Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 19, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.01.066

Association of Electrocardiographic and Imaging Surrogates of Left Ventricular Hypertrophy With Incident Atrial Fibrillation

MESA (Multi-Ethnic Study of Atherosclerosis)

Jonathan Chrispin, MD,* Aditya Jain, MD,* Elsayed Z. Soliman, MD, MSc, MS,† Eliseo Guallar, MD, PhD,‡ Alvaro Alonso, MD, PhD,§ Susan R. Heckbert, MD, MPH, PhD,|| David A. Bluemke, MD, PhD, MsB,¶ João A. C. Lima, MD,* Saman Nazarian, MD, PhD*‡

Baltimore and Bethesda, Maryland; Winston-Salem, North Carolina; Minneapolis, Minnesota; and Seattle, Washington

Objectives This study sought to examine the association between left ventricular hypertrophy (LVH), defined by cardiac magnetic resonance (CMR) and electrocardiography (ECG), with incident atrial fibrillation (AF).

Background Previous studies of the association between AF and LVH were based primarily on echocardiographic measures of LVH.

Methods The MESA (Multi-Ethnic Study of Atherosclerosis) enrolled 4,942 participants free of clinically recognized cardiovascular disease. Incident AF was based on MESA-ascertained hospital-discharge *International Classification of Diseases* codes and Centers for Medicare and Medicaid Services inpatient hospital claims. CMR-LVH was defined as left ventricular mass ≥95th percentile of the MESA population distribution. Eleven ECG-LVH criteria were assessed. The association of LVH with incident AF was evaluated using multivariable Cox proportional hazards models adjusted for CVD risk factors.

Results During a median follow-up of 6.9 years, 214 incident AF events were documented. Participants with AF were more likely to be older, hypertensive, and overweight. The risk of AF was greater in participants with CMR-derived LVH (hazard ratio [HR]: 2.04, 95% confidence interval [CI]: 1.15 to 3.62). AF was associated with ECG-derived LVH measure of Sokolow-Lyon voltage product after adjusting for CMR-LVH (HR: 1.83, 95% CI: 1.06 to 3.14, $p = 0.02$). The associations with AF for CMR-LVH and Sokolow-Lyon voltage product were attenuated when adjusted for CMR left atrial volumes.

Conclusions In a multiethnic cohort of participants without clinically detected cardiovascular disease, both CMR and ECG-derived LVH were associated with incident AF. ECG-LVH showed prognostic significance independent of CMR-LVH. The association was attenuated when adjusted for CMR left atrial volumes. (J Am Coll Cardiol 2014;63:2007–13)

Atrial fibrillation (AF), initially described over 100 years ago (1), is the most common chronic dysrhythmia in the United States, affecting over 2 million people, and is associated with heart failure, cardiovascular mortality, stroke, and total mortality (2–4). Participants with AF are 5× more likely to suffer from stroke and have a 1.5- to 1.9-fold increase in mortality (2,4,5). Due to the advancing age of the population, and improved survival from cardiovascular events and cardiac

See page 2014

From the *Department of Medicine, Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Maryland; †Departments of Epidemiology and Prevention and Internal Medicine, Cardiology Section, Epidemiological Cardiology Research Center (EPICARE), Wake Forest University School of Medicine, Winston-Salem, North Carolina; ‡Welch Center for Prevention, Epidemiology and Clinical Research, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; §Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota; ||Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, Washington; and the ¶Radiology and Imaging Sciences, National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health Clinical Center and National Institute of Biomedical Imaging and Bioengineering, Bethesda, Maryland. This research was supported by contracts N01-HC-95159 through N01-HC-95169 from the National Heart, Lung, and Blood Institute and by grants UL1-RR-024156 and UL1-RR-025005 from the National Center for Research Resources. Dr. Nazarian is supported by grants K23HL089333 and R01HL116280 from the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Dr. Nazarian is a scientific advisor and principle investigator for Biosense-Webster Incorporated and has received research funding to Johns Hopkins University from Biosense-Webster Incorporated. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Chrispin and Jain contributed equally to this manuscript. Kristian Wachtell, MD, acted as Guest Editor for this paper.

Manuscript received November 21, 2013; revised manuscript received January 14, 2014, accepted January 24, 2014.

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
CMR = cardiac magnetic resonance
ECG = electrocardiogram
HR = hazard ratio
LA = left atrium
LVH = left ventricular hypertrophy
LVM = left ventricular mass

surgery, the burden of AF will likely increase. Importantly, up to 1 of 6 individuals over 40 years of age will develop AF in the absence of heart failure or myocardial infarction (5). Known risk factors associated with the development of AF include advanced age, hypertension, diabetes, myocardial infarction, congestive heart failure, and valvular heart disease (2,3,5). Analysis in the Niigata Preventive Medicine Study showed electrocardiographic (ECG) left ventricular hypertrophy ([LVH], defined by Minnesota code 3.1/3.3), ST-T wave abnormalities with left ventricular hypertrophy, and premature complexes are also associated with increased risk for AF (6).

A number of studies have evaluated the predictive ability of echocardiographic measurements as risk factors for the development of AF. Such predictive measures include left atrial enlargement, increased ventricular wall thickness, and decreased left ventricular fractional shortening (2,7–9). Cardiac magnetic resonance (CMR) provides a more accurate assessment of myocardial size than echocardiography does (10–13), but the association of CMR findings with incident risk of AF has not been explored. We also sought to define the association of baseline ECG-defined LVH with future development of AF, and the extent to which these associations are mediated by CMR-confirmed hypertrophy.

Methods

Study sample. The MESA (Multi-Ethnic Study of Atherosclerosis) is a prospective, longitudinal study initiated in July 2000, in 6 U.S. centers, to evaluate the presence and progression of subclinical cardiovascular disease. The study objectives and design have been previously reported (14). The MESA study includes 6,814 participants 45 to 84 years of age without clinically recognized cardiovascular disease (stroke, myocardial infarction, or coronary heart disease) and with no history of AF at enrollment. A total of 4,942 participants underwent ECG and CMR examinations at baseline during 2000 to 2002 and are included in the analysis. Incident AF events were based on MESA-ascertained hospital-discharge International Classification of Diseases-Ninth Revision codes (427.31) and Centers for Medicare and Medicaid Services inpatient hospital claims. AF events that occurred during a hospital stay with coronary artery bypass surgery or valve replacement surgery were not counted as incident events.

CMR. The MESA CMR protocol, image analysis, and inter-reader and intrareader reproducibility have been previously reported (15). Briefly, base to apex short-axis fast gradient echo images (slice thickness 6 mm, slice gap 4 mm, field of view 360 to 400 mm, matrix 256 × 160, flip angle 20°, echo time 3 to 5 ms, repetition time 8 to 10 ms) were acquired using 1.5-T CMR scanners (15). Left ventricular mass (LVM) was measured as the sum of the myocardial area (the difference between endocardial and epicardial contours) times slice thickness plus image gap in the end-diastolic phase multiplied by the specific gravity of the myocardium (1.05 g/ml) (16). The reproducibility of this protocol was assessed on 79 participants with a technical measurement error of 6% and an intraclass correlation coefficient of 0.98. The threshold for CMR LVH was set at >95th percentile of the MESA population.

The original MESA CMR protocol did not measure left atrium (LA) size. Using the software cmr42 (Cardiac MRI Software version 4.1, Circle Cardiovascular Imaging, Alberta, Canada), the baseline LA volume of all participants with AF and interpretable CMR images along with a 1:1 matched (age, sex, and race) population were measured. Measurements were obtained at the end of atrial diastole (just prior to the opening of the mitral valve) in the long-axis 2- and 4-chamber cine views. The software then calculated a final biplane measurement, which was used in the analysis.

Electrocardiography. LVH by ECG was assessed using 11 different criteria (Table 1). LVM was estimated from the ECG based on the model by Rautaharju et al. (27), which adjusts for weight, race, and sex based on ECG and echocardiographic LVH associations in the multicenter Cardiovascular Health Study cohort.

Statistical analyses. Continuous data are presented as a mean ± SD. Categorical data are presented as frequency. The baseline characteristics and CMR- and ECG-derived variables were compared among participants with and without incident AF using the chi-square test and Student *t* test where appropriate. Univariable and multivariable Cox proportional hazards models were used to determine association with AF. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). The multivariable models adjusted for cardiovascular risk factors (age, sex, race, body mass index, cigarette smoking status, systolic blood pressure, diabetes, total cholesterol, high-density lipoprotein cholesterol, and use of digitalis, antiarrhythmic, antihypertensive, and lipid medications) to examine the association of LVH as defined by CMR and ECG with incident AF. Each of the 11 ECG criteria for LVH was independently assessed for their association with AF. When appropriate, the CMR-LVH group was compared with the CMR group with LVM ≤50th percentile. We also tested for 2-way interactions of LVH (by CMR and ECG) with sex and ethnicity. Finally, because the original MESA MRI measurement protocols did not measure LA volume, we performed a nested case-control study to assess the potential mediating effect of LA volume for the relationship of CMR-LVH with incident AF. We measured LA volume in all incident cases of AF and in age-, sex-, and ethnicity-matched cases and controls. LA volume assessment was done blinded to case-control status. We then used Cox

Table 1 ECG Criteria

Model (Ref. #)	Criteria	
Sokolow-Lyon voltage (17)	$SV_1 + RV_5/V_6 \geq 3.5$ mV and/or RaVL ≥ 1.1 mV	
Sex-specific Cornell voltage (18)	SV_3 + RaVL >2.8 mV (for men) and >2.0 mV (for women)	
Romhilt-Estes point score (19)	Diagnostic ≥5 points and probable ≥4 points	
	Criteria	**Points**
	Voltage criteria	
	R or S wave in limb leads ≥20 mm	3
	S wave in V_1 or V_2 ≥30 mm	3
	R wave in V_5 or V_6 ≥30 mm	3
	ST-T wave abnormality	
	ST-T vector opposite to QRS complex without digitalis	3
	ST-T vector opposite to QRS complex with digitalis	1
	Negative terminal P mode in V_1 1 mm in depth and 0.04 s in duration	3
	Left axis deviation	2
	QRS duration ≥0.09 s	1
	Delayed intrinsicoid deflection in V_5 or V_6 (>0.05 s)	1
Perugia score (20)	Positivity of ≥1 of the following 3 criteria: SV_3 + RaVL >2.4 mV (men) or >2.0 mV (women), left ventricular strain, or Romhilt-Estes score ≥5	
Perugia 2 score (21)	Positivity of ≥1 of the following 2 criteria: SV_3 + RaVL >2.4 mV (men) or >2.0 mV (women), or left ventricular strain	
Minnesota code 3.1 (22)	RV_5/V_6 >2.6 mV or RI/II/III/aVF >2 mV or RaVL >1.2 mV	
Lewis index (23)	[(RI + SIII) − (RIII + SI)] >1.7 mV	
Framingham-adjusted Cornell voltage (24)	men: $[RaVL + SV_3 + 0.0174 \times (age - 49) + 0.191 \times (BMI - 26.5)] \geq 2.8$ mV; women: $[RaVL + SV_3 + 0.0387 \times (age - 50) + 0.212 \times (BMI - 24.9)] \geq 2.0$ mV	
Cornell voltage product (25)	([RaVL + SV_3] × QRS duration) ≥243,600 μVms	
Sokolow-Lyon voltage product (25)	$(SV_1 + RV_5/RV_6) \times$ QRS duration ≥371,000 μVms	
Gubner and Ungerleider voltage (26)	RI + SIII ≥2.2 mV	

BMI = body mass index; ECG = electrocardiogram.

proportional hazards models with shared frailty (by matching variable) with time to incident AF as outcome and CMR-LVH (defined as 95th percentile of the MESA cohort), systolic blood pressure, and use of antihypertensive medications as independent variables, followed by the addition of LA volume to examine the role of LA volume as a mediator of the association between CMR-LVH and incident AF. Statistical analyses were performed using STATA statistical software (version 9.0, College Station, Texas). A p value <0.05 was considered statistically significant.

Results

The total number of MESA participants with CMR-LVM and ECG measures was 4,942. There were 214 incident AF events documented during a median follow-up of 2,533 days (6.9 years).

Participants with AF were more likely to be older, Caucasian, male, taller, overweight, have underlying systolic hypertension, have a history of smoking, and have slightly lower total cholesterol (Table 2). There were no differences in the prevalence of diabetes or high-density lipoprotein levels among participants with or without AF.

Participants with incident AF had significantly higher prevalence of LVH at baseline by 6 of 11 ECG criteria (Sokolow-Lyon, Sokolow-Lyon voltage product, Cornell voltage product, Perugia score, Perugia 2 score, Romhilt-Estes score) and CMR-LVH (Table 3). The risk of incident AF was higher in participants with ECG-LVM >95th percentile compared with those with LVM <50th percentile (HR: 2.7, 95% CI: 1.7 to 4.1, $p \leq 0.001$), but this association was attenuated and lost its significance after adjustment for traditional cardiovascular risk factors (Table 4).

Eleven ECG-LVH criteria were analyzed for their association with incident AF in both the unadjusted and adjusted models (Table 5). Six of the 11 models had a significant association in the unadjusted models: Sokolow-Lyon voltage; Sokolow-Lyon voltage product; Cornell voltage product; Romhilt-Estes score; Perugia score; and Perugia 2 score. After adjustment for cardiovascular risk factors, only 3 of 11 ECG-LVH criteria had significant associations with AF: Sokolow-Lyon voltage; Sokolow-Lyon voltage product; and Perugia score (HR: 1.57, 95% CI: 1.06 to 2.32, $p = 0.02$; HR: 2.24, 95% CI: 1.33 to 3.76, $p = 0.002$; HR: 1.71, 95% CI: 1.09 to 2.81, $p = 0.03$, respectively) (Table 5). Further analysis adjusting for CMR-LVH showed Sokolow-Lyon voltage product retained significant associations with AF (HR: 1.83, 95% CI: 1.06 to 3.14, $p = 0.02$). Sokolow-Lyon voltage and Perugia score did not retain significance after adjusting for CMR-LVH.

JACC Vol. 63, No. 19, 2014
May 20, 2014:2007–13

Table 2 Baseline Characteristics of the Study Population (n = 4,942)

	No AF (n = 4,728)	AF (n = 214)	p Value
Age, yrs	61.0 ± 10.0	70.0 ± 7.7	**<0.001**
Men	2,223 (47.02)	130 (60.8)	**<0.001**
Ethnicity			**<0.001**
Caucasians	1,808 (38.2)	118 (54.1)	
Chinese	633 (13.4)	15 (7.0)	
African American	1,229 (26.0)	42 (19.6)	
Hispanics	1,058 (22.4)	39 (18.2)	
Height, cm	166.3 ± 9.9	168.6 ± 10.4	**0.0008**
Weight, kg	76.9 ± 16.2	80.1 ± 16.5	**0.005**
Cigarette smoking status			**0.041**
Never	2,441 (51.8)	96 (45.3)	
Former	1,668 (35.4)	93 (43.9)	
Current	607 (12.9)	23 (10.9)	
Systolic blood pressure, mm Hg	124.9 ± 21.1	134.8 ± 23.4	**<0.001**
Diabetes	538 (11.4)	27 (12.6)	0.59
Total cholesterol, mg/dl	194.6 ± 35.5	188.8 ± 32.5	**0.02**
HDL cholesterol, mg/dl	51.2 ± 15.0	50.0 ± 14.2	0.22
Hypertension medication	1,612 (34.1)	122 (57.3)	**<0.001**
Lipid-lowering medication	742 (15.7)	40 (18.8)	0.22
Any antiarrhythmic drug	20 (0.4)	4 (1.8)	**0.003**
Digitalis	6 (0.13)	4 (1.9)	**<0.001**

Values are mean ± SD or n (%). **Bold** values are statistically significant.
AF = atrial fibrillation; HDL = high-density lipoprotein.

There were no multiplicative interactions with sex (p = 0.504) or race (p = 0.533).

The risk of incident AF increased with CMR LVM in both the unadjusted and adjusted models (Table 4). In the unadjusted and adjusted models, participants with LVM ≥95th percentile were more likely to have incident AF (HR: 2.77, 95% CI: 1.84 to 4.16, p = <0.001; and HR: 2.04, 95% CI: 1.15 to 3.62, p = 0.01, respectively) than were those with LVM <50th percentile.

Of 214 participants with AF, 206 had an interpretable CMR LA volume at baseline. The average baseline LA volume for participants with AF was 65.63 ml, and the average LA volume for the matched control group was 56.77 ml. When measurements of LA volume were incorporated into the conditional (shared frailty) Cox proportional hazards model, the association of CMR-LVH (adjusted for hypertension medications and systolic blood pressure) with incident AF was attenuated but statistical significance was preserved (HR: 2.17, 95% CI: 1.42 to 3.31, p < 0.001 to HR: 1.67, 95% CI: 1.07 to 2.60, p = 0.024).

Table 3 Baseline CMR and ECG-Derived Variables of the Study Population (n = 4,942)

	No AF (n = 4,728)	AF (n = 214)	p Value
CMR-LVH	217 (4.6)	28 (13.1)	**<0.001**
Sokolow-Lyon voltage	398 (8.5)	33 (15.7)	**<0.001**
Cornell voltage	170 (3.6)	11 (5.2)	0.22
Framingham-adjusted Cornell voltage	171 (3.6)	11 (5.2)	0.23
Minnesota code 3.1	247 (5.3)	18 (8.6)	0.04
Lewis index	566 (12.1)	26 (12.4)	0.88
Gubner and Ungerleider	278 (5.9)	18 (8.6)	0.115
Sokolow-Lyon voltage product	155 (3.3)	17 (8.1)	**<0.001**
Cornell voltage product	276 (5.9)	23 (11.0)	**0.003**
Romhilt-Estes score ≥4	58 (1.3)	6 (3.1)	**0.03**
Perugia score	229 (5.3)	19 (10.0)	**0.004**
Perugia 2 score	215 (4.8)	16 (8.4)	**0.026**

Values are n (%). **Bold** values are statistically significant.
CMR = cardiac magnetic resonance; LVH = left ventricular hypertrophy; other abbreviations as in Tables 1 and 2.

Discussion

The main finding of this study is that CMR-defined LVH in the MESA population is associated with development of incident AF. Participants with a LVM ≥95th percentile were 2× more likely to develop AF in this population. In addition, we found that LVH defined by certain ECG criteria can also be predictive of AF, and the Sokolow-Lyon voltage product ECG criteria retained association with incident AF independent of CMR-LVH.

CMR. The association of CMR-defined LVH with AF risk is consistent with previous echocardiographic studies. Previous echocardiographic studies evaluating LVH with the development of AF showed a HR of 1.28 (95% CI: 1.03 to 1.6) with each 4-mm incremental increase in septal or posterior left ventricular wall thickness (7). To the best of our knowledge, no previous studies have evaluated the association of CMR-LVH with the development of AF. CMR has been shown to be superior to echocardiography in its multiplanar capabilities, soft tissue resolution, and accuracy of measuring LVM and LV volumes. Confirmation of the association of LVH with AF using this superior imaging modality reinforces the importance of LVH as a risk factor for the development of AF. Importantly, the association of CMR-LVH with incident AF was attenuated when adjusted for CMR LA volume; however, borderline statistical significance was retained. This suggests that some, but not all, of the association of CMR-LVH with incident AF is mediated by LA enlargement.

ECG. There are a number of established ECG criteria for the diagnosis of LVH and recent publications have shown that ECG-based criteria have a low sensitivity but high specificity for magnetic resonance imaging–defined LVH (28,29). Among the 11 ECG criteria, the 3 that retained a significant association with AF in adjusted models were the Sokolow-Lyon voltage, Sokolow-Lyon voltage product, and Perugia score. Importantly, however, the Sokolow-Lyon voltage product remained predictive of AF even after adjusting for CMR-LVH. This suggests that the Sokolow-Lyon voltage product may be a surrogate of other electrical or structural features associated with the development of AF beyond anatomical LVH. Furthermore, previous studies

Table 4 HR and 95% CI for Incident AF by LVM

Measure	Model 1* Unadjusted	p Value	Model 2† Multivariable-Adjusted*	p Value
CMR-derived				
LVM†‡	1.50 (1.34–1.687)	**<0.001**	1.45 (1.23–1.70)	**<0.001**
LVM, intervals				
≤50th percentile	1.00 (reference)		1.00 (reference)	
50th–90th percentile	1.33 (0.84–2.10)	0.21	1.23 (0.76–2.00)	0.39
90th–95th percentile	1.55 (0.99–2.43)	**0.05**	1.29 (0.76–2.20)	0.33
>95th percentile	2.77 (1.84–4.16)	**<0.001**	2.04 (1.15–3.62)	**0.015**
ECG-derived‡				
LVM†	1.33 (1.17–1.52)	**<0.001**	1.01 (0.75–1.36)	0.11
LVM, intervals				
≤50th percentile	1.00 (reference)		1.00 (reference)	
50th–90th percentile	1.87 (1.18–2.95)	**0.007**	1.39 (0.84–2.31)	0.19
90th–95th percentile	1.93 (1.22–3.05)	**0.005**	0.99 (0.54–1.83)	0.99
>95th percentile	2.67 (1.73–4.12)	**<0.001**	1.31 (0.61–2.81)	0.47

Values are hazard ratio (95% confidence interval). **Bold** values are statistically significant. *Adjusted for cardiovascular risk factors (age, sex, ethnicity, weight, height, systolic blood pressure, diabetes, total and HDL cholesterol, smoking, and hypertension/lipid/arrhythmia/digitalis medication. †Standardized (centered at 0 and scaled to standard deviation units). ‡ECG-LVM derived from Rautaharju models.
CI = confidence interval; HR = hazard ratio; LVM = left ventricular mass; other abbreviations as in Tables 1 to 3.

analyzed ECG time-voltage product in the assessment of LVH and found QRS duration to be an independent predictor of LVH (25,30). This suggests that compared with the Sokolow-Lyon and Perugia score, the association with incident AF of the Sokolow-Lyon voltage product may be due to the inclusion of the QRS duration in its determination.

Study limitations. First, there were a limited number of AF events, which may explain why some ECG-LVH definitions were not significantly associated with AF risk. Second, the ascertainment of AF was based on U.S. inpatient data. This might have led to underestimation of AF cases not requiring hospitalization or that were managed abroad. Additionally, in some cases of asymptomatic AF, time to incident AF may be overestimated. Third, this study does not differentiate between cases of paroxysmal, persistent, or permanent AF. Fourth, LA volume was measured in a subset of the total population. Finally, the model we used for determination of ECG-LVM was developed using Caucasian and African American populations and adjusted only for those ethnicities. In our analysis, we combined Chinese and Hispanic patients into the same group with Caucasians. The assumption was made that ECG criterion for LVH is similar within those particular groups, but this may not be appropriate and thus may have contributed to the lack of association between ECG-LVM and incident AF.

Conclusions

The findings of this study demonstrate that LVH by CMR is associated with future risk of AF in participants with

Table 5 HR and 95% CI for Incident AF by ECG-LVH Criteria

ECG Measure	Model 1*	p Value	Model 2†	p Value	Model 3‡	p Value
Voltage-only criteria						
Sokolow-Lyon voltage	1.97 (1.36–2.80)	**<0.001**	1.57 (1.06–2.32)	**0.02**	1.37 (0.92–2.07)	0.12
Cornell voltage	1.49 (0.81–2.73)	0.19	1.36 (0.72–2.58)	0.33	—	—
Framingham-adjusted Cornell voltage	1.48 (0.80–2.72)	0.20	1.36 (0.76–2.58)	0.33	—	—
Minnesota code 3.1	1.65 (1.01–2.69)	**0.04**	1.26 (0.76–2.08)	0.35	—	—
Lewis index	1.02 (0.68–1.54)	0.89	0.72 (0.47–1.11)	0.14	—	—
Gubner and Ungerleider	1.45 (0.89–2.36)	0.12	1.02 (0.62–1.68)	0.91	—	—
Voltage-duration product						
Sokolow-Lyon voltage product	2.56 (1.56–4.21)	**<0.001**	2.24 (1.33–3.76)	**0.002**	1.83 (1.06–3.14)	**0.02**
Cornell voltage product	1.97 (1.28–3.04)	**0.002**	1.69 (0.94–2.31)	0.09	—	—
Composite criteria						
Romhilt-Estes score ≥4	2.45 (1.08–5.53)	**0.03**	1.48 (0.64–3.39)	0.94	—	—
Perugia score	2.07 (1.28–3.32)	**0.003**	1.71 (1.09–2.81)	**0.03**	1.35 (0.79–2.28)	0.26
Perugia 2 score	1.83 (1.10–3.06)	**0.020**	1.38 (0.80–2.38)	0.25	—	—

Values are hazard ratio (95% confidence interval). **Bold** values are statistically significant. Dashes indicate that data was not available. *Unadjusted. †Adjusted for cardiovascular risk factors (age, sex, ethnicity, weight, height, systolic blood pressure, diabetes, total and HDL cholesterol, smoking, and hypertension/lipid/arrhythmia/digitalis medication. ‡Adjusted for cardiovascular risk factors (age, sex, ethnicity, weight, height, systolic blood pressure, diabetes, total and HDL cholesterol, smoking, hypertension/lipid/arrhythmia/digitalis medication, and CMR-LVH).
Abbreviations as in Tables 1 to 4.

no clinically evident underlying cardiovascular disease. The recent statement from the Working Group on Electrocardiographic LVH called for validation of ECG criteria as prognostic determinants (31). Here we have validated 3 ECG algorithms for LVH as prognostic determinants of incident AF in a multiethnic population (16,26,28). We have also demonstrated that 1 algorithm (the Sokolow-Lyon voltage product) has prognostic value beyond structural LVH as defined by CMR. Importantly, the Sokolow-Lyon voltage product and Perugia score are simple ECG measures of LVH that can be performed at the bedside without the need for digital acquisition of tracings. Given that most individuals in the general practice do not have CMR images to assess for LVH, the previously mentioned ECG criteria can more widely be used to identify individuals at higher risk for AF. There has been promising evidence in a number of secondary analysis in large clinical trials (LIFE [Losartan Intervention for Endpoint Reduction in Hypertension], VALUE [Valsartan Antihypertensive Long-Term Use Evaluation], CHARM [Candesartan in Heart Failure–Assessment of Reduction in Mortality and Morbidity], Val-HeFT [Valsartan Heart Failure Trial]), and meta-analyses suggesting that the role of inhibiting the renin-angiotensin system in reducing the incidence of AF (32–38). Inhibition of the renin-angiotensin system has also been shown to decrease LVM, particularly in individuals with hypertension. Further research is needed to analyze preventive strategies for the development of AF in participants with subclinical cardiovascular disease.

Acknowledgments

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

Reprint requests and correspondence: Dr. Jonathan Chrispin, Division of Cardiology, Carnegie 568, 600 N. Wolfe Street, Baltimore, Maryland 21287. E-mail: chrispin@jhmi.edu.

REFERENCES

1. Lewis T. Report CXIX. Auricular fibrillation: a common clinical condition. Br Med J 1909;2:1528.
2. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946–52.
3. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 1995;98:476–84.
4. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med 2002;113:359–64.
5. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 2004;110:1042–6.
6. Watanabe H, Tanabe N, Makiyama Y, et al. ST-segment abnormalities and premature complexes are predictors of new-onset atrial fibrillation: the Niigata preventive medicine study. Am Heart J 2006;152:731–5.
7. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation: the Framingham Heart Study. Circulation 1994;89:724–30.
8. Verdecchia P, Reboldi G, Gattobigio R, et al. Atrial fibrillation in hypertension: predictors and outcome. Hypertension 2003;41:218–23.
9. Kizer JR, Bella JN, Palmieri V, et al. Left atrial diameter as an independent predictor of first clinical cardiovascular events in middle-aged and elderly adults: the Strong Heart Study (SHS). Am Heart J 2006;151:412–8.
10. Bellenger NG, Burgess MI, Ray SG, et al. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? Eur Heart J 2000;21:1387–96.
11. Bottini PB, Carr AA, Prisant LM, Flickinger FW, Allison JD, Gottdiener JS. Magnetic resonance imaging compared to echocardiography to assess left ventricular mass in the hypertensive patient. Am J Hypertens 1995;8:221–8.
12. Malayeri AA, Johnson WC, Macedo R, Bathon J, Lima JA, Bluemke DA. Cardiac cine MRI: quantification of the relationship between fast gradient echo and steady-state free precession for determination of myocardial mass and volumes. J Magn Reson Imaging 2008;28:60–6.
13. Grothues F, Smith GC, Moon JC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol 2002;90:29–34.
14. Bild BE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–81.
15. Natori S, Lai S, Finn JP, et al. Cardiovascular function in multi-ethnic study of atherosclerosis: normal values by age, sex, and ethnicity. AJR Am J Roentgenol 2006;186 Suppl 2:S357–65.
16. Jain A, Tandri H, Dalal D, et al. Diagnostic and prognostic utility of electrocardiography for left ventricular hypertrophy defined by magnetic resonance imaging in relationship to ethnicity: the Multi-Ethnic Study of Atherosclerosis (MESA). Am Heart J 2010;159:652–8.
17. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am Heart J 1949;37:161–86.
18. Casale PN, Devereux RB, Alonso DR, Campo E, Kligfield P. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: validation with autopsy findings. Circulation 1987;75:565–72.
19. Romhilt DW, Estes EH Jr. A point-score system for the ECG diagnosis of left ventricular hypertrophy. Am Heart J 1968;75:752–8.
20. Schillaci G, Verdecchia P, Borgioni C, et al. Improved electrocardiographic diagnosis of left ventricular hypertrophy. Am J Cardiol 1994;74:714–9.
21. Verdecchia P, Angeli F, Reboldi G, et al. Improved cardiovascular risk stratification by a simple ECG index in hypertension. Am J Hypertens 2003;16:646–52.
22. Prineas RJ, Crow RS, Blackburn H. The Minnesota Code Manual of Electrocardiographic Findings. Littleton, MA: John Wright–PSG; 1982.
23. Lewis T. Observations upon ventricular hypertrophy with special reference to preponderance of one or the other chamber. Heart 1914;5:367–402.
24. Norman JE Jr., Levy D, Campbell G, Bailey JJ. Improved detection of echocardiographic left ventricular hypertrophy using a new electrocardiographic algorithm. J Am Coll Cardiol 1993;21:1680–6.
25. Okin PM, Roman MJ, Devereux RB, Kligfield P. Electrocardiographic identification of increased left ventricular mass by simple voltage-duration products. J Am Coll Cardiol 1995;25:417–23.
26. Hsieh BP, Pham MX, Froelicher VF. Prognostic value of electrocardiographic criteria for left ventricular hypertrophy. Am Heart J 2005;150:161–7.
27. Rautaharju PM, Park LP, Gottdiener JS, Siscovick D, Boineau R, Smith V, Powe NR. Race- and sex-specific ECG models for left ventricular mass in older populations: factors influencing overestimation of left ventricular hypertrophy prevalence by ECG criteria in African-Americans. J Electrocardiol 2000;33:205–18.

28. Pewsner D, Jüni P, Egger M, Battaglia M, Sundström J, Bachmann LM. Accuracy of electrocardiography in diagnosis of left ventricular hypertrophy in arterial hypertension: systematic review. BMJ 2007;335:711.
29. 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.
30. Okin PM, Roman MJ, Devereux RB, Borer JS, Kligfield P. Electrocardiographic diagnosis of left ventricular hypertrophy by time-voltage integral of the QRS complex. J Am Coll Cardiol 1994;23:133–40.
31. Bacharova L, Estes H, Bang L, et al. The first statement of the Working Group on Electrocardiographic Diagnosis of Left Ventricular Hypertrophy. J Electrocardiol 2010;43:197–9.
32. Ducharme A, Swedberg K, Pfeffer MA, et al., for the CHARM Investigators. Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Am Heart J 2006;152:86–92.
33. Wachtell K, Lehto M, Gerdts E, et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention for End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol 2005;45:712–9.
34. Schmieder RE, Kjeldsen SE, Julius S, et al., for the VALUE Trial Group. Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. J Hypertens 2008;26:403–11.
35. Maggioni AP, Latini R, Carson PE, et al., for the Val-HeFT Investigators. Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). Am Heart J 2005;149:548–57.
36. Healey JS, Baranchuk A, Crystal E, et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J Am Coll Cardiol 2005;45:1832–9.
37. Schneider MP, Hua TA, Böhm M, Wachtell K, Kjeldsen SE, Schmieder RE. Prevention of atrial fibrillation by renin-angiotensin system inhibition: a meta-analysis. J Am Coll Cardiol 2010;55:2299–307.
38. Cuspidi C, Muiesan ML, Valagussa L, et al., for the CATCH Investigators. Comparative effects of candesartan and enalapril on left ventricular hypertrophy in patients with essential hypertension: the Candesartan Assessment in the Treatment of Cardiac Hypertrophy (CATCH) study. J Hypertens 2002;20:2293–300.

Key Words: atrial fibrillation ■ cardiac magnetic resonance imaging ■ electrocardiography ■ left ventricular hypertrophy.