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ORIGINAL RESEARCH

Left Atrial Remodeling and Stroke in Patients With Sinus Rhythm and Normal Ejection Fraction: ARIC-NCS

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BACKGROUND: Age-related left atrial (LA) structural and functional abnormalities may be related to subclinical cerebral infarcts (SCIs) and stroke. We evaluated the association of 3-dimensional echocardiographic LA contractility parameters with SCIs and stroke across the spectrum of tertiles of age increment in elderly patients with sinus rhythm, normal ejection fraction, and no history of atrial fibrillation.

METHODS AND RESULTS: We enrolled 407 participants (mean age, 76±8 years; 40% men) from ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study) undergoing a brain magnetic resonance imaging and 3-dimensional echocardiographic examinations in 2011 to 2013. The sample was analyzed among age tertiles and subgroups: no cerebral magnetic resonance imaging–detectable infarcts (n=315), magnetic resonance imaging–diagnosed SCIs (n=58), and clinically diagnosed stroke (n=34). The frequency of SCIs significantly increased over age tertiles (*P* trend 0.023). LA global longitudinal strain—a 3-dimensional echocardiographic index of LA reservoir function—and E/e' divided by LA global longitudinal strain—an index of LA stiffness—worsened across age tertiles (*P* trend 0.014 and 0.001, respectively), and only in the categories of SCIs (*P* trend <0.001 and 0.045, respectively) and stroke (*P* trend 0.001 and 0.011, respectively). LA global longitudinal strain was negatively associated with increased odds of SCIs (*P*=0.036, *P*=0.008, and *P*=0.001, respectively) and strokes (*P*=0.043, *P*=0.015, and *P*=0.001, respectively) over age tertiles, with a significant interaction between age tertiles (interaction *P*=0.043 and *P*=0.010, respectively). E/e' divided by LA global longitudinal strain was positively associated with the presence of SCIs (*P*=0.037, *P*=0.007, and *P*=0.001, respectively) and strokes (*P*=0.045, *P*=0.007, and *P*=0.003, respectively) over age tertiles, with a significant interaction only for SCIs (interaction *P*=0.040) and not for clinical stroke.

CONCLUSIONS: In a large cohort study of elderly patients, among participants with sinus rhythm, normal ejection fraction, and no history of atrial fibrillation, measures of worse age-related LA reservoir function and stiffness are associated with higher odds of SCIs and stroke.

Key Words: 3-dimensional echocardiography ■ left atrial function ■ left atrial stiffness ■ left atrial strain ■ subclinical cerebral infarctions

Stroke is a well-recognized health problem that affects ≈795 000 people every year and accounts for 1 in 20 deaths in the United States.[1] Changes in left atrial (LA) structure and function are well-recognized factors that contribute to the development of atrial fibrillation (AF), heart failure (HF),[2] and ischemic

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CLINICAL PERSPECTIVE

What Is New?

- The pathophysiology of cardioembolic stroke classically implies left atrial (LA) clot formation, and embolization, only in the presence of atrial fibrillation or reduced left ventricular ejection fraction.
- We demonstrated that in elderly patients, LA stiffness and reservoir function impairment is likely sufficient in LA clot formation and cerebral embolization.

What Are the Clinical Implications?

- These findings suggest the brain is an organ at risk for subclinical cerebral infarcts caused by LA senescence, raising the hypothesis that minor forms of LA dysfunction, early detectable by 3-dimensional echocardiography, may cause LA blood stasis.
- As a clinical prospective, LA global longitudinal strain routine assessment could serve as an early marker of atrial senescence and guide anticoagulation therapy, even in the absence of atrial fibrillation.

Nonstandard Abbreviations and Acronyms

3DE	3-dimensional echocardiography
ARIC	Atherosclerosis Risk in Communities
GLS	global longitudinal strain
LAV	left atrial volume
SCI	subclinical cerebral infarct

stroke.[3,4] Only 0.2% to 0.4% of cerebral thromboembolic events are clinically apparent; the majority are asymptomatic, and thus defined as subclinical cerebral infarcts (SCIs).[5] The presence of SCIs is associated with more severe stroke later in life.[5,6]

Approximately 25% of ischemic strokes are caused by cardioembolism, with the most common mechanism being AF.[1,7] Blood stasis in the left atrium from AF increases the risk of thromboembolism secondary to clot formation.[3,4] Changes in LA structure and function (conduit, reservoir, and pump) can be related to several conditions, including amyloidosis and other cardiomyopathies,[8,9] but LA remodeling may also occur as a result of aging and in the presence of age-related comorbidities, such as increased vascular stiffness, longstanding hypertension, and HF with preserved ejection fraction (EF).[2]

Speckle tracking echocardiography has recently emerged as a quantitative technique to estimate myocardial function by the analysis of the motion of speckles in 2-dimensional ultrasound images. This technique allows a non-Doppler angle-independent objective analysis of myocardial deformation, with the possibility to quantify the thickening, shortening, and rotation dynamics of the heart muscle.[10] A specific application of speckle tracking echocardiography, the LA global longitudinal strain (GLS), measures LA reservoir function and LA stiffness—the ratio of mitral inflow E/e' to LA (GLS) and LA EF—seems to lessen with age.[11,12]

Therefore, we hypothesized that age-related alterations in LA structure and function (reservoir and stiffness, in particular) in individuals with sinus rhythm and normal EF would be associated with SCIs and clinical stroke independently from the presence and history of AF. So, we aimed at assessing whether LA remodeling and impairment in contractility, detected by 3-dimensional echocardiography (3DE) and observed across the spectrum of tertiles of age increments, are associated with SCIs and clinical stroke among participants with normal EF, in sinus rhythm, and with no history of AF in the large cohort of ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study).

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files.

Study Population and Design

From 1987 to 1989, the ARIC (Atherosclerosis Risk in Communities) study enrolled and examined 15 792 men and women aged 45 to 64 years recruited from 4 communities in the United States (Forsyth County, NC; Jackson, MS; Minneapolis suburbs, MN; and Washington County, MD). Participants were mostly of White race in the Minneapolis and Washington County sites, of White and Black race in Forsyth County, and only of Black race in Jackson. After their baseline examination, participants underwent follow-up visits in 1990 to 1992, 1993 to 1995, 1996 to 1998, 2011 to 2013, 2016 to 2017 (visits 2–6), and 2018 to 2019 (visit 7). Participants have since then been followed up via annual phone calls (semiannual since 2012).[13]

A detailed rationale of the study design and procedures has been previously published.[14] Of 6538 participants seen at visit 5 (2011–2013), 1906 participants underwent brain magnetic resonance imaging (MRI) examination. Of these, 1184 underwent a 3DE examination and were considered for this study. Patients were randomly selected for the examinations

mentioned above. Of these 1184 participants, we included patients in sinus rhythm, without history of AF or atrial flutter, and with normal EF (≥50%) on visit 5 transthoracic echocardiogram, excluding participants with insufficient 3DE image quality (n=336) (Table S1). We also excluded 777 participants: 207 presenting with moderate or severe valvular regurgitation and 170 with valvular stenoses. Previous surgery for valve replacement was also considered an exclusion criterion (n=64).

The history of AF or atrial flutter was ascertained from hospitalization discharge records during follow-up (from visit 3–5), or by an ECG performed during any ARIC study visit, including visit 5.[15] Ultimately, a total of 407 participants constituted the sample for the present analysis. A flow chart of the patient selection in the study is presented in Figure S1.

The institutional review board of each center approved the ARIC study protocol and informed consent was obtained from every participant.

Variable Definitions

SCIs and Stroke

At each field center, brain MRI was performed on 3-Tesla Siemens scanners (various models) using a common, and also recommended,[16] set of sequences that included 3-dimensional volumetric magnetization-prepared gradient echo and fluid-attenuated inversion recovery (diffusion-weighted imaging, fluid-attenuated inversion recovery MRI, and T2-weighted imaging). SCIs were defined as focal, nonmass, and nonlacunar lesions of ≥3 mm, bright on T2-weighted sequences and dark on T1-weighted images.[14] The infarcts were identified, measured, and counted by a trained imaging technician and confirmed by radiologists as previously described.[17]

Stroke was adjudicated by a panel of physicians based on diagnosis of stroke from hospital records and death certificates using validated criteria from the National Survey of Stroke by the National Institute of Neurological Disorders and Stroke classification and supported by a computerized algorithm.[18] In this study, we evaluated ischemic stroke.

Echocardiography

Methods for conventional and 3DE acquisition and quantitative analysis, including reproducibility metrics, have been previously reported.[19,20] All echocardiograms were performed using dedicated Philips iE33 Ultrasound systems with Vision 2011; each examination was performed using an X3-1 iE33 transducer (Philips Medical Systems). Images were transferred to the Echocardiography Reading Center at the Brigham and Women's Hospital, Boston, MA, where echocardiographic measures were performed and over-read, blinded to the clinical characteristics of participants. Conventional echocardiographic measures including left ventricular (LV) linear dimensions and volumes, LV EF, LA parasternal linear dimensions, and right ventricular functional parameters were measured according to the recommendations from the American Society of Echocardiography guidelines.[21] Deformation analysis, including 3-dimensional LA strain measurements, were measured using semiautomated quantification software 4-dimensional left ventricle analyses 2.0 (TomTec Imaging Systems), as previously described.[2]

Three-Dimensional LA Analysis

The 3DE acquisition protocol and analysis have been previously described in detail.[2] In the 3-dimensional real-time data sets, the TomTec software automatically selects the 2-, 3-, and 4-chamber views, from 4 consecutive cardiac cycles, and then detects the blood-tissue interface with an offline contour-tracking algorithm. Where required, a manual adjustment was also systematically applied. The LA appendage and the pulmonary veins orifices were excluded from the tracing. LA endocardial surface was reconstructed throughout the cardiac cycle, resulting in a dynamic cast of LA cavity. For each consecutive frame, the voxel count inside the 3-dimensional surface was used to measure LA volume (LAV), resulting in a smooth interpolated LAV time curve allowing detection of the maximal (LAV max) and minimal (LAV min) LAVs. In this way, LA EF and stroke volume, two measures of LA contractile function, were assessed.

LA emptying fraction, an estimate of LA reservoir function, was calculated as ([LAV max–LAV min]/LAV max×100), while LA conduit volume was assessed by the following formula: LV stroke volume–(LAV max–LAV min).[4] In addition, 3DE LA speckle-tracking analysis was automatically performed throughout the cardiac cycle, using the P wave as the reference point, with measurements of LA GLS as a surrogate of LA reservoir function. The ratio of mitral inflow E/e' to LA GLS and LA EF was used to estimate LA stiffness.[12]

Image quality was judged based on stitch/artifacts ratio and quality resolution of LA segments throughout the whole cardiac cycle. In the presence of stitching artifacts or dropout of >2 LA segments, the image was excluded from analysis. 3DE LAV measurements were repeated in a randomly selected group of 40 participants by 2 additional investigators at least 1 month later, both blinded to the results of all previous measurements.[2]

Other Variables

The ARIC staff obtained baseline demographic data, medication use, and medical history from the participants during visit 5.[22] We included in our analysis age, sex, race, body mass index, body surface area (according to the Du Bois formula: body surface area m^2=0.007184×(height (cm) 0.725×weight (kg) 0.425)), CHA_2DS_2-VASc score, cigarette smoking status, presence of coronary heart disease, HF with preserved EF, diabetes, use of antihypertensive, antiplatelet and anticoagulant drugs, systolic and diastolic blood pressure, and blood biomarkers.

The definition of HF with preserved EF was based on a prior history of hospitalization for HF or a self-reported physician diagnosis of HF or HF medication use at visit 5 and an LV EF ≥50% by visit 5 echocardiogram.[9] The use of HF medications was obtained by asking cohort patients whether they had taken HF medications in the 2 weeks before the study visit.[9]

Myocardial infarction was defined based on the presence of adjudicated events according to previously published criteria.[23] Body mass index was defined as weight/(height)^2 (in kilograms per squared meters). Diabetes was defined as a fasting (minimum of 8 hours) glucose level ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, self-reported use of oral hypoglycemic agents or insulin, or self-reported physician diagnosis of diabetes. Smoking status was self-reported. Participants were classified as current smokers and noncurrent smokers.[22]

Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or medication being taken for high blood pressure during the past 2 weeks before the visit. Total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were measured in a centralized laboratory.[24] NT-pro BNP (N-terminal pro-B-type natriuretic peptide) was measured using electrochemiluminescent immunoassay (Roche Diagnostics) with a lower detection limit of 5 pg/mL.[2,25] Concentrations of high-sensitivity cardiac troponin were measured with a high-sensitivity sandwich immunoassay from stored plasma samples (–80°C) drawn at visits 2, 4, and 5. The samples were analyzed at the University of Minnesota (Minneapolis) and Baylor College of Medicine (Houston, TX) using a high-sensitivity assay (Elecsys Troponin T; Roche Diagnostics) on an automated analyzer (Cobas e411; Roche Diagnostics).[25] The limit of detection for high-sensitivity cardiac troponin T level was 5 ng/L, and the limit of blank was 3 ng/L.[26] Estimated glomerular filtration rate was calculated based on circulating creatinine and cystatin C levels using the Chronic Kidney Disease Epidemiology Collaboration formula.[27]

Statistical Analysis

We analyzed the sample across the spectrum of tertiles of age increments (age tertile 1=68±2 years, age tertile 2=76±2 years, and age tertile 3=83±3 years), and then categorized participants into 3 groups: group 1 (n=315) consisted of those with no cerebral infarcts on brain MRI scans and without previous history of stroke; group 2 (n=58) consisted of those without clinical history of stroke but with MRI evidence of SCI; and group 3 (n=34) consisted of participants with both a history of clinical stroke as well as MRI evidence of cerebral infarcts.

Categorical values are expressed as absolute number and percentage, while continuous variables are expressed as mean±SD or median and interquartile intervals (quartile 1–quartile 3), as appropriate. Mean values of echocardiographic characteristics and corresponding SEs are presented according to tertiles of age increment and cerebral infarcts, after adjusting for sex, race, body mass index, body surface area, comorbidities, and medications. Comorbidities included hypertension, diabetes, previous myocardial infarction, and renal function. Medications included the use of anticoagulants, antiplatelet agents, β-blockers, and loop diuretics. Statistical comparisons across age tertiles and types of cerebral infarcts (no cerebral infarcts, SCIs, and stroke––all of the possible phenotypes of ischemic cerebral infarcts) were made with linear regression and chi-square tests for trend.

We used a stepwise ordered multivariable logistic regression (forward adding all of the variables with a P<0.05) to estimate the odds ratios (ORs) and 95% CIs of both clinical and echocardiographic variables for 2 outcomes: (1) MRI-determined SCIs, and (2) clinically diagnosed stroke. Covariates were selected based on their potential relationship with SCIs and strokes, stratified for age tertiles. All of the potentially relevant covariates[2,5,8,11,12] that showed statistically significant associations (P<0.05) on the trend test were included in the models: sex, race, body surface area, body mass index, blood pressure, heart rate, hypertension, previous myocardial infarction, diabetes, renal function, NT-proBNP, troponin levels, use of anticoagulants and antiplatelet agents, CHA_2DS_2-VASc score, and relevant echocardiographic parameters (LV indexed volumes and linear measures, EF, LV mass index, diastolic function parameters, and all of the LA structure and function parameters). The interaction term for outcomes (SCIs and stroke) between age tertiles and predictors were then assessed through a logistic regression model.

All statistical analyses were performed with Stata version 14.1 (StataCorp LLC). P values <0.05 were considered statistically significant.

RESULTS

Participant Characteristics

The final analytic sample consisted of 407 ARIC participants (mean age, 76±8 years; 40% men). More than half were women (60%) and 21% were of Black race. Hypertension was present in more than two thirds of the sample and diabetes in approximately one third, while 63% of patients were current smokers. A total of 26 (6%) patients had HF with preserved EF; its frequency slightly increased across the age tertiles but not to a statistically significant level. Aspirin was the antiplatelet agent in our sample, with 69% of patients being current users; only 2% were taking anticoagulants and almost half were on statin treatment.

Demographic and clinical characteristics stratified by age tertiles are presented in Table 1. Age distribution among tertiles was age tertile 1=68±2 years (n=136), age tertile 2=76±2 years (n=136), and age tertile 3=83±3 years (n=135). The frequency of SCIs significantly increased over age tertiles (*P* trend 0.023), while no increase was found with respect to clinical stroke (Figure S2). As expected, and even if in sinus rhythm, patients of older ages had a higher CHA_2DS_2-VASc score (*P* trend <0.001), higher blood pressure values (*P* trend<0.001), and reduced estimated glomerular filtration rate (*P* trend <0.001). Significant trend differences were also found with respect to troponin and NT-proBNP levels (both *P* trend=0.001) (Table 1).

Echocardiographic Characteristics

After adjustments, LV end-systolic and end-diastolic diameters and end-diastolic volume diminished in those of older ages (*P* trend=0.005, 0.002, and 0.012, respectively), even when volumes were indexed (*P* trend=0.01 and 0.004) (Table 2). Similarly, the interventricular septum thickness and LV relative wall thickness were greater in age tertile 3 than age tertiles 2 and 1 (*P* trend 0.024 and 0.004, respectively). The E/e' ratio increased through the age tertiles, while there was no statistically significant trend difference in LV EF according to age increment.

Adjusted mean 2-dimensional echocardiographic and 3DE characteristics according to age tertiles and cerebral infarcts subgroups phenotypes (SCI and stroke) are presented in Table 3. In the SCI group, the E/e' ratio significantly increased according to tertiles of age increment (*P* trend *P*<0.001), while in the stroke group, along with E/e' ratio growth, we also observed an LV relative wall thickness increase from age tertile 1 to 3 (*P*=0.015 and *P*=0.042, respectively). No differences were found regarding LV volumes and linear dimensions, LV EF, and diastolic function (E/A and E/e' ratio) in the no cerebral infarcts subgroups (Table S2).

LA Structural and Functional Characteristics

LA structural and functional parameters are presented in Tables 2 and 3; all values are shown after adjustments. While still within the normal range (≤34 mL/m^2),[21] LA indexed volume significantly increased across age tertiles in the SCIs group (*P* trend=0.003). This was accompanied by a decrease in LA EF and emptying fraction (*P* trend=0.008 and 0.009, respectively). No differences were found regarding the abovementioned 3DE parameters in the clinical stroke group.

LA GLS—a 3DE index of LA reservoir function—decreased across age tertiles (*P* trend 0.014) and worsened across both SCIs and stroke groups (*P* trend <0.001 and 0.045, respectively) (Figure), while E/e' divided by LA GLS—an index of LA stiffness—increased among age tertiles (*P* trend 0.001) and was progressively impaired over SCIs and stroke groups (*P* trend=0.001 and 0.011, respectively) (Tables 2 and 3). No differences were found regarding the abovementioned 3DE parameters in the no cerebral infarcts group (Table S1).

Outcome Analysis

The results of multivariable analysis are shown in Table 4. NT-proBNP (per 1 ng/L) and CHA_2DS_2-VASc score (per 1 point) were both significantly associated with increased odds of SCIs, while the latter variables plus high-sensitivity troponin T (per 1 ng/mL) with stroke.

LA GLS was negatively associated with increased odds of SCIs (*P*=0.036, *P*=0.008, and *P*=0.001, respectively) and strokes (*P*=0.043, *P*=0.015, and *P*=0.001, respectively) among age tertiles, with a significant interaction between age tertiles (interaction *P*=0.043 and *P*=0.010, respectively). E/e' divided by LA GLS was positively associated with the presence of SCIs (*P*=0.037, *P*=0.007, and *P*=0.001, respectively) and strokes (*P*=0.045, *P*=0.007, and *P*=0.003, respectively) over age tertiles, with a significant interaction only for SCIs (interaction *P*=0.040) and not for clinical stroke.

DISCUSSION

In the present analysis of the ARIC-NCS, among elderly participants who were in sinus rhythm, with normal EF (≥50%) and no history of AF, we observed an increased frequency of MRI-diagnosed SCIs across tertiles of age increment. After adjustments for potential confounders, we also observed that changes in atrial reservoir function and stiffness significantly worsened across the spectrum of cerebral infarcts phenotypes, from SCIs to stroke. In addition, these echocardiographic

Table 1. Clinical Characteristics of Study Participants According to Age Tertiles: the ARIC-NCS, 2011 to 2013

General characteristics	Total N=407	Age tertile 1 n=136	Age tertile 2 n=136	Age tertile 3 n=135	*P* for trend
Age, y	76±8	68±2	76±2	83±3	0.001*
SCIs, n (%)	58 (15)	14 (12)	17 (13)	27 (22)	0.023*
Stroke, n (%)	34 (10)	15 (12)	6 (5)	13 (12)	0.89
White race, n (%)	323 (79)	99 (73)	110 (81)	114 (84)	0.018*
Men, n (%)	165 (40)	56 (41)	56 (41)	53 (39)	0.75
Heart rate, beats per min	61±10	62±9	60±11	60±10	0.11
Systolic blood pressure, mm Hg	133±19	128±19	135±18	136±18	0.001*
Diastolic blood pressure, mm Hg	67±10.4	68±10	68±10	64±10	0.001*
CHA_2DS_2-VASc score	4 (3–4)	3 (3–4)	4 (3–4)	6 (5–7)	0.001*
Height, cm	165±9	166±9	165±9	163±8	0.008*
Weight, kg	75±15	77±16	75±15	71±14	0.001*
BMI, kg/m^2	27±5	28±5	27±5	26±5	0.020*
Previous myocardial infarction, n (%)	21 (5)	7 (5)	7 (5)	7 (5)	0.94
HF with preserved EF, n (%)	26 (6)	7 (5)	8 (6)	11 (8)	0.31
Diabetes, n (%)	152 (37)	54 (40)	51 (37)	47 (35)	0.41
Hypertension, n (%)	334 (82)	103 (76)	111 (82)	120 (90)	0.005*
Current and former smoker, n (%)	255 (63)	83 (61)	91 (67)	81 (60)	0.86
Chronic kidney disease, n (%)	26 (6.3)	7 (5)	8 (6)	11 (8)	0.31
Blood samples					
eGFR	75±19	80.7±17.2	72.9±20.3	72±20	0.001*
Total cholesterol, mg/dL	180±41	183.8±42.4	182.0±42.7	175±38	0.08
LDL, mg/dL	103±33	106.3±34.0	105.4±33.7	98±33	0.06
HDL, mg/dL	52±14	52.4±13.8	52.5±15.1	52±13	0.88
Triglycerides, mg/dL	124±58	129.5±64.7	120.9±55.0	123±54	0.33
Glucose, mg/dL	113±33	116.3±41.2	112.9±30.4	111±26	0.16
Creatinine, mg/dL	1±0.4	0.9±0.2	1±0.5	1±0.3	0.07
hs-CRP, mg/dL	1.6 (0.8–3.5)	1.7 (0.7–3.2)	1.5 (0.8–3.8)	1.8 (1–3.8)	0.27
High-sensitivity troponin T, ng/mL	1 (0.7–1.5)	0.8 (0.5–1.3)	1 (0.7–1.4)	1.2 (0.8–1.7)	0.001*
NT-proBNP, ng/L	131 (70–233)	79 (45–135)	132 (69–240)	192 (121–344)	0.001*
Medications					
Statins, n (%)	193 (48)	66 (48)	63 (47)	64 (48)	0.90
Anticoagulants, n (%)	9 (2)	4 (3)	3 (2)	2 (1)	0.42
Aspirin, n (%)	279 (69)	88 (65)	89 (66)	102 (76)	0.043*
β-blockers, n (%)	110 (27)	41 (30)	32 (24)	37 (28)	0.64
Antiangiotensin II, n (%)	42 (10)	8 (6)	11 (8)	23 (17)	0.002*
ACEI, n (%)	88 (22)	23 (17)	36 (27)	29 (22)	0.34
Loop diuretics, n (%)	36 (9)	15 (11)	13 (9)	8 (6)	0.15

Data are described as mean (±SD) or median (quartile 1–quartile 3) for quantitative variables, and counts (proportions) for categorical variables. ACEI indicates angiotensin-converting enzyme inhibitor; ARIC-NCS, Atherosclerosis Risk in Communities Neurocognitive Study; BMI, body mass index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and SCIs, subclinical cerebral infarcts.

*Denotes statistcally significant differences across groups for the selected variable.

indices were significantly associated with increased odds of SCIs and stroke, demonstrating a significant interaction with age for SCIs.

Traditionally, the pathophysiology of cardioembolic stroke implies the presence of AF[28] and a structurally abnormal or dilated atrium producing blood stasis and thrombus formation, in accordance with the Virchow triad.[7] In this regard, previous studies have demonstrated that abnormal P-wave axis and prolonged P-wave duration (ECG surrogates of LA abnormality) are associated with an increased risk of AF[29] and cerebrovascular events.[25] In addition, Cogswell et al[8] recently reported an increased prevalence

Table 2. Adjusted Mean 2DE and 3DE Characteristics According to Age Tertiles: ARIC-NCS, 2011 to 2013

	Total	Age tertile 1	Age tertile 2	Age tertile 3	*P* for trend
	N=407	n=136	n=136	n=135	
2DE					
LV dimensions and function					
LV end-diastolic diameter, cm	4.3±0.50	4.42 (0.04)	4.32 (0.04)	4.24 (0.04)	0.005*
LV end-systolic diameter, cm	2.5±0.40	2.55 (0.04)	2.47 (0.04)	2.37 (0.04)	0.002*
Interventricular septum thickness, cm	1.1±0.20	1.04 (0.01)	1.09 (0.01)	1.10 (0.01)	0.024*
Posterior wall thickness, cm	0.9±0.10	0.88 (0.01)	0.95 (0.01)	0.92 (0.01)	0.05
LV end-diastolic volume, mL	83±23	86 (1.64)	82 (1.50)	80 (1.60)	0.012*
LV end-systolic volume, mL	27±11	28 (0.84)	27 (0.77)	26 (0.82)	0.06
LV end-diastolic volume indexed, mL/m^2	45±11	47 (0.91)	45 (0.83)	44 (0.89)	0.011*
LV end-systolic volume indexed, mL/m^2	15±50	15 (0.46)	14 (0.42)	14 (0.45)	0.06
LV EF, %	67±50	67 (0.51)	67 (0.56)	67 (0.58)	0.71
LV mass, g	146±43	144 (3.30)	151 (30)	144 (3.20)	0.93
LV mass index, g/m^2	80±19	79 (1.80)	83 (1.60)	78 (1.80)	0.76
LV relative wall thickness, cm	0.43±0.08	0.40 (0.01)	0.44 (0.01)	0.44 (0.01)	0.004*
LV diastolic function					
E/A ratio	0.9±0.30	0.96 (0.03)	0.87 (0.03)	0.90 (0.03)	0.20
E/e' ratio, average	12±40	10 (0.40)	11 (0.36)	12 (0.39)	0.004*
Deceleration time, ms	216±46	210 (4.70)	220 (4.30)	222 (4.60)	0.07
3DE					
LAVs					
LA maximal volume, mL	61±20	60 (1.60)	59 (1.50)	61 (1.60)	0.61
LA minimum volume, mL	29±12	27 (1.00)	28 (0.91)	30 (0.99)	0.08
LA maximal volume indexed, mL/m^2	33±90	33 (0.90)	32 (0.87)	33 (0.88)	0.78
LA minimum volume indexed, mL/m^2	16±60	15 (0.50)	15 (0.54)	16 (0.59)	0.16
LA contractile function					
LA stroke volume indexed, mL/m^2	18±60	18 (0.60)	17 (0.66)	17 (0.69)	0.48
LA EF, %	53±11	54 (1.20)	52 (1.01)	52 (1.10)	0.13
LA emptying fraction, %	0.5±0.10	0.54 (0.01)	0.52 (0.01)	0.51 (0.01)	0.13
LA reservoir function					
LA GLS, %	19±60	21 (0.60)	19 (0.66)	18 (0.68)	0.014*
LA expansion index	125±59	138 (6.10)	122 (5.60)	118 (6)	0.040*
LA conduit function					
LA emptying volume, mL	32±12	33 (1.20)	31 (1.10)	31 (1.20)	0.47
LA conduit volume, mL	15±80	6 (0.30)	11 (0.34)	4 (0.36)	0.64
LA stiffness					
E/e' divided by LA GLS	0.63±0.50	0.52 (0.04)	0.61 (0.04)	0.72 (0.04)	0.001*
E/e' divided by LA EF	0.20±0.20	0.19 (0.01)	0.21 (0.01)	0.24 (0.01)	0.018*

Overall characteristics are described as mean (±SD); after-adjustments variables according to cerebral infarcts are presented as mean (SE). All *P* values are adjusted for sex, race, body surface area, body mass index, blood pressure, heart rate, previous myocardial infarction, hypertension, diabetes, renal function, NT-proBNP (N-terminal pro-B-type natriuretic peptide)—troponins levels, anticoagulants usage, and antiplatelet agents. Age tertile 1=68±2 years, age tertile 2=76±2 years, and age tertile 3=83±3 years. 2DE indicates 2-dimensional echocardiography; 3DE, 3-dimensional echocardiography; ARIC-NCS, Atherosclerosis Risk in Communities Neurocognitive Study; EF, ejection fraction; GLS, global longitudinal strain; LA, left atrial; LAV, left atrial volume; and LV, left ventricular.

*Denotes statistcally significant differences across groups for the selected variable.

of SCIs among ARIC participants in the presence HF and sinus rhythm, while Sugimoto and colleagues[12] showed that LA reservoir function and stiffness modified with age.

Cardiac senescence is a complex process and is partially driven by age-related comorbidities such as long-standing hypertension, vascular stiffness, and HF.[2,30] Remodeling of cardiac chambers caused by aging[31] involves both LA electrical remodeling and enlargement, and this increase in LA dimension has been demonstrated to be a robust and well-established

Table 3. Adjusted Mean 2DE and 3DE Characteristics According to Tertiles of Age and Cerebral Infarcts Phenotypes: the ARIC-NCS, 2011 to 2013

	Total	Age tertile 1	Age tertile 2	Age tertile 3	*P* for trend
Subclinical cerebral infarct	N=58	n=20	n=19	n=19	
LV dimensions and function					
LV end-diastolic diameter, cm	4.35±0.52	4.28 (0.04)	4.32 (0.04)	4.31 (0.04)	0.55
LV end-systolic diameter, cm	2.59±0.50	2.46 (0.04)	2.46 (0.04)	2.40 (0.04)	0.28
LV end-diastolic volume indexed, mL/m^2	49±12	45 (0.84)	44 (0.84)	44 (0.85)	0.47
LV end-systolic volume indexed, mL/m^2	18±70	15 (0.40)	14 (0.40)	14 (0.40)	0.39
LV relative wall thickness	0.45±0.10	0.42 (0.01)	0.44 (0.01)	0.45 (0.01)	0.35
LV EF, %	67±50	67 (0.50)	68 (0.50)	68 (0.50)	0.36
E/e' ratio, average	11±40	9 (0.39)	11 (0.41)	12 (0.45)	0.001*
LAVs					
LA maximal volume indexed, mL/m^2	36±12	31 (0.92)	32 (0.95)	35 (0.96)	0.003*
LA minimum volume indexed, mL/m^2	17±10	14 (0.55)	16 (0.57)	17 (0.58)	0.001*
LA contractile function					
LA stroke volume indexed, mL/m^2	19±65	17 (0.61)	17 (0.64)	17 (0.67)	0.66
LA EF (%)	54±14	55 (10)	52 (20)	51 (30)	0.008*
LA emptying fraction, %	54±0.14	55 (0.01)	51 (0.01)	50 (0.01)	0.009*
LA reservoir function					
LA GLS, %	21±66	21 (0.60)	19 (0.62)	17 (0.63)	0.001*
LA expansion index	138±76	134 (5.50)	119 (5.44)	114 (5.56)	0.009*
LA conduit function					
LA emptying volume, mL	35±14	31 (1.00)	31 (1.12)	32 (1.50)	0.70
LA conduit volume, mL	15±80	6 (0.32)	11 (0.35)	4 (0.38)	0.64
LA stiffness					
E/e' divided by LA GLS	0.58±0.37	0.53 (0.04)	0.60 (0.04)	0.81 (0.04)	0.001*
E/e' divided by LA EF	0.22±0.16	0.18 (0.01)	0.22 (0.01)	0.26 (0.01)	0.001*
Stroke	**n=34**	**n=12**	**n=11**	**n=11**	
LV dimensions and function					
LV end-diastolic diameter, cm	4.54±0.58	4.57 (0.19)	4.46 (0.20)	4.58 (0.19)	0.96
LV end-systolic diameter, cm	2.58±0.54	2.62 (0.17)	2.72 (0.18)	2.39 (0.18)	0.35
LV end-diastolic volume indexed, mL/m^2	50±15	50 (51)	52 (53)	47 (58)	0.72
LV end-systolic volume indexed, mL/m^2	17±80	17 (2.60)	19 (2.70)	15 (2.60)	0.52
LV relative wall thickness	0.46±0.10	0.44 (0.09)	0.46 (0.01)	0.50 (0.01)	0.042*
LV EF, %	67±50	66 (1.74)	65 (1.75)	69 (1.77)	0.31
E/e' ratio, average	10±50	8 (1.52)	9 (1.65)	14 (1.57)	0.015*
LAVs					
LA maximal volume indexed, mL/m^2	35±90	34 (30)	34 (32)	38 (33)	0.32
LA minimum volume indexed, mL/m^2	16±60	14 (1.92)	16 (1.95)	18 (1.99)	0.19
LA contractile function					
LA stroke volume indexed, mL/m^2	19±60	20 (20)	17 (21)	20 (23)	0.72
LA EF (%)	54±12	57 (3.50)	51 (3.61)	54 (3.66)	0.54
LA emptying fraction, %	54±0.12	57 (0.03)	52 (0.04)	53 (0.03)	0.47
LA reservoir function					
LA global longitudinal strain, %	20±70	23 (0.52)	20 (1.50)	18 (20)	0.045*
LA expansion index	129±50	145 (15)	115 (15)	126 (15)	0.40
LA conduit function					
LA emptying volume, mL	37±13	37 (40)	34 (43)	39 (46)	0.76

(Continues)

Table 3. Continued

	Total	Age tertile 1	Age tertile 2	Age tertile 3	*P* for trend
LA conduit volume, mL	15±80	6 (0.25)	11 (0.35)	4 (0.37)	0.64
LA stiffness					
E/e' divided by LA GLS	0.68±0.68	0.41 (0.19)	0.48 (0.20)	1.18 (0.20)	0.011*
E/e' divided by LA EF	0.21±0.13	0.16 (0.04)	0.19 (0.04)	0.28 (0.04)	0.048*

Total characteristics are described as mean (±SD); after-adjustments variables according to cerebral infarcts are presented as mean (SE). All of the *P* values are adjusted for age, sex, race, body surface area, body mass index, heart rate, blood pressure, NT-proBNP (N-terminal pro-B-type natriuretic peptide)—troponins levels, previous myocardial infarction, hypertension, diabetes, renal function, anticoagulants usage, and antiplatelet agents. Subclinical cerebral infarcts: age tertile 1=68±1 years, age tertile 2=76±1 years, and age tertile 3=82±3 years. Stroke: age tertile 1=68±1 years, age tertile 2=76±2 years, and age tertile 3=83±2 years. 2DE indicates 2-dimensional echocardiography; 3DE, 3-dimensional echocardiography; ARIC-NCS, Atherosclerosis Risk in Communities Neurocognitive Study; EF, ejection fraction; GLS, global longitudinal strain; LA, left atrial; LAV, left atrial volume; and LV, left ventricular.

*Denotes statistcally significant differences across groups for the selected variable.

predictor of cardiovascular events.[32] In addition, studies in both animals and humans have shown that LA size increases with LAV and LA pressure, with an associated initial gain in contractile shortening and elevated LA GLS values.[4] However, with progressive deterioration of LA function and structure, atrial shortening and contractility begin to decline.[4] In this way, independently from the presence of AF and reduced EF, the solely atrial senescence could probably be sufficient to LA clot formation, causing SCIs first and, subsequently, clinically apparent stroke.

The left atrium is an extremely sensitive cardiac chamber, capable of detecting early effects of increased LV volume, pressure overload, and diastolic dysfunction.[2] A strong linear relationship between LAV and longitudinal deformation echocardiographic indices have been demonstrated in a wide variety of diseases and settings.[11,33] Speckle tracking imaging techniques may serve as a surrogate of LV diastolic dysfunction and can also be used to quantify atrial phasic function and stiffness.[12] In our analysis, E/e' divided by LA GLS and LA GLS—2 indices of both LA stiffness

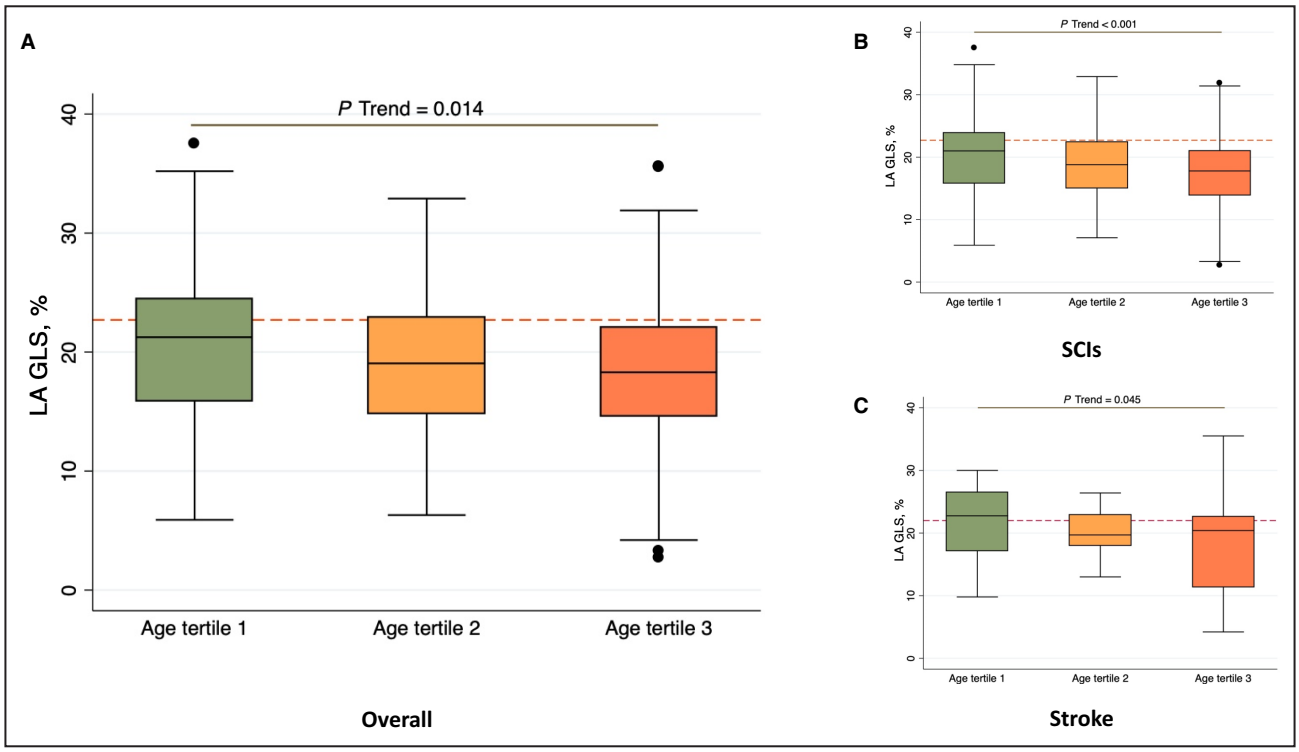

Figure. Differences of left atrial (LA) global longitudinal strain (GLS) 3-dimensional echocardiography strain analysis according to age tertiles in the overall population and through the spectrum of cerebral infarcts phenotypes, from subclinical cerebral infarcts (SCIs) to stroke.

A, The overall population: age tertile 1=68±2 years, age tertile 2=76±2 years, and age tertile 3=83±3 years. **B**, SCIs: age tertile 1=68±1 years, age tertile 2=76±1 years, and age tertile 3=82±3 years. **C**, Stroke: age tertile 1=68±1 years, age tertile 2=76±2 years, and age tertile 3=83.

Table 4. Correlates of SCIs and Stroke and Their Interactions for Age Tertiles in Participants With Sinus Rhythm, Normal EF, and No History of AF: ARIC-NCS, 2011 to 2013

Age tertiles	Predictors	Subclinical cerebral infarcts			Interaction *P* value	Stroke			Interaction *P* value
		OR	95% CI	*P* value		OR	95% CI	*P* value	
First tertile	CHA2DS2-VASc score, per 1 point	1.42	1.24–5.27	0.003*	0.58	1.53	1.26–3.63	0.017*	0.45
Second tertile	…	1.55	1.32–5.07	0.018*		1.62	1.16–2.25	0.005*	
Third tertile	…	2.02	2.72–5.66	0.0001*		3.50	3.36–4.75	0.001*	
First tertile	NT-proBNP, per 1 ng/L	1.62	1.16–2.25	0.005*	0.65	1.26	1.03–5.33	0.028*	0.66
Second tertile	…	1.65	1.18–2.27	0.007*		2.96	2.03–4.33	0.002*	
Third tertile	…	2.71	1.51–4.87	0.001*		2.45	2.23–3.23	0.0001*	
First tertile	High-sensitivity troponin T, per 1 ng/mL	1.67	0.61–4.32	0.33	0.34	2.71	1.51–5.87	0.016*	0.27
Second tertile	…	1.76	0.72–5.68	0.78		3.02	1.71–4.89	0.005*	
Third tertile	…	2.53	0.85–7.63	0.99		3.76	2.05–4.73	0.001*	
First tertile	LA EF, per 1%	0.35	0.25–0.98	0.004*	0.27	0.43	0.15–1.24	0.11	0.16
Second tertile	…	0.77	0.47–0.88	0.001*		0.65	0.24–1.28	0.55	
Third tertile	…	0.95	0.92–0.99	0.0001*		0.98	0.05–1.39	0.71	
First tertile	LA GLS, per 1%	0.32	0.30–0.97	0.036*	0.043*	0.21	0.19–0.99	0.043*	0.040*
Second tertile	…	0.58	0.52–0.69	0.008*		0.50	0.36–0.66	0.015*	
Third tertile	…	0.75	0.70–0.78	0.001*		0.56	0.53–0.60	0.001*	
First tertile	E/e' divided by LA GLS, per unit	1.53	1.42–1.67	0.037*	0.010*	1.02	1.01–1.22	0.045*	0.08
Second tertile	…	1.75	1.68–1.79	0.007*		1.25	1.22–2.34	0.007*	
Third tertile	…	2.53	2.50–2.57	0.001*		1.38	1.25–1.63	0.003*	

Stratified multivariable logistic regression over age tertiles and interactions between age tertiles and predictors for subclinical cerebral infarcts (SCIs) and stroke. AF indicates atrial fibrillation; ARIC-NCS, Atherosclerosis Risk in Communities Neurocognitive Study; EF, ejection fraction; GLS, global longitudinal strain; LA, left atrial; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and OR, odds ratio.

*Denotes statistcally significant OR.

and LA reservoir function—were the LA function parameters found to be associated with increased odds of overall cerebral events (SCIs and clinical stroke), and these indexes showed a significant interaction with age for SCIs.

Therefore, 3DE LA indexes of reservoir impairment and stiffness appear to be altered early because of aging, even before any other change in traditional LA echocardiographic volume-related parameter.[31] Consequently, LA GLS analysis may be a much more sensitive tool in detecting subclinical atrial dysfunction before the occurrence of changes in traditional echocardiographic parameters.

Limitations

The relatively small study sample and the cross-sectional design of this study are the principal limitations of our investigation. In addition, it may have been underpowered to detect differences in other echocardiographic parameters, especially those related to the LV structure and both systolic and diastolic function. Moreover, we cannot exclude the presence of subclinical AF since we do not have data regarding continuous ECG monitoring, but from visit 3 to 5, our participants did not experience hospitalizations attributable to AF and were always found in sinus rhythm at the examinations. Next, 336 3DE images were excluded from our analysis because of insufficient 3DE image quality. However, these missing data were likely random in nature and should not have biased our results. Finally, although we adjusted our analysis for potential confounders, we cannot exclude residual confounding.

CONCLUSIONS

In a large cohort study of elderly patients, among participants with normal EF, sinus rhythm, and no history of AF, measures of worsening age-related LA reservoir function and stiffness are associated with higher odds of SCIs and stroke.

ARTICLE INFORMATION

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Disclosures

The authors declare no conflicts of interest as to the content of this article.

Supplemental Material

Tables S1–S2
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Clinical Characteristics of Excluded Participants due to insufficient 3DE image-quality according to age tertiles, the ARIC NCS, 2011-13

General characteristics	Total N=336	Age tertile 1 N=112	Age tertile 2 N=112	Age tertile 3 N=112
Age (yr.)	76 ± 5	67 ± 3	75 ± 2	82 ± 3
SCIs, n (%)	55 (16 %)	13 (11 %)	16 (14 %)	26 (23 %)
Stroke, n (%)	35 (10 %)	15 (14 %)	6 (5 %)	14 (12 %)
White, n (%)	322 (95 %)	100 (89 %)	110 (98 %)	111 (99 %)
Male sex, n (%)	167 (50 %)	56 (50 %)	57 (51 %)	54 (48 %)
Heart rate (bpm)	61 ± 10	63 ± 9	60 ± 11	59 ± 10
Systolic blood pressure (mmHg)	133 ± 19	128 ± 18	136 ± 18	137 ± 18
Diastolic blood pressure (mmHg)	67 ± 10	68 ± 10	67 ± 10	65 ± 10
CHA_2DS_2-VASc score	4 (3, 4)	2 (2, 3)	3 (3, 4)	4 (4, 5)
Height (cm)	167 ± 10	167 ± 9	165 ± 10	163 ± 8
Weight (kg)	78 ± 15	77 ± 15	74 ± 15	72 ± 14
BMI (kg/m^2)	28 ± 5	28 ± 4	27 ± 5	26 ± 5
Previous myocardial infarction, n (%)	24 (7 %)	6 (5 %)	8 (7 %)	10 (9 %)
HFpEF, n (%)	29 (9 %)	8 (7 %)	9 (8 %)	12 (11 %)
Diabetes, n (%)	150 (45 %)	52 (46 %)	51 (45 %)	47 (42 %)
Hypertension, n (%)	321 (95 %)	100 (89 %)	110 (98 %)	111 (99 %)
Current and former smoking, n (%)	260 (77 %)	85 (76 %)	94 (84 %)	81 (72 %)
Chronic kidney disease, n (%)	23 (7 %)	6 (5 %)	7 (6 %)	10 (9 %)
Blood samples				
eGFR	76 ± 19	81 ± 17	73 ± 20	70 ± 20
Total Cholesterol (mg/dL)	180 ± 41	184 ± 42	182 ± 43	175 ± 38
LDL (mg/dL)	103 ± 33	106 ± 34	106 ± 33	98 ± 32
HDL (mg/dL)	52 ± 14	53 ± 14	52 ± 15	52 ± 12
Triglycerides (mg/dL)	124 ± 58	129 ± 64	122 ± 55	123 ± 54
Glucose (mg/dL)	113 ± 33	116.3 ± 41.2	112.9 ± 30.4	111 ± 26
Creatinine (mg/dL)	1.15 ± 0.4	0.9 ± 0.2	1.02 ± 0.6	1.10 ± 0.4
Hs-C-Reactive Protein (mg/dL)	1.5 (0.6, 3.3)	1.7 (0.6, 3.2)	1.6 (0.8, 3.7)	1.8 (0.9, 3.7)
Hs-Troponin T (ng/mL)	1.02 (0.7, 1.5)	0.8 (0.5, 1.2)	1 (0.7, 1.5)	1.2 (0.7, 1.7)
NT-proBNP (ng/L)	132 (72, 235)	78 (46, 132)	133 (69, 240)	191 (121, 345)
Medications				
Statins, n (%)	190 (56 %)	65 (58 %)	62 (55 %)	63 (56 %)
Anticoagulants, n (%)	10 (3 %)	5 (4 %)	3 (2 %)	2 (1 %)
Aspirin, n (%)	280 (83 %)	88 (78 %)	90 (80 %)	102 (91 %)
Beta-blockers, n (%)	112 (33 %)	42 (37 %)	32 (28 %)	37 (33 %)
Anti-angiotensin II, n (%)	45 (12 %)	10 (9 %)	12 (10 %)	23 (20 %)
ACE-I, n (%)	70 (22 %)	17 (15 %)	30 (27 %)	23 (20 %)
Loop diuretics, n (%)	40 (12 %)	17 (15 %)	14 (12 %)	9 (8 %)

Legend: Data are described as mean (±SD) or median (Q1, Q3) for quantitative variables, and counts (proportions) for categorical variables. Three-dimensional echocardiography (3DE), years (yr.), milliseconds (ms), millimeters (mm), milliliters (mL), deciliters (dL), meters (m), centimeters (cm), numbers (n), estimated glomerular filtration rate (eGFR), left ventricle (LV), standard deviation (SD), subclinical cerebral infarcts (SCIs), heart failure with preserved ejection fraction (HFpEF).

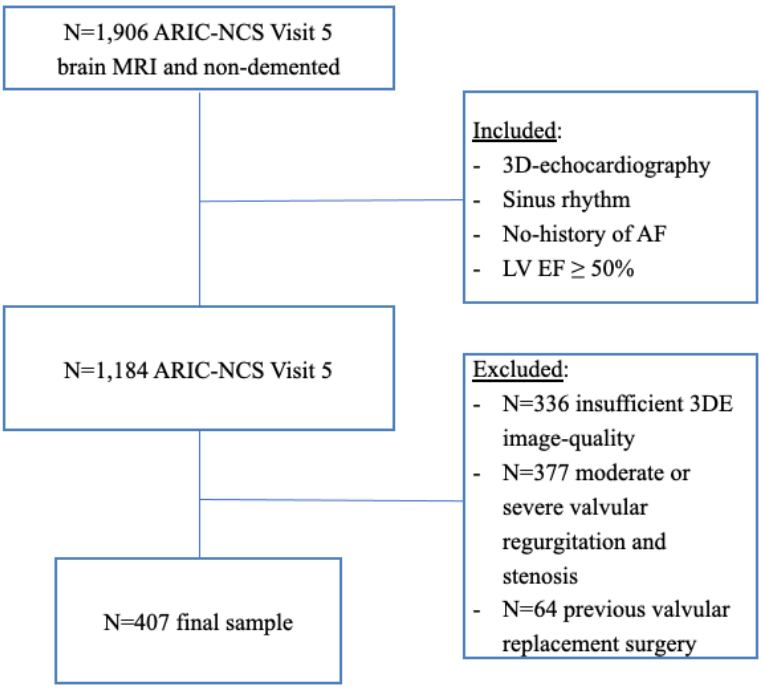
Table S2. Adjusted mean 2D/3D Echocardiographic characteristics according to tertiles of age and cerebral infarcts phenotypes, the ARIC NCS, 2011-13

No Cerebral Infarcts (NCIs)	Total N=315	Age tertile 1 N=105	Age tertile 2 N=105	Age tertile 3 N=105	P for Trend
LV dimensions and function					
LV end-diastolic diameter (cm)	4.30 ± 0.48	4.46 (0.10)	4.27 (0.10)	4.33 (0.11)	0.39
LV end-systolic diameter (cm)	2.44 ± 0.40	2.54 (0.10)	2.62 (0.10)	2.61 (0.10)	0.62
LV end-diastolic volume indexed (mL/m^2)	44 ± 9.5	49 (2.54)	51 (2.55)	46 (2.62)	0.50
LV end-systolic volume indexed (mL/m^2)	14.38 ± 4.45	17 (1.45)	19 (1.45)	16 (1.49)	0.91
LV relative wall thickness	0.44 ± 0.12	0.42 (0.01)	0.5 (0.01)	0.45 (0.02)	0.71
E/e' ratio, average	11 ± 4	9.5 (0.9)	11 (0.9)	12 (0.9)	0.40
Left atrial volumes					
LA maximal volume indexed (mL/m^2)	33 ± 9	31.9 (2.6)	40.3 (2.6)	36 (2.7)	0.26
LA minimum volume indexed (mL/m^2)	16 ± 6	13.7 (2.2)	20.8 (2.2)	16 (2.3)	0.46
LA contractile function					
LA stroke volume indexed (mL/m^2)	17 ± 6	18 (1.4)	19 (1.4)	20 (1.5)	0.31
LA ejection fraction (%)	52 ± 11	57 (3)	51 (3.1)	54 (3.2)	0.42
LA emptying fraction (%)	52 ± 0.12	58 (0.03)	51 (0.03)	54 (0.03)	0.38
Left atrial reservoir function					
LA global longitudinal strain (%)	19 ± 6	23 (1.4)	18 (1.4)	22 (1.4)	0.42
LA expansion index	122 ± 56	159 (17)	119 (18)	135 (18)	0.34
Left atrial conduit function					
LA emptying volume (mL)	31 ± 12	34 (2.5)	35 (2.5)	37 (2.6)	0.37
LA conduit volume (mL)	15 ± 8	6 (0.3)	11 (0.3)	4 (0.3)	0.64
Left atrial stiffness					
E/e’ divided by LA GLS	0.64 ± 0.42	0.45 (0.08)	0.76 (0.08)	0.54 (0.08)	0.43

E/e’ divided by LA ejection fraction	0.22 ± 0.14	0.19 (0.04)	0.27 (0.04)	0.22 (0.04)	0.49

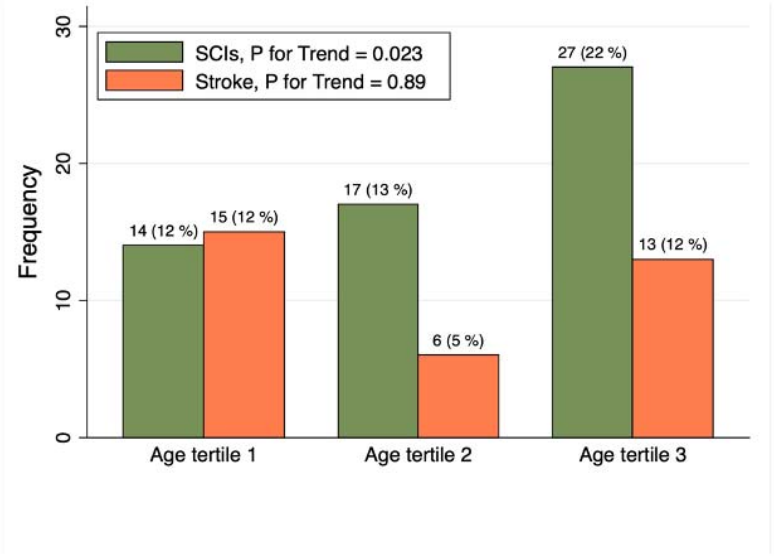
Legend: total characteristics are described as mean (±SD); after-adjustments variables according to cerebral infarcts are presented as mean (SE). Left atrium (LA), global longitudinal strain (GLS), milliseconds (ms), millimeters (mm), milliliters (mL), deciliters (dL), meters (m), centimeters (cm). All the P-values are adjusted for sex, race, body surface area (BSA), body mass index (BMI), heart rate, blood pressure, NT-proBNP - Troponins levels, previous myocardial infarction, hypertension, diabetes, renal function, anticoagulants usage and antiplatelet agents. Age tertile 1 = 68 ± 2 yr., age tertile 2 = 76 ± 2 yr., Age tertile 3 = 83 ± 3 yr.

Figure S1. Patient selection for the current study.



Abbreviations: Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS), magnetic resonance imaging (MRI), 3-dimensional (3D), atrial fibrillation (AF), ejection fraction (EF), left ventricle (LV).

Figure S2. Frequency distribution of SCIs and stroke according to age-tertiles.



Abbreviations: SCIs: Subclinical cerebral infarcts. Age-tertile 1 = 70 ± 2 yr., Age-tertile 2 = 76 ± 2 yr., Age-tertile 3 = 83 ± 3yr.