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ORIGINAL INVESTIGATIONS

# Association of Left Atrial Structure and Function With Heart Failure in Older Adults

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## ABSTRACT

**BACKGROUND** Limited data exist to characterize novel measures of left atrial (LA) structure and function in older adults without prevalent heart failure (HF).

**OBJECTIVES** The aim was to assess reference range of LA measures, their associations with N-terminal pro-B-type natriuretic-peptide (NT-proBNP) and the related risk for incident HF or death.

**METHODS** We analyzed LA structure (LA maximal [LAViMax] and minimal volume indexed by body surface area) and function (LA emptying fraction, LA reservoir, conduit, and contraction strain) in 4,901 participants from the ARIC (Atherosclerosis Risk In Communities) study (mean age 75 ± 5 years, 40% male, and 19% Black) without prevalent HF. We assessed sex-specific 10th and 90th percentile ARIC-based reference limits in 301 participants free of prevalent cardiovascular disease, and related LA measures to NT-proBNP and incident HF or death (median follow-up of 5.5 years) in the whole ARIC cohort.

**RESULTS** Approximately 20% of the overall population had LA abnormalities according to the ARIC-based reference limit. Each LA measure was associated with NT-proBNP and, except for LAViMax, with incident HF or death after multivariable adjustment (including left ventricular function and NT-proBNP). Results were consistent in participants with normal LAViMax ($P$ for interaction $> 0.05$). LA measures were prognostic for both incident HF with preserved ejection fraction or death and incident HF with reduced ejection fraction or death. When added to HF risk factors and NT-proBNP (baseline C-statistics = 0.74) all LA measures, except for LAViMax, significantly enhanced the prognostic accuracy.

**CONCLUSIONS** Novel measures of LA structure and function, but not standard assessment by LAViMax, are associated with increased risk of incident HF or death regardless of measures of left ventricular function and NT-proBNP.
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**ABBREVIATIONS AND ACRONYMS**

**AF** = atrial fibrillation

**CMR** = cardiac magnetic resonance

**CV** = cardiovascular

**HF** = heart failure

**HFpEF** = heart failure with preserved ejection fraction

**HFrEF** = heart failure with reduced ejection fraction

**LA** = left atrial/atrium

**LAEF** = left atrial emptying fraction

**LAViMax** = left atrial maximal volume

**LAViMin** = left atrial minimal volume

**LV** = left ventricle/ventricular

**LVEF** = left ventricular ejection fraction

**NT-proBNP** = N-terminal pro-B-type natriuretic peptide

**PASP** = pulmonary artery systolic pressure

**py** = person-years

The prevalence of heart failure (HF) is increasing exponentially worldwide, especially among the elderly.[1,2] Age-related changes in cardiac structure and function identify subjects at a higher risk of cardiovascular (CV) events.[3] Left atrial (LA) enlargement is a well-known marker of increased morbidity and mortality in the general population and in patients with different established cardiac diseases.[4,5] Measures of LA structure and function are significantly associated with CV events in subjects with HF with preserved and reduced ejection fraction (HFpEF and HFrEF, respectively) and in subjects at heightened risk for stroke or after an acute myocardial infarction.[6-9] Assessment of LA function has also been proposed for the early identification of left ventricular (LV) diastolic dysfunction and to identify subjects at risk of developing HF from the general population.[10,11] Nevertheless, previous data mostly derived from single-center studies, with relatively small sample size and short follow-up. Yet, the value of LA measures from a community-dwelling older population without a history of HF, has been less explored.

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Although maximal LA volume is the most used measure of LA size, and is the recommended measure by major echocardiographic societies, the prognostic role of other more novel measures of LA structure and function, including LA minimal volume and strain-derived measures, has been recently investigated.[5,12-14] These measures may show subclinical abnormalities earlier in the course of the atrial impairment and identify LA dysfunction even before the structural changes that are commonly assessed in clinical practice are identifiable. However, limited data exist on normative values of LA structure and function in a large population of older adults without prevalent HF, their association with circulating biomarkers of HF risk, and their prognostic relevance for incident HF and mortality.

To test the hypothesis that novel measures of LA structure and function may enhance prognostic accuracy more than standard measure of LA structure, we analyzed a cohort of community-dwelling adults aged above 65 years old free of prevalent HF from the ARIC (Atherosclerosis Risk In Communities) study who underwent comprehensive echocardiography and LA-dedicated analysis at the fifth study visit (2011-2013).[15] We determined reference values for LA structure and function measures in a subgroup of participants who were free of prevalent CV disease or major CV risk factors and then assessed the association of these measures with circulating N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and incident HF or death in the overall ARIC cohort.

## METHODS

**STUDY POPULATION.** The design of the ARIC study has been described previously.[15] Briefly, individuals were recruited from 4 communities (Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland) between 1987 and 1989. Of the 15,792 participants who were enrolled in ARIC at the first examination, a total of 6,538 attended the fifth visit between 2011 and 2013 for a standardized physical examination and interviewer-administered questionnaires, and 6,118 underwent a comprehensive echocardiographic examination.[16] This analysis included 4,901 participants in sinus rhythm at the time of the echocardiogram and without prevalent HF at visit 5, who had optimal echocardiographic quality to assess LA structure and function with a dedicated LA software. Institutional review boards approved the study protocol at each field center. All participants provided written informed consent, and study procedures were conducted in accordance with institutional guidelines about the protection of human subjects. Atrial fibrillation (AF) at the time of the echocardiogram was ascertained from electrocardiograms at 5 study visits[17] and during LA offline analysis. The low-risk reference subgroup[3,18] was defined by excluding prevalent CV disease or risk factors as previously described[3]: 1) prevalent CV disease, including coronary heart disease (myocardial infarction history or regional wall motion abnormality on echocardiography), prior HF hospitalization or self-report, AF, and moderate or greater valvular disease; 2) hypertension; 3) diabetes mellitus; 4) visit 5 body mass index of >30 or <18.5 kg/m$^2$; 5) chronic kidney disease defined as an estimated glomerular filtration rate <60 mL/min/1.73 m$^2$ at visit 5; 6) QRS duration ≥120 ms at visit 5; or 7) active smoking.

**ECHOCARDIOGRAPHY.** The ARIC echocardiographic study methods and design at visit 5 have been previously described in detail.[16] All studies were prospectively acquired on Philips IE33 machines by trained sonographers according to a study-specific comprehensive echocardiographic protocol. Analyses of 2-dimensional, Doppler, and tissue Doppler echocardiography were over-read by echocardiographers in a central echo core laboratory and analyzed

**TABLE 1 Clinical Characteristics of ARIC V5 Participants by Incident HF or Death and Low-Risk Reference Subgroup**

| | Overall (N = 4,901) | No Incident HF or Death (n = 4,145) | Incident HF or Death (n = 756) | *P* Value | Low-Risk Reference Subgroup (n = 301) |
|---|---|---|---|---|---|
| Clinical characteristics | | | | | |
| Visit center | | | | 0.82 | |
| Forsyth County, NC | 1,186 (24.2) | 1,012 (24.4) | 174 (23.0) | | 88 (29.2) |
| Jackson, MS | 873 (17.8) | 732 (17.7) | 141 (18.7) | | 22 (7.3) |
| Minneapolis, MN | 1,499 (30.6) | 1,268 (30.6) | 231 (30.6) | | 123 (40.9) |
| Washington County, MD | 1,343 (27.4) | 1,133 (27.3) | 210 (27.8) | | 68 (22.6) |
| Age, y | 75.2 ± 5.05 | 74.8 ± 4.8 | 78.0 ± 5.4 | <0.001 | 74.1 ± 4.4 |
| Male | 1,970 (40.2) | 1,622 (39.1) | 348 (46.0) | <0.001 | 104 (34.6) |
| Black | 965 (19.7) | 809 (19.5) | 156 (20.6) | 0.48 | 25 (8.3 ) |
| Hypertension | 3,979 (81.2) | 3,317 (80.0) | 662 (87.6) | <0.001 | – |
| Ever smoker | 2,953 (60.3) | 2,459 (59.3) | 494 (65.3) | 0.002 | 169 (56.1) |
| Current smoker | 284 (5.79) | 229 (5.7 ) | 55 (7.7 ) | 0.034 | 17 (5.7 ) |
| Coronary artery disease | 680 (13.9) | 512 (12.4) | 168 (22.2) | <0.001 | – |
| History of atrial fibrillation | 182 (3.7) | 114 (2.8) | 68 (9.0) | <0.001 | – |
| Diabetes | 1,670 (34.1) | 1,357 (32.7) | 313 (41.4) | <0.001 | – |
| BMI, kg/m$^2$ | 27.7 (24.7–31.1) | 27.8 (24.8–31.1) | 27.3 (24.2–31.1) | 0.003 | 24 (23–26) |
| SBP, mm Hg | 129 (118–141) | 128 (118–140) | 132 (121–144) | <0.001 | 120 (112–128) |
| Heart rate, beats/min | 61 (55–68) | 60 (55–67) | 63 (57–70) | <0.001 | 60 (54–66) |
| eGFR, mL/min/1.73 m$^2$ | 72.1 (59.8–83.8) | 73.2 (61.3–84.2) | 66.3 (53.1–80.4) | <0.001 | 77 (70–85) |
| NT-proBNP, ng/L | 117 (62–221) | 105 (58–195) | 215 (108–453) | <0.001 | 83 (53–155) |
| Cardiac structure and function | | | | | |
| LVMi, g/m$^2$ | 77.8 ± 18.4 | 76.3 ± 16.7 | 86.2 ± 24.4 | <0.001 | 67 ± 11 |
| LVEF, % | 65.8 ± 5.74 | 66.1 ± 5.38 | 64.3 ± 7.25 | <0.001 | 67.0 ± 4.2 |
| GLS,% | −18.1 ± 2.39 | −18.3 ± 2.29 | −17.4 ± 2.75 | <0.001 | −18.9 ± 2.0 |
| E/e′ average | 11.1 ± 3.71 | 10.9 ± 3.40 | 12.4 ± 4.90 | <0.001 | 10.0 ± 3.0 |
| PASP,[a] mm Hg | 22.8 ± 5.39 | 22.4 ± 4.92 | 24.6 ± 7.08 | <0.001 | 21.2 ± 4.3 |
| LAVi, mL/m$^2$ | 33.6 ± 11.0 | 32.9 ± 10.1 | 37.0 ± 14.6 | <0.001 | 29.3 ± 8.1 |
| LAViMin, mL/m$^2$ | 14.4 ± 7.37 | 13.7 ± 6.18 | 18.6 ± 11.09 | <0.001 | 11.3 ± 4.5 |
| LAEF, % | 58.3 ± 9.45 | 59.4 ± 8.52 | 51.6 ± 11.45 | <0.001 | 62.1 ± 7.5 |
| LA reservoir, % | 32.7 ± 7.70 | 33.8 ± 6.98 | 26.4 ± 8.38 | <0.001 | 36.2 ± 6.6 |
| LA conduit, % | 14.8 ± 5.65 | 15.4 ± 5.51 | 11.7 ± 5.49 | <0.001 | 18.2 ± 5.8 |
| LA contraction, % | 17.8 ± 5.74 | 18.4 ± 5.37 | 14.6 ± 6.54 | <0.001 | 18.1 ± 5.0 |

Values are n (%), mean ± SD, or median (IQR). [a]Data available in 2,880 subjects (58.7%).

ARIC = Atherosclerosis Risk In Communities study; BMI = body mass index; eGFR = estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration equation; GLS = global longitudinal strain; HF = heart failure; LAEF = left atrial emptying fraction; LAViMax = maximal left atrial volume index; LAViMin = minimal left atrial volume index; LV mass index; LVEF = left ventricular ejection fraction; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide; PASP = pulmonary artery systolic pressure; SBP = systolic blood pressure; V5 = visit 5.

according to the recommendations of the American Society of Echocardiography/European Society of Cardiology.[19] LA analysis was performed using a speckle-tracking vendor-dependent software with an auto-strain algorithm designed exclusively for the LA (QLAB Advanced Quantification Software 13.0, Philips Ultrasound). This software is angle-independent and identifies cardiac motion by tracking multiple chamber reference points over time. The LA endocardial borders were automatically traced at the end-diastolic frame (defined by the QRS complex or as the frame after mitral valve closure) of 2-dimensional images acquired from the apical 4-chamber views.[20] Speckles were tracked by the software frame by frame during the course of 1 cardiac cycle. Segment tracking was carefully inspected for each image and manually adjusted as needed. From LA speckle-tracking analysis, LA phasic function was measured using volumes and strain indices. LA time-volume curves were generated by calculating LA volume at each phase of the cardiac cycle (LA maximal and LA minimal volumes) using the Simpson method. From these LA volumes, LA phasic function was estimated as: LA emptying fraction = ([LA maximum volume − LA minimal volume]/LA maximum volume) × 100. Measures of LA maximal and minimal volumes were indexed by body surface area (LAViMax and LAViMin). From LA strain analysis, LA reservoir function was estimated using peak strain during ventricular systole (using a R-R electrocardiogram gating), which represents the chamber filling during LV systole. Because the LA expands during ventricular systole,

**TABLE 2 Percentile Limits for Measures of LA Structure and Function Among the 301 Low-Risk Reference Subgroup**

| | 10th Percentile (95% CI) | 50th Percentile (95% CI) | 90th Percentile (95% CI) | Prevalence of LA Abnormality in the Overall Population, % |
|---|---|---|---|---|
| LA max volume, mL/m$^2$ | | | | 21.9 |
| Overall | 19.8 (18.4–21.1) | 28.6 (27.3–29.9) | 39.4 (37.0–41.8) | |
| Female | 19.6 (17.9–21.4) | 28.6 (27.1–30.1) | 37.8 (34.8–40.9) | |
| Male | 20.6 (18.2–23.0) | 28.9 (26.2–31.6) | 42.7 (38.7–46.7) | |
| LA min volume, mL/m$^2$ | | | | 20.1 |
| Overall | 6.1 (5.5–6.6) | 10.5 (9.9–11.0) | 18.1 (16.7–19.3) | |
| Female | 5.9 (5.3–6.5) | 10.3 (9.6–11.0) | 17.7 (15.8–19.6) | |
| Male | 6.8 (5.8–7.8) | 10.8 (9.7–11.9) | 19.1 (16.0–22.2) | |
| LA emptying fraction, % | | | | 19.5 |
| Overall | 52.0 (50.2–53.8) | 62.5 (61.3–63.6) | 71.4 (69.9–72.9) | |
| Female | 52.6 (50.3–54.9) | 62.5 (60.8–64.2) | 72.4 (70.9–73.9) | |
| Male | 51.6 (48.5–54.8) | 62.4 (60.7–64.2) | 69.0 (65.8–72.1) | |
| LA reservoir, % | | | | 27.3 |
| Overall | 28.2 (27.0–29.4) | 36.0 (34.9–37.0) | 45.1 (43.7–46.4) | |
| Female | 28.6 (27.3–29.8) | 36.0 (34.7–37.2) | 45.6 (43.5–47.8) | |
| Male | 26.4 (23.3–29.6) | 36.2 (34.3–38.0) | 44.6 (43.1–46.1) | |
| LA conduit, % | | | | 26.4 |
| Overall | 11.0 (10.7–11.9) | 17.1 (16.3–17.9) | 26.0 (24.7–27.4) | |
| Female | 11.0 (9.69–12.3) | 17.1 (15.9–18.4) | 27.1 (24.9–29.2) | |
| Male | 11.0 (8.71–13.3) | 17.3 (16.0–18.5) | 23.6 (21.6–25.6) | |
| LA contraction, % | | | | 12.3 |
| Overall | 11.7 (10.5–12.7) | 18.1 (17.3–18.1) | 24.2 (23.1–25.3) | |
| Female | 11.7 (10.3–13.0) | 18.1 (17.0–19.1) | 24.4 (23.3–25.6) | |
| Male | 11.6 (9.70–13.5) | 18.1 (17.0–19.1) | 23.8 (21.5–26.1) | |

The 10th, 50th, and 90th percentile values with associated 95% CIs are derived from quantile regression models in the low-risk reference subgroup, overall and separately by sex. Low-risk reference group was defined excluding participants with coronary heart disease, prior heart failure hospitalization or self-report, atrial fibrillation, and moderate or greater valvular disease; hypertension; diabetes mellitus; visit 5 body mass index of >30 or <18.5 kg/m$^2$; chronic kidney disease defined as an estimated glomerular filtration rate <60 mL/min/1.73 m$^2$ at visit 5; QRS duration ≥120 ms at visit 5; or active smoking.

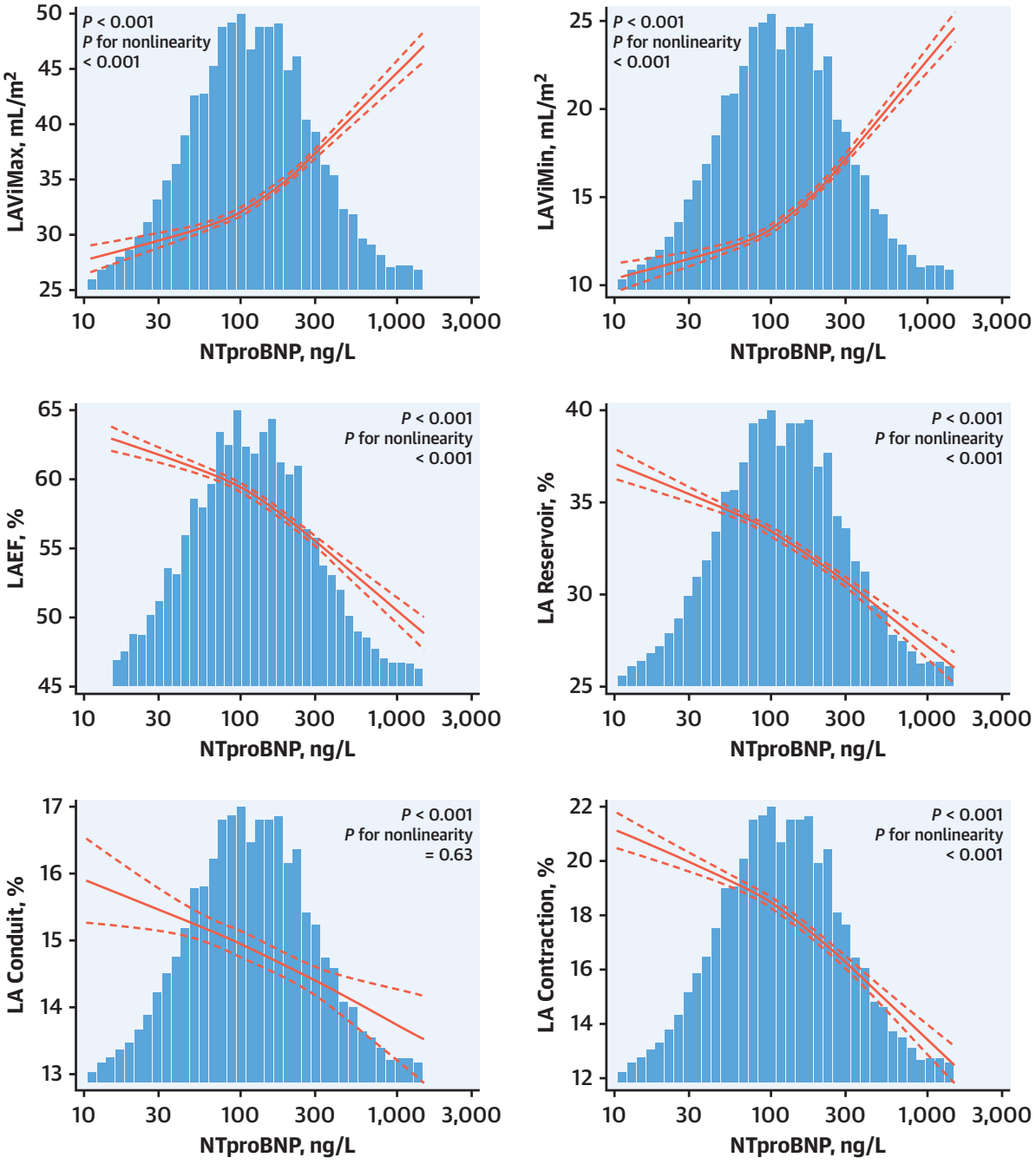
LA = left atrial.

LA reservoir strain is a positive strain value. LA conduit was estimated from the time of mitral valve opening through diastasis until the onset of LA contraction. LA contraction was assessed using peak strain during atrial contraction, which represents the LV end-diastolic filling contribution by the LA.[20] Because of the wall shortening during LA conduit and contraction, the LA strain values are negative, but for the purpose of the current analysis, the values were transformed and reported as positive. If the LA endocardial border could not be tracked for poor quality images, or there was a lack of a full cardiac cycle, missing view, non-DICOM images, or significant foreshortening of the cavity, the measurements were considered unreliable, and the patient was excluded from the analysis. All LA deformation analysis was performed by an investigator experienced in strain analyses blinded to clinical characteristics and outcome (R.M.I.). Reproducibility was assessed by a second blinded investigators (N.G.P.) using a random sample of 40 patients.[21] The coefficient of variation was 8% and the intraclass correlation coefficient was 0.98 for intraobserver variability. The coefficient of variation was 11% and the intraclass correlation coefficient was 0.91% for the interobserver variability.

**OUTCOMES.** The primary endpoint for this analysis was the composite of incident HF hospitalization or all-cause death. Incident HF after visit 5 was based on ARIC HF event classification as previously described,[22] which includes comprehensive abstraction of medical records from hospitalizations with the use of HF-related ICD-9 code and subsequent physician adjudication. All-cause mortality was ascertained by ARIC surveillance or the National Death Index. Additionally, we evaluated incident HFpEF and HFrEF. LV ejection fraction (LVEF) abstracted from the first incident adjudicated HF hospitalization was used to classify HF as HFpEF (LVEF ≥50%) or HFrEF (LVEF <50%). If LVEF was unavailable from the HF hospitalization, the most recent abstracted LVEF from a prior hospitalization, if available, was used. If the prior LVEF was normal, it was used only if it was from within 6 months before the HF hospitalization and without an interval myocardial infarction.[23]

**STATISTICAL ANALYSIS.** Summary statistics for continuous data are presented as mean ± SD or median (IQR), based on their distribution. Categorical data are presented as frequencies and percentage. Comparisons between groups according to the composite outcome of incident HF or death were assessed using Student's *t*-test for means, Wilcoxon test for medians, and chi-square test for proportions. Measures of LA structure and function were described in the low-risk reference subgroup overall and stratified by sex. We used quantile regression to define 10th, 50th, and 90th percentile limits with associated 95% CI in the low-risk reference subgroup overall and stratified by sex. The resulting 10th (for LA emptying fraction [LAEF], LA reservoir, LA conduit, and LA contraction) and 90th (for LAViMax and LAViMin) percentile limits were considered reference limits for these measures in the overall ARIC sample. Cross-sectional continuous association of measures of LA structure and function with log-transformed NT-proBNP levels was assessed with restricted cubic splines adjusted for demographics, clinical confounders, and measures of LV function. The number of knots (3-6 knots assessed) was selected to minimize the Akaike information criterion. The association of measures of LA structure and function,

**FIGURE 1** **Relationship Between LA Structure and Function and NT-proBNP Levels**




Adjusted association between measures of LA structure and function and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels at visit 5 in the entire ARIC population. **Bars** represents frequencies; the **dotted lines** indicate the 95% CIs. ARIC = Atherosclerosis Risk In Communities study; LA = left atrial; LAEF, left atrial emptying fraction; LAViMax = left atrial maximal volume; LAViMin = left atrial minimal volume.

analyzed both continuously and based on ARIC reference limits, with incident HF or death, was assessed by multivariable Cox proportional hazard models adjusted for demographics, clinical confounders, measures of LV function, and NT-proBNP. Pulmonary artery systolic pressure (PASP) was not included in the main model because it was available in only 2,880 participants (58.7%). However, sensitivity analysis was performed including PASP in the multivariable model. The continuous association

**TABLE 3 Association Between Measures of LA Structure and Function and Incident HF or Death**

| | Dichotomous[a] | | | | | | Continuous[b] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Event Rate per 100 Person-Years (95% CI) | | | | | | | | | |
| | Normal | Abnormal | HR | 95% CI | *P* Value | \|Z\| | HR | 95% CI | *P* Value | \|Z\| |
| LAViMax, mL/m$^2$ | 2.4 (2.2-2.7) | 4.2 (3.7-4.8) | 1.12 | 0.92-1.36 | 0.24 | 1.17 | 1.02 | 0.94-1.10 | 0.52 | 0.63 |
| LAViMin, mL/m$^2$ | 2.1 (1.9-2.3) | 5.8 (5.2-6.6) | 1.68 | 1.39-2.04 | <0.001 | 5.42 | 1.13 | 1.07-1.19 | <0.001 | 4.67 |
| LAEF, % | 1.8 (1.6-2.0) | 6.9 (6.2-7.7) | 2.37 | 1.97-2.84 | <0.001 | 9.33 | 1.56 | 1.42-1.70 | <0.001 | 9.56 |
| LA reservoir, % | 1.4 (1.2-1.5) | 8.0 (7.3-8.8) | 4.10 | 3.43-4.90 | <0.001 | 15.5 | 1.58 | 1.48-1.68 | <0.001 | 14.1 |
| LA conduit, % | 1.9 (1.7-2.1 | 5.9 (5.3-6.5) | 1.98 | 1.68-2.34 | <0.001 | 8.19 | 1.45 | 1.33-1.59 | <0.001 | 8.67 |
| LA contraction, % | 2.2 (2.0-2.4) | 8.8 (7.7-10.0) | 2.32 | 1.92-2.79 | <0.001 | 8.87 | 1.31 | 1.23-1.40 | <0.001 | 8.58 |

Adjustment: age, sex, race/center, history of hypertension, heart rate, eGFR, BMI, history of diabetes, history of coronary artery disease, LVMi, GLS, E/e′, NT-proBNP. [a]ARIC-based reference limits: LAViMax (mL/m$^2$) >37.8 (female), >42.7 (male); LAViMin (mL/m$^2$) >17.7 (female), >19.1 (male); LAEF (%) <52.6 (female), <51.6 (male); LA reservoir (%) <28.6 (female), <26.4 (male); LA conduit (%) <11.0 (female and male); LA contraction (%) <11.7 (female), <11.6 (male). [b]HR are shown for 10 mL/m$^2$ increase in LAViMax, 5 mL/m$^2$ increase in LAViMin, 10% decrease in LAEF, 5% decrease in LA reservoir, LA conduit, and LA contraction.

Abbreviations as in Table 1.

between the incidence rates of the composite outcome and LA structure and function was assessed by restricted cubic splines with 3 knots, resulting in the lowest model Akaike information criterion (3-6 knots were assessed). Effect modification by sex and race was further assessed. The incremental value of LA measures to improve risk stratification and correctly reclassify patients when added to relevant HF risk factors was assessed using the area under the curve derived from receiver operating characteristic curves (Harrell's C-statistic) and the continuous net reclassification improvement with time-to-event data. We finally examined cumulative incidence of HFrEF or death and HFpEF or death and the association with LA structure and function. When assessing incident HFrEF as the primary outcome, participants experiencing incident HFpEF and incident HF with unknown EF were censored at the time of that event, and vice versa for incident HFpEF. A *P* value of <0.05 was considered significant. Analyses were performed with Stata, version 14 (StataCorp) and R version 4.1.2 (R Foundation for Statistical Computing).

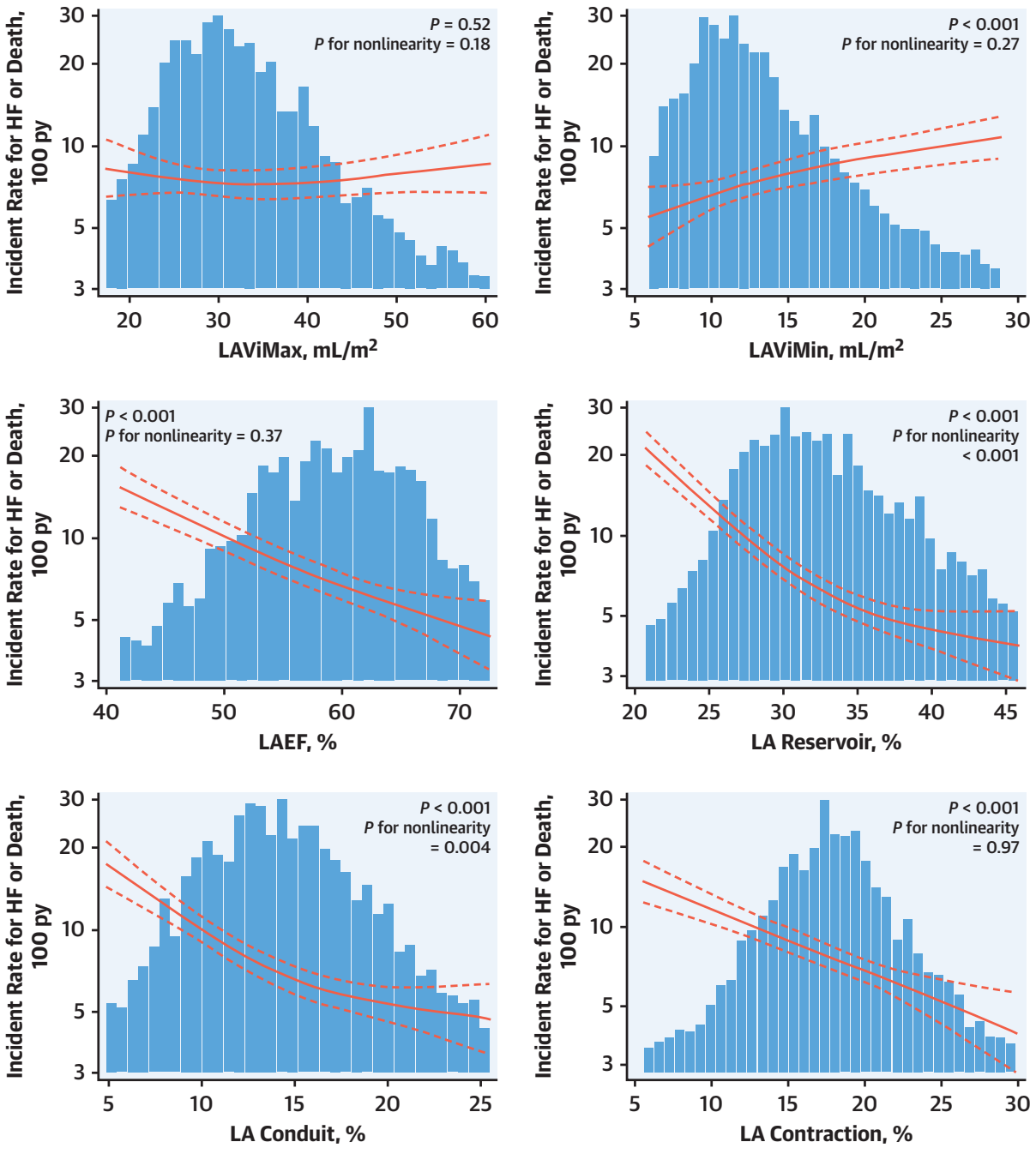
## RESULTS

**STUDY POPULATION.** Clinical and echocardiographic characteristics of the study population stratified by the composite of incident HF or death are shown in Table 1. Overall, 4,901 participants (mean age 75.2 ± 5.05 years; 40.2% male; 19.7% Black) were included in this analysis. Participants who experienced incident HF or death were older, more likely to be male, and had a greater burden of CV risk factors, higher plasma levels of NT-proBNP, and a greater impairment of cardiac structure and function.

Overall, 301 subjects (6%) were included in the low-risk reference subgroup (clinical characteristics are shown in Supplemental Table 1). The upper reference limits for LAViMax and LAViMin were 39.4 and 18.1 mL/m$^2$, respectively (Table 2). Limits for LAViMin tended to be similar between the sexes, whereas upper limits for LAViMax tended to be lower in women compared with men (37.8 and 42.7 mL/m$^2$, respectively). The lower reference limit for LAEF was 52% and was similar between the sexes. The lower reference limits for LA reservoir was 28.2% and tended to be slightly higher in women compared with men (28.6% and 26.4%, respectively). Limits for LA conduit and LA contraction were 11.0% and 11.7% respectively, without differences among men and women. In the overall ARIC population free of prevalent HF, measures of LA structure (LAViMax and LAViMin) were abnormal in 21.9% and 20.1%, respectively. LAEF was impaired in 19.5% and LA reservoir, conduit, and contraction were abnormally low in 27.3%, 26.4%, and 12.3%, respectively. Among subjects without LA enlargement (defined using LAViMax ARIC-based reference limits stratified by sex), LAViMin was high in 5.9%, LAEF was reduced in 15.9%, and LA reservoir, conduit, and contraction were impaired in 18.4%, 22.1%, and 8.7%, respectively. Similar results were observed using guideline cut-off for defining LA enlargement (LAViMax >34 mL/m$^2$).

**ASSOCIATION OF LA MEASURES WITH NT-proBNP.** All measures of LA structure and function were robustly associated with NT-proBNP levels in cross-sectional analysis after accounting for clinical confounders and measures of LV systolic and diastolic function (all $P < 0.001$) (Figure 1). These associations were nonlinear (all *P* for nonlinearity <0.001), except for LA conduit function. No significant effect modification was noted by sex or race (all *P* for interaction

**FIGURE 2** Relationship Between LA Structure and Function and HF or Death




Adjusted association between measures of LA structure and function and incident HF or death after V5 in the entire ARIC population. **Bars** represents frequencies; the **dotted line**s indicate the 95% CIs. HF = heart failure; other abbreviations as in Figure 1.

>0.05). The association between LA measures and NT-proBNP remained significant after removing subjects with LA enlargement (both defined by using ARIC-based reference limits and guideline-based cutoff).

**LA MEASURES AND THE RISK OF INCIDENT HF OR DEATH.** Over a median follow-up of 5.5 years (IQR: 5.0-6.0 years), the composite outcome occurred in 756 participants at a rate of 2.9 per 100 person-years (py) (95% CI: 2.7-3.1 per 100 py). Death occurred in

**TABLE 4 Incremental Value of LA Structure and Function for the Prediction of Incident HF or Death**

| | Dichotomous[a] | | | | Continuous | | | |
|---|---|---|---|---|---|---|---|---|
| | C-Statistics (95% CI) | *P* Value | NRI (95% CI) | *P* Value | C-Statistics (95% CI) | *P* Value | NRI (95% CI) | *P* Value |
| Basal model | 0.74 (0.72 to 0.76) | – | – | – | 0.74 (0.72 to 0.76) | – | – | – |
| LAViMax, mL/m$^2$ | 0.74 (0.72 to 0.76) | 0.87 | 0.06 (−0.09 to 0.11) | 0.29 | 0.74 (0.72 to 0.76) | 0.60 | −0.02 (−0.08 to 0.09) | 0.78 |
| LAViMin, mL/m$^2$ | 0.75 (0.72 to 0.77) | 0.036 | 0.17 (0.11 to 0.21) | <0.001 | 0.75 (0.72 to 0.77) | 0.030 | 0.01 (−0.04 to 0.06) | 0.49 |
| LAEF, % | 0.76 (0.74 to 0.78) | <0.001 | 0.27 (0.21 to 0.32) | <0.001 | 0.76 (0.74 to 0.78) | <0.001 | 0.14 (0.10 to 0.20) | <0.001 |
| LA reservoir, % | 0.79 (0.77 to 0.80) | <0.001 | 0.37 (0.31 to 0.41) | <0.001 | 0.78 (0.76 to 0.80) | <0.001 | 0.23 (0.16 to 0.27) | <0.001 |
| LA conduit, % | 0.75 (0.73 to 0.77) | 0.001 | 0.25 (0.20 to 0.30) | <0.001 | 0.76 (0.73 to 0.76) | <0.001 | 0.18 (0.13 to 0.23) | <0.001 |
| LA contraction, % | 0.75 (0.74 to 0.78) | <0.001 | 0.11 (0.03 to 0.15) | 0.013 | 0.76 (0.74 to 0.78) | <0.001 | 0.10 (0.05 to 0.15) | <0.001 |

Basal model: age, sex, race/center, history of hypertension, heart rate, eGFR, BMI, history of diabetes, history of coronary artery disease, LVMi, GLS, E/e', NT-proBNP. [a]ARIC-based reference limits: LAViMax (mL/m$^2$) >37.8 (female), >42.7 (male); LAViMin (mL/m$^2$) >17.7 (female), >19.1 (male); LAEF (%) <52.6 (female), <51.6 (male); LA Reservoir (%) <28.6 (female), <26.4 (male); LA Conduit (%) <11.0 (female and male); LA Contraction (%) <11.7 (female), <11.6 (male).

NRI = net reclassification improvement; other abbreviations as in Table 1.

568 participants (2.1 per 100 py; 95% CI: 1.9-2.3 per 100 py) and incident HF in 290 (1.1 per 100 py; 95% CI: 1.0-1.2 per 100 py). In the entire ARIC population, all measures of LA structure and function were significantly associated with incident HF or death, after accounting for clinical confounders and measures of LV systolic and diastolic function (Supplemental Table 2). With the exception of LAViMax, the association of LA measures with outcome was consistent after further adjustment for NT-proBNP plasma levels (**Table 3**). Participants with abnormal values of LA structure and function, using the ARIC-based reference limits, showed higher incident rates of events compared with subjects with normal values (**Table 3**). LAViMin, LAEF, and LA contraction showed a linear association with the outcome of interest (*P* for nonlinearity >0.05) such that impaired values were associated with higher incidence rates without evidence of a threshold (**Figure 2**). On the contrary, LA reservoir and LA conduit showed a nonlinear association with a steeper risk in incidence rates noted for values below ~28% and ~11%, respectively (**Figure 2**). Sex did not significantly modify the association of measures of LA structure and function with incident HF or death, whereas the risk associated with abnormal LA reservoir tended to be higher in black compared with white participants (adjusted *P* for interaction <0.05) (Supplemental Table 3). The relationship of all LA measures with outcome was consistent regardless of baseline LAViMax (*P* for interaction >0.05) and remained significant after removing subjects with LA enlargement (both defined by using LAViMax ARIC-based reference limits and guideline-based cutoff). Similar results were observed in sensitivity analysis including history of AF and PASP (Supplemental Tables 4 and 5) in the main model.

When added to clinical, echocardiographic HF risk factors and NT-proBNP plasma levels (baseline C-statistics = 0.74), all measures of LA structure and function, except for LAViMax, significantly increased the prediction of the composite outcome, both analyzed continuously or dichotomized using the ARIC-based reference limits (**Table 4**). Similarly, measures of LA function significantly improved the continuous net reclassification improvement when analyzed continuously or dichotomized (**Table 4**).

Incident HFrEF or death occurred in 644 participants (2.49 per 100 py; 95% CI: 2.31-2.69 per 100 py) and incident HFpEF or death in 657 (2.54 per 100 py; 95% CI: 2.35-2.74 per 100 py). Higher values of LAViMin, but not LAViMax, as well as measures of LA function were significantly associated with a higher risk of both incident HFpEF or death and incident HFrEF or death, when analyzed continuously or dichotomized using the ARIC-based reference limits (**Table 5**).

## DISCUSSION

In a large cohort of older community-dwelling adults without prevalent HF, these data provide normative values of novel measures of LA structure and function and correlate these measures to relevant HF biomarkers and clinical outcomes. We found that abnormalities of LA structure and function are present even among subjects without LA enlargement as assessed by traditional methods. Measures of LA structure and function were robustly associated with circulating NT-proBNP levels and incident HF or death regardless of HF risk factors and measure of LV systolic and diastolic function (**Central Illustration**). Nevertheless, the standard measure of LA size used by virtually all echocardiography laboratories, LA

**TABLE 5 Association Between Measures of LA Structure and Function and Incident HFpEF, HFrEF, or Death**

| | Incident HFrEF or Death | | | Incident HFpEF or Death | | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* Value | \|Z\| | HR (95% CI) | *P* Value | \|Z\| |
| Dichotomous[a] | | | | | | |
| LAViMax, mL/m$^2$ | 0.97 (0.78–1.21) | 0.84 | 0.20 | 1.04 (0.84–1.29) | 0.67 | 0.42 |
| LAViMin, mL/m$^2$ | 1.55 (1.26–1.92) | <0.001 | 4.12 | 1.63 (1.33–2.00) | <0.001 | 4.68 |
| LAEF, % | 2.43 (1.99–2.96) | <0.001 | 8.78 | 2.47 (2.03–3.00) | <0.001 | 9.06 |
| LA reservoir, % | 4.03 (3.32–4.89) | <0.001 | 14.10 | 4.26 (3.52–5.16) | <0.001 | 14.90 |
| LA conduit, % | 2.04 (1.70–2.44) | <0.001 | 7.80 | 1.96 (1.64–2.34) | <0.001 | 7.44 |
| LA contraction, % | 2.22 (1.80–2.73) | <0.001 | 7.54 | 2.30 (1.88–2.83) | <0.001 | 8.05 |
| Continuous[b] | | | | | | |
| LAViMax, mL/m$^2$ | 0.96 (0.88–1.05) | 0.40 | 0.83 | 1.00 (0.91–1.09) | 0.96 | 0.04 |
| LAViMin, mL/m$^2$ | 1.10 (1.03–1.17) | 0.001 | 3.18 | 1.12 (1.06–1.19) | <0.001 | 4.01 |
| LAEF, % | 1.55 (1.40–1.72) | <0.001 | 8.59 | 1.59 (1.44–1.76) | <0.001 | 9.29 |
| LA reservoir, % | 1.56 (1.45–1.67) | <0.001 | 12.50 | 1.59 (1.48–1.70) | <0.001 | 13.20 |
| LA conduit, % | 1.43 (1.30–1.57) | <0.001 | 7.67 | 1.45 (1.32–1.59) | <0.001 | 8.01 |
| LA contraction, % | 1.29 (1.21–1.39) | <0.001 | 7.46 | 1.32 (1.23–1.41) | <0.001 | 8.18 |

Adjustment: age, sex, race/center, history of hypertension, heart rate, eGFR, BMI, history of diabetes, history of coronary artery disease, LVMi, GLS, E/e′, NT-proBNP. [a]ARIC-based reference limits: LAViMax (mL/m$^2$) >37.8 (female), >42.7 (male); LAViMin (mL/m$^2$) >17.7 (female), >19.1 (male); LAEF (%) <52.6 (female), <51.6 (male); LA reservoir (%) <28.6 (female), <26.4 (male); LA conduit (%) <11.0 (female and male); LA contraction (%) <11.7 (female), <11.6 (male). [b]HR are shown for 10 mL/m$^2$ increase in LAViMax, 5 mL/m$^2$ increase in LAViMin, 10% decrease in LAEF, 5% decrease in LA reservoir, LA conduit, and LA contraction.

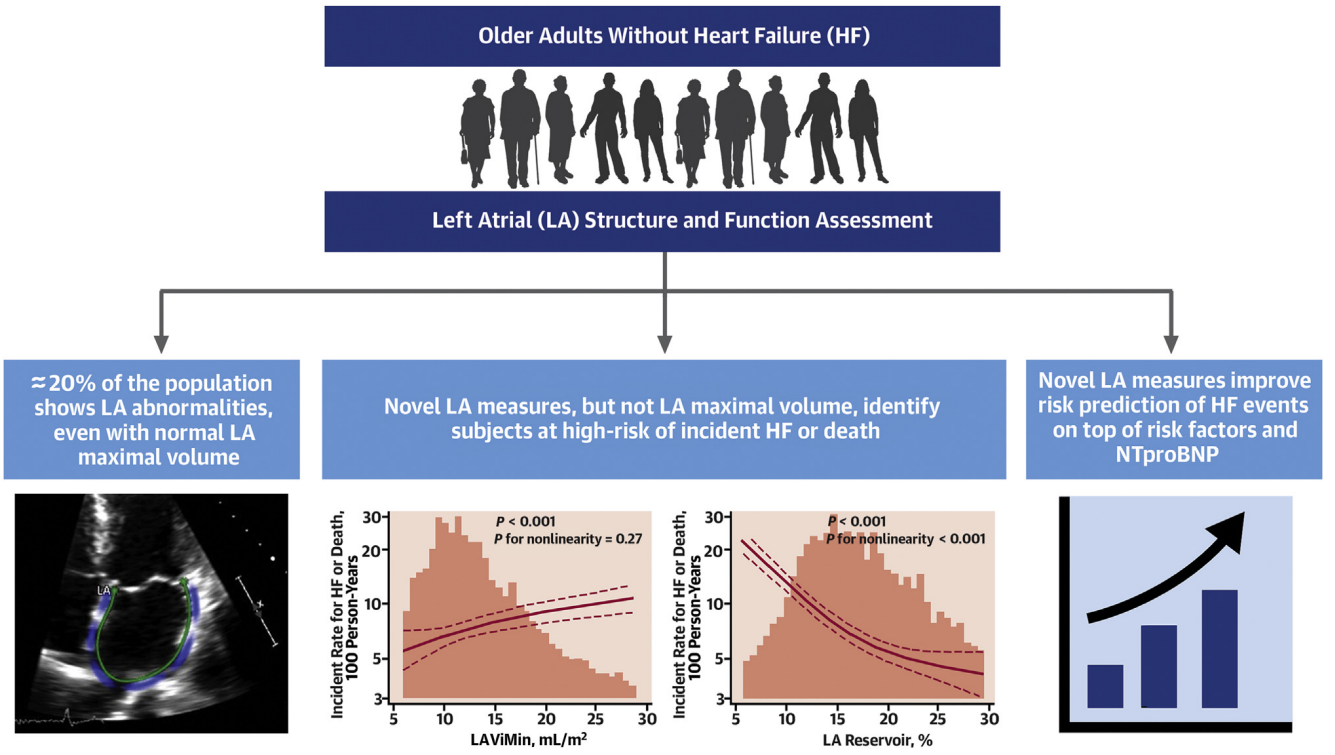
HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; other abbreviations as Tables 1 and 3.

maximal volume, was considerably less robust as a prognostic marker than LA minimal volume and other novel measures of LA function, including strain assessment.

Our study is one of the largest to explore the normative data of LA structure and function by 2-dimensional echocardiography in a biracial cohort of older adults. A previous meta-analysis[24] assessed the normal value of measure of LA function, including studies from the general population free of CV disease (mean age 25–68 years), reporting a mean LA reservoir of 39.4%, LA conduit of 23.0%, and LA contraction of 17.4%. The lower normality cutoffs found in our study can be explained by the older age of our population compared with previous reports. Indeed, as previously shown from cross-sectional studies, age-related decline of cardiac structure and function is well recognized and may suggest that the cutoffs derived from our low-risk reference group may occur as a part of healthy aging.[3] This is particularly relevant for the guidelines-recommended estimation of LA maximal volume, as the upper cutoff values found in our population, along with previous reports, question the current value of normality of LA maximal volume for adults aged 65 years and above.[25,26]

Although each measure of LA structure and function was robustly associated with circulating NT-proBNP levels, after accounting for confounders including measures of LV systolic and diastolic function, the standard measure of LA dimension, LA maximal volume, was not related to incident HF or death. On the contrary, LA minimal volume and measures of LA function (including LA phasic functions and LAEF), were significantly associated with worse outcomes and enhanced prognostic risk stratification. The present results support previous studies that showed the incremental value of LA minimal volume and LA function over standard measures of LA dimension, by LA maximal volume, for the risk assessment in patients with and without prevalent heart disease.[12,27] Measures of LA function have been shown to better classify LV diastolic function compared with LA maximal volume in patients at risk of developing HF.[10] Also, larger LA minimal volume and LA functional impairment represent strong predictors of CV outcomes in patients with HF and reduced or preserved ejection fraction, and in patients with known CV diseases.[9,13,14] Our analysis extends previous results with a direct comparison of novel LA measures, including LA minimal volume and strain-derived measures, in a population without prevalent HF. On top of the additional time consumption, we believe that the feasibility of these measures, particularly for the LA minimal volume and LAEF, and their relevant clinical implications, support the clinical need to incorporate such novel measures into a more comprehensive evaluation of cardiac structure and function alongside the guideline-recommended LA assessment by LA maximal volume. Along with the echocardiographic

**CENTRAL ILLUSTRATION** **Clinical Implication of Measures of Left Atrial Structure and Function Assessment**




**Inciardi RM, et al. J Am Coll Cardiol. 2022;79(16):1549–1561.**

Among older adults free of prevalent heart failure (HF), impairment of left atrial (LA) structure and function is encountered in approximately 20% of individuals, even with normal LA maximal volume (LAViMax). Novel LA measures identify individuals at risk of developing future HF events.

assessment, LA dysfunction detected by cardiac magnetic resonance (CMR), has been also shown to be strongly associated with HF events and mortality in patients with and without HF.[5,28] CMR has also the advantage of being the imaging gold standard for the assessment of tissue characterization, particularly fibrosis.[29] Although the cost/effectiveness and clinical value of using CMR, instead of echocardiography, needs to be demonstrated, an integrated multilevel imaging approach should be considered in patients undergoing CMR for clinical purposes.

The LA has been commonly considered a buffer chamber between the pulmonary circulation and the LV, and its changes have been thought to be indirectly related to LV function.[11,30,31] Nevertheless, the current analysis showed that LA impairment is predictive of worse outcomes regardless of common measures of LV structure and function, such as LV hypertrophy and LV global longitudinal strain. Although it might be questioned whether LA abnormalities occur before the LV impairment is detected, our analysis suggests that a comprehensive imaging assessment is advocated. From this perspective, LA "remodeling" does not represent an innocent bystander but plays an active role in the pathophysiology of HF. LA impairment may occur even before LA enlargement contributing to the risk for symptomatic HF and subsequent mortality.[32,33] Indeed, the term *atrial failure* has been recently proposed as a unique clinical entity, encompassing any anatomical, mechanical, or electrical dysfunction causing impaired heart performance and symptoms.[32]

The loss of LA contractile function may directly affect LV output, and the impairment of reservoir function, by reducing LA wall compliance, may result in elevated LA pressure which consequently leads to increased pulmonary arterial pressure and thus HF symptoms.[31,34] Because LA dysfunction is common in both HFrEF and HFpEF,[35] detection of these abnormalities, by using novel echocardiographic tools,

before the onset of overt HF could identify patients at risk for future HF events. Although we found that impairment of LA function equally accounted for the risk of both HFrEF and HFpEF, higher LA minimal volume, but not the commonly utilized LA maximal volume, was associated with both incident HFrEF and HFpEF. The potential prognostic benefit of LA minimal volume over LA maximal volume may be due to the fact that LA minimal volume is more reflective of LV filling pressure, as minimal LA volume occurs when the LA is more directly exposed to LV pressure at end-diastole.[14,36,37] Given this consideration, LA minimal volume may represent an early marker of diastolic dysfunction and high filling pressure, occurring before LA enlargement. Promising data have shown that HF medical therapy may favor LA reverse remodeling.[38] Our data may be useful for the design of future interventional studies assessing whether initiation of therapeutic interventions when LA dysfunction is detected will result in restored function and potentially improvement in clinical outcomes. Yet, clinical challenges to widespread the routinely application of LA assessment are related to time-consuming issues and the lack of standardization data across intervendor packages. From this perspective, significant efforts have been made by scientific societies and task forces[20] to lead to a more patient-oriented software utilization, better tailored to clinical needs.

**STUDY LIMITATIONS.** Given the small number of black participants in the low-risk reference subgroup (8%), we were unable to determine a normative cut-point separately by race. Ascertainment of HF was essentially based on HF hospitalizations, because outpatient diagnosis and management were not uniformly available.[3] Nevertheless, the strength of the study was the prospective adjudicated ascertainment of incident HF. Available follow-up time after echocardiography at ARIC visit 5 and the multiple stratification steps may have limited our power to assess the relationship between LA measures and outcome. Our analysis did not account for incident AF during the follow-up time, potentially confounding the interpretation of the results. Nevertheless, we performed a sensitivity accounting for history of AF for the assessment of the prognostic value of LA measures. LA measures were acquired only from apical 4-chamber view, although this is the current recommended approach,[20] and the reproducibility analysis was performed in a limited sample size subgroup. Finally, as with all observational analyses, we cannot rule out the possibility of residual confounding.

## CONCLUSIONS

In a large biracial cohort of community-dwelling older adults free of prevalent HF, impairment of LA structure and function is encountered in approximately 20% of individuals. Novel LA measures are robustly associated with NT-proBNP and incident HF or death, regardless of LV function or NT-proBNP, and even in participants with normal LA structural measurements by guidelines. Importantly, LA maximal volume, the standard and generally only measure of LA size used in the majority of echocardiography laboratories worldwide, may be considerably less prognostic than other measures of LA size and function, including LA minimal volume and strain-derived parameters, which may better identify patients at increased risk for HF.

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## PERSPECTIVES

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** Structural and functional remodeling of the LA contributes to the pathophysiology of HF. Compared with standard measures, LA minimal volume and strain-derived parameters indicative of LA impairment better identify patients with HF at risk of adverse events.

**TRANSLATIONAL OUTLOOK:** Future studies and clinical trials are necessary to determine whether earlier initiation of therapeutic interventions upon detection of LA dysfunction improves clinical outcomes in patients with HF.

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**KEY WORDS** heart failure, left atrium, speckle tracking

**APPENDIX** For supplemental tables, please see the online version of this paper.