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Atrial fibrillation pattern, left atrial diameter and risk of cardiovascular events and mortality. A prospective multicenter cohort study

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Abstract

Background: There are conflicting evidence on the association between atrial fibrillation (AF) pattern, such as persistent/permanent (Pers/Perm) and paroxysmal (PAF) AF and risk of ischemic events. We investigated if left atrial diameter (LAd) may affect the risk of cardiovascular outcomes according to AF pattern.

Methods: Prospective multicenter observational including 1,252 non-valvular AF patients (533 PAF and 719 Pers/Perm AF). Study endpoints were cardiovascular events (CVEs), major adverse cardiac events (MACE) and CV death. LA antero-posterior diameter (LAd) was obtained by transthoracic echocardiography.

Results: Pers/Perm AF patients had a higher proportion of LAd above median than PAF (≥44 mm, 59.5% vs. 37.5% respectively, p<0.001). In a mean follow-up of 42.2±31.0 months (4,315 patients/year) 179 CVEs (incidence rate [IR] 4.2%/year), 133 MACE (IR 3.1%/year), and 97 CV deaths (IR 2.2%/year) occurred. Compared to patients with LAd below median, those with LAd above the median had a higher rate of CVEs (log-rank test, p<0.001), MACE (log-rank test p<0.001), and CV death (log-rank test p<0.001). Multivariable Cox regression analysis showed that LAd above the median was associated with CVEs, (HR 1.569, 95%CI 1.129-2.180, p=0.007) MACE (HR 1.858, 95%CI 1.257-2.745, p=0.002) and CV death (HR 2.106, 95%CI 1.308-3.390, p=0.002). The association between LAd and outcomes was evident both in PAF and Pers/Perm AF patients. No association between AF pattern and outcomes was found.

Conclusion: LAd is a simple parameter that can be obtained in virtually all AF patients and can provide prognostic information on the risk of CVEs, MACE and CV death regardless of AF pattern.

Keywords: atrial fibrillation; left atrium; echocardiography; cardiovascular events; AF pattern.

What's already known about this topic?

1. Patients with atrial fibrillation (AF) and one additional risk factor beyond sex are candidate to receive an oral anticoagulation treatment independently of AF pattern.

2. LA enlargement was shown to be a risk factor for new-onset AF and was associated with an increased risk of stroke both in non-AF and AF patients.

What does this article add?

1. Left atrium diameter (LAd) above median (≥44 mm) is associated with a higher rate of cardiovascular events (CVEs), major adverse cardiac events (MACEs), and cardiovascular (CV) death.

2. No association between atrial fibrillation pattern and CVEs, MACE or CV death was found.

3. LAd is a simple parameter that can provide prognostic information on the risk of CVEs, MACE and CV death regardless of AF pattern.

Introduction

Patients with atrial fibrillation (AF) and one additional risk factor beyond sex are candidate to receive an oral anticoagulation treatment independently of AF pattern[1,2]. This recommendation is supported by the evidence that patients with paroxysmal (PAF) and persistent/permanent (Pers/Perm) AF showed a similar risk for stroke, any thrombo-embolism, and cardiovascular mortality[3].

Recent studies have challenged this evidence and suggested that thromboembolic risk may vary according to AF type. In a post-hoc analysis of SPORTIF III and V trials, Pers/Perm AF had a nearly doubled risk of ischaemic stroke (IS) and systemic embolism (SE) than PAF[4]. A pre-specified secondary analysis of the ARISTOTLE trial, showed a higher rate of IS/SE in Pers/Perm AF patients compared to those with PAF (1.52 vs. 0.98%; p= 0.003)[5]. In a more recent post-hoc analysis of the ENGAGE AF-TIMI 48 trial, a reduced stroke/SE event rate in PAF patients compared to those with persistent and permanent AF (1.49, 1.83 and 1.95%/year, respectively)was found[6]. These findings are clinically relevant considering that it is estimated that 10-20% of patients at 1 year progress from PAF to Pers/Perm AF[7], this rate raising to 50-77% at 12 years[8].

A systematic review and metanalysis showed a reduced risk of thromboembolic events in PAF compared with non-paroxysmal AF (risk ratio: 0.72)[9]. However, many studies included patients not treated with oral anticoagulants, and the effect of AF pattern on thromboembolic risk was progressively mitigated by the increasing proportion of anticoagulation[9].

However, reasons for the association between specific AF pattern and risk of cardiovascular events (CVEs) were not investigated. Among factors, left atrium (LA) may be of particular interest, as LA enlargement was shown to be a risk factor for new-onset AF[10] with an estimated increased risk of 39% per 5-mm increment[11], and was associated with an increased risk of stroke both in non-AF[12] and AF patients[13].

Based on this, we studied in a large cohort of anticoagulated AF patients, the relationship between cardiovascular outcomes and LA antero-posterior diameter (LAd), which is easy and rapid to perform and can be repeated over time.

Methods

We conducted a multicentric, prospective, observational study, which included 1,252 non-valvular AF patients treated with oral vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) from Sapienza University of Rome and Magna Graecia University of Catanzaro, as previously described **from 2007 and it is still ongoing[14].** The study started in Patients were enrolled during their first visit in the outpatient clinic. **All patients were kept at an INR range of 2.0-3.0 and quality of anticoagulation was assessed by the time in therapeutic range (TTR), as previously described[15].**

We included all patients with non-valvular AF aged ≥18 years old. Exclusion criteria were the presence of valvular AF defined as the presence of mechanical prosthetic heart valve **or moderate-severe mitral stenosis**, any chronic infectious or autoimmune diseases, active cancer, degenerative disease which may affect adherence to VKA treatment (such as Alzheimer or Parkinson's diseases). advanced liver disease (cirrhosis).

At baseline we collected patient's medical history, information on their medications and comorbidities. Every patient underwent a 12-lead electrocardiogram and a resting transthoracic echocardiogram (TTE). LAd was measured by 2D anteroposterior linear dimension obtained from the parasternal long-axis view according to ASE guidelines[16]. Ejection fraction (EF, %) was measured by 2D measurement with the biplane method of disks (modified Simpson's rule) [16].

Follow-up and definition of cardiovascular endpoints

Patients were then regularly followed for the monitoring of International Normalized Ratio (INR) and management of oral anticoagulation every 20-30 days. Patients missing 1 or more INR controls were contacted by phone.

When a patient reported the occurrence of a complication of any type, he was asked to bring medical record to verify the type of event. Only the first event recorded during the follow-up was used for the analysis. Data of patients who were lost during follow-up were censored.

As endpoints for the study we used CVEs, major adverse cardiac events (MACE) and cardiovascular mortality, defined as follows.

CVEs included fatal/non-fatal ischemic stroke and myocardial infarction (MI), cardiac revascularization/coronary bypass surgery, cardiovascular death and transient ischemic attack (TIA). The diagnosis of MI was formulated according to the universal definition proposed by the Joint ESC/ACCF/AHA/WHF[17]. If a patient died within 4 weeks of a stroke or MI, this event was classified as fatal. Death was considered as of cardiovascular origin unless a clear unequivocal non-cardiovascular cause of death was identified. Cardiovascular death included sudden death, progressive heart failure, death related to surgical or percutaneous revascularization procedures. The diagnosis of ischemic stroke was determined by clinical manifestations then confirmed by radiological findings. The TIA was defined according to the Classification of cerebrovascular disease III[18].

We also analyzed the occurrence of MACE, which consisted of fatal-nonfatal MI, cardiac revascularization and cardiovascular death (excluding fatal and non-fatal stroke and TIA).

Validation of endpoints

Data on CVEs, MACE and CV death were prospectively collected during follow-up. When an event occurred, a standardized form was filled in by the investigators. Details on each event were registered, as well as death certificates, hospital discharge letter or copy of the medical records of hospitalization, and other clinical documentation (i.e. radiology and laboratory data) were also obtained from patients, or in case of death, from relatives of patients or from general practitioner. Adjudication of cardiovascular events was performed by a committee composed by physicians who did not participate to the recruitment of patients and was unaware of the clinical and laboratory characteristics of any enrolled patient. Each member of the committee independently evaluated and adjudicated events in a blinded manner. In case of discordant evaluation or difficult adjudication of an event, the committee decided to award the event in a collegial way.

Ethical statement

All patients signed an informed written consent at study entry. The study was approved by the local ethic committee of "Sapienza" University of Rome (No. 1306/2007) and was conducted according to the declaration of Helsinki.

Statistical analysis

Categorical variables were reported as counts (percentage). Continuous variables were reported as mean ± standard deviation. The Student t-test was used to compare means. Pearson's Chi square test (χ^2) was used to compare proportions. Descriptive analyses according to AF pattern (PAF vs. Pers/Perm AF) and LAd above and below the median were performed. Then a multivariable logistic regression analysis was used to calculate the Odds Ratio (OR) and 95% confidence interval (95%CI), of factors associated to the LAd above the median. We estimated the cumulative incidence of CVEs, MACE and cardiovascular death by Kaplan-Meier curves, which were compared with the log-rank test. We used Cox proportional hazard regression analysis to calculate the relative adjusted Hazard Ratio (HR) and 95%CI by each variable. Three different models were used for CVEs, MACE and CV death. All models were adjusted for the same variables as follows: female sex, age, hypertension, diabetes, heart failure, previous ischemic heart disease, previous stroke/TIA were grouped in the CHA_2DS_2VASC score. In addition, antiplatelet, beta blockers, verapamil, amiodarone, digoxin and statins were entered as covariates. ACE inhibitors/ Sartans and Calcium channel blockers were excluded as collinear with arterial hypertension.

Statistical significance was set at a p value <0.05. all tests were two tailed and analyses were performed using computer software packages (SPSS-25.0, SPSS Inc.).

Data availability statement

All data generated or analysed during this study are included in this published article. Data are however available from the authors upon reasonable request and in accordance to current privacy policy and after the permission of all site investigators.

Results

Characteristics of patients according to AF pattern

The study included 1,252 patients, of whom 42.6% were affected by PAF. The characteristics of populations according to AF pattern are shown in **Table 1**. Patients with PAF were younger (p<0.001), with a lower prevalence of hypertension, diabetes, heart failure, and previous ischemic heart disease (**Table 1**). Furthermore, PAF patients were less likely to be treated with beta blockers, and digoxin and more frequently on amiodarone (**Table 1**).

The TTE evaluation showed a reduction of systolic function in patients with Pers/Perm AF compared to patients with PAF (EF 52.9 vs. 56.4 %, p<0.001), along with a higher tele diastolic left ventricular diameter (**Table 1**). LAd was increased in Pers/Perm AF compared to PAF ones (45.61 vs. 41.82 mm, p<0.001 **Table 1)**. In particular, a higher proportion of LAd above the median was present in Pers/Perm AF patients (p<0.001, **Table 1**).

Correlates of LA diameter

Analysis of characteristics of patients according to LAd showed that patients with LAd above the median were less frequently women, older, more likely to have Pers/Perm AF with a higher prevalence of hypertension, diabetes, heart failure, previous ischemic heart disease (**Table 2**). Regarding treatments, Patients with LAd above median were more treated with digoxin and less with amiodarone compared to those with LAd below the median (**Table 2**).

Multivariate logistic regression analysis investigating clinical factors associated with LAd above the median showed an inverse association with female sex, and a direct association of Pers/Perm AF pattern, age, hypertension and heart failure with LAd above the median (**Table 3**).

LAd and cardiovascular outcomes

During follow-up, 24 patients were lost and 1,228 were included in the survival analysis. The mean follow-up was 42.2±31.0 months (4,315 patients/year) and during follow up occurred 179 CVEs (incidence rate [IR] 4.2%/year, 95%CI 3.6-4.9), 133 MACE (IR 3.1%/year, 95%CI 2.6-3.7), 97 CV death (IR 2.2%/year, 95%CI 1.8-2.7).

When we analysed incidence of cardiovascular outcomes according to the median of LAd, we found that, compared to patients with LAd below median, those with LAd above the median had a higher rate of CVEs (59 vs. 120, log-rank test, p<0.001), MACE (40 vs. 93, log-rank test p<0.001), and CV death (26 vs. 71, log-rank test p<0.001) (**Figure 1**).

Multivariable Cox proportional hazard regression analysis showed that LAd above the median was associated with CVEs, (HR 1.569, 95%CI 1.129-2.180, p=0.007) MACE (HR 1.858, 95%CI 1.257-2.745, p=0.002) and CV death (HR 2.106, 95%CI 1.308-3.390, p=0.002). No association between AF pattern and outcomes was found (**Table 4 Panels A-C**).

To further investigate the relationship between LAd and AF pattern for outcomes prediction, we performed the multivariable Cox proportional hazard regression analysis separately in PAF and Pers/Perm AF patients. At univariable analysis, LAd above the median was associated with CVEs, MACE and CV death both in PAF and Pers/Perm AF patients (**Figure 2**).

Other parameters of LA size and CVEs

To further investigate the association of LA size parameters and CVEs we also tested the predictive value of LA area and LA volume/BSA. We found a significant correlation of LA diameter with LA area (r=0.675, p<0.001) and with LA volume/BSA (r=0.584, p<0.001). LA area and LA volume/BSA were higher in patients with Pers/Perm AF compared to PAF ones (Table 1).

However, while LAd was higher in patients with CVEs (p<0.001), neither LA area (p=0.791) or LA volume/BSA (p=0.446) were increased.

At survival analysis, increased LA area >21 cm^2 (HR 0.851, 95%CI 0.563-1.288) and LA volume/BSA >34 ml/m^2 (HR 1.094, 95%CI 0.713-1.677) were not associated with CVEs after adjustment for CHA_2DS_2 VASc score and AF pattern.

Anticoagulation, TTR and CVEs

Of the 1228 patients with data during follow-up, 1109 patients were on VKAs and 119 on DOACs. TTR was available for 771/1109 patients. Mean TTR was 63.1±22.8%. and 37.8% had a TTR <70%. Low TTR <70% was associated with CVEs (n=101, HR 2.106 95%CI 1.348-3.290, p=0.001). LAd above median remained associated with CVEs (HR 1.570, 95%CI 1.255-1.618, p<0.001) along with TTR <70% (HR 2.083, 95%CI 1.333-3.256, p=0.001) after adjustment for CHA_2DS_2 VASc score and AF pattern.

Discussion

This multicentric, prospective, observational study showed a similar incidence of CVEs and CV death in patients with PAF and Pers/Perm AF. We found that LA enlargement, as assessed by the easy antero-posterior LAd, was increased in Pers/Perm AF patients and was a predictor of CVEs, MACE and CV mortality both in PAF and Pers/Perm AF patients.

In our cohort of consecutive AF patients referring to an outpatient clinic, 42.6% of patients had PAF. The proportion of patients with PAF is higher than previous studies such as 24% in ACTIVE-A and AVERROES trials[19], 25% in the ENGAGE-AF TIMI 48[6], and 15.3% from the ARISTOTLE trial[5]. This higher proportion may be explained by the fact that this is a real-world study of patients usually referred to an anticoagulation clinic shortly after new-onset AF, when paroxysmal form is still commonly observed[20]. However, characteristics of our PAF patients are in keeping with previous studies, showing a that PAF patients were younger and with lower cardiovascular comorbidity burden than Pers/Perm AF. Regarding anti-arrhythmic treatments, PAF patients were more treated with amiodarone, similarly to the ENGAGE trial[6], and less with beta blockers as already observed in the ARISTOTLE trial[5], while Pers/Perm AF were more frequently on digoxin, in keeping with findings from ACTIVE-A and AVERROES trials[19].

Our data do not confirm previous findings from randomized clinical trials on this topic showing a higher risk of ischemic complications in Pers/Perm AF compared to PAF[4-6]. However, some real-world studies seem to corroborate our findings. A recent study performed on a Chinese AF registry that included 8,529 AF patients showed an increased risk of thromboembolism (a composite endpoint of stroke, TIA and systemic embolism) in Pers/Perm AF patients compared to PAF patients only if they were not treated with anticoagulant (HR 1.521, 95%CI 1.152-2.008), but this association was not evident in the group of patients on anticoagulation (HR 0.988, 95%CI 0.647-1.509)[21].

Furthermore, a sub-analysis of the GISSI-AF trial, which enrolled 1,234 patients, (771 PAF and 463 Pers/Perm AF) showed similar rates of thromboembolic events between PAF and Pers/Perm AF patients (HR 2.14, 95%CI 0.68-6.79) during 1 year of follow-up[22].

The controversial evidence on this topic raises the concern whether AF pattern is associated *per se* to the risk of ischemic complications, or rather if this risk may be attributable to a specific still unexplored underlying cause. As a possible mediator for this risk we investigated LA size

according to AF pattern, based on previous studies showing a graded increase in LA size from PAF to permanent AF[23]. Our study confirms a higher LAd in Pers/Perm AF patients compared to PAF ones, with 59.5% and 37.5% of patients with enlarged LAd, respectively in line with previous findings from the SPAF trial[24].

We also investigated clinical characteristics of patients with increased LAd (i.e. ≥44 mm) and found that patients with LAd above this value represent a high-risk subgroup of patients, who are more frequently men, elderly and with a high cardiovascular burden.

When we examined the risk of cardiovascular outcomes in relation to LA size, we found a significant association of LAd with risk of CVEs, MACE and CV death, regardless of the AF pattern considered. This association remained significant after adjustment for traditional CV risk factors and common treatments. While the association between LA enlargement and stroke has been previously reported, the novel finding of our study consists in the association between LA enlargement and cardiac outcomes, such as MI and CV death. This finding is of clinical relevance considering that patients with AF still experience a high rate of cardiac complications[25], which are only partially prevented by oral anticoagulants[15].

Our findings suggest that LAd might be considered as an additional risk factor especially in patients with low thromboembolic risk such as those with CHA_2DS_2VASc 0-1, for whom anticoagulation is based on risk-benefit evaluation. Furthermore, the association of LAd with MACE may identify a subgroup of patients at higher cardiovascular risk, who therefore may benefit from a more intense management of cardiovascular comorbidities[26].

Of note, we did not find a similar association using other measures of LA size, such as LA area and indexed LA volume. These parameters were higher in patients with Pers/Perm AF compared to PAF, and significantly correlated with LAd. However, only the LAd was associated with CVEs during follow-up. This difference may be explained by several factors including the need of more experienced clinicians to correctly estimate LA area and LA volume resulting in a more intrinsic variability of these indexes. A recent metanalysis that investigated the predictive value of different LA parameters showed that LAd was the strongest predictor of CVEs in AF patients, while LA volume was not associated with stroke, thromboembolism and death[27].

Limitations and implications

The study has limitations and implications. Our findings come from a prospective multicenter study, which is a strength of the study. However, to evaluate LA size we used the LAd, which despite not being the most accurate parameter to estimate LA dimension, is a standardized measure that is easy to perform and available in most clinics. Of note, the median value of LAd used in this study is very close to that previously related to an increased risk of AF recurrences and stroke/systemic embolism[13]. Thus, in the Fushimi AF Registry[13], which included 2,713 AF patients, LAd >45 mm was associated with stroke/systemic embolism despite treatment with oral anticoagulants (HR 1.83, 95%CI 1.21-2.82). Furthermore, the use of LAd may be of usefulness in obese patients, in whom the LA volume is usually difficult to measure and underestimated.

Our results come from a cohort of elderly Caucasian patients, thus generalizability of these findings to other populations is uncertain. Furthermore, the majority patients were treated with VKAs and results should be confirmed also in patients on DOACs. Furthermore, the presence of valve disease in addition to LA size should be investigated as it may affect cardiovascular risk.

Conclusions

In conclusion, patients with an increased LAd showed a higher rate of CVEs, MACE and CV death, which was not related to the AF pattern. The simple measurement of LAd may help identifying a subgroup of patients at higher risk not only for stroke but also for MI and CV death.

Declarations

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Appendix: *ATHERO-AF study group members: Mirella Saliola, Marco Antonio Casciaro, Tommasa Vicario, Giulia Astorri

Disclosures: none.

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Table 1. Population characteristics based on atrial fibrillation pattern.

	PAF (n=533)	Pers/Perm AF (n=719)	p value
Women (%)	45.0	40.5	0.118
Age (mean)	71.5±9.7	73.9±8.6	<0.001
Age >75 years (%)	40.5	47.8	0.011
Hypertension (%)	85.2	89.6	0.023
Diabetes (%)	18.9	24.0	0.038
Heart Failure (%)	12.0	21.9	<0.001
Previous ischemic heart disease (%)	19.1	25.3	0.010
Previous Stroke/TIA (%)	13.1	13.3	0.944
CHA_2DS_2 VASc score (mean±SD)	3.3±1.5	3.6±1.5	<0.001
Treatments			
Antiplatelet (%)	19.8	19.9	0.973
ACE inhibitors/ Sartans (%)	69.0	72.1	0.255
Beta blockers (%)	38.0	50.6	<0.001
Digoxin (%)	8.8	23.1	<0.001
Calcium channel blockers (%)	27.8	27.9	0.964
Verapamil (%)	10.0	10.8	0.698
Amiodarone (%)	32.3	11.1	<0.001
Echocardiographic characteristics			
LVEF Simpson's method (%)	56.4±7.9	52.9±9.7	<0.001
Intraventricular septum diameter (cm)	1.1±0.2	1.2±0.2	0.002
Posterior wall diameter (cm)	1.0±0.2	1.0±0.2	0.621
LVTD (cm)	5.0±0.6	5.2±0.7	<0.001
LAd (mm)	41.8±6.1	45.6±7.3	<0.001
LAd above median (%)	37.5	59.5	<0.001
LA area (cm^2)	22.1±4.4	26.4±5.7	<0.001
LA volume (ml)	67.9±21.3	87.4±28.2	<0.001
LA volume/BSA (ml/m^2)	36.5±10.8	46.6±14.3	<0.001

ACE: Angiotensin-converting-enzyme, AF: Atrial fibrillation, BSA: Body surface area, IVSd: Intraventricular septum diastolic, LA: Left atrium, LAd: Left atrial antero-posterior diameter, LVEF: Left ventricular ejection fraction, LVTD: Left ventricular tele diastolic diameter, PAF: Paroxysmal AF, Pers/Perm AF: Persistent/Permanent AF, TIA: Transient ischemic attack.

Table 2. characteristics of patients according to left atrial diameter (LAd) above or below the median.

	Below the median (n=625)	Above the median (n=627)	p value
Women (%)	46.2	38.4	0.005
Age (mean)	72.1±9.7	73.7±8.5	0.002
Age >75 years (%)	42.1	47.4	0.061
Pers/Perm AF (%)	46.6	68.0	<0.001
Hypertension (%)	83.4	91.7	<0.001
Diabetes (%)	19.2	24.3	0.029
Heart Failure (%)	10.1	25.2	<0.001
Previous ischemic heart disease (%)	16.6	28.6	<0.001
Previous Stroke/TIA (%)	12.0	14.5	0.212
CHA_2DS_2 VASc score (mean)	3.25±1.5	3.72±1.5	<0.001
Treatments			
Antiplatelet (%)	18.9	21.0	0.393
ACE inhibitors/ Sartans (%)	69.0	72.6	0.170
Beta blockers (%)	43.3	46.8	0.231
Digoxin (%)	12.3	22.0	<0.001
Calcium channel blockers (%)	27.2	28.7	0.569
Verapamil (%)	9.0	11.9	0.103
Amiodarone (%)	23.7	14.9	<0.001
Echocardiographic characteristics			
LVEF Simpson's method (%)	56.6±7.5	52.5±9.8	<0.001
Intraventricular septum diameter (cm)	1.1±0.2	1.2±0.2	<0.001
Posterior wall diameter (cm)	1.0±0.2	1.1±0.2	<0.001
LVTD (cm)	4.9±0.6	5.3±0.7	<0.001

Table 3. Multivariable logistic regression of clinical factors associated with left atrial diameter above the median (≥44 mm).

	p value	Odds ratio	95% Confidence Interval	
AF Pattern (Pers/Perm AF vs. PAF)	<0.001	2.283	1.714	3.041
Age	0.043	1.033	1.001	1.067
Female sex	0.020	0.709	0.531	0.948
Hypertension	0.010	1.829	1.154	2.901
Diabetes	0.345	1.177	0.840	1.649
Previous Stroke/TIA	0.632	1.115	0.715	1.739
Previous ischemic heart disease	0.234	1.248	0.866	1.799
Heart failure	0.002	1.918	1.280	2.874

AF: atrial fibrillation, PAF: paroxysmal AF, Pers/Perm AF: persistent/permanent AF.

Table 4. Multivariable Cox proportional hazard regression of factors associated with cardiovascular events during follow up.

Panel A. CVEs	p	Hazard ratio	95.0% confidence interval	
Pers/Perm AF	0.232	0.824	0.600	1.132
Antiplatelet	0.529	1.116	0.792	1.573
LA above median	0.007	1.569	1.129	2.180
Beta blockers	0.056	0.727	0.525	1.008
Amiodarone	0.290	0.813	0.554	1.194
Verapamil	0.277	0.766	0.474	1.238
Digoxin	0.028	1.458	1.041	2.042
Statin	0.794	1.041	0.769	1.409
CHA_2DS_2VASc score	<0.001	1.362	1.239	1.498

Panel B. MACE	p	Hazard ratio	95.0% confidence interval	
Pers/Perm AF	0.204	0.789	0.548	1.137
Antiplatelet	0.851	1.039	0.695	1.553
LA above median	0.002	1.858	1.257	2.745
Beta blockers	0.025	0.641	0.434	0.945
Amiodarone	0.696	0.917	0.594	1.415
Verapamil	0.821	0.942	0.562	1.579
Digoxin	0.257	1.260	0.845	1.879
Statin	0.382	1.168	0.824	1.657
CHA_2DS_2VASc score	<0.001	1.356	1.215	1.514

Panel C. CV death	p	Hazard ratio	95.0% confidence interval	

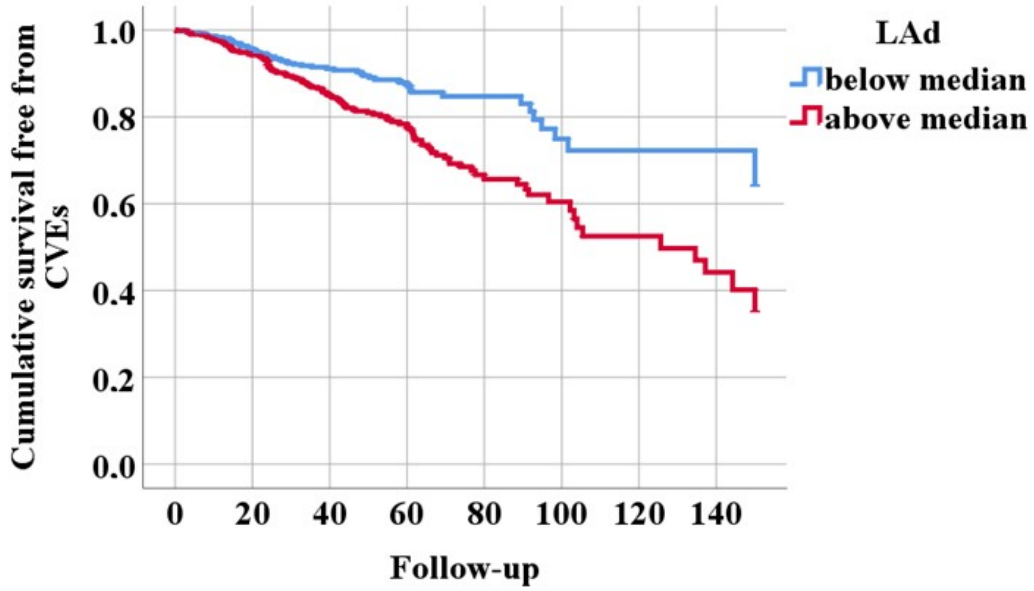
Pers/Perm AF	0.239	0.772	0.502	1.187
Antiplatelet	0.023	1.656	1.074	2.553
LA above median	0.002	2.106	1.308	3.390
Beta blockers	0.005	0.493	0.301	0.808
Amiodarone	0.167	0.687	0.404	1.169
Verapamil	0.695	0.889	0.494	1.600
Digoxin	0.055	1.557	0.991	2.446
Statin	0.093	0.688	0.445	1.065
CHA_2DS_2VASc score	0.000	1.347	1.184	1.532

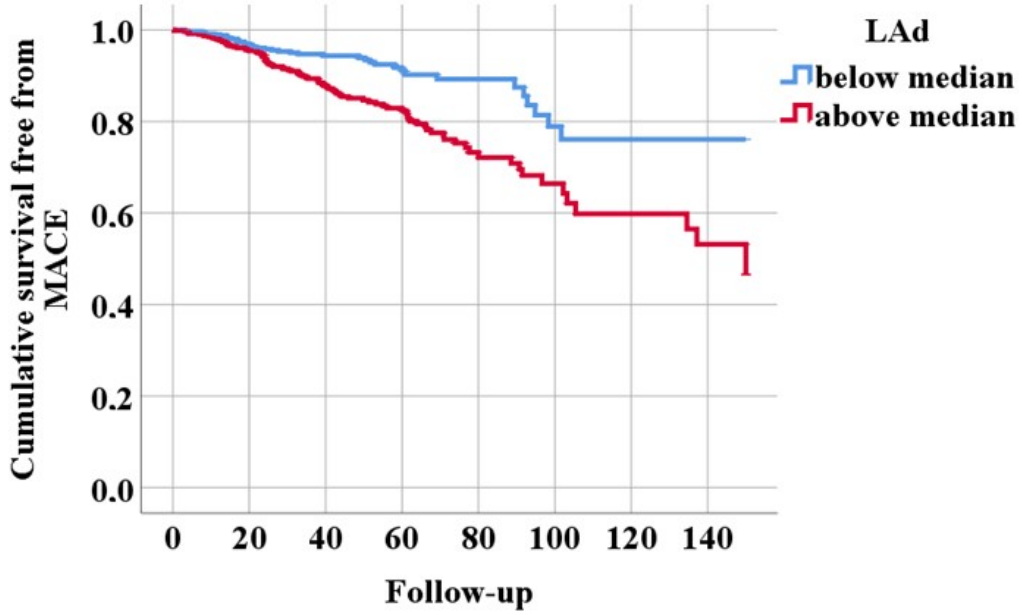
AF: Atrial Fibrillation, LA: Left atrium, Pers/Perm: Persistent/Permanent atrial fibrillation.

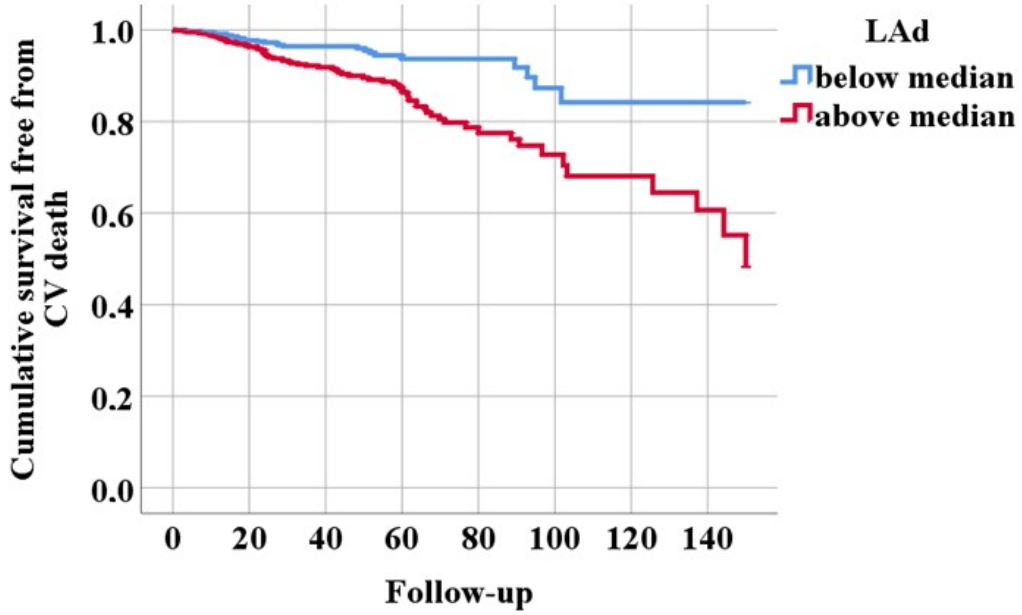
Figures Legend

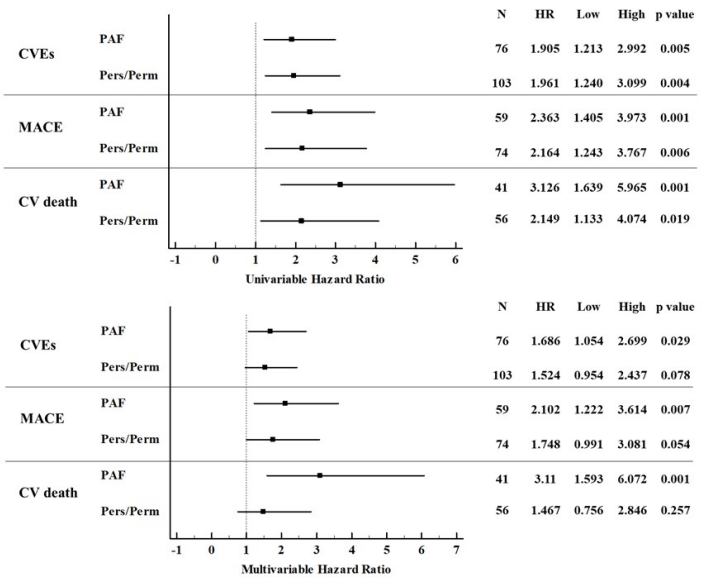
Figure 1. Kaplan Meier survival curves for cardiovascular events (CVEs), major adverse cardiac events (MACE) and Cardiovascular death according to left atrial diameter (LAd) above or below the median.

Figure 2. Forest plot of hazard ratio (HR) for left atrial diameter (LAd) above the median for cardiovascular events (CVEs), major adverse cardiac events (MACE) and CV death according to paroxysmal (PAF) or persistent/permanent (Pers/Perm AF) AF pattern.









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