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ORIGINAL RESEARCH

Association of Left Atrial Function Index with Atrial Fibrillation and Cardiovascular Disease: The Framingham Offspring Study

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***Background*—**Left atrial (LA) size, a marker of atrial structural remodeling, is associated with increased risk for atrial fibrillation (AF) and cardiovascular disease (CVD). LA function may also relate to AF and CVD, irrespective of LA structure. We tested the hypothesis that LA function index (LAFI), an echocardiographic index of LA structure and function, may better characterize adverse LA remodeling and predict incident AF and CVD than existing measures.

***Methods and Results*—**In 1786 Framingham Offspring Study eighth examination participants (mean age, 66±9 years; 53% women), we related LA diameter and LAFI (derived from the LA emptying fraction, left ventricular outflow tract velocity time integral, and indexed maximal LA volume) to incidence of AF and CVD on follow-up. Over a median follow-up of 8.3 years (range, 7.5–9.1 years), 145 participants developed AF and 139 developed CVD. Mean LAFI was 34.5±12.7. In adjusted Cox regression models, lower LAFI was associated with higher risk of incident AF (hazard ratio=3.83, 95% confidence interval=2.23–6.59, lowest [Q1] compared with highest [Q4] LAFI quartile) and over 2-fold higher risk of incident CVD (hazard ratio=2.20, 95% confidence interval=1.32–3.68, Q1 versus Q4). Addition of LAFI, indexed maximum LA volume, or LA diameter to prediction models for AF or CVD did not significantly improve model discrimination for either outcome.

***Conclusions*—**In our prospective investigation of a moderate-sized community-based sample, LAFI, a composite measure of LA size and function, was associated with incident AF and CVD. Addition of LAFI to the risk prediction models for AF or CVD, however, did not significantly improve their performance. **(*J Am Heart Assoc*. 2018;7:e008435. DOI: 10.1161/JAHA.117.008435.)**

Key Words: atrial fibrillation • cardiovascular disease • echocardiography • epidemiology • left atrium

Increased left atrial (LA) size and impaired phasic function are distinct echocardiographic phenotypes that capture different aspects of LA remodeling.[1] Measures of increased LA size, including anteroposterior LA diameter, area, or volume, are measures of LA structural remodeling.[1] Adverse atrial structural remodeling has been associated with cardiovascular disease (CVD) and atrial fibrillation (AF) risk factors, including advancing age, hypertension, and diabetes mellitus.[2–13] Although measures of LA structural remodeling have been associated with incident AF and CVD, associations have been modest, and these measures do not incrementally improve clinical AF and CVD risk prediction tools.[2–12,14,15]

Intermediate phenotypes that characterize functional LA remodeling may potentially enhance AF and CVD risk prediction. Recent reports have emphasized that impaired LA phasic function is associated with incident and recurrent CVD and AF, independent of LA size.[16–19] However, the incremental predictive value of functional LA remodeling over

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An accompanying Data S1 is available at http://jaha.ahajournals.org/content/7/7/e008435/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- This study investigated the prognostic significance of left atrial function index, a composite echocardiographic measure of atrial structural and functional remodeling in a medium-sized community-based sample.
- Left atrial function index impairment was associated with an increased risk of developing incident atrial fibrillation and cardiovascular disease, independent of validated clinical risk prediction scores and echocardiographic measures of adverse cardiac remodeling.

What Are the Clinical Implications?

- Although the left atrial enlargement is widely utilized clinically as a measure of left atrial remodeling, our findings suggest an independent association of impaired left atrial function index with adverse outcomes even in the presence of normal left atrial size.
- Left atrial function index can be measured using widely available 2-dimensional echocardiography.

clinical prediction models is currently unknown. Furthermore, LA function is strongly correlated with LA structure and is also influenced by left ventricular (LV) systolic function.[9,20] In this context, the LA function index (LAFI) has been advocated as a composite echocardiographic measure of both LA structure *and* function that also adjusts for LV systolic function.[21] LAFI can be derived using LA and LV measures obtained routinely as part of standard 2-dimensional echocardiography.[21] Recent data suggest that LAFI is strongly associated with risk for developing AF recurrence, heart failure, and stroke in select CVD-based samples.[22–25] We recently reported on the distribution of LAFI as well as its clinical and echocardiographic correlates in the community-based FHS (Framingham Heart Study) Offspring Cohort.[26] In the current investigation, we related LAFI to incident AF and CVD in FHS Offspring participants and assessed its incremental contribution to prediction of these outcomes.

Methods

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Sample

The Framingham Offspring Study is a longitudinal, community-based cohort study.[27] Starting in 1971, the children of the

Table 1. Baseline Characteristics of Study Participants and Excluded Participants

Variable	Study Participants (N=1786)	Excluded Participants (N=1102)	*P* Value
Age, y	66±9	66±9	0.21
Women	957 (54%)	612 (56%)	0.33
Body mass index, kg/m^2	28±5	29±6	0.006
Current smoker	171 (10%)	90 (8%)	0.20
Systolic blood pressure, mm Hg	128±17	129±18	0.19
Diastolic blood pressure, mm Hg	73±10	74±10	0.011
Antihypertensive medication use	938 (53%)	606 (55%)	0.21
Diabetes mellitus	279 (16%)	165 (15%)	0.63
Prevalent AF	133 (8%)	77 (7%)	0.64
Prevalent heart failure	43 (2%)	32 (3%)	0.42
Prevalent CVA or TIA	79 (4%)	43 (4%)	0.49
Prevalent coronary heart disease	192 (11%)	117 (11%)	0.90
Estimated glomerular filtration rate less than 60 mL/min per 1.73 m^2	287 (16%)	182 (17%)	0.81
Total/HDL cholesterol ratio	3.47±1.05	3.49±1.07	0.68
Incident AF*	145 (9%)	102 (10%)	0.64
Incident CVD†	139 (9%)	82 (9%)	0.56

AF indicates atrial fibrillation; CVA, cerebrovascular accident; CVD, cardiovascular disease; HDL, high-density lipoprotein; TIA, transient ischemic attack.
*Incident AF is reported for the participants who were free of AF at baseline.
†Incident CVD is reported for the participants who were free of CVD at baseline).

Table 2. Baseline Clinical and Echocardiographic Characteristics of Study Participants by Sex-Specific LAFI Quartile Groups

Variable	LAFI Quartile 1 (N=446)	LAFI Quartile 2 (N=446)	LAFI Quartile 3 (N=446)	LAFI Quartile 4 (N=446)	*P* Value
LAFI, mean±SD	19.9±5.6	30±2.6	37.1±3	51.1±8.8	<0.001
Age, y	70±9	66±9	65±9	64±8	<0.001
Body mass index, kg/m^2	27.8±5	28.1±5	28.1±5.3	28.3±5.4	0.58
Current smoker	42 (9)	43 (10)	41 (9)	45 (10)	0.97
Systolic blood pressure, mm Hg	130±19	129±17	127±16	128±16	0.08
Diastolic blood pressure, mm Hg	71±11	73±10	73±10	74±9	<0.001
Antihypertensive agent use	302 (67)	228 (51)	207 (46)	201 (45)	<0.001
Diabetes mellitus	97 (22)	61 (14)	62 (14)	59 (13)	<0.001
Prevalent AF	85 (19)	21 (5)	16 (3)	11 (2)	<0.001
Prevalent heart failure	31 (7)	3 (1)	3 (1)	6 (1)	<0.001
Prevalent CVA or TIA	39 (9)	14 (3)	11 (2)	10 (2)	<0.001
Prevalent peripheral arterial disease	21 (5)	11 (2)	8 (2)	6 (1)	0.007
Prevalent coronary heart disease	80 (18)	43 (10)	36 (8)	33 (7)	<0.001
10-y FHS CVD risk, %*	31±19	25±17	23±16	22±16	<0.001
CHARGE-AF risk, %†	8.7±10.3	5.6±6.9	4.9±5.9	4.3±5.8	<0.001

AF indicates atrial fibrillation; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; CVA, cerebrovascular accident; CVD, cardiovascular disease; FHS, Framingham Heart Study; LAFI, left atrial function index; TIA, transient ischemic attack.

*10-year FHS CVD risk was calculated for the participants who were free of CVD at baseline and had information available for individual components of FHS-CVD risk, which are age, male sex, systolic blood pressure, antihypertensive medication use, current smoker, diabetes mellitus, and body mass index (n=1501).

†CHARGE-AF risk was calculated for the participants who were free of AF at baseline and had information available for individual components of CHARGE-AF risk score, which are age, race, height, weight, systolic blood pressure, diastolic blood pressure, current smoking, antihypertensive medication use, diabetes mellitus, heart failure, myocardial infarction, and left ventricular hypertrophy and PR interval by ECG (n=1638).

original cohort of the FHS and their spouses were enrolled and have been evaluated every 4 to 8 years. Transthoracic echocardiography was performed in 2888 participants with digital image acquisition during their eighth examination cycle (2005–2008).[28] After excluding participants with absent or poor imaging of the atrium (n=1093), and moderate to severe or greater degrees of mitral regurgitation (n=9), 1786 participants remained eligible for the present analysis. Characteristics of FHS participants who were included in comparison with those excluded are presented in Table 1. For incident AF outcome analyses, participants with history of baseline AF were excluded, whereas for CVD outcome analyses, the participants with history of baseline CVD were excluded. Methodology for the ascertainment of cardiovascular risk factors, CVD, and AF are presented in Data S1.

The protocol for the FHS Offspring Study was approved by the Boston University Medical Center Institutional Review Board, and all analyses were approved by the University of Massachusetts Medical School. All participants provided written informed consent.

Echocardiographic Measurements

Routine M-mode and 2-dimensional echocardiography were performed at the eighth examination cycle using a standard protocol as described previously.[28] M-mode measurements were made using the leading-edge technique, and the final measures were derived by averaging the measurements over ≥3 cardiac cycles. For the current investigation, we used the following end-diastolic M-mode measurements in the parasternal long axis view: LV septal wall thickness (SWT_d), posterior wall thickness (PWT_d), LV internal diameter ($LVID_d$), and LA anteroposterior diameter (LAD). LV mass was calculated by using a previously validated formula: $0.8\ [1.04\ (LVID_d+SWT_d+PWT_d)^3-(LVID_d)^3]+0.6$ g.[29] In the apical-2 chamber view, LV end-diastolic and end-systolic volumes were measured using Simpson's method. Stroke volume was calculated as (LV end-diastolic volume−LV end-systolic volume), and LV ejection fraction was calculated as (Stroke volume/LV end-diastolic volume)×100. LV outflow tract (LVOT) diameter was measured in the parasternal long-axis view.[30] LVOT velocity-time integral (LVOT−VTI) was calculated by dividing the stroke volume by LVOT area $(3.14\times(\text{LVOT diameter}/2)^2)$.

Echocardiographic image acquisition was performed with settings optimal for LV assessment. For LA volume measurement, 2 sonographers converted saved images into a digital format. The Digisonics DigiView System Software (version 3.7.9.3; Digisonics Inc, Houston, TX) was then used by 1 of 2 FHS sonographers to measure LA volumes. Maximum and minimum LA volumes (LAmax, LAmin) were derived by

Table 3. Association of LAFI With Incident AF in Cox Proportional Hazards Regression Model

Sample	No. of Eligible Participants	No. of Incident AF Events	LAFI Quartile	Events	Person-Years Follow-up	*P* For Linear Trend	Model 1 Hazard Ratio (95% Confidence Interval)	Model 2 Hazard Ratio (95% Confidence Interval)
Participants free of AF at baseline	1638	141‡	Q1	54	2224	<0.001	3.83 (2.23–6.59)	3.83 (2.23–6.59)
			Q2	39	2918		2..41 (1.37–4.25)	2.39 (1.35–4.22)
			Q3	30	3051		1.86 (1.04–3.33)	1.86 (1.04–3.33)
			Q4	18	3277		1.00	1.00
Participants free of CVD and AF at baseline	1437	104	Q1	37	1836	<0.001	2.77 (1.53–5.01)	2.76 (1.53–4.99)
			Q2	29	2596		2.02 (1.11–3.67)	1.98 (1.08–3.63)
			Q3	21	2771		1.35 (0.72–2.53)	1.35 (0.72–2.54)
			Q4	17	2997		1.00	1.00
Normal left atrial volume (LAmax index <34 mL/m^2)	1242†	80	Q1	18	951	<0.01	3.52 (1.80–6.91)	3.71 (1.87–7.35)
			Q2	23	2022		2.31 (1.21–4.43)	2.37 (1.22–4.59)
			Q3	21	2687		1.44 (0.75–2.76)	1.50 (0.77–2.91)
			Q4	18	3231		1.00	1.00

AF indicates atrial fibrillation; CVD, cardiovascular disease; LAFI, left atrial function index.
Model 1 was adjusted for CHARGE-AF (Cohorts for Heart and Aging Research in Genomic Epidemiology - atrial fibrillation) risk. Model 2 was adjusted for model 1, ln(left ventricular mass), and ln(left ventricular ejection fraction).
†These participants were free of AF at baseline.
‡A total of 145 participants developed incident AF events, but 4 did not have 1 or more of the variables required to calculate CHARGE-AF score reducing the eligible number of incident AF events to 141.

averaging the respective volumes in apical 2- and 4-chamber views measured using the area-length method.[31] LAmax index was calculated by dividing LAmax by the body surface area. LA emptying fraction was derived as ([LAmax − LAmin]/LAmax)×100. LAFI was calculated using a previously derived formula.[21]

$$\text{LAFI} = \frac{\text{LA emptying fraction} \times \text{LVOT-VTI}}{\text{LAmax index}}$$

Statistical Analyses

The study sample was divided into 4 groups based on LAFI, with quartile 1 (Q1) having the lowest LAFI values and quartile 4 (Q4) having the highest LAFI values. Because women have higher LAFI,[26] we generated sex-specific LAFI quartiles based on previously observed distributions of LAFI among men and women. Baseline characteristics of study participants are presented as means±SD for continuous variables and as numbers and percentages for nominal variables across each LAFI quartile. Natural logarithmic transformation was performed for the variables with skewed distribution (LV ejection fraction and LV mass). Scatter plots were generated to depict the correlation of LAFI with LAD, LAmax index, LV ejection fraction, and LV mass.

We used Cox proportional hazards regression models to study associations between LAFI and incident AF or CVD. The assumption of proportionality of hazards was confirmed for each model. The Fine and Grey subdistribution method was used to adjust the Cox proportional hazards models for competing risk of death.[32] The CHARGE-AF risk model used in our analyses were previously validated using the Framingham Offspring Cohort as predictors of incident AF.[33,34] For CVD, we utilized the 10-year FHS-CVD model, which has previously been validated as a predictor of CVD in the FHS-Offspring cohort.[35] We opted to use the FHS-CVD model instead of the contemporary American College of Cardiology and American Heart Association's 10-year pooled risk model[36] because the pooled risk model only estimates the risk of coronary death, nonfatal myocardial infarction, and nonfatal stroke, whereas our CVD outcome also included coronary insufficiency, angina, transient ischemic attack, intermittent claudication, and heart failure, in addition to coronary death, nonfatal myocardial infarction, and nonfatal stroke. Because of our sample size and to reduce the risk of overfitting our models, we adjusted for each individual's predicted risk score as a covariate instead of the individual component variables in the regression models.

Two models were generated to examine the associations between LAFI and AF. In model 1, we adjusted for CHARGE-AF risk and in model 2 we adjusted for CHARGE-AF risk as well as LV mass and ejection fraction. LAFI quartiles were included as categorical variables in all models, and the hazards of AF were calculated utilizing the highest quartile of LAFI as the reference. In these models, only participants free from AF

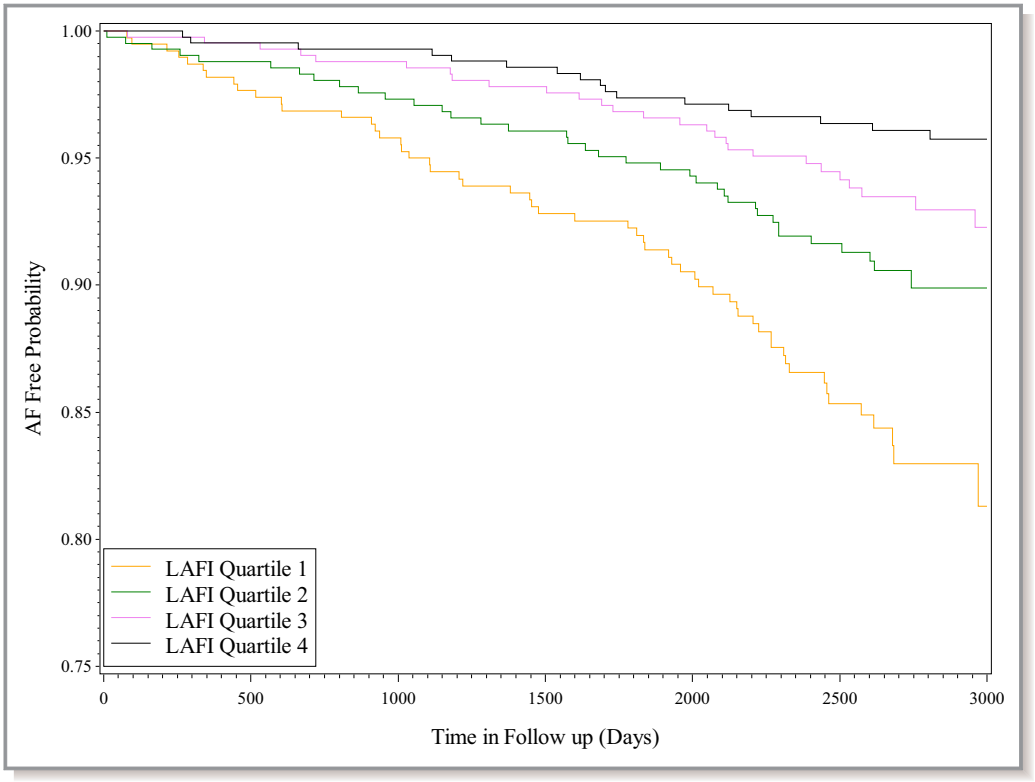

Figure 1. Kaplan–Meier curves depicting the risk of incident atrial fibrillation stratified by quartiles of LAFI. AF indicates atrial fibrillation; LAFI, left atrial function index.

were included (n=1638). Two separate models were created to examine the associations between LAFI and CVD. In model 1, we adjusted for FHS-CVD risk and in model 2 we adjusted for FHS-CVD risk score as well as LV mass and ejection fraction. In CVD-specific models, only participants free from CVD were included (n=1501). Kaplan–Meier curves were generated for both AF and CVD outcomes by quartile of LAFI.

To further refine our understanding of LAFI and its relation to relevant clinical outcomes in select subgroups, we examined relations between LAFI and incident AF or CVD in 2 subgroups: (1) those free from both AF and CVD and (2) those with normal LA volume index (LA volume index <34 mL/m^2; n=1298).[31] For both subgroups, we performed secondary analyses using proportional hazards regression analyses similar to those used in other analyses.

We examined the incremental benefit of LAFI, LAD, or LAmax index to existing clinical risk prediction tools for prediction of AF and CVD, respectively, by examining change in model discrimination based on Cox proportional hazards regressions models including the appropriate clinical prediction models after addition of LAFI, LAD, or LAmax index. We compared model discrimination using the Nam and D'Agostino C-statistic.[37] We also calculated categorical net reclassification improvement, and Integrative Discrimination Index to measure the incremental discrimination by addition of LAFI, LAD, or LAmax index to the clinical prediction models.[38] Categories for net reclassification improvement were defined a priori as tertiles of clinical risk (lowest, intermediate, and highest) for both AF and CVD as estimated by CHARGE-AF and FHS-CVD risk prediction models. Finally, we also assessed model calibration using the Akaike information criterion.[39] A *P* value of <0.05 in 2-tailed tests was considered statistically significant. All statistical analyses were performed using SAS (v9.3; SAS Institute Inc., Cary, NC) and SPSS (version 24; IBM SPSS, Chicago, IL) software.

Results

Baseline demographic, clinical, and echocardiographic characteristics of the study sample are presented by LAFI quartile in Table 2. Participants included in our analyses were middle-aged to older adults (mean age, 66±9 years; 54% women), and the mean LAFI for the overall cohort was 34.5±12.7. Excluded participants were more likely to have a larger body mass index, reflecting the difficult atrial imaging for larger individuals (Table 1). For included participants, those with LAFI measures in the lowest quartile (Q1) were older, had a greater burden of cardiovascular and AF risk factors (including diabetes mellitus and hypertension), and were more likely to have prevalent AF and CVD when compared with participants with LAFI values in the highest quartile (Q4). Predicted risk for incident AF and CVD by clinical prediction models was higher for the participants in Q1 when compared with Q4 participants.

Table 4. Association of LAFI With Incident CVD in Cox Proportional Hazards Regression Model

Sample	No. of Eligible Participants	No. of Incident CVD Events	LAFI Quartile	Events	Person-Years Follow-up	*P* for Linear Trend	Model 1 Hazard Ratio (95% Confidence Interval)	Model 2 Hazard Ratio (95% Confidence Interval)
Participants free of CVD at baseline	1501	139	Q1	47	2295	<0.001	2.20 (1.32–3.67)	2.20 (1.32–3.68)
			Q2	35	3025		1.58 (0.93–2.69)	1.57 (0.92–2.67)
			Q3	34	3128		1.49 (0.87–2.54)	1.49 (0.87–2.54)
			Q4	23	3343		1.00	1.00
Participants free of CVD and AF at baseline	1443	126	Q1	40	2071	<0.001	2.36 (1.37–4.05)	2.37 (1.38–4.08)
			Q2	33	2945		1.66 (0.95–2.89)	1.65 (0.95–2.87)
			Q3	32	3060		1.57 (0.90–2.73)	1.56 (0.90–2.73)
			Q4	21	3314		1.00	1.00
Normal left atrial volume (LAmax index <34 mL/m^2)	1149[†]	90	Q1	17	972	0.018	2.17 (1.14–4.12)	2.21 (1.15–4.24)
			Q2	23	2166		1.44 (0.80–2.59)	1.45 (0.80–2.61)
			Q3	27	2750		1.34 (0.77–2.35)	1.36 (0.77–2.40)
			Q4	23	3290		1.00	1.00

AF indicates atrial fibrillation; CVD, cardiovascular disease; LAFI, left atrial function index.
Model 1 was adjusted for FHS-CVD risk. Model 2 was adjusted for model 1, ln(left ventricular mass), and ln(left ventricular ejection fraction) .
[†]These participants were free of CVD at baseline.

Association of LAFI With Incident AF

Over a median follow-up of 8.3 years (interquartile range, 7.5–9.1), 145 participants developed new-onset AF. In a Cox proportional hazards model adjusting for CHARGE-AF risk, participants with LAFI values in Q1 were 3.8-fold more likely to develop AF compared with participants in the Q4 (model 1, Table 3). Even after adjustment for their CHARGE-AF risk score, echocardiographic LV mass, and ejection fraction (model 2, Table 3), lower LAFI remained associated with higher hazards of incident AF (hazard ratio [HR] for AF among participants in Q1 of LAFI compared with Q4=3.83; 95% confidence interval [CI], 2.23–6.59; *P*<0.001). Figure 1 depicts Kaplan–Meier curves for incident AF stratified by the quartiles of LAFI. In a prespecified secondary subgroup analysis including participants free from both AF and CVD, lower LAFI was similarly associated with higher hazards for incident AF (HR for Q1 versus Q4, 2.76; 95% CI, 1.53–4.99; *P*<0.001; Table 3). Also, in participants with normal LA volume index (<34 mL/m^2), lower LAFI was associated with higher hazards of incident AF (HR for Q1 versus Q4, 3.71; 95% CI, 1.87–7.35; *P*<0.001; Table 3).

Association of LAFI With Incident CVD

Over a median duration of follow-up of 8.3 years (interquartile range, 7.5–9.1), 139 participants developed CVD. In a Cox proportional hazards regression model adjusting for 10-year FHS-CVD risk, lower LAFI was associated with significantly higher hazards of incident CVD (HR for Q1 versus Q4 of LAFI, 2.20; 95% CI, 1.32–3.67; *P*=0.003; model 1, Table 4). Even after including LV mass, ejection fraction, and FHS-CVD risk score (model 2, Table 4) in Cox models, lower LAFI remained associated with higher hazards of incident CVD (HR for Q1 versus Q4=2.20; 95% CI, 1.32–3.68; *P*=0.003). Kaplan–Meier curves depicting the risk of CVD stratified by quartiles of LAFI are presented in the Figure 2. In prespecified secondary analyses including only participants free from both AF and CVD, lower LAFI was associated with higher hazards for incident CVD in multivariable-adjusted models (HR for Q1 versus Q4=2.37; 95% CI, 1.38–4.08; *P*=0.002; Table 4). In our other prespecified secondary analyses including the participants with normal LAmax index, lower LAFI was associated with higher risk of incident AF (HR for Q1 versus Q4=2.21; 95% CI, 1.15–4.24; *P*=0.018; Table 4).

LAFI, LA Size, and Other Measures of Cardiac Remodeling

LAFI correlated poorly with LAD as well as other echocardiographic variables (Figures 3 through 5), including LV ejection fraction (Spearman rho=0.11; *P*<0.001), and LV mass (Spearman rho=−0.14; *P*<0.001). LAFI correlated inversely with LAmax index (Spearman rho=−0.71; *P*<0.001; Figure 6). Despite its poor correlation with LAFI, LAD was associated with incident AF and CVD (Tables 5 and 6).

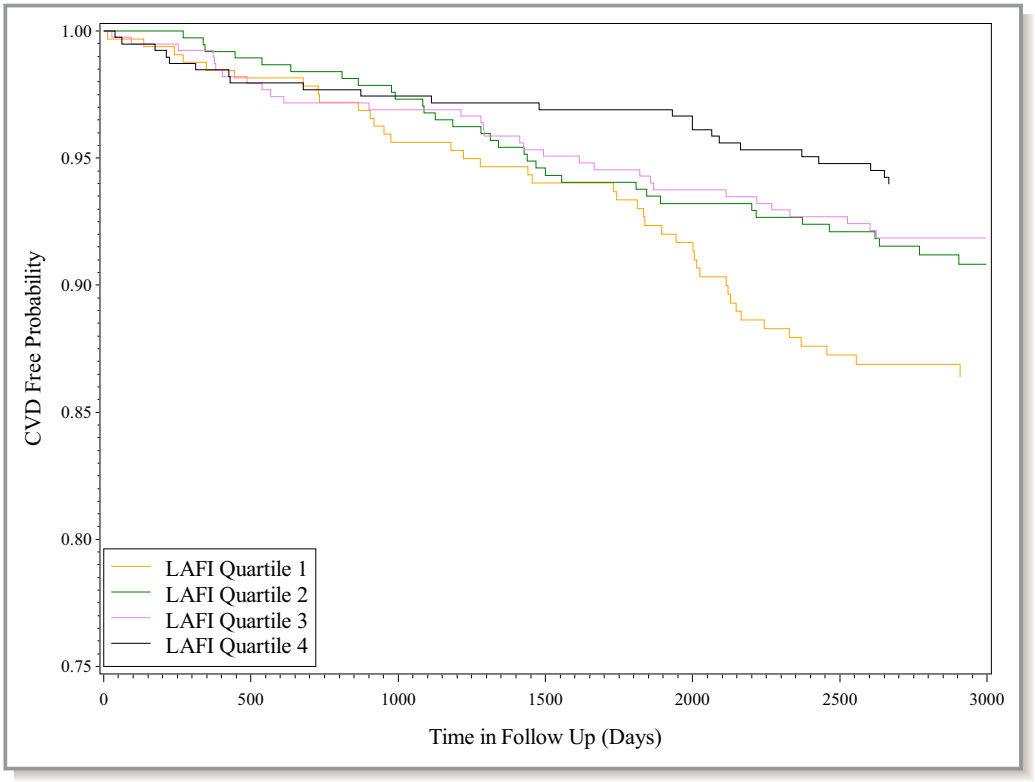

Figure 2. Kaplan–Meier curves depicting the risk of incident cardiovascular disease stratified by quartiles of LAFI. CVD indicates cardiovascular disease; LAFI, left atrial function index.

Improvement in Risk Prediction by Clinical Prediction Models With Addition of LAFI, LAD, and LAmax index

In Cox-proportional hazards models, CHARGE-AF score demonstrated excellent performance for predicting AF in our sample (C-statistic=0.733). Despite the association of LAFI and LAD with incident AF in models including CHARGE-AF score, neither the addition of LAFI nor LAD significantly improved risk prediction models (C-statistic difference=−0.031 for LAFI and −0.009 for LAD; Table 7). Similarly, the addition of LAmax index to CHARGE-AF score

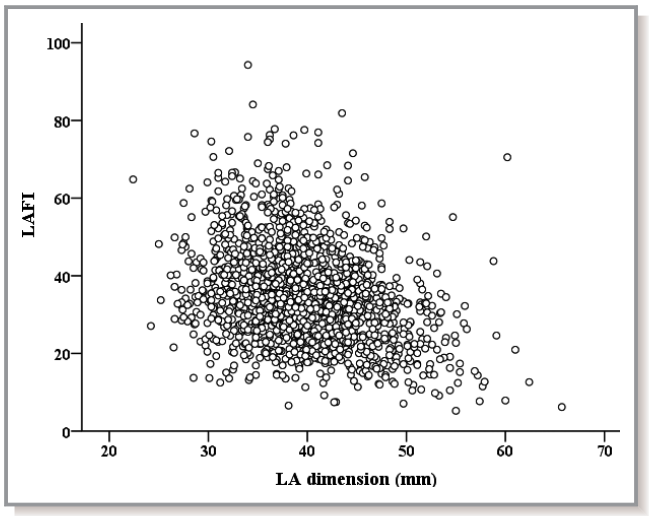

Figure 3. Scatter plot depicting the correlation of LAFI with LA dimension. LA indicates left atrium; LAFI, left atrial function index.

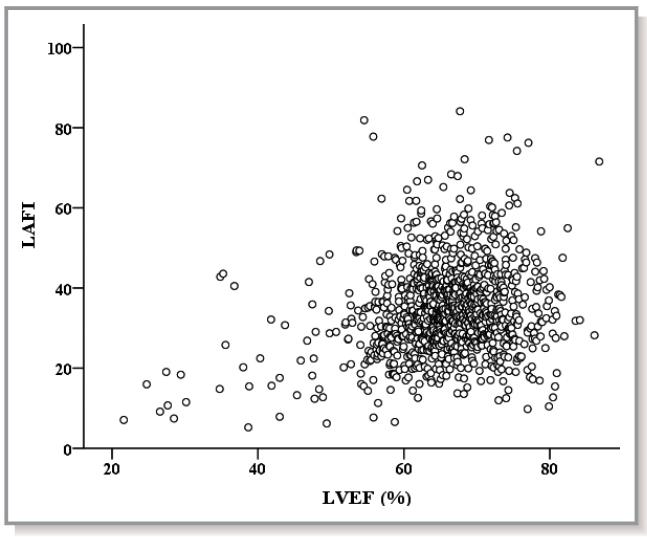

Figure 4. Scatter plot depicting the correlation of LAFI with left ventricular ejection fraction. LAFI indicates left atrial function index; LVEF, left ventricular ejection fraction.

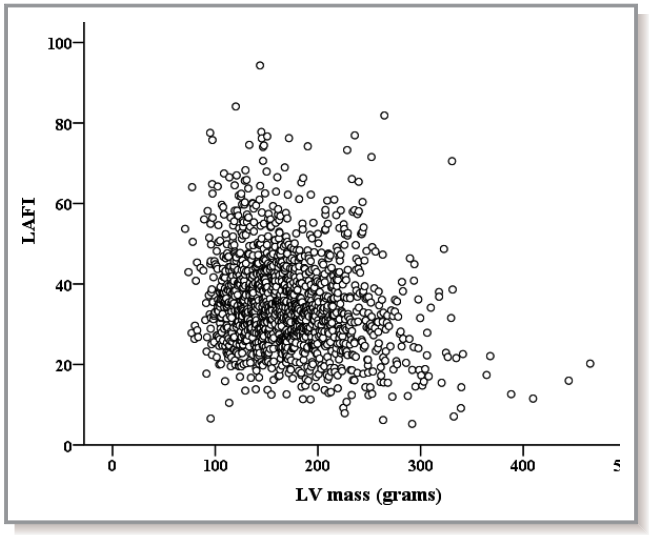

Figure 5. Scatter plot depicting the correlation of LAFI with left ventricular mass. LAFI indicates left atrial function index; LV, left ventricle.

did not improve the risk prediction (C-statistic difference=−0.037). We also observed no significant change in categorical net reclassification improvement or Integrative Discrimination Index with addition of LAFI, LAD, or LAmax index to clinical prediction models. We observed minimal reduction in the Akaike information criterion (lower Akaike information criterion indicating better model fit): 38-point reduction with addition of LAFI; 74-point reduction with addition of LAD; and 34-point reduction with addition of LAmax to clinical prediction models. C-statistic of LAFI alone for prediction of AF was 0.638, whereas the C-statistic values for LAD and LAmax index were 0.671 and 0.635, respectively

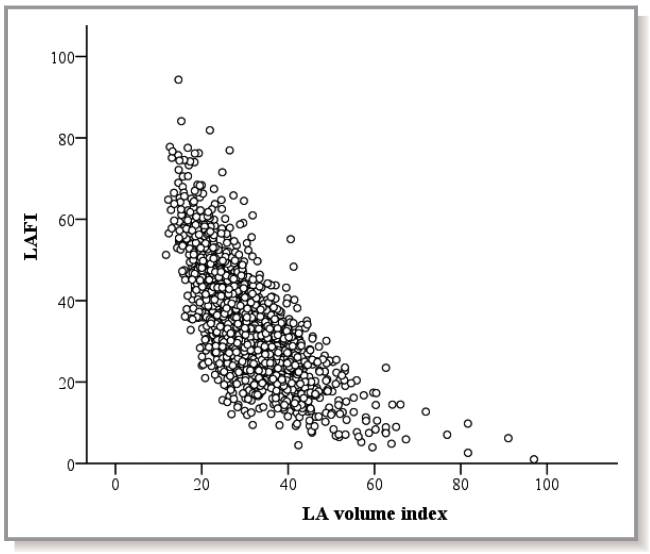

Figure 6. Scatter plot depicting the correlation of LAFI with LA volume index. LA indicates left atrium; LAFI, left atrial function index.

(Table 8). When LAFI, LAD, or LAmax index was added to a baseline risk model with CHARGE-AF risk score *and* other echocardiographic variables (LV mass and ejection fraction), there was no significant improvement in AF risk discrimination (Table 9).

For CVD prediction, 10-year FHS-CVD risk also demonstrated good performance for predicting CVD events in our sample (C-statistic=0.682). We observed no significant change in C-statistic with addition of LAFI, LAD, or LAmax index to clinical prediction models (C-statistic change=0.004 for LAFI, −0.004 for LAD, and 0.004 for LAmax index; Table 7). Furthermore, there was no significant reclassification of CVD risk prediction by clinical prediction models with the addition of LAFI, LAD, or LAmax index. We observed minimal change in Akaike information criterion with the addition of LAFI, LAD, or LAmax index to the clinical prediction models (4-point reduction with addition of LAFI, 48-point reduction with addition of LAD, and 8-point reduction with addition of LAmax index). C-statistic of LAFI alone for prediction of CVD was 0.583, whereas the C-statistic values for LAD and LAmax index were 0.595 and 0.605, respectively (Table 8).

Discussion

In our prospective analysis of a community-based sample, LAFI was associated with incident AF and CVD, which persisted after adjustment for clinical prediction scores and echocardiographic measures associated with AF and CVD, respectively. LAFI remained associated with AF and CVD among those with normal LA size, supporting the hypothesis that measure of LA functional impairment adds to prediction of AF and CVD events beyond LA structure. LAFI, however, did not improve the model discrimination or reclassification of the risk for either AF or CVD predicted by clinical risk estimators. Similar to LAFI, LAD was associated with incident AF and CVD events and was measurable in the majority of participants with echocardiographic images suboptimal for the measurement of LA volumes, suggesting that LAD remains a valid and clinically relevant marker of LA remodeling and cardiovascular risk.[2] Similar to LAFI, LAD and LAmax index failed to improve the performance of the clinical risk prediction models for AF or CVD.

LAFI as a Composite Echocardiographic Marker of LA Remodeling

LA volume indexed to body surface area (LAmax index) is currently recommended by consensus guidelines for assessment of LA structure.[31] LA emptying fraction and emptying volume have also been examined as measures of LA reservoir function.[1] Compensatory changes in LA function might occur with change in LA size.[40] Furthermore, LV systolic function is associated with LA reservoir function.[20] LAFI is a composite

Table 5. Association of LA Diameter With Incident AF in Cox Proportional Hazards Regression Models

Sample	No. of Eligible Participants	No. of Incident AF Events	LAD Quartile	Events	Person-Years Follow-up	*P* for Linear Trend	Model 1 Hazard Ratio (95% Confidence Interval)	Model 2 Hazard Ratio (95% Confidence Interval)
Participants free of AF at baseline	1638	141	Q1	24	3120	<0.001	1.00	1.00
			Q2	29	2938		1.35 (0.79–2.30)	1.36 (0.80–2.33)
			Q3	37	2972		1.47 (0.87–2.50)	1.49 (0.86–2.58)
			Q4	51	2440		2.30 (1.42–3.71)	2.33 (1.39–3.88)
Participants free of CVD and AF at baseline	1437	104	Q1	21	2869	0.02	1.00	1.00
			Q2	25	2672		1.43 (0.80–2.56)	1.38 (0.76–2.50)
			Q3	29	2606		1.68 (0.95–2.98)	1.60 (0.87–2.94)
			Q4	29	2055		1.64 (0.93–2.90)	1.56 (0.85–2.87)

AF indicates atrial fibrillation; CVD, cardiovascular disease; LAD, left atrial diameter.
Model 1 was adjusted for CHARGE-AF (Cohorts for Heart and Aging Research in Genomic Epidemiology - atrial fibrillation) risk. Model 2 was adjusted for model 1, ln(left ventricular mass), and ln(left ventricular ejection fraction).

echocardiographic measure that adjusts LA function for LA size, and attempts to isolate atrial remodeling from the ventricular systolic function by incorporating LV stroke volume (LVOT-VTI).[21] Thus, LAFI may be better able to account for both structural and functional LA remodeling than other echocardiographic measures when they are considered in isolation.

LA Remodeling and Incident AF

Echocardiographic LA anteroposterior diameter, maximal LA volume, minimal LA volume, and LA emptying fraction are associated with incident AF in community-based samples[2–5,8–10] and cohorts with CVD.[6,7] In a past investigation involving participants in the original FHS cohort, every 5-mm increase in LAD was associated with increase in the hazards of AF by 39% over a median follow-up of 7.2 years.[2] More recently, in participants of the community-based MESA (Multi-Ethnic Study of Atherosclerosis), higher LAmax index (HR, 1.38; *P*=0.042) and lower LA emptying fraction (HR, 0.70; *P*=0.020) as measured by magnetic resonance imaging were associated with higher hazards of developing AF, after adjusting for clinical risk factors and LV mass. Despite the association of LA size with incident AF, the addition of LAD to clinical risk models has not led to a significant improvement in model discrimination,[12,15] whereas the incremental model discrimination with the addition of LAmax or LA emptying fraction to clinical risk scores has not been reported before.

Consistent with past investigations, we observed that lower LAFI (ie, greater LA remodeling) was associated with

Table 6. Association of LA Diameter With Incident CVD in Cox Proportional Hazards Regression Models

Sample	No. of Eligible Participants	No. of Incident CVD Events	LAD Quartile	Events	Person-Years Follow-up	*P* For Linear Trend	Model 1 Hazard Ratio (95% Confidence Interval)	Model 2 Hazard Ratio (95% Confidence Interval)
Participants free of CVD at baseline	1501	139	Q1	26	3212	<0.001	1.0	1.00
			Q2	36	3026		1.42 (0.86–2.36)	1.41 (0.85–2.35)
			Q3	26	3016		0.96 (0.56–1.65)	0.95 (0.55–1.65)
			Q4	51	2536		1.84 (1.14–2.98)	1.83 (1.13–2.97)
Participants free of CVD and AF at baseline	1443	126	Q1	24	3177	<0.001	1.00	1.00
			Q2	32	2985		1.37 (0.81–2.33)	1.37 (0.80–2.33)
			Q3	26	2940		1.06 (0.61–1.84)	1.06 (0.60–1.85)
			Q4	44	2288		1.98 (1.19–3.28)	1.97 (1.18–3.27)

AF indicates atrial fibrillation; CVD, cardiovascular disease; LAD, left atrial diameter.
Model 1 was adjusted for FHS-CVD risk. Model 2 was adjusted for model 1, ln(left ventricular mass), and ln(left ventricular ejection fraction).

Table 7. Change in the Parameters of Model Discrimination With the Addition of LAFI, LA Diameter, or LA Volume Index to the Hazards Models for Incident AF and CVD

Outcome	Parameter	Clinical Prediction Model*	Clinical Risk+LAFI	Clinical Risk+LA Diameter	Clinical Risk+LA Volume Index
AF	C-statistic	0.733 (0.679–0.787)	0.702 (0.638–0.767)	0.724 (0.669–0.779)	0.696 (0.633–0.759)
	NRI†	…	0.123	0.072	0.104
	IDI†	…	0.019	0.028	0.026
	AIC	1910.3	1872.4	1835.7	1876.3
CVD	C-statistic	0.682 (0.629–0.735)	0.686 (0.634–0.738)	0.678 (0.623–0.732)	0.686 (0.633–0.738)
	NRI†	…	0.021	0.038	0.059
	IDI†	…	0.004	0.004	0.009
	AIC	1939.4	1934.8	1891.3	1931.2

AF indicates atrial fibrillation; AIC, Akaike information criterion; CVD, cardiovascular disease; IDI, Integrated Discrimination Improvement; LAFI, left atrial function index; NRI, net reclassification index.
*CHARGE-AF (Cohorts for Heart and Aging Research in Genomic Epidemiology - atrial fibrillation) model for AF, and FHS-CVD model for CVD.
†Outcomes at 5 years were used to calculate NRI and IDI.

higher hazards of incident AF, even after adjustment for clinical AF risk (CHARGE-AF risk)[33] and the measures of LV remodeling (mass and ejection fraction). Similarly, increase in LAD was significantly associated with AF in models analogous to the LAFI models. However, the addition of LAFI, LAD, or LAmax index to the models with CHARGE-AF risk score did not lead to a significant improvement in AF risk prediction, likely because of the excellent overall performance of the clinical AF risk prediction model in our sample and perhaps also related to the moderate sample size.

CHARGE-AF risk is based on clinical and electrocardiographic associates of incident AF (such as age, smoking, weight, height, hypertension, diabetes mellitus, and prevalent CVD).[33] Our results suggest that LAFI detects subtle structural and functional LA derangements resulting from higher intensity or duration of exposure to clinical AF risk factors among individuals exposed to these risk factors. Although the C-statistic of LAFI alone for prediction of AF was significantly lower than CHARGE-AF risk score, we noticed improvement in model fit (38-point reduction in AIC) with addition of LAFI to the baseline CHARGE-AF model. Our findings suggest that LAFI adds prognostic information to the clinical risk model, but does not reclassify the risk of incident AF. Of note, LAD was measurable in the majority of participants with image quality suboptimal for the measurement of LA volumes (and LAFI) and was associated with AF. Our findings suggest that LAD should still be considered a clinically relevant marker of atrial remodeling. Our observation that LAFI relates to AF among those with normal LA size would suggest that LAFI may represent an attractive intermediate phenotype to consider in addition to clinical factors for studies examining the effects of novel therapies to reduce or slow pathological LA remodeling and prevent AF.[41,42]

LA Remodeling and Incident CVD

Past investigations involving participants from community-based samples and cohorts with CVD have demonstrated a significant association between LA size and incident and recurrent CVD.[6–9,11,43] For example, among participants in the original FHS cohort, every 10-mm increase in LAD was associated with 1.4- to 2.4-fold higher hazards of stroke and 1.3- to 1.4-fold higher hazards of death over median follow-up of 8 years, even after adjustment for CVD risk factors.[11] Two recent community-based studies have shown that LA reservoir function (LA emptying volume and fraction) is associated with incident CVD and all-cause mortality, even after adjustment for the measures of LV remodeling and LAmax.[16,18]

Table 8. Association of LAFI, LA Diameter, and LA Volume Index in Hazards Models for Incident AF and CVD

Outcome	Parameter	LAFI	LA Diameter	LA Volume Index
AF	C-statistic	0.638 (0.573–0.704)	0.671 (0.612–0.730)	0.635 (0.570–0.701)
	AIC	1964.7	1923.2	1958.9
CVD	C-statistic	0.583 (0.522–0.644)	0.595 (0.530–0.660)	0.605 (0.541–0.668)
	AIC	1983	1929.1	1975

AF indicates atrial fibrillation; AIC, Akaike information criterion; CVD, cardiovascular disease; LAFI, left atrial function index.

Table 9. Change in the Parameters of Model Discrimination With the Addition of LAFI, LA Diameter, or LA Volume Index to the Hazards Models for Incident AF and CVD (Clinical and Echocardiographic Baseline Model)

Outcome	Parameter	Baseline Model	Baseline Model+LAFI	Baseline Model+LA Diameter	Baseline Model+LA Volume Index
AF	C-statistic	0.738 (0.684–0.792)	0.705 (0.642–0.769)	0.733 (0.680–0.787)	0.698 (0.636–0.761)
	NRI†	…	0.088	0.113	0.078
	IDI†	…	0.018	0.028	0.024
	AIC	1913.3	1875.7	1837.4	1880.1
CVD	C-statistic	0.684 (0.631–0.737)	0.689 (0.638–0.741)	0.678 (0.624–0.733)	0.686 (0.634–0.739)
	NRI†	…	0.021	0.015	0.033
	IDI†	…	0.004	0.004	0.009
	AIC	1943.2	1938.7	1895.2	1935.2

AF indicates atrial fibrillation; CVD, cardiovascular disease; NRI, net reclassification index; IDI, Integrated Discrimination Improvement, LAFI, left atrial function index; AIC, Akaike information criterion.
Baseline model for AF consisted of CHARGE-AF+ln(left ventricular mass)+ln(left ventricular ejection fraction). Baseline model for CVD consisted of FHS-CVD model for CVD+ln(left ventricular mass)+ln(left ventricular ejection fraction).
†Outcomes at 5 years were used to calculate NRI and IDI.

Consistent with the past literature, we observed that LAFI was associated with incident CVD, overall and among those with normal LA volume, even after adjustment for clinical and echocardiographic CVD risk factors. An increase in LAD was similarly associated with an increased risk of CVD. However, similarly to the AF models, addition of LAFI, LAD, or LAmax index to the clinical CVD risk prediction models did not improve model discrimination or reclassification of predicted CVD risk, again likely related to the excellent performance of the FHS-CVD risk prediction instrument in our moderately sized sample.

Strengths and Limitations

The results from our study should be analyzed in the context of its strengths and weaknesses. We utilized data from a medium-sized, community-based sample with rigorous CVD risk factor and end point adjudication to examine associations between an echocardiographic measure of LA remodeling (LAFI) with incident AF and CVD events. However, our study has several limitations. First, our sample was comprised largely of participants of white ancestry and the application of our results to the participants of other ethnicities needs further investigation in multiethnic samples. Second, we utilized 2-dimensional echocardiography to measure LA volumes, which have lower correlation with magnetic resonance imaging–measured volumes than those measured by 3-dimensional echocardiography.[44] However, imaging time and the lack of large studies with normative values limit the widespread clinical use of 3-dimensional echocardiography currently. Future studies should assess the prognostic value of LAFI derived from 3-dimensional echocardiography in community-based cohorts. Third, although we adjusted for LV mass, and ejection fraction in our echocardiographic survival models, echocardiographic measures of diastolic function were not available and it is plausible that LV diastolic function could mediate associations observed between LAFI with AF and/or CVD. Fourth, nonvolumetric measures of atrial function, such as atrial strain, were not available for our analyses. Therefore, we were unable to directly compare the predictive ability of LAFI with atrial strain. Fifth, although we adjusted for clinical risk factors for AF and CVD using previously validated risk scores, it is plausible that certain risk factors (eg, obstructive sleep apnea, dietary practices, and physical activity),[45,46] which are not captured by clinical risk scores, might have been differentially distributed in the various LAFI quartile groups and could have, in part, accounted for the association of LAFI with incident AF and/or CVD.

Conclusions

In this investigation including data from participants in a medium-sized, community-based sample with echocardiographic imaging and rigorously adjudicated AF and CVD events over an 8-year follow-up period, we observed strong associations between LAFI, incident AF, and incident CVD in adjusted models. Our findings suggest that LAFI captures subtle and clinically relevant pathological changes in LA structure and function. Our study findings also support the notion that LAD and LAFI sit along the causal pathway from risk factor exposure to AF and CVD. Future studies should validate our findings in large, multiethnic cohorts with longitudinal follow-up for AF and investigate whether LAFI can be used to better target individuals at high clinical risk for AF for further monitoring or AF prevention.

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Author Contributions

Sardana, Lessard, Vaze, Tsao, Barton, Nah, Thomas, Parikh, Schiller, and McManus contributed to study design, analysis, and draft of article. Cheng, Aragam, Mitchell, Benjamin, Vasan, and McManus contributed toward obtaining data and funding. All authors were involved in the acquisition and/or interpretation of the data, made critical revision of the article for important intellectual content, and provided final approval of the version to be published

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References

1. Hoit BD. Left atrial size and function: role in prognosis. *J Am Coll Cardiol*. 2014;63:493–505.
2. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. *The Framingham Heart Study. Circulation*. 1994;89:724–730.
3. Vasan RS, Larson MG, Levy D, Galderisi M, Wolf PA, Benjamin EJ; National Heart, Lung, and Blood Institute, National Institutes of Health. Doppler transmitral flow indexes and risk of atrial fibrillation (the Framingham Heart Study). *Am J Cardiol*. 2003;91:1079–1083.
4. Tsang TS, Barnes ME, Bailey KR, Leibson CL, Montgomery SC, Takemoto Y, Diamond PM, Marra MA, Gersh BJ, Wiebers DO, Petty GW, Seward JB. Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. *Mayo Clin Proc*. 2001;76:467–475.
5. Tsang TS, Abhayaratna WP, Barnes ME, Miyasaka Y, Gersh BJ, Bailey KR, Cha SS, Seward JB. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? *J Am Coll Cardiol*. 2006;47:1018–1023.
6. Rossi A, Cicoira M, Zanolla L, Sandrini R, Golia G, Zardini P, Enriquez-Sarano M. Determinants and prognostic value of left atrial volume in patients with dilated cardiomyopathy. *J Am Coll Cardiol*. 2002;40:1425.
7. Moller JE, Hillis GS, Oh JK, Seward JB, Reeder GS, Wright RS, Park SW, Bailey KR, Pellikka PA. Left atrial volume: a powerful predictor of survival after acute myocardial infarction. *Circulation*. 2003;107:2207–2212.
8. Laukkanen JA, Kurl S, Eranen J, Huttunen M, Salonen JT. Left atrium size and the risk of cardiovascular death in middle-aged men. *Arch Intern Med*. 2005;165:1788–1793.
9. Gottdiener JS, Kitzman DW, Aurigemma GP, Arnold AM, Manolio TA. Left atrial volume, geometry, and function in systolic and diastolic heart failure of persons > or =65 years of age (the Cardiovascular Health Study). *Am J Cardiol*. 2006;97:83–89.
10. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. *The Framingham Heart Study. JAMA*. 1994;271:840–844.
11. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. *The Framingham Heart Study. Circulation*. 1995;92:835–841.
12. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr, Newton-Cheh C, Yamamoto JF, Magnani JW, Tadros TM, Kannel WB, Wang TJ, Ellinor PT, Wolf PA, Vasan RS, Benjamin EJ. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet*. 2009;373:739–745.
13. McManus DD, Xanthakis V, Sullivan LM, Zachariah J, Aragam J, Larson MG, Benjamin EJ, Vasan RS. Longitudinal tracking of left atrial diameter over the adult life course: clinical correlates in the community. *Circulation*. 2010;121:667–674.
14. Alonso A, Norby FL. Predicting atrial fibrillation and its complications. *Circ J*. 2016;80:1061–1066.
15. Bekwelem W, Misialek JR, Konety S, Solomon SD, Soliman EZ, Loehr LR, Lopez FL, Fox ER, Mosley TH, Alonso A. Echocardiographic measures of cardiac structure and function are associated with risk of atrial fibrillation in blacks: the Atherosclerosis Risk in Communities (ARIC) study. *PLoS One*. 2014;9:e110111.
16. Russo C, Jin Z, Homma S, Rundek T, Elkind MS, Sacco RL, Di Tullio MR. LA phasic volumes and reservoir function in the elderly by real-time 3-D echocardiography: normal values, prognostic significance, and clinical correlates. *JACC Cardiovasc Imaging*. 2016;10:976–985.
17. Habibi M, Samiei S, Ambale Venkatesh B, Opdahl A, Helle-Valle TM, Zareian M, Almeida AL, Choi EY, Wu C, Alonso A, Heckbert SR, Bluemke DA, Lima JA. Cardiac magnetic resonance-measured left atrial volume and function and incident atrial fibrillation: results from MESA (Multi-Ethnic Study of Atherosclerosis). *Circ Cardiovasc Imaging*. 2016;9:e004299.
18. Gupta S, Matulevicius SA, Ayers CR, Berry JD, Patel PC, Markham DW, Levine BD, Chin KM, de Lemos JA, Peshock RM, Drazner MH. Left atrial structure and function and clinical outcomes in the general population. *Eur Heart J*. 2013;34:278–285.
19. Abhayaratna WP, Fatema K, Barnes ME, Seward JB, Gersh BJ, Bailey KR, Casaclang-Verzosa G, Tsang TS. Left atrial reservoir function as a potent marker for first atrial fibrillation or flutter in persons > or = 65 years of age. *Am J Cardiol*. 2008;101:1626–1629.
20. Barbier P, Solomon SB, Schiller NB, Glantz SA. Left atrial relaxation and left ventricular systolic function determine left atrial reservoir function. *Circulation*. 1999;100:427–436.
21. Thomas L, Hoy M, Byth K, Schiller NB. The left atrial function index: a rhythm independent marker of atrial function. *Eur J Echocardiogr*. 2008;9:356–362.
22. Sardana M, Ogunsua AA, Spring M, Shaikh A, Asamoah O, Stokken G, Browning C, Ennis C, Donahue JK, Rosenthal LS, Floyd KC, Aurigemma GP, Parikh NI, McManus DD. Association of left atrial function index with late atrial fibrillation recurrence after catheter ablation. *J Cardiovasc Electrophysiol*. 2016;27:1411–1419.
23. Sargento L, Vicente Simoes A, Longo S, Lousada N, Palma Dos Reis R. Left atrial function index predicts long-term survival in stable outpatients with systolic heart failure. *Eur Heart J Cardiovasc Imaging*. 2017;18:119–127.
24. Welles CC, Ku IA, Kwan DM, Whooley MA, Schiller NB, Turakhia MP. Left atrial function predicts heart failure hospitalization in subjects with preserved ejection fraction and coronary heart disease: longitudinal data from the Heart and Soul Study. *J Am Coll Cardiol*. 2012;59:673–680.
25. Wong JM, Welles CC, Azarbal F, Whooley MA, Schiller NB, Turakhia MP. Relation of left atrial dysfunction to ischemic stroke in patients with coronary heart disease (from the heart and soul study). *Am J Cardiol*. 2014;113:1679–1684.

26. Sardana M, Nah G, Tsao CW, Ogunsua AA, Vittinghoff E, Thomas RC, Cheng S, Vaze A, Aragam JR, Mitchell GF, Benjamin EJ, Vasan RS, Aurigemma GP, Schiller NB, McManus DD, Parikh NI. Clinical and echocardiographic correlates of left atrial function index: the Framingham Offspring Study. *J Am Soc Echocardiogr*. 2017;30:904–912.
27. Schnabel RB, Larson MG, Yamamoto JF, Sullivan LM, Pencina MJ, Meigs JB, Tofler GH, Selhub J, Jacques PF, Wolf PA, Magnani JW, Ellinor PT, Wang TJ, Levy D, Vasan RS, Benjamin EJ. Relations of biomarkers of distinct pathophysiological pathways and atrial fibrillation incidence in the community. *Circulation*. 2010;121:200–207.
28. Cheng S, McCabe EL, Larson MG, Merz AA, Osypiuk E, Lehman BT, Stantchev P, Aragam J, Solomon SD, Benjamin EJ, Vasan RS. Distinct aspects of left ventricular mechanical function are differentially associated with cardiovascular outcomes and all-cause mortality in the community. *J Am Heart Assoc*. 2015;4:e002071. DOI: 10.1161/JAHA.115.002071.
29. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol*. 1986;57:450–458.
30. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Iung B, Otto CM, Pellikka PA, Quinones M; American Society of Echocardiography and European Association of Echocardiography. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr*. 2009;22:1–23; quiz, 101–102.
31. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.e14.
32. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.
33. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, Sinner MF, Sotoodehnia N, Fontes JD, Janssens AC, Kronmal RA, Magnani JW, Witteman JC, Chamberlain AM, Lubitz SA, Schnabel RB, Agarwal SK, McManus DD, Ellinor PT, Larson MG, Burke GL, Launer LJ, Hofman A, Levy D, Gottdiener JS, Kaab S, Couper D, Harris TB, Soliman EZ, Stricker BH, Gudnason V, Heckbert SR, Benjamin EJ. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc*. 2013;2:e000102. DOI: 10.1161/JAHA.112.000102.
34. Pencina MJ, D'Agostino RB Sr, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the framingham heart study. *Circulation*. 2009;119:3078–3084.
35. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753.
36. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 Suppl 2):S49–S73.
37. D'Agostino RB Sr, Pencina MJ, Massaro JM, Coady S. Cardiovascular disease risk assessment: insights from Framingham. *Glob Heart*. 2013;8:11–23.
38. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157–172; discussion, 207–212.
39. Ju H, Brasier AR, Kurosky A, Xu B, Reyes VE, Graham DY. Diagnostics for statistical variable selection methods for prediction of peptic ulcer disease in helicobacter pylori infection. *J Proteomics Bioinform*. 2014;7:1000307.
40. Anwar AM, Geleijnse ML, Soliman OI, Nemes A, ten Cate FJ. Left atrial Frank-Starling law assessed by real-time, three-dimensional echocardiographic left atrial volume changes. *Heart*. 2007;93:1393–1397.
41. Wachtell K, Lehto M, Gerdts E, Olsen MH, Hornestam B, Dahlof 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;45:712–719.
42. Milliez P, Deangelis N, Rucker-Martin C, Leenhardt A, Vicaut E, Robidel E, Beaufils P, Delcayre C, Hatem SN. Spironolactone reduces fibrosis of dilated atria during heart failure in rats with myocardial infarction. *Eur Heart J*. 2005;26:2193–2199.
43. Yaghi S, Moon YP, Mora-McLaughlin C, Willey JZ, Cheung K, Di Tullio MR, Homma S, Kamel H, Sacco RL, Elkind MS. Left atrial enlargement and stroke recurrence: the Northern Manhattan Stroke Study. *Stroke*. 2015;46:1488–1493.
44. Boyd AC, Thomas L. Left atrial volumes: two-dimensional, three-dimensional, cardiac magnetic resonance and computed tomography measurements. *Curr Opin Cardiol*. 2014;29:408–416.
45. Tung P, Levitzky YS, Wang R, Weng J, Quan SF, Gottlieb DJ, Rueschman M, Punjabi NM, Mehra R, Bertisch S, Benjamin EJ, Redline S. Obstructive and central sleep apnea and the risk of incident atrial fibrillation in a community cohort of men and women. *J Am Heart Assoc*. 2017;6:e004500. DOI: 10.1161/JAHA.116.004500.
46. Garg PK, O'Neal WT, Ogunsua A, Thacker EL, Howard G, Soliman EZ, Cushman M. Usefulness of the American Heart Association's Life Simple 7 to Predict the Risk of Atrial Fibrillation (from the REasons for Geographic And Racial Differences in Stroke [REGARDS] Study). *Am J Cardiol*. 2017;121:199–204.

SUPPLEMENTAL MATERIAL

Data S1.

Ascertainment of Prevalent Cardiovascular Risk Factors

During each examination cycle, participants undergo a physician-administered medical history and cardiovascular-targeted physical examination, 12-lead electrocardiography and phlebotomy for assessment of CVD risk factors.[1,2] For our study, left ventricular hypertrophy on electrocardiogram was defined using voltage-based criteria previously described.[3] The PR interval was measured from the beginning of the P-wave to the end of the PR segment. Body mass index was calculated by dividing the weight in kilograms by the square of height in meters. The participants who reported smoking ≥1 cigarettes on a daily basis during the year preceding their Heart Study examination were considered current smokers. Participants were categorized to have hypertension if they had a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg and/or were taking antihypertensive medications.[4] Diabetes was defined as fasting plasma glucose ≥126 mg/dL and/or use of medications for lowering blood sugar. Cohorts for Heart and Aging Research in Genomic Epidemiology-AF (CHARGE-AF) risk and 10-year FHS-CVD risk were calculated using formulae previously validated in the Framingham Offspring Cohort.[4, 5]

Ascertainment of AF Events

The 12-lead electrocardiograms obtained during the FHS examination and from all inpatient and outpatient medical records were reviewed to ascertain for AF. Also, telemetry data obtained

during hospitalizations was adjudicated for the presence of AF. In addition, inpatient telemetric data were adjudicated for possible AF. Potential AF cases were adjudicated by 2 or more FHS cardiologists.[6] The participants were considered to have AF if a diagnosis of AF was made on any FHS or clinically obtained electrocardiogram, telemetry recordings, on a Holter monitor recording, or if a diagnosis of AF was documented by a treating physician in the hospital records.

Ascertainment of CVD Events

A committee comprised of three physicians reviewed the all pertinent medical records, including emergency and hospital notes, consultations, and outpatient visits and adjudicated CVD outcome events using previously published criteria.[7] Events included in the composite CVD outcome included fatal or non-fatal coronary insufficiency, angina, myocardial infarction, transient ischemic attack, ischemic stroke, hemorrhagic stroke, intermittent claudication, heart failure, and cardiovascular death, as has previously been reported.[8-10]

Definitions of CVD events

Angina Pectoris

Angina was defined by presence of brief recurrent episodes of chest discomfort (up to 15 mins in duration), precipitated by emotional stress or exertion, and relieved by rest or nitroglycerine.

Coronary Insufficiency

Coronary insufficiency was defined by presence of prolonged ischemic chest pain (more than 15 mins), with concomitant presence of transient ischemic ST segment and T wave changes on

electrocardiogram, but with lack of Q waves on electrocardiogram or election of serum biomarkers of myocardial damage.

Myocardial Infarction

A myocardial infarction was determined to be present when 2 of 3 following findings were present in the medical record: (1) symptoms suggestive of cardiac ischemia; (2) increase in biomarkers of myocardial damage; and (3) serial changes in electrocardiograms suggesting the evolution of infarction. Old myocardial infarction was defined by the presence of a stable electrocardiographic changes including either a pathologic Q wave or loss of precordial R waves. An acute, new, or recent myocardial infarction documented in an autopsy report was also accepted as the evidence of a myocardial infarction.

Intermittent Claudication

Intermittent claudication was defined as presence of cramping discomfort in the calf that was clearly precipitated by walking some distance and relieved by a few minutes of rest. Symptoms were assessed using the standard structured forms by the study physicians for the uniformity of assessment. Additionally, a second study physician confirmed all the cause of suspected claudication during the examination.

Heart Failure

Congestive heart failure was defined by the concurrent presence of minimum of 2 major or 1 major and 2 minor criteria. Other conditions capable of producing the symptoms and signs were considered while evaluating the findings.

Major criteria:

1) Paroxysmal nocturnal dyspnea
2) Distended neck veins (in other than the supine position)
3) Ventricular S3 gallop
4) Rales
5) Increasing heart size by X-ray
6) Acute pulmonary edema described in hospital record
7) Increased venous pressure (greater than 16 cm of water from the right atrium)
8) Circulation time (greater than 24 seconds, arm to tongue)
9) Hepatojugular reflux
10) Pulmonary edema, visceral congestion, cardiomegaly on autopsy

Minor criteria:

1) Night cough
2) Dyspnea with day-to-day activities
3) Tachycardia (120 beats per minute or more)
4) Bilateral ankle edema
5) Hepatomegaly
6) Pleural effusion
7) Decrease in vital capacity by one-third from maximum record

Arbitrary major or minor criterion: Weight loss (ten pounds or more in five days) while on therapy for congestive heart failure.

Stroke

The criteria for defining stroke included abrupt onset of a localizing neurologic deficit (such as hemiplegia, aphasia, homonymous hemianopia) lasting for more than 24 hours in duration. A neurologist and study physician reviewed hospital and clinic records to determine the presence and to differentiate the type of stroke (ischemic Vs. hemorrhagic).

Transient Ischemic Attack

A documented localizing neurologic deficit lasting for less than 24 hours in duration was considered a transient ischemic attack.

Cardiovascular Death

Death certificate, hospital, autopsy, and pathology records were reviewed by a panel of study physicians to ascertain the cause of death. Cardiovascular death was designated when the responsible cause was considered to be either coronary heart disease (angina pectoris, coronary insufficiency, myocardial infarction, intermittent claudication, congestive heart failure, stroke, or transient ischemic attack).

Inter-observer and Intra-observer Variability in Measurement of LA volumes

To reduce the inter- and intra-observer variability in LA volume measurement, serial quality control iterations were performed. Both sonographers measured LAmax and LAmin for 20 randomly selected participants during each iteration cycle. Sonographers received training for LA volume measurement between serial iterations. Intra-observer and inter-observer coefficients of variation were less than 5% for both LAmax and LAmin. If images were deemed suboptimal for the measurement of LA volume (endocardial borders not well visualized, posterior wall of

LA was not visualized, or recorded cardiac cycles contained a premature beat), the sonographer coded the measure as “inadequate”. LA volumes were then reviewed by a second sonographer or a study investigator (DDM) to confirm. Of note, the M-mode image quality was optimal for LAD measurement in nearly all of the included and excluded participants (**Table 1**).

Supplemental References:

1. Feinleib M, Kannel WB, Garrison RJ, McNamara PM and Castelli WP. The Framingham Offspring Study. Design and preliminary data. *Prev Med*. 1975;4:518-25.
2. Magnani JW, Newton-Cheh C, O'Donnell CJ and Levy D. Development and application of a longitudinal electrocardiogram repository: the Framingham Heart Study. *J Electrocardiol*. 2012;45:673-6.
3. Kannel WB, Gordon T, Castelli WP and Margolis JR. Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease. The Framingham study. *Ann Intern Med*. 1970;72:813-22.
4. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM and Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743-53.
5. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, Sinner MF, Sotoodehnia N, Fontes JD, Janssens AC, Kronmal RA, Magnani JW, Witteman JC, Chamberlain AM, Lubitz SA, Schnabel RB, Agarwal SK, McManus DD, Ellinor PT, Larson MG, Burke GL, Launer LJ, Hofman A, Levy D, Gottdiener JS, Kaab S, Couper D, Harris TB, Soliman EZ, Stricker BH, Gudnason V, Heckbert SR and Benjamin EJ. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc*. 2013;2:e000102.
6. McManus DD, Yin X, Gladstone R, Vittinghoff E, Vasan RS, Larson MG, Benjamin EJ and Marcus GM. Alcohol Consumption, Left Atrial Diameter, and Atrial Fibrillation. *J Am Heart Assoc*. 2016;5.

7. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ and Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994;271:840-4.
8. Pencina MJ, D'Agostino RB, Sr., Larson MG, Massaro JM and Vasan RS. Predicting the 30-year risk of cardiovascular disease: the framingham heart study. *Circulation*. 2009;119:3078-84.
9. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D and Framingham Heart S. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation*. 2002;106:3068-72.
10. Lubitz SA, Yin X, Rienstra M, Schnabel RB, Walkey AJ, Magnani JW, Rahman F, McManus DD, Tadros TM, Levy D, Vasan RS, Larson MG, Ellinor PT and Benjamin EJ. Long-term outcomes of secondary atrial fibrillation in the community: the Framingham Heart Study. *Circulation*. 2015;131:1648-55.