Published in final edited form as:
J Am Coll Cardiol. 2014 May 20; 63(19): 2007–2013. doi:10.1016/j.jacc.2014.01.066.

Association of Electrocardiographic and Imaging Surrogates of Left Ventricular Hypertrophy with Incident Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis

Jonathan Chrispin, MD[1,*], **Aditya Jain, MD**[1,*], **Elsayed Z. Soliman, MD, MSc, MS**[2], **Eliseo Guallar, MD, PhD**[3], **Alvaro Alonso, MD, PhD**[4], **Susan R. Heckbert, MD, MPH, PhD**[5], **David A. Bluemke, MD, PhD, MsB**[6], **Joao A.C. Lima, MD**[1], and **Saman Nazarian, MD, PhD**[1,3]

[1]Johns Hopkins University School of Medicine, Baltimore, MD

[2]Wake Forest University School of Medicine, Winston-Salem, NC

[3]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

[4]University of Minnesota, Minneapolis, MN

[5]University of Washington, Seattle, WA

[6]National Institutes of Health Clinical Center and National Institute of Biomedical Imaging and Bioengineering, Bethesda, MD

Abstract

Objectives—To examine the association between LVH, defined by cardiovascular magnetic resonance (CMR) and electrocardiography (ECG), with incident AF.

Background—Previous studies of the association between atrial fibrillation (AF) and left ventricular hypertrophy (LVH) were based primarily on echocardiographic measures of LVH.

Methods—The Multi-Ethnic Study of Atherosclerosis (MESA) study enrolled 4942 participants free of clinically recognized cardiovascular disease. Incident AF was based on MESA ascertained hospital discharge ICD codes and Centers for Medicare and Medicaid Services (CMS) 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.

Address for Correspondence: Jonathan Chrispin, MD, Fellow, Division of Cardiology, Carnegie 568, 600 N. Wolfe Street, Baltimore, MD 21287, chrispin@jhmi.edu, Phone: (516) 984-8124, Fax: (410) 502-4854.
*Both authors contributed equally to this manuscript

Disclosures: Dr Nazarian is a scientific advisor to and PI for research funding to Johns Hopkins University from Biosense-Webster Incorporated. The other authors declare no conflicts of interest.

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% CI 1.15-3.62]. AF was associated with ECG-derived LVH measure of Sokolow-Lyon voltage product after adjusting for CMR-LVH [HR=1.83 (1.06, 3.14), p= 0.02]. The associations with AF for CMR LVH and Sokolow-Lyon voltage product were attenuated when adjusted for CMR LA volumes.

Conclusion—In a multi-ethnic cohort of participants without clinically detected CVD, 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 LA volumes.

Keywords

Atrial Fibrillation; Left Ventricular Hypertrophy; Cardiac MRI; ECG

Introduction

Atrial fibrillation (AF) is the most common chronic dysrhythmia in the United States, affecting over 2 million people, and is associated with heart failure (HF), cardiovascular mortality, stroke and total mortality (3,4). Participants with AF are five times more likely to suffer from stroke and have a 1.5-1.9 fold increase in mortality (2,4,5). Due to the advancing age of the population, and improved survival from cardiovascular events and cardiac surgery, the burden of AF will likely increase. Importantly, up to 1 of 6 individuals over 40 will develop AF in the absence of HF or myocardial infarction (MI) (5). Known risk factors associated with the development of AF include advanced age, hypertension, diabetes, myocardial infarction, CHF, and valvular heart disease (2,3,5). Analysis in the Niigata Preventive Medicine Study showed electrocardiographic (ECG) left ventricular hypertrophy (defined by Minnesota code 3.1/3.3), ST-T 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 (2,7,8,9). Cardiovascular magnetic resonance (CMR) provides a more accurate assessment of myocardial size compared to echocardiography (10,11,13), 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 left ventricular hypertrophy with future development of AF, and the extent to which these associations are mediated by CMR confirmed hypertrophy.

Methods

Study sample

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective, longitudinal study initiated in July 2000, in six US centers, to evaluate the presence and progression of subclinical cardiovascular disease. The study objectives and design have been previously

reported (17). The MESA study includes 6814 participants 45-84 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 4942 participants underwent ECG and CMR examinations at baseline during 2000-2002 and are included in the analysis. Incident AF events were based on MESA ascertained hospital discharge ICD-9 codes (427.31) and Centers for Medicare and Medicaid Services (CMS) 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.

Cardiovascular Magnetic Resonance

The MESA CMR protocol, image analysis, and inter- and intra reader reproducibility have been previously reported (14). Briefly, base to apex short-axis fast gradient echo images (slice thickness 6 mm, slice gap 4 mm, field of view 360-400 mm, matrix 256×160, flip angle 20, echo time 3-5 msec, repetition time 8-10 msec) were acquired using 1.5 Tesla CMR scanners (14). 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) (15).The reproducibility of this protocol was assessed on 79 participants with a technical measurement error of 6% and an intra-class correlation coefficient of 0.98. The threshold for CMR LVH was set at greater than the 95^{th} percentile of the MESA population.

The original MESA CMR protocol did not measure left atrium (LA) size. Using the software cmr42 (Circle Cardiovascular Imaging, Cardiac MRI Software Version 4.1; Alberta, Canada), the baseline LA volume of all participants with atrial fibrillation 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 two and four chamber cine views. The software then calculated a final biplane measurement, which was used in the analysis.

Electrocardiography

LVH by ECG was assessed using eleven different criteria (Table 1). Left ventricular mass was estimated from the ECG based on the model by Rautaharju et al, which adjusts for weight, race, and sex based upon ECG and echocardiographic LVH associations in the multicenter Cardiovascular Health Study Cohort (16).

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 Squared test and Student's 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. The multivariable models adjusted for cardiovascular risk factors (age, sex, race, BMI, cigarette smoking status, systolic blood pressure, diabetes, total cholesterol, high-density lipoprotein cholesterol, and use of digitalis, anti-arrhythmic, anti-

hypertensive and lipid medications,) to examine the association of LVH as defined by CMR and ECG with incident AF. Each of the eleven ECG criteria for LVH was independently assessed for their association with AF. When appropriate the CMR-LVH group was compared to the CMR group with LVM <=50th percentile.

We also tested for two-way interactions of LVH (by CMR and ECG) with sex and ethnicity. Finally, since 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, gender and ethnicity matched cases and controls. LA volume assessment was done blinded to case-control status. We then used Cox 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, TX). A p-value <0.05 was considered significantly significant.

Results

The total number of MESA participants with CMR-LVM and ECG measures was 4942. There were 214 incident AF events documented during a median follow-up of 2533 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 HDL levels among participants with or without AF.

Participants with incident AF had significantly higher prevalence of LVH at baseline by six of eleven 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 greater than 95th percentile compared to those with LVM <50th percentile (2.7 (1.7, 4.1), p=<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 eleven 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 three of eleven ECG-LVH criteria had significant associations with AF; Sokolow-Lyon voltage, Sokolow-Lyon voltage product and Perugia score (HR 1.57 (1.06, 2.32), p= 0.02; HR= 2.24 (1.33, 3.76), p= 0.002; HR 1.71 (1.09, 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 (1.06, 3.14), p= 0.02). Sokolow-Lyon voltage and Perugia score did not retain significance after adjusting for CMR-LVH. There were no multiplicative interactions with gender (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 (1.84, 4.16), p = <0.001; and HR = 2.04 (1.15, 3.62), p= 0.01, respectively) compared to those with LVM <50th percentile.

A total of 206 of 214 participants with AF 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 (1.42-3.31), p<0.001 to HR 1.67, 95% CI (1.07-2.60), p=0.024).

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 two times 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 prior echocardiographic studies. Previous echocardiographic studies evaluating LVH with the development of AF, showed a HR of 1.28 (95% CI, 1.03-1.6) 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 multi-planar capabilities, soft tissue resolution, and accuracy of measuring left ventricular mass and 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 MRI-defined LVH (27,28). Among the eleven ECG criteria, the three 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. Further, previous studies analyzed ECG time-voltage product in the assessment of LVH and found QRS duration to be an independent predictor of LVH (25,29). This suggests that compared to 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.

Limitations

Our study has 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 US inpatient data. This might have led to underestimation of AF cases not requiring hospitalization, or 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, which may not be appropriate and thus may have contributed to the lack of association between ECG-LVM and incident AF.

Clinical Implications

The findings of this study demonstrate that LVH by CMR is associated with future risk of AF in participants with 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. Here we have validated three ECG algorithms for LVH as prognostic determinants of incident AF in a multi-ethnic population (15,26,27). We have also demonstrated that one algorithm (the Sokolow-Lyon voltage product) has prognostic value beyond structural LVH as defined by CMR. Importantly, the Sokolow-Lyon 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, VALUE, CHARM, Val-HeFT), and meta-analyses suggesting the role of inhibiting the renin-angiotensin system (RAS) in reducing the incidence of AF (30-35). Inhibition of the RAS has also been shown to decrease LVM, particularly in individuals with hypertension (36). 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.

Funding Sources: 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 NCRR. Dr. Nazarian is supported by grants K23HL089333 and R01HL116280 from the National Institutes of Health (NIH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Lewis T. Auricular Fibrillation: a common clinical condition. BMJ. 1909; 2:1528. [PubMed: 20764769]
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; 98:946–952. [PubMed: 9737513]
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; 98:476–484. [PubMed: 7733127]
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; 113:359–364. [PubMed: 12401529]
5. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation. 2004; 110:1042–1046. [PubMed: 15313941]
6. Watanabe H, Tanabe N, Makiyama Y, Chopra SS, Okura Y, Suzuki H, Matsui K, Watanabe T, Kurashina Y, Aizawa Y. 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. [PubMed: 16996849]
7. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation. 1994; 89:724–30. [PubMed: 8313561]
8. Verdecchia P, Reboldi G, Gattobigio R, Bentivoglio M, Borgioni C, Angeli F, Carluccio E, Sardone MG, Porcellati C. Atrial fibrillation in hypertension: predictors and outcome. Hypertension. 2003; 41:218–23. [PubMed: 12574085]
9. Kizer JR, Bella JN, Palmieri V, Liu JE, Best LG, Lee ET, Roman MJ, Devereux RB. 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. [PubMed: 16442908]
10. Bellenger NG, Burgess MI, Ray SG, Lahiri A, Coats AJ, Cleland JG, Pennell DJ. 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. [PubMed: 10952828]
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. [PubMed: 7794570]
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. [PubMed: 18581356]
13. Grothues F, Smith GC, Moon JC, Bellenger NG, Collins P, Klein HU, Pennell DJ. 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. [PubMed: 12088775]
14. Natori S, Lai S, Finn JP, Gomes AS, Hundley WG, Jerosch-Herold M, Pearson G, Sinha S, Arai A, Lima JA, Bluemke DA. Cardiovascular function in multi-ethnic study of atherosclerosis: normal values by age, sex, and ethnicity. AJR Am J Roentgenol. 2006; 186:S357–65. [PubMed: 16714609]
15. Jain A, Tandri H, Dalal D, Chahal H, Soliman EZ, Prineas RJ, Folsom AR, Lima JA, Bluemke DA. 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. [PubMed: 20362725]

16. 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. Journal of Electrocardiology. 2000; 33:3.
17. Bild BE, Bluemke DA, Burke GL, Detrano R, Diez AV, Folsom AR, Greenland P, Jacobs DR, Kronmal R, Liu K, Clark Nelson J, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-Ethnic Study of Atherosclerosis: Objectives and Design. Am J Epidemiol. 2002; 156:871–81. [PubMed: 12397006]
18. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am Heart J. 1949; 37(2):161–186. [PubMed: 18107386]
19. Casale PN, Devereux RB, Alonso DR, et al. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: validation with autopsy findings. J Am Coll Cardiol. 1987; 3:565–72.
20. Romhilt DW, Estes EH Jr. A point-score system for the ECG diagnosis of left ventricular hypertrophy. Am Heart J. 1968; 75:752–8. [PubMed: 4231231]
21. Schillaci G, Verdecchia P, Borgioni C, Ciucci A, Guerrieri M, Zampi I, Battistelli M, Bartoccini C, Porcellati C. Improved electrocardiographic diagnosis of left ventricular hypertrophy. Am J Cardiol. 1994; 74:714–9. [PubMed: 7942532]
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, et al. Improved detection of echocardiographic left ventricular hypertrophy using a new electro-cardiographic algorithm. J Am Coll Cardiol. 1993; 21:1680–6. [PubMed: 8496537]
25. Okin PM, Roman MJ, Devereux RB, et al. Electrocardiographic identification of increased left ventricular mass by simple voltage- duration products. J Am Coll Cardiol. 1995; 25:417–23. [PubMed: 7829796]
26. Hsieh BP, Pham MX, Froelicher VF. Prognostic value of electrocar-diographic criteria for left ventricular hypertrophy. Am Heart J. 2005; 150:161–7. [PubMed: 16084164]
27. 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; 335:71. [PubMed: 17626957]
28. 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; 81:815–820. [PubMed: 2137733]
29. 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. [PubMed: 8277071]
30. Ducharme A, Swedberg K, Pfeffer MA, Cohen-Solal A, Granger CB, Maggioni AP, Michelson EL, McMurray JJV, Olsson L, Rouleau JL, Young JB, Olofsson B, Puu M PhD, Yusuf S. 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. [PubMed: 16838426]
31. Wachtell K, Lehto M, Gerdts E, Olsen MH, Hornestam B, Dahlöf B, Ibsen H, Julius S, Kjeldsen SE, Lindholm LH, Nieminen MS, Devereux RB. 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. [PubMed: 15734615]
32. Schmiedera RE, Kjeldsen SE, Julius S, McInnes GT, Zanchettie A, Hua TA. Reduced incidence of new-onset atrial fibrillation with angiotensinII receptor blockade: the VALUE trial. J Hypertens. 2008; 26:403–411. [PubMed: 18300848]

33. Maggioni AP, Latini R, Carson PE, Singh SN, Barlera S, Glazer R, Masson S, Cere E, Tognoni G, Cohn JN. 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. [PubMed: 15864246]

34. Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, Connolly SJ. Prevention of Atrial Fibrillation With Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers A Meta-Analysis. J Am Coll Cardiol. 2005; 45:1832–9. [PubMed: 15936615]

35. Schneider MP, Hua TA, Böhm M MD, 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. [PubMed: 20488299]

36. Cuspidi C, Muiesan ML, Valagussa L, Salvetti M, Di Biagio C, Agabiti-Rosei E, Magnani B, Zanchetti A. 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. [PubMed: 12409969]

37. Bacharova L, Estes H, Bang L, Rowlandson I, Schillaci G, Verdecchia P, Macfarlane PW. The first statement of the Working Group on Electrocardiographic Diagnosis of Left Ventricular Hypertrophy. J Electrocardiol. 2010; 43:197–9. [PubMed: 20399348]

38. Verdecchia P, Angeli F, Reboldi G, Carluccio E, Benemio G, Gattobigio R, et al. Improved cardiovascular risk stratification by a simple ECG index in hypertension. Am J Hypertens. 2003 Aug; 16(8):646–652. [PubMed: 12878370]

Common Abbreviations

AF	Atrial Fibrillation
ECG	Electrocardiogram
LVH	Left Ventricular Hypertrophy
CMR	Cardiovascular Magnetic Resonance
LVM	Left Ventricular Mass
LA	Left Atrium
MI	Myocardial Infarction
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

Table 1

ECG Criteria

	Criteria	
Sokolow-Lyon voltage[18]	SV1 + RV5/V6 ≥3.5 mV and/or RaVL ≥1.1 mV	
Sex-specific Cornell voltage[19]	SV3 + RaVL >2.8 mV [for men] and >2.0 mV [for women]	
Romhilt-Estes point score[20]	Diagnostic ≥5 points and probable ≥4 points	
	Criteria	**Points**
	Voltage Criteria	
	- R or S in limb leads ≥ 20mm	3
	- S in V1 or V2 ≥ 30mm	3
	- R in V5 or V6 ≥ 30mm	3
	ST-T Abnormality -ST-T vector opposite to QRS w/o digitalis	3
	-ST-T vector opposite to QRS w/digitalis	1
	Negative terminal P mode in V_1 1 mm in depth and 0.04 sec in duration	3
	Left axis deviation	2
	QRS duration ≥0.09 sec	1
	Delayed intrinsicoid deflection in V_5 or V_6 (>0.05 sec)	1
Perugia score[21]	Positivity of at least 1 of the following 3 criteria: SV3 + RaVL >2.4 mV [men] or >2.0 mV [women], left ventricular strain, or Romhilt-Estes score of ≥5	
Perugia 2 Score[38]	Positivity of at least 1 of the following 2 criteria: SV3 + RaVL >2.4 mV [men] or >2.0 mV [women], or left ventricular strain	
Minnesota code 3.1[22]	RV5/V6 >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 + SV3 + 0.0174*{age − 49} + 0.191*{body mass index (BMI) - 26.5}] ≥2.8 mV; women: [RaVL + SV3 + 0.0387*{age − 50} + 0.212* {BMI − 24.9}] ≥2.0 mV	
Cornell voltage product[25]	([RaVL + SV3] *QRS duration ≥243,600 μVms	
Sokolow- Lyon voltage product[25]	[SV1 + RV5/RV6]*QRS duration ≥371,000 μVms	
Gubner and Ungerleider voltage[26]	RI + SIII ≥2.2 mV	

Table 2
Baseline characteristics of the study population (n=4942)

Variable	No Afib (n=4728)	Afib (n=214)	P-value
Age, years	61.0 ± 10.0	70.0 ± 7.7	**<0.001**
Men, n (%)	2223(47.02)	130(60.8)	**<0.001**
Ethnicity, n (%)			**<0.001**
Caucasians	1808 (38.2)	118 (54.1)	
Chinese	633 (13.4)	15 (7.0)	
African American	1229 (26.0)	42 (19.6)	
Hispanics	1058 (22.4)	39 (18.2)	
Height, cm	166.3 ± 9.9	168.6 ± 10.4	**0.0008**
Weight, kgs	76.9 ± 16.2	80.1 ± 16.5	**0.005**
Cigarette smoking status, n (%)			**0.041**
Never	2441 (51.8)	96 (45.3)	
Former	1668 (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, n (%)	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, n (%)	1612 (34.1)	122 (57.3)	**<0.001**
Lipid-lowering medication, n (%)	742 (15.7)	40 (18.8)	0.22
Any antiarrhythmic drug, n (%)	20 (0.4)	4 (1.8)	**0.003**
Digitalis, n (%)	6 (0.13)	4 (1.9)	**<0.001**

Table 3
Baseline CMR and ECG-derived variables of the study population (n=4942)

Variable, n (%)	No Afib (n=4728)	Afib (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**

Table 4
Hazard ratios (HR) and 95% Confidence Intervals (CI) for Incident AF by LV mass

	HR (95% CI)			
Measure	**Model 1[*] Unadjusted**	**P-value**	**Model 2[†] Multivariable-adjusted[*]**	**P-value**
CMR-derived				
LV mass[†‡]	1.50 (1.34, 1.687)	**<0.001**	1.45 (1.23, 1.70)	**<0.001**
LV mass (intervals)				
≤50th percentile	1 (ref.)		1 (ref.)	
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[‡]				
LV mass[†]	1.33 (1.17, 1.52)	**<0.001**	1.01 (0.75, 1.36)	0.11
LV mass (intervals)				
≤50th percentile	1 (ref.)		1 (ref.)	
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

[*] Adjusted for cardiovascular risk factors (age, sex, ethnicity, weight, height, systolic BP, diabetes, total and HDL cholesterol, smoking, and hypertension/lipid/arrhythmia/digitalis medication

[†] Standardized (centered at 0 and scaled to SD units)

[‡] ECG-LV mass derived from Rautaharju models

Table 5

Hazard ratios (HR) and 95% Confidence Intervals (CI) for Incident AF by ECG-LVH criteria

	HR (95% CI)					
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(0.7 9, 2.28)	0.26
Perugia 2 score	1.83 (1.10, 3.06)	**0.020**	1.38 (0.80, 2.38)	0.25	-	-

*Unadjusted

†Adjusted for cardiovascular risk factors (age, sex, ethnicity, weight, height, systolic BP, diabetes, total and HDL cholesterol, smoking, and hypertension/lipid/arrhythmia/digitalis medication

‡Adjusted for cardiovascular risk factors (age, sex, ethnicity, weight, height, systolic BP, diabetes, total and HDL cholesterol, smoking, hypertension/lipid/arrhythmia/digitalis medication and CMR-LVH)

J Am Coll Cardiol. Author manuscript; available in PMC 2015 May 20.