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Left atrial volume predicts atrial fibrillation recurrence after radiofrequency ablation: a meta-analysis

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Aims Left atrial (LA) diameter is a predictor of atrial fibrillation (AF) recurrence following radiofrequency catheter ablation (RFA). However, LA volume (LAV) is more accurate in assessing LA size. Studies evaluating LAV as a predictor of AF recurrence are contradictory; therefore, we performed a meta-analysis to assess whether LAV is an independent predictor of AF recurrence following RFA.

Methods and results All studies reporting LAV/LAV index (LAVi) as a predictor of AF recurrence following RFA were included. For studies reporting mean LAV/ LAVi in patients with and without AF recurrence, standard difference in means (SDM) and standard errors were calculated, and combined using meta-analytical techniques. For studies reporting adjusted odds ratio (OR) for AF recurrence based on LAV/LAVi, log ORs were combined using generic inverse variance. Twenty one studies (3822 subjects) were included. Meta-analysis of 11 studies (1559 subjects) reporting LAV, showed that patients with AF recurrence had a higher mean LA volume compared to patients with no recurrence (SDM 0.801; CI 0.387–1.216). Data from 9 studies (1425 subjects) comparing LAVi showed that, patients with AF recurrence had a higher mean LAVi compared to patients with no recurrence (SDM-0.596; CI 0.305–0.888). Thirteen studies (2886 patients) reporting ORs for AF recurrence based on LAV/ LAVi, showed that LAV/ LAVi was independently predictive of AF recurrence post-RFA (OR-1.032, CI- 1.012–1.052).

Conclusions Patients with AF recurrence following RFA have a higher mean LAV/LAVi compared to patients with no recurrence. Large LAV/LAVi increases the odds of AF recurrence post RFA.

Keywords Atrial fibrillation • Atrial fibrillation recurrence • Radiofrequency ablation • Left atrial volume • Meta-analysis

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a projected prevalence of about 16 million by the year 2050. AF leads to thromboembolic strokes, myocardial infarction and heart failure, and is associated with increased mortality, costing the US health care system an approximate 6 billion dollars a year.[1] Pulmonary vein isolation (PVI) by radiofrequency ablation (RFA) is now an established therapeutic option for AF and is commonly used in patients with symptomatic AF who have failed anti-arrhythmic drug therapy. The rate of success after pulmonary vein isolation varies between 50–80%.[2] Although a majority of patients with AF recurrence after PVI have pulmonary vein reconnection,[3] many patients with PV reconnection do not develop AF recurrence,[4] suggesting complex underlying mechanisms beyond pulmonary vein triggers instigating AF recurrence. Multiple studies have focused on understanding risk factors and predictors of AF recurrence after RFA. Left atrial size has been studied mostly in a retrospective fashion by various groups, and

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What's new?

- Previous studies have shown large left atrial (LA) diameter to be a predictor of atrial fibrillation (AF) recurrence following radiofrequency catheter ablation (RFA).
- However, LA diameter does not truly reflect the size of an asymmetric LA, whereas LA volume (LAV) is more accurate.
- Studies evaluating LAV as a predictor of AF recurrence following RFA are contradictory; therefore, we performed a meta-analysis to assess the same.
- Meta-analyses of observational studies show that while patients with AF recurrence post-AF ablation have significantly higher LAV compared to patients without recurrence, the difference in LA dimensions and the risk of AF recurrence due to an increased LA size is only modest.
- Large patient registries with post-AF ablation patients and extensive outcomes data may shed further light into the impact of LAV and LAVi on AF recurrence and other outcomes following catheter ablation for AF.

the results have been mixed. A meta-analysis of 22 studies with 3750 patients showed that increased antero-posterior diameter of the LA was associated with increased recurrence of AF after RFA.[5] Prior evidence shows that LA dilation is asymmetric and is predominantly in the medial-lateral and superior-inferior axes as antero-posterior dilation is limited by the thoracic cavity. Therefore, diameter is not an accurate way of assessing LA dimension, as it frequently underestimates LA size. Studies evaluating large LA volume (LAV) as a predictor of AF recurrence are small, retrospective, and contradictory. Therefore, we aimed to perform a systematic review and meta-analysis of these studies. In this meta-analysis, we compared: (1) the mean LAV and LA volume index (LAVi) in patients who develop AF recurrence after RFA compared to patients who do not; (2) the incidence of AF recurrence and odds ratio for recurrence in patients based on LAV/LAVi.

Methods

Our meta-analysis is in accordance with recommendations of the Meta-analysis of Observational studies in the Epidemiology Group (MOOSE).[6]

Search strategies

We searched MEDLINE/PubMed (1966–2014), Cochrane Database of systematic reviews (1999–2014), and Google Scholar using keywords: 'atrial fibrillation ablation,' 'atrial fibrillation,' 'recurrence post ablation,' 'left atrial volume', and 'left atrial volume index.' 'Related article' feature on PubMed, and a manual search of references was also used to identify additional studies. We reviewed full text of relevant articles. English translations, if necessary, were obtained. Titles and abstracts were independently reviewed by two reviewers (A.N and R.A) and cross-verified for inclusion. Details of search strategy are reported in *Figure 1*.

Inclusion criteria

For the analysis of mean LAV and or LAVi in patients with post-RFA AF recurrence: Studies (retrospective and prospective) comparing mean LAV and or LAVi in patients with AF recurrence after RFA to that of patients without recurrence were included. Studies with a minimum follow-up of 6 months post RFA were included.

For the analysis of risk of AF recurrence post RFA based on LAV/LAVi: Studies reporting the risk of AF recurrence after RFA based on per unit increase in LAV/LAVI by univariate or multivariate logistic regression analysis were included. Studies with minimum follow-up of 6 months post RFA were included.

For both groups of studies, LAV/LAVI was assessed by one of the following modalities: Transthoracic Echocardiogram (TTE), Cardiac Computed Tomography (CT), or Magnetic Resonance Imaging (MRI).

Exclusion criteria

Studies were excluded if they (i) Lacked a control group, (ii) compared mean LAV/LAVi in patients with AF recurrence post direct current cardioversion, (iii) reported only systolic and diastolic LAV, (iv) did not report baseline variables, (v) were published only in abstract form, (vi) were non-English studies with no English translation, and (vii) reported odds ratio for AF recurrence post-RFA based on an arbitrary cut-off value (Only for studies evaluating the risk of AF recurrence post-RFA based on LAV/LAVI).

Data extraction and assessment of study quality

For each included study, all data elements uniformly reported across most studies were extracted by two reviewers (A.N and R.A) and cross-verified by a third (M.K) and is shown in *Tables 1* and *2*. The quality of each study was evaluated in accordance with the guidelines of United States Preventive Task Force and the Evidence-Based Management Group.[7,8] The following characteristics were assessed: (i) clear inclusion and exclusion criteria; (ii) study sample representative of the population; (iii) explanation of sample selection; (iv) full specification of clinical and demographic variables; (v) reporting loss of follow-up; (vi) clear definition of outcomes and outcome assessment; and (vii) adjustment of possible confounders in multivariate analysis. Studies were graded as 'poor' if they met less than three of the criteria, 'fair' if they met three to five of the criteria, and 'good' if they met more than five of the criteria. The quality assessment of individual studies is reported alongside baseline variables in *Tables 1* and *2*. All disagreements between reviewers were resolved by consensus.

Statistical methods

For the analysis of mean LAV and LAVi in patients with AF recurrence, mean LAV/LAVi values were extracted for patients with AF recurrence and patients without AF recurrence, and weighted mean differences (WMD) and 95% confidence interval (CI) were calculated for each study. For the analysis of the risk of AF recurrence post RFA based on LAV/LAVi, univariate and multivariate odds ratio for AF recurrence reported using logistic regression analysis was extracted. For studies reporting Hazard ratio (HR) only, HR was adopted as the best estimate of OR. ORs were transformed logarithmically, then standard error was calculated from Log OR and the corresponding 95% confidence interval (CI). Inverse variance method was used to achieve a weighted estimate of the combined overall effect. Adjusted ORs were used whenever individual studies employed Cox proportional hazard model to adjust for potential confounders. For all the analyses, we assessed the results for heterogeneity in our analysis by examining the forest plots and then calculating a Q statistic, which we then compared with the I^2 index. We considered the presence of significant heterogeneity at the 5% level of significance (for the Q test) and values of I^2 exceeding 56% as an indicator of significant heterogeneity. For the mean LAV and LAVi in AF recurrence analysis, Q statistic (*P*-0.00 for both) and I^2 index (92.2 for LAV and 79.65 for LAVi) indicated moderate to severe heterogeneity between studies. This prompted us to adopt the random effect model to pool WMD. For the analysis of studies, reporting the risk of AF

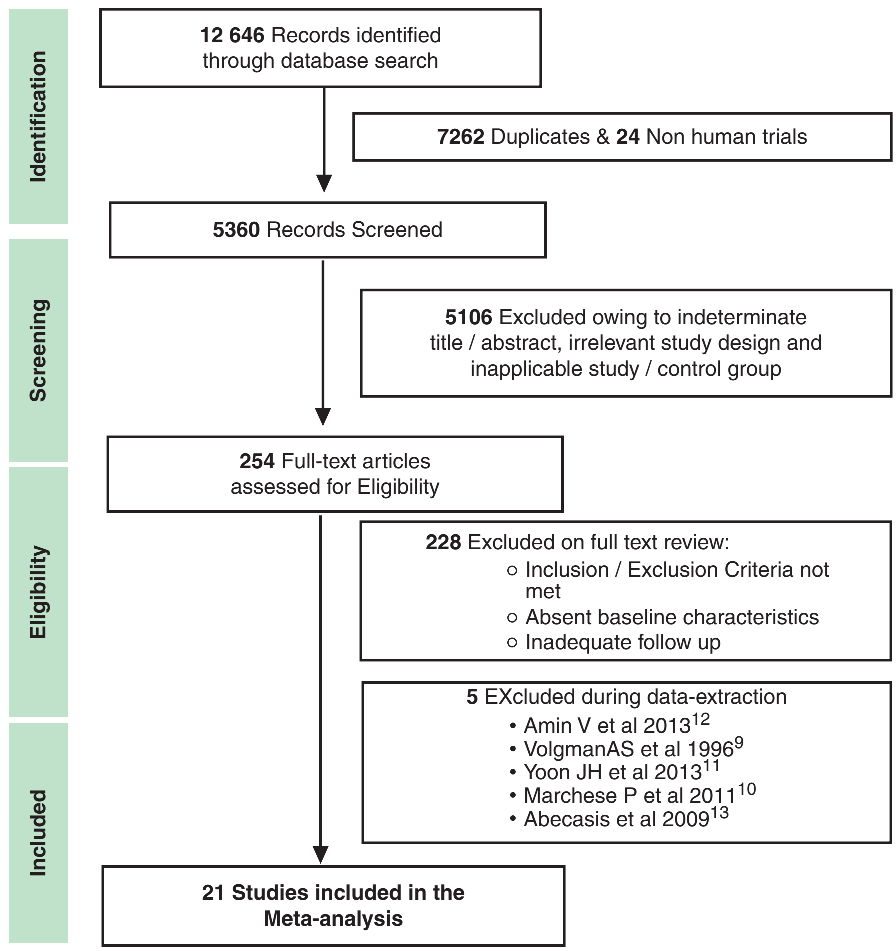


Figure 1 PRISMA flow diagram. Search strategies and screening of studies for inclusion in the meta-analysis.

recurrence based on LAV/LAVi, Q statistic (*P*-0.00) and I^2 index of 89 indicated severe heterogeneity again prompting us to adopt the random effect model to pool effect sizes. All analyses were performed using Comprehensive Meta-Analysis version 3, BiostatInc, Englewood, NJ, USA.

The underlying heterogeneity further prompted us to perform a meta-regression analysis to investigate factors contributing to heterogeneity, and to explore if our study outcome (mean LAV/LAVi and OR for AF recurrence) was affected by factors other than our primary variable. To achieve this, we adopted a weighted regression random effect model and carried out a multivariate regression of pre-determined factors using comprehensive meta-analysis version 3. These factors were selected based on factors shown to affect AF recurrence in individual studies and on data availability for majority of the studies included. A two-sided *P*-value <0.05 was regarded as significant for all analyses. Data was represented as forest plots, and potential publication bias was assessed with the Egger test and represented graphically with Begg funnel plots of the natural log of the OR vs. its standard error.

Results

A total of 21 studies fulfilled our criteria for inclusion. Details of search strategy are reported in *Figure 1*. Five studies were excluded for the following reasons: (i) two studies reported LAV/LAVI in patients with AF recurrence post-direct current cardioversion,[9,10] (ii) one study reported LAV/LAVI in patients with AF recurrence after spontaneous conversion,[11] and (iii) one study by Amin V. *et al.*[12] was considered poor quality because there was no reported baseline variables, no continuous monitoring for symptomatic AF recurrence, no mean LAV reported (only systolic and diastolic), and there was a large variation in follow up duration from less than 6 months to 24 months and (iv) one study by Abecasis *et al.*[13] was excluded as the authors analysed risk of AF recurrence based on an arbitrary cut-off value for LAV/LAVI.

Meta-analysis of the difference in left atrial volume between patients with and without atrial fibrillation recurrence post-radiofrequency catheter ablation

Eleven studies, mostly singe centre cohorts, with 1559 subjects were included in the meta-analysis (*Table 1*). Seven studies were prospective and four were retrospective. The average follow up duration for the studies was 16.9 months. Studies used ECHO, CT, and MRI to assess the LAV. Most studies performed circumferential PVI alone, and 4 of

Table 1 Characteristics of 16 studies included in the meta-analysis of difference in LAV/LAVi between patients with and without post-RFA AF recurrence

Study, year	Region	No. of patients	Study design	Mean follow-up, months	Imaging used	Mean LAV Recurrence	Mean LAV No Recurrence	Mean LAVi Recurrence	Mean LAVi No Recurrence	RFA details	Blanking Period, months	Recurrence detection	Qualit Assessment
Maciel et al., 2006[15]	South America	104	Single centre, prospective cohort	6	CT, MRI	105.1	69.5	NA	NA	CPVI	1.5	Holter	Good
Parikh et al., 2010[25]	North America	88	Single centre, prospective cohort	12	CT, TTE, TEE (LAD+)	102	74.2	NA	NA	CPVIPLUS	NR	Holter	Good
Hof et al., 2010[16]	Europe	79	Single centre, prospective cohort	24	MRI (LAD+)	105	103	NA	NA	CPVI	3	Holter	Good
Shin et al., 2007[27]	ASIA	68	Single centre, prospective cohort	6	TTE	NA	NA	39.1	22.4	CPVI	NR	Holter	Good
Kohari et al., 2013[14]	Europe	125	Single centre, retrospective cohort	12	TTE (LAD +)	107.3	92.7	49	42.5	CPVI	NR	Transtelephonic monitoring	Good
Helms et al., 2009[28]	North America	73	Single centre, prospective cohort	12	CT	119	98	56	49	CPVI PLUS	1	Holter and event monitoring	Good
Bergau et al., 2014[29]	Europe	120	Single centre, prospective cohort	12	MDCT	113	103	NA	NA	CPVI	3	Holter	Good
Sohns et al., 2013[30]	Europe	279	Single centre, prospective cohort	12	MDCT (LAD+)	117	107	NA	NA	CPVI	3	Holter	Good
Kim et al., 2014[31]	Asia	130	Single centre, Prospective cohort	24	TTE	NA	NA	39.3	35.2	CPVI PLUS	3	Holter	Good
Linhart et al., 2013[32]	Europe	205	Single centre, prospective cohort	12	TTE	NA	NA	40.1	33	CPVI	3	Holter	Good
Yoshida et al., 2011[17]	North America	79	Single centre, prospective cohort	6	TTE	NA	NA	48	49	CPVI PLUS	3	30 day event monitor	Good
Nedios et al. 2015[33]	Europe	103	Single centre, retrospective cohort	36	TTE, CT (LAD +)	144	116	68	59	CPVIPLUS	3	Holter	Good
Hof et al. 2009[26]	Europe	146	Single centre, prospective cohort	19	CT	135	118	NA	NA	CPVI	3	Holter	Good
Montefusco et al., 2010[34]	Europe	240	Single centre, retrospective study of prospective cohort	6	MRI	209.8	122.1	NA	NA	CPVI PLUS	2	Holter	Good
Uijl et al., 2011[35]	Europe	170	Single centre, prospective cohort	12	TTE (LAD+)	NA	NA	46	40.2	CPVI	3	Holter	Good
Bary et al., 2012[36]	Europe	202	Multi centre, Retrospective non randomized	6	MDCT, MRI	96	80	44	41	CPVI	1	Holter	Good

For complete study names, see Reference.

CPVI, circumferential pulmonary vein isolation; CPVI PLUS, includes CPVI with one or more of adjuvant ablations in cavotricuspid isthmus, mitral isthmus, left atrial roof, the basal posterior wall, superior vena cava or complex fractionate atrial electrograms; CT, computed tomography(cardiac); LAD+, left atrial diameter was measured in the study; LAV, left Atrial Volume; LAVi, left atrial volume index; MDCT, multidetector computed tomography; MRI, magnetic resonance imaging (Cardiac); NR, not reported; RFA, radiofrequency ablation; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Table 2 Baseline variables of 16 studies included in the meta-analysis of difference in LAV/LAVi between patients with and without post-RFA AF recurrence

Study, Year	Mean Age, years	Male, %	Hypertension, %	Diabetes, %	CAD, %	Type of AF, %			Valvular heart disease, %
						Paroxysmal	Persistent	Long standing persistent	
Maciel *et al.*, 2006	60	69.78	58.22	NA	33.74	NA	NA	NA	0
Parikh *et al.*, 2010	57.6	74.17	61.3	9.64	10.36	45.4	54.6	0	5.7
Hof *et al.*, 2010	56	76	29	NA	NA	70	25	5	1
Shin *et al.*, 2007	55	95.72	45.58	8.99	13.77	58.8	41.2	0	NA
Kohari *et al.*, 2013	61.3	79.66	68.23	14.97	13.76	0	77	23	0
Helms *et al.*, 2009	56	81.50	50.83	13.13	17.21	66	34	0	14
Bergau *et al.*, 2014	63	61.11	64.24	14.24	NA	58.3	41.7	0	44.1
Sohns *et al.*, 2013	62	76.05	95.33	21.23	NA	71	29	0	16
Kim *et al.*, 2014	54.6	86.01	40.53	5.26	NA	0	100	0	NA
Linhart *et al.*, 2013	60	68.33	58	9.74	16.09	67	33	0	NA
Yoshida *et al.*, 2011	62	83.16	50.35	22.2	20.57	0	100	0	NA
Nedios *et al.* 2015	59	69.29	60.28	16.17	9.95	61.2	38.8	0	NA
Hof *et al.*, 2009	57	83.00	47	NA	NA	55	18	27	NA
Montefusco *et al.*, 2010	60	68.09	29.23	NA	NA	65.4	34.6	0	3.3
Uijl *et al.*, 2011	55.9	77.00	45	NA	NA	71	29	0	0
Bary *et al.*, 2012	60	56.91	40.74	NA	21.24	100	0	0	NA

For complete study names, see reference.
AF, atrial fibrillation; CAD, coronary artery disease; LAV, left atrial volume; LAVi, left atrial volume index; NA, not available; RFA, radiofrequency ablation.

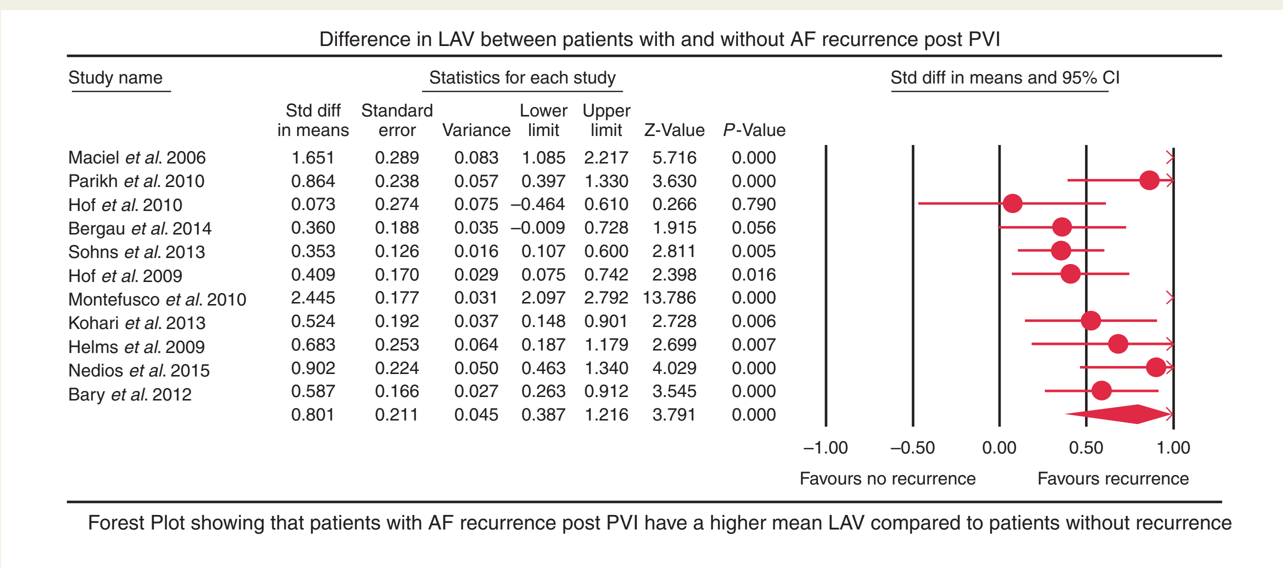
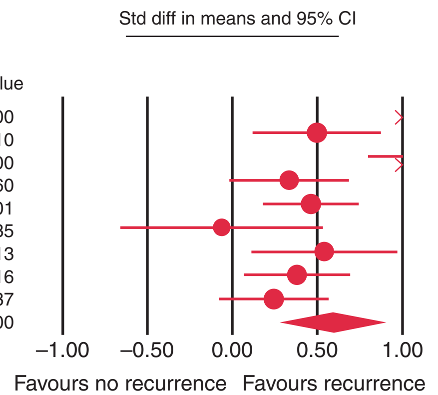


Figure 2 Forest plot showing the difference in LAV between patients with and without post-RFA AF recurrence. Meta-analysis showed patients with post-RFAAF recurrence had a higher mean Left Atrial volume compared to patients with no recurrence.

the 11 studies performed additional linear ablations. All the studies used holter monitoring for diagnosis of asymptomatic AF recurrence except one,[14] which used trans-telephonic monitoring. Blanking periods for AF recurrence post-RFA varied between 1 and 3 months across studies. Two studies excluded patients with low EF,[14,15] and one excluded patients based on LA size.[16] Baseline study variables are shown in *Table* 2. Analysis of the funnel plot showed no significant publication bias (see Supplementary material online, *Figure S1*). In our pooled analysis (*Figure* 2), we found that patients with AF recurrence had a higher mean LA volume compared to patients with no

Difference in LAVI between patients with and without AF recurrence post PVI

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	*P*-Value
Shin *et al.* 2007	2.129	0.345	0.119	1.454	2.805	6.176	0.000
Kohari *et al.* 2013	0.497	0.192	0.037	0.121	0.873	2.589	0.010
Helms *et al.* 2009	1.333	0.270	0.073	0.803	1.862	4.932	0.000
Kim *et al.* 2014	0.333	0.177	0.031	−0.014	0.680	1.880	0.060
Linhart *et al.* 2013	0.462	0.142	0.020	0.184	0.739	3.261	0.001
Yoshida *et al.* 2011	−0.063	0.303	0.092	−0.658	0.532	−0.208	0.835
Nedios *et al.* 2015	0.542	0.218	0.048	0.114	0.969	2.483	0.013
Uijl *et al.* 2011	0.380	0.158	0.025	0.070	0.690	2.401	0.016
Bary *et al.* 2012	0.243	0.163	0.027	−0.077	0.564	1.488	0.137
	0.596	0.149	0.022	0.305	0.888	4.009	0.000



Forest Plot showing that patients with AF recurrence post PVi have a higher mean LAVI compared to patients without recurrence

Figure 3 Forest plot showing the difference in LAVI between patients with and without post-RFA AF recurrence. Meta-analysis showed patients with post-RFA AF recurrence had a higher mean Left Atrial volume index compared to patients with no recurrence.

recurrence (SDM 0.801 mm; CI 0.387–1.216; *P*-0.00). A separate sensitivity analysis was performed by excluding the only study that excluded patients based on LA size (Hof *et al.*)[16] and the results do not change the inference (SDM-0.870; CI 0.435–1.305; $P < 0.05$). A univariate meta-regression analysis showed that age, gender, history of hypertension (HTN) or diabetes (DM), duration of follow up, detection method used for the diagnosis of asymptomatic AF recurrence, and the region where the study was conducted did not significantly affect the outcome of the individual studies and did not add heterogeneity to the meta-analysis. More importantly, the type of imaging to obtain LAV in individual studies did not affect the outcome.

Meta-analysis of the difference in left atrial volume index between patients with and without atrial fibrillation recurrence post-radiofrequency catheter ablation

Nine studies with 1425 subjects were included in the meta-analysis (*Table 1*) comparing the difference in LAVi following RFA between patients with AF recurrence and no recurrence. Six studies were prospective and three were retrospective. Mean follow up duration of the studies was 17.2 months. Baseline study variables are shown in *Table 2*. LAVi was assessed using ECHO, CT, or MRI across various studies with some studies using multiple modalities within the study. Five studies performed circumferential PVI alone, and four studies performed additional linear ablations. All the studies used holter monitoring for diagnosis of asymptomatic AF recurrence except two, one of which used trans-telephonic monitoring[14] and the other used event monitoring.[17] Blanking periods for AF recurrence post-RFA varied between 1 and 3 months across studies. One study excluded patients with low EF[14] and another excluded patients based on LA size.[17] Analysis of the funnel plot showed no significant publication bias (see Supplementary material online, *Figure S2*).

Our meta-analysis (*Figure 3*) showed that patients with AF recurrence had a higher mean LAVi compared to patients with no recurrence (SDM-0.596; CI 0.305–0.888; *P*-0.00). A separate sensitivity analysis was performed by excluding the only study that excluded patients based on LA size (Yoshida *et al.*)[17] and the results do not change the inference (SDM-0.661; CI 0.358–0.964; *P*-0.0). A univariate meta-regression analysis showed that the WMD of LAVI between patients with and without AF recurrence was larger in studies with higher percentage of males ($P < 0.05$), thus explaining some of the heterogeneity between the studies (see Supplementary material online, *Figure S3*). Other factors including age, history of HTN or DM, duration of follow up, detection method used for the diagnosis of asymptomatic AF recurrence, region where the study was performed, and imaging modality used to obtain LAVi did not influence the individual study outcomes; therefore they failed to further explain heterogeneity in our analysis.

Meta-analysis of studies evaluating risk of atrial fibrillation recurrence post-radiofrequency catheter ablation based on left atrial volume/left atrial volume index

Thirteen studies (*Table 3*) which analysed the risk of AF recurrence post-RFA based on LAV/LAVi in 2886 subjects were included in the meta-analysis. Nine studies were prospective and four were retrospective. Mean follow up duration was 18 months. Baseline study variables are shown in *Table 4*. LAV/LAVi was assessed using ECHO, CT, or MRI across various studies with some studies using multiple modalities within the study. Six of the included studies performed PVI alone, while seven studies performed additional linear lines and cavo-tricuspid isthmus ablation during AF ablation. All the studies used holter monitoring to diagnose asymptomatic AF recurrence except one by Yoshida *et al.*,[17] which used 30 days event monitors. Only one

Table 3 Characteristics of 13 studies included in the meta-analysis of studies evaluating the risk of post-RFA AF recurrence based on LAV/LAVi

Study, year	Region	No. of patients	Study design	Mean follow-up, months	Imaging used	Univariate OR/HR	Multivariate OR/HR	RFA details	Blanking period, months	Recurrence detection method	Quality assessment
Costa *et al.*, 2015[37]	Europe	809	Prospective Cohort	29	CT	1.14	1.16	CPVIPLUS	3	Holter	Good
Yoshida *et al.*, 2011[17]	North America	79	Prospective Cohort	6	ECHO	NA	1.05	CPVIPLUS	3	30 day event monitor	Good
Kim et al 2014[31]	Asia	130	Prospective Cohort	24	ECHO	0.613	0.51	CPVI PLUS	3	Holter	Good
Kiliszek *et al.*, 2014[38]	Europe	168	Retrospective Cohort	17	ECHO	1.01	NA	CPVI	3	Holter	Good
Nedios *et al.*, 2015[33]	Europe	103	Single centre, Retrospective cohort	36	ECHO and CT (LAD+)	1.016	1.011	CPVI PLUS	3	Holter	Good
Uijl *et al.*, 2011[35]	Europe	170	Single centre, Prospective cohort	12	TTE (LAD+)	1.011	2.796	CPVI	3	Holter	Good
Nedios *et al.*, 2011[39]	Europe	115	Single centre, pro-spective cohort	25	CT (LAD+)	NA	0.97	CPVI	3	Holter	Good
Hof *et al.*, 2009[26]	Europe	146	Single centre, Prospective cohort	19	CT	NA	1.14	CPVI	3	Holter	Good
Montefusco *et al.*, 2010[34]	Europe	240	Single centre, Retrospective study of prospective cohort	30	MRI	1.1	1.09	CPVIPLUS	2	Holter	Good
Park *et al.*, 2014[40]	ASIA	454	Single centre, pro-spective cohort	13	ECHO and 3D CT(LAD+)	1.008	NA	CPVIPLUS	3	Holter	Good
Linhart *et al.*, 2013[32]	Europe	205	Single centre, Prospective cohort	12	ECHO	1.16	1.11	CPVIPLUS	3	Holter	Good
Akutsu *et al.*, 2011[18]	ASIA	65[a]	Single, centre, pro-spective cohort	6	MDCT (LAD+)	1.04	1.04	CPVI	1	Holter	Good
Bary *et al.*, 2012[36]	Europe	202	Retrospective non randomized multicentre	6	MDCT and MRI (LAD+)	NA	0.76	CPVI	1	Holter	Good

For complete study names, see reference.
CPVI, circumferential pulmonary vein isolation; CPVI PLUS, includes CPVI with one or more of adjuvant ablations in cavotricuspid isthmus, mitral isthmus, left atrial roof, the basal posterior wall, superior vena cava or complex fractionate atrial electrograms; CT, computed tomography(cardiac); ECHO, echocardiography; LAD+, left atrial diameter was measured in the study; LAV, left atrial volume; LAVi, left atrial volume index; MDCT, multidetector computed tomography; MRI, magnetic resonance imaging (cardiac); NR, not reported; RFA, radiofrequency ablation; 3D CT, three dimensional computed tomography.
[a]Reduced LVEF excluded from study.

Table 4 Baseline variables of 15 studies included in the meta-analysis of studies evaluating the risk of post-RFA AF recurrence based on LAV/LAVi

Study, year	Mean age, years	Male, %	Hypertension, %	Diabetes, %	Type of AF, %			Valvular heart disease, %
					Paroxysmal	Persistent	Long standing persistent	
Costa *et al.*, 2015	57	72.2	37.8	NA	73.2	19.9	0	NA
Yoshida *et al.*, 2011	64	83.16	50.35	22.2	0	100	0	NA
Kim *et al.*, 2014	54.6	86.15	40.53	5.26	0	100	0	NA
Kiliszek *et al.*, 2014	56	68.45	56	9	71.4	28.6	0	0
Nedios *et al.*, 2015	59	69.29	60.28	16.17	61.2	38.8	0	NA
Uijl *et al.*, 2011	55.9	77	45	NA	71	29	0	0
Nedios *et al.*, 2011	59	62.6	53.9	7.8	54.8	29.6	15.6	0
Hof *et al.*, 2009	57	83	47	NA	55	18	27	NA
Montefusco *et al.*, 2010	60	68.1	36.02	NA	65.4	34.6		3.3
Park *et al.*, 2014	58	76.7	46.26	15.42	71.8	28.2	0	NA
Linhart *et al.*, 2013	60.4	68.33	58	9.74	67	33	0	NA
Akutsu *et al.*, 2011	59	85.65	48.47	13.4	100	0	0	0
Bary *et al.*, 2012	60	56.9	40.74	NA	100	0	0	NA

For complete study names, see reference.
AF, atrial fibrillation; LAV, left atrial volume; LAVi, left atrial volume index; NA, not available; RFA, radiofrequency ablation.

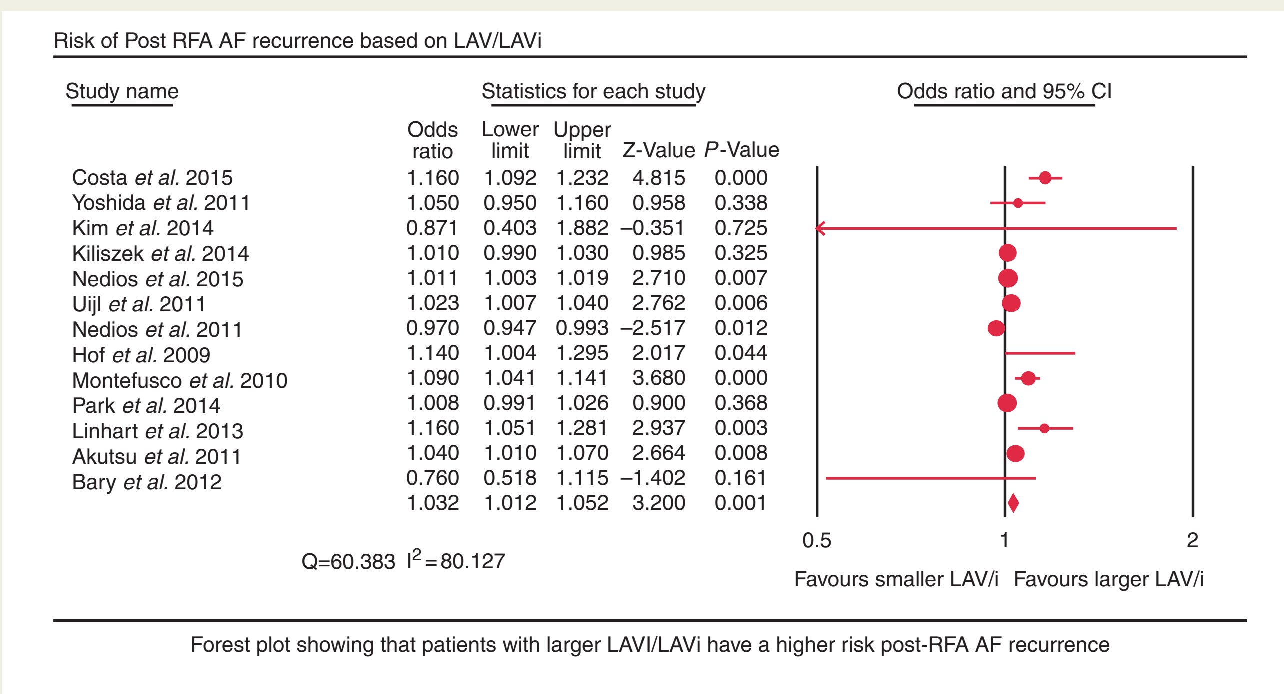


Figure 4 Forest plot showing the incidence of AF recurrence based on LA volume. Meta-analysis showed patients with a larger left atrial volume had higher odds of AF recurrence following RFA.

study with a relatively smaller sample size excluded patients with heart failure[18] and one additional study excluded patients based on LA size.[17] Analysis of the funnel plot showed no significant publication bias (see Supplementary material online, *Figure S4*). Our meta-analysis (*Figure 4*) showed that large LAV/LAVi was independently associated with significantly increased odds of AF recurrence (OR-1.032, CI- 1.012–1.052; *P*-0.001). A multivariate meta-regression showed that the imaging modality used for LAV/LAVi measurement did not add to the heterogeneity between the studies. Moreover age, gender, history of HTN or DM, follow up period, type of monitoring to diagnose asymptomatic AF recurrence, and region of study did not significantly influence individual study outcome or add to the heterogeneity of the meta-analysis.

Discussion

AF recurrence at 5 years post-RFA can be as high as 70% after a single ablation procedure. Thus, the need for predictors of AF recurrence to plan patient management post-RFA, including duration of anti-arrhythmic drug therapy, monitoring for asymptomatic recurrence, and setting realistic patient expectations cannot be overstated. Our meta-analysis showed that compared to patients without AF recurrence, patients with AF recurrence post-RFA had higher mean LAV/LAVi and the measurements were independently associated with significantly increased odds of AF recurrence. Notably, our meta-analysis is the first to report the odds of AF recurrence post-RFA based on LA size assessed by LAV/LAVi. Interestingly, our results suggest that between patients with and without AF recurrence, the mean difference in LAV (0.8 mL, CI 0.387–1.216) and LAVi (0.6 mL/m^2, CI-0.305–0.888) is very small.

While it remains unclear if left atrial enlargement is a cause or a consequence of AF, a large body of evidence indicates that a large LA size contributes to the vicious cycle of atrial remodelling and AF. In addition, structural remodelling, atrial hypertrophy, and stretch can lead to alterations in ionic currents and electrical remodelling. Cardiac endothelin-1 (ET-1) expression responds to wall stress, can promote myocyte hypertrophy and interstitial fibrosis and correlates with enlarged LA size.[19] Patchy atrial fibrosis can lead to areas of slow conduction and altered repolarization dynamics that may form atrial rotors,[20] thereby moving the focus of initiation and sustenance of AF from the pulmonary veins to the LA. PVI in such patients may be insufficient and may predict higher rates of recurrence.

Enlarged LA size is an independent predictor of new onset AF.[21] Relatively large studies evaluating LA diameter as a predictor of AF recurrence post-RFA show mixed results.[22,23] However, LA antero-posterior diameter is not considered a true reflection of LA size. Recently, Abecasis *et al.*[13] showed that LA volume was related to AF recurrence post-RFA ablation, whereas the LA anterior–posterior diameter (LAD) was not. While a meta-analysis of observational studies showed that patients with AF recurrence had a mean LAD that was 1.84 mm more than patients without recurrence, it did not provide a risk estimate.[5]

The weighted mean difference of 1.84 mm in the anteroposterior diameter of the LA between patients with and without AF recurrence in the previous meta-analysis of studies reporting LA diameter, translates approximately to 0.62 mL weighted mean difference in LAV, assuming that the LA is roughly a cube. In reality, however, LAV difference is probably higher, as the anteroposterior diameter is the smallest and the most restricted. Our meta-analysis found a 0.8 mL weighted mean difference in the LAV between the two groups thus confirming the previous LA diameter meta-analysis. Moreover, our meta-analysis is the first to report the odds of AF recurrence post-RFA based on LA size showing that there is a 3% increase in the odds of AF recurrence per unit increase in LAV/LAVi. Studies dividing post-AF ablation patients into two groups based on LAV/LAVi quote dimensions between 95 and 165 mL for LAV and 26 and 42.5 mL/m^2 for LAVi as increasing the risk for AF recurrence. A recently published study validated a scoring system, which included: history of DM & HTN, renal dysfunction, persistent form of AF, LA diameter > 45 mm, age > 65 years, and female sex, in predicting a LA substrate favourable for AF recurrence and actual AF recurrence post-RFA.[24]

Limitations

Our study is a meta-analysis of observational studies; therefore, it carries inherent limitations of the study design. Adjusted HR/OR from multivariate analysis in individual studies were included when available in our analysis mitigating the effect of confounding variables but it does not completely remove it. The imaging modalities to assess LAV and LAVi varied considerably in our studies but a meta-regression using modality of imaging did not show any effect on the outcome of AF recurrence. Additionally, the studies included different proportions of paroxysmal, persistent, and long-standing persistent atrial fibrillation patients (*Tables 2 and 4*). However, a meta-regression using AF type failed to show any significant effect on the outcome of AF recurrence (*P*-values-0.9182 for the LAV analysis, 0.4293 for the LAVi analysis and 0.7084 for the risk of AF recurrence based on LAV/LAVi analysis)

Conclusions

Meta-analyses of observational studies show that while patients with AF recurrence post-AF ablation have significantly higher LAV/LAVi compared to patients without recurrence, the difference in LA dimensions and the risk of AF recurrence due to an increased LA size is modest. Although there are limitations to determine a linear relationship between LA volume and AF-recurrence using this meta-analysis, a one-size-fits-all approach may not be optimal in the selection of patients for RFA. LA volume in our view is a risk assessment tool that when combined with other prognosticators of AF recurrence, may help refine patient selection for RFA. Furthermore, an increased LA volume should raise suspicion and prompt search for other correctable comorbidities that have been shown to independently increase AF recurrence post RFA. However, while awaiting further studies to clarify if increased LA volume is an effect of AF or a risk modifier, excluding patients for RFA based only on modest increase in LA volume may not be warranted. Large patient registries with post-AF ablation patients and extensive outcomes data may shed further light into the impact of LAV and LAVi on AF recurrence and other outcomes following catheter ablation for AF.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of Interest: none declared.

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