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ORIGINAL ARTICLE

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

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Disclosures: None.

Abstract

Background: Recurrence rates of atrial fibrillation (AF) remain high even after complete wide area circumferential pulmonary vein isolation (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 rates 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 either persistent or paroxysmal AF (PAF) 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 exhibited a substantial reduction in the risk of AF recurrence (RR: 0.51; 95% CI: 0.42–0.63, $p < .00001$), as well as all atrial arrhythmias (RR: 0.58; 95% CI: 0.49–0.68, $p < .00001$). On subgroup analysis, in patients with only PAF, adjunct PWI resulted in significant reduction in recurrence risk of AF (RR: 0.56; 95% CI: 0.41–0.76, $p = .0002$) as well. There was no significant difference in adverse events between both groups (RR: 0.90; 95% CI: 0.44–1.86; $p = .78$), whereas total ablation time was significantly increased in PVI + PWI group (MD: 21.75; 95% CI: 11.13–32.37, $p < .0001$).

Conclusion: Adjunct PWI when compared to PVI alone decreases recurrence rates of atrial fibrillation after CBA of patients with persistent as well as paroxysmal atrial fibrillation.

KEYWORDS

meta-analysis, persistent atrial fibrillation, posterior wall isolation, pulmonary vein isolation

1 | INTRODUCTION

The incidence of atrial fibrillation (AF) is rising 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 are more frequent in patients with persistent AF,[7] impact quality of life, requiring repeat ablation procedures in 20%–40% of patients.[8] Adjunctive ablation strategies targeting arrhythmia substrates outside of the pulmonary veins (PV)[9] such as ablation of complex fragmented electrograms, posterior wall (PW) ablation with radiofrequency energy,[10] left atrial (LA) 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 (PWI) in reducing recurrence rates of atrial tachy-arrhythmias using cryoballoon ablation (CBA) in patients with persistent and/or PAF.

2 | METHODS

2.1 | Search strategy and selection

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[11] 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, 2023. 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.

2.2 | Inclusion criterion

We incorporated studies that compared PVI alone to a combination of PVI and PWI in a group of patients aged 18 years or older who were undergoing catheter ablation for either persistent AF (continuous AF for more than 7 days), long-standing persistent AF (continuous AF for over 12 months), or PAF.

2.3 | Exclusion criterion

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

2.4 | 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),[12,13] 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 trials.[14–16]

2.5 | Interventions

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

PWI was performed by delivery of at least two cryo-balloon freezes applied to each quadrant of the LA 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 PV supported by pushing in the Achieve catheter (Medtronic Inc.) to apply pressure to the LAPW. All the included studies employed box lesion sets for ablation of LAPW which involved creation of overlapping CBA forming a roof line connecting the superior aspect of PVs and a lower line connecting the inferior aspect of PVs. The cryo-balloon position was monitored on intracardiac ultrasound. Postablation 3-dimensional (3D) voltage maps were created after each procedure.

2.6 | 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 s 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.

2.7 | 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.[17] A p value of <.05 was considered statistically significant. The publication bias was depicted graphically using funnel plots (Figure S1).

3 | RESULTS

3.1 | Literature search

The preliminary literature search yielded 30 524 of which 30 012 were screened for title and abstract. Consequently 3389 were assessed for eligibility and full text screening, which led to the inclusion of 5 studies with a total of 1000 participants.[12–16] The PRISMA flow chart is shown in Figure 1. The search strategy and the quality assessment of included studies is summarized in the Table S1.

3.2 | Study characteristics

These trials randomly assigned 483 patients to the PVI group and 517 to the PVI + PWI group. The follow-up period ranged from 12 to 60 months. The baseline demographics, characteristics, and comorbidities are summarized in Table 1. The average age was 67 years in the PVI group, as compared to 66 years in the PVI + PWI group while 321/483 patients were male in the PVI group and 339/517 patients were male in the PVI + PWI group. Out of total study population 466 patients had persistent AF (continuous AF for >7 days), 134 patients had long-standing persistent AF (continuous AF for >12 months), and 180 patients had PAF. Out of five studies that we included in our meta-analysis, two were randomized controlled trials[12,13] while the other three studies were non-randomized trials,[14–16] CBA was performed in both the PVI and PVI + PWI groups with adjunct touch-up radiofrequency ablation (RFA) performed in three of the five studies.[13,15,16]

3.3 | Results of meta-analysis

3.3.1 | Recurrence of all atrial arrhythmias

Four out of five studies[12,13,15,16] reported recurrence of atrial arrhythmias (AF, atrial flutter, and atrial tachycardia). Recurrence occurred in 149 of 485 (31%) patients who underwent PVI + PWI and 229 of 432 patients (53%) who underwent PVI alone. Our meta-analysis revealed that the PVI + PWI group was associated with a significantly lower recurrence of atrial arrhythmias as compared to the PVI group (RR: 0.58; 95% CI: 0.49–0.68, $p < .00001$) (Figure 2). In other words, there was a 42% reduction in the recurrence risk of any type of atrial arrhythmia in the PVI + PWI group with 0% heterogeneity among studies $I^2 = 0\%$.

Subgroup analysis

On subgroup analysis, patients with persistent and/or long-standing persistent AF showed significant reduction in the recurrence of all atrial arrhythmias in PVI + PWI group as compared to PVI alone (RR: 0.57; 95% CI: 0.47–0.70, $p < .00001$) (Figure 2). Patients with PAF also showed significant reduction in recurrence of all atrial arrythmias in PVI + PWI group vs PVI alone (RR: 0.59; 95% CI: 0.45–0.77, $p < .0001$) (Figure 2).

3.3.2 | Recurrence of AF

All five studies[12–16] reported AF recurrences. Recurrence occurred in 105 of 515 patients (20%) who were undergoing PVI + PWI while 190 of 482 patients (39%) undergoing PVI alone. Our meta-analysis revealed a significant reduction in AF recurrences in PVI + PWI arm when compared to the PVI arm (RR: 0.51; 95% CI: 0.42–0.63, $p < .00001$) (Figure 2), or a 49% reduction in the risk of AF recurrence with 0% heterogeneity among studies, $I^2 = 0\%$.

Subgroup analysis

On subgroup analysis, patients with persistent and/or long-standing persistent AF had significant reduction in recurrence of AF in the PVI + PWI group as compared to PVI alone (RR: 0.48; 95% CI: 0.36–0.64, $p < .00001$) (Figure 2). Similarly, patients with PAF showed significant reduction in recurrence of AF in the PVI + PWI group vs PVI alone (RR: 0.56; 95% CI: 0.41–0.76, $p = .0002$) (Figure 2).

3.3.3 | Adverse events

Four out of five studies[12,13,15,16] reported adverse events. Our meta-analyses did not find any significant difference in adverse events between both groups (RR: 0.90; 95% CI: 0.44–1.86; $p = .78$) (Figure 2) with no heterogeneity among studies, $I^2 = 0$.

Subgroup analysis

Patients with persistent and/or long-standing persistent AF did not show any difference in adverse events between both groups (RR: 1.05; 95% CI: 0.43–2.56, $p = .91$), however, patients with PAF showed a non-significant reduction of adverse events in PVI + PWI group as compared to PVI alone (RR: 0.67; 95% CI: 0.19–2.32, $p = .52$) (Figure 2).

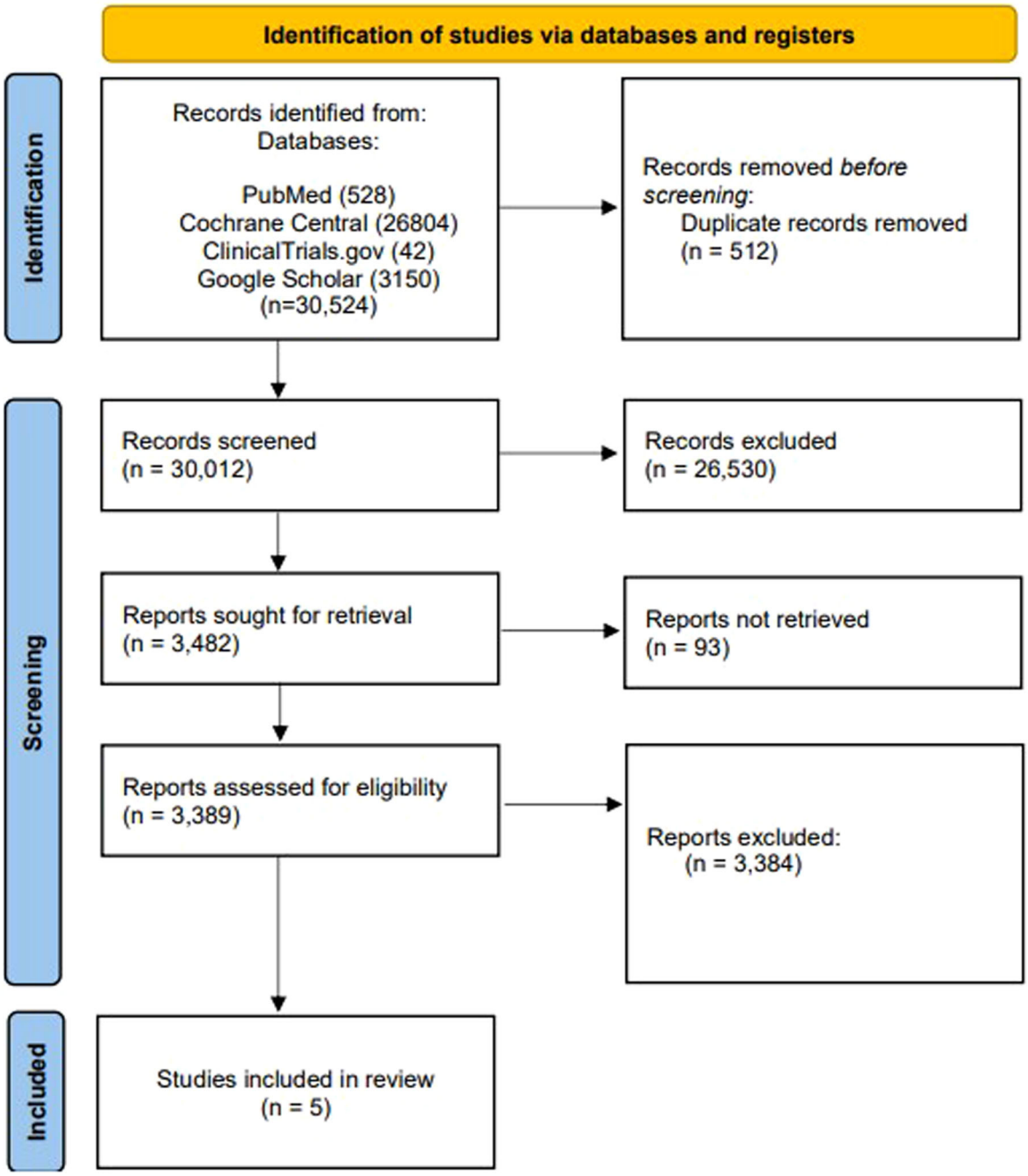


FIGURE 1 PRISMA flow diagram of study search and selection. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

3.3.4 | Total ablation time

Four out of five studies[12,13,15,16] reported total ablation time. Our meta-analysis showed significantly decreased ablation time required to achieve PVI alone as compared to PVI + PWI (MD: 21.75; 95% CI: 11.13–32.37, $p < .0001$) with high heterogeneity among studies, $I^2 = 99\%$ (Figure 2).

Subgroup analysis

In patients with persistent and/or long-standing persistent AF, subgroup analysis showed a significant reduction in ablation time in PVI group as compared to the PVI + PWI group (MD: 22.67; 95% CI: 7.61–37.73, $p < .003$). In patients with PAF results were similar (MD: 19.00; 95% CI: 16.70–21.30, $p < .00001$) (Figure 2).

4 | DISCUSSION

The addition of PWI to PVI resulted in a considerably higher chance of freedom from AF and all atrial arrhythmias over a follow-up ranging from 12 to 60 months compared to PVI alone in patients with symptomatic persistent/paroxysmal AF who were referred for CBA.

TABLE 1 Base line demographics, comorbidities, and study characteristics.

Studies Variable	Aryana (2018)	Aryana (2020)	Aryana (2023)	Bisignani (2020)	Ahn (2021)
Sample (*n*)	168/222	55/55	160/160	50/30	50/50
PVI/PVI + PWI					
Age	67 ± 11/67 ± 9	70 ± 9/67 ± 8	63 ± 11/63 ± 10	67.4 ± 8.5/68.4 ± 9.16	65.9 ± 8.8/65.1 ± 8.6
Male (*n*)	108/146	33/35	106/99	29/20	45/39
CAD risk factors					
Hypertension	123/173	37/35	113/107	35/17	45/38
Diabetes Mellitus	37/46	15/14	30/26	7.0/7.0.	20/23
Left atrial size mean (*SD*) (mm)	44 ± 7/44 ± 9	44 ± 5/44 ± 4	44 ± 7/44 ± 5	43.9 ± 9.5/44.8 ± 4.7	48.5 ± 8.1/48.1 ± 7.4
LV ejection fraction mean (*SD*), %	55 ± 13/54 ± 12	61 ± 8/60 ± 7	58 ± 10/57 ± 11	50.8 ± 12/49.8 ± 13.7	58.5 ± 8.4/57.6 ± 9.4
CHA2DS2-VASc score	2.5 ± 1.4/2.7 ± 1.5	2.8 ± 1.6/2.4 ± 1.5	2.2 ± 1.6/2.1 ± 1.5	2.5 ± 1.6/2.3 ± 1.3	3.0 ± 1.4/3.0 ± 1.6
Type of AF	Persistent AF	Persistent AF	Paroxysmal AF	Paroxysmal AF	Persistent AF
Type of CA	Cryoballoon	Cryoballoon	Cryoballoon	Cryoballoon	Cryoballoon
Monitoring	12 Lead ecg and mobile cardiac telemetry	12 Lead ecg and mobile cardiac telemetry	12 Lead ecg and mobile cardiac telemetry	12 Lead ecg and Holter monitoring	12 lead ecg and 24 h holter monitoring
Oral anticoagulation	142/194	51/52	119/125		NA
Study design					
Study	Non-randomized (prospective)	Randomized prospective	Non-randomized (Retrospective)	Non-randomized cohort study	Randomized prospective
Year	2018	2020	2023	2020	2022
Centre	Multicentre	Multicentre	Multicentre	Single centre	NA
Study period	2014–2017	2017–2019	2014–2018	2018–19	2019–2020
Sample size	390	110	320	80	100
Follow-up duration	18 Months	12 Months	60 Months	12 Months	12 Months

(Continues)

TABLE 1 (Continued)

Studies Variable	Aryana (2018)	Aryana (2020)	Aryana (2023)	Bisignani (2020)	Ahn (2021)
Main outcome	Freedom from atrial fibrillation, freedom from atrial flutter, freedom from all atrial arrhythmias	Atrial fibrillation recurrence, atrial flutters/tachycardias recurrence, all atrial arrhythmias recurrence	Freedom from atrial fibrillation, freedom from atrial flutter, freedom from all atrial arrythmias	Recurrence of Atrial fibrillation	Recurrence of atrial fibrillation, recurrence of all tachyarrthmias
Results	PVI + PWI was superior to PVI only.	PVI + PWI was superior to PVI only.	long-term follow-up 3 years or more shows PVI + PWI with improved outcomes	PVI + PWI does not seem to improve an outcome compared with PVI-only strategy	PVI + PWI was superior to PVI only.

Abbreviations: AF, atrial fibrillation; PVI, pulmonary vein isolation; PWI, posterior wall isolation.

Furthermore, PWI was not associated with increased adverse events when compared to PVI alone, while total ablation time was significantly longer in the PWI + PVI group as compared to PVI group with a mean of 45.7 ± 11 min and 23.9 ± 7 min, respectively. These results are 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] This can be explained by the fact that LAPW isolation achieved by RF and by cryoballoon may not share the same pathological or pathophysiological consequence as the created lesion sets are different.

To our knowledge, this is the first meta-analysis that has compared patients with AF undergoing PVI to PVI + PWI using CBA exclusively. Previous meta-analyses[18–20] 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 and/or paroxysmal AF.

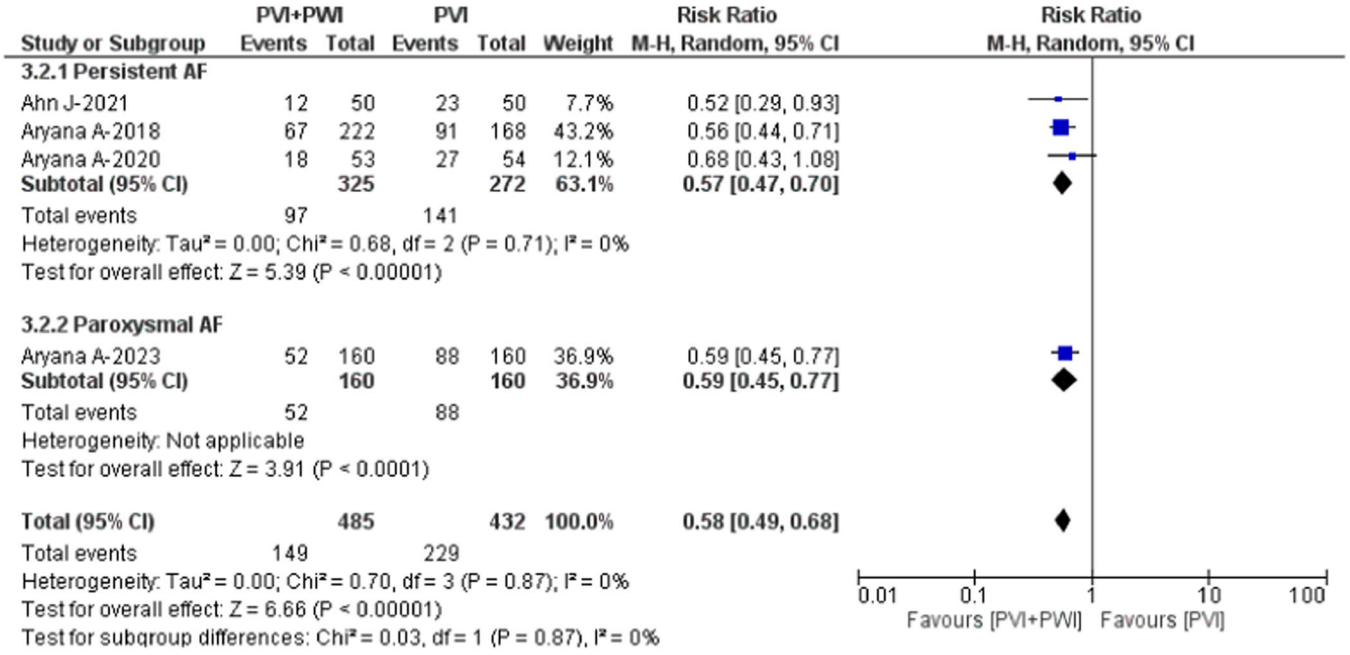
The front section of the LA wall yields the majority of LA contractility, while the PW appears to play a rather minor role. Hence, LA PWI does not result in a substantial loss in atrial mechanical function.[21]

The LAPW and the PV share the same embryological origin in which the primitive mesodermal PV develops four different branches, and thus, the LAPW and PV exhibit similar histology.[22] The LAPW is a complicated structure made up of many layers of muscle bundles with varying wall thicknesses.[22,23] In comparison to other sections of the LA, the LAPW frequently gives rise to rotors and spontaneous triggers.[24,25] The LAPW and septum are the most common locations of structural atrial remodeling seen in AF.[26] Consequently, the LAPW similar to the PVs may be a relevant contributor to arrhythmogenesis. When compared to other LA sites, the LAPW has more frequent delayed afterdepolarizations, greater 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.[24]

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.[27] Furthermore, wide area circumferential PV isolation often leaves a narrow PW channel that may be a viable reentry substrate. Fibrosis of the PW, may account for slow conduction and functional reentry.[28] “Debulking” the left atrium by PWI may diminish critical mass required to sustain AF,[29] and the PW's epicardial fat pads containing ganglionic plex can be modified by ablation.[30] The DECAAF multicenter prospective study demonstrated that among patients with AF undergoing catheter ablation, atrial fibrosis estimated by delayed enhancement MRI was independently associated with the likelihood of recurrent arrhythmia.[31] However the DECAAF II trial did not demonstrate any incremental benefit of additional MRI-guided scar ablation when compared to conventional ablation in patients undergoing PVI.[32]

A meta-analysis from 2022 found no difference in outcomes between PVI + PWI and PVI alone in patients with PAF.[33] The discrepancy of this observation can be attributed to the small sample size and the inclusion of different ablation techniques in the analyzed

(A) **Recurrence of all atrial arrhythmias**



(B) **Recurrence of Atrial Fibrillation**

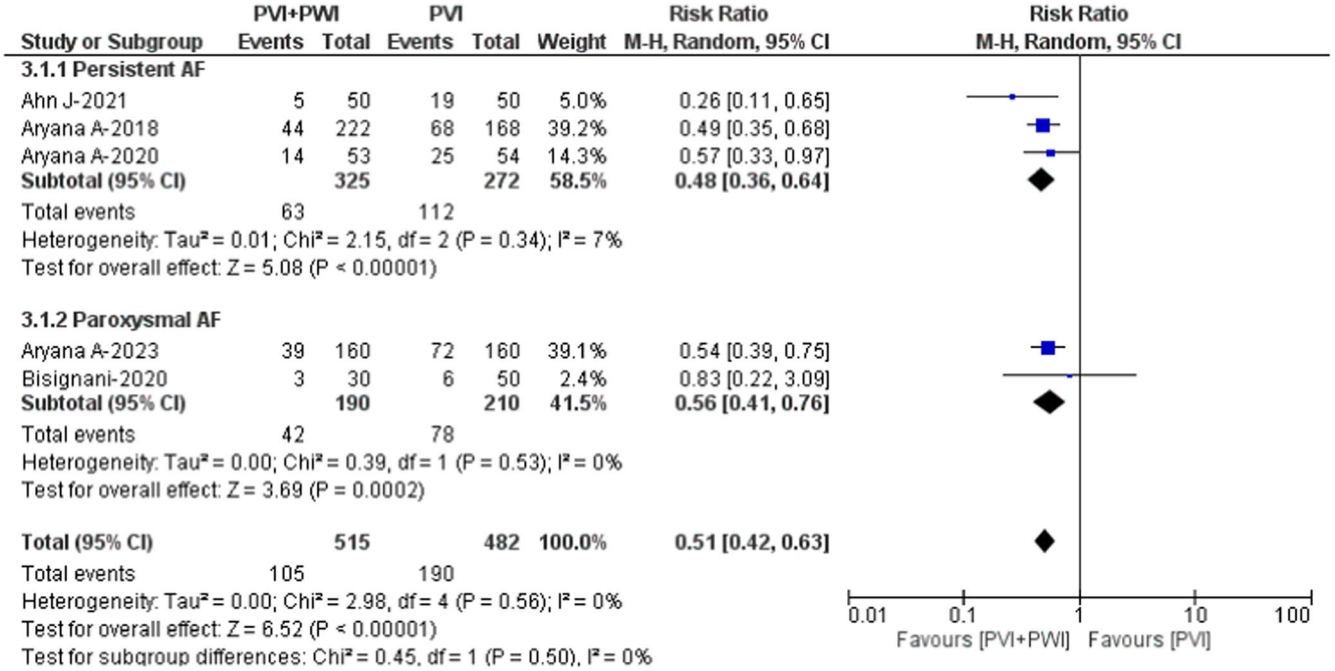
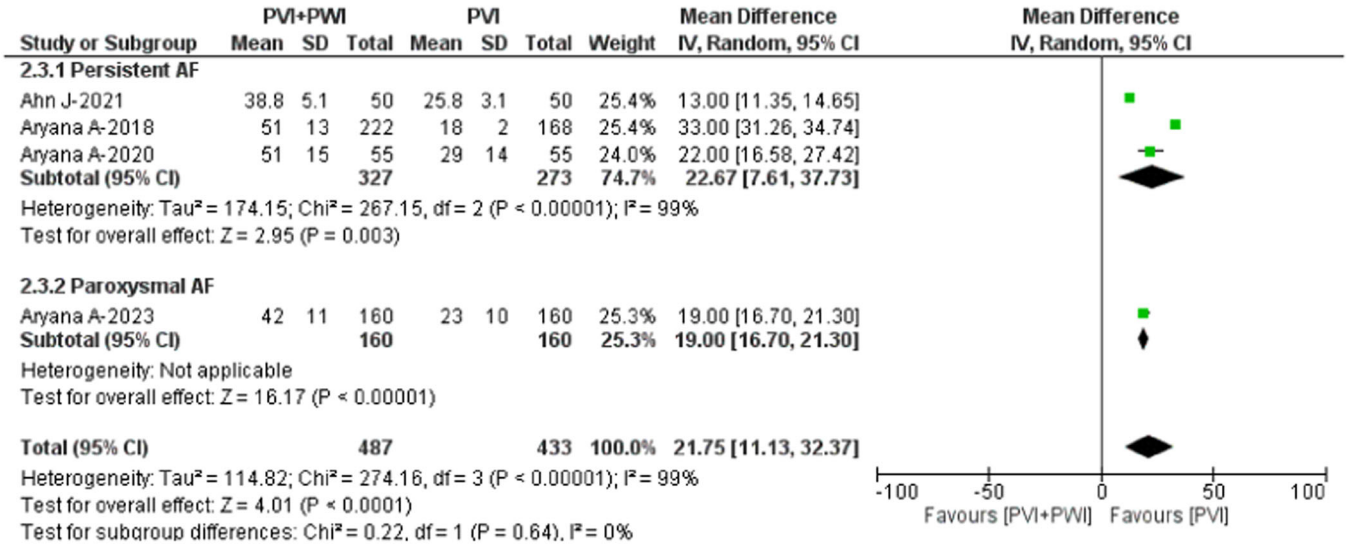


FIGURE 2 Forest plots comparing patients with persistent/paroxysmal atrial fibrillation who underwent PWI + PVI versus PVI. (A) Recurrence of all atrial arrhythmias. (B) Recurrence of atrial fibrillation. (C) Total ablation time. (D) Adverse events. AF, atrial fibrillation; CI, confidence interval; PVI, pulmonary vein isolation; PWI, posterior wall isolation.

(C) **Total Ablation Time**



(D) **Adverse Events**

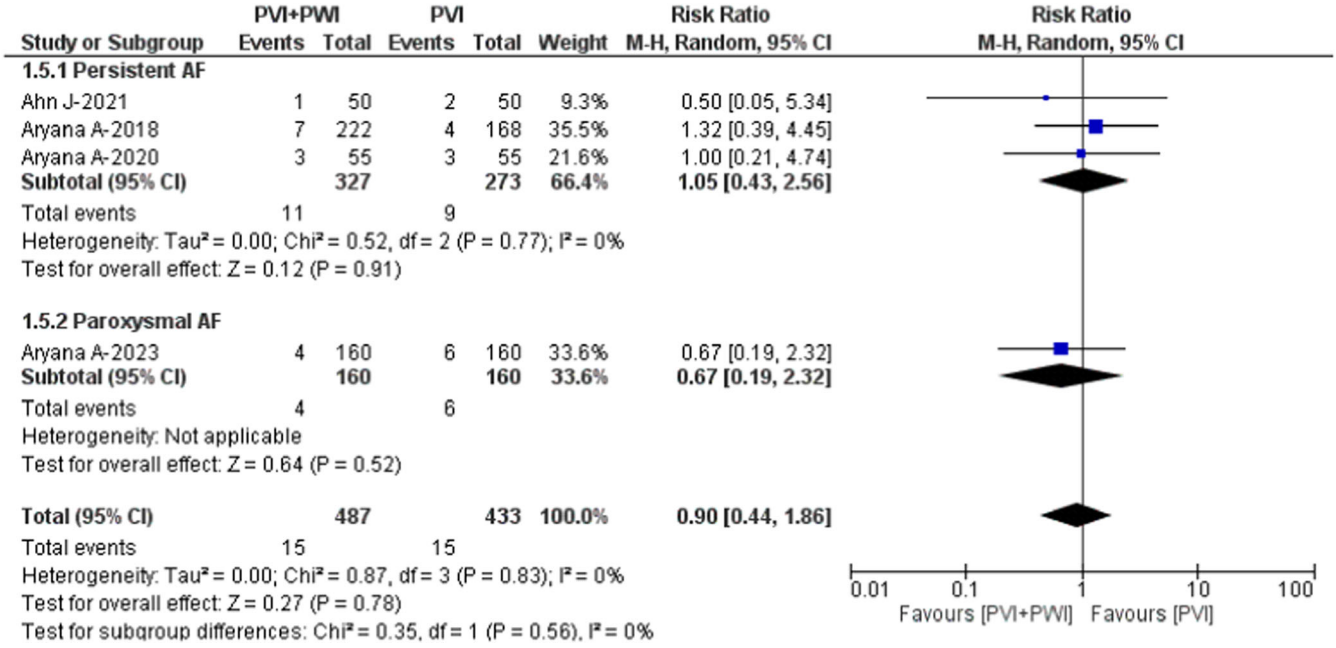


FIGURE 2 (Continued)

studies. Only one study employed CBA for PW ablation, while the remaining two studies utilized RFA. A subgroup analysis focusing solely on the studies employing CBA for PW ablation demonstrated a significant reduction in the recurrence of AF. Hence, the authors propose that the addition of PWI to PVI can confer benefits not only to patients with persistent AF but also to those with PAF. We need randomized controlled clinical trials focusing especially on patients with PAF. It is important to highlight that the frequency of arrhythmia recurrences in patients with PAF is generally lower compared to those with persistent AF. Further, recurrences following catheter ablation are more likely to be asymptomatic. Hence, in the absence of larger sample sizes, longer follow-up durations, and more sensitive surveillance methods, a significant difference between these two ablation strategies in this patient population could potentially go unnoticed.[15,34] This could explain the findings reported by Bisignani et al.,[14] as their study had a relatively short follow-up period of only 12 months, which might account for the lack of observed difference between PVI + PWI and PVI alone. The fact that PV and PW share similar embryologic origin and complex anatomy may support an ablation approach targeting both, PW and the PV segments.[35]

Depending on the operator's choice and expertise, different techniques of PWI 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 PW 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 resulting in recovery of conduction in deeper epicardial layers of the PW and LA roof.

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

Advantages of CBA of the PW 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.[13,16] A trade of is the higher risk of phrenic nerve palsy. High output right atrial phrenic nerve stimulation (>10 mA) from the superior vena cava was performed in all three studies to avoid phrenic nerve injury.[12,13,16] Our meta-analysis found no evidence of a greater risk of complications with adjunctive PWI compared to PVI alone, including AE fistula.

5 | LIMITATIONS

First, the included studies had different study protocols, including both randomized and non-randomized trials. Second, the precise techniques of CBA for PVI and PWI might differ between different operators, while three of our studies used adjunct RFA, which might explain the high heterogeneity found in total ablation time. Third, our sample size is too small to compare rare events such as AE fistula. Fourth, there were only two studies that met the inclusion criterion which solely focused on patients with paroxysmal AF, leading to a limited sample size for this particular group. Therefore, randomized controlled trials with larger patient populations are needed.

6 | CONCLUSION

Adjunctive PWI using CBA significantly reduces the recurrence rates of atrial tachy-arrhythmias, including AF, in patients with persistent and paroxysmal 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.

AUTHOR CONTRIBUTIONS

Mishal Mumtaz, Ahmad Danial, Sidra Jabeen, Muhammad Tayyab Muzaffar Chaychi, and Muhammad Kashan Zaheer: contributed to the conception or design of the manuscript. **Muhammad Tayyab Muzaffar Chaychi, Sidra Jabeen, Mishal Mumtaz, and Ahmad Danial**: contributed to the acquisition of the data. **Sidra Jabeen, Aymen Mumtaz, and Mishal Mumtaz**: contributed to the analysis of data. **Mishal Mumtaz and Ahmad Danial**: contributed to the interpretation of the analysis. **Mishal Mumtaz, Muhammad Tayyab Muzaffar Chaychi, Ahmad Danial, and Sidra Jabeen**: drafted the manuscript. **Tayebah Mumtaz and Bengt Herweg**: 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.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Pubmed at https://pubmed.ncbi.nlm.nih.gov/.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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