

Extent of Left Atrial Ablation Lesions and Atrial Fibrillation Recurrence after Catheter Ablation – A Systematic Review and Meta-Analysis

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Abstract

Background: Atrial fibrillation (AF) is known to induce atrial remodeling, which promotes fibrosis related to arrhythmogenesis. Accordingly, since scars induced by catheter ablation (CA) can reduce unablated fibrotic areas, greater extent of left atrial (LA) scarring may be associated with less AF recurrence after CA.

Objectives: This study aims to investigate, through systematic review and meta-analysis, whether the amount of LA scarring, seen on late gadolinium enhancement magnetic resonance imaging, is associated with less AF recurrence after CA.

Methods: The recommendations of the MOOSE guideline were followed. Database search was conducted in PubMed and Cochrane Central Register of Controlled Trials (comentário 1) until January 2019 (comentário 2). Two authors performed screening, data extraction, and quality evaluation. All studies were graded as good quality. A funnel plot was generated, showing no publication bias. Statistical significance was defined as p value < 0.05.

Results: Eight observational studies were included in the systematic review, four of which were included in the meta-analysis. Six of the eight studies included in the systematic review showed that greater extension of LA scarring is associated with less AF recurrence after CA. Meta-analysis showed that greater extension of LA scarring is associated with less AF recurrence (SMD = 0.52; 95% CI 0.27 – 0.76; p < 0.0001).

Conclusion: Greater extension of LA scarring is possibly associated with less AF recurrence after CA. Randomized studies that explore ablation methods based on this association are fundamental. (Arq Bras Cardiol. 2020; 114(4):627-635)

Keywords: Atrial Fibrillation; Catheter Ablation; Heart Atria/injuries; Meta-Analysis as Topic; Databases, Bibliographic.

Introduction

Radiofrequency catheter ablation (RFCA) is a standard procedure for correction of atrial fibrillation (AF) in patients who have not responded to previous antiarrhythmic drug therapies.¹ However, this procedure is related to high AF recurrence rates, even in the best hands.² Accordingly, electrophysiologists and interventional cardiologists are seeking techniques that aim to reduce AF recurrence.

AF is known to induce atrial remodeling, increasing the amount of fibrotic tissue in the myocardium, which can promote atrial arrhythmogenesis, reinforcing the vicious cycle of AF.³⁻⁵ In this manner, since the scars induced by catheter ablation (CA) can reduce unablated fibrotic areas, the extent of the left atrial (LA) scars could be associated with less AF recurrence after CA. However, there are currently no systematic reviews or meta-analyses that have investigated this relationship, although they are the highest quality of evidence available.

Accordingly, this systematic review and meta-analysis aims to investigate if the amount of LA scarring, visualized by late gadolinium-enhanced magnetic resonance imaging (LGE-MRI), could be associated with less AF recurrence after CA, which can provide a solid background for designing new ablation strategies that improve patient outcomes.

Methods

A systematic review was performed according to the criteria established by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group.⁶

Search strategies

Two investigators (ETOC and ETM) searched the PubMed and Cochrane Central Register of Controlled Trials, until January 2019. The search strategy comprised a combination of English terms and Medical Subject Headings (MeSH) descriptors, consisting of nine keywords [(left atrial OR left atrium) AND (scar OR scarring OR remodelling OR fibrosis OR enhancement) AND (ablation OR pulmonary vein isolation)]. A manual search of references was also used to identify possible studies for inclusion. Each title and abstract were independently analyzed by both investigators, who selected the articles which were relevant to the review. Subsequently, the full texts of the remaining articles were reviewed to select which

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would be included for qualitative or quantitative analysis. In the event of disagreement, the authors reached a decision through discussion and consensus.

Inclusion criteria for qualitative analysis

We included observational studies (with prospective or retrospective design) in humans, whose objective was to study the association between post-ablation LA scarring and AF recurrence after CA.

Studies that met the following criteria were included: 1) The study evaluated AF or total arrhythmia recurrence after CA in human subjects; 2) The publication was an original study; 3) The mean follow-up period was equal to or longer than 3 months; 4) The study included more than 20 subjects; 5) The study evaluated LA scarring by LGE-MRI after CA.

Inclusion criteria for quantitative analysis

Meta-analysis included studies that met the previous qualitative analysis criteria and reported means and 95% confidence intervals (CI) of total LA scarring in patients with and without AF recurrence after CA.

Quality assessment

Risk of bias in the studies was evaluated by the National Heart, Lung and Blood Institute Quality Assessment Tool for Case Series Studies.⁷ Evaluation was independently conducted by two raters (ETOC and LMSB), and, in the event of disagreement, the raters reached a decision by consensus. The following characteristics were assessed: 1) Was the study question or objective clearly stated? 2) Was the study population clearly and fully described, including a case definition? 3) Were the cases consecutive? 4) Were the subjects comparable? 5) Was the intervention clearly described? 6) Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? 7) Was the length of follow-up adequate? 8) Were the statistical methods well-described? 9) Were the results well described?

Following assessment of those characteristics, the authors assigned a quality rating (good, fair, or poor) to each of the studies. Studies were rated as 'poor' if they met fewer than three criteria; 'fair' if they met three to five criteria; and 'good' if they met more than five criteria. All studies selected met almost all of the criteria and received a good quality rating from both raters. Quality assessment of the included studies is reported in Table 1.

Data extraction

Using a standard data extraction form, two researchers (ETOC and LMSB) performed data extraction, which was cross-verified by a third researcher (ETM). Extracted data included the following: 1) First author's last name and publication year; 2) Characteristics of included studies: number of patients, study region, study design, ablation strategy, measurement method of LA scarring, method of AF detection, length of follow-up period, and main findings; 3) Outcome results: means and 95% CI of total LA scarring in patients with and without AF recurrence after CA.

Statistical analysis

The association between AF recurrence and total LA scarring following RFCA was measured by standardized mean difference (SMD) with 95% CI, and standard errors were determined using the corresponding 95% CI. The inverse variance method was used to weigh studies for combined statistical analysis. Statistical significance was defined as p value < 0.05 . Heterogeneity between studies was assessed using Cochran's Q test and I^2 statistics and subsequently evaluated by I^2 values. I^2 values below 30% were defined as low heterogeneity; values between 30% and 60% were considered moderate heterogeneity; and values above 60% were considered high heterogeneity.⁸ The fixed-effects model was chosen due to the small number of studies included and the low heterogeneity. Meta-regression was not carried out due to the small number of studies included. The results are reported in a forest plot with 95% CI. Publication bias was verified using a funnel plot. All analyses were conducted using Review Manager 5.3 software.

Results

Study selection

Initially, a total of 790 studies were identified by the database search, 695 in PubMed and 95 in the Cochrane Central Register of Controlled Trials. Duplicate analysis revealed 28 duplicates, which were subsequently eliminated. After careful reading of the title and abstract, 742 of the 762 studies were excluded, because they were not related to the present review. Twenty studies were analyzed in full text, twelve of which were excluded, because they were not related to the present review. Finally, eight studies⁹⁻¹⁶ were included in the qualitative analysis, and four were included in the meta-analysis.^{9-11,15} The study selection flow diagram is shown in Figure 1.

Characteristics of the included studies

Eight studies were included in this review,⁹⁻¹⁶ comprising six prospective single center observational studies and two prospective multicenter studies (Table 1). The systematic review included a total of 703 patients, and meta-analysis included 295. The follow-up period ranged from 3 to 12 months. All studies used LGE-MRI to identify post-CA LA scarring. Pulmonary vein isolation (PVI) was the ablation strategy in all of the studies. The studies by Akoum et al.¹⁴ and Hunter et al.¹⁶ used both catheter and cryoballoon ablation. Table 1 and Table 2 summarize the characteristics of all included studies.

Total LA scarring post-ablation and AF recurrence

Six of the eight included studies^{8-12,14} found that the extent of LA scarring was associated with less AF recurrence after CA.

In the study by Hunter et al.,¹⁶ there was no significant association between identification of ablation lesions and freedom from AF (53% with ablation lesions identified remained free from AF vs. 65% in those with no lesions

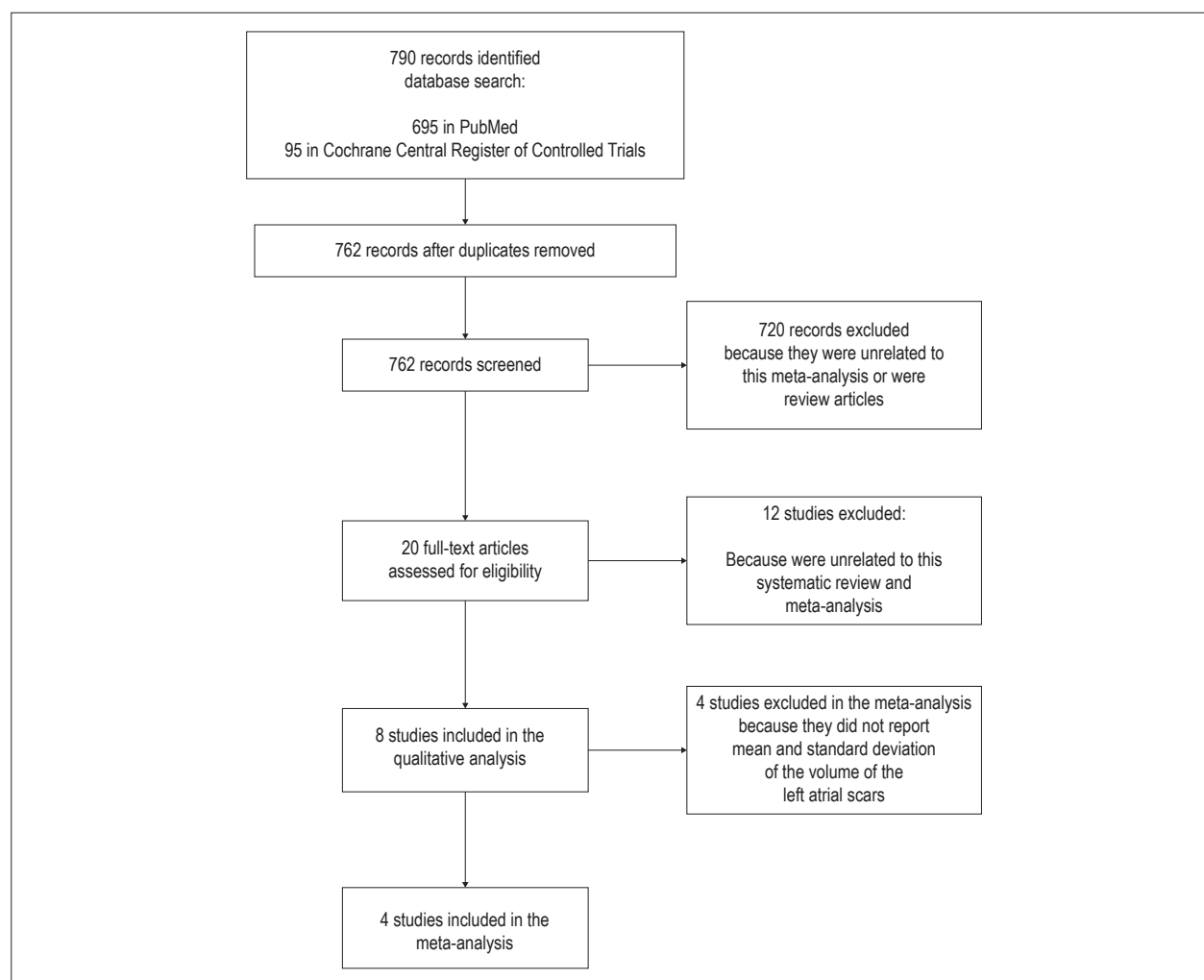


Figure 1 – Study selection flow diagram.

identified, $p = 0.560$). The study also performed binary logistic regression, which confirmed that there was no significant association between identification of ablation lesions and freedom from AF.¹⁶

The 2015 study by Akoum et al.¹⁴ found that ablation-induced scarring was not a statistically significant predictor of less AF recurrence (hazard ratio = 0.95; $p = 0.097$). However, according to this same study, when performing scar homogenization, inducing ablation lesions in prior fibrotic tissue leads to a lower recurrence rate, because less heterogeneous fibrotic tissue remains.¹⁴

Meta-analysis

The present meta-analysis shows that total LA scarring post-ablation is associated with less AF recurrence after CA (SMD = 0.52, 95% CI 0.27 – 0.76, $p < 0.0001$), as shown in Figure 2. The heterogeneity test showed that there were no significant differences between studies ($p = 0.4$, $I^2 = 0\%$). A funnel plot (Figure 3) was used to verify the existence of publication bias. There was no obvious asymmetry, suggesting that there was no publication bias.

Discussion

The importance of CA for AF correction has grown since its introduction. A recent meta-analysis by Kheiri et al. that included seven randomized controlled trials showed that CA was associated with better outcomes in patients with AF and heart failure, in comparison with medical treatment.¹⁷ Therefore, interventional cardiologists should seek ablation strategies that reduce AF recurrence and procedural risks. This systematic review and meta-analysis shows that the extent of LA scarring after ablation is possibly associated with less AF recurrence after CA, paving the way for future research on ablation methods with lower chances of post-procedural recurrence.

Substrate modification

Previous studies in animal models have established the concept that “AF begets AF” by atrial remodeling.¹⁸ In this manner, AF stimulates atrial fibrotic alterations that maintain and increase the AF burden, leading to a vicious cycle.¹⁹ Furthermore, in spite of some limitations, studies in humans have shown that patients with paroxysmal AF have increased LA stiffness, possibly due to an increase in LA fibrosis.^{20,21}

Table 1 – Characteristics of the included studies and quality evaluation

Study, year	Region	Type of Study	N	Paroxysmal, N (%)	AF detection method	Follow up	Quality	p threshold
McGann et al., 2008 ⁹	North America	Single center, prospective, observational	46	22 (48%)	Patient reports, event monitoring, Holter monitoring, and ECG data.	3 months	Good	0.05
Peters et al., 2009 ¹⁰	North America	Single center, prospective, observational	35	19 (54%)	7-day event monitor at multiple intervals	6.7 ± 3.6 months	Good	0.05
Badger et al., 2010 ¹¹	North America	Single center, prospective, observational	144	57 (40%)	8-day Holter monitoring and ECG at 3 months, 6 months, and 1 year	10.23 ± 5.14 months (range, 6 to 20 months)	Good	0.05
Akoum et al., 2011 ¹²	North America	Single center, prospective, observational	120	50 (42%)	12-lead ECG and 8-day Holter monitor at 3 months after ablation and in 3-month intervals thereafter. Additional ECG were obtained when patients reported symptoms.	283 ± 167 days	Good	0.05
McGann et al., 2011 ¹³	North America	Single center, prospective, observational	37	NR	NR	1 year	Good	0.05
Hunter et al., 2013 ¹⁶	Europe	Multicenter, prospective, observational	50	50 (100%)	7 days of ambulatory ECG monitoring at 3 and 6 months	6 months	Good	0.05
Akoum et al., 2015 ¹⁴	North America, Europe, and Oceania	Multicenter, prospective, observational	177	116 (66%)	ECG or ambulatory monitor recordings	At least 1 year	Good	0.05
Parmar et al., 2015 ¹⁵	North America	Single center, prospective, observational	94	45 (48%)	12-lead ECG and 30-day event monitor at 3 and 6 months and 1 year, and every 6 months thereafter. Patients who experienced symptoms were given additional ECG and Holter monitors	Mean follow up of 336 days	Good	0.05

AF: atrial fibrillation; ECG: electrocardiogram; LA: left atrium; LGE-MRI: Late gadolinium enhanced magnetic resonance imaging; NR: not reported.

In addition to that, animal studies have demonstrated that 80% of AF triggers are located in the posterior wall, including the pulmonary vein (PV) region.²² A previous meta-analysis has shown that isolation of a part of the posterior LA reduces the recurrence of AF after CA.²³ Therefore, an increase in the extent of LA ablation may promote greater substrate modification, decreasing the amount of viable LA tissue capable of harboring AF by overlapping PV and non-PV triggers with ablation lesions.

PV scarring

The clinical application of real-time MRI may make it possible to visualize LA scarring during the procedure, making it easier to induce scarring.²⁴ However, as real-time MRI is still a new and expensive imaging method, alternatives such as driver-guided CA by electroanatomic mapping to visualize LA scars might be an option for optimizing outcomes. A recent meta-analysis by Ramirez et al.²⁵ reported an association between driver-guided CA for AF and increased freedom from AF, in comparison with conventional strategies. However, this meta-analysis included primarily nonrandomized studies of moderate quality. Future observational studies can help build evidence to prove whether electroanatomic mapping can assist in creating contiguous scar lesions around the PV.

Risks of targeting more LA scarring

Even though this meta-analysis shows that more extensive ablation reduces the risk of AF recurrence, this strategy is not risk free, given that the procedure may decrease LA compliance, LA volume, and LA systolic function, which may induce the development of the stiff left atrial syndrome (SLAS).²⁶ SLAS, which was described in 1988 by Pilote et al.,²⁷ is characterized by a decline in LA diastolic function and pulmonary hypertension.²⁸ Although this may represent a severe consequence of RFCA, in a case series study by Gibson et al., the condition was reported in only 1.4% of patients who underwent RFCA.²⁸

Furthermore, previous studies found that LA scar volume after CA was associated with depressed LA systolic function.^{26,29} Ablation scars in the posterior LA wall, however, had less effect on LA systolic function.²⁶

Another risk of CA that extensive ablation may increase is the possibility of esophageal injury due to the anatomical relationship between the esophagus and the posterior LA wall.²⁹ The esophagus is separated from the posterior LA by a thin layer of fat, being prone to injury during AF ablation.³⁰ Possible esophageal injuries include perforation, atrio-esophageal fistula formation, and peri-esophageal nerve injury.³⁰ To minimize the potential risks of esophageal

Table 2 – Characteristics of the included studies and main findings

Study, year	Ablation method	Ablation strategy	Catheter used	Time of LGE-MRI	Main Findings
McGann et al., 2008 ⁹	RFCA	PVI in addition to LA posterior wall and septal debulking.	Externally irrigated ablation catheter	3 months after ablation	Patients with scar ratios > 13% are 18.5 times more likely to have a favorable outcome and freedom from AF at 3 months
Peters et al., 2009 ¹⁰	RFCA	PVI without routine addition of empiric ablation lines in the LA.	8-mm standard tip: N = 29 (83%); 3.5-mm externally irrigated tip ablation catheter: N = 6 (17%)	46 ± 28 days after ablation	AF recurrence during the first year is associated with a lesser degree of PV and LA scarring after ablation
Badger et al., 2010 ¹¹	RFCA	PVA isolation with posterior wall and septal debulking	3.5-mm Thermocool irrigated tip ablation catheter	3 months after ablation	Patients with successful AF termination had higher average total LA wall scar after ablation of 16.4 ± 9.8% (p = 0.004) and percent PVA scar of 66.2 ± 25.4 (p = 0.01)
Akoum et al., 2011 ¹²	RFCA	PVI in a circular fashion in the PVA and additional debulking in LA posterior wall and septum	10-pole circular mapping catheter: N = NR; 3.5 mm Thermocool ablation catheter: N = NR	3 months after ablation	Overall post-ablation LA wall scarring predicts recurrence in moderate fibrosis stages
McGann et al., 2011 ¹³	RFCA	PVI in addition to posterior wall and septal debulking	3.5-mm Thermocool ablation catheter	Immediately following ablation and 3 months after ablation	At 1-year follow-up, patients with moderate scar formation 3 months after ablation had no AF recurrence. In comparison, all recurrences occurred in patients with mild scar formation 3 months after ablation (p = 0.02).
Hunter et al., 2013 ¹⁶	RFCA and cryoballoon ablation	PVI by WACA or ostial ablation with a cryoballoon	3.5-mm irrigated ablation catheter: N = NR For cryoballoon ablation an 11F FlexCath sheath delivered a 23- or 28-mm cryoablation balloon: N = NR	Pre-ablation and 3 months after ablation	The proportion of patients free from AF was unaffected by whether ablation lesions could be identified on imaging: 16 of 30 patients (53%) with ablation lesions identified remained free from AF compared to 13 of 20 patients (65%) with no lesions identified (p = 0.560).
Akoum et al., 2015 ¹⁴	RFCA and cryoballoon ablation	PVI with CFAE ablation, linear ablation lines of the CTI, and other ablations in the LA (roof line, mitral isthmus line, posterior wall)	Cryo-balloon: N = 12 (6.7 %); Multi-electrode duty-cycled phased radiofrequency ablation: N = 8 (4.5 %); Nonirrigated and open-irrigation radiofrequency catheters: N = 157 (88.7 %)	3 months after ablation	The more scarring overlaps fibrosis, the better the arrhythmia-free survival
Parmar et al., 2015 ¹⁵	RFCA	PVI and additional debulking of the LA posterior wall	3.5-mm ablation catheter	3 months after ablation	Poor scar formation on LGE-MRI was associated with higher rates of AF recurrence

AF: atrial fibrillation; CFAE: complex fractionated atrial electrogram; CTI: cavotricuspid isthmus; LA: left atrium; LGE-MRI: Late gadolinium enhanced magnetic resonance imaging; NR: not reported; PV: pulmonary vein; PVA: pulmonary vein antrum; PVI: pulmonary vein isolation; RFCA: radiofrequency catheter ablation; WACA: wide area circumferential radiofrequency ablation

injuries, strategies, such as reducing power in the posterior LA wall, monitoring temperature in the esophagus, irrigating the esophagus with cold water, and pre-procedural imaging, should be adopted.³¹⁻³³

Reproducibility

A previous study by Chubb et al.,³⁴ which investigated post-ablation atrial scar, using LGE-MRI, in 40 subjects undergoing first time ablation for AF, showed that post-ablation visualization of induced scars in the LA is reproducible. Moreover, they concluded that imaging should be performed at least 20 minutes after administration of gadolinium-based contrast for better reproducibility.³⁴ However, the study by Hunter et al. analyzed in the present review, which included

50 patients, concluded that LGE imaging of atrial scar is not yet sufficiently accurate to identify ablation lesions or determine lesion distribution reliably. A published consensus by the European Heart Rhythm Association stated that there is still neither recommendation nor expert consensus on the role of LGE-MRI to assist AF ablation procedures. The consensus, nevertheless, states that the available data are intriguing enough to warrant further research.³⁵

STAR AF II and DECAAF II

Although previous studies have demonstrated the positive impact of targeting ablation strategies beyond circumferential pulmonary vein isolation (CPVI), the STAR AF II trial showed a different scenario.^{23,36} The STAR AF II was a randomized

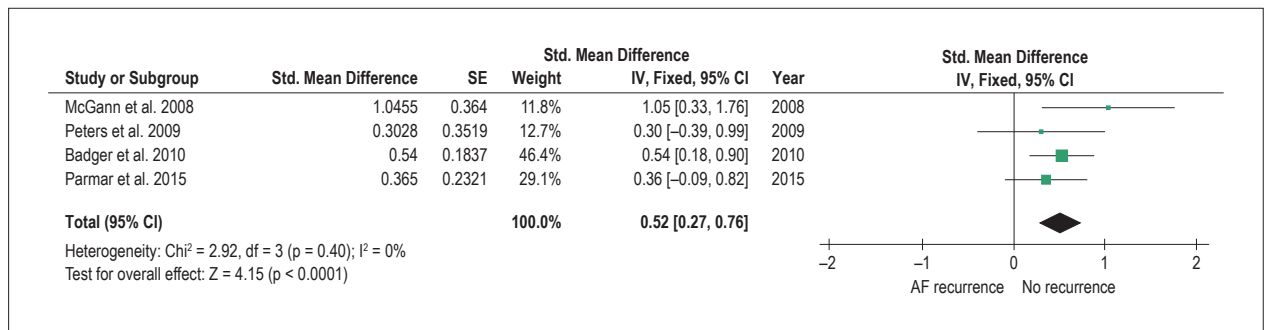


Figure 2 – Forest plot showing that the extent of left atrial scarring is associated with less atrial fibrillation recurrence after catheter ablation. CI: confidence interval; IV: inverse variance

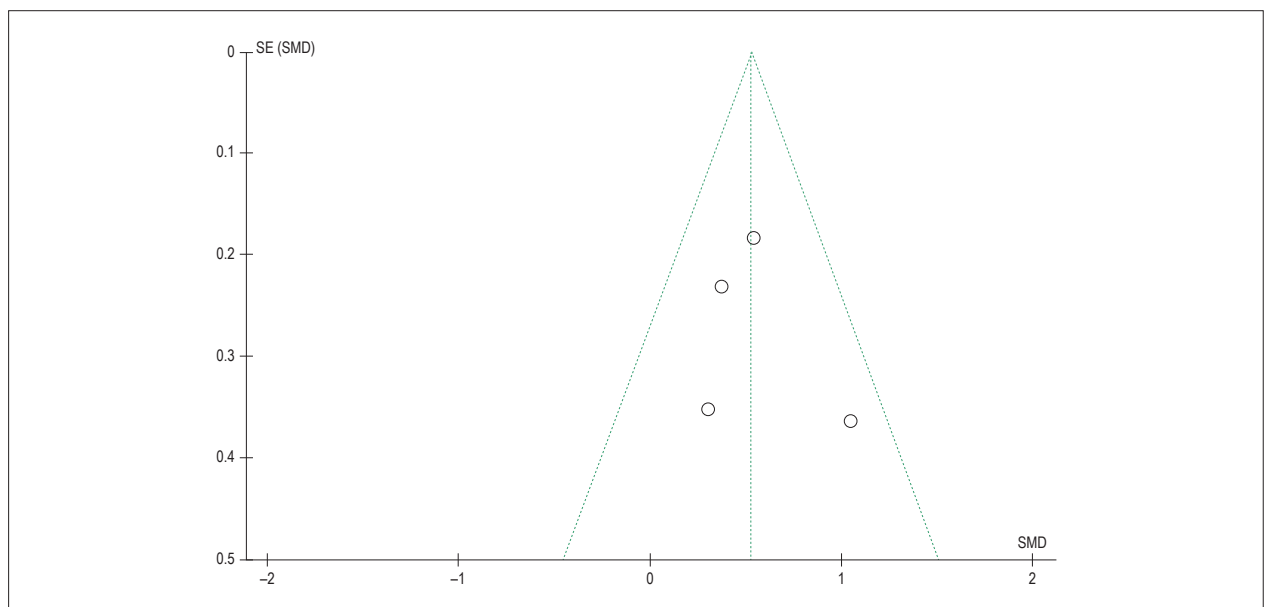


Figure 3 – Funnel plot showing no publication bias.

multicenter study, which, in patients with persistent AF, compared CPVI alone, CPVI plus linear ablation across the LA roof and mitral valve isthmus, and CPVI plus ablation of complex fractionated electrograms. No reduction was found in the recurrence of AF when additional strategies beyond CPVI were performed.³⁶

The DECAAF study showed that LA fibrosis visualized by LGE-MRI was a strong predictor of ablation outcome, and the more ablation-induced scarring overlapped fibrotic tissue, the better the outcome.³⁷ Accordingly, the DECAAF II study will randomize patients with persistent AF to receive either conventional PVI ablation or PVI guided by LGE-MRI.³⁸

Future studies

The increased use of CA for AF correction in clinical practice requires better strategies to reduce post procedural failures. It is necessary to conduct randomized controlled trials that compare driver-guided CA by electroanatomic mapping

with traditional ablation methods. Moreover, it is important to standardize LGE-MRI to detect LA scars in order to guarantee its reproducibility. In addition to that, developing real-time MRI on a larger scale might reduce its costs, making it possible to use in the future.

Limitations

Although the present systematic review and meta-analysis provides a significant increase in the number of patients analyzed, the number of patients included is limited. Moreover, only four studies were included in the quantitative analysis, and all of them were observational studies. Although LGE-MRI is feasible to detect post-ablation atrial scar, its reproducibility needs to be further studied.

Conclusion

The present review shows that the extent of post-ablation LA scars is possibly associated with less AF recurrence after

CA (SMD = 0.52; 95% CI 0.27 – 0.76; $p < 0.0001$), which paves the way for scar-guided ablation strategies. However, the reproducibility of this imaging method needs to be further studied and improved. It is necessary to conduct randomized controlled trials, such as the DECAAF II trial, that investigate ablation methods based on this association in order to provide patients with the best treatment option, with minimal risk of AF recurrence and complications.

Author contributions

Conception and design of the research, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Correia ETO, Barbetta LMS, Mesquita ET; Acquisition of data: Correia ETO, Barbetta LMS; Statistical analysis: Correia ETO.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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