BACKGROUND: Left atrial (LA) volumes and emptying fraction in the general population may address structural and functional aspects of atrial cardiomyopathy associated with long-term risk of ischemic stroke in the absence of atrial fibrillation or prior stroke. We investigated the association between LA volumes and function and ischemic stroke.

METHODS AND RESULTS: In a community-based cohort, we measured LA minimal volume, LA maximal volume, and LA emptying fraction by transthoracic echocardiography. The primary end point was ischemic stroke. Participants with known atrial fibrillation or prior ischemic stroke were excluded, which resulted in 1866 participants. The mean age was 58±16 years, and 57% were women. During a median follow-up of 16.5 years (interquartile range: 11.4–16.8 years), 176 (9.4%) ischemic strokes occurred. In multivariable cause-specific regression models and competing risk models with death as a competing risk, LA emptying fraction was associated with ischemic stroke (hazard ratio [HR], 1.14 per 10% decrease [95% CI, 1.02–1.28]) and (subdistribution HR, 1.14 [95% CI, 1.01–1.29]). This association remained when adjusting for participants who developed atrial fibrillation during follow-up (HR, 1.12 per 10% decrease [95% CI, 1.00–1.26]). Indexed LA volumes were not associated with ischemic stroke in the same models. LA emptying fraction and indexed LA volumes were not associated with all-cause mortality.

CONCLUSIONS: Lower LA emptying fraction measured by transthoracic echocardiography was associated with future ischemic stroke independently of incident atrial fibrillation.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02993172.

Key Words: echocardiography ■ epidemiology ■ ischemic stroke ■ left atrium
size and functional parameters to the risk of ischemic vascular events. Nonetheless, only 1 study has previously associated LA volumetric and functional parameters with a first incident ischemic cardiovascular event, defined as either ischemic stroke or transient ischemic attack (TIA) in a population free of AF or prior stroke. This study used cardiac magnetic resonance (CMR) to assess LA function and demonstrated that reduced LAEF was associated with the combined end point of ischemic cardiovascular event. CMR has excellent spatial resolution and contrast but is hampered by high costs and limited availability.

Additional studies are needed to substantiate these findings. To our knowledge, no study has investigated long-term follow-up of LA volumes and LAEF measured with transthoracic echocardiography (TTE) and the risk of ischemic stroke as the primary end point in the general population without evident AF or prior ischemic stroke. We examined whether increasing baseline LA volumes and reduced LAEF are associated with the development of ischemic stroke independently of incident AF.

**METHODS**

The data used in this study hold potentially identifiable or sensitive information and therefore cannot be shared publicly. However, anyone can apply for the use of data by contacting the secretariat director of the Copenhagen City Heart Study. For contact information, please see [https://www.frederiksberghospital.dk/afdelinger-og-klinikker/oeesterbrounderosagenskontakt/Sider/default.aspx](https://www.frederiksberghospital.dk/afdelinger-og-klinikker/oeesterbrounderosagenskontakt/Sider/default.aspx).

**Study Population**

We examined participants from the fourth round of the Copenhagen City Heart Study (CCHS) who underwent a TTE. The CCHS has been described in detail previously. Briefly, the CCHS is a longitudinal cohort study in the general population >20years of age that examines cardiovascular risk factors and outcomes in an age-stratified random sample. The fourth round enrolled participants between 2001 and 2003. The echocardiographic substudy included randomly selected men and women between 20 and 93 years of age from the primary cohort independently of their health status. In this study, we excluded participants with known AF, prior stroke, or inability to measure LA volumes (Figure 1). All subjects gave informed consent before participation. The study was approved by the Regional Scientific Ethics Committee and was performed according to the Second Helsinki Declaration.

**Health Examination and Definitions**

All participants underwent a health examination, including a physical examination, a self-administered questionnaire, and blood tests. We defined hypertension as self-reported, use of antihypertensive medication, or resting systolic blood pressure of >140 mmHg or diastolic >90 mmHg. Diabetes was defined as self-reported, plasma glucose ≥11.1 mmol/L, hemoglobin A1c >7%, or use of antidiabetic drugs. Ischemic heart disease was defined as a history of hospital admission because of acute coronary syndrome, percutaneous coronary intervention, or coronary artery bypass grafting.

**Echocardiography**

The echocardiographic acquisition and analysis have been described previously, including reproducibility
measures. Relevant to the present study, LA volumes were measured by the biplane area–length method at end-systole, that is, LA maximal volume, and end-diastole, that is, LA minimal volume, in the apical 4- and 2-chamber views. The total LAEF was calculated as \((\text{LA maximal volume} - \text{LA minimal volume})/\text{LA maximal volume}\). LA volumes were indexed to body surface area: LA maximal volume/body surface area (LAVI\text{max}) and LA minimal volume/body surface area (LAVI\text{min}).

**Follow-Up and End Points**

The primary end point was incident ischemic stroke, and the competing event was death from any cause. Follow-up was until December 2018. Death from any cause was retrieved from The Danish Register of Causes of Death. End points were retrieved from the Danish National Patient Registry using the following International Classification of Disease Tenth Revision (ICD-10) codes: Ischemic stroke I63x, unspecified stroke I64x, transient ischemic attack G45x, and atrial fibrillation or atrial flutter I48x. The follow-up rate was 100%.

**Statistical Analysis**

Baseline continuous variables with normal distribution are presented as mean±SD. Non-normally distributed data are shown as median with interquartile ranges. Categorical variables are presented with frequencies and percentages. Student *t* test, Fisher exact test, and Wilcoxon rank-sum test compared baseline factors as appropriate.

We used Cox proportional hazard models to estimate the cause-specific hazard of continuous LA parameters (LAVI\text{min}, LAVI\text{max}, LAEF) with ischemic stroke as the outcome and death as a censoring event. Because of the high number of deaths during follow-up, we used the Fine–Gray subdistribution hazard model to estimate the same LA parameters with death as a competing risk. Confounding covariates were selected based on their relationship with LA parameters and risk factors associated with ischemic stroke. The final multivariable model included age, sex, body mass index, smoking, systolic blood pressure, diastolic blood pressure, heart rate, hypertension, diabetes, ischemic heart disease, estimated glomerular filtration rate, total cholesterol, and NT-proBNP (N-terminal pro-brain natriuretic peptide). To ensure that we controlled for after-load as thoroughly as possible, the final model included both systolic and diastolic blood pressure as continuous variables and hypertension as a dichotomous variable acknowledging the close association between blood pressure and LA volume and function. Since these variables are correlated, this could lead to problems of multicollinearity. However, since the objective was not to outline the association between blood pressure and hypertension with ischemic stroke, we chose to add all 3 variables. This approach was supported by an improved fit of the multivariable model using the likelihood-ratio test. We added AF as a time-dependent variable.
covariate to the final Cox proportional hazard model to assess whether the risk of ischemic stroke associated with LA parameters was mediated by participants developing AF. Harrell C-statistics were calculated from a Cox regression model with the participants’ CHA2DS2-VASc score (Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, Prior stroke, transient ischemic attack, or thromboembolism, Vascular disease, Age 65 to 74 years, Sex category female) and added LA measures. We used the likelihood ratio test to examine whether the C-statistics improved.

In a sensitivity analysis, we assessed exploratory models with additional echocardiographic covariates with missing values to assess the stability of the primary models. Furthermore, we evaluated the combined end point of either first ischemic stroke or TIA. We used the likelihood-ratio test to assess the interaction of sex, age, hypertension, and CHA2DS2-VASc score with LA measures in fully adjusted models and found none. Finally, we tested the association between LA measures and death. The proportional hazard assumption was tested and confirmed using Schoenfeld residuals. We used the cumulative incidence function accounting for the competing risk of death to graphically assess tertiles of LAEF and ischemic stroke. We used Gray’s test to compare the groups. A 2-sided $P$ value $<0.05$ was considered statistically significant. We performed all analyses with STATA version 13.1 (StataCorp, College Station, TX).

RESULTS

Study Population
In this study, 1866 participants were included, with a median follow-up of 16.5 years (interquartile range 11.4–16.8 years). Baseline characteristics of the whole population and according to incident ischemic stroke during follow-up are shown in Table 1. Participants who developed ischemic stroke were older, had more cardiovascular comorbidity, higher CHA2DS2-VASc score, higher levels of NT-proBNP and cholesterol, larger LA volumes, and lower LAEF.

Outcomes
During follow-up, 176 participants had an ischemic stroke (9.4%, 6.9 ischemic strokes/1000 person-years), 248 developed incident AF (13.3%, 9.9 incident AF/1000 person-years), and 73 had a TIA (3.9%, 2.8 TIA/1000 person-years). A total of 219 patients had the combined end point of first ischemic stroke or TIA (11.7%, 8.6 events/1000 person-years). Fifty-five participants developed both AF and ischemic stroke. Of these, 32 had an AF diagnosis before the ischemic stroke (58.2%). In total, 617 subjects died (33.1%, 23.3 deaths/1000 person-years).

LA Measures and Ischemic Stroke
Table 2 shows indexed LA volumes and LAEF and their associations with the primary outcome of ischemic stroke. Indexed LA volumes (per 10 mL/m² increase) and LAEF decrease (per 10% decrease) were associated with the primary outcome of ischemic stroke in both univariable Cox regression and univariable competing risk regression. When adjusting for baseline confounders, this association did not remain for LAVImax and LAVImin. Total LAEF remained associated with ischemic stroke also after adjusting for AF as a time-dependent covariate (hazard ratio [HR]: 1.12 per 10% decrease [95% CI, 1.00–1.25, $P=0.049$]).

Figure 2 shows a significant difference in the unadjusted cumulative incidence of ischemic stroke according to tertiles of LAEF. When adjusting for baseline covariates as in model 1, the association remained significant for the lowest tertile of LAEF compared with the highest tertile (HR: 1.57 [95% CI, 1.04–2.38], $P=0.032$) but attenuated to insignificant when modeling AF as a time-dependent covariate (HR, 1.51 [95% CI, 0.99–2.28, $P=0.053$]). Figure 3 shows the rate of ischemic stroke according to tertiles of LAEF and stratified on CHA2DS2-VASc score (0, 1, ≥2) with a significant difference between the tertiles (stratified log-rank test $P=0.024$, test for trend $P=0.008$). Adding LAEF to the CHA2DS2-VASc score (0–9) significantly improved the C-statistics (C-statistic for CHA2DS2-VASc 0.752 versus CHA2DS2-VASc+LAEF 0.762; $P=0.014$).

Sensitivity Analysis
To assess whether the association of LAEF was influenced by echocardiographic parameters of diastolic dysfunction and left ventricular remodeling, we performed a sensitivity analysis by adding covariates with missing values for some participants. Adding left ventricular mass index and left ventricular hypertrophy to model 1 did not change the results significantly (HR, 1.15 per 10% decrease [95% CI, 1.01–1.31, n=1517]). Further adjustment for E/A ratio and E/e’ did not attenuate the results (HR, 1.17 per 10% decrease [95% CI, 1.02–1.34, n=1384]). Adding AF as a time-dependent covariate in the same models showed similar results (HR, 1.14 per 10% decrease [95% CI, 1.00–1.30] and HR, 1.16 per 10% decrease [95% CI, 1.02–1.34]).

The association of LA-measures in multivariable analysis with the combined end point of first ischemic stroke or TIA remained unchanged compared to the primary end point of ischemic stroke. LAEF was the only measure associated with the combined end point with the same adjustments used in Model 1 (LAVImin HR, 1.17 per 10 mL/m² increase [95% CI, 0.85–1.61]) and (LAVI max HR: 0.91 per 10 mL/m² increase [95% CI, 0.73–1.14]) and (LAEF HR, 1.12 per 10% decrease [95% CI, 1.01–1.24]). However, the association with
LAEF was insignificant when adjusting for AF as a time-dependent covariate (LAEF HR, 1.10 per 10% decrease [95% CI, 1.25–1.59]) and (LAEF HR, 1.25 per 10% decrease [95% CI, 1.18–1.32]). This association disappeared when adjusting for baseline confounders as in model 1 (LAVI_min HR, 1.08 per 10 mL/m² increase [95% CI, 0.89–1.32]) and (LAVI_max HR, 1.05 per 10 mL/m² increase [95% CI, 0.92–1.20]) and (LAEF HR, 1.00 per 10% decrease [95% CI, 0.94–1.07]).

In univariate models of LA-measures there was an association with death from any cause. (LAVI_min HR, 2.44 per 10 mL/m² increase [95% CI, 2.07–2.87]) and (LAVI_max HR, 1.41 per 10 mL/m² increase [95% CI, 1.25–1.59]) and (LAEF HR, 1.10 per 10% decrease [95% CI, 0.99–1.22]).

Table 1. Baseline Characteristics Stratified by Ischemic Stroke

|                       | All          | No ischemic stroke | Ischemic stroke | P value |
|-----------------------|--------------|--------------------|-----------------|---------|
| N                     | 1866         | 1690               | 176             |         |
| Age, y                | 58.3±15.7    | 57.2±15.7          | 69.5±10.8       | <0.001  |
| Male                  | 793 (42.5)   | 726 (43.0)         | 67 (38.1)       | 0.21    |
| Body mass index, kg/m²| 25.6±4.0     | 25.5±3.9           | 26.4±4.3        | 0.002   |
| Body surface area, m² | 1.84±0.20    | 1.84±0.20          | 1.81±0.20       | 0.037   |
| Systolic blood pressure, mmHg | 135.2±22.5 | 133.8±22.1         | 148.6±21.8      | <0.001  |
| Diastolic blood pressure, mmHg | 78.2±12.2 | 77.8±12.1          | 81.8±12.7       | <0.001  |
| Resting heart rate, beats/min | 66.9±11.1 | 66.8±11.2          | 67.5±10.2       | 0.48    |
| Hypertension          | 787 (42.3)   | 666 (39.5)         | 121 (69.5)      | <0.001  |
| Diabetes              | 181 (9.7)    | 157 (9.3)          | 24 (13.7)       | 0.080   |
| Ischemic heart disease | 102 (5.5)    | 89 (5.3)           | 13 (7.4)        | 0.22    |
| CHA2DS2-VASc 1–2      | 1 (0–2)      | 1 (0–2)            | 2 (1–2)         | <0.001  |
| CHA2DS2-VASc ≥3       | 623 (33.4)   | 512 (30.3)         | 111 (63.1)      |         |

Smoking status, %

|                | No ischemic stroke | Ischemic stroke | P value |
|----------------|--------------------|-----------------|---------|
| Never smoked   | 597 (32.7)         | 544 (32.9)      | 53 (30.5) | 0.65    |
| Former smoker  | 606 (33.2)         | 543 (32.8)      | 63 (36.2) |         |
| Current smoker | 625 (34.2)         | 567 (34.3)      | 58 (33.3) |         |

Values are n (%), mean±SD, or median (interquartile range). CHA2DS2-VASc indicates congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female; DT, deceleration time; eGFR, estimated glomerular filtration rate; LAD, left atrial diameter; LAEF, left atrial emptying fraction; LAVI_min, minimal left atrial volume indexed; LAVI_max, maximal left atrial volume indexed; LVEF, left ventricular ejection fraction; E/A, transmitral E-wave velocity/transmitral A-wave velocity; LVIDd, left ventricular internal diameter at end diastole; and LVMI, left ventricular mass index.
DISCUSSION

The principal finding of our study is an association between LAEF and ischemic stroke in a community-based cohort from the general population free of known AF and prior ischemic stroke. The association was consistent in both cause-specific regressions adjusting for participants developing incidental AF during follow-up and competing risk regressions accounting for the high proportion of deaths. The addition of LAEF to the CHA2DS2-VASc score modestly improved the C-statistics. Our results add to the growing body of evidence associated with LA measures and adverse outcomes. In our study, LAEF was associated with ischemic stroke in adjusted models, while indexed LA volumes were not. A possible explanation is that a decline in LA function manifests before enlargement of the LA and thus reflects an earlier, more sensitive risk

Table 2. Cox Regression and Competing Risk Regression Showing the Association Between Continuous LA-Measures and Ischemic Stroke

|                        | Hazard Ratio. Ischemic stroke with death as a censored event | P value | Subdistribution Hazard Ratio. Ischemic stroke with death as a competing event | P value |
|------------------------|--------------------------------------------------------------|---------|--------------------------------------------------------------------------------|---------|
| **Univariable**         |                                                              |         |                                                                                |         |
| LAVimin, 10 mL/m² increase | 2.72 (2.03–3.66)                                             | <0.001  | 2.20 (1.84–2.95)                                                              | <0.001  |
| LAVimax, 10 mL/m² increase | 1.45 (1.16–1.82)                                             | 0.002   | 1.34 (1.08–1.71)                                                              | 0.014   |
| LAEF, 10% decrease      | 1.32 (1.19–1.47)                                             | <0.001  | 1.27 (1.15–1.41)                                                              | <0.001  |
| **Multivariable Model 1** |                                                              |         |                                                                                |         |
| LAVimin, 10 mL/m² increase | 1.30 (0.93–1.87)                                             | 0.143   | 1.24 (0.87–1.78)                                                              | 0.230   |
| LAVimax, 10 mL/m² increase | 0.98 (0.77–1.26)                                             | 0.889   | 0.97 (0.75–1.25)                                                              | 0.795   |
| LAEF, 10% decrease      | 1.14 (1.02–1.28)                                             | 0.025   | 1.14 (1.01–1.29)                                                              | 0.034   |
| **Multivariable Model 2** |                                                              |         |                                                                                |         |
| LAVimin, 10 mL/m² increase | 1.21 (0.85–1.72)                                             | 0.296   |                                                                                |         |
| LAVimax, 10 mL/m² increase | 0.94 (0.74–1.21)                                             | 0.641   |                                                                                |         |
| LAEF, 10% decrease      | 1.12 (1.00–1.25)                                             | 0.049   |                                                                                |         |

Model 1: Adjusted for: Age, sex, body mass index, smoking, systolic blood pressure, diastolic blood pressure, heart rate, hypertension, diabetes, ischemic heart disease, estimated glomerular filtration rate, total cholesterol, and NT-proBNP. Model 2: Includes the same covariates as model 1 and incident atrial fibrillation as a time-dependent covariate. LAEF indicates left atrial emptying fraction; LAVimin, minimal left atrial volume indexed; LAVimax, maximal left atrial volume indexed; and NT-proBNP, N-terminal pro-brain natriuretic peptide.

Figure 2. Cumulative incidence of ischemic stroke by tertiles of left atrial emptying fraction.

Cumulative incidence failure of ischemic stroke according to tertiles of the left atrial emptying fraction. The first tertile is those with the lowest LAEF and is represented by the blue line. The orange line represents the second tertile. The third tertile is those with the highest LAEF, represented by the green line. A significant difference was seen between the groups. LAEF indicates left atrial emptying fraction.

Figure 3. Incidence of ischemic stroke per 1000 patient-years by tertiles of LAEF and CHA2DS2-VASc score with 95% CI.

An increase in the rates of ischemic stroke was observed with increasing CHA2DS2-VASc score and decreasing LAEF. 1st Tertile LAEF 1–46%; 2nd Tertile LAEF 47–57%; 3rd Tertile LAEF 58–87%. CHA2DS2-VASc, congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female. LAEF indicates left atrial emptying fraction.
marker of atrial dysfunction. Furthermore, as seen in the athlete’s heart, enlargement of the LA may be exercise-induced without a decline in the function of the LA, suggesting that atrial function is a more sensitive marker of atrial pathology. Notably, we have recently demonstrated an increase in LA phasic volumes over time, but no change in LAEF, between 2 CCHS visits 10 years apart.

LA Measures and Risk of Ischemic Stroke
A study investigating the association of ischemic stroke and LA volume and function by CMR in 4261 participants without known clinical cardiovascular disease from the MESA (Multi-Ethnic Study of Atherosclerosis) population showed results similar to the present study with a HR of 0.85 per increasing SD of LAEF (95% CI, 0.74–0.98) after adjusting for interim AF. In agreement with our results, no association of LA phasic volumes with ischemic stroke in adjusted analyses was found. However, the study had a shorter follow-up period and used a combined end point of ischemic stroke and TIA. Several other studies have demonstrated an association between LA size or volume measures and incidence of ischemic stroke, which could not be reproduced in our adjusted models. A case–control study in 352 patients from the Northern Manhattan Stroke Study showed an adjusted odds ratio of 1.47 per 10 mm index increase in LA diameter (95% CI, 1.03–2.11). In a study of 1554 randomly selected residents from Olmsted County, LA volume >32 mL/m² was associated with a HR of 1.63 (95% CI, 1.08–2.46). In the Framingham Heart Study, every 10-mm increase in LA diameter was associated with a relative risk of stroke of 2.4 in men (95% CI, 1.6–3.7) and 1.4 in women (95% CI, 1.1–1.7). Possible explanations for these disagreements are different study populations with more comorbidity, more pronounced atrial enlargement, and cruder measures of the atrial size such as monoplane anterior–posterior diameter as opposed to biplane volume measures.

LA Emptying Fraction and Other Adverse Outcomes
We previously showed that LAEF is associated with incident AF in the CCHS. Decreasing LAEF was independently associated with mortality in 1802 participants from the Dallas Heart Study with a HR of 1.56 per decreasing SD of LAEF (95% CI, 1.32–1.87). Another study of 664 patients with heart failure showed that decreasing LAEF was associated with heart failure hospitalization, cardiovascular mortality, all-cause mortality, and AF. In 971 patients with AF, LAEF, but not LA size, was correlated with an increased risk of cardiovascular death and heart failure independently of heart rhythm at the time of examination. We could not demonstrate an association between LA volumes or LAEF and all-cause death.

Value of LA Function as a Risk Marker of Ischemic Stroke
Approximately 25% of ischemic strokes are without an identified cause. Undetected paroxysmal AF is often suspected as the cause. Several studies using prolonged cardiac rhythm monitoring after cryptogenic ischemic stroke have shown increased detection rates of AF lasting >2 minutes within the first year. However, the clinical significance and consequence of short runs of subclinical AF poststroke are still subject to debate, and detection of AF beyond the first year could represent natural progression rather than causation of ischemic stroke. These questions have prompted an increasing interest in elucidating an atrial cardiomyopathy entity as a potential substrate of both AF and ischemic stroke. Furthermore, it has been speculated that ischemic stroke could be the first clinical manifestation of atrial cardiomyopathy even before the onset of AF. In this context, reduction of LA global function as reflected by LAEF in our study could be an early marker of a functional component of atrial cardiomyopathy. Interestingly, a correlation between LAEF, diastolic measures, and more extensive fibrosis has been demonstrated, signifying the intricate interplay between cardiac structure and function. The hypothesis of atrial cardiomyopathy and a possible correlation to ischemic stroke is supported by CMR imaging studies of the LA with late gadolinium enhancement as a surrogate of LA fibrosis. These studies have shown increased LA with late gadolinium enhancement in patients with embolic stroke of undetermined source and stroke of undetermined cause. On the other hand, as others have shown, reduced LAEF could be associated with subclinical AF, which results in the observed increased risk of ischemic stroke. LAEF is also a risk marker of other adverse outcomes such as subclinical cerebrovascular disease, heart failure, and death. Thus, another possibility is that reduced LAEF signifies a more pronounced vascular risk profile that contributes to an increased risk of ischemic cerebrovascular events through established pathways such as small vessel occlusion or large-artery atherosclerosis. Because data on the type of ischemic stroke are not available for this study, we cannot investigate this hypothesis. Interestingly, in patients with stroke attributed to either large- or small-vessel disease, a recent study demonstrated implantable cardiac monitor detected AF in 12.1% at 12 months. This is equal to what has been reported in patients with cryptogenic stroke and probably reflects the shared risk factors of patients with
stroke.36 Future studies in patients with stroke of non-cardioembolic mechanism with indices of atrial cardiomyopathy are needed to understand whether atrial cardiomyopathy could guide poststroke management both in terms of AF detection and prevention of new stroke. Regardless of the potential stroke mechanism, we believe that LAEF provides relevant prognostic information and is readily available from most standard echocardiographic examinations.

**Translational Perspective**

Our data suggest that reduced LAEF is associated with future ischemic stroke and that LAEF is a potential biomarker of atrial cardiomyopathy, readily available from routine TTE. Nonetheless, the concept of atrial cardiomyopathy as a clinical entity that necessitates medical treatment in either primary or secondary prevention needs confirmation in carefully designed prospective trials. A recent secondary analysis of the NAVIGATE ESUS (New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source) trial examined whether patients with indications of atrial cardiomyopathy could benefit from an anticoagulation strategy in secondary prevention of ischemic stroke.38 They suggested a moderate benefit in patients with a LA diameter >4.6 cm. Whether this post hoc analysis translates to a real clinical benefit in patients with indices of atrial cardiomyopathy is investigated by the currently recruiting ARCADIA (Atrial cardiomyopathy and antithrombotic drugs in prevention after cryptogenic stroke) trial.39

**Study Limitations**

Outcomes of AF and ischemic stroke were obtained from registries using ICD-10 codes and were not adjudicated, so we cannot exclude some degree of diagnostic misclassification. We cannot state how the patients were monitored and thus identified with AF. However, we have previously demonstrated high sensitivity and specificity for the AF diagnosis.40 Participants did not have continuous heart rhythm monitoring for subclinical AF, which could be a mediating factor of stroke, and we cannot examine whether this would have changed our results. The ischemic stroke diagnosis (I63x) from the Danish National Patient Registry has been validated with a high positive predictive value.41,42 We used a combined diagnosis of I63x and I64x as the primary end point, and we cannot exclude that some of the patients with an I64x diagnosis could have a hemorrhagic and not an ischemic stroke. A study investigating this issue showed that ~60% of unspecified strokes were ischemic, and 8% were hemorrhagic.41 However, we believe that this misclassification and possible dilution of the data would only lead to more conservative estimates of associations. Intraobserver and interobserver variability of LA measures with TTE is operator dependent, underestimates LA volumes, and is less reproducible than CMR.43 We have only measured total LAEF and not specified the passive and active LA-function, which might have provided additional information. We cannot exclude residual confounding because specific ischemic stroke risk factors were not measured at baseline, such as carotid stenosis and plaques. Finally, while a long follow-up period increases the number of events, it also introduces potential confounders as risk factors change over time. The study cannot capture these confounders. Thus, our findings should be applied with caution to other populations.

**CONCLUSIONS**

In this community-based cohort, lower LAEF as measured by TTE is associated with future ischemic stroke independently of detected AF. Our findings support the growing body of evidence related to the concept of atrial cardiomyopathy and increased risk of ischemic stroke potentially independent of AF.

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