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Clinical research

Left atrial volume predicts cardiovascular events in patients originally diagnosed with lone atrial fibrillation: three-decade follow-up

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KEYWORDS
Lone atrial fibrillation;
Left atrial volume;
Echocardiography;
Cerebral infarction

Aims The objectives of this study were to determine the long-term outcome and the predictors of adverse events in patients originally diagnosed with lone atrial fibrillation (AF).
Methods and results This population-based historical cohort study comprised 46 residents of Olmsted County, MN, USA, with well-documented, clinically defined lone AF and a complete two-dimensional echocardiographic examination. The original echocardiographic videotape recordings were analysed in a blinded fashion for left atrial volume (LAV) and left ventricular ejection fraction. With 1296 person-years of follow-up, the median duration of AF was 27 (first quartile = 24, third quartile = 33) years. Twenty-three (50%) patients developed events. Cerebral infarction occurred in seven patients, myocardial infarction in 11, and congestive heart failure in 16. In a multivariable analysis, patients with indexed LAV $\geq$32 mL/m^2 had a significantly worse event-free survival (adjusted HR, 4.46; 95% CI, 1.56–12.74; $P = 0.005$). All cerebral infarctions occurred in patients with an indexed LAV $>$32 mL/m^2.
Conclusion Patients originally diagnosed with benign lone AF follow divergent courses based on LAV. Those originally diagnosed with lone AF and normal sized atria had a benign clinical course throughout the long-term follow-up. Patients with increased LAV at diagnosis or later during the follow-up experienced adverse events.

Introduction

Atrial fibrillation (AF) is the most common cardiac rhythm disorder, affecting more than two million adults in the United States.[1] By consensus, lone AF is clinically defined as a separate, less commonly encountered entity that occurs in the absence of overt cardiovascular disease or any other known causal factor.[2] Lone AF was observed by our group and others to be a benign disorder in younger patients ($<$60 years)[3–5] and a disorder associated with adverse events in older persons ($>$60 years).[6,7] On the basis of this evidence, the American College of Cardiology/American Heart Association/European Society of Cardiology guidelines state that 'by virtue of aging or the development of cardiac abnormalities', young patients move out of the low-risk lone AF category into a high-risk group, which may warrant anticoagulation for stroke prevention.[2] However, to date, no study has followed a lone AF cohort of patients sufficiently long enough to test this hypothesis. To the best of our knowledge, no specific cardiac changes have been identified that would predict adverse events in patients originally diagnosed with lone AF.

Increased left atrial volume (LAV), which is an indicator of chronic diastolic dysfunction,[8,9] as well as reduced left ventricular ejection fraction (EF), which denotes impaired systolic function, are independent markers of cardiovascular risk.[10–12] We hypothesized that also in patients with lone AF, LAV enlargement and lower left ventricular EF would be independent predictors of cardiovascular and cerebrovascular events.

In order to test this hypothesis, we chose a geographically defined cohort of patients with clinically lone AF and with an established benign intermediate-term outcome.[3] The objectives of our study were to determine the long-term outcome of patients with lone AF and to investigate whether the development of diastolic or systolic dysfunction predicted the transition from originally diagnosed benign lone AF to AF associated with adverse events.

Methods

Patient selection

This study was carried out in Olmsted County, MN, USA, where Mayo Clinic is the principal provider of healthcare and patient records are accumulated within a single dossier. Previous studies have shown

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that the Olmsted population can be considered representative of the US white population.[13] Patients with lone AF were identified among 3623 Olmsted County residents presenting with new onset AF between 1950 and 1980. All medical records were thoroughly reviewed to identify subjects with lone AF and to confirm Olmsted County residency status. Exclusion criteria were applied at the onset of AF and included lack of electrocardiographic documentation of AF; age >60; coronary artery disease according to clinical or laboratory criteria; hyperthyroidism; valvular heart disease including mitral valve prolapse; congestive heart failure (CHF), cardiomyopathy, chronic obstructive pulmonary disease, cardiomegaly apparent on the chest radiograph; treated hypertension or blood pressure above 140 mmHg systolic or 90 mmHg diastolic measured on three separate occasions; life-shortening disease, including diabetes mellitus; or AF due to trauma, surgery, or acute medical illness. All of these patients had been thoroughly investigated, followed-up for 14.8 years, and confirmed as having benign lone AF by peer review.[3] For inclusion in the current study, all patients needed to have had one or more complete transthoracic echocardiographic examinations since the beginning of the era of two-dimensional echocardiography in 1976. All of the original echocardiographic data were available for the offline measurement of LAV and EF.

Follow-up

Subjects were followed until death or 1 July 2002. Complete follow-up was possible because Olmsted County is relatively isolated from other urban areas and medical care is concentrated at the Mayo Clinic and a small number of other providers that use a unified medical record system whereby all medical information on each individual is accumulated in a single dossier. Approximately 96% of the County population is seen at Mayo Clinic or Olmsted Medical Centre within a 3-year period.[13] With approval by the Mayo Foundation Institutional Review Board, the complete patient records and echocardiographic video tapes were reviewed in a blinded fashion.

A cardiologist (F.B.) who was unaware of the echocardiographic measurements reviewed the complete clinical history to determine the AF type (paroxysmal or persistent, according to published guidelines[2]). The date of onset of classic cardiovascular risk factors was recorded, including dyslipidaemia, hypertension (blood pressure more than 140/90 mmHg or antihypertensive treatment), and diabetes mellitus requiring treatment with oral antidiabetic medication or insulin. A history of smoking at any time was also noted.

Medical records were reviewed for study outcomes including: (1) cerebrovascular event, including cerebral infarction or intracerebral haemorrhage but not including transient ischaemic attacks; (2) acute myocardial infarction (MI) defined according to the World Health Organization criteria[14] (symptoms and typical electrocardiographic changes or elevated cardiac enzymes); (3) a clinical diagnosis of CHF requiring hospitalization; and (4) death. The clinical records were reviewed and a definitive diagnosis of a cerebrovascular event was adjudicated by an experienced neurologist (R.D.B.) who was blinded to the echocardiographic data. The date and cause of death were established by review of the medical record, including death certificates and autopsy reports.

Echocardiographic measurements

In patients with more than two echocardiograms, the first and the last echocardiogram were chosen for detailed analysis. This was done to cover most of the follow-up duration, while keeping the time-dependent statistical models feasible. For all patients, the original videotape recordings of echocardiograms were quantitatively remeasured for volumetric LAV and volumetric left ventricular EF. LAV was measured using the biplane area-length method[15] and indexed to body surface area. Left ventricular EF was measured using the biplane Simpson's method. Indexed LAV $\geq$32 mL/m^2, that is, above the 95th percentile in a large reference sample based on the Olmsted County population,[16] and EF <50% were considered abnormal. Because the echocardiograms were performed over a period of approximately three decades, additional state-of-the-art assessment such as Doppler diastolic function was not consistently available. Echocardiographic measures were obtained independently by two experienced investigators (M.O., J.B.S.) who were blinded to the clinical history of the patients. Measurements were repeated by each observer over at least three different cardiac cycles and averaged. Interobserver agreement was strong, with an intraclass correlation of 0.86 and a Pearson correlation coefficient of 0.93.

Statistical analysis

Continuous variables are presented as mean and SD, and categorical variables as percentages. All *P*-values are two-tailed and a value $\leq$0.05 is considered statistically significant. SAS Version 8 (SAS Institute Inc., 2000, Cary, NC, USA) was used for all statistical analyses.

Multiple linear regression was used to identify the predictors of LAV (at first echocardiogram). Predictors included were age (at time of echocardiogram), sex, history of any event (CHF, stroke, or MI), persistent type of AF (at time of echocardiogram), and duration of AF (from onset to echocardiogram).

Expected survival free of cerebral infarction was determined from age- and sex-specific cerebral infarction rates of the Rochester, Olmsted County, MN, USA, population database during 1955–94.[17] Survival free of cerebral infarction was estimated using the Kaplan–Meier product limit method and comparisons were made by use of the log-rank test.

A Cox model was fit with covariates of sex and age at onset and three time-dependent covariates: total number of four possible clinical risk factors, left ventricular EF, and LAV. The time-dependent modelling of these variables allowed for their realistic representation during the long follow-up. To treat the two echocardiographic variables as time-dependent, it was necessary to impute their values at times other than the actual times of measurement. To internally validate our results, three different methods were used to either reduce assumptions or attempt to model the two variables throughout the whole follow-up. All methods use the date of AF onset as baseline.

Method 1 (strict dichotomized analysis): LAV and left ventricular EF were modelled dichotomously, with normal values defined as LAV <32 mL/m^2 and EF $\geq$50%. Patients were left-censored before an abnormal measurement and right-censored after a normal measurement because the exact point of possible progression could not be known.

Method 2 (dichotomized analysis): dichotomized variables together with interpolation were used to allow for complete follow-up. Before the first measurement, that is, without any evidence of disease, all patients were assumed to have normal values. Between echocardiograms, the status of LAV and EF (normal or abnormal) was ascertained by means of linear interpolation of measurements. After the last measurement, the values were held constant. This method represented the most conventional approach.

Method 3 (continuous analysis): for this innovative method, the variables were treated as continuous. LAV and EF were linearly interpolated between two measurements and held constant after the last measurement until last follow-up. The normal indexed LAV remains constant throughout life at $\sim 22 \pm 6$ mL/m^2, similarly, the normal EF remains at 65%.[16,18] Thus, LAV before the first measure was extrapolated back to the normal value of 22 mL/m^2 at age 30 if the measurement was >22 mL/m^2 and otherwise held constant before that measurement. EF was treated in an analogue fashion.

A full clinical model was fit, including age, sex, and the number of present conventional cardiovascular risk factors (dyslipidaemia, hypertension, diabetes mellitus, and smoking). Significant clinical predictors were then included in a model that was used to assess the incremental value of EF and LAV to predict events.

Results

Fourty-six patients with lone AF fit the inclusion criteria. The median duration of follow-up was 27 (first quartile = 24, third quartile = 33) years, totalling 1296 person-years of follow-up. The mean age was 45.8 ± 12.1 at the onset of AF and 74 ± 11.3 at last follow-up; 38 patients (83%) were men. Up to the time of the first echocardiographic examination, 35 patients (76%) were in paroxysmal AF and 11 (24%) in persistent AF. These values changed to 27 (59%) for paroxysmal AF and 19 (41%) for persistent AF at the end of follow-up. The mean LAV at the initial echocardiographic examination was 38.1 ± 22.3 mL/m^2 and the mean EF was 57.3 ± 12.8%.

According to the clinical definition of benign lone AF, all patients were younger than 60 years and free of cardiovascular risk factors or any history of cardiac disease at the onset of AF. During the three decades of follow-up, all but three patients subsequently developed one or more cardiovascular risk factors (*Table 1*): 18 developed one, 16 developed two, eight developed three, and one developed four. Of the 46 patients, 23 experienced a cardiovascular or cerebrovascular event: 15 experienced one, five experienced two, and three experienced three types of events (*Table 1*). Eighteen patients died at a mean age of 81.7 ± 7.6: nine died of a cardiovascular cause, four of cancer, and four of a respiratory tract infection; for one patient the cause of death was undetermined. The observed mortality at 25 years after onset of lone AF was lower (15.9%) than expected (32.5%) based on age- and sex-specific rates from the general Minnesota white population life tables. This comparison accounted for the censored nature of the data using the Kaplan–Meier method and approached statistical significance (log-rank test, $P = 0.055$).

Survival free of stroke

No patient was receiving continuous anticoagulation therapy because of the reported benign nature of lone AF.[2,3] Seven cerebral infarctions and no intracranial haemorrhages were observed. An eighth patient, with significantly enlarged atria, experienced bilateral retinal artery occlusion but never had a cerebral infarction, and was not included in the stroke endpoint analyses.

Table 1 Incident risk factors and events

Patients ($n = 46$)	N (%)	Age at onset or occurrence, years, mean ± SD
Risk factor		
Diabetes mellitus	10 (22)	59.3 ± 12.9
Dyslipidaemia	20 (43)	61.7 ± 12.1
Hypertension	27 (59)	64.5 ± 12.1
Smoking	21 (46)	N/A[a]
Event		
Death	18 (39)	81.7 ± 7.6
Cerebral infarction	7 (15)	77.1 ± 7.8
Myocardial infarction	11 (24)	69.4 ± 11.3
Congestive heart failure	16 (35)	76.8 ± 9.1

[a]Not applicable.

The survival free of cerebral infarction for patients with lone AF was not significantly different from that expected in the general population ($P = 0.54$) (*Figure 1*).[17]

Predictors of adverse cardiovascular events

Sixteen (70%) of 23 patients without adverse cardiovascular events retained a LAV index <32 mL/m^2 throughout follow-up (*Figure 2*). Twenty (87%) of 23 patients experiencing events had a LAV index ≥32 mL/m^2 before the event (*Figure 3*). In all of the multivariable Cox models predicting any first event, the echocardiographic measurements (LAV and EF) provided incremental information to clinical variables (risk factors and age). LAV was significantly incremental to all other variables combined (*Figure 4*). Gender or the number of risk factors were not independent predictors in any of the final multivariable models.

The adjusted hazard ratio for a LAV ≥32 mL/m^2 predicting any event was 4.46 (95% CI, 1.56–12.74; $P = 0.005$) for the dichotomous model with linear interpolation (Method 2).

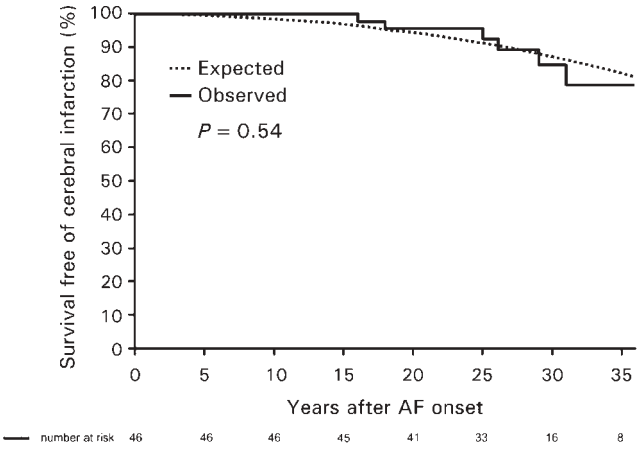

Figure 1 Survival free of cerebral infarction. The observed survival free of cerebral infarction is not different from the expected survival based on the data from Rochester, Olmsted County, MN, USA.

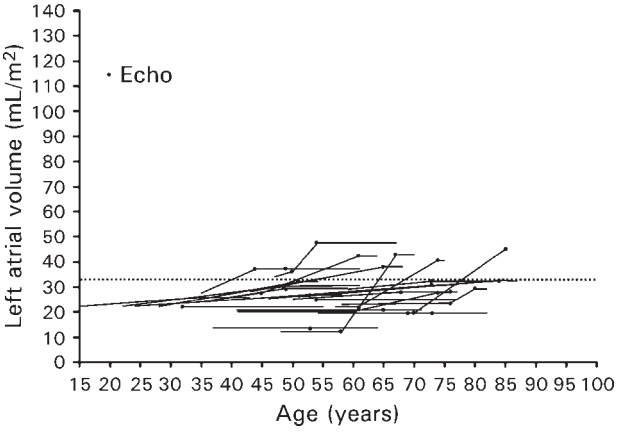

Figure 2 LAV over time for 23 patients without events. LAV indexed to body surface area from the onset of atrial fibrillation to the end of follow-up for each patient who did not experience an event is shown. LAV was linearly interpolated between a normal value of 22 mL/m^2 at age 30 and the values measured at the examinations and plotted constant thereafter. The median length of follow-up in this group was 26 (first quartile = 23, third quartile = 31) years. Note that inspite of atrial fibrillation the LAV remained <32 mL/m^2 (dotted line) for many years. Echo denotes echocardiographic examination.

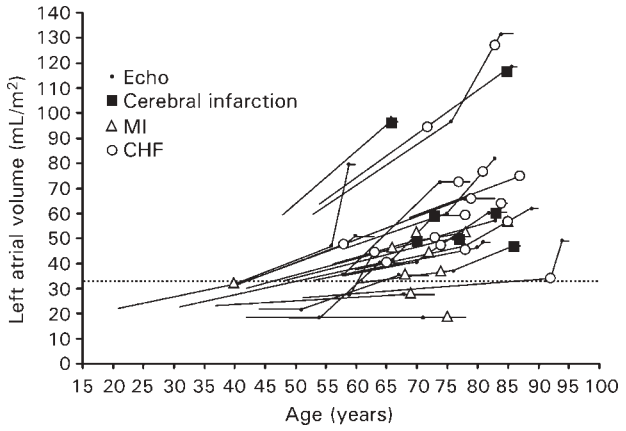

Figure 3 LAV over time for 23 patients with events. LAV indexed to body surface area for each patient who experienced an event is shown. The median length of follow-up in this group was 29 (first quartile = 25, third quartile = 34) years. The three types of event as well as the echocardiographic examinations (Echo) are marked as icons.

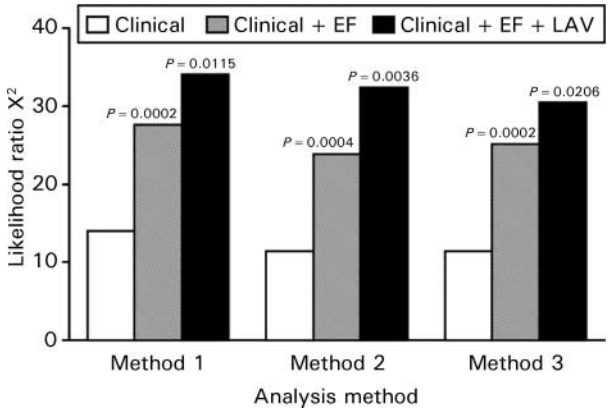

Figure 4 Cox models predicting any cardiovascular or cerebrovascular event. The χ^2 of each model predicting events when including clinical data (age, number of risk factors), EF, and LAV is shown. The *P*-values above the bars are testing for significant incremental addition to the models, specifically, the incremental value of EF (vs. clinical) and then LAV (vs. clinical with EF).

For the continuous model (Method 3), the adjusted hazard ratio for a 10 mL/m^2 increase in LAV was 1.24 (95% CI, 1.04–1.49; $P = 0.017$). The adjusted hazard ratio for LAV in the dichotomous model (Method 1) could not be calculated because all events occurred in patients with abnormal LAV. Using log-likelihood methods, a lower 95% bound for the hazard ratio was 1.9. All three models confirmed the independent and strong predictive value of LAV.

A multivariable analysis for cerebral infarction was not feasible with only seven events. All cerebral infarctions, however, occurred in patients whose LAV was measured >32 mL/m^2 before or at the time of the event, while only four (57%) cerebral infarctions occurred in patients with a measured EF $<50\%$. At any time during follow-up, the rate of cerebral infarction for patients with a LAV $>$ 32 mL/m^2 was 1.19 per 100 person-years.

Factors associated with LAV

Multiple linear regression analysis was performed to investigate the predictors of LAV at the first echocardiogram. Predictors included in the model were age at time of echocardiogram, sex, history of events (yes/no; any of CHF, stroke, or MI), persistent type of AF (yes/no), and duration of AF (from the onset of lone AF to the time of echocardiogram). The results suggested that persistent type of AF was associated with increased LAV ($P = 0.001$). Age at the time of echocardiogram ($P = 0.07$) and occurrence of prior events ($P = 0.09$) were marginally associated with increased LAV. Importantly, the duration of AF ($P = 0.49$) was not associated with an increase in LAV.

Discussion

In the present study, half of the patients with originally diagnosed lone AF experienced cardiovascular events after a median follow-up of 27 years. Increased LAV, which is documented to correlate with increased filling pressure,[8,9] was the strongest independent predictor of adverse events, even after adjustment for age and clinical risk factors. Cerebral infarction occurred only in patients with significantly enlarged LAV, many years after the diagnosis of supposedly benign lone AF. The duration of AF was not related to the development of either cerebral infarction or atrial enlargement.

Age and lone AF

Two separate cohorts of patients with lone AF from Olmsted County, only distinguished by age at the time of diagnosis, a 'young' cohort aged <60[3] (mean age 44) and an 'elderly' cohort >60[6] (mean age 74), have been published. The 'young' cohort was observed to have a low risk of cerebrovascular events (0.3 per 100 person-years). In contrast, the 'elderly' lone AF cohort study experienced an increased rate of cerebral infarction (0.9 per 100 person-years).[6] These and similar[4,5,7] apparently contradictory findings in the absence of any other overt cardiovascular disease, were interpreted as an inevitable transition of benign lone AF that occurs with aging. Thus, the recommended clinical diagnosis of benign lone AF has been confined to patients younger than 60 years.[2] This conclusion has however been drawn from separate patient samples varying in age, and with different comparison groups. In the present study, we have extended the follow-up of a single 'young' cohort of patients with lone AF in order to determine whether the continued presence of lone AF into older age would by itself determine adverse outcome. With nearly three decades of follow-up we found that, as expected, most events occurred at older age, but contrary to other studies we did not observe an increased risk attributable to AF. The age- and sex-specific stroke rate in the group of 'young' lone AF patients remained similar to the general population (0.5 per 100 person-years). In our study, the mean age at which 'young' lone AF patients experienced incident cerebral infarction was similar to that in the general population and to that in the published group of 'elderly' patients with lone AF (77.1 vs. 78.1 years), despite a longer mean duration of AF preceding cerebral infarction (26.7 vs. 5.3 years). This observation indicated that the pathophysiological mechanisms responsible for the development of a cerebrovascular event were unrelated to the continued presence of AF. The current very long-term follow-up study was designed to better understand the pathophysiological changes occurring with age that were

most closely associated with the development of adverse events, irrespective of the presence of lone AF.

LAV and cardiovascular risk in lone AF

Epidemiological studies have observed that in healthy subjects, LAV indexed for body size does not increase with age.[16,18] Increased LAV is a morphological expression of chronic diastolic dysfunction[8,9] and a measure of cardiovascular risk burden.[19] Increased LA size has been shown to be highly predictive of AF and stroke in the community,[10,11,20] and superior to EF in the prediction of mortality in patients with MI[12] and dilated cardiomyopathy.[21]

In the present study, LAV was strongly predictive of adverse events in lone AF, independent of age and the development of clinical risk factors. As the 'young' lone AF population aged, we found that the cohort separated into two distinct groups. One group retained a normal LAV throughout the follow-up and experienced a benign clinical course. The second group who already had or developed enlarged atria experienced almost all of the events. Specifically, cerebral infarction occurred only when LAV exceeded 32 mL/m^2. These results suggest that the development of adverse cardiovascular events in patients with lone AF was more directly related to a measurable pathophysiological change than age alone.

Left ventricular filling pressure, LAV, and AF

Commonly encountered AF in older patients with cardiovascular disease is preceded by atrial enlargement[10] and increased left ventricular filling pressures.[20] Increased atrial afterload increases wall tension,[8,9] atrial effective refractory period dispersion,[22] and fibrosis.[23] The pathophysiological mechanisms of benign lone AF are not completely understood, but it is assumed to represent a primary or focal atrial arrhythmia which is often related to increased parasympathetic tone.[24,25]

Left atrial diameter has been investigated in the setting of lone AF and has been variably reported as either normal[4] or abnormal,[26] with the latter being associated with the development of persistent AF. Until recently, there has been no agreement whether lone AF causes an increase in left atrial size.[4,26,27] Earlier studies however were limited to one-dimensional measurements and relatively short follow-up. As the atria enlarge asymmetrically, a volumetric approach best reflects atrial size.[28] The current study shows that longstanding paroxysmal or persistent AF by itself does not cause an increase in LAV. The observation of a normal LAV in benign lone AF in the present study is consistent with the findings from animal models. Atria subjected to rapid atrial pacing develop AF; however, when protected from heart failure and increased left ventricular filling pressure by atrioventricular block, do not exhibit atrial enlargement or the pathological changes of AF associated with heart failure.[29,30]

Implications

Our findings have important implications for the correct diagnosis and management of AF. Despite the application of a strict clinical definition of lone AF including age <60, it was observed that some of these patients had an unrecognized abnormal LAV at diagnosis. On the basis of epidemiological and animal research, chronic elevation of cardiac filling pressures is likely to be the cause of AF in these patients, despite the absence of clinically overt cardiovascular risk factors. According to our observations, patients with increased LAV should not be considered to have benign lone AF. We have found that adverse cardiovascular events in lone AF were not directly related to chronological aging, but mediated by an increase in age-associated cardiovascular burden. Further studies are needed to investigate the potential of increased LAV to better guide therapeutic decisions for patients with lone AF.

Limitations and strengths

A limitation of our study is the small sample size, which is a reflection of the relatively low prevalence of rigorously defined lone AF within the general population. Like in other studies on lone AF, the small cohort limits the statistical power to detect a difference compared with the general population. While we acknowledge this limitation, we were able to identify a significant predictor of outcome. The study design is historical, however, a prospective study spanning approximately three decades would be unrealistic. The unique strength of this study is the ability to obtain complete follow-up for the cohort, including all of the original echocardiographic studies and medical records. The inclusion criterion of an existing echocardiogram may have resulted in the selection of a cohort with a different risk profile. Thus, our conclusions may only be applied to patients with an echocardiogram. We did not include medical treatment strategies in our analysis, as considerable changes within patients were present due to the long follow-up starting in the 1950s. In addition, although Olmsted County can be considered representative of the Caucasian US population,[13] extrapolation of our findings to other ethnic groups should be made with caution.

Conclusion

In this historical cohort study, we demonstrated that patients originally diagnosed with lone AF may follow divergent courses based on LAV. Those patients who retained small atria throughout the three decade follow-up consistently experienced a benign clinical course. Patients originally diagnosed with benign lone AF, who had unrecognized LAV enlargement at diagnosis or later during the long-term follow-up, experienced adverse events. LAV measurement is a promising tool for risk stratification and monitoring of patients presenting with AF.

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Conflict of interest: none declared.

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