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

MESA (Multi-Ethnic Study of Atherosclerosis)

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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

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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