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Left ventricular hypertrophy as a predictor of coronary heart disease mortality and the effect of hypertension

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Background Although associations between hypertension, left ventricular hypertrophy (LVH), and coronary heart disease (CHD) have been described, it is less clear whether LVH is associated with increased rates of CHD in the absence of hypertension.

Methods We examined this association with Cox regression analyses of data from 7924 adults 25 to 74 years of age from the Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study (1976 to 1992). Covariates included age, race, sex, history of cardiovascular diseases and diabetes, cholesterol, body mass index, blood pressure, and smoking.

Results During 16.8 follow-up years, there were 462 (26%) deaths from CHD (ICD-9 410-414) and 667 (38%) deaths from diseases of the heart (ICD-9 390-398, 402, 404, 410-414, 415-417, 420-429). LVH prevalence was 13.3 per 1000 population. Hypertension prevalence was 29.1%. LVH prevalence was higher among hypertensive adults than among normotensive adults (29.9 vs 6.4 per 1000, $P < .001$). Persons with LVH were twice as likely to die of CHD (relative risk, 2.0; 95% confidence interval, 1.2, 3.5) and diseases of the heart (relative risk, 1.9; 95% confidence interval, 1.1, 3.0) after adjustment for hypertension and covariates. In age-adjusted predicted survival, probability plots for CHD, and diseases of the heart, normotensives with LVH had survival similar to hypertensive adults with LVH and lower survival than normotensive and hypertensive adults with no LVH.

Conclusions Our results confirm previous findings that the presence of LVH is a strong predictor of future cardiovascular death. Although LVH appears to be rare among normotensives, clinicians should be aware that such individuals may have an increased risk for death similar to that of hypertensive adults with LVH. (*Am Heart J* 2000;140:848-56.)

Left ventricular hypertrophy (LVH) is a strong risk factor for cardiovascular disease. Numerous studies have found it to be associated with adverse cardiovascular outcomes including stroke, sudden death, myocardial infarction (MI), congestive heart failure, and coronary heart disease (CHD).¹⁻⁴ In addition, data from the Framingham Heart Study and the Bronx Longitudinal Aging Study suggest that the presence of electrocardiographically defined LVH (ECG-LVH) is an independent predictor of all-cause death.⁵

Hypertension is a major risk factor for both LVH and cardiovascular disease. Among hypertensive patients, the presence of ECG-LVH increases the risk of cardiovas-

cular disease nearly 3-fold.⁶ Although hypertension is more strongly associated with heart failure and stroke, it has been observed to account for a greater absolute and excess risk of CHD than for these other events.⁶ A similar result was observed for ECG-LVH.⁷

Although the association between hypertension, LVH, and death has been well described, it is less clear whether LVH in the absence of hypertension is associated with increased CHD mortality rates. Data from the Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study were used to examine the association between ECG-LVH and CHD death among a nationally representative sample of whites and blacks with and without hypertension. In addition, analyses were repeated for deaths associated with diseases of the heart.

Methods

The National Center for Health Statistics of the Centers for Disease Control and Prevention conducted the Second National Health and Nutrition Examination Survey between February 1976 and February 1980. NHANES II, a nationwide probability sample of approximately 28,000 persons, was designed to be representative of the civilian, noninstitutional-

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ized population of the United States, 6 months to 74 years of age. A detailed description of the NHANES II survey and sampling procedures has been provided elsewhere.⁸

Briefly, data were collected through responses to questions on individual medical history, food consumption, and health-related behavior.⁸ In addition, persons underwent a physical examination by a licensed physician who followed a standardized procedure to complete the examination and to record examination results. Serum cholesterol (mg/dL), height (cm), weight (kg), and systolic and diastolic blood pressure (mm Hg) were measured. To obtain a more accurate measure of blood pressure, 3 blood pressure readings were recorded. The blood pressure used in this analysis was the mean value of the second and third readings.

For persons 25 to 74 years of age, electrocardiographic signal data were collected by means of a Novacode ECG program.⁹ Electrocardiographic data were coded according to the Minnesota code. Presence of probable LVH was defined by means of code 3.1 (Left: R amplitude >26 mm in either V₅ or V₆, or R amplitude >20.0 mm in any of leads I, II, III, and aVF, or R amplitude >12.0 mm in lead aVL measured only on second-to-last complete normal beat) and one of the following codes: 5.1 (T amplitude negative 5.0 mm or more in lead II, or in lead aVF when QRS is mainly upright), 5.2 (T amplitude negative or biphasic with negative phase at least 1.0 mm but not as deep as described in 5.1), or 5.3 (T amplitude flat, negative, or biphasic (negative-positive type only) with less than 1.0 mm negative phase in lead II; not coded in lead aVF).

The two outcome variables of interest were death from CHD and death from diseases of the heart. CHD death was defined by ICD-9 codes 410-414 and diseases of the heart death by ICD-9 codes 390-398, 402, 404, 410-414, 415-417, and 420-429.

Baseline data from NHANES II was merged with follow-up data from the NHANES II Mortality Study. As part of the NHANES II Mortality Study, data from the National Death Index, which has been shown to capture 93% to 98% of all deaths,¹⁰⁻¹² and from the Social Security Administration Death Master File were used to ascertain the vital status of each cohort member through December 31, 1992 (approximately 16.8 years of follow-up). Information obtained from the Mortality Study data includes the month and year in which an individual was last known to be alive and the ICD-9 code for the underlying cause of death. Because only month and year of the date of death were ascertained, the 15th day of the month was analyzed as the day of the date last known to be alive for decedents. For all others, December 31, 1992, was assigned as the last known date alive. Follow-up (ie, survival) time was calculated as the difference between the NHANES II baseline examination date for each subject and the last known date alive obtained from the NHANES II Mortality Study. As a result of the last known day alive assignment, one subject who was examined after the 15th of the month and who died within days of the baseline examination had a calculated negative value for follow-up time. This individual was assigned a follow-up time value of zero.

Of the 9250 persons followed prospectively by the NHANES II Mortality Study, 8159 received a baseline electrocardiogram. Our analysis was limited to 7924 of these who were white or black and who had complete information for height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), total

serum cholesterol, history of cardiovascular disease, physical activity, and education. Cox proportional hazards regression was used to assess the independent relation between LVH and death from CHD and diseases of the heart in age-adjusted and multivariate-adjusted analyses. The multivariate-adjusted analysis took into account age, race, sex, SBP, total cholesterol level, body mass index (BMI), smoking status, and history of cardiovascular disease and diabetes mellitus. Age, SBP, cholesterol level, and BMI were entered into the model as continuous variables.

Analyses were completed by use of the full sample ($n = 7924$) as well as stratified by hypertensive status. Normotensive persons ($n = 5158$) were defined as having SBP <140 mm Hg, DBP <90 mm Hg at baseline examination, and not taking antihypertensive medications. Hypertensive persons ($n = 2756$) were defined as those having a baseline SBP ≥ 140 mm Hg, DBP ≥ 90 mm Hg, or currently using antihypertensive medication.

Differences in survival among hypertensive and normotensive persons with or without LVH were assessed for each cause of death. Using a Cox proportional hazards model, we obtained the effect on survival time for age and for each of the following groups: hypertensive-LVH, hypertensive-no LVH, and normotensive-LVH. The reference group was normotensive-no LVH. The baseline survival probability at time t was calculated as the exponent of the baseline cumulative hazard at time t obtained from Sudaan. Predicted survival probabilities were then calculated for each group by using the baseline survival probability and the regression coefficient for each group evaluated at the mean age of the sample ($\mu = 49.2$ years). The predicted survival probabilities were then plotted against the survival time.

To make the NHANES representative of the US population, sample weights were used in all analyses. A χ^2 test was used to compare differences in categorical variables across groups, and a 2-sided t test was used for continuous variables. Ordinal trend tests used logistic regression with either CHD death or diseases of the heart death as the dependent variable and an ordinal independent variable. To account for the complex sampling design and to achieve accurate variance estimates, we used Sudaan 7.0 (Research Triangle Institute, 1996) to complete all analyses. All statistical inferences were based on a significance level of .05.

Results

At baseline, persons with probable LVH were more likely than those without LVH to be older, black, and male (Table I). They were also more likely to be physically inactive and to have completed less than a high school education. The mean BMI was nearly the same for those with and those without LVH. Mean SBP and DBP were significantly higher in persons with LVH.

History of cardiovascular disease differed significantly between the two groups. Compared with persons without LVH, a greater proportion of persons with LVH reported MI (11.3% vs 4.0%, $P < .05$) and stroke (6.4% vs 2.0%, $P < .05$). Persons with LVH were also more likely to report a history of hypertension (52.2% vs 29.3%, $P < .001$) and diabetes (8.2% vs 4.2%, $P < .05$).

The unadjusted prevalence of LVH in the sample was

Table I. Correlates of LVH

	LVH (n = 147)	No LVH (n = 7777)	All persons (n = 7924)
Male ¹ (%)	62.6		47.6
Black ² (%)	31.6	47.4	9.6
Age,† mean (y)	58.2 (1.30)	9.3	49.2 (0.22)
Age group (%)			
<40 y	8.5		28.4
40-49 y	17.2	28.7	23.4
50-59 y	22.6	23.5	23.6
60-69 y	32.7	23.6	18.4
≥70 y	19.0	18.2	6.3
Education (%)		6.1	
High school education* ³	20.0		35.9
College education ⁴	24.2	36.1	30.4
Physical activity (%)		30.4	
Very active	7.4		10.2
Moderately active	77.3	10.3	79.7
Inactive ⁵	15.3	79.7	10.1
Smoking status (%)		10.0	
Current smoker	35.2		35.9
Former smoker	26.2	35.9	25.7
Never smoked	38.6	25.7	38.4
BMI, mean (kg/m ²)	25.9 (0.41)	38.4	25.9 (0.08)
SBP,† mean (mm Hg)	150.9 (2.88)	25.9 (0.08)	130.5 (0.65)
DBP,‡ mean (mm Hg)	90.2 (2.10)	130.5 (0.65)	130.8 (0.65)
H _c MI (%)	11.3	83.1 (0.57)	83.2 (0.57)
H _c hardening of arteries (%)	4.7	4.0	4.1
H _c stroke (%)	6.4	3.4	3.4
H _c heart failure (%)	1.3	2.0	2.0
H _c hypertension ⁶ (%)	52.2	1.1	1.1
H _c diabetes (%)	8.2	4.2	29.6
Left ventricular mass ⁷ (g)	170.6 (3.45)	4.2	4.2
Left ventricular mass index ⁷ (g/m ²)	136.7 (3.45)	149.8 (0.49)	150.1 (0.50)
Follow-up time,† mean (y)	11.6 (0.49)	99.7 (0.41)	100.2 (0.41)
Death		13.9 (0.14)	13.9 (0.14)
Diseases of the heart ⁸ (%)	17.7		5.3
CHD ⁹ (%)	13.3	5.2	3.7

Standard error reported in parentheses.

Diseases of the heart defined by ICD-9 codes 390-398, 402, 404, 410-414, 415-417, and 420-429.

CHD defined by ICD-9 codes 410-414.

*Completed education through grade 12.

†Completed at least some college education.

‡Statistically significant differences between LVH and No LVH, $P < .001$.§Statistically significant differences between LVH and No LVH, $P < .01$.¶Statistically significant differences between LVH and No LVH, $P < .05$.

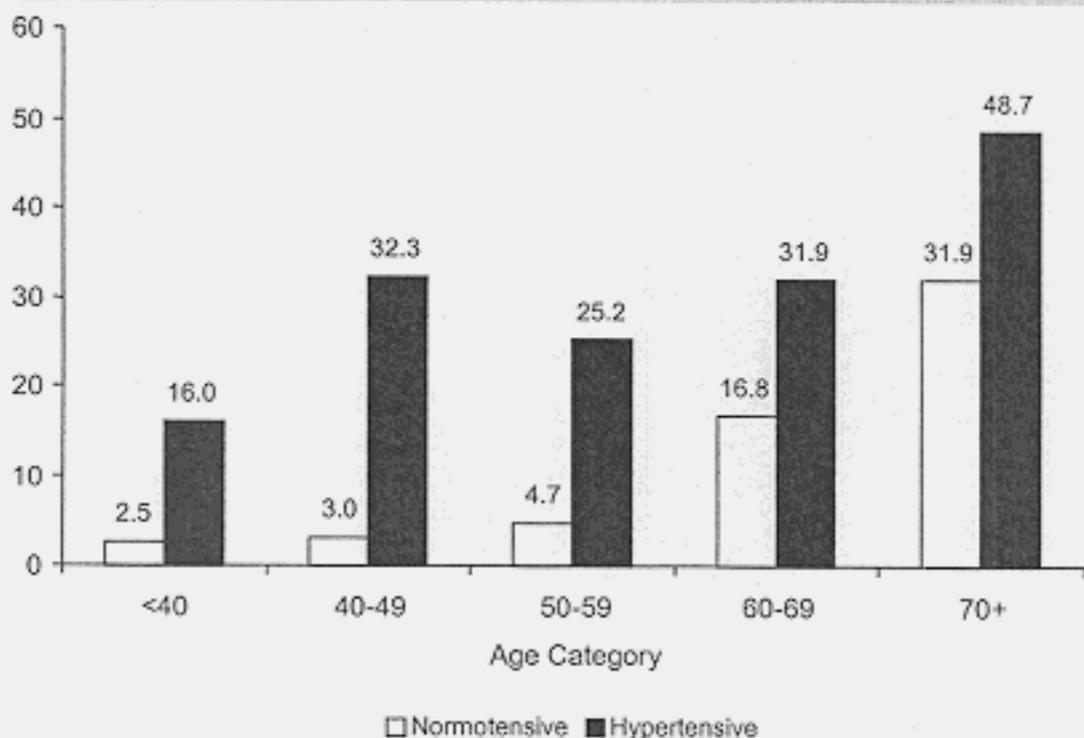
13.3 per 1000 population. The age-adjusted prevalence of LVH per 1000 population was 4.0 among those <40 years of age; 9.8 among those 40 to 49 years of age; 12.7 among those 50 to 59 years of age; 23.6 among those 60 to 69 years of age; and 40.2 among those ≥70 years of age. The unadjusted prevalence of LVH among hypertensive persons was significantly higher than among normotensive persons (29.9 vs 6.4 per 1000, $P < .001$). This result persisted across age categories (Figure 1). Within the 3 age groups under 60 years, a large difference in prevalence was observed between the hypertensive and normotensive groups.

Sex, increasing age, smoking status, education, physical activity, BMI, cholesterol level, and history of car-

diovascular disease, hypertension, and diabetes were risk factors significantly associated with death from CHD (Table II). Similar relations were observed for diseases of the heart (data not shown). Race was significantly associated with CHD death only. Among those in this study whose underlying cause of death was CHD, 13.3% had evidence of probable LVH. Among those who died of diseases of the heart, 17.7% had LVH.

The median follow-up time for the sample was 14.6 years. The crude mortality rate from CHD among persons with LVH was >5 times that for persons without LVH (1153.7 vs 259.1 per 100,000 person-years) (Table III). After adjusting for cardiovascular disease risk factors, we found persons with LVH were twice as likely

Figure 1



Prevalence of LVH per 1000 population by hypertensive status and age. Normotensive status is defined as SBP <140 mm Hg, DBP <90 mm Hg, and not currently taking antihypertensive medications. Hypertensive status includes controlled hypertension and uncontrolled hypertension. Controlled hypertension is defined as SBP <140 mm Hg or DBP <90 mm Hg and currently taking blood pressure medication. Uncontrolled hypertension is defined as SBP \geq 140 mm Hg or DBP \geq 90 mm Hg.

to die of CHD (95% confidence interval [CI], 1.20-3.45). Similarly, for diseases of the heart death, the crude mortality rate for persons with LVH was 1530 per 100,000 person-years; for persons without LVH, it was 370.2. The association between LVH and death from diseases of the heart was similar to that for CHD death. Persons with LVH were 1.86 (95% CI, 1.14-3.03) times more likely to die of diseases of the heart than were those without LVH.

For normotensives with LVH, the crude mortality rates for CHD and diseases of the heart were 6 and 10 times the respective rates for normotensives without LVH (Table IV). Although the relative difference was not as great among hypertensives, mortality rates were more than twice as high for those with LVH than for those without. For both persons with and those without hypertension, the presence of LVH was associated with a 2-fold increase in risk of dying of CHD or diseases of the heart. The relative risk (RR) of CHD death, after controlling for age, was 2.19 for both hypertensive and normotensive persons. For diseases of the heart death, normotensives with LVH were at signifi-

cantly increased risk of death, but in neither model did normotensives have significantly increased risk. Hypertensives with LVH were also at increased risk of death. The estimates were not statistically significant, however, and their magnitude was considerably less than that observed among normotensives.

A plot of the age-adjusted predicted survival probability showed that for both CHD death and diseases of the heart death, the proportion of normotensives without LVH who survived to the end of follow-up was greater than that of any of the other 3 groups (Figures 2 and 3). For CHD death, the proportion of hypertensives with LVH who survived to the end of the follow-up period was lower than that of normotensives with LVH or without LVH and hypertensives without LVH (Figure 2). Also, normotensives with LVH had a lower predicted survival probability than did hypertensives without LVH. For death from diseases of the heart, however, there was little difference between the proportion of hypertensives with LVH and normotensives with LVH who survived to the end of the follow-up period (Figure 3).

Table II. Risk factors for CHD death

	Sample size	CHD death [†]		P value
		% Yes (n = 462)	% No (n = 7462)	
Black	850	6.04	9.77	.001
Male	3744	65.47	46.90	<.001
Age				<.001*
<40 y	1611	2.19	29.42	
40-49 y	1272	7.51	24.00	
50-59 y	1305	19.69	23.74	
60-69 y	2783	45.93	17.30	
≥70 y	953	24.69	5.54	
Smoking status				.008*
Current smoker	2573	37.26	35.81	
Former smoker	2145	34.46	25.37	
Never smoked	3206	28.28	38.81	
High school [‡]	2584	30.82	36.05	.072
College education [§]	2019	17.35	30.86	<.001
Very active	815	6.70	10.35	.018
Moderately active	6216	75.86	79.84	.146
BMI (kg/m ²)				.009*
14.1-22.7	1981	20.76	26.27	
22.7-25.4	1981	23.86	26.03	
25.4-28.6	1981	30.91	23.87	
28.6-61.1	1981	24.47	23.83	
Cholesterol (mg/dL)				<.001*
80-192	1987	16.97	27.67	
193-223	2004	20.99	25.75	
224-254	1958	24.18	24.04	
255-268	1975	37.87	22.53	
H _x MI	460	25.18	3.30	<.001
H _x hardening of arteries	408	16.60	2.93	<.001
H _x stroke	238	6.62	1.87	<.001
H _x heart failure	119	7.14	0.85	<.001
H _x hypertension	2688	57.57	28.51	<.001
H _x diabetes	444	13.10	3.89	<.001

*Ordinal trend test.

[†]CHD defined by ICD-9 codes 410-414.[‡]Completed education through grade 12.[§]Completed at least some college education.

Discussion

By using data from a nationally representative sample of black and white adults, we observed that the prevalence of ECG-LVH was greater among hypertensives than normotensives across all age groups. The unadjusted prevalence of LVH in this sample with Minnesota Code criteria was 13.3 per 1000 population. The prevalence of LVH with Minnesota Code in NHANES I was 19 per 1000 for white men, 83 per 1000 for black men, 18 per 1000 for white women, and 66 per 1000 for black women.¹³ The prevalence of ECG-LVH in 1980 in the Framingham Study was 25 per 1000 population among men 55 to 59 years of age, 42 per 1000 among men 60 to 64 years of age, 11 per 1000 among women 55 to 59 years of age, and 27 per 1000 among women 60 to 64 years of age.² Differences in prevalence estimates may be the result of different diagnostic criteria and population samples.

Our results confirm previous findings that the presence of LVH is a strong predictor of future cardiovascular death. After controlling for a set of traditional cardiovascular disease risk factors, we found that the risk of death from CHD or from diseases of the heart was nearly twice as high among persons with LVH than among those without. Within 5 years of the appearance of LVH, one can expect mortality rates of 33% for men and 21% for women.² Data from the Framingham Study demonstrate that ECG-LVH increases the age-adjusted risk of CHD >3-fold, the age-adjusted risk of all cardiovascular events 4- to 7-fold, and the risk of sudden death 3- to 5-fold.²

The current study also demonstrates that normotensive persons with LVH have a risk of death from CHD and diseases of the heart that is equal to or greater than that of hypertensive persons with LVH. For CHD death, normotensives with LVH were at a modestly increased

Table III. Association between LVH and death: Cox proportional hazards model

		Crude mortality rate [‡] (standard error)	CHD death*			
			Age-adjusted RR	95% CI	Multivariate RR [§]	95% CI
LVH	No = 7777	259.9 [275.48]	1.00	—	1.00	—
	Yes = 147	1153.7 [2586.09]	2.44	(1.46, 4.05)	2.03	(1.20, 3.45)
Diseases of heart death[†]						
LVH	No = 7777	370.2 [286.83]	1.00	—	1.00	—
	Yes = 147	1530.0 [2956.22]	2.29	(1.40, 3.74)	1.86	(1.14, 3.03)

*CHD defined by ICD-9 codes 410-414.

[†]Diseases of the heart defined by ICD-9 codes 390-398, 402, 404, 410-414, 415-417, and 420-429.

[‡]Rate per 100,000 person-years.

[§]Adjusted for age, race, sex, SBP, prior cardiovascular disease (stroke, congestive heart failure, hardening of the arteries, MI), diabetes, cholesterol, BMI, smoking status.

Table IV. Association between LVH and death by hypertensive status: Cox proportional hazards model

		Crude mortality rate [‡] (standard error)	CHD death*			
			Age-adjusted RR	95% CI	Multivariate RR [§]	95% CI
Normotensive						
No LVH = 5114		164.7 (146.75)	1.00	—	1.00	—
LVH = 54		856.7 [1992.38]	2.19	(0.90, 5.32)	1.66	(0.60, 4.61)
Hypertensive[¶]						
No LVH = 2663		508.7 (901.60)	1.00	—	1.00	—
LVH = 93		1303.2 (3709.18)	2.19	(1.19, 4.01)	2.04	(1.05, 3.95)
Diseases of the heart death[†]						
Normotensive						
No LVH = 5114		233.7 (153.80)	1.00	—	1.00	—
LVH = 54		1723.6 [4174.27]	3.14	(1.59, 6.17)	2.41	(1.17, 4.98)
Hypertensive[¶]						
No LVH = 2663		731.2 (944.97)	1.00	—	1.00	—
LVH = 93		1432.6 [3793.58]	1.70	(0.97, 2.99)	1.51	(0.82, 2.77)

*CHD defined by ICD-9 codes 410-414.

[†]Diseases of the heart defined by ICD-9 codes 390-398, 402, 404, 410-414, 415-417, and 420-429.

[‡]Rate per 100,000 person-years.

[§]Adjusted for age, race, sex, SBP, prior cardiovascular disease (stroke, congestive heart failure, hardening of arteries, MI), diabetes, cholesterol, BMI, smoking status.

^{||}Normotensive status defined as SBP <140 mm Hg or DBP <90 mm Hg at baseline measurement.

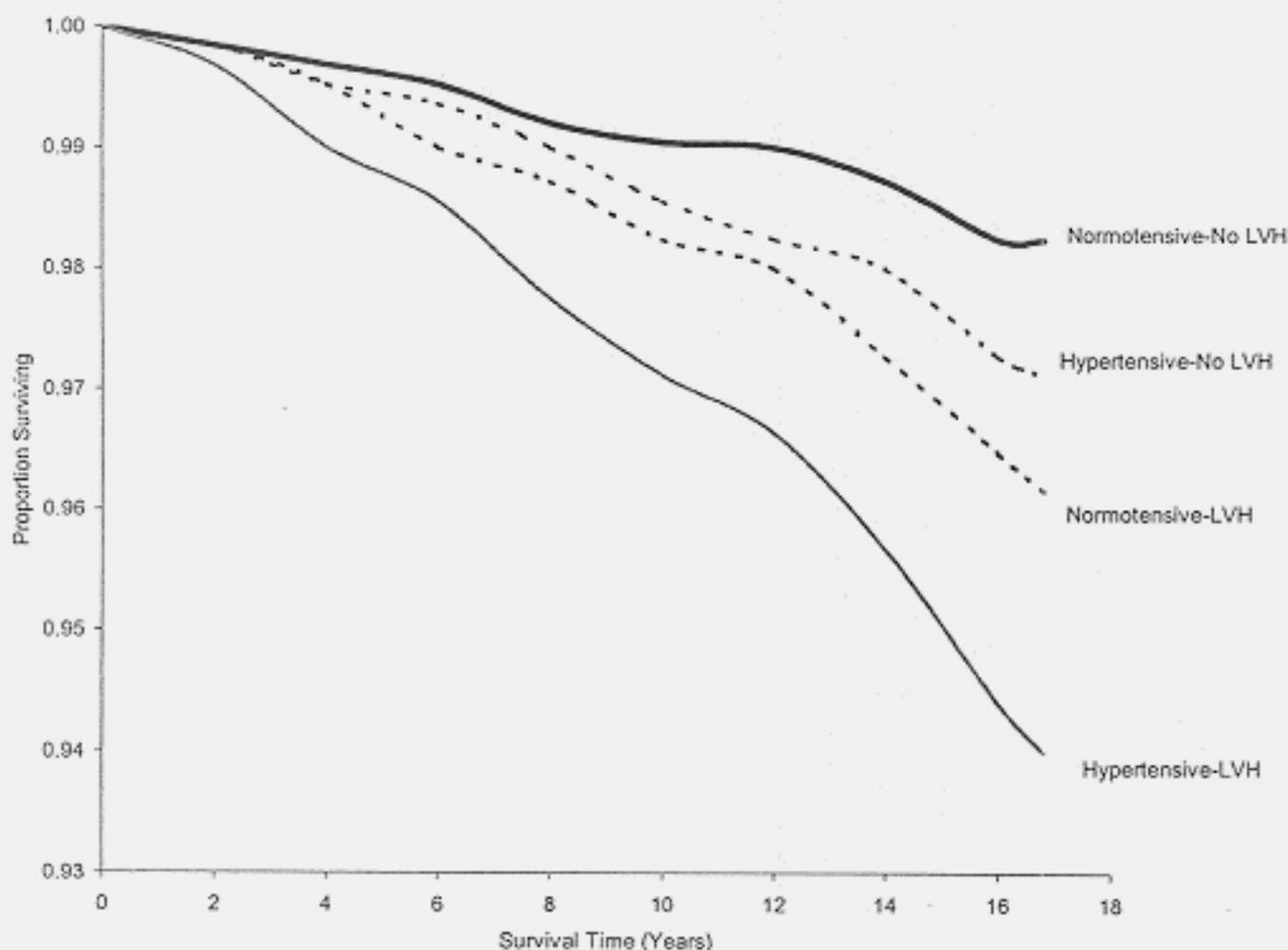
[¶]Hypertensive status includes controlled hypertension and uncontrolled hypertension. Controlled hypertension defined as SBP <140 mm Hg or DBP <90 mm Hg and currently taking blood pressure medication at baseline measurement. Uncontrolled hypertension defined as SBP ≥140 mm Hg or DBP ≥90 mm Hg at baseline measurement.

risk of death, although the risk estimates failed to achieve statistical significance. These individuals also had a lower survival probability for CHD death than did hypertensives without LVH, and for diseases of the heart, their survival probability was similar to that of hypertensives with LVH. These results should be viewed with some caution, however, because the number of normotensives with LVH was small (n = 54).

The increased risk of death among normotensives with LVH compared with hypertensives has several possible explanations. First, the cause of LVH may influ-

ence the likelihood of a fatal event. Causes of LVH other than hypertension, such as valvular heart diseases (eg, aortic stenosis and mitral regurgitation), may be associated with a higher probability of death. The normotensive persons in our study might have had a form of LVH stemming from a cause more lethal than that of the hypertensives. Secondary analyses found 18.9% of normotensives with LVH had evidence of a systolic murmur, a proportion nearly equal to that of hypertensives with LVH (18.1%) and greater than that of hypertensives without LVH (5.5%).

Figure 2



Age-adjusted CHD survival probability based on Cox proportional hazards model.

Second, the classification of persons as either normotensive or hypertensive may have resulted in a misclassification bias. Baseline systolic and diastolic blood pressure measurements were obtained by taking the mean value of the second and third measurements, all of which were obtained on the same day. Ideally, blood pressure would be measured on different days. Therefore, as a result of the measurement process, a fraction of persons classified as normotensive on the basis of blood pressure measurements may actually have been hypertensive.

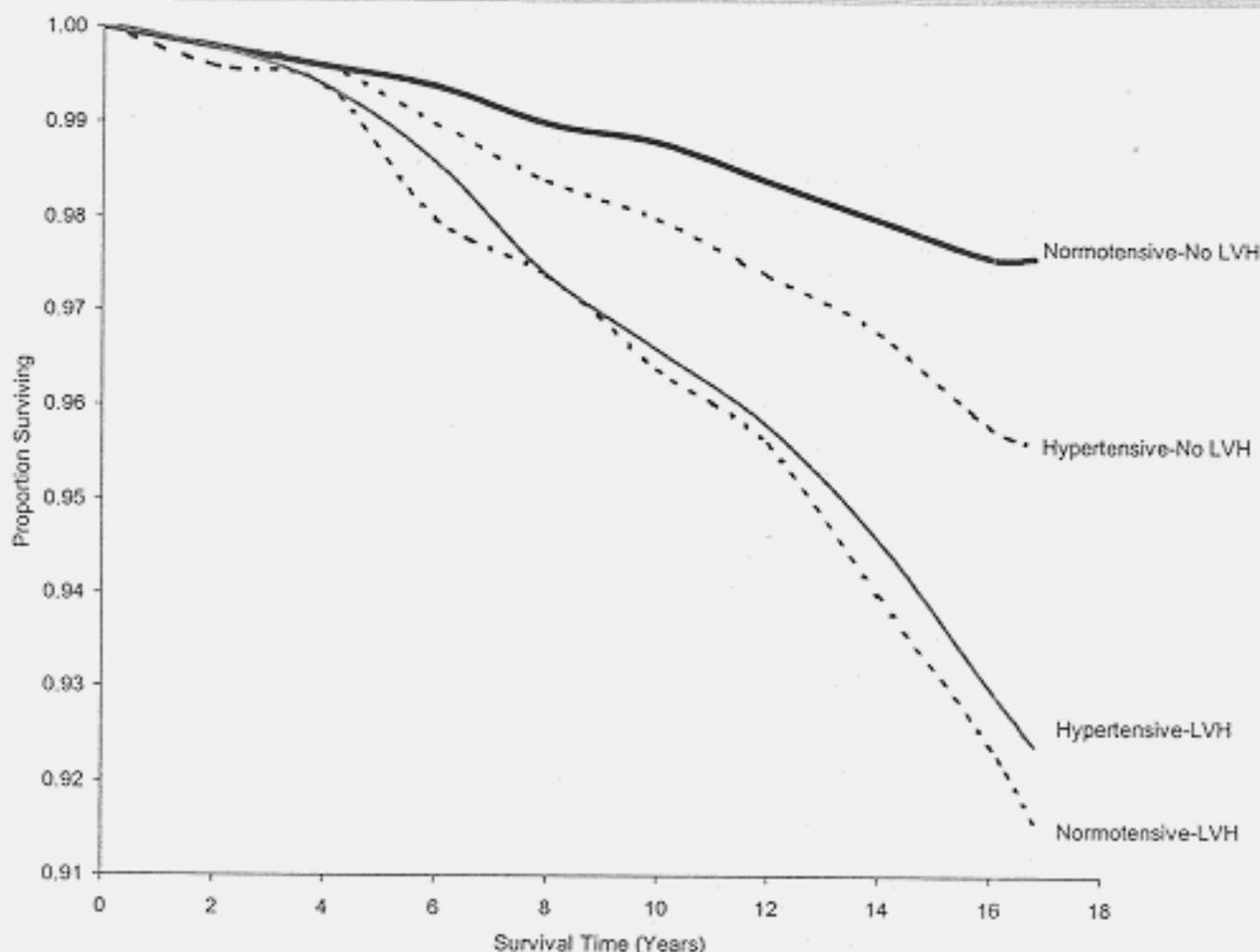
A third possibility is related to findings suggesting that the use of antihypertensive medication may result in the regression of LVH.¹⁴⁻¹⁶ By our definition, normotensives were persons having SBP <140 mm Hg or DBP <90 mm Hg and not taking antihypertensive medication. Normotensives with LVH in this study, therefore, would not be able to realize the possible benefit

of the medication on the regression of LVH. This may partly explain the higher mortality rates among normotensives with LVH.

One possible limitation to the findings of this study is that NHANES II relies on electrocardiographic evidence of LVH, but the sensitivity and specificity of the electrocardiogram, compared with that of echocardiography, has been questioned. ECG-LVH occurs less frequently among patients than does echocardiographic LVH.¹⁷ Electrocardiographic data may thus be associated with a misclassification of patients with LVH, and therefore any observed association between LVH and death is probably a conservative estimate.

Another possible limitation is our coding of electrocardiographic data. Several studies have demonstrated that the prevalence of LVH is dependent on the criteria used to detect LVH.¹⁸⁻²⁰ Our measure of LVH, based on

Figure 3



Age-adjusted diseases of heart survival probability based on Cox proportional hazards model.

the Minnesota Code, may have resulted in a misclassification of LVH in the study population, which we would expect to produce a downward bias on the observed association between LVH and cardiovascular death. Finally, this study assumes that the risk factor status for an individual does not change during the follow-up period; therefore, we probably underestimate the association between risk factors and death.

Conclusions

Our results confirm previous findings of an increased risk of death associated with the presence of LVH. In addition, we observed that normotensives with LVH are at increased risk of cardiovascular death. Although LVH among normotensive patients appears to be rare, clinicians should be aware that these individuals, like hypertensive patients with LVH, are at increased risk for

death. Further research is also needed to examine the prognostic importance of identifying the cause of the detected LVH. Should the cause of LVH be associated with risk of death, the diagnosis of the more lethal causes may have an important role in the treatment of patients with LVH.

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