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Cardiovascular Risk Reduction in Hypertensive Black Patients With Left Ventricular Hypertrophy

The LIFE Study

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OBJECTIVES We report on a subanalysis of the effects of losartan and atenolol on cardiovascular events in black patients in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study.

BACKGROUND The LIFE study compared losartan-based to atenolol-based therapy in 9,193 hypertensive patients with left ventricular hypertrophy (LVH). Overall, the risk of the primary composite end point (cardiovascular death, stroke, myocardial infarction) was reduced by 13% ($p = 0.021$) with losartan, with similar blood pressure (BP) reduction in both treatment groups. There was a suggestion of interaction between ethnic background and treatment ($p = 0.057$).

METHODS Exploratory analyses were performed that placed LIFE study patients into black ($n = 533$) and non-black ($n = 8,660$) categories, overall, and in the U.S. (African American [$n = 523$]; non-black [$n = 1,184$]).

RESULTS A significant interaction existed between the dichotomized groups (black/non-black) and treatment ($p = 0.005$); a test for qualitative interaction was also significant ($p = 0.016$). The hazard ratio (losartan relative to atenolol) for the primary end point favored atenolol in black patients (1.666 [95% confidence interval (CI) 1.043 to 2.661]; $p = 0.033$) and favored losartan in non-blacks (0.829 [95% CI 0.733 to 0.938]; $p = 0.003$). In black patients, BP reduction was similar in both groups, and regression of electrocardiographic-LVH was greater with losartan.

CONCLUSIONS Results of the subanalysis are sufficient to generate the hypothesis that black patients with hypertension and LVH might not respond as favorably to losartan-based treatment as non-black patients with respect to cardiovascular outcomes, and do not support a recommendation for losartan as a first-line treatment for this purpose. The subanalysis is limited by the relatively small number of events. (J Am Coll Cardiol 2004;43:1047–55) © 2004 by the American College of Cardiology Foundation

The recently published Losartan Intervention For Endpoint reduction in hypertension (LIFE) study (1) was the first to demonstrate, in a head-to-head comparison of two antihypertensive agents, that a "new generation" antihypertensive agent (losartan) offers better cardiovascular protection than therapy with a traditional agent (atenolol), despite comparable blood pressure (BP) reduction. In the overall LIFE study, the risk of the occurrence of the primary composite cardiovascular end point (cardiovascular death, stroke, and myocardial infarction [MI]) was significantly reduced by 13% ($p = 0.021$) with losartan (compared to atenolol) in the primary analysis, which adjusted for Framingham risk score and the degree of electrocardiographic-left ventricular hypertrophy (ECG-LVH) at baseline (unadjusted reduction with losartan was 15%; $p = 0.009$). Among the components of the primary composite end point, losartan was associated with a significant reduction in the risk of stroke (fatal and nonfatal) by 25% ($p < 0.001$). Treatment differences in other components of the primary composite end point (fatal and nonfatal MI and cardiovascular mortality) were not significant in the main study. In addition, patients randomized to losartan experienced a significantly greater reduction in LVH, as assessed by ECG. Reduction of BP was similar in the treatment groups. At the last visit before a primary end point or end of follow-up, systolic BP was reduced by 30.2 and 29.1 mm Hg in the losartan and atenolol groups, respectively ($p = 0.015$); diastolic BP was reduced by 16.6

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Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
ALLHAT	= Antihypertensive therapy and Lipid Lowering Heart Attack prevention Trial
BP	= blood pressure
CHD	= coronary heart disease
CI	= confidence interval
ECG	= electrocardiogram/electrocardiographic
ISH	= isolated systolic hypertension
LIFE	= Losartan Intervention For Endpoint reduction in hypertension study
LVH	= left ventricular hypertrophy
MI	= myocardial infarction
SOLVD	= Studies Of Left Ventricular Dysfunction
VA	= Veterans Administration

and 16.8 mm Hg in the losartan and atenolol groups, respectively (p = NS).

Patients with diabetes (n = 1,195) and those with isolated systolic hypertension (ISH) (n = 1,326) at baseline were prespecified to be of special interest in the LIFE study. Subgroup analyses in these patients found losartan was associated with a 25% reduction in the risk of the primary composite end point compared with atenolol in both groups (p = 0.031 for diabetics [2] and p = 0.059 in patients with ISH [3]). In addition, the LIFE study analysis plan predefined analyses of the primary composite end point in 23 demographic, geographic, disease-history, and disease-severity subgroups. Although no significant interactions occurred between treatment and any of the predefined subgroups, there was a suggestion of interaction between ethnic background and treatment (p = 0.057). This analysis was based on the five ethnic groups reported by the investigators, some of which included small sample sizes; therefore, further exploratory analyses were subsequently performed to investigate this finding. Results of these analyses are presented here.

METHODS

The complete LIFE study protocol (4), patient baseline characteristics (5), primary study results (1), and results in patients with diabetes (2) and ISH (3) have been published.

Participants and procedures. Patients age 55 to 80 years with previously treated or untreated hypertension (n = 9,193), ECG signs of LVH (by Cornell voltage-duration product or Sokolow-Lyon voltage criteria), and sitting BP (after one to two weeks on placebo) of 160 to 200 mm Hg systolic and/or 95 to 115 mm Hg diastolic, were randomized either to losartan-based or atenolol-based treatment at more than 900 centers in seven countries (Denmark, Finland, Iceland, Norway, Sweden, United Kingdom, U.S.). Study therapy was initiated with 50 mg of blinded losartan or atenolol and the matching placebo of the other agent. Study drug dosage was increased, if necessary, to achieve target BP (<140/90 mm Hg) by the addition of hydrochlorothiazide 12.5 mg, followed by an increase of blinded medication to 100 mg and subsequent increase of hydrochlorothiazide or addition of other medication, with the exception of angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, or beta-blockers. All patients were to be followed for at least four years and until at least 1,040 patients experienced a primary cardiovascular end point (cardiovascular mortality, stroke, or MI). The study ran its full course, and at termination of the study (September 16, 2001, as determined by the LIFE Steering Committee) 1,096 patients had experienced a primary event that was confirmed by the Endpoint Classification Committee; mean duration of follow-up was 4.8 years.

Statistical methods. As previously described (4), the statistical significance of the effect of losartan compared with atenolol on the primary composite end point was assessed by a Cox regression model that included the baseline variables of the Framingham risk score and ECG measures of LVH. The effect of losartan versus atenolol treatment among subgroups (treatment-by-factor interactions) was also analyzed; ethnic group was included as a predefined subgroup because data were intended to be submitted to regulatory agencies. A set of indicator variables was defined for each factor, which was included in the Cox regression analyses with the treatment indicator and the products of the treatment indicator with each of the subgroup factor indicators. Factors considered for subgroup analysis of the primary composite end point are listed in Table 1. Under the prespecified analysis plan, significant interactions were to be further examined to determine whether the interaction was qualitative or quantitative (6).

Differences between the treatment groups with respect to mean changes in BP and ECG measures of LVH from baseline were assessed with a rank-transformed analysis-of-variance model. Note that there were no formal adjustments for multiplicity.

RESULTS

Worldwide subgroup analyses. As described in the previous text, the statistical significance of the differing effect of losartan compared with atenolol on the primary composite end point was analyzed. No significant interactions were seen between treatment and any of the predefined subgroups (Table 1); however, there was a suggestion of interaction between ethnic background and treatment (p = 0.057). The prespecified test for interaction between ethnic background and treatment was based on a comparison of the effect of losartan among the five different ethnic background categories reported by the investigators: white (n = 8,503), black (n = 533), Hispanic (n = 100), Asian (n = 43), and other (n = 14). Primary composite end point results for the prespecified ethnic groups are shown in Figure 1 (ethnic group identified as "other" [n = 14] is not shown). White patients had lower risk with losartan (hazard ratio: 0.819 [95% confidence interval (CI) 0.724 to 0.928]), whereas

Table 1. Results of Test for Interaction Between Baseline Subgroup and Treatment for the Primary End Point

Subgroup	Test for Interaction (p Value)
Demographics	
Age	0.185
Gender	0.420
Country	0.607
Ethnic group	0.057
Disease history	
MI	0.316
Stroke	0.211
IHD	0.209
Angina	0.250
Heart failure	0.733
Diabetes	0.170
Microalbuminuria	0.383
ISH	0.176
Clinical characteristics	
Smoking status	0.282
Alcohol intake	0.420
Exercise status	0.892
BMI	0.290
Systolic BP	0.725
Diastolic BP	0.402
Total cholesterol	0.975
HDL cholesterol	0.114
ECG-LVH (Cornell)	0.485
ECG-LVH (Sokolow-Lyon)	0.422
Framingham risk score	0.922

BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; HDL = high-density lipoprotein; IHD = ischemic heart disease; ISH = isolated systolic hypertension; LVH = left ventricular hypertrophy; MI = myocardial infarction.

black patients appeared to have lower risk with atenolol (hazard ratio: 1.598 [95% CI 1.004 to 2.543]). Because the data for all but the white and black groups were limited, a further exploratory analysis was performed that divided patients into black (n = 533) and non-black groups (n = 8,660). This analysis yielded a statistically significant interaction (p = 0.005). Further, a test for qualitative interaction (i.e., effect of losartan differs in direction between blacks and non-blacks, not just in magnitude) was also statistically significant (p = 0.016).

The hazard ratio adjusted for baseline Framingham risk score and degree of LVH for the primary composite end point favored atenolol in black patients and favored losartan in non-black patients; similar results were found for the secondary component end points (Table 2A).

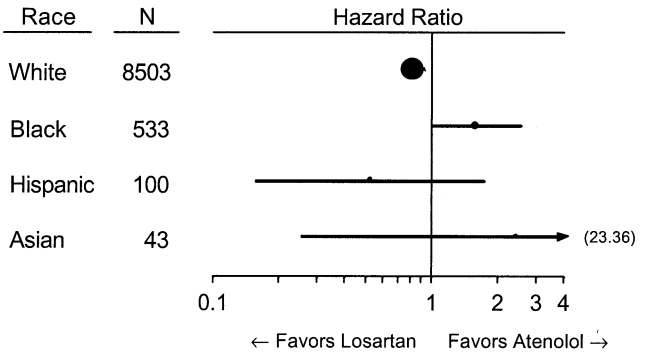

Figure 1. Results of primary composite end point by ethnic group. The **dots** represent the hazard ratio; **dot size** is proportional to the number of patients for each ethnic group, as shown to the **left.** The **line through each dot** corresponds to the 95% confidence interval.

U.S. Almost all black patients were enrolled in the U.S. (523 of 533 black patients). It is important to note that differences existed between the baseline characteristics of patients enrolled in the U.S. relative to the overall study population (Table 3). The overall rate of occurrence of primary end points in the U.S. was also higher than in other countries (U.S. primary composite event rate per 1,000 years of patient follow-up was 30.6 and 32.1 for the losartan and atenolol groups, respectively, versus 22.4 and 27.0 for the non-U.S. losartan and atenolol groups, respectively). Therefore, to avoid the confounding effects of region, further analyses to explore the apparent differences in response in black and non-black patients compared African-American (n = 523) and non-black (n = 1,184) patients within the U.S.

The primary end point results in the African-American and non-black U.S. population were similar to those found in the overall population; results for the secondary component end points also trended similarly (Table 2B).

Figure 2 shows the Kaplan-Meier curves for the primary composite end point in the African-American and non-black U.S. patients. The trend for atenolol in African Americans appears to differ during the first two years compared to later. In the first two years of the study, the primary composite end point crude incidence rates in African Americans were similar in each treatment group (two-year crude composite end point rate: 8.6% and 6.4% in the losartan and atenolol groups, respectively) but, thereafter, the incidence of new events on atenolol appears to decline (four-year crude composite end point rate: 15.3% and 9.7% in the losartan and atenolol groups, respectively).

The baseline characteristics of African-American and non-black U.S. patients are shown in Table 3. A number of differences existed between African Americans and non-black U.S. patients. For example, at baseline, African Americans were younger and were more likely to have diabetes, a history of cerebrovascular disease, or to be smokers. African Americans had higher baseline serum creatinine, serum uric acid, and urine albumin levels and were more likely to have received prior treatment with calcium channel blockers or diuretics. African Americans had a lower Framingham risk score; they were less likely to be female, likely to have a history of coronary heart disease, and to have been treated with a beta-blocker or renin-angiotensin system inhibiting agent.

However, as depicted in Figure 3, the difference in the primary end point rate between African Americans and non-black U.S. patients was unaffected by adjustment for various baseline factors.

The BP response in African Americans showed results similar to the overall LIFE study. Similar reductions occurred in both treatment groups in African-American pa-

Table 2. Primary Composite and Secondary Component End Points in Black and Non-Black Patients

	Losartan (n = 270)		Atenolol (n = 263)		Adjusted Hazard Ratio§ (95% CI)	p Value‖
	Rate‡	N (%)	Rate‡	N (%)		
A: Worldwide Black and Non-Black Patients						
Worldwide Black Patients						
Crude Rate						
Composite	41.8	46 (17.0)	25.9	29 (11.0)	1.666 (1.043–2.661)	0.033*
Components of Primary Composite End Point—Secondary End Points						
Cardiovascular mortality	19.1	22 (8.1)	13.1	15 (5.7)	1.483 (0.764–2.879)	0.244
MI (fatal/nonfatal)	11.8	13 (4.8)	5.5	6 (2.3)	2.074 (0.786–5.473)	0.141
Stroke (fatal/nonfatal)	21.9	24 (8.9)	11.0	12 (4.6)	2.179 (1.079–4.401)	0.030*
Worldwide Non-Black Patients						
Crude Rate						
	Losartan (n = 4,355)		**Atenolol (n = 4,325)**		**Adjusted Hazard Ratio§ (95% CI)**	**p Value‖**
	Rate‡	**N (%)**	**Rate‡**	**N (%)**		
Composite	22.8	462 (10.7)	28.0	559 (12.9)	0.829 (0.733–0.938)	0.003†
Components of Primary Composite End Point—Secondary End Points						
Cardiovascular mortality	8.7	182 (4.2)	10.5	219 (5.1)	0.842 (0.692–1.025)	0.087
MI (fatal/nonfatal)	9.0	185 (4.3)	8.9	182 (4.2)	1.036 (0.844–1.271)	0.735
Stroke (fatal/nonfatal)	10.2	208 (4.8)	14.7	297 (6.9)	0.700 (0.586–0.836)	<0.001†
B: U.S. Black and Non-Black Patients						
U.S. Black Patients						
Crude Rate						
	Losartan (n = 264)		**Atenolol (n = 259)**		**Adjusted Hazard Ratio‡ (95% CI)**	**p Value‖**
	Rate‡	**N (%)**	**Rate‡**	**N (%)**		
Composite	42.7	46 (17.4)	26.4	29 (11.2)	1.665 (1.042–2.659)	0.033*
Components of Primary Composite End Point—Secondary End Points						
Cardiovascular mortality	19.5	22 (8.3)	13.4	15 (5.8)	1.480 (0.763–2.872)	0.246
MI (fatal/nonfatal)	12.0	13 (4.9)	5.6	6 (2.3)	2.078 (0.787–5.486)	0.140
Stroke (fatal/nonfatal)	22.4	24 (9.1)	11.2	12 (4.6)	2.181 (1.080–4.403)	0.030*
U.S. Non-Black Patients						
Crude Rate						
	Losartan (n = 605)		**Atenolol (n = 579)**		**Adjusted Hazard Ratio‡ (95% CI)**	**p Value‖**
	Rate‡	**N (%)**	**Rate‡**	**N (%)**		
Composite	25.6	68 (11.2)	34.7	86 (14.9)	0.722 (0.525–0.994)	0.046*
Components of Primary Composite End Point—Secondary End Points						
Cardiovascular mortality	11.2	31 (5.1)	16.2	42 (7.3)	0.650 (0.408–1.036)	0.070
MI (fatal/nonfatal)	11.0	29 (4.8)	11.2	28 (4.8)	0.987 (0.587–1.660)	0.962
Stroke (fatal/nonfatal)	11.3	30 (5.0)	16.1	40 (6.9)	0.679 (0.422–1.092)	0.110

*p values <0.05. †p values <0.01. ‡Per 1,000 patient-years of follow-up. §Baseline left ventricular hypertrophy degree (Cornell product and Sokolow-Lyon) and baseline Framingham risk score are included in Cox proportional hazard model as covariates. ‖p Values and estimates of hazard ratio of experiencing the end point on losartan compared to atenolol are based on the Cox proportional hazard model.

CI = confidence interval; MI = myocardial infarction.

tients (Fig. 4). In African Americans, sitting systolic BP at the last visit before a primary end point occurred, or at end of follow-up, decreased by 30.3 and 29.1 mm Hg to 141.7 and 142.7 mm Hg in the losartan and atenolol groups, respectively. Sitting diastolic BP in African Americans decreased by 17.3 and 17.2 mm Hg to 80.6 and 80.5 mm Hg in the losartan and atenolol groups, respectively. In non-black U.S. patients, sitting systolic BP decreased by 31.1 and 30.3 mm Hg to 140.4 and 140.3 mm Hg in the losartan and atenolol groups, respectively. Sitting diastolic

Table 3. Baseline Characteristics of Patients

	All Patients (n = 9,193)	U.S. Non-Black Patients (n = 1,184)	U.S. Black Patients (n = 523)	p Values (U.S. Non-Black vs. U.S. Black Patients)
Age (yrs)	66.9	67.4	65.0	< 0.001
Female (%)	54.0	52.1	46.5	0.036
Current smoker (%)	16.3	13.2	25.0	< 0.001
BMI (kg/m^2)	28.0	28.9	29.5	0.066
Prior CHD (%)	16.0	32.4	23.1	< 0.001
Prior stroke/TIA (%)	8.1	9.8	11.1	0.435
Diabetes (%)	13.0	19.6	25.4	0.007
FRS	22.4	23.5	22.2	0.006
Serum creatinine (mg/dl)	0.98	1.18	1.26	< 0.001
Serum glucose (mg/dl)	108.5	115.2	117.5	0.302
Serum uric acid (mg/dl)	5.6	5.7	6.1	< 0.001
Urine albumin (mg/dl)	6.4	12.0	16.9	0.019
Prior RAS drugs (%)	25.4	43.2	36.3	0.009
Prior BB (%)	25.9	27.0	21.2	0.011
Prior CCB (%)	25.5	36.7	48.4	0.001
Prior diuretics (%)	27.6	31.6	38.6	0.005

A *t* test was used to test for racial differences in continuous variables (age, FRS, and laboratory values). The Fischer exact test was used to test for differences in dichotomous variables.

BB = beta-blocker; BMI = body mass index; CCB = calcium channel blocker; CHD = coronary heart disease; FRS = Framingham risk score; RAS = renin angiotensin system; TIA = transient ischemic attack.

BP in non-black U.S. patients decreased by 16.5 and 17.5 mm Hg to 77.8 and 76.4 mm Hg in the losartan and atenolol groups, respectively.

Also similar to the overall LIFE study, there was a larger regression of ECG-LVH in losartan-treated African Americans compared with atenolol-treated African Americans. In African Americans, mean Cornell voltage-duration product at last visit before a primary end point occurred, or at end of follow-up, was reduced by 193 and 79 mm·ms, respectively, in the losartan and atenolol groups ($p = 0.056$), and Sokolow-Lyon voltage was reduced by 5.9 and 4.0 mm, respectively, in the losartan and atenolol groups ($p = 0.018$).

Distribution of study drug dosages and the use of concomitant medication were similar in African-American and non-black U.S. patients; study drug discontinuation rates were also similar in these groups (Table 4). African-American and non-black U.S. patients received hydrochlorothiazide or another diuretic for 78% and 73% of days of study follow-up (through occurrence of primary end point), respectively. In addition, an on-drug analysis of the primary composite end point including only those events occurring while patients were on study drug found a similar result to the overall analysis favoring atenolol in black patients. The changes in laboratory measures in the losartan and atenolol groups, such as serum glucose and uric acid, were similar among black and non-black patients.

DISCUSSION

The finding in the LIFE study that black patients seem to have a greater reduction in the risk of cardiovascular events with atenolol relative to losartan, whereas the rest of the LIFE-study participants, including the non-black U.S. patients, benefited substantially more from losartan than from atenolol, is fascinating. However, there are limitations of subanalyses, in general, and in particular the post hoc

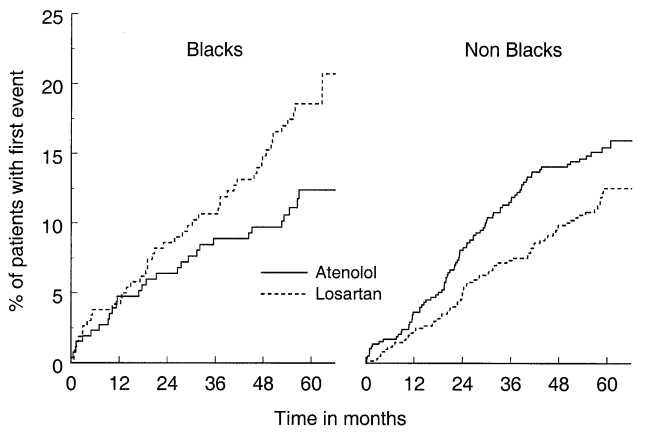

Figure 2. Results of primary composite end point by ethnic group in the U.S.: blacks versus non-blacks.

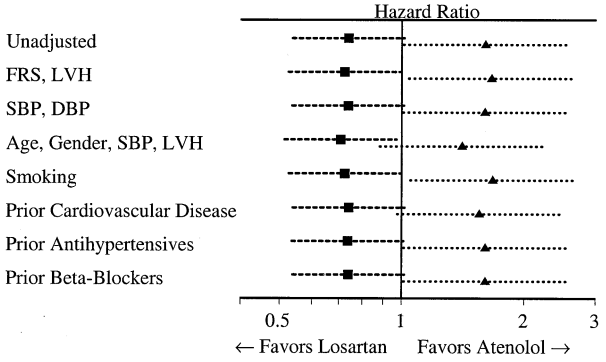

Figure 3. Primary composite end point: unadjusted and adjusted for baseline covariates in U.S. blacks **(triangles)** versus non-blacks **(squares)**. **Symbols** represent the hazard ratio; the **line through each symbol** corresponds to the 95% confidence interval. DBP = diastolic blood pressure; FRS = Framingham risk score; LVH = left ventricular hypertrophy; SBP = systolic blood pressure.

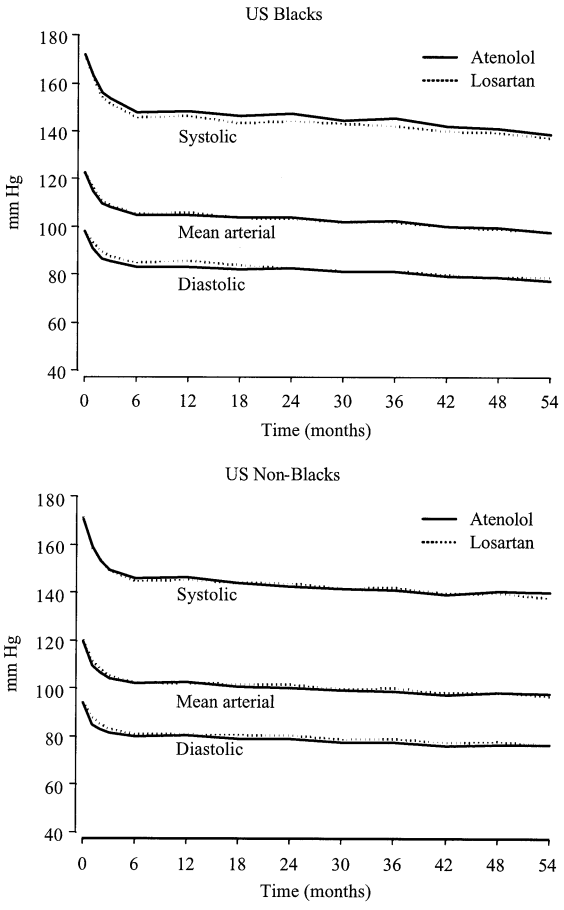

Figure 4. Blood pressure results in the U.S.: blacks versus non-blacks.

nature of the grouping of black and non-black patients, that must be considered. In addition, relatively few primary cardiovascular events occurred in black patients (46 of 270 losartan-treated patients and 29 of 263 atenolol-treated patients), which may seriously limit the stability of the finding. It must also be recognized that it is not appropriate to make comparisons of the individual treatments across the black and non-black subgroups as observed differences might be due to confounding factors and that there were no adjustments to the analyses for multiplicity.

Three elements led to our decision to report this observation, which might well be a chance finding. First, we believed that full disclosure is sound scientific practice. Second, we hope to generate discussion in the medical community as to whether real differences exist in outcomes between black and non-black patients treated with the same drug, and whether these differences can be used to guide clinical practice. Third, we firmly believe that this issue will remain open until targeted, well-powered trials are designed and conducted to resolve it.

Unfortunately, the literature does not provide a complete framework to evaluate our findings. Contrary to the statement by Schwartz (7) that "attributing differences in a biologic endpoint to race is not only imprecise but also of no proven value in treating an individual patient," differences between ethnic groups have been documented in cardiovascular research. Several cardiovascular phenotypes differ between people who are considered black and those who are not, although the cause of these differences may be environmental/behavioral rather than racial/genetic. Black patients with hypertension more often have low plasma renin values (8), appear to be more salt sensitive (8), and fit the Laragh and Sealey model of volume-expanded hypertension (9). It has been proposed that black patients are more responsive to treatment with diuretics or calcium antagonists (10). The Veterans Administration (VA) study evaluating BP responsiveness to six antihypertensive drugs provided support for this concept (11), although only in elderly black men. This study of six antihypertensive agents was the first to analyze the effect of race and treatment on a cardiovascular outcome, namely regression of LVH. Although various drugs had different effects on the regression

Table 4. Distribution of Study Drug Dosage at Time of End Point or End of Follow-Up

	LIFE: Study Therapy U.S. Black vs. U.S. Non-Black Patients at End Point or End of Follow-Up			
	Black (n = 523)		Non-Black (n = 1,184)	
	Losartan (%) (n = 264)	Atenolol (%) (n = 259)	Losartan (%) (n = 605)	Atenolol (%) (n = 579)
50 mg alone	5	3	3	6
50 mg with additional drugs	14	15	15	17
With HCTZ only	8	9	7	9
With other drugs only	2	2	4	3
With HCTZ and other drugs	4	4	4	5
100 mg with or without additional drugs	48	45	49	39
Alone	0	2	2	2
With HCTZ only	11	9	12	11
With other drugs only	4	5	7	5
With HCTZ and other drugs	33	29	29	21
Off-study drug	33	37	33	38

HCTZ = hydrochlorothiazide.

of LVH, there was no evidence of an interaction between race and outcome.

The recently reported results of the Antihypertensive therapy and Lipid Lowering Heart Attack prevention Trial (ALLHAT) (12) reinforce the observation from the LIFE trial that black patients with hypertension may respond differently from other ethnic groups to different treatment regimens. In the ALLHAT study, no difference was seen between treatment regimens (amlodipine vs. chlorthalidone and lisinopril vs. chlorthalidone) with respect to the primary end point of fatal coronary heart disease (CHD) or nonfatal MI. Black patients represented approximately 35% of the ALLHAT population. In subgroup analyses, there was no interaction between ethnic group and treatment with respect to the primary end point. In the comparison of lisinopril to chlorthalidone, interactions between race and treatment were observed with respect to two secondary end points in ALLHAT: stroke ($p = 0.01$) and combined cardiovascular disease ($p = 0.04$). The hazard ratios for lisinopril relative to chlorthalidone for stroke were 1.40 (95% CI 1.17 to 1.68) and 1.00 (95% CI 0.85 to 1.17) for black and non-black patients, respectively. The hazard ratios for combined cardiovascular disease end points were 1.19 (95% CI 1.09 to 1.30) and 1.06 (95% CI 1.00 to 1.13) for black and non-black patients, respectively. It is important to note, however, that differences existed in BP control in the treatment arms of the ALLHAT study. In black patients, there was a 4 mm Hg lesser reduction in systolic BP with lisinopril in comparison to chlorthalidone. In addition, when comparing to the LIFE results it should be noted that the treatment regimens were very different. First, ALLHAT did not include an angiotensin II antagonist. Second, diuretics could not be added to the lisinopril arm in ALLHAT, whereas in the LIFE study, approximately 90% of black patients received a diuretic at any time. Overall, these results do not provide definitive information with which to evaluate the LIFE results.

Other hypertension studies comparing effects of different active agents on cardiovascular outcomes had too few black patients to analyze separately.

Studies of the effects of ACE inhibitors and beta-blockers on cardiovascular outcomes in patients with heart failure report conflicting data regarding differences in response among black and white patients. Analyses of data from the two Vasodilator-Heart Failure Trials (V-HeFT I and II) indicated that enalapril therapy (compared with treatment with a combination of hydralazine and isosorbide dinitrate) was associated with a significant reduction in the risk of death from any cause among white but not among black patients (13). Two recent reports present analyses from the Studies Of Left Ventricular Dysfunction (SOLVD) (14,15). One report combining data from the Treatment and Prevention arms found that enalapril therapy (compared with placebo) reduced the risk of hospitalization for heart failure among white patients with left ventricular dysfunction, but not among black patients. The second report analyzing primary end point data from the Prevention arm found that enalapril was equally efficacious in black and white patients. Both of these reports found a higher rate of cardiovascular outcomes in black patients relative to white patients.

In the Beta-Blocker Evaluation of Survival Trial (16) it was found that white, but not black, patients with heart failure appear to benefit from the beta-blocker bucindolol. However, in another report (17), carvedilol reduced the risk of death from any cause or hospitalization for any reason (and other end points) to a similar magnitude in both black and non-black subjects.

Thus, conflicting published data suggest, but do not prove, the hypothesis that interruption of the renin-angiotensin system may be somewhat less effective in preventing cardiovascular events in black than in non-black subjects. The only way we can evaluate our findings is to discuss, as even-handedly as possible, which aspects of our observations favor the conclusion that the black patients benefited more from atenolol and which aspects militate against interpreting the results in such a fashion.

The strongest argument favoring the conclusion that the finding reported herein might represent a true and reproducible difference is a statistical one. There were similar findings for the primary and secondary component end points, and a test for qualitative interaction was statistically significant ($p = 0.016$) using the Gail and Simon test, although interpretation of this test must be influenced by its post hoc nature (6). In addition, the difference between the groups in treatment effects on outcomes remained significant after adjustment for a wide variety of baseline covariates.

The most fascinating and perplexing observation that speaks against accepting our findings at face value is that losartan-based treatment had similar physiologic and hemodynamic effects in black and non-black patients. As in the overall LIFE study, for black patients, BP control throughout the study was similar in both treatment groups, and the losartan-based treatment induced a larger decrease in ECG-LVH than the atenolol-based treatment. These findings suggest that losartan-based treatment was used in appropriate doses and support the primary hypothesis of the LIFE study, namely that the angiotensin II receptor blocking agent losartan would antagonize the trophic effects of angiotensin on cardiac muscle cell hypertrophy in addition to lowering BP in black as well as non-black patients.

In a study comparing the effects of losartan versus atenolol treatment on vascular structure and function in non-black patients, ex vivo evaluation of gluteal arterioles found treatment with losartan was associated with regression of vascular hypertrophy and improvement in endothelial function, relative to atenolol, despite comparable control of BP (18). The fact that, in the LIFE study, the regression of ECG-LVH similarly favored losartan over atenolol in black patients suggests that losartan had similar antitrophic effects in this group.

It is difficult to conceive of a mechanism whereby, in the

face of good hemodynamic and antihypertrophic responses, a losartan-based treatment might have some negative cardiovascular effects in one subgroup of patients. Conversely, there are no established mechanisms by which an atenolol-based treatment might have a positive effect on cardiovascular outcomes only in black patients.

We diligently sought to analyze relevant factors that could potentially explain the differential cardiovascular outcome in black subjects in our study, and we were unable to determine a mechanism for this finding. Although we are fully aware that there might be an unknown ethnic difference in basic physiology or in pharmacologic responses, the fact that the lesser cardiovascular protection with losartan in black patients is contrary to any expectation, and against the known physiologic frame of reference, gives reason for caution.

Another important factor to consider in interpreting these data are the findings to the contrary cited in the recent guidelines for management of hypertension in African Americans published by the International Society on Hypertension in Blacks (19). Treatment algorithms in these guidelines recommend initiating antihypertensive therapy with renin aldosterone system-blocking agents in African Americans with renal disease based on results of the African American Study of Kidney Disease and Hypertension (AASK) trial with the ACE inhibitor ramipril (20,21), and in African Americans with diabetic nephropathy based on results of the Reduction of Endpoints in patients with Non–insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan in Diabetic Nephropathy Trial (IDNT) trials with the angiotensin II receptor antagonists losartan and irbesartan, respectively (22,23).

We believe that our finding is sufficiently convincing to generate the hypothesis that black patients with hypertension and LVH might not respond as favorably to losartan-based treatment as non-black patients, with respect to cardiovascular outcomes, and that these data do not support a recommendation for losartan as a first-line treatment for this purpose. However, this subanalysis is limited by a relatively small number of events among black patients in the LIFE study, and the data are insufficient to conclude that atenolol is superior to losartan with regard to reduction of cardiovascular events in black patients with hypertension and LVH. Properly powered studies in black hypertensive patients, in general, and in those with LVH, would be useful to address these questions.

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