The Influence of Left Ventricular Hypertrophy on Survival in Patients With Coronary Artery Disease: Do Race and Gender Matter?

Mark A. East, MD,* James G. Jollis, MD, FACC,* Charlotte L. Nelson, MS,* David Marks, MD, FACC,†
Eric D. Peterson, MD, MPH, FACC*

Durham, North Carolina; and Milwaukee, Wisconsin

OBJECTIVES	We sought to determine the overall prognostic importance of left ventricular hypertrophy (LVH) among patients with coronary artery disease (CAD), as well as to determine whether this risk varies as a function of race or gender.
BACKGROUND	Left ventricular hypertrophy is more prevalent among blacks and women than their counterparts. Blacks and women also have higher mortality with coronary disease.
METHODS	We studied records of 2,461 patients (19% black, 42% women) diagnosed with CAD at cardiac catheterization between 1990 and 1998 from a single academic center. Left ventricular hypertrophy was defined using standard echocardiographic measures. Cox proportional hazards models were used for adjusted survival analyses. Mean patient follow-up was three years.
RESULTS	Patients with LVH were older (68 vs. 65 years, p < 0.01), more often women (54% vs. 36%, p < 0.01), and black (25% vs. 16%, p < 0.01), and had higher unadjusted three-year mortality rates than patients without LVH (42% vs. 34%, p < 0.01). Left ventricular hypertrophy remained an independent predictor of mortality after adjusting for other clinical risk factors (hazard ratio 1.56, 95% confidence interval 1.35 to 1.80) with prognostic importance equivalent to that of left ventricular ejection fraction. Although the relative risk of LVH did not vary by race or gender, the attributable risk of LVH was greater in blacks and women.
CONCLUSIONS	Clinicians should consider the prognostic importance of LVH when assessing risk in patients with CAD. Because LVH is more common among black and women patients with CAD, it partially accounts for racial and gender differences in survival. (J Am Coll Cardiol 2003;41: 949–54) © 2003 by the American College of Cardiology Foundation

Estimating long-term prognosis is an important component in determining appropriate care for patients with coronary artery disease (CAD). Risk assessment has traditionally been based on the patient's demographics (age, gender, race), disease severity (extent of coronary occlusions, left ventricular [LV] ejection fraction), and other cardiac risk factors (diabetes mellitus, hypertension, smoking status, hyperlipidemia). Beyond this traditional risk assessment, investigators have identified left ventricular hypertrophy (LVH), defined by echocardiography, as an additional predictor of cardiovascular and all-cause mortality (1–4). Despite such evidence, in practice clinicians neither routinely assess for LVH nor adjust for it when they estimate a patient's prognosis (5–7).

Additionally, LVH is more prevalent in blacks than whites and in women than men (2–4,8), and prior studies have postulated that the relative risk (RR) associated with it may be greater in these subgroups (2,3,9). Combined, the differential effects of LVH could be an important explanation for known racial or gender differences in long-term survival among patients with coronary disease.

The primary purpose of this study was to determine the incremental prognostic importance of LVH in a large, contemporary, racially diverse population of patients with CAD. We explored whether the RR associated with LVH varied as a function of patient race or gender, and we examined to what extent LVH explained survival differences between blacks and whites and/or between women and men.

METHODS

Study patients. All patients underwent an initial cardiac catheterization at Duke University Medical Center between 1990 and 1998 and had an echocardiogram performed within one month, during which left ventricular mass (LVM) and body surface area (BSA) indices were obtained. Patients were eligible for the study if they were found to have significant obstructive coronary disease as we defined. Patients were excluded from our analysis if their race was classified as other than black or white.

Cardiac catheterization. Patients underwent standard left heart cardiac catheterization, and coronary cineangiograms

---

Abbreviations and Acronyms

BSA	=	body surface area
CAD	=	coronary artery disease
CI	=	confidence interval
HR	=	hazard ratio
$IVST_d$	=	interventricular septal thickness at end-diastole
LV	=	left ventricular
LVH	=	left ventricular hypertrophy
$LVID_d$	=	left ventricular internal dimension at end-diastole
LVM	=	left ventricular mass
LVMI	=	left ventricular mass index
PAR	=	population attributable risk
PWT_d	=	posterior wall thickness at end-diastole
RR	=	relative risk

---

were obtained in the standard projections. Significant CAD was defined as a ≥75% reduction in the cross-sectional diameter of a major coronary artery. The extent of CAD was summarized with the Coronary Artery Disease Index, a composite score that takes into account both disease location and severity (10).

Echocardiography. Echocardiograms were performed using standard two-dimensional measurements. The LV measurements included interventricular septal thickness at end-diastole ($IVST_d$), the posterior wall thickness at end-diastole (PWT_d), and left ventricular internal dimension at end-diastole ($LVID_d$). Corrected LV mass was calculated using this formula (11): $LVM = 1.04 [(IVST_d + LVID_d + PWT_d)^3 - (LVID_d)^3] [(0.8 + 0.6)]$. Left ventricular mass index (LVMI, g/m^2) was calculated as LVM/BSA (12). Finally, the diagnostic criteria for LVH using LVMI (g/m^2) were ≥134 g/m^2 for men and ≥110 g/m^2 for women, representing the gender-specific 97th percentile of a previously published reference in a normal population (13).

Data collection and follow-up. Baseline clinical and demographic information and informed consent were obtained by a physician at the time of cardiac catheterization (14,15). Patients were contacted by telephone six months after the index catheterization and annually thereafter. Follow-up was complete in 95% of the patients. The National Death Index was used to search for patients we were unable to locate (16).

Statistical analysis. Medians and interquartile ranges (25th to 75th percentile) were used to describe baseline characteristics in continuous variables, and percentages were used to describe discrete variables. The associations between these characteristics and LVH were analyzed using a chi-square or Wilcoxon rank-sum test as appropriate.

We analyzed LVH both as a continuous and as a dichotomous variable using the previously described cutoff points. For descriptive purposes, the dichotomous results were presented; however, the results of LVH on overall prognosis and by race and gender were similar regardless of the method of analysis of the variable. Because of censoring, we considered survival to three years the primary end point.

The incremental effect of LVH on the three-year survival rate was performed using a Cox survival model that adjusted for known prognostic baseline indicators including age, gender, race, coronary artery disease severity (CAD index), LV ejection fraction, diabetes mellitus, chronic obstructive pulmonary disease, peripheral vascular disease, mitral insufficiency, and congestive heart failure (17). Hypertension was also considered for inclusion in this model but was not found to be a significant independent predictor after adjusting for other factors. We formally analyzed whether the RR of LVH varied by race or gender by testing the significance of interaction terms (LVH by race, LVH by gender) in the Cox survival model. Risk ratios (hazards ratio) and the 95% confidence intervals (CIs) were derived from the Cox coefficients and associated standard error. We calculated the population attributable risk (PAR) by race and by gender, which takes into account both the prevalence of LVH and the RR of death associated with LVH, using the formula: $PAR = LVH$ prevalence $(RR - 1)/[LVH$ prevalence $(RR - 1) + 1]$.

RESULTS

Baseline characteristics. We identified 4,953 patients who had significant CAD at catheterization and underwent echocardiography within one month of catheterization. Of these, 2,461 patients had echocardiographic measurements necessary for LVM calculation, had BSA information, and were either black or white. Comparison of patients included in our study versus those excluded because of missing echocardiographic information revealed no significant differences in baseline clinical risk factors.

Cumulative LVM by BSA ranged from 94 to 156 g/m^2. Using standard echocardiographic criteria, LVH was identified in 35% of our CAD population (Table 1). Patients with LVH were slightly older (68 vs. 65 years) and more likely to have hypertension (75% vs. 61%), diabetes (39% vs. 31%), and peripheral vascular disease (25% vs. 20%) than patients without LVH.

LVH as a risk factor for all-cause mortality. The mean follow-up duration was 3 ± 2 years. The overall unadjusted and adjusted survival rates were significantly lower among patients with LVH compared with patients having normal LVM (Fig. 1). Unadjusted survival rates at one, three, and five years were 75%, 56%, and 42% respectively for those with LVH versus 88%, 76%, and 67% (p < 0.01) respectively for those without LVH. The unadjusted risk ratio for patients with LVH at three years was 2.1 (95% CI 1.96 to 2.23).

After adjusting for demographic, clinical, and angiographic risk factors (Table 2), LVH remained an independent predictor of three-year mortality (RR 1.56, 95% CI 1.35 to 1.80). Ranking these risk factors by their overall contribution to model, we found LVH to be the third most powerful prognostic factor, after patient age and coronary disease severity (Table 2).

Table 1. Baseline Characteristics of the Study Population

Variable	LVH (n = 862)	Non-LVH (n = 1,599)	p Value
Age (yrs)	68 (60,75)	65 (56,73)	< 0.01
Blacks	25	16	< 0.01
Female	54	36	< 0.01
Hypertension	75	61	< 0.01
Diabetes mellitus	39	31	< 0.01
Hyperlipidemia	50	52	0.37
Peripheral vascular disease	25	20	< 0.01
Chronic obstructive pulmonary disease	9	11	0.20
Ejection fraction	40 (28,55)	50 (38,60)	< 0.01
NYHA class IV congestive heart failure	20	9	< 0.01
Severe mitral insufficiency, 3 +	13	7	< 0.01
Severe mitral insufficiency, 4 +	6	4	< 0.01
Number of diseased vessels			< 0.01
1 vessel	30	36	
2 vessel	26	26	
3 vessel	44	38	
Treatment			< 0.01
Medicine	63	49	
PTCA	19	31	
CABG	18	20	

CABG = coronary artery bypass graft; LVH = left ventricular hypertrophy; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty.

LVH risk as a function of race or gender. We also assessed whether the RR of LVH varied with patient race or gender. Although LVH was more common among blacks than whites (46% vs. 33%, p < 0.01) and among women than men (45% vs. 28%, p < 0.01), its impact on unadjusted and adjusted survival estimates in these groups was similar (Figs. 2 and 3). The adjusted LVH hazard ratio (HR) was 1.54 (95% CI 1.11 to 2.13) in blacks versus 1.56 (95% CI 1.33 to 1.84) in whites. In women, the adjusted LVH HR was 1.48 (95% CI 1.20 to 1.83) versus 1.63 (95% CI 1.34 to 1.98) in men. Additionally, formal statistical testing revealed no significant interaction between LVH and race or gender. Although blacks and women had similar RR, their higher prevalence of LVH led to differences in the PAR. The PAR was 20% among blacks versus 16% among whites, and 18% among women versus 15% among men.

Prognostic implications for higher mortality among blacks and women. In the overall CAD population, blacks had higher unadjusted mortality rates than whites at three years: 43% versus 23% for those with LVH and 30% versus 23% for those without. After adjusting for traditional clinical risk factors, blacks continued to have higher mortality risk (HR 1.16, 95% CI 0.98 to 1.37). However, after adjusting for traditional factors and LVH, the mortality differences narrowed (HR 1.10, 95% CI 0.93 to 1.31).

Women also had higher unadjusted three-year mortality rates than men: 40% versus 24% for those with LVH and 30% versus 21% for those without. After adjusting for baseline traditional risk factors, women and men had similar three-year mortality rates (HR 1.01, 95% CI 0.88 to 1.17). Interestingly, after accounting for traditional risk factors and LVH, women actually had a trend toward lower long-term mortality than men did (HR 0.93, 95% CI 0.81 to 1.08).

DISCUSSION

Clinical practice guidelines have not traditionally emphasized the need to consider LVH in the risk assessment of those with coronary disease (6,7). However, our contemporary study confirmed that the presence of LVH had important prognostic implications in a large, racially diverse patient cohort. Although its relative impact on prognosis was similar across race and gender, differences in LVH prevalence can partly explain why blacks and women with coronary disease have higher mortality rates than their counterparts.

The Framingham Heart Study was one of the first investigations to identify the prognostic importance of LVH (4). M-mode echocardiography was used to classify LVH status in 3,220 subjects without baseline cardiac disease. After adjusting for cardiac risk factors, all-cause mortality risk with LVH was 1.49 (95% CI 1.14 to 1.94) in men and 2.01 (95% CI 1.44 to 2.81) in women. However, this study was limited to a predominately white patient population and reflects care patterns from the 1980s.

Liao et al. (2) studied echocardiographic-measured LVH in a predominately black cohort undergoing concomitant cardiac catheterization between 1983 and 1991. After adjusting for baseline risk factors and angiographic findings, these investigators also found that LVH doubled a patient's five-year mortality risk. They further concluded that the RR of LVH was higher in women than men, particularly among those patients with insignificant coronary disease. They also proposed that LVH may play a differential role in blacks versus whites, but their study lacked an adequate representation of whites to test this hypothesis (3).

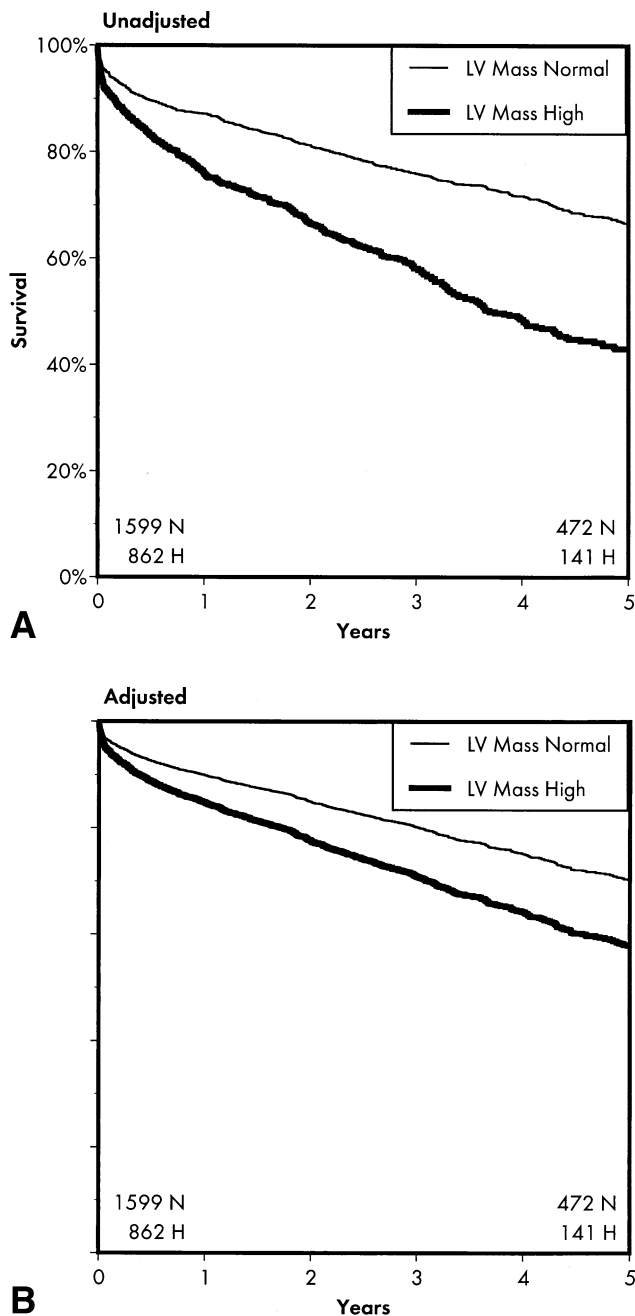Our study confirms and expands our understanding of the

Figure 1. Survival curves for patients with and without left ventricular (LV) hypertrophy showing unadjusted **(A)** and adjusted **(B)** comparisons of the two groups. **Numbers at the bottom of the plots** show the number of patients at risk at 0 and 5 years of follow-up. H = LV mass high; N = LV mass normal.

Table 2. Predictors of All-Cause Three-Year Mortality

Variable	All-Cause Mortality	
	Wald Chi-Squared	HR (95% CI)
Age*	76	1.30 (1.26–1.44)
Coronary artery disease†	52	1.58 (1.34–1.86)
Left ventricular mass index	36	1.56 (1.35–1.80)
Ejection fraction‡	34	1.16 (1.11–1.22)
Diabetes	19	1.37 (1.19–1.58)
Chronic obstructive pulmonary disease	17	1.51 (1.24–1.85)
Congestive heart failure	15	1.09 (1.05–1.15)
Peripheral vascular disease	15	1.35 (1.16–1.57)
Mitral insufficiency	8	1.33 (1.10–1.61)
Black race	1	1.10 (0.93–1.31)
Female gender	0.9	0.93 (0.81–1.08)

*Relative risk per decade of life increase. †Relative risk associated with single-vessel disease versus multivessel disease. ‡Relative risk for ejection fraction expressed as a 10% decrease. All other variables are categorical.

CI = confidence interval; HR = hazard ratio.

Although the RR of LVH was constant among patient subgroups, racial and gender differences in disease prevalence of LVH may have important prognostic implications. Specifically, multiple studies have reported that blacks and women have higher mortality with coronary disease than their counterparts (1,18–20). However, these prior studies had not considered the influence of LVH. We found much of the race and gender differences in prognosis accounted for by the higher prevalence of LVH among blacks and women.

Biologic influence of LVH on prognosis. Left ventricular hypertrophy has multiple potential mechanisms for detrimental end organ sequelae. Activation of the renin-angiotensin system leads to cardiac hypertrophy and LVH (21). Angiotensin II has been shown to induce vasoconstriction by local release of norepinephrine (22,23). Angiotensin II has also been directly linked to the coagulation and fibrinolytic pathways and vascular smooth muscle proliferation and thus progression of atherosclerosis (24,25). Therefore, angiotensin II may be the common mediator explaining the strong association of LVH with CAD.

Left ventricular hypertrophy may also increase the risk of death in those patients having coronary disease. Studies have demonstrated that LVH is associated with increases in whole-blood viscosity, white blood cell counts, and plasma fibrinogen levels, all increasing patients' likelihood for a coronary event (26,27). Additionally, the Framingham Heart Study showed that hypertensive patients with LVH are at increased risk of sudden arrhythmic death (4,28). Of patients with LVH 92% will demonstrate re-entry rhythms in response to programmed ventricular stimulation versus 17% in those without, suggesting an anatomic substrate for ventricular arrhythmias (29).

Although the prognostic implications of LVH were clear, less had been understood regarding effective treatment for LVH. Proposed therapies include diuretics, calcium-channel blockers, beta-blockers, angiotensin-converting en-
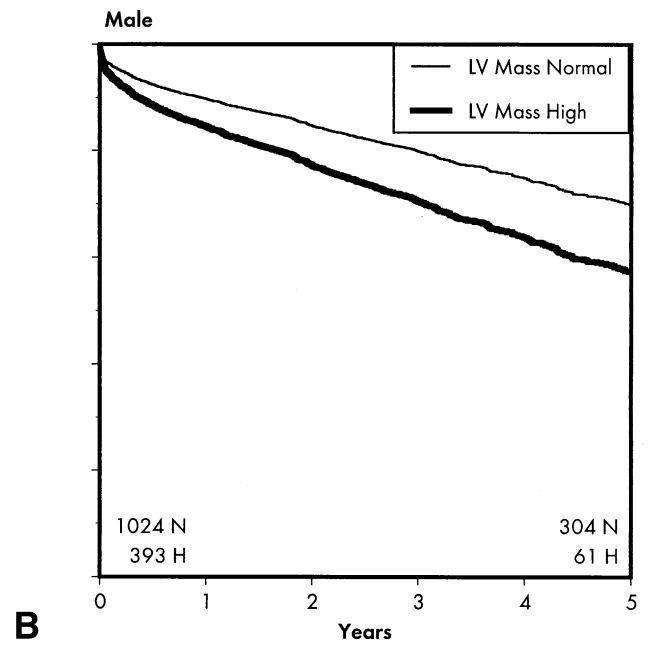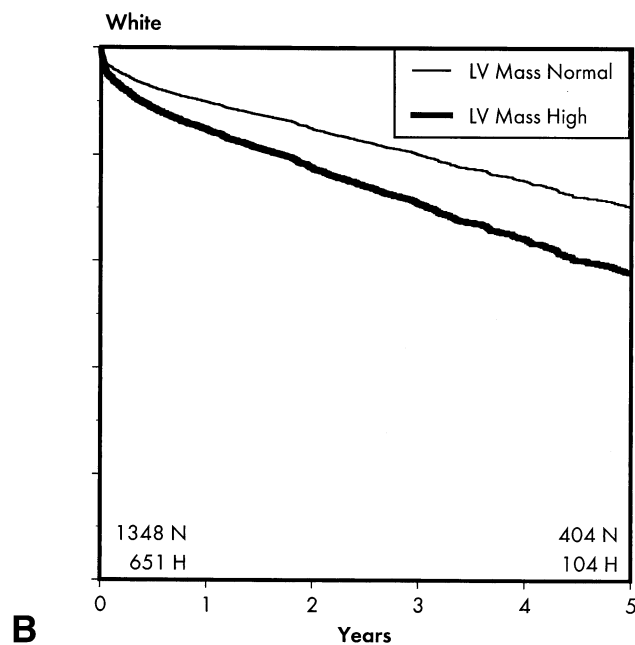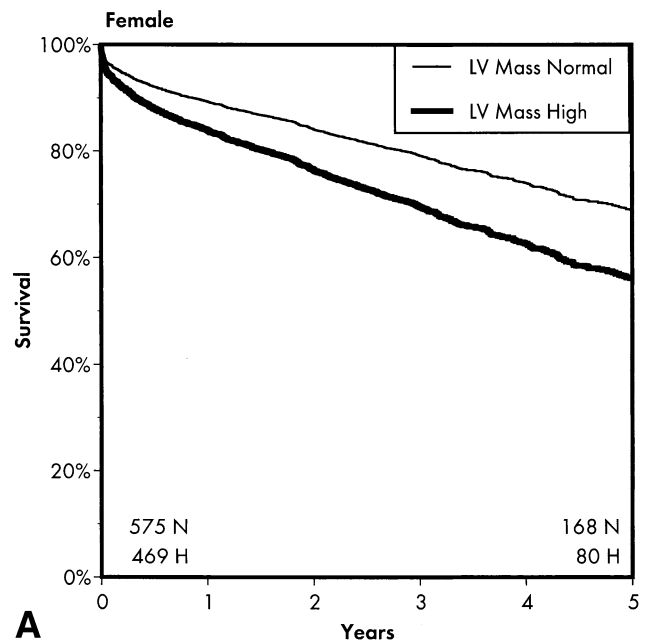
prognostic importance of assessing LVH in those with CAD. We found that the identification of LVH by echocardiography had similar prognostic importance to knowing a patient's LV ejection fraction (Table 2). Contrary to prior reports and speculation, however, we found that the RR of LVH was almost identical in blacks and whites and women and men. Differences between our results and prior studies may be due to our more racially diverse population and our inclusion of only patients with known coronary disease.
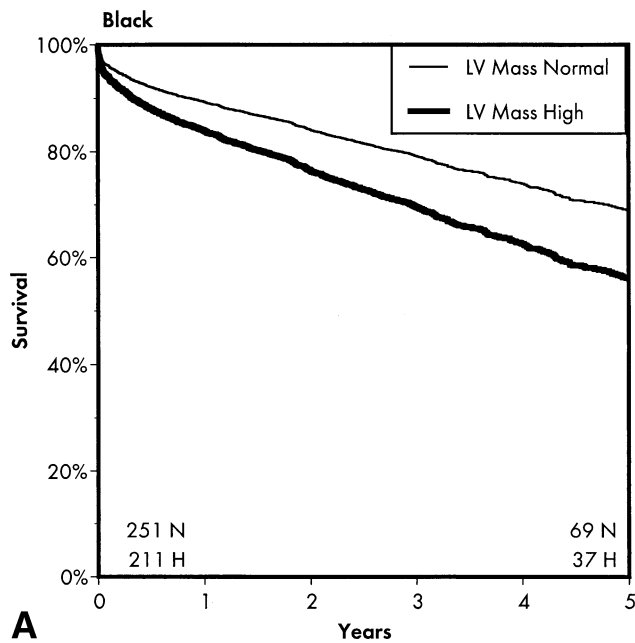
Figure 2. Survival curves for patients with and without left ventricular (LV) hypertrophy showing black **(A)** and white **(B)** patients adjusted for demographic and clinical characteristics. **Numbers at the bottom of the plots** show the number at risk at 0 and 5 years of follow-up. H = LV mass high; N = LV mass normal.

Figure 3. Survival curves for patients with and without left ventricular (LV) hypertrophy showing female **(A)** and male **(B)** patients adjusted for demographic and clinical characteristics. **Numbers at the bottom of the plots** show the number of patients at risk at 0 and 5 years of follow-up. H = LV mass high; N = LV mass normal.

zyme inhibitors, and angiotensin II blockers. However, the recently completed Losartan Intervention For End point reduction in hypertension (LIFE) trial provided some comparative data, randomizing patients with hypertension and LVH to an angiotensin II blocker (losartan) versus a beta-blocker (atenolol). The study found that those treated with losartan had greater regression in the LVH and 13% lower RR for acute myocardial infarction, stroke, and death than those treated with a beta-blocker (30).

Study limitations. Our study was limited to those with CAD and does not address LVH in those without CAD. Our study was retrospective and thus limited to those patients undergoing echocardiography and catheterization, a population that is generally sicker than patients undergoing catheterization alone. Serial LVH measurements were not obtained and there were no data on patients' medication profiles.

Conclusions and clinical application. Our study suggests that current CAD risk stratification algorithms should be

re-evaluated to consider the strong incremental prognostic influence of LVH. Assessment of LVH can significantly improve assessment of an individual patient's long-term prognosis. Unfortunately, LVH is common in patients with coronary disease, particularly in blacks and women, and may partially explain poor prognosis in these latter groups. Primary and secondary prevention of LVH through appropriate pharmacologic therapy is indicated. Further studies, however, are needed to determine which form of treatment is most effective and whether treatment selection varies as a function of patient race or gender.

Acknowledgment

Reprint requests and correspondence: Dr. Mark A. East, Duke Clinical Research Institute, P.O. Box 17969, Durham, North Carolina 27715. E-mail: east0001@onyx.dcri.duke.edu.

REFERENCES

1. Cooper RS, Simmons BE, Castaner A, Santhanam V, Ghali J, Mar M. Left ventricular hypertrophy is associated with worse survival independent of ventricular function and number of coronary arteries severely narrowed. Am J Cardiol 1990;65:441–5.
2. Liao Y, Cooper RS, McGee DL, Mensah GA, Ghali JK. The relative effects of left ventricular hypertrophy, coronary artery disease, and ventricular dysfunction on survival among black adults. JAMA 1995;273:1592–7.
3. Liao Y, Cooper RS, Mensah GA, McGee DL. Left ventricular hypertrophy has a greater impact on survival in women than in men. Circulation 1995;92:805–10.
4. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322:1561–6.
5. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non–ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2000;36:970–1062.
6. Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J Am Coll Cardiol 1999;34:890–911.
7. Peterson ED, Shaw LJ, Califf RM. Risk stratification after myocardial infarction. Ann Intern Med 1997;126:561–82.
8. Savage DD, Henry WL, Mitchell JR, et al. Echocardiographic comparison of black and white hypertensive subjects. J Natl Med Assoc 1979;71:709–12.
9. Levy D, Labib SB, Anderson KM, Christiansen JC, Kannel WB, Castelli WP. Determinants of sensitivity and specificity of electrocardiographic criteria for left ventricular hypertrophy. Circulation 1990;81:815–20.
10. Smith LR, Harrell FE Jr., Rankin JS, et al. Determinants of early versus late cardiac death in patients undergoing coronary artery bypass graft surgery. Circulation 1991;84 Suppl:III:245–53.
11. Troy BL, Pombo J, Rackley CE. Measurement of left ventricular wall thickness and mass by echocardiography. Circulation 1972;45:602–11.
12. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450–8.
13. Devereux RB, Lutas EM, Casale PN, et al. Standardization of M-mode echocardiographic left ventricular anatomic measurements. J Am Coll Cardiol 1984;4:1222–30.
14. Peterson ED, Shaw LK, DeLong ER, Pryor DB, Califf RM, Mark DB. Racial variation in the use of coronary-revascularization procedures. Are the differences real? Do they matter? N Engl J Med 1997;336:480–6.
15. Califf RM, Harrell FE Jr., Lee KL, et al. The evolution of medical and surgical therapy for coronary artery disease. A 15-year perspective. JAMA 1989;261:2077–86.
16. Fisher SG, Weber L, Goldberg J, Davis F. Mortality ascertainment in the veteran population: alternatives to the National Death Index. Am J Epidemiol 1995;141:242–50.
17. Mark DB, Nelson CL, Califf RM, et al. Continuing evolution of therapy for coronary artery disease. Initial results from the era of coronary angioplasty. Circulation 1994;89:2015–25.
18. Judge KW, Pawitan Y, Caldwell J, Gersh BJ, Kennedy JW. Congestive heart failure symptoms in patients with preserved left ventricular systolic function: analysis of the CASS registry. J Am Coll Cardiol 1991;18:377–82.
19. Kannel WB, Castelli WP, McNamara PM, McKee PA, Feinleib M. Role of blood pressure in the development of congestive heart failure. The Framingham study. N Engl J Med 1972;287:781–7.
20. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971;285:1441–6.
21. Malhotra R, Sadoshima J Brosius FC III, Izumo S. Mechanical stretch and angiotensin II differentially upregulate the renin-angiotensin system in cardiac myocytes in vitro. Circ Res 1999;85:137–46.
22. Goldsmith SR, Hasking GJ, Miller E. Angiotensin II and sympathetic activity in patients with congestive heart failure. J Am Coll Cardiol 1993;21:1107–13.
23. Lyons D, Webster J, Benjamin N. Angiotensin II: adrenergic sympathetic constrictor actions in humans. Circulation 1995;91:1457–60.
24. Vaughan DE, Lazos SA, Tong K. Angiotensin II regulates the expression of plasminogen activator inhibitor-1 in cultured endothelial cells: a potential link between the renin-angiotensin system and thrombosis. J Clin Invest 1995;95:995–1001.
25. Feener EP, Norhtrup JM, Aiello LP, et al. Angiotensin II induces plasminogen activator inhibitor-1 and -2 expression in vascular endothelial and smooth muscle cells. J Clin Invest 1995;95:1353–62.
26. Lip GY, Blann AD, Jones AF, Lip PL, Beevers DG. Relation of endothelium, thrombogenesis, and hemorheology in systemic hypertension to ethnicity and left ventricular hypertrophy. Am J Cardiol 1997;80:1566–71.
27. Devereux RB, Drayer JI, Chien S, et al. Whole blood viscosity as a determinant of cardiac hypertrophy in systemic hypertension. Am J Cardiol 1984;54:592–5.
28. Casale PN, Devereux RB, Milner M, et al. Value of echocardiographic measurement of left ventricular mass in predicting cardiovascular morbid events in hypertensive men. Ann Intern Med 1986;105:173–8.
29. Coste P, Clementy J, Besse P, Bricaud H. Left ventricular hypertrophy and ventricular dysrhythmic risk in hypertensive patients: evaluation by programmed electrical stimulation. J Hypertens 1988;6 Suppl:S:116–8.
30. Dahlof B, Devereux RB, Kjedlsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study: a randomized trial against atenolol. Lancet 2002;359:995–1003.