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Left and right atrial echocardiographic parameters and outcome in patients with atrial fibrillation

Short title: Atrial echocardiographic parameters in atrial fibrillation patients

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WHAT'S NEW?

To our knowledge, this is one of the first studies to comprehensively evaluate the correlation between a broad set of both left atrial and right atrial echocardiographic parameters and outcomes (defined as a composite of all-cause death, stroke or systemic embolism, any acute coronary syndrome and hospitalization for new/worsening heart failure) in a real-world cohort of atrial fibrillation patients.
We found that atrial echocardiographic parameters, particularly those related to the left atrial, were associated with long-term adverse outcomes, thus highlighting the importance of a comprehensive echocardiographic evaluation in the clinical practice, since this assessment may provide valuable insights into the extent of atrial remodeling and underlying atrial cardiomyopathy.

ABSTRACT

Background: This study evaluates the association between left and right atrial (LA, RA) parameters and a composite endpoint (CEP) of all-cause death, thromboembolism, acute coronary syndrome, and heart failure hospitalization in atrial fibrillation patients.

Methods: Patients were prospectively enrolled. At baseline, the following echocardiogram parameters were measured: LA and RA antero-posterior diameter indexed (iLAAPD, iRAAPD), LA and RA volume indexed (LAVi, RAVi), LA and RA sphericity index (LASI, RASI), LA and RA emptying fraction.

Results: A total of 489 patients (61.3% males) with a median age of 75 (66–80) years and a median CHA_2DS_2VASc score of 3 (2–5) were enrolled (92.2% receiving anticoagulation). Permanent atrial fibrillation was present in 40.5% of the total cohort. After a median follow-up of 1114 (392–1384) days, 129 patients (26.3%) reached the CEP. The highest sensitivity for CEP was for LA emptying fraction <28% and iRAAPD >24 mm/m^2 (72% and 73%, respectively) while the best negative predictive values were for iLAAPD and LAVi (both 81%). Right atrial parameters were not associated with CEP. Discrimination analysis using net reclassification improvement (NRI) showed that iLAAPD, and LAVi significantly improved patient reclassification compared to a null model without atrial parameters (iLAAPD NRI 0.30; $P = 0.005$; LAVi NRI 0.32; $P = 0.002$). Multivariable Cox regression analysis found that LA dimensions, volume, and function were associated with a higher risk of adverse outcomes and significantly improved risk prediction for the CEP.

Conclusions: LAVi and iLAAPD enhance discrimination and risk prediction for adverse outcomes in AF patients.

Key words: atrial cardiomyopathy, atrial fibrillation, atrial remodeling, echocardiography, outcome

INTRODUCTION

Atrial fibrillation (AF) poses a significant challenge to healthcare systems, especially in Western countries, due to the rising number of affected patients, associated adverse outcomes and costs of care [1]. Research on AF pathophysiology has focused on the remodeling process of the left and right atria. AF and atrial remodeling share a bidirectional link, each being both a cause and effect of the other [2, 3]. In clinical practice, structural remodeling is commonly assessed by measuring atrial dimensions and function. Various imaging techniques, including echocardiography and cardiac magnetic resonance (MR) are used to evaluate atrial remodeling and underlying atrial cardiomyopathy [4]. There is no consensus on the optimal parameter for assessing atrial remodeling.

Left atrial (LA) volume indexed by the body surface area (BSA) is the most commonly used measure in daily clinical practice [5]. LA enlargement is a known factor associated with progression to permanent AF, affecting up to 22% of patients with first-diagnosed or paroxysmal AF, as recently reported in a large European cohort. Adding moderate-to-severe enlargement of the left atrium to the HATCH score (hypertension, age ≥75 years, stroke or transient ischemic attack, chronic obstructive pulmonary disease, and heart failure [HF]) resulted in a significant improvement in predicting the progression to permanent AF compared to the HATCH score alone [6]. In the context of AF ablation, increased left atrial antero-posterior diameter (iLAAPD) indexed by BSA was a predictor of AF recurrences [7, 8]; however, conflicting results remain [9, 10].

Recently, three-dimensional (3D) echocardiography techniques have been introduced. Schaaf et al. reported that patients with paroxysmal AF had greater LA volumes and impaired LA function compared to patients without AF [11]. Moreover, LA strain has been studied as a marker of AF recurrence after catheter ablation [12, 13] and a predictor of new onset of AF in patients with HF with preserved ejection fraction [14] and risk of ischemic stroke [15]. Atrial remodeling can be also evaluated using the left and right atrial sphericity indices (LASI and RASI). In a study analyzing left and right atrial sphericity with MR, LA sphericity was found to be associated with AF pattern, while right atrial (RA) sphericity was correlated with AF recurrences after catheter ablation [16].

In daily practice, advanced echocardiographic and MR methods for assessing anatomical atrial remodeling are not easily available. Therefore, we aimed to compare LA and RA echocardiographic parameters, which can be obtained through a simple echocardiographic assessment, to identify the best predictors of outcome in an unselected cohort of AF patients.

METHODS

The Fibrillazione Atriale in Modena (FAMo) registry is a prospective single-center observational study conducted at the Cardiology Division of the tertiary-care University Hospital in Modena. From March 2016 to December 2021, we enrolled in- and outpatients with AF in our tertiary center. The enrollment criteria included: 1) age ≥18 years; 2) an electrocardiogram (ECG) (standard 12-lead ECG recording or a single-lead ECG tracing ≥30 seconds showing no discernible repeating P waves and irregular RR intervals) documenting an AF episode within 1 year; 3) written and informed consent and 4) no participation in clinical trials at the time of enrollment. At enrollment, we collected demographic, clinical, laboratory, pharmacotherapy, and echocardiographic data. The protocol was approved by the local ethical committee (approval number: 237/16) and the study was performed according to the European Union Note for Guidance on Good Clinical Practice (CPMP/ECH/135/95) and the Declaration of Helsinki.

Diagnosis and pattern of AF, EHRA score, CHA_2DS_2VASc, and HAS-BLED scores were assessed according to 2020 European Society of Cardiology guidelines [1, 17].

Valvular heart disease was defined if aortic, mitral, tricuspid or pulmonary valves stenosis or a regurgitation was graded at least moderate-to-severe. Chronic kidney disease (CKD) was defined as Chronic Kidney Disease Epidemiology Collaboration group (CKD-EPI) formula value <60 ml/min/1.73 m. Anemia was defined by hemoglobin levels <13 g/dl for males and 12 g/dl for females. Major and clinically relevant non major bleedings were defined according to International Society of Thrombosis and Hemostasis criteria [18].

For the purpose of this analysis, we included patients with available information concerning the echocardiographic parameters as detailed below. Therefore, all patients who did not have a complete echocardiographic evaluation, with high-quality echocardiographic images allowing the measurement of atrial parameters included in the present analysis were excluded.

Echocardiographic parameters

The echocardiographic parameters considered included LA and RA volumes indexed by BSA (LAVi and RAVi), indexed LA and RA antero-posterior end-diastolic diameters (iLAAPD and iRAAPD), LA and RA emptying fraction (LAEF and RAEF), LASI and RASI.

A complete transthoracic echocardiographic evaluation was performed within 3 months after enrollment, using a commercial ultrasound system (EPIQ CVx, Philips Healthcare) with a X5-1 transducer, or an ACUSONSC200 (Siemens Healthineers) machine, with a 4V1c transducer. All measurements were obtained over three different cardiac cycles for patients in sinus rhythm and over five beats for patients in AF, with the final value being the mean of these and then indexed by BSA where appropriate. iLAAPD and iRAAPD were both measured in B-mode, in parasternal long-axis and in 4-chamber view respectively, at the end of ventricular systole (corresponding at the end of the QRS in the electrocardiographic trace), when their dimension is maximal, using the inner-to-inner edge method. iLAAPD was considered abnormal when greater than 22 mm/m^2. Using both apical 4- and 2-chambers views, LAVi was measured and calculated with the biplanar Simpson method, while RAVi was measured in the 4-chamber view using single plane disc summation [5]. LAVi was classified as normal up to 34 ml/m^2, mildly dilated 35–41 ml/m^2, moderately dilated 42–48 ml/m^2, and severely dilated values greater than 48 ml/m^2 [19]. LAEF and RAEF were calculated using the formula: ([maximum volume – minimum volume]/maximum volume) × 100 [20]. The sphericity indices were calculated as the ratio between the antero-posterior and longitudinal diameter, obtained in the 4-chamber view in B-mode.

In the absence of standardization, RA and LA parameters were grouped according to indexed tertile values, with the higher tertile considered abnormal (LASI, iRAAPD, RAVi, RASI). For LAEF and RAEF, the lowest tertile was considered abnormal. All echocardiograms were performed by expert physicians and reviewed offline by the echo-lab team leader (AB) if needed. A good interrater reliability, with an interclass correlation coefficient of 98.4%–99.1%, was previously proven in our echo-lab for the measurements of atrial parameters [21].

Follow-up protocol and endpoints

Data were collected through the hospital Electronic Healthcare Records (EHRs), during in-office consultations or by phone calls for patients not attending scheduled visits. Patients were generally followed up after 1 month and every 6 months thereafter, unless clinically relevant events occurred. For this analysis, the date of censoring follow-up was May 2022.

The primary endpoint was defined as a composite endpoint (CEP) of all-cause death, stroke or systemic embolism, any acute coronary syndrome and hospitalization for new/worsening HF. The secondary exploratory outcomes were the single components of the CEP. The aim of this post-hoc analysis was to compare LA and RA parameters in predicting the CEP, and the secondary exploratory outcomes.

Statistical analysis

Numerical variables are presented as median and interquartile range and analyzed with Mann–Whitney test, while categorical variables are shown as count and percentage and compared with χ^2 test. Kaplan–Meier curves were built to describe the survival-free from the CEP based on different atrial parameters. We dichotomized atrial values according to literature standards (iLAAPD and LAVi) or by comparing the higher tertile values against the lower and middle tertiles (LASI, iRAAPD, RAVi, RASI), while for LAEF and RAEF, the lower tertile was compared to the middle and higher tertiles. Then, we performed multivariable Cox proportional regression analysis, and 2 adjusted models were built. Model 1 (the “null model”) was adjusted for CHA_2DS_2VASc score, AF type, and oral anticoagulant therapy, while Model 2 included also for chronic obstructive pulmonary disease , smoking history (current or former), and CKD, as well as the same covariates as in Model 1. Results are reported as adjusted hazard ratio with 95% confidence interval (CI). Then, we added to the “null model” each atrial parameter, one by one, to determine if it was an independent predictor of the outcome when adjusted for the variables in the "null model." The models were compared using the likelihood ratio test (LRT), and we checked the proportional hazard assumption using Schoenfeld residuals.

We built receiver-operating characteristic (ROC) curves and calculated the area under the curve (AUC) to evaluate the discrimination power of each atrial parameter vs. the CEP. The AUCs were compared using the DeLong test [22], with the ROC curve analysis of LAVi used as a reference.

In accordance with the method described by Pencina et al. [23], we performed a reclassification analysis, with the "null model" as reference; then, we added each atrial parameter in the analyses, in order to quantify the improvement offered by these atrial measurements. We calculated the integrated discrimination improvement (IDI), and the net reclassification improvement (NRI) for each atrial parameter included, to assess their predictive ability to reclassify the risk of events.

Finally, we used multivariable RCS [24] with 3 knots to illustrate the association between each LA and RA parameter as a continuous variable and the hazard of reaching the CEP. Each model was adjusted for CHA_2DS_2VASc score, AF type, and oral anticoagulant therapy.

A two-tailed *P*-value <0.05 was considered significant. Statistical analysis was conducted using R v.4.1.2 and its interface RStudio using predictABEL, survival, survminer, pROC and rms packages.

RESULTS

From the 856 AF patients enrolled, 489 (57.1%) with complete data were included in the present analysis. The flow-chart of the study is shown in Supplementary material, *Figure S1*. The study cohort comprised 300 males (61.3%) with a median age of 75 (66–80) years, a median CHA_2DS_2VASc score of 3 (2–5) and a median HAS-BLED score of 1 (1–2). Among them, 451 (92.2%) were on anticoagulant therapy. The AF types were as follows: 87 (17.8%) patients had paroxysmal AF, 141 (28.8%) had persistent AF, 198 (40.5%) had permanent AF, and 63 (12.9%) had first-detected AF. The clinical characteristics of the study cohort are detailed in Table 1.

The threshold for identifying the highest tertile were as follows: LASI >0.71, iRAAPD >24 mm/m^2, RAVi >32 ml/m^2 and RASI >0.82. The lowest tertile thresholds for LAEF and RAEF were <28% and <25%, respectively.

After a median follow-up of 1114 (392–1384) days, 84 (17.2%) patients died and 129 (26.4%) reached the CEP. These patients were older, more frequently enrolled in the hospital setting, had permanent AF, higher CHA_2DS_2VASc and HAS-BLED scores and higher history of coronary artery disease, valvular heart disease and HF (all *P* <0.001) (Table 1).

Crude rates of adverse events, according to LA dilation, are reported in Table 2. Patients with moderate-to-severe atrial dilation (based on LAVi categories) had a higher rate of death (*P* = 0.001), more frequent admissions for new/worsening HF (*P* = 0.013) and higher rates of the CEP (*P* <0.001)

compared to those with no-to-mild dilation. Both atrial diameters and volumes, and reduced LAEF were significantly associated with a higher rate of the CEP (all P <0.001) (Table 3). Conversely, RAEF < 25% and both sphericity indexes were not (Table 3).

Kaplan–Meier curves showed a lower survival free from the CEP for the vast majority of left atrial parameters (iLAAPD, LAVi, LAEF), and some right atrial parameters (iRAAPD and RAVi), as detailed in Figure 1, except for LASI, RASI, and RAEF (Supplementary material, *Figure S2*). Table 4 shows the results of multivariable Cox regression analysis for the CEP: iLAAPD (adjusted hazard ratio, 95% CI, 1.78; 1.24–2.57), LAVi (1.50, 1.03–2.19), LAEF (1.74; 1.21–2.48) and iRAAPD (1.65; 1.10–2.47) were significantly associated with a higher risk of CEP, while, when adjusting also for chronic obstructive pulmonary disease, smoking and CKD, these results were confirmed only for iLAAPD and LAVi (1.63, 1.14–2.34; 1.47, 1.03–2.09, respectively). Concerning the secondary exploratory outcomes (Supplementary material, *Table S1*), iLAAPD (1.92, 1.23–3.00), LAVi (1.87, 1.20–2.92), LAEF (1.80, 1.05–3.07), and RAVi (1.97, 1.09–3.55) were associated with a higher risk of death, and both LAEF (3.02, 1.27–7.17) and RAVi (6.44, 1.98–21.0) were associated also with a higher risk of hospitalization for HF. No statistically significant differences were observed regarding the other secondary exploratory outcomes (Supplementary material, *Table S1*).

The ROC analysis showed moderate power in discriminating patients who met the CEP (AUC always <0.7). However, LAVi ≥42 ml/m^2 and iLAAPD >22 mm/m^2 had better, though not optimal, negative predictive values (Supplementary material, *Table S2*).

At reclassification analysis, iLAAPD >22mm/m^2 (NRI 0.30; 95% CI, 0.09–0.50; P = 0.005; IDI 0.02; 95% CI, 0.01–0.04; P = 0.008), LAVi ≥42 ml/m^2 (NRI 0.32; 95% CI, 0.12–0.53; P = 0.002; IDI 0.03; 95% CI, 0.01–0.05; P = 0.014), and LAEF <28% (NRI 0.26; 95% CI, 0.05–0.46; P = 0.014; IDI 0.01; 95% CI, 0.002–0.02; P = 0.021) were effective in reclassifying the hazard of reaching the CEP (Table 4), when added to the "null model". On the contrary, the sphericity indexes and RA parameters did not show significant reclassification ability.

Finally, Figure 2 and *Figure S3* show the association between each atrial parameter, modelled as a continuous, non-linear variable, and the risk of CEP. Both iLAAPD and LAVi refined risk prediction. In details, Figure 2A shows that for iLAAPD values above 21 mm/m^2 the risk of events of the CEP progressively and gradually increases until 27 mm/m^2, then tends to plateau for higher values. Figure 2B depicts the relationship between LAVi and the risk of CEP: LAVi values higher than 40 ml/m^2 are associated with a progressive increase in the risk of CEP, which then plateaus for values above 60 ml/m^2.

DISCUSSION

The main finding of our study is that left atrial parameters, particularly iLAAPD, LAVi, and, to a lesser extent, LAEF, were significantly associated with an increased risk of the adverse cardiovascular (CV) events. Conversely, neither sphericity indexes nor RA parameters correlated with these adverse outcomes in AF patients.

To our knowledge, this is one of the first studies to comprehensively evaluate the correlation between a broad set of both LA and RA echocardiographic parameters and outcomes in a real-world cohort of AF patients. According to literature, there is a lack of conclusive evidence regarding the predictive capability of atrial measurements obtained by transthoracic echocardiography in terms of clinical outcomes [9]. Previous studies primarily focused on fewer atrial parameters — mainly LA-related ones — and on outcomes following catheter ablation or predicting thromboembolic events [25]. Our study provides a holistic and broader assessment of atrial remodeling by exploring its implications not only for thromboembolic events but also for survival and major adverse CV events, which has considerable clinical value.

The present analysis was focused on AF patients and allowed to integrate prior knowledge, by identifying LAVi, iLAAPD and, to a lesser extent, LAEF as reliable predictors of adverse outcomes in AF patients. We found that an increase in iLAAPD and LAVi, simple atrial parameters, was statistically associated with adverse outcomes, likely reflecting chronic diastolic dysfunction and increased atrial filling pressures. Historically, LA size has been recognized as a predictor of CV outcomes in both AF and non-AF patients. Since AF can be considered a manifestation of atrial cardiomyopathy and LA remodeling is a well-known factor associated with AF progression, understanding atrial remodeling and its association with outcomes is crucial [26–31]. Tsang et al. [32] found that LAVi, considered the most reliable outcome predictor in sinus rhythm patients, had a poor role in predicting adverse CV events in AF patients. These preliminary results could be justified by the relatively small sample size and the complex nature of atrial remodeling which goes beyond mere dilation. Of note, atrial dilation is not symmetrical, as it spreads more in superior-inferior and medial-lateral directions. This asymmetry limits the utility of some bidimensional indices, such as sphericity indices, in capturing true atrial size and shape. Given the growing relevance of a deeper evaluation of the atria, a recent consensus statement revised the concept of atrial cardiomyopathy, which encompasses structural, electrical, and mechanical abnormalities of the atrial myocardium that extend beyond AF and result in changes in contractility, electrophysiology and chamber architecture, potentially related to clinically relevant events [33]. This definition highlights the central interplay of structural and functional remodeling.

Similarly, LAEF, although less robust in our analyses, was associated with a higher risk of the composite endpoint, driven primarily by increased risks of death and HF hospitalization. Reduced

LA ejection force, defined as the force exerted by the atrium in propelling blood into the ventricle during atrial systole, was associated with negative outcomes after ablation for paroxysmal AF, but LAEF did not seem to differ between recurrent and non-recurrent AF patients [34, 35]. A lower LAEF highlights negative atrial dynamics and can be considered as the result of the arrhythmia itself combined with an underlying atrial myopathy [36, 37]. In line with these results, the importance of LA function is emphasized especially in HF management, since its loss might lead to exacerbation of symptoms and might contribute to a refractory or worsening HF [38], particularly in patients with history of AF.

Moreover, there is a growing interest concerning the right heart structures and function and their association with AF, as recent evidence suggest that the RA share the same substrate, electrical and structural remodeling (e.g. patchy fibrosis, inflammation, vascular degeneration) as the LA [16, 39, 40]. However, to the best of our knowledge, no previous studies have extensively investigated their role in predicting adverse CV events. While we observed an association between RAVi and the composite endpoint on univariable analysis, this was not confirmed on multivariable models nor at reclassification analysis. Nonetheless, RAVi was associated with a higher risk of death and HF hospitalization, consistent with previous findings by Ko et al. [41]. Notably, RA enlargement may reflect a more advanced atrial remodeling, and most AF patients with increased RAVi had also LA dilation.

Our study has some limitations that should be highlighted. Firstly, this is an observational monocentric study with the intrinsic relatively short follow-up duration and limited granularity of available data (in particular concerning concurrent medications and comorbidities), which may limit the generalizability of our findings. Given the observational design, our study should be considered as hypothesis-generating and reports associations rather than implying causality. Most of the echocardiograms were performed by the echo-lab team leader, who also took the majority of the measurements, minimizing inter-operator variability. Measurements by other physicians were reviewed by the team leader to ensure consistency [21]. Nonetheless, minor inter- and intra-operator discrepancies cannot be excluded and are acknowledged as a potential limitation of our study. Moreover, echo-parameters were not always obtained in the same rhythm for all patients, thus introducing heterogeneity in the evaluation. We did not use 3D imaging or LA strain evaluation, since they were not routinely employed in daily clinical practice, despite their potential role [42–45], and we focused on simple measurements, that can be easily obtained. One of the advantages of 3D echocardiography is a more detailed analysis of LA volumes in various phases of the cardiac cycle and the reservoir function [46]. Similarly, LA strain provides useful information concerning atrial function. Previous studies analyzed the role of LA strain and 3D LA volume in patients with embolic

strokes of unknown origin and in predicting the risk of stroke in patients with AF [47, 48]. The pathophysiological mechanisms are partially unknown; however, it has been hypothesized that there might be an association among reduced LA strain, LA fibrosis, and lower LA appendage flow velocity. Thus, the development of thrombi might be due to the reduced LA compliance during the LA reservoir phase, resulting in blood flow stasis in the atrium and increased risk of stroke [48, 49]. These advanced imaging techniques are particularly relevant for the characterization of atrial cardiomyopathy, as these methods provide detailed insights into atrial structure and function (e.g. fibrosis, compliance, and reservoir function), which were not fully captured by mere dimension. For this reason, given the more widespread availability of these advanced echocardiographic techniques in the recent years, incorporating these techniques in future research could improve risk stratification by identifying specific atrial dysfunction patterns contributing to adverse outcomes. Finally, despite controlling for many covariates, residual or unmeasured confounding in this analysis could not be excluded.

CONCLUSIONS

Atrial echocardiographic parameters, particularly those related to the LA, are associated with long-term adverse outcomes in AF patients. Our study highlights the importance of a comprehensive echocardiographic evaluation in the clinical practice, since this assessment may provide valuable insights into the extent of atrial remodeling and underlying atrial cardiomyopathy, and integrate clinical risk stratification and decision making in AF patients.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

Conflict of interest: GB — small speaker fee from Boston, Boehringer Ingelheim, Bayer, Daiichi-Sankyo, Janssen and Sanofi and he is Study Coordinator of ARISTOTELES (Grant from Horizon Europe (HORIZON-HLTH-2022-STAYHLTH-01 — Grant 101080189). The other authors declare no conflicts of interest. No conflict exists for any of the authors with regard to the data presented in the current study.

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REFERENCES

1. Van Gelder IC, Rienstra M, Bunting KV, et al. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2024; 45(36): 3314–3414, doi: 10.1093/eurheartj/ehae176, indexed in Pubmed: 39210723.
2. Boriani G, Vitolo M, Diemberger I, et al. Optimizing indices of atrial fibrillation susceptibility and burden to evaluate atrial fibrillation severity, risk and outcomes. Cardiovasc Res. 2021; 117(7): 1–21, doi: 10.1093/cvr/cvab147, indexed in Pubmed: 33913486.
3. Goette A, Kalman J, Aguinaga L, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: Definition, characterization, and clinical implication. Europace. 2016; 18(10): 1455–1490, doi: 10.1093/europace/euw161.
4. Deneke T, Kutyifa V, Hindricks G, et al. Pre- and post-procedural cardiac imaging (computed tomography and magnetic resonance imaging) in electrophysiology: a clinical consensus statement of the European Heart Rhythm Association and European Association of Cardiovascular Imaging of the European Society of Cardiology. Europace. 2024; 26(5): euae108, doi: 10.1093/europace/euae108, indexed in Pubmed: 38743765.
5. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015; 16(3): 233–270, doi: 10.1093/ehjci/jev014, indexed in Pubmed: 25712077.
6. Malavasi VL, Fantecchi E, Tordoni V, et al. Atrial fibrillation pattern and factors affecting the progression to permanent atrial fibrillation. Intern Emerg Med. 2021; 16(5): 1131–1140, doi: 10.1007/s11739-020-02551-5, indexed in Pubmed: 33161524.
7. D'Ascenzo F, Corleto A, Biondi-Zoccai G, et al. Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation?: A meta-analysis. Int J Cardiol. 2013; 167(5): 1984–1989, doi: 10.1016/j.ijcard.2012.05.008, indexed in Pubmed: 22626840.
8. Zhuang J, Wang Y, Tang K, et al. Association between left atrial size and atrial fibrillation recurrence after single circumferential pulmonary vein isolation: a systematic review and meta-analysis of observational studies. Europace. 2012; 14(5): 638–645, doi: 10.1093/europace/eur364, indexed in Pubmed: 22117033.

9. Choi SH, Yu HT, Kim D, et al. Late recurrence of atrial fibrillation 5 years after catheter ablation: predictors and outcome. Europace. 2023; 25(5): euad113, doi: 10.1093/europace/euad113, indexed in Pubmed: 37099677.
10. Charitakis E, Dragioti E, Stratinaki M, et al. Predictors of recurrence after catheter ablation and electrical cardioversion of atrial fibrillation: An umbrella review of meta-analyses. Europace. 2023; 25(1): 40–48, doi: 10.1093/europace/euac143, indexed in Pubmed: 36037026.
11. Schaaf M, Andre P, Altman M, et al. Left atrial remodelling assessed by 2D and 3D echocardiography identifies paroxysmal atrial fibrillation. Eur Heart J Cardiovasc Imaging. 2017; 18(1): 46–53, doi: 10.1093/ehjci/jew028, indexed in Pubmed: 26976357.
12. Ma XX, Boldt LH, Zhang YL, et al. Clinical relevance of left atrial strain to predict recurrence of atrial fibrillation after catheter ablation: A meta-analysis. Echocardiography. 2016; 33(5): 724–733, doi: 10.1111/echo.13184, indexed in Pubmed: 26857344.
13. Marchandise S, Garnir Q, Scavée C, et al. Prediction of left atrial fibrosis and success of catheter ablation by speckle tracking echocardiography in patients imaged in persistent atrial fibrillation. Front Cardiovasc Med. 2022; 9: 856796, doi: 10.3389/fcvm.2022.856796, indexed in Pubmed: 35694674.
14. Jasic-Szpak E, Marwick TH, Donal E, et al. Prediction of AF in heart failure with preserved ejection fraction: Incremental value of left atrial strain. JACC Cardiovasc Imaging. 2021; 14(1): 131–144, doi: 10.1016/j.jcmg.2020.07.040, indexed in Pubmed: 33413883.
15. Mannina C, Ito K, Jin Z, et al. Association of left atrial strain with ischemic stroke risk in older adults. JAMA Cardiol. 2023; 8(4): 317–325, doi: 10.1001/jamacardio.2022.5449, indexed in Pubmed: 36753086.
16. Gunturiz-Beltrán C, Nuñez-Garcia M, Althoff TF, et al. Progressive and simultaneous right and left atrial remodeling uncovered by a comprehensive magnetic resonance assessment in atrial fibrillation. J Am Heart Assoc. 2022; 11(20): e026028, doi: 10.1161/JAHA.122.026028, indexed in Pubmed: 36216438.
17. Imberti JF, Mei DA, Vitolo M, et al. Comparing atrial fibrillation guidelines: Focus on stroke prevention, bleeding risk assessment and oral anticoagulant recommendations. Eur J Intern Med. 2022; 101: 1–7, doi: 10.1016/j.ejim.2022.04.023, indexed in Pubmed: 35525635.
18. Mei DA, Imberti JF, Bonini N, et al. Performance of HAS-BLED and DOAC scores to predict major bleeding events in atrial fibrillation patients treated with direct oral anticoagulants: A report from a prospective European observational registry. Eur J Intern Med. 2024; 128: 63–70, doi: 10.1016/j.ejim.2024.06.022, indexed in Pubmed: 38969571.

19. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28(1): 1–39.e14, doi: 10.1016/j.echo.2014.10.003, indexed in Pubmed: 25559473.
20. Blume GG, Mcleod CJ, Barnes ME, et al. Left atrial function: Physiology, assessment, and clinical implications. Eur J Echocardiogr. 2011; 12(6): 421–430, doi: 10.1093/ejechocard/jeq175, indexed in Pubmed: 21565866.
21. Barbieri A, Bursi F, Zanasi V, et al. Left atrium reclassified: application of the American Society of Echocardiography/European Society of Cardiology cutoffs to unselected outpatients referred to the echocardiography laboratory. J Am Soc Echocardiogr. 2008; 21(5): 433–438, doi: 10.1016/j.echo.2007.08.025, indexed in Pubmed: 17904802.
22. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. Biometrics. 1988; 44(3): 837–845, indexed in Pubmed: 3203132.
23. Pencina MJ, D'Agostino RB, D'Agostino RB, et al. Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond. Stat Med. 2008; 27(2): 157–172; discussion 207–212, doi: 10.1002/sim.2929, indexed in Pubmed: 17569110.
24. Gauthier J, Wu QV, Gooley TA. Cubic splines to model relationships between continuous variables and outcomes: A guide for clinicians. Bone Marrow Transplant. 2020; 55(4): 675–680, doi: 10.1038/s41409-019-0679-x, indexed in Pubmed: 31576022.
25. Galderisi M, Donal E, Magne J, et al. Rationale and design of the EACVI AFib Echo Europe Registry for assessing relationships of echocardiographic parameters with clinical thrombo-embolic and bleeding risk profile in non-valvular atrial fibrillation. Eur Heart J Cardiovasc Imaging. 2018; 19(3): 245–252, doi: 10.1093/ehjci/jex322, indexed in Pubmed: 29474699.
26. Guichard JB, Nattel S. Atrial cardiomyopathy: A useful notion in cardiac disease management or a passing fad? J Am Coll Cardiol. 2017; 70(6): 756–765, doi: 10.1016/j.jacc.2017.06.033, indexed in Pubmed: 28774383.
27. Vitolo M, Proietti M, Imberti JF, et al. Factors associated with progression of atrial fibrillation and impact on all-cause mortality in a cohort of European patients. J Clin Med. 2023; 12(3): 768, doi: 10.3390/jcm12030768, indexed in Pubmed: 36769416.
28. Boriani G, Vitolo M, Imberti JF. The search for a gold standard to clinically diagnose and monitor atrial cardiomyopathy. Eur J Intern Med. 2022; 101: 34–36, doi: 10.1016/j.ejim.2022.05.019, indexed in Pubmed: 35606288.

29. Tufano A, Lancellotti P. Atrial cardiomyopathy: Pathophysiology and clinical implications. Eur J Intern Med. 2022; 101: 29–31, doi: 10.1016/j.ejim.2022.03.007, indexed in Pubmed: 35288030.
30. Stalikas N, Doundoulakis I, Karagiannidis E, et al. Prevalence of markers of atrial cardiomyopathy in embolic stroke of undetermined source: A systematic review. Eur J Intern Med. 2022; 99: 38–44, doi: 10.1016/j.ejim.2022.01.024, indexed in Pubmed: 35065879.
31. Boriani G, Gerra L, Mantovani M, et al. Atrial cardiomyopathy: An entity of emerging interest in the clinical setting. Eur J Intern Med. 2023; 118: 14–21, doi: 10.1016/j.ejim.2023.10.023, indexed in Pubmed: 39492265.
32. Tsang TSM, Abhayaratna WP, Barnes ME, et al. Prediction of cardiovascular outcomes with left atrial size: Is volume superior to area or diameter? J Am Coll Cardiol. 2006; 47(5): 1018–1023, doi: 10.1016/j.jacc.2005.08.077, indexed in Pubmed: 16516087.
33. Goette A, Corradi D, Dobrev D, et al. Atrial cardiomyopathy revisited-evolution of a concept: A clinical consensus statement of the European Heart Rhythm Association (EHRA) of the ESC, the Heart Rhythm Society (HRS), the Asian Pacific Heart Rhythm Society (APHRS), and the Latin American Heart Rhythm Society (LAHRS). Europace. 2024; 26(9): euae204, doi: 10.1093/europace/euae204, indexed in Pubmed: 39077825.
34. Kishima H, Mine T, Takahashi S, et al. Left atrial ejection force predicts the outcome after catheter ablation for paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2018; 29(2): 264–271, doi: 10.1111/jce.13387, indexed in Pubmed: 29125704.
35. Manning WJ, Silverman DI, Katz SE, et al. Atrial ejection force: A noninvasive assessment of atrial systolic function. J Am Coll Cardiol. 1993; 22(1): 221–225, doi: 10.1016/0735-1097(93)90838-r, indexed in Pubmed: 8509545.
36. Boriani G, Vitolo M, Imberti JF. Atrial cardiomyopathy: A derangement in atrial volumes, geometry, function, and pathology with important clinical implications. J Cardiovasc Med (Hagerstown). 2022; 23(6): 359–362, doi: 10.2459/JCM.0000000000001316, indexed in Pubmed: 35645026.
37. Schnabel RB, Marinelli EA, Arbelo E, et al. Early diagnosis and better rhythm management to improve outcomes in patients with atrial fibrillation: The 8th AFNET/EHRA consensus conference. Europace. 2023; 25(1): 6–27, doi: 10.1093/europace/euac062, indexed in Pubmed: 35894842.
38. Inoue K, Smiseth OA. Left atrium as key player and essential biomarker in heart failure. J Cardiol. 2025; 85(1): 8–16, doi: 10.1016/j.jjcc.2024.07.006, indexed in Pubmed: 39084316.

39. Sun ZY, Li Q, Li J, et al. Echocardiographic evaluation of the right atrial size and function: Relevance for clinical practice. Am Heart J Plus. 2023; 27: 100274, doi: 10.1016/j.ahjo.2023.100274, indexed in Pubmed: 38511096.
40. Prabhu S, Voskoboinik A, McLellan AJA, et al. A comparison of the electrophysiologic and electroanatomic characteristics between the right and left atrium in persistent atrial fibrillation: Is the right atrium a window into the left? J Cardiovasc Electrophysiol. 2017; 28(10): 1109–1116, doi: 10.1111/jce.13297, indexed in Pubmed: 28730651.
41. Ko KY, Jang JH, Choi SH, et al. Impact of right atrial enlargement on clinical outcome in patients with atrial fibrillation. Front Cardiovasc Med. 2022; 9: 989012, doi: 10.3389/fcvm.2022.989012, indexed in Pubmed: 36211539.
42. Di Biase L, Zou F, Lin AN, et al. Feasibility of three-dimensional artificial intelligence algorithm integration with intracardiac echocardiography for left atrial imaging during atrial fibrillation catheter ablation. Europace. 2023; 25(9): euad211, doi: 10.1093/europace/euad211, indexed in Pubmed: 37477946.
43. Matei LL, Popescu RM, Popescu AC, et al. Early echocardiographic predictors for atrial fibrillation propensity: The left atrium oracle. Rev Cardiovasc Med. 2022; 23(6): 205, doi: 10.31083/j.rcm2306205, indexed in Pubmed: 39077189.
44. Mandoli GE, Cameli M, Pastore MC, et al. Speckle tracking echocardiography in early disease stages: a therapy modifier? J Cardiovasc Med (Hagerstown). 2023; 24(Suppl 1): e55–e66, doi: 10.2459/JCM.0000000000001422, indexed in Pubmed: 37052222.
45. Jing M, Li D, Xi H, et al. Value of imaging in the non-invasive prediction of recurrence after catheter ablation in patients with atrial fibrillation: An up-to-date review. Rev Cardiovasc Med. 2023; 24(8): 241, doi: 10.31083/j.rcm2408241, indexed in Pubmed: 39076720.
46. Russo C, Jin Z, Homma S, et al. LA phasic volumes and reservoir function in the elderly by real-time 3D echocardiography: Normal values, prognostic significance, and clinical correlates. JACC Cardiovasc Imaging. 2017; 10(9): 976–985, doi: 10.1016/j.jcmg.2016.07.015, indexed in Pubmed: 28017387.
47. Vera A, Cecconi A, Ximénez-Carrillo Á, et al. Advanced echocardiography with left atrial strain and indexed left atrial three-dimensional volume for predicting underlying atrial fibrillation after cryptogenic stroke. Am J Cardiol. 2022; 185: 87–93, doi: 10.1016/j.amjcard.2022.09.004, indexed in Pubmed: 36307348.
48. Hsu PC, Lee WH, Chu CY, et al. Prognostic role of left atrial strain and its combination index with transmitral E-wave velocity in patients with atrial fibrillation. Sci Rep. 2016; 6: 17318, doi: 10.1038/srep17318, indexed in Pubmed: 26833057.

49. Obokata M, Negishi K, Kurosawa K, et al. Left atrial strain provides incremental value for embolism risk stratification over CHA_2DS_2-VASc score and indicates prognostic impact in patients with atrial fibrillation. J Am Soc Echocardiogr. 2014; 27(7): 709–716.e4, doi: 10.1016/j.echo.2014.03.010, indexed in Pubmed: 24767972.

Table 1. Patient characteristics according to the primary composite endpoint

	CEP no (n = 360)	**CEP yes (n = 129)**	***P*-value**
Age, median (IQR)	73 (65–78.2)	78 (73–83)	<0.001
Age ≥75 years, n (%)	156 (43.3)	90 (69.8)	<0.001
Female, n (%)	145 (40.3)	44 (34.1)	0.259
Enrollment site, n (%)			<0.001
Outpatient	245 (68.1)	53 (41.4)	
Ward	115 (31.9)	76 (58.6)	
BMI, median (IQR)	27 (24.1–29.7)	26.1 (23.4–29.4)	0.184
AF type, n (%)			<0.001
Paroxysmal	77 (21.4)	10 (7.8)	
Persistent	112 (31.1)	29 (22.5)	
Permanent	128 (35.6)	70 (54.3)	
First detected	43 (11.9)	20 (15.5)	
AF on baseline ECG, n (%)	205 (56.9)	105 (81.4)	<0.001
EHRA score, median (IQR)	1 (1–2)	1 (1–2)	0.339
CHA_2DS_2VASc, median (IQR)	3 (2–4)	4 (3–5)	<0.001
HASBLED, median (IQR)	1 (1–2)	2 (2–3)	<0.001
Smoker, n (%)	125 (34.8)	60 (46.5)	0.025
Diabetes, n (%)	60 (16.7)	31 (24.0)	0.087
Dyslipidemia, n (%)	176 (48.9)	64 (50.4)	0.851
Hypertension, n (%)	259 (71.9)	99 (76.7)	0.347
CAD, n (%)	82 (22.8)	53 (41.1)	<0.001
Cardiomyopathy, n (%)	19 (5.3)	16 (12.4)	0.013
VHD, n (%)	81 (23.3)	57 (44.9)	<0.001
EF, median (IQR)	56 (50–60)	52 (38–60)	<0.001
EF<40%, n (%)	54 (18.4)	48 (42.5)	<0.001

HF (%)			<0.001
No	293 (81.4)	57 (44.2)	
NYHA I	20 (5.6)	16 (12.4)	
NYHA II	31 (8.6)	31 (24.0)	
NYHA III	15 (4.2)	22 (17.1)	
NYHA IV	1 (0.3)	3 (2.3)	
Stroke/SE, n (%)	45 (12.5)	21 (16.3)	0.354
Major or intracranial bleeding, n (%)	11 (3.1)	5 (3.9)	0.872
PAD, n (%)	46 (12.8)	27 (20.9)	0.037
CKD-EPI ml/min/1.73 m^2, median (IQR)	75.7 (61.3–88.2)	58.8 (43.6–73.8)	<0.001
CKD, n (%)	84 (23.3)	66 (51.2)	<0.001
COPD, n (%)	27 (7.5)	19 (14.7)	0.025
Anemia, n (%)	70 (19.5)	64 (49.6)	<0.001
Liver disease, n (%)	9 (2.5)	9 (7.0)	0.041
Malignancy, n (%)	76 (21.1)	32 (24.8)	0.457
aMMSE, median (IQR)	27.7 (26–29)	26.7 (24.7–28.7)	0.025
CI, n (%)	39 (12.6)	28 (23.5)	0.008
CCI, median (IQR)	1 (0–3)	3 (2–5)	<0.001
AC pattern, n (%)			0.008
None	20 (5.6)	1 (0.8)	
APT only	10 (2.8)	7 (5.4)	
AC only	282 (78.3)	93 (72.1)	
AC+APT	48 (13.3)	28 (21.7)	
Correctly anticoagulated (%)	328 (91.1)	121 (93.8)	0.442

Abbreviations: AC, anticoagulation; AF, atrial fibrillation; aMMSE, adjusted mini mental state examination; APT, antiplatelet therapy; BMI, body mass index; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack, vascular disease, age 65–75 years, sex category; CI, cognitive impairment; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; EF, ejection fraction; EHRA, European Heart Rhythm Association; HF, heart failure; IQR, interquartile range; NYHA, New York Heart Association; PAD, peripheral artery disease; SE, systemic embolism; VHD, valvular heart disease

Table 2. Outcomes in patients according to left atrial dilation (no-mild vs. moderate-severe)

	No or mild LA dilation (n = 276)	Moderate to severe LA dilation (n = 213)	*P*-value
CEP, n (%)	53 (19.2)	76 (35.7)	<0.001
Death, n (%)	33 (12.0)	51 (23.9)	0.001
Thromboembolism, n (%)			0.575
Stroke	3 (1.1)	5 (2.3)	
TIA	1 (0.4)	0 (0)	
Peripheral embolism	1 (0.4)	1 (0.5)	
ACS, n (%)			0.722
UA	6 (2.2)	6 (2.8)	
NSTEMI	9 (3.3)	5 (2.3)	
STEMI	1 (0.4)	0 (0)	
HF hospitalization, n (%)	20 (7.2)	31 (14.6)	0.013
Follow-up days, median (IQR)	1133 (392–1399)	1077 (404–1371)	0.815

Abbreviations: ACS, acute coronary syndrome; CEP, composite endpoint; HF, heart failure; IQR, interquartile range; LA, left atrial; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction; TIA, transient ischemic attack; UA, unstable angina

Table 3. Atrial parameters and the primary composite endpoint

	CEP no (n = 360)	CEP yes (n = 129)	*P*-value
iLAAPD, median (IQR)	21 (18–24)	23 (20–26)	<0.001
iLAAPD > 22 mm/m^2, n (%)	125 (35)	73 (57)	<0.001
LAVi, median (IQR)	37 (27–48)	46 (35–55)	<0.001
LA enlargement, n (%)			<0.001
No	161 (45)	29 (23)	
Mild	62 (17.2)	24 (18.6)	
Moderate	52 (14.4)	20 (15.5)	
Severe	85 (23.6)	56 (43.4)	
LASI, median (IQR)	0.66 (0.60–0.74)	0.67 (0.60–0.75)	0.353

LASI higher tertile, n (%)	118 (32.8)	46 (35.7)	0.627
LAEF basal, median (IQR)	36 (27–48)	30 (19–39)	<0.001
LAEF <28% (%)	93 (27.8)	59 (46.5)	<0.001
iRAAPD, median (IQR)	21 (18–24)	23 (20–27)	0.001
iRAAPD higher tertile, n (%)	75 (27.3)	57 (52.3)	<0.001
RAVi, median (IQR)	27 (20–35)	32 (26–44)	<0.001
RAVi higher tertile, n (%)	84 (28.7)	56 (46.7)	0.001
RASI, median (IQR)	0.75 (0.67–0.84)	0.76 (0.69–0.84)	0.756
RASI higher tertile, n (%)	92 (33.5)	35 (32.1)	0.895
RAEF basal, median (IQR)	33 (22–45)	31 (19–42)	0.043
RAEF <25%, n (%)	90 (32.3)	45 (38.5)	0.284

Abbreviations: CEP, composite endpoint; iLAAPD, indexed left atrial antero-posterior diameter; iRAAPD, indexed right atrial antero-posterior diameter; LA, left atrial; LAEF, left atrial emptying fraction; LASI, left atrial sphericity index; LAVi, left atrial volume indexed by body surface area; RAEF, right atrial emptying fraction; RASI, right atrial sphericity index; RAVi, right atrial volume indexed by body surface area

Table 4. Multivariable Cox regression analysis and reclassification analysis

	aHR[a] (95% CI)	**aHR[b] (95% CI)**	***P*-value (LRT)**	**NRI (95% CI)**	***P*-value**	**IDI (95% CI)**	***P*-value**
Null Model	–	–	ref	ref	ref	ref	ref
iLAAPD >22 mm/m²	1.78 (1.24–2.57) **0.002**	1.63 (1.14–2.34) **0.008**	**0.002**	0.30 (0.09–0.50)	**0.005**	0.02 (0.01–0.04)	**0.008**
LAVi ≥42 ml/m²	1.50 (1.03 - 2.19) **0.036**	1.47 (1.03 - 2.09) **0.033**	**0.035**	0.32 (0.12 - 0.53)	**0.002**	0.03 (0.01 - 0.05)	**0.014**
LASI > 0.71	1.35 (0.93 - 1.95) *0.110*	1.19 (0.81 - 1.73) *0.371*	0.116	0.05 (-0.15 - 0.25)	0.640	0 (0 - 0)	0.525

LAEF < 28%	1.74 (1.21 - 2.48) **0.003**	1.37 (0.91 - 2.05) *0.130*	**0.003**	0.26 (0.05 - 0.46)	**0.014**	0.01 (0.002 - 0.02)	**0.021**
iRAAPD > 24 mm/m^2	1.65 (1.10 - 2.47) **0.015**	1.01 (0.65 - 1.55) *0.972*	0.015	0.16 (-0.07 - 0.39)	0.177	0.01 (-0.002 - 0.02)	0.098
RAVi > 32 ml/m^2	1.41 (0.97 - 2.07) *0.074*	1.54 (0.99 - 2.39) *0.054*	0.074	0.21 (-0.01 - 0.42)	0.063	0.01 (-0.004 - 0.03)	0.128
RASI > 0.82	0.84 (0.56 - 1.27) *0.420*	0.93 (0.61 - 1.41) *0.739*	0.415	0.05 (-0.17 - 0.28)	0.653	0 (0 - 0)	0.858
RAEF < 25%	1.37 (0.94 - 2.00) *0.104*	1.51 (1.01 - 2.26) *0.046*	0.108	0.20 (-0.02 - 0.42)	0.073	0.01 (-0.003 - 0.03)	0.125

The *P*-value separately shown in the third column relates to the comparison of the atrial parameters' Cox regression model against the "null model" (our reference) using the LRT

[a]The analysis was adjusted for CHA_2DS_2-VASc, AF type and use of OAC. The number below the 95% CI refers to the multivariable Cox regression analysis p value. [b]The analysis was adjusted for CHA_2DS_2-VASc, AF type and use of OAC, COPD, CKD, and smoking. The number below the 95% CI refers to the multivariable Cox regression analysis p value.

Abbreviations: AF, atrial fibrillation; aHR, adjusted hazard ratio; CHA_2DS_2VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack, vascular disease, age 65–75 years, sex category; CKD, chronic kidney disease, CI, confidence interval; COPD, chronic obstructive pulmonary disease; IDI, integrated discrimination index; iLAAPD, indexed left atrial antero-posterior diameter; iRAAPD, indexed right atrial antero-posterior diameter; LAEF, left atrial emptying fraction; LASI, left atrial sphericity index; LAVi, left atrial volume indexed by body surface area; LRT, likelihood ratio test; NRI, net reclassification improvement; OAC, oral anticoagulant; RAEF, right atrial emptying fraction; RASI, right atrial sphericity index; RAVi, right atrial volume indexed by body surface area.

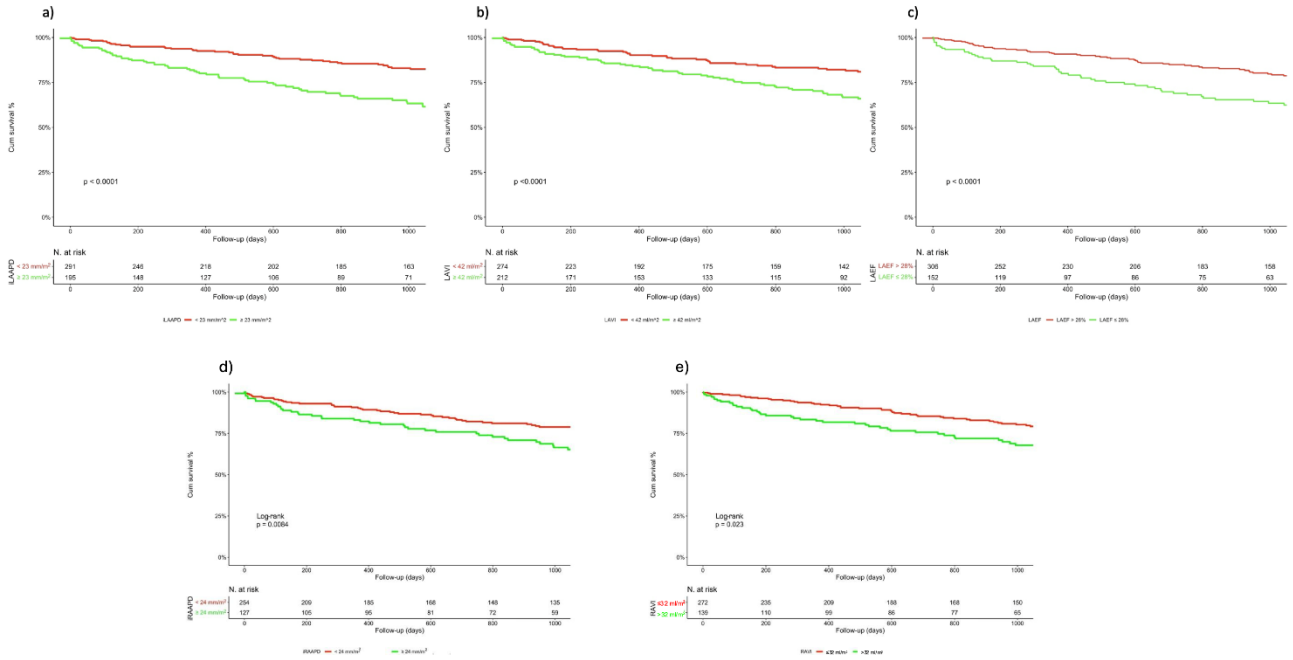

Figure 1. Kaplan–Meier survival curves for the primary composite endpoint. **A.** Kaplan–Meier curves for iLAAPD. **B.** Kaplan–Meier curves for LAVi. **C.** Kaplan–Meier curves for LAEF. **D.** Kaplan–Meier curves for iRAAPD. **E.** Kaplan–Meier curves for RAVi

Abbreviations: CEP, composite endpoint; iLAAPD, indexed left atrial antero-posterior diameter; iRAAPD, indexed right atrial antero-posterior diameter; LAEF, left atrial emptying fraction; LAVi, left atrial volume indexed by body surface area; RAVi, right atrial volume indexed by body surface area

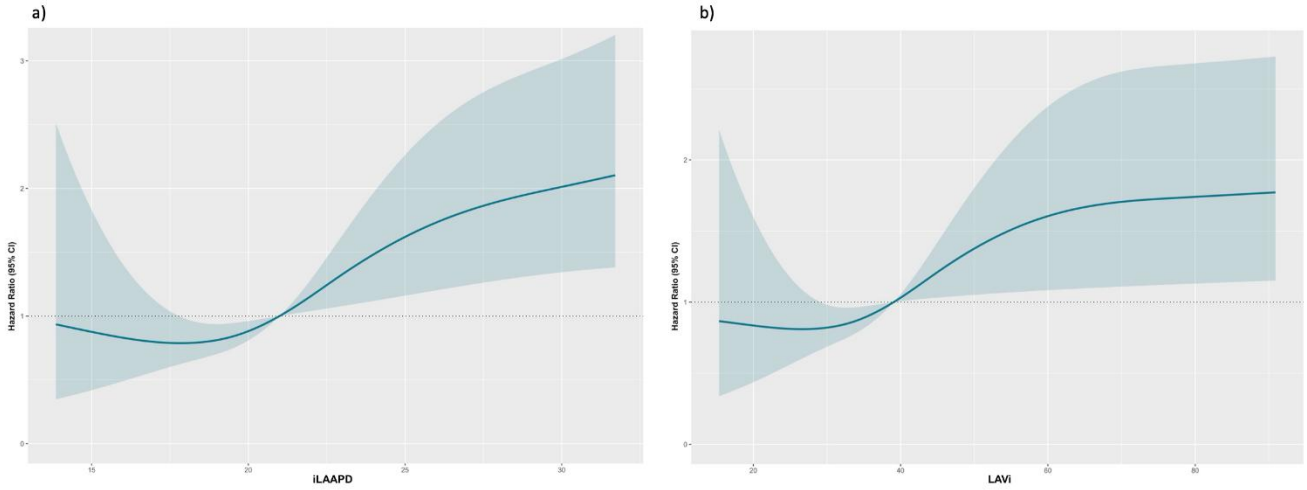

Figure 2. Multivariable Cox regression analyses plotted as restricted cubic splines curves using each atrial parameter as a continuous variable. **A.** iLAAPD modeled as a continuous variable. **B.** LAVi modeled as a continuous variable

Values over the dotted line indicate an increased hazard of CEP, while below a reduced hazard. Panel **A.** shows that for iLAAPD values above 21 mm/m^2 the risk of events of the CEP progressively and gradually increases until 27 mm/m^2, then tends to *plateau* for higher values ($P = 0.001$; P non-linearity = 0.258). Panel **B.** depicts the relationship between LAVi and the risk of CEP: LAVi values higher than 40 ml/m^2 are associated with a progressive increase in the risk of CEP, which then plateaus for values above 60 $ml/m^{2,}$ showing a non-linear relationship ($P = 0.003$, P non-linearity = 0.012). The analysis was adjusted for CHA_2DS_2-VASc, AF type and use of OAC

Abbreviations: AF, atrial fibrillation; CEP, composite endpoint; CI, confidence interval; iLAAPD, indexed left atrial antero-posterior diameter; LAVi, left atrial volume indexed by body surface area; OAC, oral anticoagulant