

# Adjunct posterior wall isolation reduces the recurrence of atrial fibrillation in patients undergoing cryoballoon ablation: a systematic review and meta-analysis.

Mishal Mumtaz<sup>1</sup>, Sidra Jabeen<sup>2</sup>, Ahmad Danial<sup>1</sup>, Muhammad Tayyab Muzaffar Chaychi<sup>1</sup>, Muhammad Kashan Zaheer<sup>2</sup>, Aymen Mumtaz<sup>3</sup>, Tayebah Mumtaz<sup>4</sup>, and Bengt Herweg<sup>5</sup>

<sup>1</sup>Quaid-e-Azam Medical College

<sup>2</sup>Liaquat National Hospital and Medical College

<sup>3</sup>CMH Lahore Medical College and Institute of Dentistry

<sup>4</sup>Saint Elizabeth's Medical Center

<sup>5</sup>University of South Florida Morsani College of Medicine

April 3, 2023

## Abstract

Background: Pulmonary vein isolation (PVI) has evolved to be an integral part of ablative therapy for atrial fibrillation (AF), however, recurrence rates of AF remain high even after complete wide area circumferential PVI. In recent years adjunct posterior wall isolation (PWI) has been performed in patients with more persistent forms of AF but the benefits remain unclear. Aim: The objective of this meta-analysis was to evaluate the efficacy of adjunct posterior wall isolation in reducing recurrence rate of AF using cryoballoon ablation (CBA). Methods: We searched PubMed, Google Scholar, Clinicaltrials.gov and Cochrane CENTRAL. We included studies comparing PVI to PVI + PWI in patients with persistent AF undergoing CBA. After data extraction and quality assessment of the studies, we assessed recurrence rates of atrial tachy-arrhythmias (AF, atrial flutter, and atrial tachycardia) as well as total ablation time and procedural adverse events. Risk ratio (RR), mean difference (MD) and 95% confidence interval (CI) were calculated using Review Manager. Results: Concomitant PWI demonstrated significant decrease in recurrence risk of AF (RR 0.48; 95% CI 0.36-0.64;  $p < 0.00001$ ) as well as all atrial arrhythmias (RR 0.57; 95% CI 0.47-0.70;  $p < 0.0001$ ). There was no significant difference in adverse events between both groups (RR 1.05; 95% CI 0.43-2.56;  $p = 0.91$ ), whereas total ablation time was significantly increased in PVI + PWI group (MD 22.67, 95% CI, 7.61-37.73,  $p = 0.003$ ). Conclusion: Adjunct PWI when compared to PVI alone decreases recurrence rates of atrial tachy-arrhythmias after CBA of persistent AF.

**Adjunct posterior wall isolation reduces the recurrence of atrial fibrillation in patients undergoing cryoballoon ablation: a systematic review and meta-analysis.**

## Author(s):

Mishal Mumtaz<sup>1</sup>, Sidra Jabeen<sup>2</sup>, Ahmad Danial<sup>1</sup>, Muhammad Tayyab Muzaffar Chaychi<sup>1</sup>, Muhammad Kashan Zaheer<sup>2</sup>, Aymen Mumtaz<sup>3</sup>, Tayebah Mumtaz<sup>4</sup>, Bengt Herweg, FHRS.<sup>5</sup>

## Affiliations:

<sup>1</sup> Quaid-e-Azam Medical College Bahawalpur, affiliated with University of Health Sciences Lahore, Pakistan.

<sup>2</sup> Liaquat National Hospital and Medical College, Affiliated with Jinnah Sindh Medical University Karachi, Pakistan.

<sup>3</sup> CMH Lahore Medical and Dental College, affiliated with National University of Medical Sciences, Pakistan

<sup>4</sup> Cardiovascular department, St. Elizabeth's Medical Centre, Boston, USA.

<sup>5</sup> Division of Cardiovascular Sciences, University of South Florida Morsani College of Medicine, Heart & Vascular Institute, Tampa General Hospital, Florida, USA.

## Corresponding author:

Mishal Mumtaz, MBBS.

Quaid-e-Azam Medical College Bahawalpur, affiliated with University of Health Sciences Lahore, Pakistan.

*Mishal.mumtaz@hotmail.com*

**Total Word Count:** 4095 (including references)

*Background:* Pulmonary vein isolation (PVI) has evolved to be an integral part of ablative therapy for atrial fibrillation (AF), however, recurrence rates of AF remain high even after complete wide area circumferential PVI. In recent years adjunct posterior wall isolation (PWI) has been performed in patients with more persistent forms of AF but the benefits remain unclear.

*Aim:* The objective of this meta-analysis was to evaluate the efficacy of adjunct posterior wall isolation in reducing recurrence rate of AF using cryoballoon ablation (CBA).

*Methods:* We searched PubMed, Google Scholar, Clinicaltrials.gov and Cochrane CENTRAL. We included studies comparing PVI to PVI + PWI in patients with persistent AF undergoing CBA. After data extraction and quality assessment of the studies, we assessed recurrence rates of atrial tachy-arrhythmias (AF, atrial flutter, and atrial tachycardia) as well as total ablation time and procedural adverse events. Risk ratio (RR), mean difference (MD) and 95% confidence interval (CI) were calculated using Review Manager.

*Results:* Concomitant PWI demonstrated significant decrease in recurrence risk of AF (RR 0.48; 95% CI 0.36-0.64;  $p < 0.00001$ ) as well as all atrial arrhythmias (RR 0.57; 95% CI 0.47-0.70;  $p < 0.0001$ ). There was no significant difference in adverse events between both groups (RR 1.05; 95% CI 0.43-2.56;  $p = 0.91$ ), whereas total ablation time was significantly increased in PVI + PWI group (MD 22.67, 95% CI, 7.61-37.73,  $p = 0.003$ ).

*Conclusion:* Adjunct PWI when compared to PVI alone decreases recurrence rates of atrial tachy-arrhythmias after CBA of persistent AF.

## Keywords:

Posterior wall isolation, pulmonary vein isolation, persistent atrial fibrillation, and meta-analysis.

**Abstract Word Count:** 249

## Introduction

Atrial Fibrillation (AF) is on a rising trend worldwide with almost 37.6 million cases in 2017.(1) Health complications due to AF, including ischemic stroke and heart failure, contribute significantly to morbidity and mortality. (2) The primary goal in the management of patients with AF is improvement of symptoms and the prevention of stroke and cardiomyopathy. (3) In recent years management of AF has shifted from pharmacologic rate and/or rhythm control to catheter ablation of AF (4) yielding superior rhythm control when compared to antiarrhythmic therapy. (5, 6)

Pulmonary vein isolation (PVI) is the cornerstone of current ablation techniques for AF. Recurrences of atrial tachy-arrhythmias after AF ablation procedure are more frequent in patients with persistent AF (7), impact quality of life, and result in repeat ablation in 20 to 40% of patients (8). Adjunctive ablation strategies targeting arrhythmia substrates outside of the pulmonary veins (9) such as ablation of complex fragmented

electrograms, posterior wall ablation with radiofrequency energy, (10) left atrial linear ablation and scar modification have failed to demonstrate incremental benefit in randomized controlled clinical trials.

The objective of this meta-analysis was to evaluate the efficacy of adjunct posterior wall isolation in reducing recurrence rates of atrial tachy-arrhythmias using cryoballoon ablation (CBA) in patients with persistent AF.

## Methods

### Search strategy and selection

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. (12) An ethical/institutional review board (IRB) approval for our systemic review and meta-analysis was not required as we retrieved and synthesized data from already published studies. Online databases such as PubMed, Clinicaltrials.gov, Google Scholar, and Cochrane CENTRAL were systematically searched from inception to June 20, 2022. No restrictions on date, language, or publication type were applied. The following combinations of MeSH terms were used using the Boolean Logic:

"Pulmonary vein isolation", "posterior wall isolation", "cryoballoon ablation", "atrial fibrillation". Previously published meta-analyses on this topic were also cross-checked.

### *Inclusion criterion*

We included studies comparing PVI with PVI+PWI in a patient population >18 years undergoing catheter ablation for persistent AF (continuous AF for >7 days) or long standing persistent AF (continuous AF for >12 months).

### *Exclusion criterion*

Patients <18 years, patients with any history of AF ablation or cardiac surgery, paroxysmal AF, congenital heart disease, left ventricular ejection fraction (LVEF) < 40, cardiomyopathy, or cerebral ischemic events were excluded.

### *Data extraction and quality assessment*

The retrieved articles were initially reviewed by two independent reviewers (SJ and AD). They screened titles and abstracts and removed the duplicates using the EndNote X9 software. The extracted data were further verified by the reviewers. The third investigator (MM) was then consulted to address any discrepancies concerning the evaluation of studies. The study design, baseline characteristics, and various outcomes were extracted. For the quality assessment of the included randomized control trials (RCTs) (13, 14), the Revised Cochrane Risk of Bias tool (ROB-2) was used. The modified Newcastle Ottawa scale was used for quality assessment of the remaining non-randomized trial (15).

### Interventions

Operators performed PVI under fluoroscopic guidance by advancing an inflated cryoballoon (CB) catheter (Medtronic Inc., Minneapolis, MN) to each pulmonary vein antrum and freezing the tissue.

PWI was performed by delivery of at least two cryo-balloon freezes applied to each quadrant of the left atrial posterior wall (LAPW) under fluoroscopic guidance. This was accomplished by clocking/counter clocking of the sheath and balloon catheter after positioning the cryo-balloon in the individual pulmonary veins supported by pushing in the Achieve catheter (Medtronic Inc., Minneapolis, MN) to apply pressure to the LAPW. The cryo-balloon position was monitored on intracardiac ultrasound. Post ablation 3-dimensional (3D) voltage maps were created after each procedure.

### Study definitions and end points

The primary outcome of interest was the recurrence of AF after the 90-day blanking period. Recurrence of any type of atrial tachyarrhythmia was defined as >30 seconds on any cardiac rhythm recording following the specified blanking period after the index CBA procedure.

Secondary outcomes included recurrence of all atrial arrhythmias (AF, atrial flutter, and atrial tachycardia), total ablation time, and adverse events.

### Statistical analysis

We used the Review Manager (RevMan) computer program, version 5.4, to perform statistical analysis. A random effects model with Mantel-Haenszel weighting was then used to analyze our primary and secondary endpoints. The outcomes were reported as risk ratios (RR) and mean difference (MD) with a 95% confidence interval (CI). For assessment of study heterogeneity, the Higgins-I-squared ( $I^2$ ) model was used with values < 25%, 25–50%, 50–75%, and > 75% corresponding to no, low, moderate, and high degrees of heterogeneity, respectively. (16) A p-value of <0.05 was considered statistically significant. The publication bias was depicted graphically using funnel plots

(Supplementary figures).

## Results

### Literature Search

The preliminary literature search yielded 13,022, of which 12,747 were screened for title and abstract. Consequently 7,159 were assessed for eligibility and full text screening, which led to the inclusion of 3 studies with a total of 600 participants (13, 14, 15). The PRISMA flow chart is shown in **Figure 1**. The search strategy and the quality assessment of included studies is summarized in the **Supplementary Tables**.

*Study Characteristics* These trials randomly assigned 273 patients to the PVI group and 327 to the PVI+PWI group. The follow-up period ranged from 1 to 18 months. The baseline demographics, characteristics, and comorbidities are summarized in **Table 1**. The average age was 68 years in the PVI group, as compared to 66 years in the PVI+PWI group while 186/273 patients were male in the PVI group and 220/327 patients were male in the PVI+PWI group. Out of total study population 466 patients had persistent AF (continuous AF for > 7 days) and 134 patients had long-standing persistent AF (continuous AF for > 12 months). Out of 3 studies that we included in our meta-analysis, two were randomized controlled trials (13, 14). One study was a prospective non-randomized trial. (15) CBA was performed in both the PVI and PVI+PWI groups with adjunct radiofrequency ablation (RFA) performed in 2 of the studies (14, 15).

### Results of Meta-Analysis

#### Recurrence of all atrial arrhythmias

All 3 studies reported recurrence of all atrial arrhythmias (AF, atrial flutter, and atrial tachycardia). Recurrence occurred in 97 of 325 (30%) patients who underwent PVI+PWI and 141 of 272 (52%) patients who underwent PVI alone. Our meta-analysis revealed that the PVI+PWI group was associated with a significantly lower recurrence of all atrial arrhythmias as compared to the PVI group (RR 0.57; 95% CI, 0.47-0.70,  $p < 0.00001$ ) (**Figure 2**). In other words, there was a 43% reduction in the recurrence risk of any type of atrial arrhythmia in the PVI+PWI group with 0% heterogeneity among studies  $I^2 = 0\%$ .

#### Recurrence of atrial fibrillation

All 3 studies reported AF recurrences. Recurrence occurred in 63 of 325 (19%) patients were undergoing PVI+PWI arm while 112 of 272 (41%) patients undergoing PVI arm. Our meta-analysis revealed a significant reduction in AF recurrences in PVI+PWI arm when compared to the PVI arm (RR 0.48; 95% CI, 0.36-0.64,  $p < 0.00001$ ) (**Figure 2**), or a 52% reduction in the risk of AF recurrence with 7% heterogeneity among studies,  $I^2 = 7\%$ .

#### Adverse events

All 3 studies reported adverse events (13, 14, 15). Our meta-analyses did not find any significant difference in adverse events between both groups (RR 1.05; 95% CI 0.43-2.56;  $p = 0.91$ ) (**Figure 2**) with no heterogeneity among studies,  $I^2 = 0$ .

#### *Total ablation time*

All 3 studies reported total ablation time (13, 14, 15). Our meta-analysis showed significantly decreased ablation time required to achieve PVI as compared to PVI + PWI (MD 22.67minutes, 95% CI, 7.61-37.73,  $p = 0.003$ ) with high heterogeneity among studies,  $I^2 = 99\%$  (**Figure 2**).

### **Discussion**

The addition of posterior wall isolation (PWI) to pulmonary vein isolation (PVI) resulted in a considerably higher chance of freedom from AF over 12 months compared to PVI alone in patients with symptomatic persistent AF who were referred for CBA. Adding PWI to PVI also significantly reduced the recurrence risk of all atrial tachyarrhythmias. Furthermore, PWI was not associated with increased adverse events when compared to PVI, while total ablation time was significantly longer in the PWI + PVI group as compared to PVI group with a mean of  $47 \pm 33$  minutes and  $24 \pm 19$  minutes, respectively. This result is remarkable considering that a recently published RCT in patients with persistent AF using RF ablation did not show any significant difference in freedom from atrial arrhythmias with adjunct PWI as compared to PVI alone. (10)

To our knowledge, this is the first meta-analysis that has compared patients with atrial fibrillation undergoing PVI to PVI + PWI using CBA exclusively. Previous meta-analyses (17, 18, 19) also compared PVI with PVI+PWI, but they included studies that used RFA, whereas our meta-analysis explores the outcomes of only CBA in patients with persistent AF.

The front section of the LA wall yields the majority of left atrial (LA) contractility, while the posterior wall (PW) appears to play a rather minor role. Hence, LA posterior wall isolation does not result in a substantial loss in atrial mechanical function. (20)

The LA PW and the pulmonary veins (PV) share the same embryological origin in which the primitive mesodermal PV develops four different branches, and thus, the LA PW and PV exhibit similar histology. (21) The LA PW is a complicated structure made up of many layers of muscle bundles with varying wall thicknesses. (21, 22) In comparison to other sections of the LA, the LAPW frequently gives rise to rotors and spontaneous triggers. (25) (23) The LA PW and septum are the most common locations of structural atrial remodeling seen in AF. (24) Consequently, the LA PW similar to the PVs may be a relevant contributor to arrhythmogenesis. When compared to other LA sites, the LA PW has a greater rate of delayed afterdepolarizations, late sodium currents, but relatively small inward rectifier potassium currents, higher intracellular calcium transients, and sarcoplasmic reticulum calcium storage, and greater protein expression of the ryanodine receptor. (23)

Among individuals undergoing surgical ablation for AF, the routine inclusion of PWI with PVI has been shown to favorably impact the long-term procedural success. (11) Further, wide area circumferential PV isolation often leaves a narrow posterior wall channel that may be a viable reentry substrate. Fibrosis of the PW, may account for slow conduction and functional reentry. (27) "Debulking" the left atrium by PWI may diminish critical mass required to sustain AF (28), and the PW's epicardial fat pads containing ganglionic plex can be modified by ablation. (26) The DECAAF multicenter prospective study demonstrated that among patients with atrial fibrillation undergoing catheter ablation, atrial fibrosis estimated by delayed enhancement MRI was independently associated with the likelihood of recurrent arrhythmia. (29). However the DECAAF II trial did not demonstrate the incremental benefit of additional MRI-guided scar ablation when compared to conventional ablation in patients undergoing PVI (30).

Targeting LAPW following PVI may be a viable option for preventing AF recurrence in persistent AF. Depending on the operator's choice and expertise, different techniques of PW can be utilized using either radiofrequency or cryo energy. Isolation can be accomplished via a "box lesion set," connecting the superior

and inferior PV lesion sets with a roof and a low posterior line. A single ring has also been described that employs a single circle to include the PVs and the PW. Another technique is to eliminate all viable atrial potentials on the posterior wall with RF ablation. A potential explanation why PWI with RF ablation may not result in improved clinical outcomes may be that RF ablation in the area of the PW at altered energy settings may frequently result in incomplete lesion sets as a result of insufficient lesion debt and recovery of conduction in deeper epicardial layers of the posterior wall and left atrial roof.

Thorough PWI isolation is associated with longer procedure times. Another drawback of PWI is the possibility of complications, such as an atrio-esophageal (AE) fistula which appear to be more common using radiofrequency ablation (10). Operators have tried to decrease the risk of AE fistula by esophageal temperature monitoring, (31) employing high power short duration ablation, altered irrigation settings and rigorous contact monitoring, as well as (31) esophageal deflection. (32)

Advantages of CBA of the posterior wall may be a lower risk of esophageal injury and the creation of a more homogenous lesion set. Luminal esophageal temperature monitoring was done in 2 of the 3 included studies (14, 15). A trade off is the higher risk of phrenic nerve palsy. High output right atrial phrenic nerve stimulation (>10mA) from the superior vena cava was performed in all three studies to avoid phrenic nerve injury (13, 14, 15). Our meta-analysis found no evidence of a greater risk of complications with PWI than with PVI alone, particularly the development of an AE fistula.

### Limitations:

Firstly, the included studies had different study protocols, including both randomized and nonrandomized trials. Secondly, the precise techniques of CBA for PVI and PWI might differ between different operators, while two of our studies used adjunct RFA, which might explain the high heterogeneity found in total ablation time. Thirdly, our sample size is small, too small to compare rare events such as AE fistula. Therefore, more randomized trials with larger populations are needed in the future.

### Conclusion

Adjunctive PWI using CBA significantly reduces the recurrence rates of atrial tachy-arrhythmias, including AF, in patients with persistent AF without significantly increasing the risk of adverse events. In contrary, a recently published RCT of PWI using RF ablation did not demonstrate improved outcomes.

### Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

### Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Authors' Contributions

MM, AD, SJ, MTMC and MKZ contributed to the conception or design of the manuscript. MTMC, SJ MM and AD contributed to the acquisition of the data. SJ, AM and MM contributed to the analysis of data. MM and AD contributed to the interpretation of the analysis. MM, MTMC, AD and SJ drafted the manuscript. TM and BH were involved in critical revision for important intellectual content. All authors critically revised the manuscript, gave final approval, and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

**Acknowledgments:** None to declare.

### References

1. Chung S-C, Sofat R, Acosta-Mena D, Taylor JA, Lambiase PD, Casas JP, et al. Atrial fibrillation epidemiology, disparity and healthcare contacts: a population-wide study of 5.6 million individuals. *Lancet Reg Health Eur.* 2021 Aug;7:100157.

2. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: An increasing epidemic and public health challenge. *Int J Stroke*. 2021 Feb;16(2):217–21.
3. Padanilam BJ, Prystowsky EN. Atrial fibrillation: goals of therapy and management strategies to achieve the goals. *Cardiol Clin*. 2009 Feb;27(1):189–200, x.
4. Mulder BA, Rienstra M, Van Gelder IC, Blaauw Y. Update on management of atrial fibrillation in heart failure: a focus on ablation. *Heart*. 2022 Mar;108(6):422–8.
5. Alrumayh A, Alobaida M. Catheter ablation superiority over the pharmacological treatments in atrial fibrillation: a dedicated review. *Ann Med*. 2021 Dec;53(1):551–7.
6. Razzack AA, Lak HM, Pothuru S, Rahman S, Hassan SA, Hussain N, et al. Efficacy and Safety of Catheter Ablation vs Antiarrhythmic Drugs as Initial Therapy for Management of Symptomatic Paroxysmal Atrial Fibrillation: A Meta-Analysis. *Rev Cardiovasc Med*. 2022 Mar 19;23(3):112.
7. Stabile G, Lepillier A, De Ruvo E, Scaglione M, Anselmino M, Sebag F, et al. Reproducibility of pulmonary vein isolation guided by the ablation index: 1-year outcome of the AIR registry. *J Cardiovasc Electrophysiol*. 2020 Jul;31(7):1694–701.
8. Darby AE. Recurrent atrial fibrillation after catheter ablation: considerations for repeat ablation and strategies to optimize success. *J Atr Fibrillation*. 2016 Jul;9(1):1427.
9. Stiles MK, Sanders P, Lau DH. Targeting the substrate in ablation of persistent atrial fibrillation: recent lessons and future directions. *Front Physiol*. 2018 Sep 18;9:1158.
10. Kistler PM, Chieng D, Sugumar H, Ling LH, Segan L, Azzopardi S, Al-Kaisey A, Parameswaran R, Anderson RD, Hawson J, Prabhu S, Voskoboinik A, Wong G, Morton JB, Pathik B, McLellan AJ, Lee G, Wong M, Finch S, Pathak RK, Raja DC, Sterns L, Ginks M, Reid CM, Sanders P, Kalman JM. Effect of Catheter Ablation Using Pulmonary Vein Isolation With vs Without Posterior Left Atrial Wall Isolation on Atrial Arrhythmia Recurrence in Patients With Persistent Atrial Fibrillation: The CAPLA Randomized Clinical Trial. *JAMA*. 2023 Jan 10;329(2):127–135. doi: 10.1001/jama.2022.23722. PMID: 36625809; PMCID: PMC9856612.
11. Thiagarajah A, Kadhim K, Lau DH, Emami M, Linz D, Khokhar K, et al. Feasibility, Safety, and Efficacy of Posterior Wall Isolation During Atrial Fibrillation Ablation: A Systematic Review and Meta-Analysis. *Circ Arrhythm Electrophysiol*. 2019 Aug 12;12(8):e007005
12. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009 Jul 21;6(7):e1000097.
13. Ahn J, Shin DG, Han S-J, Lim HE. Does isolation of the left atrial posterior wall using cryoballoon ablation improve clinical outcomes in patients with persistent atrial fibrillation? A prospective randomized controlled trial. *Europace*. 2022 Feb 9;
14. Aryana A, Allen SL, Pujara DK, Bowers MR, O'Neill PG, Yamauchi Y, et al. Concomitant pulmonary vein and posterior wall isolation using cryoballoon with adjunct radiofrequency in persistent atrial fibrillation. *JACC Clin Electrophysiol*. 2021 Feb;7(2):187–96.
15. Aryana A, Baker JH, Espinosa Ginic MA, Pujara DK, Bowers MR, O'Neill PG, et al. Posterior wall isolation using the cryoballoon in conjunction with pulmonary vein ablation is superior to pulmonary vein isolation alone in patients with persistent atrial fibrillation: A multicenter experience. *Heart Rhythm*. 2018 Aug;15(8):1121–9.
16. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine*. 2002; 21: 1539–1558
17. He X., Zhou Y., Chen Y., Wu L., Huang Y., and He J. Left atrial posterior wall isolation reduces the recurrence of atrial fibrillation: a meta-analysis. *J Interv Card Electrophysiol*. 2016;46:267–74.

18. Lupercio F., Lin A.Y., Aldaas O.M., Romero J., Briceno D., Hoffmayer KS., Han F.T., Di Biase L., Feld G.K., and Hsu JC. Role of adjunctive posterior wall isolation in patients undergoing atrial fibrillation ablation: a systematic review and meta-analysis. *J Interv Card Electrophysiol*. 2019 [Epub ahead of print]
19. Salih M, Darrat Y, Ibrahim AM, Al-Akchar M, Bhattarai M, Koester C, Ayan M, Labedi M, Elayi CS. Clinical outcomes of adjunctive posterior wall isolation in persistent atrial fibrillation: A meta-analysis. *J Cardiovasc Electrophysiol*. 2020 Jun;31(6):1394-1402. doi: 10.1111/jce.14480. Epub 2020 Apr 20. PMID: 32270562.
20. Verma, A., Kilicaslan, F., Adams, J. R., Hao, S., Beheiry, S., Minor, S., . . . Natale, A. (2006). Extensive ablation during pulmonary vein antrum isolation has no adverse impact on left atrial function: an echocardiography and cine computed tomography analysis. *J Cardiovasc Electrophysiol*, 17(7), 741-746. doi:10.1111/j.1540-8167.2006.00488.x
21. Ho, S. Y., Cabrera, J. A., & Sanchez-Quintana, D. (2012). Left atrial anatomy revisited. *Circ Arrhythm Electrophysiol*, 5(1), 220-228. doi:10.1161/circep.111.962720
22. Markides, V., Schilling, R. J., Ho, S. Y., Chow, A. W., Davies, D. W., & Peters, N. S. (2003). Characterization of left atrial activation in the intact human heart. *Circulation*, 107(5), 733-739. doi:10.1161/01.cir.0000048140.31785.02
23. Suenari, K., Chen, Y. C., Kao, Y. H., Cheng, C. C., Lin, Y. K., Chen, Y. J., & Chen, S. A. (2011). Discrepant electrophysiological characteristics and calcium homeostasis of left atrial anterior and posterior myocytes. *Basic Res Cardiol*, 106(1), 65-74. doi:10.1007/s00395-010-0132-1
24. Rohr, S. (2012). Arrhythmogenic implications of fibroblast-myocyte interactions. *Circ Arrhythm Electrophysiol*, 5(2), 442-452. doi:10.1161/circep.110.957647
25. Elayi, C. S., Di Biase, L., Bai, R., Burkhardt, J. D., Mohanty, P., Santangeli, P., . . . Natale, A. (2013). Administration of isoproterenol and adenosine to guide supplemental ablation after pulmonary vein antrum isolation. *J Cardiovasc Electrophysiol*, 24(11), 1199-1206. doi:10.1111/jce.12252
26. Corradi, D., Callegari, S., Gelsomino, S., Lorusso, R., & Macchi, E. (2013). Morphology and pathophysiology of target anatomical sites for ablation procedures in patients with atrial fibrillation: part II: pulmonary veins, caval veins, ganglionated plexi, and ligament of Marshall. *Int J Cardiol*, 168(3), 1769-1778. doi:10.1016/j.ijcard.2013.06.141
27. Iwasaki, Y. K., Nishida, K., Kato, T., & Nattel, S. (2011). Atrial fibrillation pathophysiology: implications for management. *Circulation*, 124(20), 2264-2274. doi:10.1161/circulationaha.111.019893
28. Lee, A. M., Aziz, A., Didesch, J., Clark, K. L., Schuessler, R. B., & Damiano, R. J., Jr. (2013). Importance of atrial surface area and refractory period in sustaining atrial fibrillation: testing the critical mass hypothesis. *J Thorac Cardiovasc Surg*, 146(3), 593-598. doi:10.1016/j.jtcvs.2012.04.021
29. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, Kholmovski E, Burgon N, Hu N, Mont L, Deneke T, Duytschaever M, Neumann T, Mansour M, Mahnkopf C, Herweg B, Daoud E, Wissner E, Bansmann P, Brachmann J. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA*. 2014 Feb 5;311(5):498-506. doi: 10.1001/jama.2014.3. Erratum in: *JAMA*. 2014 Nov 5;312(17):1805. PMID: 24496537.
30. Marrouche NF, Wazni O, McGann C, Greene T, Dean JM, Dagher L, Kholmovski E, Mansour M, Marchlinski F, Wilber D, Hindricks G, Mahnkopf C, Wells D, Jais P, Sanders P, Brachmann J, Bax JJ, Morrison-de Boer L, Deneke T, Calkins H, Sohns C, Akoum N; DECAAF II Investigators. Effect of MRI-Guided Fibrosis Ablation vs Conventional Catheter Ablation on Atrial Arrhythmia Recurrence in Patients With Persistent Atrial Fibrillation: The DECAAF II Randomized Clinical Trial. *JAMA*. 2022 Jun 21;327(23):2296-2305. doi: 10.1001/jama.2022.8831. PMID: 35727277; PMCID: PMC9214588.



31. Thiagarajah A, Kadhim K, Lau DH, Emami M, Linz D, Khokhar K, Munawar DA, Mishima R, Malik V, O'Shea C, Mahajan R, Sanders P. Feasibility, Safety, and Efficacy of Posterior Wall Isolation During Atrial Fibrillation Ablation: A Systematic Review and Meta-Analysis. *Circ Arrhythm Electrophysiol.* 2019 Aug;12(8):e007005. doi: 10.1161/CIRCEP.118.007005. Epub 2019 Aug 12. PMID: 31401853.

32. Sommer P. Posterior Wall of the Left Atrium: Is It Arrhythmogenic Enough for Empiric Isolation? *JACC Clin Electrophysiol.* 2019 Nov;5(11):1262-1264. doi: 10.1016/j.jacep.2019.10.012. PMID: 31753430.

Figures

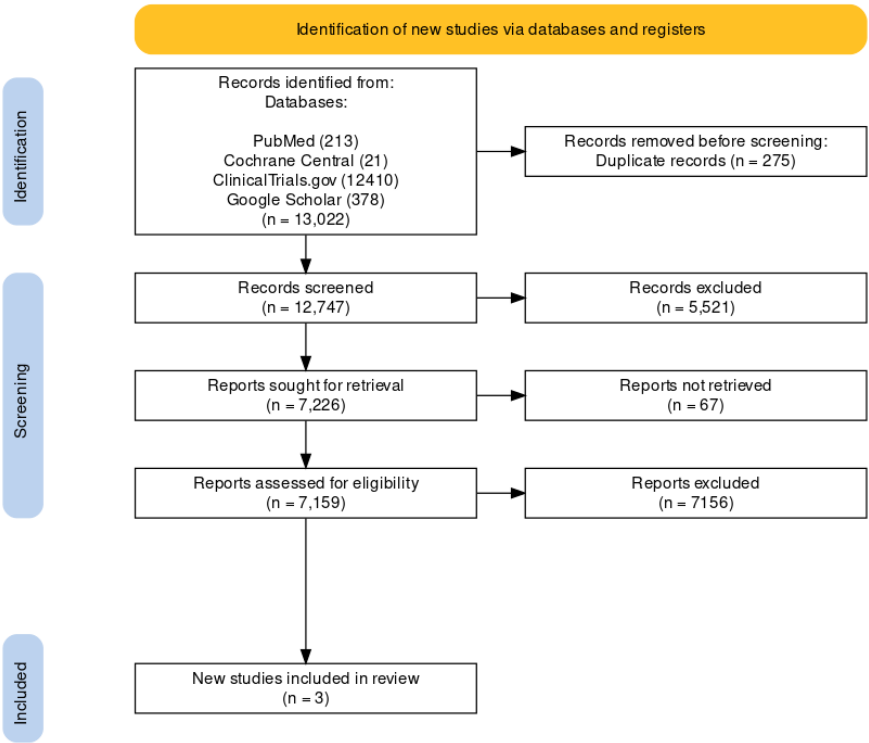


Figure 1 . PRISMA Flow diagram of study search and selection

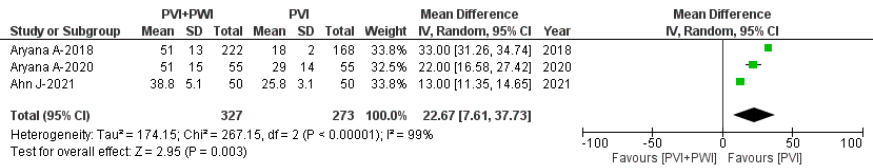
Table 1. Base line demographics, comorbidities and study characteristics

Figure 2 Forest Plots comparing patients with persistent atrial fibrillation who underwent PWI+PVI versus PVI. **A** Recurrence of all atrial arrhythmias, **B** Recurrence of atrial fibrillation, **C** Total ablation time, **D** Adverse events.

Recurrence of All Atrial Arrhythmias

Recurrence of Atrial Fibrillation

Total Ablation Time



Adverse Events

