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TITLE OF THE DOCTORAL THESIS

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

S.S.D. MED/11 MALATTIE DELL'APPARATO CARDIOVASCOLARE

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Summary (Italian)

Esiste un`associazione fra le alterazioni strutturali e funzionali dell'atrio sinistro e lo sviluppo di malattie cardiovascolari. Tuttavia esistono dei dati limitati volti a caratterizzare l'impatto clinico di nuovi parametri atriali, elaborati attraverso metodica ecocardiografica avanzata, nella popolazione generale adulta.

La prevalenza di scompenso cardiaco sta crescendo esponenzialmente in tutto il mondo e le alterazioni cardiache strutturali e funzionali rappresentano dei marker che permettono di identificare i soggetti a rischio elevato di sviluppare scompenso cardiaco e successivamente morte cardiovascolare.

Lo scopo del seguente studio e' volto ad analizzare in modo comprensivo nuovi parametri strutturali e funzionali atriali in soggetti adulti senza storia di scompenso cardiaco, arruolati nello studio ARIC (Atherosclerosis Risk in Communities, 4901 soggetti, età media 75 ± 5 anni, 40% maschi), con lo scopo di valutarne i range di normalità, l'associazione con biomarkers di scompenso cardiaco e la loro associazione con insorgenza di scompenso cardiaco o morte.

Il nostro studio ha dimostrato alterazioni strutturali e funzionali atriali in circa il 20% della popolazione, anche fra i soggetti con stimata struttura atriale normale secondo in base ai parametri classici indicati dalle attuali linee guida. Inoltre, abbiamo rilevato una significativa associazione fra i nuovi parametri atriali, quali il volume minimo e lo strain di parete, ma non i parametri standard normalmente utilizzati in pratica clinica, ed il rischio di sviluppare scompenso cardiaco o morte anche dopo aggiustamento per la funzione sistolica ventricolare sinistra ed il NTproBNP.

Questi nuovi parametri, sono in grado di incrementare la capacità di predire nuovi eventi di scompenso cardiaco nella popolazione generale e potrebbero essere utilizzari come di marker di rischio per stratificare i soggetti adulti ad aumentato rischio di sviluppare ospedalizzazioni.

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: To assess reference range of LA measures, their associations with N-terminal pro-brain-natriuretic-peptide (NTproBNP) and the related risk for incident HF or death.

Methods: We analyzed LA structure [LA maximal and minimal volume indexed by body surface area (LAViMax and LAViMin)] and function [LA emptying fraction, LA reservoir, conduit and contraction strain] in 4901 participants from the Atherosclerosis Risk in Communities (ARIC) study (mean age 75±5 years, 40% male and 19% black) without prevalent HF. We assessed gender-specific 10th and 90th percentile ARIC-based reference limits in 301 participants free of prevalent cardiovascular disease, and related LA measures to NTproBNP 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 NTproBNP and, except for LAViMax, with incident HF or death after multivariable adjustment. Results were consistent in participants with normal LAViMax (p for interaction>0.05). LA measures were prognostic for both incident HFpEF or death and incident HFrEF or death. When added to HF risk factors and NTproBNP (baseline C-statistics=0.74) all LA measures, except for LAViMax, significantly enhanced the prognostic accuracy.

Conclusion: 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 LV function and NTproBNP.

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Introduction

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). 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). Contrary to left ventricular (LV) volume and ejection fraction (EF), which are landmark parameters used in cardiovascular disease, the clinical usefulness of left atrium (LA) has been essentially neglected for a long time. In the last decade there has been an increasing interest in LA structural and functional remodeling, especially for identifying high risk subjects, for diagnosis of underlying diseases, and potentially as a target for medical treatment.

Measures of LA structure and function are significantly associated with CV events in subjects with heart failure (HF) with preserved and reduced ejection fraction (HFpEF and HFrEF), 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 ventricle (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.

While maximal LA volume is the most utilized 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.

How to Assess LA Structure and Function

The interest in the LA started with the advent of echocardiography in cardiovascular clinical practice. Previously, other imaging techniques such as angiography, allowed a sharp visualization of LV but blurred imaging of the LA. In opposition, echocardiography provides optimal visualization of the LA chamber. Until recently, the most widely used echocardiographic LA measurement was the antero-posterior diameter (15). However, since the LA can enlarge in not-uniform fashion, mono-dimensional assessment has proven to be inaccurate. In 2015, the American/European Societies of Echocardiography guidelines recommended analyzing LA volume with two dimensional (2D) transthoracic echocardiography (TTE) as the method of choice (16) (Figure 1).

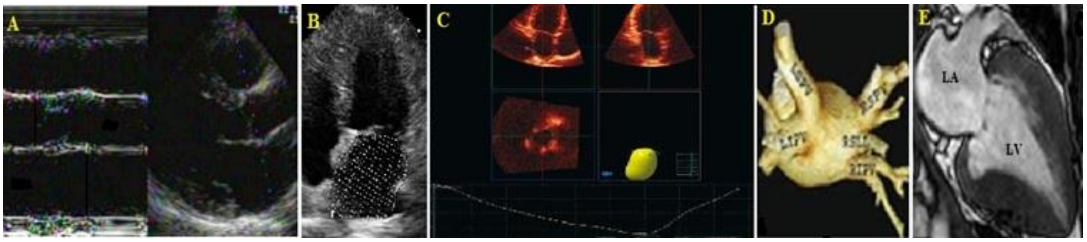


Figure 1: Evolution of LA imaging.

A. LA diameter measurement on 1-dimensional M-mode echocardiography; B. LA volume on 2-dimensional echocardiography; C. 3-dimensional Echocardiographic assessment; D. LA computer tomography reconstruction; D. LA evaluation using magnetic resonance imaging.

This was based not only on the demonstration that LA volume provides a more accurate estimate of the overall LA size when compared with cardiac magnetic resonance (CMR) and computerized tomography (CT) (17,18), but mainly on the demonstration that LA volume has a stronger association with cardiovascular outcome compared to LA diameter or area (19, 20).

Since the major limitation of 2D-TTE is the underestimation of LA volume, the latest guidelines also suggest the use of three-dimensional TTE (3D-TTE) as a new technique for a better assessment of this measurement (15) (Figure 1).

With less geometric assumptions, 3D-TTE provides better correlation with CMR (21, 22) and CT-derived LA volumes (21). 3D-TTE also showed a better reproducibility with a minor variability compared with 2D-TTE (23).

In addition to echocardiographic measurements, cardiac CT and CMR provide an accurate evaluation of LA without geometric assumptions (21). Particularly, CMR is considered the gold standard for LA volume measure, providing accurate endocardial border definition (24).

An additional ability of CMR is to provide further details, beyond structure and function, by directly detecting pathological tissue characteristics, such as myocardial scarring and fibrosis, with the use of late gadolinium enhancement (25).

LA influences cardiac function upon 3 phases (13): the reservoir phase, during LV systole when LA collects blood from the pulmonary veins; the conduit phase, during early LV diastole when blood passively transfers to the ventricle; and the LA contraction phase at end-diastole when blood is forced to fill LV.

A promising technique recently introduced to evaluate LA function is 2D-speckle-tracking echocardiography (2D-STE), which is based on the analysis of the speckle pattern (acoustic backscatter generated by the reflected ultrasound beam) followed frame-by-frame during the cardiac cycle (26) (Figure 2).

During LV systole, the LA is stretched and longitudinal LA strain increases, reaching a positive peak at the end of LA filling (peak atrial longitudinal strain - PALS). This phase is also influenced by the mitral annulus movement toward the LV apex, as a result of LV contraction. Hence, PALS reflects not only LA compliance, but also LV longitudinal contraction due to the LA-LV interdependency (26). During the conduit phase, LA strain decreases to a plateau, corresponding with LA diastasis that mainly depends on aging and LV diastolic function. The subsequent LA shortening leads to a further decrease in LA strain (peak atrial contraction strain - PACS) and reflects the LA booster pump function that is dependent on intrinsic LA contractility and LV filling pressures (27). Although 2D-STE is a promising tool, several considerations must be taken into account such as the need of a specific consensus for analysis of LA tracking, the inter-software discordance of LA strain values, and the interdependency of LA-LV strain imaging.

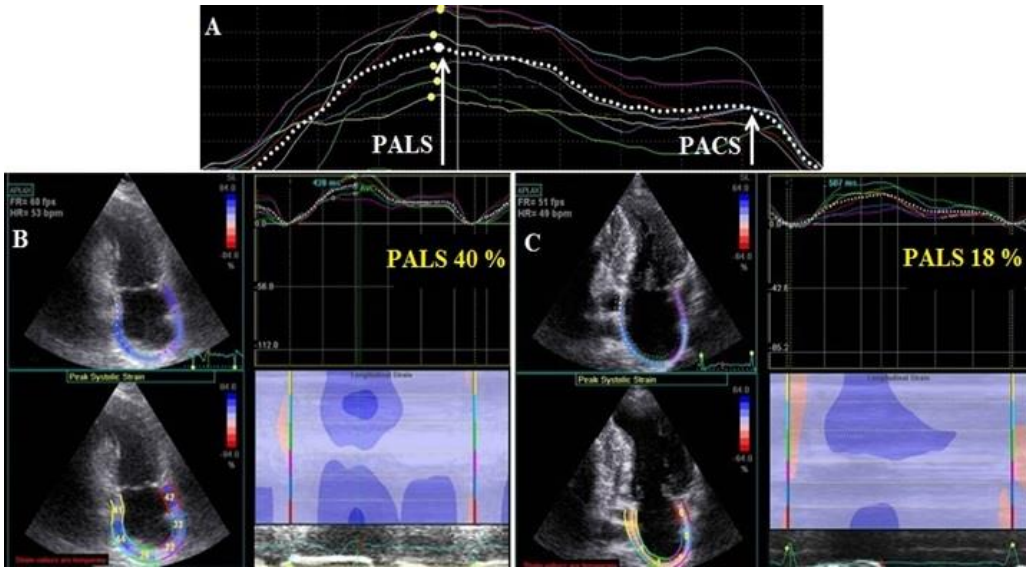


Figure 2: LA strain imaging

On A, measurement of peak atrial longitudinal strain (PALS) at the end of reservoir phase and peak atrial contraction strain (PACS) before the start of atrial systole. The dashed curve is representative of the average atrial longitudinal strain during the cardiac cycle. On B and C examples of respectively an healthy control with normal LA strain in and a patients with HF and consequent impaired LA function.

Even though the LA reservoir phase is modulated by atrial compliance during ventricular systole, it has been hypothesized that it is also influenced by downward motion of the mitral plane, driven by LV longitudinal shortening, casting doubts about its significance beyond LV function (13). Thus, further studies are needed to assess whether LA function assessment may give information of intrinsic LA properties per se beyond LV longitudinal displacement.

Finally, increasing interest is raising on the assessment of LA minimal volume. 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 (13, 28, 29). Given this consideration, LA minimal volume may represent an early marker of diastolic disfunction and high filling pressure, occurring before LA enlargement.

Might Left Atrial Remodeling Help Clinicians to Manage Patients?

Numerous studies showed that LA remodeling could be useful in several clinical applications potentially enhancing the care of patients with different cardiovascular diseases.

In the general population, the assessment of cardiovascular risk is based on evaluation of clinical conditions such as hypertension, diabetes and hyperlipidemia without considering mechanistic markers which might predict various outcomes.

LA structural remodeling is associated with increased mortality and cardiovascular events both in middle age (30) and elderly (31) asymptomatic persons recruited from the general population. The prognostic value can be explained by the powerful association between the LA and different clinical entities such as HF, ischemic heart disease (IHD), AF and stroke, all intrinsically associated with consistent morbidity and mortality. LA remodeling makes patients at an increased risk for these conditions.

Asymptomatic elderly patients with enlarged LA had a 2-fold increased risk of incident HF independently and incrementally to clinical risk factors (32) (Figure 3). Similarly, reduced LA function measured by CMR represents a marker for HF development in the general population (33).

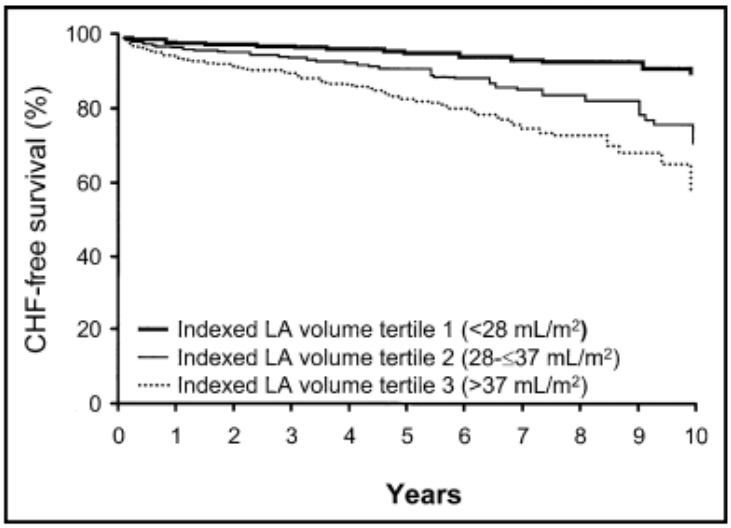


Figure 3: LA volume and the risk of developing HF

Risk of developing incident HF among patients aged ≥ 65 years old from the general population. From reference 32.

The predictive value of LA for IHD has been inconsistently reported in literature. The Cardiovascular Health Study suggested that LA dimension was not independently associated with coronary artery events after adjustment for traditional risk factors (31). On the contrary, other investigations based on LA volume measurement, were able to clearly demonstrate an independent association between LA volume and the risk of acute myocardial infarction (AMI) (32-35).

Furthermore, LA volume might be a marker of atherosclerotic burden since it was shown to be an independent predictor of normal stress echocardiography (36).

In non-diabetic patients with preserved LVEF, impaired LA function was associated with renal function degradation showing how LA remodeling could be considered a marker of systemic arterial impairment as a result of the complex cardiorenal interactions (37).

LA size, moreover, plays a central role in the prediction of the incidence of AF in the general population (38), in fact a 30% increase in LA volume was associated with a 43% greater risk of AF. Similarly, in a population of patients at particularly high risk for AF such as those undergoing to cardiac surgery, LA volume (>32 ml/m2) were associated with 6.5-fold increased risk of post-operative AF compared to patients with small LA (39).

O'Neal et al. recently found that in the HF with preserved EF (HFpEF) population, impaired atrial function resulted as an independent predictor of AF onset, underlying the potential of LA functional remodeling to be a marker of subtle electro-anatomical disease (40).

Finally, a considerable association has been described between LA and stroke. In male patients from the general population, the relative risk for stroke for 1 cm increments in LA size was 2.4 after adjustment for traditional stroke risk factors (41). A second population-based study confirmed that patients with LA volume ≥32ml/m2 had a 67% increased risk of stroke independent of age, diabetes, IHD and hyperlipidemia, even after censoring for ad interim AF development (42).

Study aim

To test the hypothesis that novel measures of LA structure and function may enhance prognostic accuracy to identify subjects at a high-risk of developing HF, 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 Atherosclerosis Risk in Communities (ARIC) Study who underwent comprehensive echocardiography and LA-dedicated analysis at the fifth study visit (2011-2013) (43). 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-brain natriuretic peptide (NTproBNP) levels and incident HF or death in the overall ARIC cohort.

Methods

Study population

The design of the ARIC study has been described previously (43). Briefly, individuals were recruited from 4 communities (Forsyth County, NC; Jackson, MS; Minneapolis, MN; and Washington County, MD) between 1987 and 1989. Of the 15,792 participants who were enrolled in ARIC at the first examination, a total of 6538 attended the fifth visit between 2011 and 2013 for a standardized physical examination, interviewer-administered questionnaires, and 6118 underwent a comprehensive echocardiographic examination (44). This analysis included 4901 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 (Figure 4).

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 at the time of the echocardiogram was ascertained from ECGs at 5 study visits (45) and during LA offline analysis.

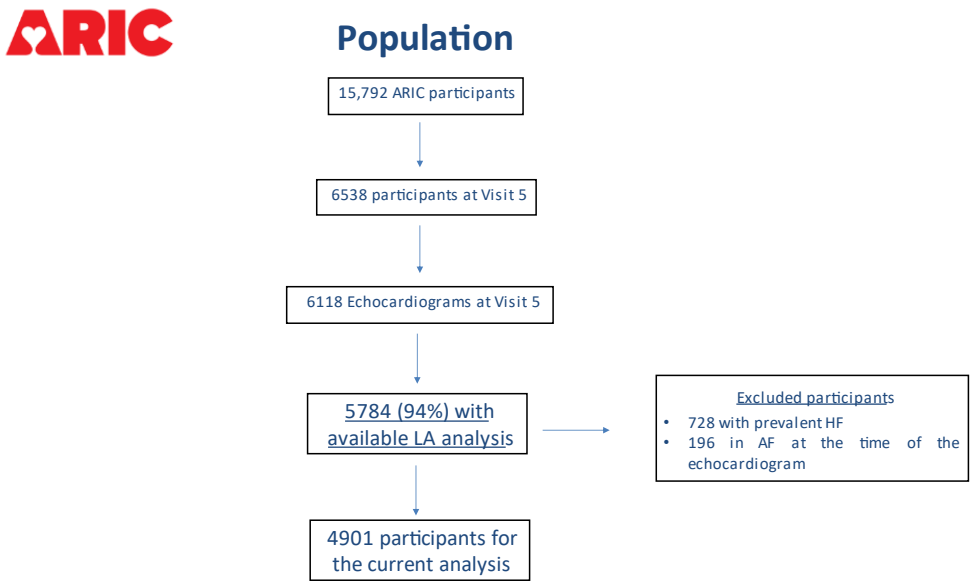


Figure 4: Study Population

The low-risk reference subgroup (3, 46) was defined by excluding prevalent cardiovascular disease or risk factors as previously described (3): [1] prevalent cardiovascular disease, including coronary heart disease (myocardial infarction history or regional wall motion abnormality on echocardiography), prior HF hospitalization or self-report, atrial fibrillation, and moderate or greater valvular disease; [2] hypertension; [3] diabetes mellitus; [4] visit 5 body mass index of >30 or <18.5 kg/m2; [5] chronic kidney disease defined as an estimated glomerular filtration rate <60 mL·min−1·1.73 m−2 at visit 5; [6] QRS duration ≥120 milliseconds at visit 5; or [7] active smoking.

Echocardiography

The ARIC echocardiographic study methods and design at visit 5 have been previously described in detail (44). 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 according to the recommendations of the

American Society of Echocardiography/European Society of Cardiology (16). 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, Inc. 3000 Minuteman Road Andover, MA). 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 (47). 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, 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 (47). 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. Reproducibility was assessed by a second blinded investigators using a random sample of 40 patients (48). The coefficient of variation (CoV) was 8% and the intraclass correlation coefficient (ICC) was 0.98 for intraobserver variability. CoV was 11% and ICC 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 (49) 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 (50).

Statistical analysis

Summary statistics for continuous data are presented as mean (± standard deviation) or median (25th, 75th percentiles), 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-squared test for proportions. Measures of LA structure and function were described in the low-risk reference subgroup overall and stratified by gender. We used quantile regression to define 10th, 50th, and 90th percentile limits with associated 95% confidence interval (CI) in the low-risk reference subgroup overall and stratified by gender. The resulting 10th (for LAEF, LA Reservoir, LA Conduit and LA Contraction) and 90^{th} (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 NTproBNP 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, 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 NTproBNP. Pulmonary artery systolic pressure (PASP) was not included in the main model as it was available in only 2880 (58.7%) participants. However, sensitivity analysis was performed including PASP in the multivariable model. The continuous association 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 gender 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, College Station, TX) and R version 4.1.2.

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.

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.

Overall, 4901 participants (mean age 75.2 ± 5.05, 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 NTproBNP and a greater impairment of cardiac structure and function.

Overall, 301 (6%) subjects were included in the low-risk reference subgroup. The upper reference limits for LAViMAx and LAViMin, were 39.4 and 18.1 ml/m2, respectively (Table 2). Limits for LAViMin tended to be similar between gender, whereas upper limits for LAViMax tended to be lower in women compared with men (37.8 and 42.7 ml/m2, respectively). The lower reference limit for LAEF was 52% and was similar between gender. 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%. 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 gender), 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/m2).

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)	

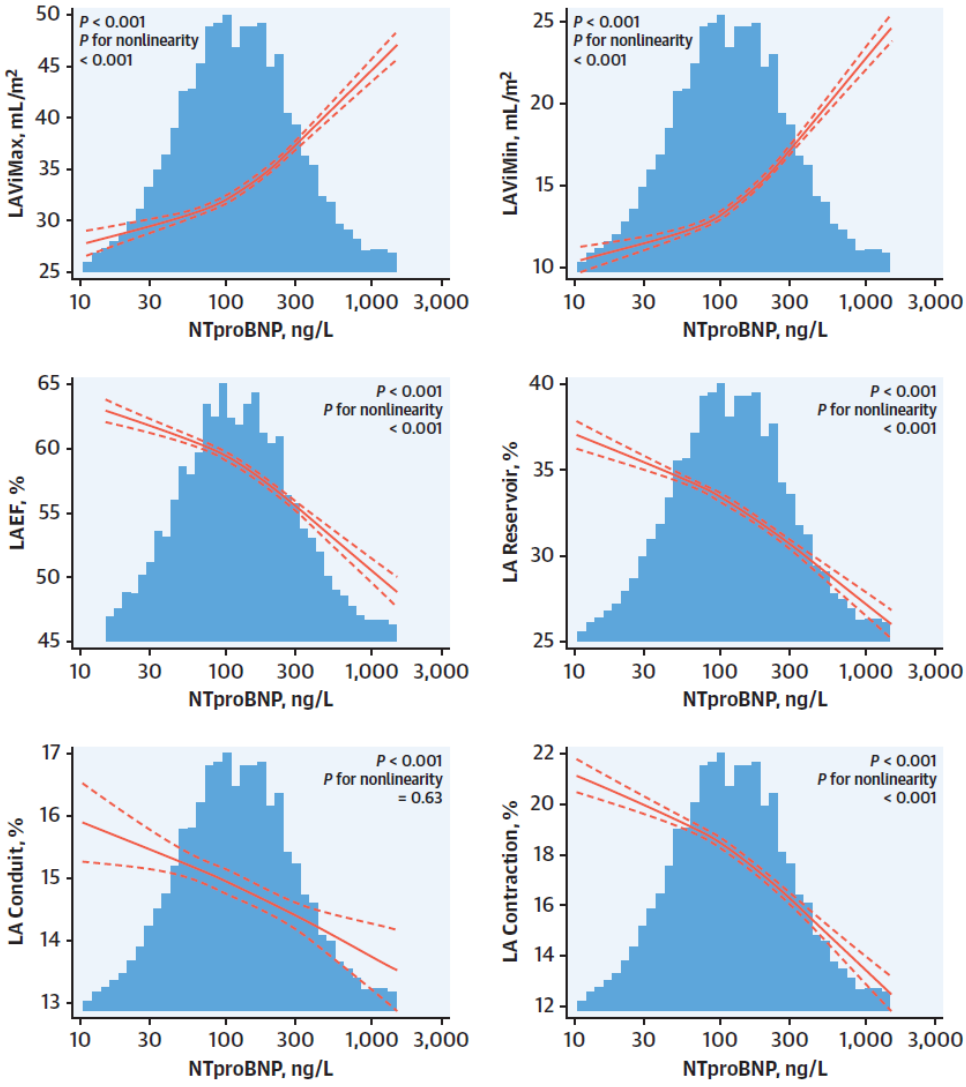
The 10th, 50th, and 90th percentile values with associated 95% CIs are derived from quantile regression models in the low-risk reference subgroup, overall and separately by sex. Low-risk reference group was defined excluding participants with coronary heart disease, prior heart failure hospitalization 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.

Association of LA measures with NTproBNP

All measures of LA structure and function were robustly associated with NTproBNP levels in cross-sectional analysis after accounting for clinical confounders and measures of LV systolic and diastolic function (all p<0.001; Figure 5). These associations were non-linear (all p for non-linearity < 0.001), except for LA conduit function. No significant effect modification was noted by gender or race (all p for interaction > 0.05). The association between LA measures and NTproBNP remained significant after removing subjects with LA enlargement (both defined by using ARIC-based reference limits and guideline-based cut-off).

Figure 5. Relationship between LA structure and function and NTproBNP 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.

LA measures and the risk of incident HF or death

Over a median follow-up of 5.5 years (25^{th}-75^{th} percentiles: 5.0 – 6.0), the composite outcome occurred in 756 participants at a rate of 2.9 per 100 person-years (py) [95% confidence interval (95%CI): 2.7 – 3.1]. Death occurred in 568 participants (2.1 per 100-py; 95%CI: 1.9 – 2.3) and incident HF in 290 (1.1 per 100-py; 95%CI:1.0-1.2). 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. With the exception of LAViMAx, the association of LA measures with outcome was consistent after further adjustment for NTproBNP 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 to subjects with normal values (Table 3).

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

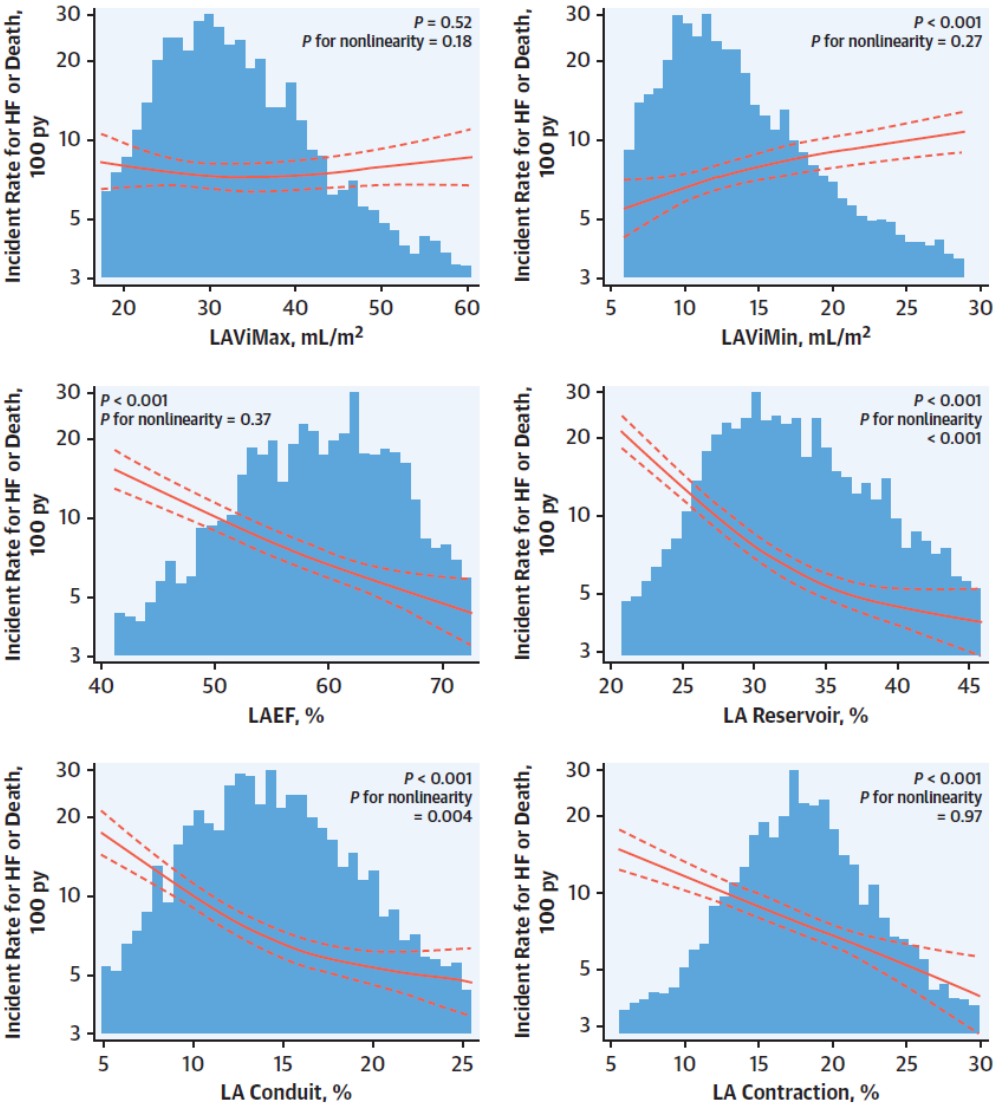
Adjustment: age, sex, race/center, history of hypertension, heart rate, eGFR, BMI, history of diabetes, history of coronary artery disease, LVMi, GLS, E/e', NT-proBNP. [a]ARIC-based reference limits: LAViMax (mL/m^2) >37.8 (female), >42.7 (male); LAViMin (mL/m^2) >17.7 (female), >19.1 (male); LAEF (%) <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.

LAViMin, LAEF and LA contraction showed a linear association with the outcome of interest (p for non-linearity > 0.05) such that impaired values were associated with higher incidence rates without evidence of a threshold (Figure 6). On the contrary, LA reservoir and LA conduit showed a non-linear association with a steeper risk in incidence rates noted for values below ~28% and ~11% respectively (Figure 6). Gender 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). 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 cut-off). Similar results were observed in sensitivity analysis including history of AF and PASP in the main model.

Figure 6. 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 lines** indicate the 95% CIs. HF = heart failure; other abbreviations as in Figure 1.

Finally, history of hypertension and anti-hypertensive drugs as well as diabetes and obesity, did not modify the association between LA structure and function and outcome. When added to clinical, echocardiographic HF risk factors and NTproBNP 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).

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.

Incident HFrEF or death occurred in 644 participants (2.49 per 100-py; 95%CI: 2.31 – 2.69) and incident HFpEF or death in 657 (2.54 per 100-py; 95%CI:2.35-2.74). 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).

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.

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 NTproBNP levels and incident HF or death regardless of HF risk factors and measure of LV systolic and diastolic function. Nevertheless, the standard measure of LA size utilized by virtually all echocardiography laboratories, LA 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 metanalysis (51) assessed the normal value of measure of LA function, including studies from the general population free of CV disease (mean age ranges 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 cut-offs found in our study can be explained by the older age of our population compared to 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 cut-offs 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 cut-off 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 (52, 53).

Although each measure of LA structure and function was robustly associated with circulating NTproBNP levels, after accounting for confounders including measures of LV systolic and diastolic function, 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, 54). Measures of LA function have been shown to better classify LV diastolic function compared to 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 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 (5,55). CMR has also the advantage of being the imaging gold standard for the assessment of tissue characterization, particularly fibrosis (56). 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, 57, 58). 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 suggest 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 (59,60). 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 (59).

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 (58, 61). As LA dysfunction is common in both HFrEF and HFpEF (62), detection of these abnormalities, by using novel echocardiographic tools, before the onset of overt HF could identify patients at risk for future HF events. While 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, 28, 29). Given this consideration, LA minimal volume may represent an early marker of diastolic disfunction and high filling pressure, occurring before LA enlargement. Promising data have been shown that HF medical therapy may favor LA reverse remodeling (63,64). 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 inter-vendor packages. From this perspective, significant efforts have been made by Scientific Societies and Task Force (20) to lead to a more patient oriented software utilization, better tailored to clinical needs.

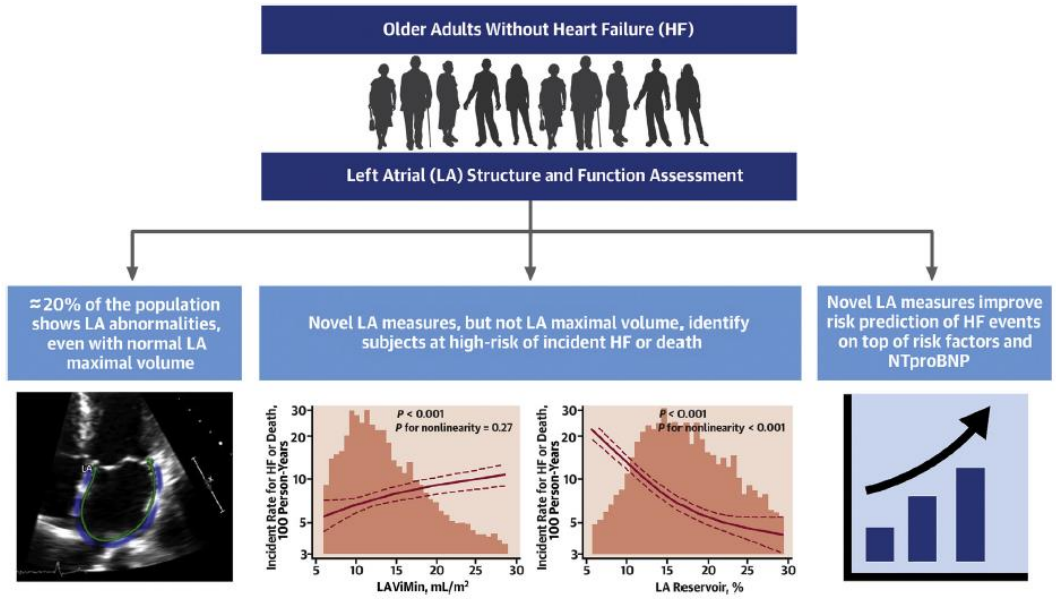
Limitations

Several limitations of this study should be acknowledged. Given the small number of black participants in the low-risk reference subgroup (8%), we were unable to determine normative cut-point separately by race. Ascertainment of HF was essentially based on HF hospitalizations, as 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 four-chamber view, although this is the current recommended approach (47), and 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 conclusion, in a large biracial cohort of community-dwelling older adults free of prevalent HF, impairment of LA structure and function is often encountered in approximately 20% of individuals. Novel LA measures are robustly associated with NTproBNP and incident HF or death, regardless of LV function, NTproBNP, and even in participants with normal LA structural measurements by guidelines. Importantly, LA maximal volume, the standard and generally only measure of LA size utilized 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 heart failure (Figure 7) (65).

Figure 7. 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.

References

1. Lloyd-Jones DM, Larson MG, Leip EP, et al., ; Framingham Heart Study. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation. 2002;106:3068–3072.

2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, et al., ; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2013 update: a report from the American Heart Association. Circulation. 2013;127:e6–e245.

3. Shah AM, Claggett B, Kitzman D, et al., . Contemporary Assessment of Left Ventricular Diastolic Function in Older Adults: The Atherosclerosis Risk in Communities Study. Circulation. 2017 Jan 31;135(5):426-439.

4. Gupta S, Matulevicius SA, Ayers CR, et al., . Left atrial structure and function and clinical outcomes in the general population. Eur Heart J 2013;34:278 –285

5. Pellicori P, Zhang J, Lukaschuk E, et al., . Left atrial function measured by cardiac magnetic resonance imaging in patients with heart failure: clinical associations and prognostic value. Eur Heart J. 2015 Mar 21;36(12):733-42.

6. Rossi A, Triposkiadis F, Solomon SD, Pieske B, Butler J. Left Atrium in Heart Failure With Preserved Ejection Fraction Structure, Function, and Significance. Circ Heart Fail. 2014;7:1042-1049

7. Malagoli A, Rossi L, Bursi F, et al., Left Atrial Function Predicts Cardiovascular Events in Patients With Chronic Heart Failure With Reduced Ejection Fraction. J Am Soc Echocardiogr 2019;32:248-56

8. Inciardi, R. M., Giugliano, R. P., Claggett, B., et al., Left atrial structure and function and the risk of death or heart failure in atrial fibrillation. European journal of heart failure, 21(12), 1571–1579.

9. Santos AB, Roca GQ, Claggett B, et al., Prognostic Relevance of Left Atrial Dysfunction in Heart Failure With Preserved Ejection Fraction. Circ Heart Fail. 2016;9:e002763.

10. Morris DA, Belyavskiy E, Aravind-Kumar R, et al., Potential Usefulness and Clinical Relevance of Adding Left Atrial Strain to Left Atrial Volume Index in the Detection of Left Ventricular Diastolic Dysfunction. JACC Cardiovasc Imaging. 2018 Oct;11(10):1405-1415.

11. Potter EL, Ramkumar S, Kawakami H, et al., Association of Asymptomatic Diastolic Dysfunction Assessed by Left Atrial Strain With Incident Heart Failure. JACC Cardiovasc Imaging. 2020 Nov;13(11):2316-2326.

12. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA*. 2003;289:194–202.

13. Hoit BD. Left atrial size and function: role in prognosis. J Am Coll Cardiol. 2014;63:493– 505.

14. Shin SH, Claggett B, Inciardi RM, et al., Prognostic Value of Minimal Left Atrial Volume in Heart Failure with Preserved Ejection Fraction. J Am Heart Assoc 2021;10(15):e019545.

15. Rosca M, Lancellotti P, Popescu BA, Pierard LA. Left atrial function: pathophysiology, echocardiographic assessment, and clinical applications. Heart 2011;97:1982-9

16. Lang RM, Badano LP, Mor-Avi V, et al., 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

17. Messika_Zeitoun D, Bellamy M, Avierinos JF, Breen J et al., Left atrial remodelling in mitral regurgitation methodologic approach, physiological determinants and outcome implications: a prospective quantitative Doppler-echocardiographic and electron beam-computed tomographic study. Eur Heart J 2007;28:1773-81.

18. Keenan NG, Cueff C, Cimadevilla C et al., Usefulness of left atrial volume versus diameter to assess thromboembolic risk in mitral stenosis. Am J Cardiol. 2010;106:1152-6.

19. Tsang TS, Abhayaratna WP, Barnes ME et al., Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? J Am Coll Cardiol. 2006;47:1018-23.

20. Dini FL, Ballo P, Badano L et al., Validation of an echo-Doppler decision model to predict left ventricular filling pressure in patietns with heart failure independently of ejection fraction. Eur J Echocardiography 2010;11:703-10.

21. Kuhl JT, Lonborg J, Fuchs A, et al. Assessment of left atrial volume and function: a comparative study between echocardiography, magnetic resonance imaging and multi slice computed tomography. Int J Cardiovasc Imaging 2012;28:1061–71.

22. Buechel RR, Stephan FP, Sommer G, Bremerich J, Zellweger MJ, Kaufmann BA. Head-to- head comparison of two-dimensional and three-dimensional echocardiographic methods for left atrial chamber quantification with magnetic resonance imaging. J Am Soc Echocardiogr 2013; 26:428–35.

23.Jenkins C, Bricknell K, Marwick TH. Use of real-time three-dimensional echocardiography to
measure left atrial volume: comparison with other echocardiographic techniques. J Am Soc Echocardiogr 2005;18:991–7.

24. Benfari G, Vinco G, Sayegh K, Friedrich M, Rossi A. A New Method to Evaluate Atrial Hemodynamic and Quantify Mitral Regurgitation using Cardiovascular Magnetic Resonance: The Pulmonary Venous Flow Approach. J Heart Valve Dis. 2017 Jul;26(4):456-459.

25. Oakes RS, Badger TJ, Kholmovski EG et al., Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. Circulation. 2009;119:1758-1767

26. Mor-Avi V, Lang RM, Badano LP, et al., Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. J Am Soc Echocardiogr 2011;24:277-313.

27. Vieira MJ, Teixeira R, Goncalves L, Gersh BJ, Left Atrial Mechanics: Echocardiographic Assessment and Clinical Implications. J Am Soc Echocardiogr. 2014 May;27(5):463-78

28. Inciardi RM, Rossi A. Left atrium: a forgotten biomarker and a potential target in cardiovascular medicine. J Cardiovasc Med (Hagerstown). 2019 Dec;20(12):797-808

29. Russo C, Jin Z, Homma S, Rundek T, Elkind MS, Sacco RL, Di Tullio MR. Left atrial minimum volume and reservoir function as correlates of left ventricular diastolic function: impact of left ventricular systolic function. Heart. 2012;98:813-820

30. Laukkanen JA, Kurl S, Eränen J, Huttunen M, Salonen JT. Left atrium size and the risk of cardiovascular death in middle-aged men. Arch Intern Med. 2005 Aug 8-22;165(15):1788-93.

31. Gardin JM, McClelland R, Kitzman D et al. M-mode echocardiographic prdictors of six to seven year incidence of coronary artery disease, stroke, congestive heart failure and mortality in an elderly cohort (the Cardiovascular Health Study). Am J Cardiol 2001;87:1051-17.

32. Tsang TS, Barnes ME, Gersh BJ et al., Prediction of risk for first age-related cardiovascular events in an elderly population: the incremental value of echocardiography J Am Coll Cardiol. 2003;42:1199-205

33. Takemoto Y, Barnes ME, Seward JB et al. Usefulness of left atrial volume in predicting first congestive heart failure in patients > 65 years of age with well-preserved left ventricular systolic function. Am J Cardiol 2005;96:832-36.

34. Habibi M, Chahal H, Opdahl A et al., Association of CMR-measured LA function with heart failure development: results from the MESA study. J Am Coll Cardiol Img 2014;7:570–9.

35. Osranek M, Bursi F, Bailey KR et al. Left atrial volume predicts cardiovascular events in patients originally diagnosed with lone atrial fibrillation : three-decade follow-up. Eur Heart J 2005;26:2556-61.

36. Alsaileek AA, Osranek M, Fatema K, McCully RB, Tsang TS, Seward JB. Predictive value of normal left atrial volume in stress echocardiography. J Am Coll Cardiol. 2006;47:1024-8.

37. Hsiao SH and Chiou KR. Renal function decline predicted by left atrial expansion index in non-diabetic cohort with preserved systolic heart function. European Heart Journal - Cardiovascular Imaging (2017) 18, 521–528

38. Tsang TS, Barnes ME, Bailey KR et al., Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. Mayo Clin Proc. 2001;76:467-75.

39. Osranek M, Fatema K, Qaddoura F et al., Left atrial volume predicts the risk of atrial fibrillation after cardiac surgery: a prospective study. J Am Coll Cardiol. 2006;48:779-86.

40. O'Neal WT, Sandesara P, Patel N, et al., Echocardiographic predictors of atrial fibrillation in patients with heart failure with preserved ejection fraction. European Heart Journal - Cardiovascular Imaging (2017) 18, 725–729

41. 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;92:835-41.

42. Barnes ME, Miyasaka Y, Seward JB et al., Left atrial volume in the prediction of first ischemic stroke in an elderly cohort without atrial fibrillation. Mayo Clin Proc 2004;79:1008-14

43. Wright JD, Folsom AR, Coresh J, et al. The ARIC (Atherosclerosis Risk In Communities) Study: JACC Focus Seminar 3/8. J Am Coll Cardiol. 2021 Jun 15;77(23):2939-2959.

44. Shah AM, Cheng S, Skali H et al., Rationale and design of a multicenter echocardiographic study to assess the relationship between cardiac structure and function and heart failure risk in a biracial cohort of community-dwelling elderly persons: the Atherosclerosis Risk in Communities study. Circ Cardiovasc Imaging. 2014;7:173–181.

45. Alonso A, Agarwal SK, Soliman EZ, et al., . Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J. 2009;158:111–117. doi: 10.1016/j. ahj.2009.05.010.

46. Shah AM, Claggett B, Loehr LR, et al., Heart Failure Stages Among Older Adults in the Community. The Atherosclerosis Risk in Communities Study. Circulation. 2017;135:224–240

47. Badano LP, Kolias TJ, Muraru D, et al., ; Industry representatives; Reviewers: This document was reviewed by members of the 2016–2018 EACVI Scientific Documents Committee. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging. 2018 Jun 1;19(6):591-600.

48. Minamisawa M, Inciardi RM, Claggett B, et al., . Left atrial structure and function of the amyloidogenic V122I transthyretin variant in elderly African Americans. Eur J Heart Fail. 2021 Aug;23(8):1290-1295.

49. Rosamond WD, Chang PP, Baggett C et al., Classification of heart failure in the atherosclerosis risk in communities (ARIC) study: a comparison of diagnostic criteria. Circ Heart Fail. 2012 Mar 1;5(2):152-9.

50. Myhre PL, Claggett B, Ballantyne CM, et al., Association Between Circulating Troponin Concentrations, Left Ventricular Systolic and Diastolic Functions, and Incident Heart Failure in Older Adults. JAMA Cardiol. 2019 Oct 1;4(10):997-1006.

51. Pathan F, D'Elia N, Nolan MT, Marwick TH, Negishi K. Normal Ranges of Left Atrial Strain by Speckle-Tracking Echocardiography: A Systematic Review and Meta-Analysis. J Am Soc Echocardiogr. 2017 Jan;30(1):59-70.e8

52. Badano LP, Muraru D, Parati G. Do we need different threshold values to define normal left atrial size in different age groups? Another piece of the puzzle of left atrial remodelling with physiological ageing. Eur Heart J Cardiovasc Imaging. 2020 May 1;21(5):508-510

53. Rønningen PS, Berge T, Solberg MG, et al., Sex differences and higher upper normal limits for left atrial end-systolic volume in individuals in their mid-60s: data from the ACE 1950 Study. Eur Heart J Cardiovasc Imaging. 2020 May 1;21(5):501-507

54. Thadani SR, Shaw RE, Fang Q, Whooley MA, Schiller NB. Left Atrial End-Diastolic Volume Index as a Predictor of Cardiovascular Outcomes: The Heart and Soul Study. Circ Cardiovasc Imaging. 2020;13:e009746.

55. Chirinos JA, Sardana M, Ansari B, et al., Left Atrial Phasic Function by Cardiac Magnetic Resonance Feature Tracking Is a Strong Predictor of Incident Cardiovascular Events. Circ Cardiovasc Imaging. 2018 Dec;11(12):e007512

56. Marrouche NF, Wilber D, Hindricks G, et al., Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA 2014; 311:498–506.

57. Triposkiadis F, Pieske B, Butler J, Parissis J, Giamouzis G, Skoularigis J. Global left atrial failure in heart failure. Eur J Heart Fail 2016;18:1307–1320.

58. Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left Atrial Structure and Function, and Left Ventricular Diastolic Dysfunction: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019 Apr 23;73(15):1961-1977.

59. Bisbal F, Baranchuk A, Braunwald E, Bayés de Luna A, Bayés-Genís A. Atrial Failure as a Clinical Entity: JACC Review Topic of the Week. J Am Coll Cardiol. 2020 Jan 21;75(2):222-232

60. Shen MJ, Arora R, Jalife J. Atrial Myopathy. JACC Basic Transl Sci. 2019 Sep 23;4(5):640-654

61. Inciardi RM, Rossi A, Bergamini C, et al., . Mitral regurgitation, left atrial structural and functional remodelling and the effect on pulmonary haemodynamics. Eur J Heart Fail. 2020 Mar;22(3):499-506.

62. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circ Heart Fail. 2015 Mar;8(2):295-303.

63. Thomas L, Abhayaratna WP. Left atrial reverse remodeling mechanisms, evaluation, and clinical significance. JACC Cardiovasc Imaging 2017;10:65–77.

64. Inciardi RM, Bonelli A, Biering-Sorensen T, Cameli M, Pagnesi M, Lombardi CM, Solomon SD, Metra M. Left atrial disease and left atrial reverse remodelling across different stages of heart failure development and progression: a new target for prevention and treatment. Eur J Heart Fail. 2022 Jun;24(6):959-975

65. Inciardi RM, Claggett B, Minamisawa M, Shin SH, Selvaraj S, Gonçalves A, Wang W, Kitzman D, Matsushita K, Prasad NG, Su J, Skali H, Shah AM, Chen LY, Solomon SD. Association of Left Atrial Structure and Function With Heart Failure in Older Adults. J Am Coll Cardiol. 2022 Apr 26;79(16):1549-1561.