was particularly evident in blacks and in women. Compared with amlodipine, the RR of lisinopril for stroke in blacks was 1.51 (95% CI, 1.22 to 1.86) compared

with 1.07 (95% CI, 0.89 to 1.28) in nonblacks and in women 1.45 (95% CI, 1.17 to 1.79) compared with 1.10 (95% CI, 0.92 to 1.31) in men. This observed benefit of amlodipine over lisinopril for stroke can be attributed at least in part to its better BP-lowering effect. This difference in BP was most pronounced in black women. A meta-analysis of 61 observational studies suggests that an average systolic BP difference of 4 mm Hg could account for about a 10% reduction in stroke mortality.¹⁹ However, the slope for BP versus stroke may be more steep in the high-risk blacks studied in ALLHAT.

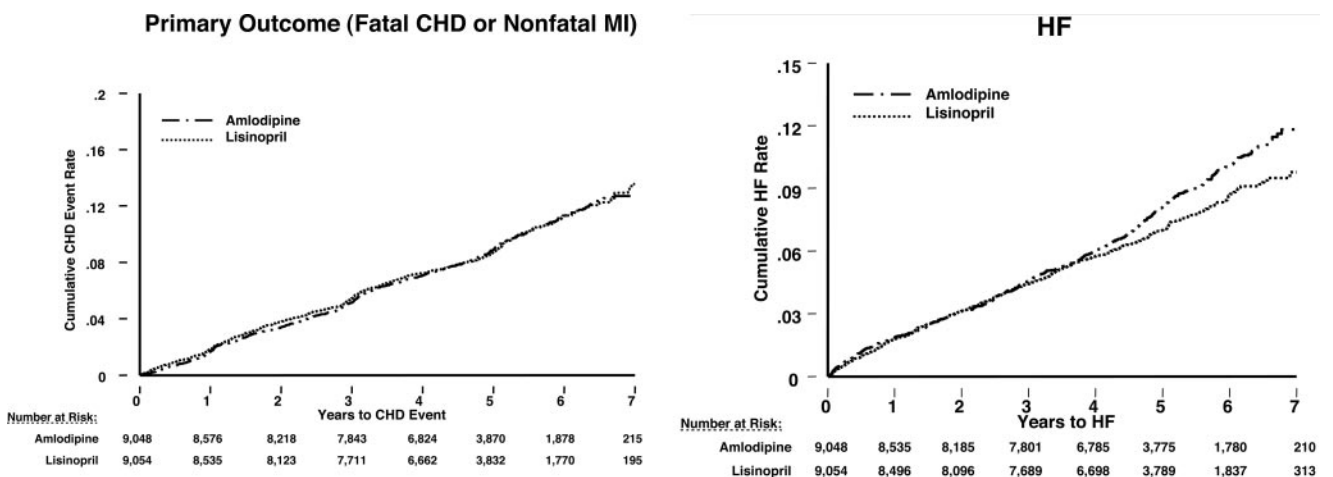


Figure 2. Cumulative event rates for the primary outcome (fatal CHD or nonfatal MI) and hospitalized or treated HF, by treatment group.

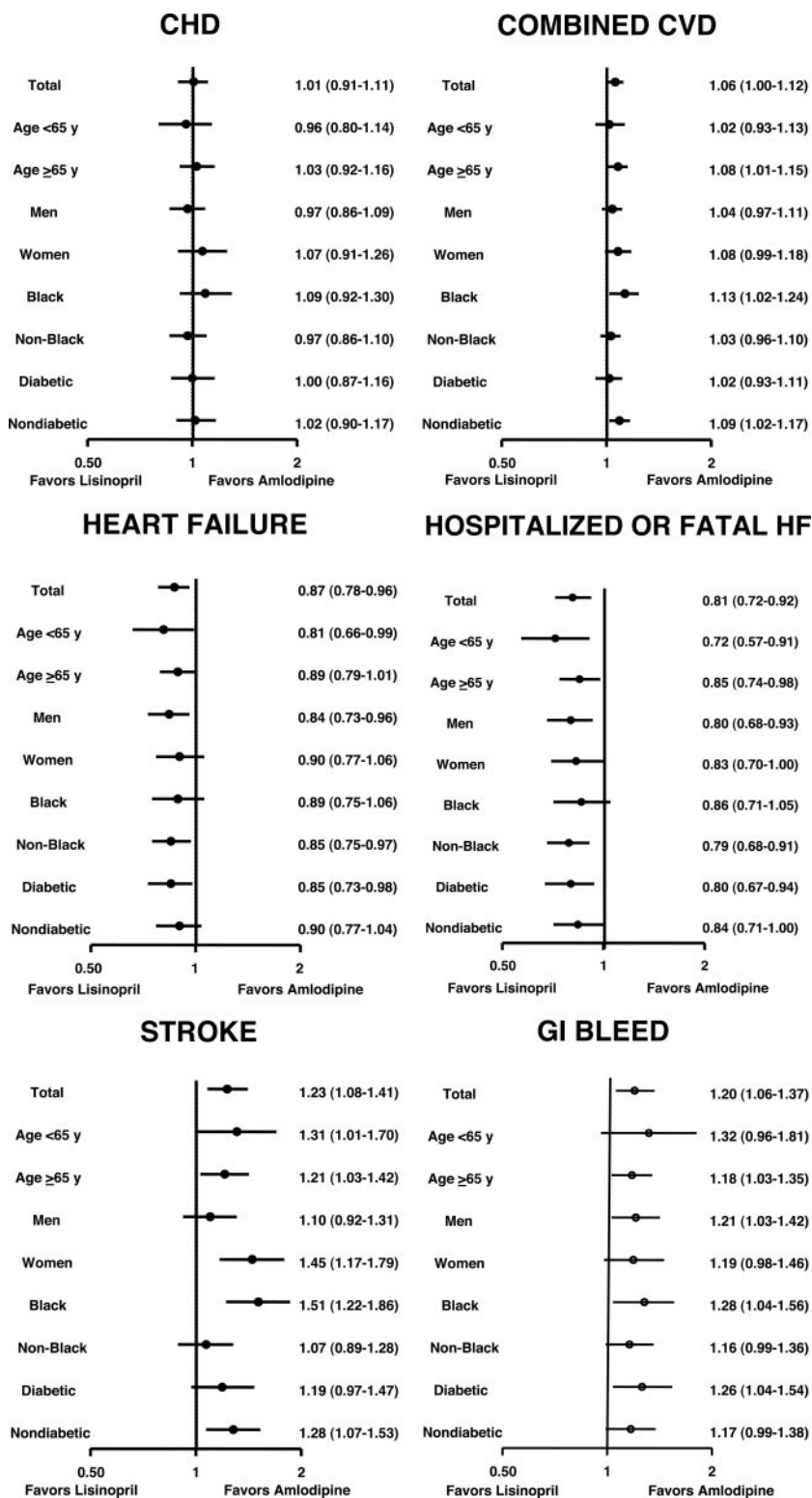


Figure 3. RRs (<1 favors lisinopril/>1 favors amlodipine) and 95% CIs for treatment comparisons in prespecified subgroups.

Chinese hypertensive patients show a steeper relationship between BP and stroke rates compared with Western populations.²⁰ The Felodipine Event Reduction (FEVER) Study enrolled Chinese patients, and an average BP difference of 4.2/2.1 mm Hg was associated with a 27% difference in stroke rates,²¹ considering also the 95% CI (0.60 to 0.89) consistent with the findings in blacks in ALLHAT. On the other hand, in nonblack women, BP may not explain the

higher (+37%) stroke rates on lisinopril versus amlodipine, because the average systolic BP between the 2 treatment arms differed by only 1.3 mm Hg. The beneficial findings in stroke for amlodipine over lisinopril are consistent with a trend toward a CCB-ACE inhibitor difference for stroke in the BPLTTC meta-analysis.¹⁸ Considering also the results from the monotherapy arm in Perindopril PROtection aGainst REcurrent Stroke Study (PROGRESS),²² the ALLHAT find-

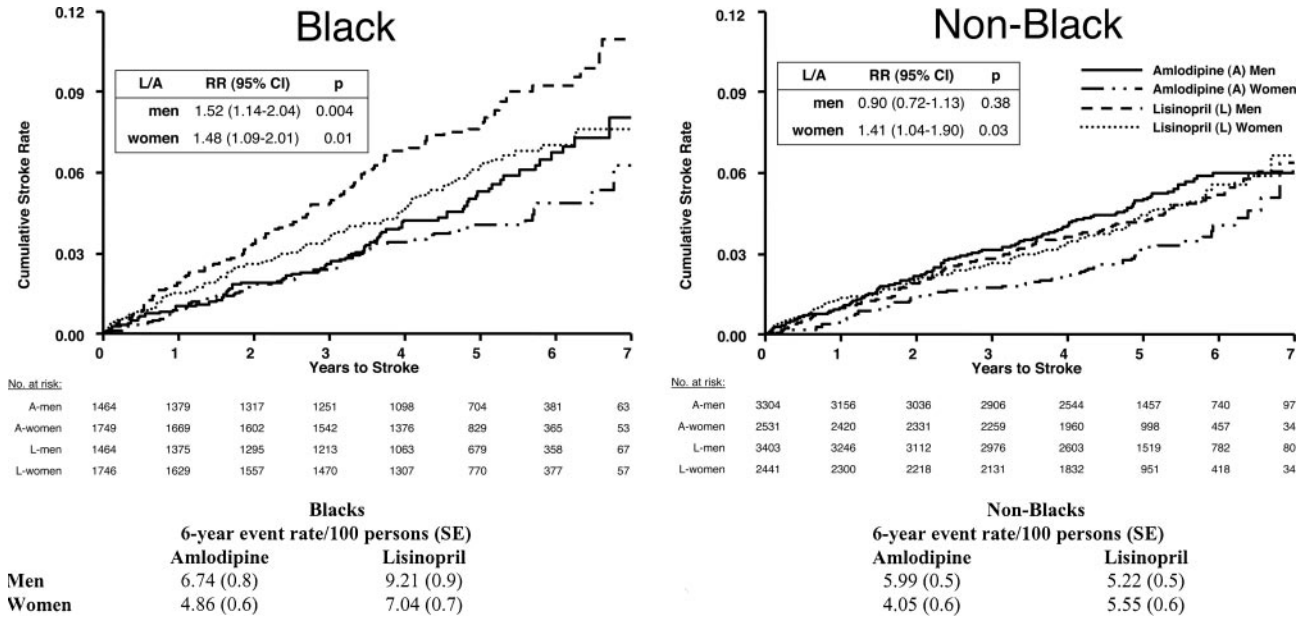


Figure 4. Cumulative event rates for stroke by race and treatment group.

ings raise the possibility that ACE inhibitors somehow prevent strokes less effectively. However, one should keep in mind that occasional BP measurements obtained in the office do not necessarily reflect the actual BP load over time. Inclusion of 24-hour BP or central aortic BP monitoring in clinical trials may provide more accurate data.

Combined CVD is a composite end point that includes components rather dissimilar in terms of clinical importance. Some of the components were discussed above. HF, a clinically important component of the CVD composite outcome with high case-fatality rate, showed a statistically significant greater risk with amlodipine versus lisinopril. This difference was not

apparent until after the third year of follow-up. The delayed separation of the treatment HF curves is similar to the results reported in Valsartan Antihypertensive Long-term Use Evaluation (VALUE) for the comparison of the angiotensin receptor blockers valsartan and amlodipine.²³ On the other hand, hospitalized angina and PAD, both also components of the CVD composite, were statistically, but marginally, different in favor of amlodipine over lisinopril.

Based on results from placebo-controlled trials such as Heart Outcomes Prevention Evaluation Study⁶ or European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA),²⁴ it is commonly assumed that

TABLE 4. Cardiovascular Events by CHD Status at Baseline

Variable	CHD at Baseline			No CHD at Baseline		
	Amlodipine	Lisinopril	P Value Lisinopril vs Amlodipine	Amlodipine	Lisinopril	P Value Lisinopril vs Amlodipine
Time point, N of participants (%)						
Baseline	2202	2270		6777	6715	
Year 1	1869 (85)	1877 (83)		5678 (84)	5578 (83)	
Year 2	1669 (76)	1651 (73)		5155 (81)	4991 (74)	
Year 4	1395 (63)	1362 (60)		4199 (62)	3917 (58)	
% <140/90 at year 4	70.7	66.7	0.03	64.1	62.1	0.06
Events, N (6-year rate per 100 persons)						
CHD	282 (16.1)	300 (17.0)	0.69	507 (9.6)	494 (9.4)	0.78
All-cause mortality	358 (19.8)	418 (21.6)	0.06	882 (15.7)	883 (15.7)	0.82
Combined CHD	575 (31.0)	619 (33.2)	0.38	877 (16.3)	876 (16.6)	0.86
Stroke	105 (6.5)	138 (7.2)	0.05	268 (5.0)	314 (6.0)	0.04
Combined CVD	906 (48.1)	940 (48.9)	0.86	1500 (26.8)	1555 (28.0)	0.16
HF	250 (15.1)	231 (12.7)	0.20	453 (8.7)	377 (7.4)	0.01
Angina	467 (24.8)	469 (24.3)	0.65	474 (8.5)	538 (9.8)	0.025
Coronary revascularization	308 (16.9)	319 (18.0)	0.95	410 (7.7)	394 (7.5)	0.65
PAD	109 (5.8)	102 (5.8)	0.47	153 (2.9)	207 (3.9)	0.003

in patients with CHD, treatment with ACE inhibitors results in improved outcome beyond what may be expected from the BP decrease. In a post hoc analysis of ALLHAT, no significant interactions were noted for the 2 treatments for patients with versus without CHD at baseline. In both HOPE and EUROPA, modest but clinically important (see above) differences in BP between the ACE inhibitors and placebo arms were present. In ALLHAT, at equivalent BP control, no evidence for specific benefits by ACE inhibitor-based treatment was found in the patients with CHD. A reassessment of the evidence for special effects of ACE inhibitors in patients with CHD seems overdue.

Despite a persistently higher GFR in the CCB group, there was no difference between amlodipine and lisinopril for the prespecified outcome of ESRD. In the ALLHAT cohort, 17.8% of the participants had moderate-to-severe reduction in GFR.²⁵ The benefits of ACE inhibition in diabetic and other proteinuric renal impairment are well known.²⁶ However, in an older population, multiple mechanisms may contribute to a low GFR, and the extent of proteinuric renal disease in ALLHAT was not assessed. Moreover, differences in BP control may have offset renal benefits of ACE inhibitor therapy.

There were 975 GI bleeding end points reported among participants assigned to the lisinopril and amlodipine groups, with no differences in the use of aspirin at baseline. However, an (\approx 20%) excess of GI bleeding was observed among individuals assigned to lisinopril compared with amlodipine. This finding is at odds with the observations by Pahor et al¹¹ and Zuccala et al.¹² Other investigators^{27,28} have reported observations contrary to those of Pahor et al¹¹ and Zuccala et al¹² as well. Fogari et al²⁹ suggest that plasma fibrinogen levels are significantly decreased by treatment with lisinopril, providing a plausible mechanism to explain our observation.

There were a total of 41 reported incident cases of angioedema, with 38 (0.42%) in the lisinopril group and 3 (0.03%) in the amlodipine group. This serious and potentially fatal adverse drug reaction is well known to be associated with the use of ACE inhibitors. In blacks, the rate was 0.72% in the lisinopril group versus 0.26% in nonblacks. One plausible explanation for the excess angioedema in blacks compared with nonblacks may be because of racial differences in the kallikrein-kinin system, which, in blacks, results in greater sensitivity to ACE inhibitor-induced increases in bradykinin.³⁰

The strength of this study is that the observations reported here are from a randomized group comparison using prospective clinical information on \approx 83 292 patient years of follow-up. The total number of events observed in each outcome category were substantially greater than has been reported in similar comparisons, such as Captopril Prevention Project (CAPPP)³¹ and Swedish Trial in Old Patients-2 (STOP-2),³² enabling, therefore, the detection of clinically meaningful differences in the outcome categories of interest. The large sample size represents multiple races, ethnicities, locations, and types of clinics, making the findings reported here quite robust and making this as pure an effectiveness study as could be conducted.

Certain limitations in the comparison warrant discussion. First, the primary hypotheses of ALLHAT were based on

comparisons between the diuretic and the 3 newer classes of antihypertensive drugs. However, a head-to-head comparison of any of the other arms in the trial is still valid, involving a sample size greater than has been used in similar head-to-head comparisons.^{18,31} Second, equivalent BP control was not achieved in several major prespecified subgroups, primarily because of insufficient BP response to ACE inhibitor-based therapy in blacks. It is possible that, in blacks, in the absence of a diuretic, the second-step drugs allowed in ALLHAT do not combine well with an ACE inhibitor. In ALLHAT, nonblacks and particularly blacks randomized to amlodipine also had a greater adherence to assigned treatment and needed fewer medications to reach BP treatment goal than those randomly assigned to lisinopril. Overall, the CCB-based treatment proved, therefore, to be superior for BP lowering compared with ACE inhibitor-based treatment.

In conclusion, HF was the only secondary outcome for which the ACE inhibitor showed a superior effect over the CCB. In contrast, for stroke and several more "minor" outcomes (PAD, hospitalized angina, GI bleeding, and angioedema), the CCB was superior to the ACE inhibitor. For male and female blacks, less effective BP control by the ACE inhibitor-based regimen may play a significant role in the higher stroke rates, but this is less likely for female nonblacks. Because there were differences in opposite directions (mainly stroke and HF), the drug choice in a given patient should depend on how the clinician and patient assess the absolute risks and the importance of reducing those risks.³³

Perspectives

The long-term relative safety and efficacy of CCBs as a class have been the subject of many reports in the literature and discussions in regulatory and policy circles and in the lay media. The results that we have presented here highlight the importance of conducting randomized clinical trials, such as ALLHAT. Observational studies are an important method of evidence development to generate hypotheses, which can then be addressed with clinical trials. Researchers, clinicians and others must be cautious in the interpretation and dissemination of the findings from observational studies of drugs, lest otherwise good therapies be lost. One should also consider that premature claims of "dangers" of a particular drug (class) in the press may also jeopardize recruitment and retention of patients in ongoing clinical trials studying the drug (class), as was the case for ALLHAT.

Sources of Funding

This study was supported by contract NO1-HC-35130 from the National Heart, Lung, and Blood Institute. The ALLHAT investigators acknowledge contributions of study medications supplied by Pfizer Inc (amlodipine), AstraZeneca (atenolol and lisinopril), and Bristol-Myers Squibb (pravastatin) and financial support provided by Pfizer Inc.

Disclosures

The National Heart, Lung, and Blood Institute sponsored the study and was involved in all aspects other than direct operations of the

study centers. This included collection, analysis, and interpretation of the data plus the decision to submit the article for publication. Pfizer Inc, AstraZeneca, and Bristol-Myers Squibb had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation or approval of the article. The following conflicts of interest are disclosed: Abbott: W.C.C. (honoraria, research grant), J.N.B. (speakers bureau, honoraria), J.V.F. (speakers bureau, honoraria); Astra-Zeneca: C.E.N. (current employer), W.C.C. (research grant), J.V.F. (research grant), U.T. (speakers bureau, honoraria); Aventis: H.R.B. (speakers bureau, consultant/advisory board), W.C.C. (research grant), J.V.F. (speakers bureau, honoraria); Bristol-Myers Squibb: F.H.H.L. (ownership interest), H.R.B. (speakers bureau, consultant/advisory board), W.C.C. (consultant/advisory board), M.H.A. (speakers bureau), S.A.A. (consultant/advisory board), J.T.W. (speakers bureau, honoraria); Boehringer-Ingelheim: H.R.B. (speakers bureau), W.C.C. (honoraria), A.B.C. (speakers bureau, honoraria); Biovail: W.C.C. (honoraria), J.T.W. (speakers bureau); CV Therapeutics: H.R.B. (honoraria), U.T. (consultant/advisory board), J.T.W. (speakers bureau, honoraria); First Horizon: W.C.C. (consultant/advisory board); Forest: W.C.C. (honoraria, consultant/advisory board); Glaxo-Smith Kline: B.R.D. (consultant/advisory board), J.T.W. (research grant); Johnson & Johnson: F.H.H.L. (ownership interest); Kos: W.C.C. (research grant); Merck: F.H.H.L. (ownership interest), W.C.C. (research grant), B.R.D. (consultant/advisory board), M.H.A. (speakers bureau, honoraria, consultant/advisory board), S.A.A. (speakers bureau), A.B.C. (speakers bureau, honoraria), R.H.G. (research grant, speakers bureau, honoraria), U.T. (speakers bureau); MSD: H.R.B. (consultant/advisory board); Novartis: H.R.B. (speakers bureau, expert witness, consultant/advisory board), W.C.C. (research grant, consultant/advisory board), S.A.A. (research grant, consultant/advisory board), J.N.B. (research grant), R.H.G. (speakers bureau, honoraria), U.T. (honoraria), J.T.W. (research grant, honoraria, speakers bureau, consultant/advisory board); Pfizer: F.H.H.L. (research grant, honoraria, consultant/advisory board), H.R.B. (research grant, speakers bureau, consultant/advisory board), W.C.C. (honoraria, consultant/advisory board), J.N.B. (speakers bureau, honoraria), J.V.F. (research grant, speakers bureau, honoraria), R.H.G. (research grant, speakers bureau, honoraria, consultant/advisory board), U.T. (speakers bureau, honoraria, consultant/advisory board), J.T.W. (speakers bureau, honoraria); Reddy: W.C.C. (consultant/advisory board); Rudin Foundation: M.H.A. (research grant); Sankyo: H.R.B. (consultant/advisory board), W.C.C. (honoraria), J.N.B. (speakers bureau, honoraria); Sanofi-Synthelabo: H.R.B. (speakers bureau, consultant/advisory board), W.C.C. (consultant/advisory board), S.A.A. (speakers bureau), J.T.W. (consultant/advisory board); Schering-Plough: F.H.H.L. (ownership interest); R.H.G. (research grant, speakers bureau, honoraria); Takeda: B.R.D. (consultant/advisory board); and VA: J.V.F. (research grant). The remaining authors report no conflicts.

References

1. Psaty BM, Manolio TA, Smith NL, Heckbert SR, Gottdiener JS, Burke GL, Weissfeld J, Enright P, Lumley T, Powe N, Furberg CD. Cardiovascular Health Study. Time trends in high blood pressure control and the use of antihypertensive medications in older adults: the Cardiovascular Health Study. *Arch Intern Med.* 2002;162:2325–2332.
2. 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 to Prevent Heart Attack Trial (ALLHAT). *JAMA.* 2002;288:2981–2997.
3. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Diuretic versus α -blocker as first-step antihypertensive therapy: final results from the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT). *Hypertension.* 2003;42:239–246.
4. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Werthheimer JH, Hawkins CM. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med.* 1992;327:669–677.
5. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med.* 1992;327:685–691.
6. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med.* 2000;342:145–153.
7. Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality on patients with coronary heart disease. *Circulation.* 1995;92:1326–1331.
8. Psaty BM, Smith NL, Siscovick DS, Koepsell TD, Weiss NS, Heckbert SR, Lemaitre RN, Wagner EH, Furberg CD. Health outcomes associated with antihypertensive therapies used as first-line agents: a systematic review and meta-analysis. *JAMA.* 1997;277:739–745.
9. Pahor M, Guralnik JM, Salive ME, Corti MC, Carbonin P, Havlik RJ. Do calcium channel blockers increase risk of cancer? *Am J Hypertens.* 1996;9:695–699.
10. Pahor M, Guralnik JM, Ferrucci L, Corti MC, Salive ME, Cerhan JR, Wallace RB, Havlik RJ. Calcium-channel blockade and incidence of cancer in aged populations. *Lancet.* 1996;348:493–497.
11. Pahor M, Guralnik JM, Furberg CD, Carbonin P, Havlik RJ. Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old. *Lancet.* 1996;347:1061–1065.
12. Zuccala G, Pedone C, Cocchi A, Pahor M, Carosella L, Carbonin P, Bernabei R. Use of calcium antagonists and hemoglobin loss in hospitalized elderly patients: a cohort study. Gruppo Italiano di Farmacoepidemiologia nell'Anziano (GIFA) investigators. *Clin Pharmacol Ther.* 2000;67:314–322.
13. Davis BR, Cutler JA, Gordon DJ, Furberg CD, Wright JT, Cushman WC, Grimm RH, LaRosa J, Whelton PK, Perry HM, Alderman MH, Ford CE, Oparil S, Francis C, Proschan M, Pressel S, Black HR, Hawkins CM, for the ALLHAT Research Group. Rationale and design for the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Am J Hypertens.* 1996;9:342–360.
14. Grimm RH, Margolis KL, Papademetriou VV, Cushman WC, Ford CE, Bettencourt J, Alderman MH, Basile JN, Black HR, DeQuattro VV, Eckfeldt J, Hawkins CM, Perry HM, Proschan M, for the ALLHAT Research Group. Baseline Characteristics of Participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Hypertension.* 2001;37:19–27.
15. Barzilay JI, Davis BR, Bettencourt J, Margolis KL, Goff DC, Black H, Habib G, Ellsworth A, Force RW, Wiegmann T, Ciocon JO, Basile JN, for the ALLHAT Collaborative Research Group. Cardiovascular outcomes using doxazosin vs. chlorthalidone for the treatment of hypertension in older adults with and without glucose disorders: a report from the ALLHAT study. *J Clin Hypertens.* 2004;6:116–125.
16. Klein JP, Moeschberger ML. *Survival Analysis: Techniques for Censored and Truncated Regression.* New York, NY: Springer-Verlag; 1997.
17. Proschan MA. A multiple comparison procedure for three- and four-armed controlled clinical trials. *Statist Med.* 1999;18:787–798.
18. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomized trials. *Lancet.* 2003;362:1527–1535.
19. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, for the Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360:1903–1913.
20. Lawes CMM, Rodgers A, Bennett DA, Parag V, Suh I, Ueshima H, MacMahon S, for the Asia Pacific Cohort Studies Collaboration. Blood Pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens.* 2003;21:707–716.
21. Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A, for the FEVER Study Group. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo controlled trial in Chinese hypertensive patients. *J Hypertens.* 2005;23:2157–2172.
22. MacMahon S, Neal B, Tzourio C, Rodgers A, Woodward M, Cutler J, Anderson C, Chalmers J, for the PROGRESS Collaborative Group. Randomized trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet.* 2001;358:1033–1041.
23. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F, Schork A, Smith B, Zanchetti A, for the VALUE trial group. Outcomes in hypertensive

- patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomized trial. *Lancet*. 2004;363:2022–2031.
24. The European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362:782–788.
 25. Rahman M, Brown CD, Coresh J, Davis BR, Eckfeldt JH, Kopyt N, Levey AS, Nwachuku C, Pressel S, Reisen E, Walworth C, for the ALLHAT Collaborative Research Group. The prevalence of reduced glomerular filtration rate in older hypertensive patients and its association with cardiovascular disease. *Arch Intern Med*. 2004;164:969–976.
 26. Wright JT, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, Cheek D, Douglas-Baltimore JG, Gassman J, Glassock R, Hebert L, Jamerson K, Lweis J, Philips RA, Toto RD, Middleton JP, Rostand SG, for the African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK Trial. *JAMA*. 2002;288:2421–2431.
 27. Smalley WE, Ray WA, Daugherty JR, Griffin MR. No association between calcium channel blocker use and confirmed bleeding peptic ulcer disease. *Am J Epidemiol*. 1998;148:350–354.
 28. Kelly JP, Laszlo A, Kaufman DW, Sundstrom A, Shapiro S. Major upper gastrointestinal bleeding and the use of calcium channel blockers. *Lancet*. 1999;353:559.
 29. Fogari R, Zoppi A, Malamani GD, Marasi G, Vanasia A, Villa G. Effects of different antihypertensive drugs on plasma fibrinogen hypertensive patients. *Br J Clin Pharmacol*. 1995;39:471–476.
 30. Gainer JV, Nadeau JH, Ryder D, Brown NJ. Increased sensitivity to bradykinin among African Americans. *J Allergy Clin Immunol*. 1996;98:283–287.
 31. Hanson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmaki K, Dahlof B, de Faire U, Morlin C, Karlberg BE, Wester PO, Bjorck JE, for the Captopril Prevention Project (CAPPP) study group. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet*. 1999;353:611–616.
 32. Hansson L, Lindholm LH, Ekborn T, Dahlof B, Lanke J, Schersten B, Wester PO, Hedner T, de Faire U, for the STOP-Hypertension-2 study group. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet*. 1999;354:1751–1756.
 33. Diehr P, Williamson J, Patrick DL, Bild DE, Burke GL. Patterns of self-rated health in older adults before and after sentinel health events. *J Am Geriatr Soc*. 2001;49:36–44.