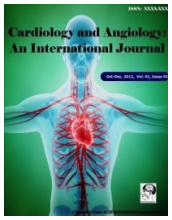

Cardiology and Angiology: An International Journal
3(1): 27-39, 2015, Article no.CA.2015.004
ISSN: 2347-520X

SCIENCEDOMAIN *international*
www.sciencedomain.org

Left Ventricular Hypertrophy and Incidence of Acute Coronary Heart Disease and Mortality in the Reasons for Geographic and Racial Differences in Stroke Study (REGARDS)

Ronald J. Prineas[1*], Anh Le[2], Stephen P. Glasser[3], Vera Bittner[4], William M. McClellan[5], Xin Wang[3], Yulia Khodneva[3] and Monika M. Safford[3]

[1]Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC, USA.
[2]Department of Biostatistics, University of Alabama at Birmingham School of Public Health, Birmingham, Alabama, USA.
[3]Division of Preventive Medicine, University of Alabama at Birmingham School of Medicine, Birmingham, AL, USA.
[4]Division of Cardiovascular Disease, University of Alabama at Birmingham School of Medicine, Birmingham, AL, USA.
[5]Department of Epidemiology, Rollins School of Public health, Emory University, Atlanta, AL, USA.

Authors' contributions

This work was carried out in collaboration between all authors. Author MMS designed the original cohort study. Author RJP designed the analysis, and wrote the first draft of the manuscript. Authors AL, YK and XW carried out a large series of analyses and statistical testing. Authors SPG and VB contributed to the clinical interpretation and all authors provided critical review and editing of the final paper. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/CA/2015/13917
Editor(s):
(1) Francesco Pelliccia, Department of Heart and Great Vessels University La Sapienza, Rome, Italy.
Reviewers:
(1) Mahnoosh Foroughi, Cardiovascular Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
(2) Nobuyuki Shiba, Cardiovascular Center, International University of Health and Welfare Hospital, Japan.
(3) Syed Ali Raza Kazmi, Institute of Biomedical and Genetic Engineering, Islamabad, Pakistan.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=641&id=26&aid=6821

Original Research Article

Received 9th September 2014
Accepted 16th October 2014
Published 5th November 2014

**Corresponding author: E-mail: rprineas@wakehealth.edu;*

ABSTRACT

Objective: To examine the relationship between left ventricular hypertrophy (LVH) and the incidence of acute coronary heart disease (CHD) and mortality in the modern era.
Methods: We studied 16, 390 black and white participants free of clinical CHD from a US national sample. The independent prognostic value of ECG-LVH was determined by Cornell voltage (CV) for risk of incident acute CHD and total mortality overall and by race and sex.
Results: 410 incident acute CHD events and 993 deaths occurred over a median follow-up of 4.8 years. CV LVH was associated with outcomes: more common in blacks (4.1%) than whites (1.2%) and in women (3.9%) than men (1.3%). However, men with CV LVH (HR 2.12 [95% CI 1.02-4.42) had greater risk for incident acute CHD than women (HR 1.29 [95% CI 0.79-2.11]) after adjusting for demographic, behavioral and clinical variables. By contrast, CV LVH conferred similar hazards for incident acute CHD among blacks (HR 1.63 [1.00-2.68; p=0.050]) and whites (HR 1.58 [95% CI 0.76-3.28; p=0.22]). Mortality associated with CV LVH was elevated overall (HR 1.31 [95% CI 1.00-1.71]) and for blacks (HR 1.36 [95% CI 1.00-1.86]) but not whites (HR 1.16 [95% CI 0.70-1.94]), with similar risk for women (HR 1.24 [95% CI 0.92-1.67] and for men (HR 1.30 [95% CI 0.72-2.35]).
Conclusion: In this contemporary cohort, CV LVH was significantly prognostic for incident acute CHD for men but not women and there was no evidence of race differences. However, CV LVH was significantly prognostic for total mortality for blacks but not whites without evidence of sex differences.

Keywords: Left ventricular hypertrophy; myocardial infarction; mortality; racial disparities.

1. INTRODUCTION

Whether defined echocardiographically or electrocardiographically, left ventricular hypertrophy (LVH) has been reported to be an independent risk factor for coronary heart disease (CHD) among both men and women [1]. In addition, LVH has been associated with three-year mortality [2]. The mechanisms leading to these excess risks include the fact that left ventricular mass (LVM) is related to depressed left ventricular ejection fraction [3]. However, LVH can occur along a continuum of LVM. Furthermore, some prospective studies indicate that the left ventricle can increase in size prior to the onset of hypertension [4,5]. Indeed, even in individuals with normal blood pressure, LVH is a risk factor for coronary events and all-cause mortality [6] and the association between LVH and incident CHD can be explained only partially by blood pressure levels. Further, there may be differences in the risks associated with LVH by sex: risk of CHD and mortality was greater in women than in men in the Framingham Study [7]. After adjusting for other CHD risk factors, LVH has been associated with a doubling of mortality in both white and black cohorts [2].

Many of the studies reporting on the relationships between LVH and CHD outcomes or death were conducted years ago, prior to the widespread use of statins and the improved sensitivity of troponin assays. In the modern era, very small so-called microsize myocardial infarctions (MIs) are now routinely detected, but were not able to be included in past studies [8]. We therefore examined the role of baseline LVH as an independent predictor of incident CHD and total mortality in the REasons for Geographic and Racial Differences in Stroke (REGARDS) cohort, a large contemporary national cohort study of cardiovascular disease. We have already shown in REGARDS that electrocardiographic LVH was greater in blacks than whites [9]. The present report examines the association between electrocardiographic LVH and incident acute CHD events and mortality overall, and by race and sex separately.

2. METHODS

The REGARDS study is prospectively following 30,239 individuals to better understand regional and racial influences on stroke and MI incidence and mortality. Details of the study are described elsewhere [10]. Briefly, recruitment was conducted from 2003-2007 using commercially available lists and a combination of mail and telephone contact to recruit English-speaking, community-dwelling adults aged 45 and older living in the continental US. The telephone response rate was 33% and the cooperation rate was 49% (similar to other reported epidemiologic studies).

The sample was designed to be balanced on race and sex, with oversampling from the Southeastern US; the final cohort was composed of 42% blacks and 58% women. Baseline data collection included computer-assisted telephone surveys assessing medical history and health status domains, and in-home exams during which trained health professionals collected blood and urine samples, recorded electrocardiograms (ECGs), measured blood pressure and height and weight, and recorded medications by pill bottle review. Participants were asked to fast overnight prior to the in-home visit. Blood and urine samples were sent to the University of Vermont central laboratory for analysis, and ECGs were transmitted to a reading center at Wake Forest University for coding.

For follow-up, living participants or their proxies were telephoned every 6 months and asked if they were hospitalized with subsequent medical records retrieval. Deaths were detected by reaching next-of-kin at a scheduled follow-up, through online sources (e.g., Social Security Death Index), or through the National Death Index. Proxies or next-of-kin were interviewed about the circumstances surrounding the death, including questions about the presence of chest pain in the hours prior to death. Death certificates and autopsy reports were also obtained. The study protocol was reviewed and approved by the University of Alabama at Birmingham Institutional Review Board, and all participants provided informed consent.

For this study, individuals with prevalent CHD at baseline were excluded. Prevalent CHD was defined as a self-reported history of MI or coronary revascularization procedure or evidence of a prior MI on a participant's baseline ECG. For the present analysis follow-up was through December 31, 2010, for a median follow-up of 4.8 years and a maximum of 6.9 years.

2.1 Outcomes

Acute CHD, acute CHD or cardiovascular disease mortality, all-cause mortality.

The CHD outcome was defined as incident definite or probable acute MI or definite or probable acute CHD death, whichever occurred first. Possible CHD events were detected at the time of telephone follow-up. Any reported hospitalizations for a heart-related condition prompted retrieval of medical records which were adjudicated by a team of experts using a standardized approach modeled on major epidemiologic studies [11]. Medical records were reviewed for the presence of signs or symptoms suggestive of ischemia, a rising and/or falling pattern of cardiac troponin or creatinine phosphokinase-MB over at least 6 hours, and ECG changes consistent with ischemia or MI, guided by the Minnesota code [12,13]. MIs were adjudicated as being definite, probable or possible. Cases were assigned to 2 adjudicators and disagreements were adjudicated by committee. The test for agreement between adjudicators, the kappa statistic, was greater than 0.80 for the presence of definite or probable MI. Definite or probable MIs that occurred through December 31, 2010 were included in this analysis.

For fatal events, hospital records, interviews with next-of-kin or proxies, and death certificate and/or National Death Index data were reviewed to adjudicate the cause of death. Definite or probable acute CHD death was defined as death where adjudicators judged that the main underlying cause of death was acute CHD [10]. For hospitalized deaths, the underlying cause was definite or probable acute CHD if the death occurred within 28 days of a hospital admission in definite or probable MI cases; postmortem findings were consistent with MI within 28 days; or the death occurred within 6 hours of hospital admission with cardiac symptoms and/or signs and other confirmatory data such as biomarkers or ECGs were absent or not diagnostic. For deaths occurring outside of the hospital, the cause of death was definite or probable acute CHD if the death was judged to be sudden death; or there was a documented definite or probable MI in the previous 28 days and there was no evidence of a non-coronary cause of death; or there was autopsy evidence of recent coronary occlusion or MI <28 days old; or there was a history of CHD and/or documented cardiac pain within 72 hours before death and there was no evidence of a non-coronary cause of death; or there was autopsy evidence of chronic CHD, including coronary atherosclerosis and myocardial scarring. Only definite or probable acute CHD deaths were included in this analysis. Cardiovascular disease (CVD) death included definite or probable acute CHD death; stroke death; death due to congestive heart failure; or death due to other CVD. The date of death recorded on death certificates or the National Death Index was used in the analyses as the date of death.

2.2 Determination of LVH

A total of 21,071 REGARDS participants underwent a standard 12-lead ECG recording. All ECGs were read centrally at the EPICARE center located at Wake Forest University School of Medicine, where the ECGs were coded by trained MD electrocardiographers and all abnormalities were over-read by a second MD electrocardiographer. The ECG variables included all ECG Minnesota codes (MC) with codes 1 through 9 [13] and continuous ECG variables: heart rate, QRS duration, QT duration (and heart rate-adjusted QTI: ([QT] / 656 * ([HR] + 100), RaVL, SV1 and SV3.

LVH in the present study was defined as: CV LVH = sex-specific Cornell voltage [14] (CV = RaVL + SV3) > 2200μV for women; > 2800μV for men

2.3 Covariates

Being aware of that change in presentation of CHD and treatment effects are well documented in the changing patterns of heart disease presentation [15], we recorded all salient risk factors and modifiers in this study. Age, race, sex, income, education, and smoking status were self-reported. Region was defined as residence in the Stroke Buckle (coastal North and South Carolina and coastal Georgia), the Stroke Belt (remainder of North and South Carolina and Georgia, plus Alabama, Mississippi, Louisiana, Arkansas, and Tennessee) or the remainder of the continental US. Annual income was categorized as <$20,000 or >$20,000. Education was dichotomized as having less than or at least a high school diploma. Alcohol consumption was classified based on the drinks per week categorization of the National Institute on Alcohol Abuse and Alcoholism: None=0, Moderate = 1-7 drinks for women, 1-14 drinks for men, Heavy = more than 7 drinks for women, or more than 14 drinks for men. Participants were classified as smokers if they reported having smoked at least 100 cigarettes in their lifetime and responded affirmatively to the question “Do you smoke cigarettes now, even occasionally?” Exercise was assessed by asking participants the number of times per week they exercised to work up a sweat, dichotomized as reporting getting any exercise or none.

Biometrics used in this analysis included body mass index (BMI) and blood pressure. Participants had their height and weight measured using a standardized protocol during the in-home visit. BMI was modeled as a continuous measure in kg/m2. Blood pressure was obtained after a seated rest of 3 minutes with both feet on the floor. Two measures were obtained following a standardized protocol and averaged. Systolic blood pressure was modeled as a continuous variable. Antihypertensive medication and statin use was based on pill bottle review.

Blood and urine markers included low density cholesterol (LDL), high density lipoprotein (HDL) cholesterol, fasting glucose, high sensitivity C-reactive protein (hsCRP), serum creatinine and urinary albumin and creatinine. LDL and HDL cholesterol were modeled as continuous variables. Diabetes was classified as present if participants reported having been told by a doctor or other health professional that they had diabetes, or if their fasting glucose was ≥126 mg/dL (≥200 mg/dL for participants who did not fast prior to their REGARDS study visit), or if they were taking diabetes medications. hsCRP was log-transformed and modeled as a continuous variable. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation [16]. Urinary albumin and creatinine were used to define the albumin-to-creatinine ratio (ACR), which was log-transformed for analysis.

2.4 Statistical Analysis

The end of follow-up for this analysis was December 31st, 2010. Follow-up time for each participant was calculated from the date of the in-home visit to the date of incident CHD event, death, or last telephone follow-up. Age- sex- and race-adjusted logistic regression models were used to estimate baseline prevalence of LVH, overall and stratified by sex and race separately. Additionally, we calculated age- sex- and race adjusted incidence rates for acute CHD, acute CHD or CVD death and all-cause mortality using Poisson regression models. Cox proportional hazards analysis was used to examine the hazard ratios (and 95% confidence interval [CI]) for all-cause mortality and acute CHD, overall and separately by race and sex. To better understand the findings, we built models incrementally with model 1 adjusting for age, race, sex and region. We included region of residence as a covariate in all models since the REGARDS study over-sampled residents of the southeastern US states. Model 2 added to the model 1 covariates income, education, alcohol use, smoking status, exercise, and BMI. Model 3

added to the model 2 covariates statin use, estimated glomerular filtration rate, anti-hypertension medication use, diabetes, systolic blood pressure, glucose, LDL cholesterol, HDL-cholesterol, log-transformed hsCRP and log-transformed ACR. We built an overall set of models, one for incident acute CHD, one for acute CHD or CVD death and one for all-cause mortality. Separate models were also constructed for blacks and whites and for men and women. Interaction terms for race and LVH and sex and LVH were also tested for significance in the overall model with all covariates included. All multivariable-adjusted Cox proportional hazards models were fitted using imputed data to account for missing covariate data. Missing data were imputed using multivariable multiple imputation by chained equations with five datasets [17,18]. Analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC) and STATA version 11 (STATA Incorporated, College Station, TX).

3. RESULTS

The exclusionary cascade for this analysis is shown in Fig. 1. Of the 30,182 REGARDS cohort participants after excluding 56 for consent errors, in order the following were excluded from the analysis: 490 missing follow-up, 9,023 with only 7 lead ECG or poor quality 12 lead ECG, 3474 with prevalent coronary heart disease at baseline, and 806 were excluded due to intraventricular conduction delays (since ECG-based measures of LVH are not valid in the presence of such delays), resulting in a final analytic sample size of 16,390 participants.

Table 1a shows the characteristics of this sample according to whether they met CV criteria for LVH. Overall, their mean age was 63 years and 42% were black, and 66% were female. As expected, those with CV LVH were older; a greater proportion was black; a greater proportion were women; they had higher systolic blood pressure, glucose, and hsCRP; and more had hypertension and diabetes and, in fact, all vascular risk factors were significantly worse.

Table 1b shows the excluded participants without baseline CHD or QRS ≥ 120ms, had significant differences in demographic and some risk variables from the study cohort. Most of these excluded participants were the first contacted in the study and only had a 7-lead ECG and so could not be included because of inability to estimate LVH. It can be seen from Table 1a that they differ from the study cohort and more resemble participants with CV LVH shown in Table1a.That is, they are older, more black, more male and have generally a modestly worse vascular risk factor profile.

Table 2 shows the relative differences in ECG LVH prevalence, overall and separately by race and sex. LVH as defined using CV LVH (2.2%). The prevalence of CV LVH was higher in blacks than in whites (4.1% vs.1.2%, respectively) and in women than in men (3.9% vs. 1.3%).

Table 3 shows the age, race and sex adjusted incidence rates per 1,000 person-years for the overall and by race and sex separately. In this sample, blacks had higher incidence of all 3 endpoints than whites (5.6 vs.4.8 per 1000 person-years for acute CHD; 7.9 vs. 5.7 per 1000 person-years for acute CHD or CVD mortality; and 14.7 vs. 8.0 per 1000 person-years for all-cause mortality, respectively). Men had a higher incidence of all 3 endpoints than women (7.8 vs. 3.5 per 1000 person-years for acute CHD; 9.8 vs. 4.7 per 1000 person-years for acute CHD or CVD mortality; and 14.2 vs. 8.5 per 1000 person-years for all-cause mortality, respectively).

In Table 4 is shown the prognostic utility of ECG LVH after adjustment for demographic, behavioral and clinical risk factors was a significant independent predictor of all 3 end points in fully adjusted models, with a hazard ratio (HR) for incident acute CHD of 1.57 (95% CI 1.04, 2.35); for incident acute CHD or CVD mortality of 1.47 (95% CI 1.05, 2.06); and for all-cause mortality of 1.31 (95% CI 1.00, 1.71).

Table 5 presents the sex-stratified results. For incident acute CHD, men with CV LVH (HR 2.12 [95% CI 1.02, 4.42]) were at greater risk than women (HR 1.29 [95% CI 0.79, 2.11]). For acute CHD or CVD death, there were no significant associations for either men or women in fully adjusted models. For all-cause mortality, there were no significant associations. Of note, for many of these stratified analyses, the number of events was modest, limiting the power of the analyses.

Table 6 presents the race-stratified results. After adjustment for covariates, both blacks and whites with CV LVH had an elevated risk for incident acute CHD, but only the HR for blacks reached statistical significance (HR 1.63 [95% CI 1.00, 2.68] for blacks; HR 1.58 [95% CI 0.76, 3.28] for whites). For acute CHD or CVD death, the HR for

blacks was 1.54 (95% CI 1.03, 2.30) and the HR for whites was 1.36 (95% CI 0.71, 2.60), a finding that was not statistically significant for whites. For all-cause mortality, the HR for blacks with CV LVH was 1.36 (95% CI 1.00, 1.95; p-value 0.05) and the HR for whites with CV LVH was 1.16 [95% CI 0.70, 1.94]).

In fully adjusted models of acute CHD, the p-value for the interaction terms between race*CV LVH was 0.79 and between sex*CV LVH was 0.34. For acute CHD or CVD death, the p-value for the interaction between race*CV LVH was 0.52 and between sex*CV LVH was 0.72. For all-cause mortality, the p-value for the interaction term for race*CV LVH was 0.70 and for sex*CV LVH was 0.96. And again of note, for many of these stratified analyses, the number of events was modest, limiting the power of the analyses.

4. DISCUSSION

In this contemporary cohort, we observed an association between CV LVH and incident acute CHD and mortality. The risks for incident acute CHD were elevated for men in a range similar to past reports, but were much lower and non-significant for women.

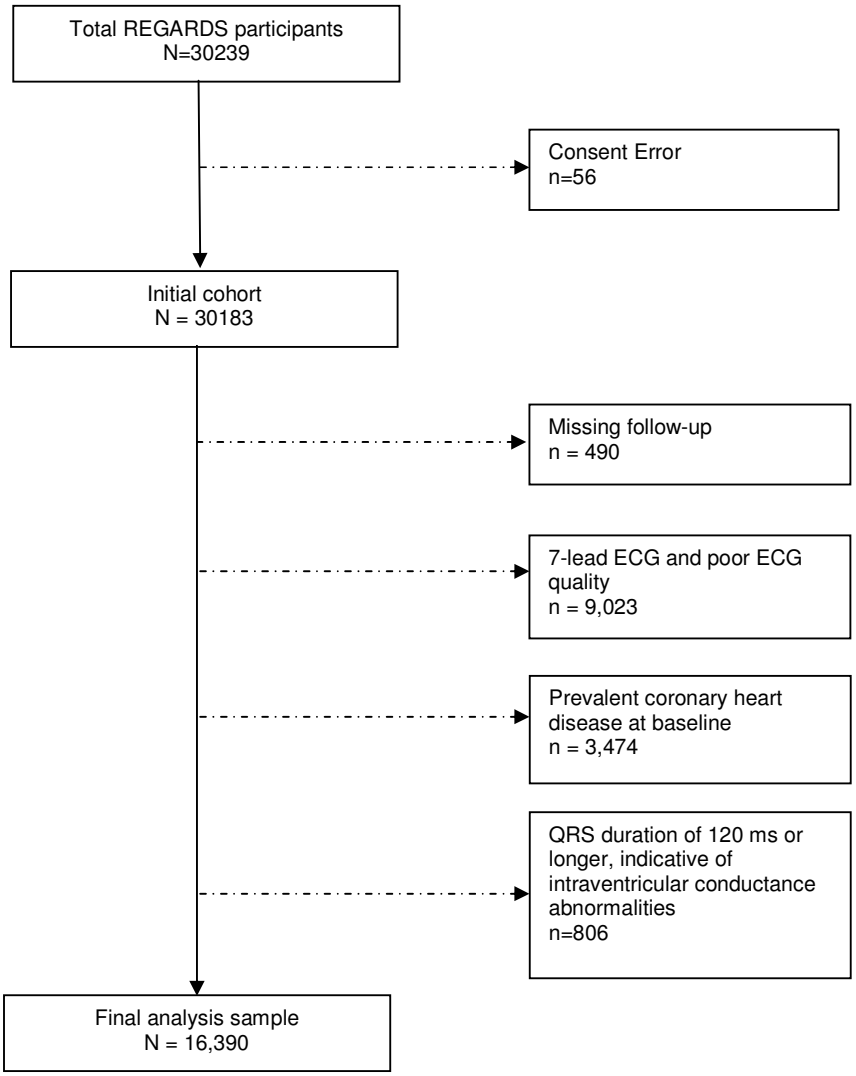

Fig. 1. Exclusion cascade

In contrast, similar to past reports, risks for CHD were similar for both blacks and whites; and risks for mortality were higher for blacks than whites and similar for men and women, albeit of lower magnitude than in past reports. Because the p-value for the interactions were not significant, we cannot exclude the possibility that these differences could be due to chance; nevertheless, if confirmed in other contemporary cohorts, these findings could suggest that the relationship between LVH and CHD may be changing.

Table 1a. Baseline characteristics of REGARDS Participants with and without left ventricular hypertrophy, based on Cornell Voltage Criteria (CV LVH)[a]

	CV LVH n=539	Without CV LVH n=15,851	p-value
Demographic factors			
Age, mean (SD), years	65.7 (9.8)	62.8 (9.5)	<.001
Black, n (%)	375 (69.6)	6,454 (40.7)	<.001
Female, n (%)	466 (86.5)	10,444 (65.9)	<.001
Region of residence, n (%)			0.30
Belt	194 (36.0)	5,470 (34.5)	
Buckle	117 (21.7)	3,907 (24.7)	
Non-belt	228(42.3)	6,474 (40.8)	
Socio-economic factors			
Annual income, n (%)			<.001
Less than $20,000	139 (25.8)	2,451 (15.5)	
$20,000-$34,000	156 (28.9)	3,570 (22.5)	
$35,000-$74,000	111 (20.6)	4,894 (30.9)	
$75,000 and over	53 (9.8)	2,889 (18.2)	
Declined to report income	80 (14.8)	2,047 (12.9)	
Education, n (%)			
Less than High School	103 (19.1)	1,588 (10.0)	<.001
High School Graduate	148 (27.5)	4,012 (25.3)	
Some College	151 (28.0)	4,414 (27.9)	
College Graduate and above	137 (25.4)	5,827 (36.8)	
Lifestyle factors			
Body mass index, mean (SD), kg/m^2	30.6 (7.1)	29.4 (6.4)	<.001
Exercise, n (%)			0.005
None	211 (49.7)	5,234 (33.5)	
1-3 times per week	195 (36.7)	5,912 (37.8)	
4 or more times per week	126 (23.7)	4,480 (28.7)	
Cigarette smoking, n (%)			0.002
Never	290 (53.9)	7,853 (49.7)	
Past	156 (29.0)	5,697 (36.1)	
Current	92 (17.1)	2,243 (14.2)	
Alcohol consumption, n (%)			0.001
None	395 (74.5)	9,709 (62.4)	
Moderate	123 (23.2)	5,200 (33.4)	
Heavy	12 (2.3)	637 (4.2)	
Vascular risk factors			
Systolic blood pressure, mean (SD), mmHg	135.6 (19.8)	125.5 (15.9)	<.001
Glucose, mean (SD), mg/dL	113.8 (56.5)	102.2 (32.9)	<.001
Low density lipoprotein cholesterol, mean (SD), mg/dL	119.0(38.7)	115.4 (34.6)	0.038
High density lipoprotein cholesterol, mean (SD), mg/dL	56.0 (17.0)	54.2 (16.5)	0.014
High sensitivity C-reactive protein, median [IQR], mg/L	3.3[1.4-7.5]	2.1[0.9-5.0]	<.001
Hypertension, n (%)	440 (81.8)	8,524(53.9)	<.001
Diabetes, n (%)	157 (30.1)	2,742 (18.0)	<.001
Atrial fibrillation, n (%)	52 (9.8)	1,001 (6.4)	0.002
Urinary albumin/creatinine ratio, median [IQR], mg/g	12.7 [6.5-40.6]	6.8 [4.5-13.2]	<.001
Estimated glomerular filtration rate < 60, ml/min/1.73m^2, n (%)	76 (14.8)	1,210(8.0)	<.001
Medication use			
On statins, n (%)	143(26.8)	4525(28.9)	0.029
On antihypertensive medications, n (%)	389(73.0)	7390(47.2)	<.001

Abbreviations: IQR, Interquartile Range; [a]LVH CV is based on sex-specific Cornell voltage criteria.

Table 1b. Baseline characteristics of REGARDS participants included into left ventricular hypertrophy analysis vs. not included participants (only those who do not have follow-up or their EKG is missing or not suitable). Participants who were excluded due to baseline CHD or QRS=>120 are not analyzed here

	Included n=16390	Not included n=7219	p
Demographic factors			
Age, mean (SD), years	62.9(9.5)	65.7(8.3)	<.001
Black, n (%)	6829 (41.7)	3317 (46.0)	<.001
Female, n (%)	10910(66.6)	3072 (42.6)	<.001
Region of residence, n (%)			<.001
Belt	5667 (34.6)	2502(34.7)	
Buckle	4024 (24.6)	941(13.0)	
Non-belt	6702(40.9)	6727(52.3)	
Socio-economic factors			
Annual income, n (%)			<.001
Less than $20,000	2590(15.8)	1450(20.1)	
$20,000-$34,000	3726(22.7)	1832(25.4)	
$35,000-$74,000	5005 (30.5)	2107(29.2)	
$75,000 and over	2942 (18.0)	1034(14.3)	
Declined to report income	2127 (13.0)	796 (11.0)	
Education, n (%)			<.001
Less than High School	1691(10.3)	1025(14.2)	
High School Graduate	4160 (25.4)	1817(25.2)	
Some College	4565(27.9)	1832 (25.4)	
College Graduate and above	5964 (36.4)	2539 (35.2)	
Lifestyle factors			
Body mass index, mean (SD), kg/m^2	29.4 (6.4)	29.0 (6.0)	<.001
Exercise, n (%)			<.001
None	5445 (33.7)	2314 (32.6)	
1-3 times per week	6107 (37.8)	2515(35.4)	
4 or more times per week	4606 (28.5)	2276(32.0)	
Cigarette smoking, n (%)			<.001
Never	8143 (49.9)	3026 (42.1)	
Past	5853(35.8)	3073 (42.7)	
Current	2335 (14.3)	1092 (15.2)	
Alcohol consumption, n (%)			0.007
None	10104(62.8)	4275(60.6)	
Moderate	5323(33.1)	2473 (35.2)	
Heavy	669(4.2)	297(4.2)	
Vascular risk factors			
Systolic blood pressure, mean (SD), mmHg	125.8(16.1)	129.6(17.0)	<.001
Glucose, mean (SD), mg/dL	102.6(34.0)	103.7(39.9)	0.03

Table 2. Baseline prevalence of left ventricular hypertrophy, percent (95%CI), adjusted for age sex and race. analytic sample N=16,390

CV* LVH n=539	
Overall, N=16,390	2.2 (2.0-2.5)
Blacks, n=6,829	4.1 (3.5-4.7)
Whites, n=9,561	1.2 (1.0-1.5)
Males, n=5,480	1.3 (1.0-1.6)
Females, n=10,910	3.9 (3.5-4.4)

**Sex-specific CV LVH: Cornell voltage; (CV = RaVL + SV3) > 2200μV for women; > 2800μV for men*

Table 3. Age, race, and sex adjusted incidence rate (IR) of acute coronary heart disease (CHD), acute CHD or cardiovascular disease (CVD) death and all-cause mortality (95% confidence interval), per 1000 person-years, on/before 12/31/2010

	Acute CHD IR (95%CI)	Acute CHD/CVD death IR (95%CI)	All-cause mortality IR (95%CI)
Overall N=16,390	5.3 (4.7-5.9)	6.8(6.2-7.5)	11.0(10.2-11.8)
Number of events	410	572	993
Blacks, n=6,829	5.6 (4.7-6.6)	7.9(6.9-9.1)	14.7 (13.3-16.3)
Number of events	179	271	507
Whites, n=9,561	4.8 (4.2-5.6)	5.7(5.0-6.6)	8.0 (7.1-8.9)
Number of events	231	301	486
Males, n=5,480	7.8 (6.7-9.0)	9.8(8.5-11.2)	14.2 (12.7-15.9)
Number of events	213	286	446
Females, n=10,910	3.5 (3.0-4.1)	4.7(4.1-5.4)	8.5 (7.7-9.4)
Number of events	197	286	547

Abbreviations: CHD coronary heart disease; Overall rates adjusted for age, race and sex. Race-specific rates adjusted for age and sex. Sex-specific rates adjusted for age and race

Table 4. Unadjusted and incrementally adjusted hazard ratios (and 95% confidence intervals) for LVH from model predicting risk of incident acute CHD and total mortality

Endpoint	CV LVH
Acute CHD n=410 events	
Unadjusted	**2.19(1.48, 3.23)**
Model 1[2]	**2.23(1.50, 3.32)**
Model 2[3]	**2.15(1.44, 3.20)**
Model 3[4]	**1.57(1.04, 2.35)**
Acute CHD/CVD death n=572 events	
Unadjusted	**2.27 (1.64,3.14)**
Model 1[2]	**2.08 (1.49,2.90)**
Model 2[3]	**2.02 (1.45,2.82)**
Model 3[4]	**1.47 (1.05,2.06)**
All-cause mortality n=993	
Unadjusted	**2.08 (1.61, 2.68)**
Model 1[2]	**1.69 (1.31, 2.19)**
Model 2[3]	**1.67 (1.29, 2.17)**
Model 3[4]	**1.31 (1.00, 1.71)**

CV LVH = based on sex-specific Cornell voltage criteria. See also text. CHD = coronary heart disease.; [2]Model 1 adjusts for age, race, sex, region; [3]Model 2 adjusts for Model 1 covariates plus income, alcohol, smoking, exercise, education, and body mass index; [4]Model 3 adjusts for Model 2 covariates plus statin use, estimated glomerular filtration rate, atrial fibrillation, hypertension medication use, diabetes, systolic blood pressure, glucose, low density lipoprotein cholesterol, high density lipoprotein cholesterol, log of high sensitivity c-reactive protein, and log of the urinary albumin/creatinine ratio. Bold p-value < 0.05

In the Framingham study, women with LVH demonstrated higher risks for CHD and death than men with LVH, which is the exact opposite of the finding in our study. The epidemiology of CHD has changed considerably since the Framingham study, with far fewer ST elevation MIs occurring in the modern era, and increasingly sensitive troponin assays able to detect smaller and smaller so-called 'microsize' MIs that were not included in previous studies of the relationship between LVH and CHD or mortality [19]. In the Atherosclerosis Risk in Communities (ARIC) study, CHD was the most common first event in men with ECG LVH, but heart failure was the most common first event in women [20]. Although that study used criteria similar to MC ECG and had longer follow-up than the present study, it speaks to possible sex differences in risks associated with LVH that may have emerged since the Framingham study.

Although blacks were not included in the Framingham study [7], the ARIC study did include blacks, and it showed that whites and blacks have a similar threshold of LVH in terms of CVD risk [21]. The similarity of risk for incident CHD that we observed is consistent with this finding. Furthermore, in a study using the National Health And Nutrition Examination Survey (NHANES) III sample conducted between

1988-94, CV LVH displayed a HR of 1.34 (95% CI 1.01-1.79) for 5-year mortality, a remarkably similar HR as the one we report here [22]. Another report using NHANES data showed higher mortality risk associated with ECG-defined LVH for blacks compared to whites, but the magnitude of risk for blacks after adjustment in that report was 2.30 (95% CI 1.55-3.42), higher than the HR reported here, [23] and the risk for whites in that study was significantly elevated (HR 1.42 [95% CI 1.14-1.76]) whereas in our study it was near 1.0 and not significant. The unadjusted HRs in that study were also considerably higher than the HR in our study. Since the confidence intervals of the fully adjusted model point estimates from the NHANES study and those of our study do overlap, we cannot exclude that these differences could be due to chance, but the consistency of the findings suggests that this association deserves further study in modern cohorts. Studies that include long-term exposures to therapeutic agents such as statins or specific antihypertensive medications could shed light on why the association between LVH and CHD outcomes could be changing, but this was beyond the scope of the current study. Such change in presentation of CHD and treatment effects are well documented in the changing patterns of heart disease presentation [15].

The superiority of CV LVH for LVH diagnosis compared to that for Sokolow-Lyon (essentially MC LVH) has been shown in other populations [24]. In addition, CV LVH has been shown to better reflect echocardiographically measured LVH than other ECG LVH measures [25].

The superiority of CV LVH for LVH diagnosis compared to that for Sokolow-Lyon (essentially MC LVH) has been shown in other populations [24]. In addition, CV LVH has been shown to better reflect echocardiographically measured LVH than other ECG LVH measures [25].

Our study's strengths include the large national cohort, with large female and black populations, its contemporary settings and rigorous adjudication of endpoints. Some limitations are worth noting. First, our study's time horizon is relatively short and a longer time horizon might have shown stronger associations. Further, our measure of LVH is based on ECG formulations that are structurally less sensitive and specific than echocardiographic LVH. As in any observational study, causal inferences should be drawn with caution. Some of the covariates were self-reported with known limitations.

Table 5. Unadjusted and incrementally adjusted hazard ratios (95% confidence intervals) for LVH from models predicting risk of incident acute CHD and total mortality, stratified by sex. (males, n=5,480; females, n=10,910)

	CV LVH[c]	
Acute CHD	**Female**	**Male**
n=410 events	**n=19 events**	**n=8 events**
Unadjusted	**2.50 (1.56,4.01)**	**3.29 (1.62,6.66)**
Model 1[d]	**1.95 (1.21,3.15)**	**3.03(1.48,6.19)**
Model 2[e]	**1.85 (1.14,2.99)**	**2.97 (1.45,6.11)**
Model 3[f]	1.29 (0.79,2.11)	**2.12 (1.02,4.42)**
Acute CHD/CVD death	**Female**	**Male**
n=572 events	**n=30 events**	**n=9 events**
Unadjusted	**2.74(1.88,4.01)**	**2.75 (1.41,5.33)**
Model 1[d]	**1.99 (1.35,2.91)**	**2.30(1.18,4.50)**
Model 2[e]	**1.88 (1.28,2.76)**	**2.37(1.21,4.66)**
Model 3[f]	1.31(0.89,1.94)	1.69(0.86,3.37)
All-Cause Mortality	**Female**	**Male**
n=993 events	**n=51 events**	**n=12 events**
Unadjusted	**2.37 (1.78,3.17)**	**2.28 (1.28,4.04)**
Model 1[d]	**1.69 (1.26,2.26)**	1.72 (0.97,307)
Model 2[e]	**1.63 (1.12,2.19)**	**1.80 (1.00,3.21)**
Model 3[f]	1.24 (0.92,1.67)	1.30 (0.72,2.35)

Abbreviations: CHD = coronary heart disease. CVD = cardiovascular disease. ECG = electrocardiogram. LVH = left ventricular hypertrophy CV LVH is based on sex-specific Cornell voltage criteria. See also text; [d]Model 1 adjusts for age, race, sex, region. [e]Model 2 adjusts for Model 1 covariates plus income, alcohol, smoking, exercise, education, and body mass index. [f]Model 3 adjusts for Model 2 covariates plus statin use, estimated glomerular filtration rate, atrial fibrillation, hypertension medication use, diabetes, systolic blood pressure, glucose, low density lipoprotein cholesterol, high density lipoprotein cholesterol, log of high sensitivity C-reactive protein, and log of the urinary albumin/creatinine ratio; Bold p-value < 0.05

Table 6. Unadjusted and incrementally adjusted hazard ratios (95% confidence Intervals) for LVH using different definitions from models predicting risk of incident acute CHD and total mortality, stratified by race. (White N=9,561; black N=6,829)

	CV LVH[c]	
Acute CHD n=410 events	**Black n=19 events**	**White n=8 events**
Unadjusted	**2.16(1.34,3.48)**	**2.08(1.03,4.21)**
Model 1[d]	**2.22(1.37,3.60)**	**2.21(1.08,4.53)**
Model 2[e]	**2.20(1.36,3.56)**	**2.11(1.03,4.33)**
Model 3[f]	**1.63(1.00,2.68)**	1.58(0.76,3.28)
Acute CHD/CVD death n=572 events	**Black n=29 events**	**White n=10 events**
Unadjusted	**2.19(1.49,3.22)**	**1.99(1.06,3.73)**
Model 1[d]	**2.15(1.46,3.18)**	1.88(0.99,3.56)
Model 2[e]	**2.11(1.42,3.12)**	1.78(0.94, 3.39)
Model 3[f]	**1.54(1.03,2.30)**	1.36(0.71, 2.60)
All-cause Mortality n=993 events	**Black n=47 events**	**White n=16 events**
Unadjusted	**1.85(1.37,2.49)**	**1.90(1.16,3.13)**
Model 1[d]	**1.84(1.36,2.49)**	1.35(0.82,2.24)
Model 2[e]	**1.79(1.32,2.43)**	1.37(0.82,2.27)
Model 3[f]	**1.36(1.00,1.86)**	1.16(0.70,1.94)

Abbreviations: CHD = coronary heart disease. CVD = cardiovascular disease. ECG = electrocardiogram. LVH = left ventricular hypertrophy; [c]CV LVH is based on sex-specific Cornell voltage criteria. See also text; [d]Model 1 adjusts for age, race, sex, region; [e]Model 2 adjusts for Model 1 covariates plus income, alcohol, smoking, exercise, education, and body mass index; [f]Model 3 adjusts for Model 2 covariates plus statin use, estimated glomerular filtration rate, atrial fibrillation, hypertension medication use, diabetes, systolic blood pressure, glucose, low density lipoprotein cholesterol, high density lipoprotein cholesterol, log of high sensitivity C-reactive protein, and log of the urinary albumin/creatinine ratio; Bold p-value < 0.05

Although this is a large cohort, the relatively modest number of events in race and sex stratified analyses limited the power of the analyses. The effect of exclusion of slightly higher risk older patients with only 7 lead ECGs cannot be assessed but is likely do little to alter the conclusions of our study analysis.

5. CONCLUSION

In conclusion, we described risks associated with LVH as defined using CV LVH ECG criteria for incident CHD, CHD or CVD mortality, and total mortality similar to findings from past studies. In contrast with past studies, we described a possible higher risk of incident acute CHD for men compared to women with CV LVH, a finding that should be confirmed in other studies. Similar to past studies, we found similar risks of incident acute CHD for blacks and whites with CV LVH. Also consistent with past studies, the risks for mortality associated with CV LVH were modest and similar for both men and women, but possibly greater for blacks than for whites. LVH as assessed by ECG continues to be an independent risk factor for incident CHD and mortality in the modern era. It is possible that some of this apparent change is contributed to by a different sampling scheme from other studies but it is no more selective than those compared from the past.

ETHICAL APPROVAL

The study protocol was reviewed and approved by the University of Alabama at Birmingham Institutional Review Board, and all participants provided informed consent.

ACKNOWLEDGEMENTS

The authors thank the other investigators, the staff, and the participants of the REGARDS study for their valuable contributions. A full list of participating REGARDS investigators and institutions can be found at http://www.regardsstudy.org.

The contributions of all authors were funded by the REGARDS study, which is supported by U01 NS041588 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, U.S. Department of Health and Human Services. The REGARDS-MI ancillary study was supported by R01 HL80477-01A1 from the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services. The

content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute, the National Institute of Neurological Disorders and Stroke, or the National Institutes of Health. Representatives of the funding agency have been involved in the review of the manuscript but not directly involved in the collection, management, analysis, or interpretation of the data. Additional funding was provided by an investigator-initiated grant-in-aid from Amgen Corporation. Amgen did not have any role in the design and conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation or approval of the manuscript

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Nichol G, Paynter NP, Schreiner PJ, Sorlie PD, Stein J, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. American heart association statistics committee and stroke statistics subcommittee. Heart disease and stroke statistics--2013 update: A report from the American Heart Association. Circulation. 2013;127:6-245.
2. East MA, Jollis JG, Nelson CL, Marks D, Peterson ED. The influence of left ventricular hypertrophy on survival in patients with coronary artery disease: Do race and gender matter? J Am Coll Cardiol. 2003;41:949-954.
3. Drazner MH, Rame JE, Marino EK, Gottdiener JS, Kitzman DW, Gardin JM, Manolio TA, Dries DL, Siscovick DS. Increased left ventricular mass is a risk factor for the development of a depressed left ventricular ejection fraction within five years: The Cardiovascular Heart Study. J Am Coll Cardiol. 2004;43(12):2207-2215.
4. Benjamin EJ, Levy D. Why is left ventricular hypertrophy so predictive of morbidity and mortality? Am J Med Sci. 1999;317(3):168-175.
5. Chambers J. Left ventricular hypertrophy: an underappreciated coronary risk factor. BMJ. 1995;311(7000):273-274.
6. 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;322:1561-1566.
7. Kannel WB. Left ventricular hypertrophy as a risk factor: the Framingham experience. J Hypertens. 1991;(suppl 2):53-59.
8. Safford MM, Brown TM, Muntner P, Durant RW, Glasser S, Halanych J, Shikany JM, Prineas R, Samdarshi T, Bittner V, Lewis CE, Gamboa C, Cushman M, Howard V. Association of race and sex with risk of incident acute coronary heart disease events in the reasons for geographic and racial differences in stroke (REGARDS) study. JAMA. 2012;308:1768-1774.
9. Prineas RJ, Le A, Soliman EZ, Zhang ZM, Howard VJ, Ostchega Y, Howard G. Reasons for geographic and racial differences in stroke (REGARDS) investigators. United States national prevalence of electrocardiographic abnormalities in black and white middle-age (45- to 64-Year) and older (≥65-Year) adults (from the Reasons for Geographic and Racial Differences in Stroke Study). Am J Cardiol. 2012;109:1223-1228.
10. Howard VJ, Cushman M, Pulley L, et al. The reasons for geographic and racial differences in stroke study: Objectives and design. Neuroepidemiology. 2005;25(3):135-143.
11. Luepker RV, Apple FS, Christenson RH, et al. Case definitions for acute coronary heart disease in epidemiology and clinical research studies: A statement from the AHA Council on Epidemiology and Prevention, AHA Statistics Committee, World Heart Federation Council on Epidemiology and Prevention, European Society of Cardiology Working Group on Epidemiology and Prevention, Centers for Disease Control and Prevention, and the National Heart Lung and Blood Institute. Circulation. 2003;108(20):2543-2549.
12. Prineas RJ, Crow RS, Blackburn H. The Minnesota code manual of electrocardiographic findings: Standards

and procedures for measurement and classification. Boston, MA: Wright-OSG; 1982.
13. Prineas RJ, Crow RS, Zhang Z-M. Minnesota code manual of electrocardiographic findings. Second ed. London: Springer-Verlag; 2010.
14. Casale PN, Devereux RB, Alonso DR, Campo E, Kligfield PSO. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: validation with autopsy findings. Circulation. 1987;75(3):565-572
15. Fox CS1, Evans JC, Larson MG, Kannel WB, Levy D. Temporal trends in coronary heart disease mortality and sudden cardiac death from 1950 to 1999: the Framingham Heart Study. Circulation. 2004;110(5):522-7. Epub 2004 Jul 19.
16. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.
17. Rubin DB, Schenker N. Multiple imputation in health-care databases: An overview and some applications. Stat Med. 1991;10(4):585-598.
18. Rubin DB. Multiple imputation after 18+ years. Journal of the American Statistical Association. 1996;91(434):473-489
19. Safford MM, Parmar G, Barasch CS, Halanych JH, Glasser S, Goff DC, Prineas R, Brown TM. Hospital laboratory reporting may be a barrier to detection of 'microsize' myocardial infarction in the US: An observational study. BMC Health Services Research. 2013;13:162.
20. Desai CS, Ning H, Lloyd-Jones DM. Competing cardiovascular outcomes associated with electrocardiographic left ventricular hypertrophy: The Atherosclerosis Risk in Communities Study. Heart. 2012;98(4):330-4.
21. Nunez E, Arnett DK, Benjamin EJ, Liebson PR, Skelton TN, Taylor H, Andrew M. Optimal threshold value for left ventricular hypertrophy in blacks: The Atherosclerosis Risk in Communities Study. Hypertension. 2005;45:58-63.
22. Havranek EP, Emserman CD, Foshaug DN, Masoudi FA, Krantz MJ, Hanratty R, Estacio RO, Dickinson LM, Steiner JF. Thresholds in the relationship between mortality and left ventricular hypertrophy defined by electrocardiography. J Electrocardiol. 2008;4:342-350.
23. Havranek EP, Foshaug DB, Emserman CD, Hanratty R, Krantz MJ, Masoudi FA, Dickinson LM, Steiner JF. Left ventricular hypertrophy and cardiovascular mortality by race and ethnicity. Am Med. 2008;12:870-875.
24. Park JK, Shin JH, Kim SH, Lim YH, Kim KS, Kim SG, Kim JH, Lim HG, Shin J. A comparison of cornell and sokolow-lyon electrocardiographic criteria for left ventricular hypertrophy in Korean patients. Korean Circ J. 2012;42:606-613.
25. Tsiachris D, Chrysohoou C, Oikonomou E, Lazaros G, Dimitriadis K, Maragiannis D, Roussos D, Andreou I, Tsantilas A, Christoforatou E, Pitsavos C, Panagiotakos D, Stefanadis C. Distinct role of electrocardiographic criteria in echocardiographic diagnosis of left ventricular hypertrophy according to age, in the general population: the Ikaria Study. J Hypertens. 2011;29:1624-1632.

© 2015 Prineas et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=641&id=26&aid=6821