The role of left atrial peak systolic strain in atrial fibrillation recurrence after catheter ablation. A systematic review and meta-analysis.

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Abstract

Background: This systematic review and meta-analysis was performed to assess the prognostic role of left atrial peak systolic longitudinal strain (LA-PLSsys) as a predictor of atrial fibrillation (AF) recurrence after catheter ablation. Methods We systematically searched major electronic databases and grey literature for studies assessing the role of preablation LA-PLSsys, measured in at least 2 segments, in post-ablation AF recurrence, after a follow up period of at least 6 months. Results: 17 eligible studies were included, resulting in 1704 patients (68.6% men) with a pooled mean age of 59.9±10.6 years, 65.9% with paroxysmal AF. Recurrence occurred in 32.7% of patients. Those without recurrence had significantly higher LA-PLSsys (pooled mean±SD: 22.22%±10.64%, weighted mean difference: 5.43%, 95%CI: 4.03-6.84%, I2: 82.7%). Subgroup analysis revealed that methodology used (echocardiographic view and segments assessed) was a significant source of heterogeneity (p=0.02), while meta-regression analysis demonstrated that the effect size was inversely related to the baseline LA volume index (p=0.004). Conclusions: Pre-ablation LA-PLSsys seems to be a useful predictor of post-ablation AF recurrence. However, data for patients with persistent AF and severe LA dilation are still lacking, thus no safe conclusion can be made for this challenging subgroup. Moreover, use of different methodology seems to introduce bias in the effort to obtain a universal cutoff value. Whether LA strain may be of clinical use, which would require better methodological definition and deriving a reference range - with adequate positive and negative predictive value for recurrence - is subject to further investigation.

INTRODUCTION

Atrial fibrillation (AF) is the most common tachyarrhythmia, with an estimated prevalence of 6% in patients older than 65 years, which is progressively increasing because of aging of the population, higher prevalence of risk factors and better strategies for detection[1]. The presence of AF is associated with a 2-fold increase in death and heart failure and a 5-fold increase in the rates of stroke and systemic thromboembolism. Additionally, AF can reduce quality of life and exercise tolerance[2].

Catheter ablation (CA), one of the most commonly performed electrophysiology procedures, has emerged as an important treatment option for patients with AF. Randomized trials demonstrated the superiority of CA compared to antiarrhythmic drugs in terms of maintaining sinus rhythm (SR), improving the quality of life and symptoms of AF patients and, the number of CA procedures grew exponentially and indications are expanding[3]. Long-term success of CA varies widely from 50 to 80% and recurrences of AF, mostly due to pulmonary vein reconnection, remain an important problem. Prior studies have recognized a number of predictive outcomes following CA of AF, such as age, type of AF, hypertension and left atrial (LA) dilation[4].

AF is associated with LA enlargement, remodeling and fibrosis, caused by LA pressure and/or volume overload[5]. Furthermore, LA structural and functional remodeling has been recognized as an important risk factor for AF recurrence. In this regard, it is interesting that LA strain, determined by 2-dimensional speckle tracking echocardiography (2DSTE), can serve as a predictor for AF recurrence after catheter ablation[6-7].

The aim of this meta-analysis is to evaluate the predictive role of LA peak systolic longitudinal strain (LA-PLSsys) on AF recurrence after CA.

METHODS

This systematic review and meta-analysis was performed in accordance with the PRISMA guidelines[8]. The predefined protocol was registered in PROSPERO database (CRD42020178248).

Search strategy

A systematic search of the literature was performed, up to July 2020, in three databases: Medline (via PubMed), Scopus and Cohrane Library, using the following search strategy based on keywords: ((atrial) OR (atria) OR (atrium)) AND ((reservoir) OR (strain) OR (stiffness)) AND ((atrial fibrillation) OR (af)). Additional hand- search was also performed using the references of the articles that were identified as relevant (snowball strategy). No date restriction was used. Articles not available in english were excluded.

Study selection

All articles that were obtained after the initial search, were screened by two independent reviewers (I.A. and M.K.) based on title and abstract. Subsequently, potentially eligible studies were further reviewed for inclusion in the final analysis based on the full text. Any disagreements were resolved after consensus with an expert (G.G.). Eligibility criteria for inclusion were: a) prospective or retrospective studies including patients with paroxysmal or/and persistent AF, b) endocardial pulmonary venous isolation (PVI) with radiofrequency catheter ablation (RFCA) or cryoballoon ablation, c) pre-procedural quantification of LA-PLSsys, averaged in at least two segments, using 2DSTE d) a follow-up of at least 6 months for post-ablation AF recurrence.

Data extraction

Data from eligible studies were extracted in a predesigned Microsoft Office Excel 2007 form by two independent reviewers (I.A. and M.K.) and crosschecked for any disagreements, which were resolved after consensus with a senior (G.G.). In case of eligible studies that did not clearly report the primary outcome of interest, we contacted authors electronically (via email) to obtain the required data. For one study that provided effect size as median with interquartile range (IQR), median was used as mean and the standard deviation was obtained from IQR (standard deviation=IQR/1.35). In 10 out of 17 studies the endpoint was defined as AF recurrence, whereas in the other 6 studies the endpoint included atrial tachyarrhythmias (AF, atrial flutter, atrial tachycardia). Furthermore, in the majority of eligible studies (11/16) the LA-PLSsys was measured in sinus rhythm, whereas, accordingly to Hang et al.[9], peak and average systolic strain and strain rate showed no statistical difference between sinus rhythm and AF at baseline echocardiographic parameters. It should be noted that all strain measurements were performed before the catheter ablation procedure.

Risk of bias

Risk of bias within studies, concerning the primary outcome of interest, was assessed in duplicate with the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies[10], modified to better fit our studies (Supplementary table 1). Disagreements were resolved by consensus. Studies with an overall score [?]80% were deemed as high quality. Publication bias was evaluated both visually – using contour-enhanced funnel plot (with the level of statistical significance set at 1%, 5% and 10%) – and with Egger's test[11].

Statistical analysis

Continuous variables were summarized as mean (standard deviation). For pooling the primary outcome of interest, the mean difference (MD) with 95% confidence interval in pre-ablation LA-PLSsys between patients with and without post-ablation AF recurrence, meta-analysis, based on aggregate data, was performed. To allow for expected effect size dispersion between studies (based on intra/inter-observer variation, different methodology/ softwares used and different sample synthesis) a random effects (DerSimonian-Laird) model was adopted. Heterogeneity was assessed using I^2, with values between 50% and 90% representing substantial heterogeneity[12]. To explore heterogeneity sensitivity analysis (including only high quality studies) and subgroup analysis were performed. Moreover meta-regression analysis was performed to explore the confounding effect of age, comorbidities and baseline echocardiographic characteristics. All analyses were performed using STATA/MP version 16.0, Texas, USA software.

RESULTS

Search results and studies characteristics

2312 articles were retrieved by the electronic search and 3 additional articles were identified by hand-search. The flow of study selection is depicted in Figure 1. 17 articles were considered to be eligible and were included in the final analysis[13-29]. We analyzed 1704 patients (68.6% men) with a pooled mean (SD) age of 59.9(10.6) years. Among them 65.9% had PAF, while the main comorbidities were hypertension (51.6%) and diabetes mellitus (11%). The baseline pre-ablation weighted mean (SD) maximum LA volume index (LAVi) and left ventricular ejection fraction were 38.38 (16.27) and 61.5% (9%), respectively. For quantification of LA-PLSsys most studies used the EchoPac PC, GE Vingmed, Horton, Norway software, with the vast majority of the researches measuring LA-PLSsys in at least 6 segments. Two studies included a mixed population of patients who underwent first and second PVI procedure[20, 22], while in one study the majority of patients were treated with electrical cardioversion prior to CA procedure (LA-PLSsys was measured before cardioversion)[29]. AF recurrence occurred in 32.7% of the patients analyzed. Studies characteristics are summarized in Table 1.

Bias assessment

The risk of bias assessment is summarized in Supplementary table 2. Five studies were deemed as low-quality, mainly due to not reporting sample size calculation. No significant publication bias was revealed after construction of the contour-enhanced funnel plot (Supplementary Figure 1) and Egger's test demonstrated no significant small study effect (p= 0.21).

Baseline LA strain and AF recurrence

Analysis of the 17 included studies revealed that the MD between baseline LA strain in patients with post-ablation SR maintenance ((N= 1147, pooled mean (SD): 22.22% (10.64)) and those with AF recurrence ((N= 557, pooled mean (SD): 15.96% (9.77)) was statistically significant (5.43%, 95%CI: 4.03-6.84%). Heterogeneity analysis showed substantial heterogeneity (I^2: 82.7%) (Figure 2).

We performed a sensitivity analysis, by including only the 12 studies that were classified as high-quality, but no significant change was noted compared to the overall results (Supplementary Figure 2). Also, when we excluded two studies[15.27] which visually introduced substantial heterogeneity, a more homogenous effect size estimation emerged (mean difference: 6, 95%CI: 5.12-6.89, I^2:42.77%). Subgroup analysis was also performed by dividing studies according to the methodology used for strain measurement (apical 4 chambers view only versus biplane and the number of LA segments assessed), a significant subgroup interaction was noted (p=0.02) (Figure 3). The pooled effect sizes presented minimal quantitative changes compared to the initial pooled effect size estimation. Heterogeneity was almost eliminated in the smaller subgroups of studies, but remained substantial in the larger subgroup of studies that used the biplane method. Moreover, subgroup analysis was performed based on the type of the ablation procedure that was used – 7 studies using radiofrequency catheter ablation PVI alone versus 9 studies using radiofrequency catheter ablation PVI plus additional lesions- but no significant interaction was found (p=0.6). Subgroup analysis based on the software used (9 studies using EchoPac and 8 studies using other softwares) no significant interaction was noted (p=0.5). Finally, after removing one subgroup of patients who underwent second radiofrequency[13] catheter ablation procedure and one study with mixed population (first and second radiofrequency catheter ablation PVI)[14] heterogeneity remained at the same levels (I^2: 84.5%) with no significant change in the effect size (MD: 5.36, 95%CI: 3.84-6.87).

Meta-regression analysis revealed no confounding effect of age (p=0.67), male gender (p=0.34), number of PAF patients included (p=0.96), number of hypertensive patients included (p=0.56) and baseline pre-ablation strain (p=0.66). However a statistically significant negative correlation was documented between the pooled effect size and the mean baseline maximum LAVi (regression coefficient= -0.184, p=0.004, one study where LAVi was measured using 3D echocardiography was excluded[27]) (Figure 4).

DISCUSSION

The main finding of this meta-analysis is that, between AF patients who maintained post-ablation sinus rhythm and those with arrhythmia recurrence, there is a significant difference in baseline LA-PLSsys measured by 2DSTE in at least two segments. According to our findings, a higher pre-ablation LA-PLSsys could identify patients who will benefit more from a PVI procedure. However, these results should be interpreted with caution because of the existing heterogeneity. The magnitude of the effect size decreases as the LAVi increases. In other words, the LA-PLS as a predictor of AF recurrence in patients with a severely dilated LA may be limited. Moreover we provide evidence that methodological issues could be a potential source of bias. Subgroup analysis based on echocardiographic views used and segments assessed, revealed that the effect size estimation is more homogenous in studies using the same methodology. An exception was noticed for studies using the global approach (apical 4 and 2 chambers- 12 segments). In this subgroup heterogeneity remained substantial (I^2: 88.2%). Visually, it can be attributed to two studies- Hongning et al.[27] and Hanaki et al.[15] - which are characterized by including patients with extreme (relative to the pooled baseline LA-PLSsys mean±SD: 20.18%±10.77%) pre-ablation strain values (36.95% and 8,64%, respectively). Thus, concern is also raised about test's utility in such patients. Nevertheless, no confounding effect of baseline LA-PLSsys was documented in meta-regression analysis.

These results are in line with previous reports[30, 31] which have included studies up to 2017. Our study adds to existing knowledge by allowing a more robust effect size estimation, independent of age, sex, comorbidities and PAF status effects. It also addresses the matter of heterogeneity across the existing literature, leading to some interesting observations, regarding the confounding effect of the baseline LAVi and the methodology used for strain quantification in the included studies.

LA enlargement and remodeling, which typically accompany AF, usually in direct proportion to AF burden, are a critical correlate of AF recurrence[32]. Kalifa et al. demonstrated that higher LA stretch constitutes a substrate for AF development, by increasing activation sources at the junction between pulmonary veins and the LA in a sheep model[33]. On the other hand, long-standing ineffective atrial contraction in the setting of persistent AF worsens LA dilatation and electric remodeling and can perpetuate the arrhythmia[34]. The pathophysiology of AF can be, thus, described as ectopic triggering in a reentry atrial environment[35]. The remodeling of the atrial interstitial matrix, which is characterized by increased fibrosis, is a prerequisite for reentry of ectopic depolarizations and the occurrence of AF. Increased fibrosis has been shown to be an independent predictor of left atrial mechanical dysfunction[36]. Reactive deposition of collagen fibers in the interstitium causes massive fibrosis with consequent alterations in normal conduction[37]. Moreover, fibrosis tends to increase progressively, favoring conversion to a permanent form. Prevention of atrial fibroblastic remodeling is fundamental; identification of an advanced stage of fibrosis can guide a specific and focused therapeutic strategy[38, 39]. Consequently, LA strain could be useful in identifying patients with LA structural and functional remodeling, that is favorable for sustaining AF propagation[9].

According to the CABANA trial and other smaller trials (CASTLE-AF, RAAFT-2), CA is associated with a decreased AF recurrence rate than drug therapy[40-42]. On the other hand, the lack of proof of definitive clinical benefit from PVI in the CABANA trial has highlighted the need to select patients more likely to benefit from this procedure. For this reason, more research is needed in order to understand whether risk factor management and lifestyle changes along with a more focused approach to pre-procedural patient assessment may reduce recurrence rates and maximize the benefits gained from ablation.

Echocardiography is a feasible, widely available, highly reproducible and low-cost examination, which may offer important information regarding parameters potentially associated with post-ablation outcome. This meta-analysis suggests that LA-PLSsys appears to be a useful predictor of AF recurrence after CA. However, it is unclear whether a clinically useful cut-off value (with a high positive and negative predictive value for recurrence) may be computed, which could be employed as a criterion to proceed with CA or not. Currently, according to the results of this meta-analysis, there is a number of potential heterogeneity sources which may limit LA-PLSsys clinical value, including methodological differences, patients with severely dilated LA, etc.

Limitations

The subpopulation of patients with persistent AF was under-represented (34%) in the pooled sample size, which may limit the applicability of the present findings in this group of patients. Data about patients with severely dilated LA (i.e. LAVi$>$ 48ml/m^2) are also lacking. Moreover, only a limited number of studies provided diagnostic accuracy analysis and performing such a meta-analysis to construct the pooled rock curve, to find the optimal cut off was impossible. Finally, PVI using cryoenergy was performed only in one study and, as a result, any possible confounding effect of this alternative procedure type could not be estimated.

Conclusion

Pre-ablation assessment of LA-PLSsys seems to be a significant predictor of AF recurrence after CA. However, current data do not permit derivation of a reference range with adequate positive and negative predictive value. More studies, using stricter methodology and also including patients at high risk for recurrence- such as those with severely dilated LA- are needed to clarify the clinical use of LA-PLSsys.

FIGURES AND TABLES WITH LEGENDS

Figure 1 Flowchart of studies selection

Figure 2 Forest plot of LA-PLSsys weighted mean difference between patients with No AF recurrence and AF recurrence

AF: atrial fibrillation

LA-PLSsys: left atrial peak systolic longitudinal strain

Figure 3 Forest plot of LA-PLSsys weighted mean difference between patients with No AF recurrence and AF recurrence, based on the echocardiographic methodology for strain quantification

A2C: apical two chambers view, A4C: apical four chambers view, S: segments

AF: atrial fibrillation

LA-PLSsys: left atrial peak systolic longitudinal strain

Figure 4 Meta-rgression analysis. Impact of pre-ablation maximum LAVi in LA-PLSsys weighted mean difference between patients with No AF recurrence and AF recurrence

AF: atrial fibrillation

LA-PLSsys: left atrial peak systolic longitudinal strain

LAVi : left atium volume index

Table 1 Summary table of included studies

Study (year)	N	Men (%)	Age (y)	HT (%)	DM (%)	DLD (%)	CAD (%)	LAVi (ml/m^2)	LVEF (%)	PAF (%)	View-Segments	Software	PVI
Hwang et al. (2009)[13]	40	85	54.1 (9,3)	35	13,8	NR	NR	31,2 (10,8)	63,28 (6,46)	100	A4C +A2C-8	EchoPac PC, GE Healthcare	RFC
Kuppahally et al. (2010)[14]	64	73,4	61,9 (14,6)	42.5		34,5	14,5	36,97 (12,32)	52,72 (11,18)	38	A2C-2	VVI,Siemens Medical Solutions	RFC
Mirza et al. (2011)[15]	63	58,7	63,1 (9,9)	53.2	14,3	55,6	11,1	33,7 (10,1)	63,5 (5,7)	74,6	A4C-6	TomTec Imaging Systems	RFC
Machino-Otsuka et al. (2013)[16]	123	84,6	60 (9)	56	7	NR	6	52,3 (24,13)	63,5 (10,24)	0	A4C +A2C-12	EchoPac PC, GE Healthcare	RFC
Morris et al. (2013)[17]	84	60,7	60,7 (9,7)	54.8	1,2	NR	8,3	27,78 (18,42)	**61,4 (6,9)**	100	A4C +A2C-12	EchoPac PC, GE Healthcare	RFC
Spethmann et al. (2014)[18]	31	61,3	62,3 (9,1)	67.7	16,1	NR	3,2	34,85 (9,19)	43,1 (8,98)	61,3	A4C-2	EchoPac PC, GE Healthcare	RFC
Motoki et al. (2014)19]	256	69,9	59 (11)	54	11	NR	14	41 (13)	58 (10)	80	A4C +A2C-12	VVI,Siemens Medical Solutions	RFC
Montserrat et al. (2015)[20]	83	73,5	54 (8,5)	37	NR	NR	NR	36,73 (12,44)	61 (5,22)	96	A4C-6	Philips QLAB	RFC
Yasuda et al. (2015)[21]	100	84	59 (11)	42	12	29	4	46,48 (14,05)	71,68 (8,83)	68	+A2C-12	EchoPac PC, GE Healthcare	RFC
Kawasaki et al. (2016)[22]	137	70,8	61,9 (10,6)	46	16,1	NR	5,8	50,97 (15,40)	63,78 (7,98)	100	A4C-2	Aquson Sequoa	RFC
Ma et al. (2017)[23]	115	60,9	64 (7)	65.2	17,4	6,9	12,2	39 (12,7)	60,2 (6,1)	46,1	A4C +A2C-12	TomTec Imaging Systems	RFC
Parwani et al. (2017)[24]	102	66,7	65,7 (9,7)	72.5	8,8	NR	24,5	30,9 (12,3)	56,8 (3,8)	0	A4C +A2C-12	EchoPac PC, GE Healthcare	RFC

Study (year)	N	Men (%)	Age (y)	HT (%)	DM (%)	DLD (%)	CAD (%)	LAVi (ml/m^2)	LVEF (%)	PAF (%)	View-Segments	Software	PVI
Bai et al. (2018)[25]	87	71,3	61,9 (10,6)	57.5	24,1	NR	12,2	23,73 (9)	61,84 (4,58)	74,7	A4C-6	EchoPac PC, GE Healthcare	RFC
Hongning et al. (2018)[26]	88	59,1	8,5 (9,6)	44.3	9,1	NR	6,8	27,05 (8,16)	68,5 (5,44)	100	A4C +A2C-12	NR	RFC
Lizewska-Springer et al. (2019) [27]	41	61	55 (11)	51	5	27	5	40 (12)	62 (6)	83	A4C-6	EchoPac PC, GE Healthcare	RFC
Koca et al. (2019)[28]	150	62,3	55,1 (11,1)	86	25	8	17	28,72 (8,66)	62,7 (5,41)	100	A4C +A2C-14	Philips QLAB	CRY
Hanaki et al. (2020)[29]	100	84	63 (9)	54	11	28	13	45,2 (15,2)	62,3 (9,2)	0	A4C +A2C-12	EchoPac PC, GE Healthcare	RFC

BMI: Body Mass Index, CAD: Coronary Artery Disease, DLD: Dyslipidemia, DM: Diabetes Mellitus, FUP: follow up, HT: Hypertension, LAVi: Left Atrium Volume index, LVEF: Left Ventricle Ejection Fraction, m: months, NR: Not Reported PAF: Paroxysmal Atrial Fibrillation, PVI: Pulmonary Venous Isolation, Rec: Recurrence, y: years

Continuous variables are summarized as mean (SD)

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REFERENCES

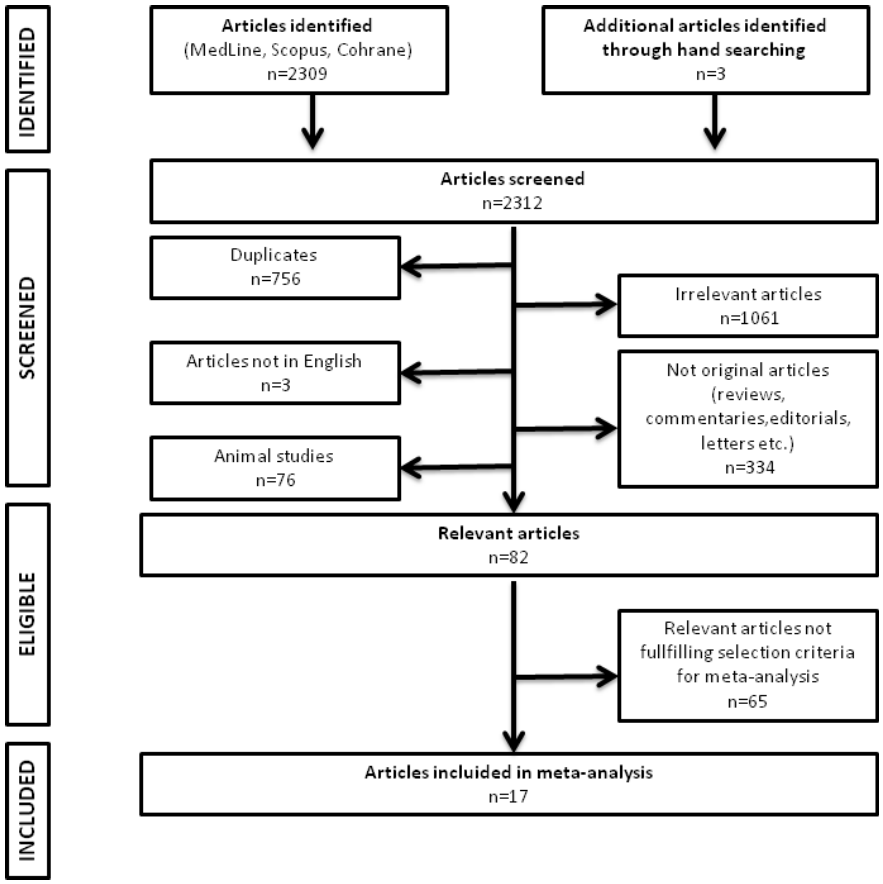
1. Chugh SS, Havmoeller R, Narayanan K. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014;129:837-847.
2. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. Circulation Research. 2017;120(9):1501-1517.
3. Mujović N, Marinković M, Lenarczyk R, Tilz R, Potpara TS. Catheter Ablation of Atrial Fibrillation: An Overview for Clinicians. Advances in Therapy. 2017;34(8):1897-1917.
4. Haegeli LM, Calkins H. Catheter ablation of atrial fibrillation: an update. European Heart Journal. 2014 Sep 21;35(36):2454-2459.
5. Patel DA, Lavie CJ, Milani RV, Shah S, Gilliland Y. Clinical implications of left atrial enlargement: a review. The Ochsner Journal. 2009;9(4):191-196.
6. Seko Y, Kato T, Haruna T, et al. Association between atrial fibrillation, atrial enlargement, and left ventricular geometric remodeling. Scientific Reports. 2018 Apr 23;8(1):6366.
7. Zacà V, Galderisi M, Mondillo S, Focardi M, Ballo P, Guerrini F. Left atrial enlargement as a predictor of recurrences in lone paroxysmal atrial fibrillation. The Canadian Journal of Cardiology. 2007

Sep;23(11):869-872.

8. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of Clinical Epidemiology. 2009;62(10):e1-e34.
9. Hwang HJ, Choi EY, Rhee SJ, et al. Left Atrial Strain as Predictor of Successful Outcomes in Catheter Ablation for Atrial Fibrillation: A Two-Dimensional Myocardial Imaging Study. Journal of Interventional Cardiac Electrophysiology. 2009;26(2):127-132.
10. National Institutes of Health (2014). Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. Available online at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools Accessed: July 10, 2020.
11. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. British Medical Journal. 1997;315(7109):629-634.
12. Ryan R. Cochrane Consumers and Communication Review Group. Heterogeneity and subgroup analyses in Cochrane Consumers and Communication Group reviews: planning the analysis at protocol stage. Accessed: July 10, 2020.
13. Hwang HJ, Choi EY, Rhee SJ, et al. Left atrial strain as predictor of successful outcomes in catheter ablation for atrial fibrillation: a two-dimensional myocardial imaging study. J Interv Card Electrophysiol. 2009 Nov;26(2):127-32.
14. Kuppahally SS, Akoum N, Badger TJ, et al. Echocardiographic left atrial reverse remodeling after catheter ablation of atrial fibrillation is predicted by preablationdelayed enhancement of left atrium by magnetic resonance imaging. American Heart Journal. 2010;160(5):877-884.
15. Mirza M, Caracciolo G, Khan U, et al. Left atrial reservoir function predicts atrial fibrillation recurrence after catheter ablation: a two-dimensional speckle strain study. Journal of Interventional Cardiac Electrophysiology. 2011;31:197-206.
16. Machino-Ohtsuka T, Seo Y, Ishizu T, et al. Significant improvement of left atrial and left atrial appendage function after catheter ablation for persistent atrial fibrillation. Circ J. 2013;77(7):1695-1704.
17. Morris DA, Parwani A, Huemer M, et al. Clinical Significance of the Assessment of the Systolic and Diastolic Myocardial Function of the Left Atrium in Patients With Paroxysmal Atrial Fibrillation and Low CHADS(2) Index Treated With Catheter Ablation Therapy. American Journal of Cardiology. 2013;111(7):1002-1011.
18. Spethmann S, Stuer K, Diaz I, et al. Left atrial mechanics predict the success of pulmonary vein isolation in patients with atrial fibrillation. Journal of Interventional Cardiac Electrophysiology. 2014;40(1):53-62.
19. Motoki H, Negishi K, Kusunose K, et al. Global left atrial strain in the prediction of sinus rhythm maintenance after catheter ablation for atrial fibrillation. Global Left Atrial Strain in the Prediction of Sinus Rhythm Maintenance after Catheter Ablation for Atrial Fibrillation. Journal of the American Society of Echocardiography. 2014;27(11):1184-1192.
20. Montserrat S, Gabrielli L, Bijnens B, et al. Left Atrial Deformation Predicts Success of First and Second Percutaneous Atrial Fibrillation Ablation. Heart Rhythm. 2015;12(1):11-18.
21. Yasuda R, Murata M, Roberts R, et al. Left Atrial Strain Is a Powerful Predictor of Atrial Fibrillation Recurrence After Catheter Ablation: Study of a Heterogeneous Population With Sinus Rhythm or Atrial Fibrillation. European Heart Journal- Cardiovascular Imaging. 2015;16(9):1008-1014.
22. Kawasaki M, Tanaka R, Miyake T, et al. Estimated pulmonary capillary wedge pressure assessed by speckle tracking echocardiography predicts successful ablation in paroxysmal atrial fibrillation. Cardiovascular Ultrasound. 2016;14:6.
23. Ma XX, Zhang YL, Hu B, et al. The Usefulness of Global Left Atrial Strain for Predicting Atrial Fibrillation Recurrence After Catheter Ablation in Patients With Persistent and Paroxysmal Atrial Fibrillation. Archives of Cardiovascular Diseases. 2017;110(8-9):447-455.
24. Parwani AS, Morris DA, Blaschke F, et al. Left atrial strain predicts recurrence of atrial arrhythmias after catheter ablation of persistent atrial fibrillation. Left atrial strain predicts recurrence of atrial

arrhythmias after catheter ablation of persistent atrial fibrillation. Open Heart. 2017;4(1):e000572.

25. Bai Y, Zhao Y, Li J, et al. Association of Peak Atrial Longitudinal Strain With Atrial Fibrillation Recurrence in Patients With Chronic Lung Diseases Following Radiofrequency Ablation. Internal Medicine Journal. 2018;48(7):851-859.
26. Hongning Y, Ruiqin X, Jing W, et al. Assessment of Left Atrial Function and Dyssynchrony by Real Time Three-Dimensional Echocardiography Predicts Recurrence of Paroxysmal Atrial Fibrillation After Radiofrequency Ablation. European Review for Medical and Pharmacological Sciences. 2018;22(10):3151-3159.
27. Liżewska-Springer A, Dąbrowska-Kugacka A, Lewicka E, et al. Biatrial strain as a new predictive marker of successful pulmonary vein ablation in patients with atrial fibrillation and preserved left ventricular function. Kardiol Pol. 2019;77(4):471-474
28. Koca H, Demirtas AO, Kaypaklı O, et al. Decreased Left Atrial Global Longitudinal Strain Predicts the Risk of Atrial Fibrillation Recurrence After Cryoablation in Paroxysmal Atrial Fibrillation. Journal of Interventional Cardiac Electrophysiology. 2020;58(1):51-59.
29. Hanaki Y, Machino-Ohtsuka T, Aonuma K, et al. Preprocedural restoration of sinus rhythm and left atrial strain predict outcomes of catheter ablation for long-standing persistent atrial fibrillation. Journal of cardiovascular electrophysiology, 31(7), 1709–1718.
30. 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.
31. Bajraktari G, Bytyçi I, Henein MY. Left atrial structure and function predictors of recurrent fibrillation after catheter ablation: a systematic review and meta-analysis. Clinical Physiology and Functional Imaging. 2020;40(1):1-13.
32. Oakes RS, Badger TJ, Kholmovski EG, et al. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. Circulation. 2009 Apr 7;119(13):1758-67.
33. Kalifa J, Jalife J, Zaitsev AV, et al. Intra-atrial pressure increases rate and organization of waves emanating from the superior pulmonary veins during atrial fibrillation. Circulation. 2003 Aug 12;108(6):668-71.
34. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. Circ Res. 2017 Apr 28;120(9):1501-1517.
35. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation. 1995 Mar 1;91(5):1588-95.
36. Lau DH, Linz D, Schotten U, Mahajan R, Sanders P, Kalman JM. Pathophysiology of Paroxysmal and Persistent Atrial Fibrillation: Rotors, Foci and Fibrosis. Heart Lung Circ. 2017 Sep;26(9):887-893.
37. Yoon YE, Kim HJ, Kim SA, et al. Left atrial mechanical function and stiffness in patients with paroxysmal atrial fibrillation. J Cardiovasc Ultrasound. 2012 Sep;20(3):140-5.
38. Verma A, Wazni OM, Marrouche NF, et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. J Am CollCardiol. 2005 Jan 18;45(2):285-92.
39. Ausma J, Wijffels M, Thone F, Wouters L, Allessie M, Borgers M. Structural changes of atrial myocardium due to sustained atrial fibrillation in the goat. Circulation. 1997 Nov 4;96(9):3157-63.
40. Packer DL, Mark DB, Robb RA, et al. Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial: Study Rationale and Design. Am Heart J. 2018 May;199:192-199.
41. Shah SR, Moosa PG, Fatima M, et al. Atrial fibrillation and heart failure- results of the CASTLE-AF trial. J Community Hosp Intern Med Perspect. 2018 Aug 23;8(4):208-210.
42. Kaba RA, Cannie D, Ahmed O. RAAFT-2: Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation. Glob CardiolSciPract. 2014 Jun 18;2014(2):53-5.


IDENTIFIED
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Articles identified
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Articles not in English
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Not original articles
(reviews,
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letters etc.)
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Animal studies
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Relevant articles
n=82
Relevant articles not
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for meta-analysis
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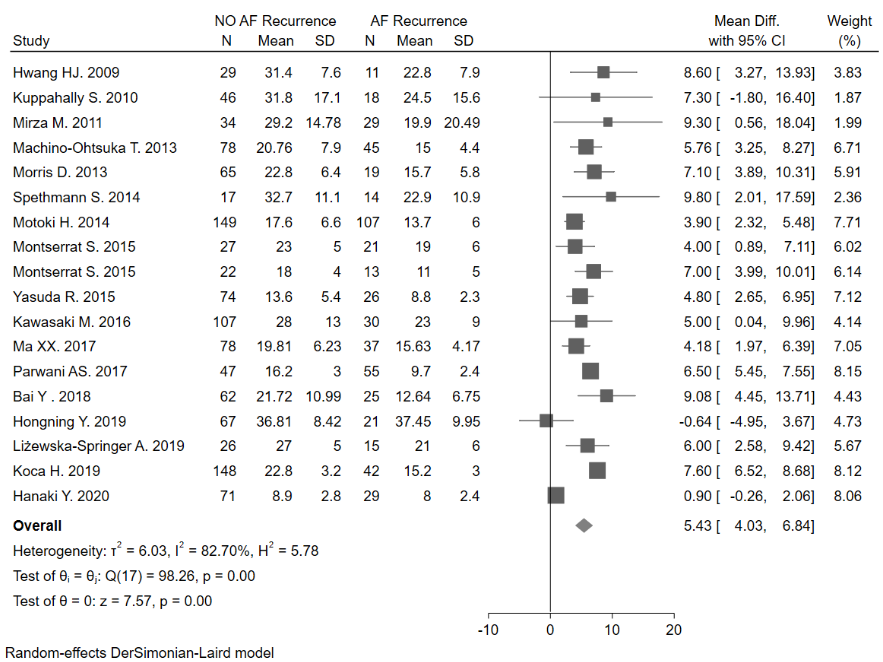
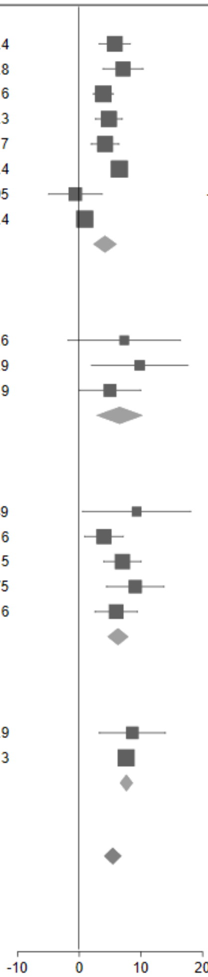
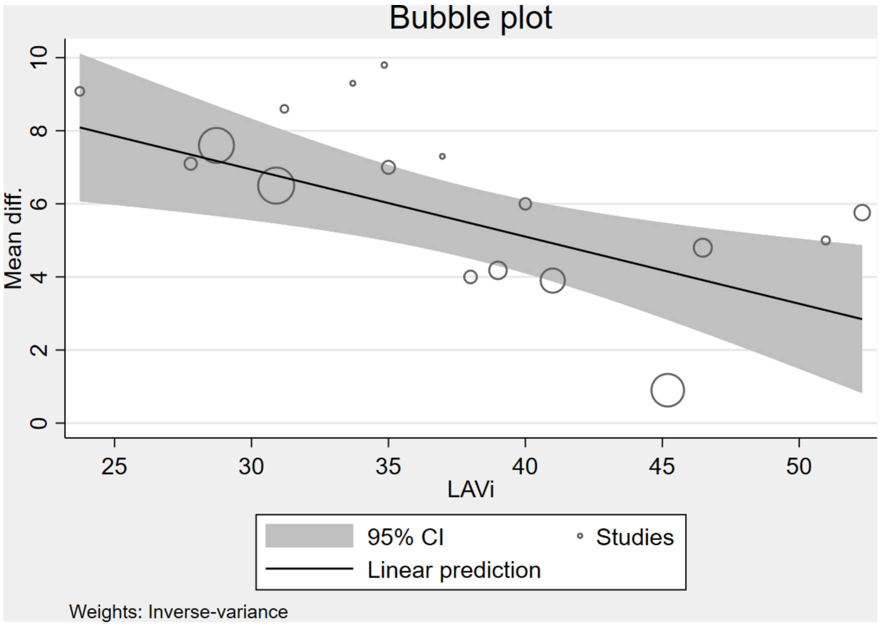

Study
NO AF Recurrence
N Mean SD
AF Recurrence
N Mean SD
Mean Diff.
with 95% CI
Weight
(%)
Hwang HJ. 2009 29 31.4 7.6 11 22.8 7.9 8.60 [3.27, 13.93] 3.83
Kuppahally S. 2010 46 31.8 17.1 18 24.5 15.6 7.30 [-1.80, 16.40] 1.87
Mirza M. 2011 34 29.2 14.78 29 19.9 20.49 9.30 [0.56, 18.04] 1.99
Machino-Ohtsuka T. 2013 78 20.76 7.9 45 15 4.4 5.76 [3.25, 8.27] 6.71
Morris D. 2013 65 22.8 6.4 19 15.7 5.8 7.10 [3.89, 10.31] 5.91
Spethmann S. 2014 17 32.7 11.1 14 22.9 10.9 9.80 [2.01, 17.59] 2.36
Motoki H. 2014 149 17.6 6.6 107 13.7 6 3.90 [2.32, 5.48] 7.71
Montserrat S. 2015 27 23 5 21 19 6 4.00 [0.89, 7.11] 6.02
Montserrat S. 2015 22 18 4 13 11 5 7.00 [3.99, 10.01] 6.14
Yasuda R. 2015 74 13.6 5.4 26 8.8 2.3 4.80 [2.65, 6.95] 7.12
Kawasaki M. 2016 107 28 13 30 23 9 5.00 [0.04, 9.96] 4.14
Ma XX. 2017 78 19.81 6.23 37 15.63 4.17 4.18 [1.97, 6.39] 7.05
Parwani AS. 2017 47 16.2 3 55 9.7 2.4 6.50 [5.45, 7.55] 8.15
Bai Y . 2018 62 21.72 10.99 25 12.64 6.75 9.08 [4.45, 13.71] 4.43
Hongning Y. 2019 67 36.81 8.42 21 37.45 9.95 -0.64 [-4.95, 3.67] 4.73
Liżewska-Springer A. 2019 26 27 5 15 21 6 6.00 [2.58, 9.42] 5.67
Koca H. 2019 148 22.8 3.2 42 15.2 3 7.60 [6.52, 8.68] 8.12
Hanaki Y. 2020 71 8.9 2.8 29 8 2.4 0.90 [-0.26, 2.06] 8.06
Overall 5.43 [4.03, 6.84]
Heterogeneity: τ^2 = 6.03, I^2 = 82.70%, H^2 = 5.78
Test of $\theta_i = \theta_j$: Q(17) = 98.26, p = 0.00
Test of θ = 0: z = 7.57, p = 0.00
-10 0 10 20
Random-effects DerSimonian-Laird model

Study	No AF Reccurence N	Mean	SD	AF Reccurence N	Mean	SD	Mean Diff. with 95% CI	Weight (%)
A2C+A4C-12S								
Machino-Ohtsuka T. 2013	78	20.76	7.9	45	15	4.4	5.76 [3.25, 8.27]	6.71
Morris D. 2013	65	22.8	6.4	19	15.7	5.8	7.10 [3.89, 10.31]	5.91
Motoki H. 2014	149	17.6	6.6	107	13.7	6	3.90 [2.32, 5.48]	7.71
Yasuda R. 2015	74	13.6	5.4	26	8.8	2.3	4.80 [2.65, 6.95]	7.12
Ma XX. 2017	78	19.81	6.23	37	15.63	4.17	4.18 [1.97, 6.39]	7.05
Parwani AS. 2017	47	16.2	3	55	9.7	2.4	6.50 [5.45, 7.55]	8.15
Hongning Y. 2019	67	36.81	8.42	21	37.45	9.95	-0.64 [-4.95, 3.67]	4.73
Hanaki Y. 2020	71	8.9	2.8	29	8	2.4	0.90 [-0.26, 2.06]	8.06
Heterogeneity: τ^2 = 6.24, I^2 = 88.20%, H^2 = 8.48							4.17 [2.26, 6.09]	
Test of $\theta_i = \theta_j$: Q(7) = 59.33, p = 0.00								
A4C-2S								
Kuppahally S. 2010	46	31.8	17.1	18	24.5	15.6	7.30 [-1.80, 16.40]	1.87
Spethmann S. 2014	17	32.7	11.1	14	22.9	10.9	9.80 [2.01, 17.59]	2.36
Kawasaki M. 2016	107	28	13	30	23	9	5.00 [0.04, 9.96]	4.14
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00							6.54 [2.74, 10.35]	
Test of $\theta_i = \theta_j$: Q(2) = 1.07, p = 0.59								
A4C-6S								
Mirza M. 2011	34	29.2	14.78	29	19.9	20.49	9.30 [0.56, 18.04]	1.99
Montserrat S. 2015	27	23	5	21	19	6	4.00 [0.89, 7.11]	6.02
Montserrat S. 2015	22	18	4	13	11	5	7.00 [3.99, 10.01]	6.14
Bai Y . 2018	62	21.72	10.99	25	12.64	6.75	9.08 [4.45, 13.71]	4.43
Liżewska-Springer A. 2019	26	27	5	15	21	6	6.00 [2.58, 9.42]	5.67
Heterogeneity: τ^2 = 0.16, I^2 = 4.05%, H^2 = 1.04							6.27 [4.55, 7.99]	
Test of $\theta_i = \theta_j$: Q(4) = 4.17, p = 0.38								
OTHER								
Hwang HJ. 2009	29	31.4	7.6	11	22.8	7.9	8.60 [3.27, 13.93]	3.83
Koca H. 2019	148	22.8	3.2	42	15.2	3	7.60 [6.52, 8.68]	8.12
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00							7.64 [6.58, 8.70]	
Test of $\theta_i = \theta_j$: Q(1) = 0.13, p = 0.72								
Overall							5.43 [4.03, 6.84]	
Heterogeneity: τ^2 = 6.03, I^2 = 82.70%, H^2 = 5.78								
Test of $\theta_i = \theta_j$: Q(17) = 98.26, p = 0.00								
Test of group differences: $Q_b(3)$ = 9.95, p = 0.02								



Random-effects DerSimonian-Laird model



Bubble plot
Mean diff.
0
2
4
6
8
10
25
30
35
40
45
50
LAVi
95% CI
Studies
Linear prediction
Weights: Inverse-variance