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Pulmonary vein isolation plus adjunctive therapy for the treatment of atrial fibrillation: a systematic review and meta-analysis

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Abstract

Background Pulmonary vein isolation (PVI) is the primary technique for ablation of atrial fibrillation (AF). It is unclear whether adjunctive therapies in addition to PVI can reduce atrial arrhythmia recurrence (AAR) compared to PVI alone in patients with AF.

Methods A meta-analysis of randomized controlled trials comparing PVI plus an adjunctive therapy (autonomic modulation, linear ablation, non-pulmonary vein trigger ablation, epicardial PVI [hybrid ablation], or left atrial substrate modification) to PVI alone was conducted. The primary outcome was AAR. Cumulative odd's ratios (OR) and 95% confidence intervals (CI) were calculated for each treatment type.

Results Forty-six trials were identified that included 8,500 participants. The mean age (± standard deviation) was 60.2 (±4.1) years, and 27.2% of all patients were female. The mean follow-up time was 14.6 months. PVI plus autonomic modulation and PVI plus hybrid ablation were associated with a relative 53.1% (OR 0.47; 95% CI 0.32 to 0.69; $p < 0.001$) and 59.1% (OR 0.41; 95% CI 0.23 to 0.75; $p = 0.003$) reduction in AAR, respectively, compared to PVI alone. All categories had at least moderate interstudy heterogeneity except for hybrid ablation.

Conclusion Adjunctive autonomic modulation and epicardial PVI may improve the effectiveness of PVI. Larger, multi-center randomized controlled trials are needed to evaluate the efficacy of these therapies.

Keywords Atrial fibrillation · Adjunctive therapy · Ablation · Pulmonary vein isolation · Autonomic modulation · Hybrid ablation

1 Introduction

Pulmonary vein isolation (PVI) is the primary technique for catheter ablation of atrial fibrillation (AF) [1, 2]. Adjunctive non-pharmacological therapies including autonomic modulation [3–10], linear ablation [11–22], non-pulmonary vein trigger isolation [21, 23–36], epicardial PVI (convergent hybrid ablation) [37, 38], and atrial substrate modification [11, 33, 39–48] have been studied for the purpose of reducing atrial arrhythmia recurrence (AAR) after PVI. The objective of the present meta-analysis was to evaluate randomized controlled trials (RCTs) comparing PVI alone to PVI plus adjunctive therapy in order to determine which adjunctive therapies are the most effective for reducing AAR.

2 Materials and methods

2.1 Literature search

Electronic databases, PubMed and Cochrane Central Register of Clinical Trials, were searched for RCTs evaluating PVI plus an adjunctive therapy compared to PVI alone regarding their effectiveness in reducing AAR by three independent

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investigators (R.B., M.A., and J.B.). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were used to conduct the literature search and report this systematic review and meta-analysis (Fig. 1). Search terms are listed in Table S1. Searched adjunctive therapies to PVI were ablation of complex fractionated atrial electrograms (CFAE), empiric non-pulmonary vein trigger (mitral annulus, fossa ovalis, eustachian ridge, crista terminalis, and superior vena cava) ablation (enPV), left atrial ganglionic plexus (GP) ablation, hybrid (convergent epicardial and endocardial) ablation, linear ablation of the left atrium, ablation of left atrial low voltage areas (LVA), magnetic resonance imaging-guided left atrial fibrosis ablation (MRI-f), posterior wall isolation (PWI), renal denervation (RD), Vein of Marshall ethanol infusion (VMEI), superior vena cava isolation (SVCI), stellate ganglion ablation, spinal cord stimulation, vagal nerve stimulation, botulinum toxin injections, and left atrial appendage closure/excision. We stratified these adjunctive therapies into the following 5 strategies: autonomic modulation, linear ablation,

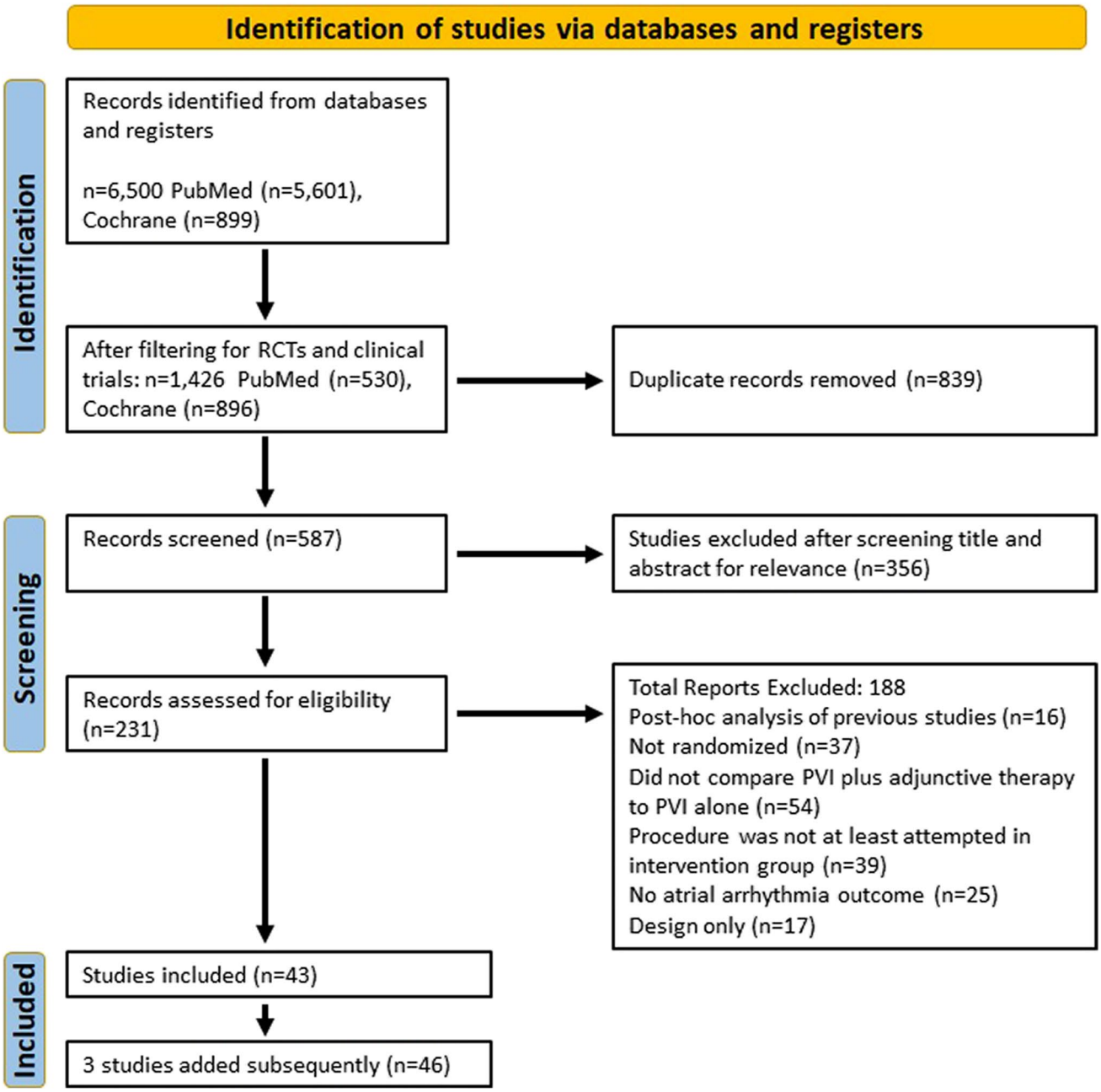

Fig. 1 Identification of Studies via Databases and Registers. PRISMA flow diagram that represents the studies identified, screened, and assessed for eligibility. Reasons for exclusions are listed

non-pulmonary vein (PV) trigger ablation, hybrid ablation, and substrate modification. Only strategies with at least 2 RCTs were included in the analysis.

All RCTs published in any language from the creation date of the databases through July 31st, 2022 were included. Studies were only included if the intervention(s) patients were randomized to was/were attempted in all patients. If a trial published another set of results after extended follow-up, the most recent published study was included. We allowed for trials to utilize operator flexibility in performing additional lesions at their discretion. Studies were excluded if they were not RCTs, if they did not directly compare PVI alone to PVI plus an adjunctive therapy, and if they did not report either AAR or atrial arrhythmia freedom. Trials that uniformly studied multiple adjunctive therapies to PVI within a single arm or that did not utilize the same PVI approach between control and intervention arms were also excluded. All included studies were independently assessed for internal validity and bias using the Cochrane Handbook for Systematic Review of Interventions by three investigators (R.B., M.A., and J.B.). Any differences were resolved by discussion until consensus was reached.

2.2 Statistical analysis

Three investigators (R.B., M.A., and J.B.) independently reviewed all studies meeting the inclusion and exclusion criteria and performed standardized data extraction. The prespecified primary outcome was AAR of each adjunctive therapy. A subgroup analysis was done for overall strategy, by whether the trial was single-center or multi-center, and by classification of AF (paroxysmal vs persistent). For the subgroup analysis comparing classification of AF, only trials that enrolled either all patients with paroxysmal AF or all patients with persistent AF were included. Analysis was performed using Comprehensive Meta-Analysis Version 3, Biostat, Englewood, NJ, 2013. Cumulative odd's ratios (OR) and 95% confidence intervals (CI) were calculated for AAR. An I^2 value of > 0% and < 30% was deemed to represent mild heterogeneity, ≥ 30% and < 60% was deemed to represent moderate heterogeneity, and ≥ 60% was deemed to represent severe heterogeneity. For endpoints with at least moderate heterogeneity, a random effects model was used, otherwise a fixed effects model was used. A sensitivity analysis for the primary outcome was performed by excluding one study at a time within each adjunctive therapy group to assess whether treatment effect or heterogeneity were sensitive to the exclusion of any one study. Lastly, a meta-regression of the primary outcome using the moderator variables left atrial diameter and year of publication was performed for adjunctive therapies with at least 4 trials and at least moderate heterogeneity. The regression coefficient, 95% CI, R^2 value, and the p-value were calculated for each regression.

3 Results

Forty-six studies [3–48] were identified that included 8,500 participants (Fig. 1). Some clinical trials had multiple intervention arms, each implementing a different adjunctive therapy. We identified 12 linear ablation trials, 11 PWI trials, 8 CFAE trials, 4 RD trials, 3 GP trials, 3 LVA trials, 3 SVCI trials, 2 epicardial PVI (hybrid ablation) trials, 1 enPV trial, 1 MRI-f trial, and 1 VMEI trial. GP, RD, and VMEI were grouped into the autonomic modulation strategy, PWI, enPV, and SVCI into the non-PV trigger elimination strategy, and CFAE, LVA, and MRI-f into the substrate modification strategy. The mean age (±SD) was 60.2 (±4.1) years, and 27.2% of all patients were female. The mean follow-up time was 14.6 months. Baseline characteristics of patients in each of the trials are listed in Table 1. The most common definition of AAR was >30s of AF or other atrial tachyarrhythmias including atrial flutter. The majority of trials utilized ECGs and continuous rhythm monitoring with Holter monitors or event monitors (Table 1). The Cochrane risk for bias assessment showed that the domain most likely to be judged an unclear or high risk of bias was blinding of outcome assessment (Table 2).

3.1 Autonomic modulation

Eight studies (3 GP, 4 RD, and 1 VMEI) were identified that included 1,253 participants. Adjunctive autonomic modulation was associated with a statistically significant 53.1% relative reduction in AAR compared to PVI alone (OR 0.47; 95% CI 0.32 to 0.69; $p < 0.001$; Fig. 2), and there was severe interstudy heterogeneity ($I^2 = 56.46$).

3.1.1 Ganglion plexus ablation

Three GP studies were identified that included 467 participants. Adjunctive GP ablation did not show a statistically significant difference in AAR compared to PVI alone (OR 0.56; 95% CI 0.27 to 1.17; $p = 0.12$; Fig. 2), and there was severe interstudy heterogeneity ($I^2 = 68.91$). Both the overall effect estimate and interstudy heterogeneity were sensitive to the exclusion of Berger et al. [3] (OR 0.40; $p = 0.001$; $I^2 = 0.00$).

3.1.2 Renal denervation

Four RD studies were identified that included 443 participants. Adjunctive RD was associated with a statistically significant 69.1% relative reduction in AAR compared to PVI alone (OR 0.31; 95% CI 0.16 to 0.62; $p = 0.001$;

Table 1 Baseline Characteristics of Randomized Controlled Trials

Study	Class of AF	Trial Arm	*n*	Duration of Follow Up (months)	Definition of AAR	Rhythm Monitoring	Blanking Period	Age	*n* Female (%)	BMI (kg/m^2)	AF Duration (months)	LA diameter (mm)	LVEF (%)
Katritsis 2011	Paroxysmal	PVI + GP	34	12	AF/AT/AFL > 30 s	ECG and Holter monitor	3 months	55.2±11.6	9 (26.5)	NR	NR	41.5±5.4	56.2±7.7
		PVI	33					53.2±11.3	7 (21.2)	NR	NR	41.1±3.3	56.1±5.3
Katritsis 2013	Paroxysmal	PVI + GP	82	24	AF/AT > 30 s	ECG and/or ILR	3 months	56±8.5	25 (30.5)	NR	NR	48±6.0	62±8.1
		PVI	78					56±7.6	25 (32.1)	NR	NR	48±7.0	63±6.8
Berger 2019	Both	PVI + GP	117	12	AF/AT/AFL > 30 s	ECG	3 months	59.5±8.2	33 (28.2)	27.6±4.3	48 (24 – 72)	42.1±5.6	47.9±18
		PVI	123					60.2±8.2	32 (26)	27.1±3.5	5 (2 – 10)	42.3±5.5	51.2±9.1
Kiuchi 2016	Both	PVI + RD	21	12	AF > 30 s	Pacemaker recordings	3 months	68±9	8 (38)	27±3	NR	45.1±3.2	62.7±6.6
		PVI	24					66±9	8 (33)	25±3	NR	44.9±3.9	63.5±6.8
Kiuchi 2018	Paroxysmal	PVI + RD	33	12	AF > 30 s	Pacemaker recordings	3 months	56.8±6.5	8 (24)	27.1±1.9	NR	NR	62.2±7.2
		PVI	36					58.4±5.1	6 (17)	26.4±1.8	NR	NR	61.2±5.7
Pokushalov 2012	Both	PVI + RD	13	12	AT > 30 s	ECG and Holter monitor	3 months	57±8	2 (15.4)	28±6	NR	49±7	65±5
		PVI	14					56±9	4 (28.6)	28±5	NR	50±6	66±4
Steinberg 2020	Paroxysmal	PVI + RD	154	12	AF/AT/AFL > 30 s	ECG	3 months	59 (54 – 65)	63 (40.9)	NR	43.2 (35 – 49)	48±3	62±5
		PVI	148					60 (58 – 65)	57 (38.5)	NR	43.2 (37 – 50)	47±3	62±5
Valderrabano 2020	Persistent	PVI + VMEI	185	12	AF/AT > 30 s	ECG and continuous monitoring	3 months	66.6±9.6	48 (26)	31.2±6.6	NR	44.8±7.9	52.1±10.1
		PVI	158					66.4±9.9	34 (22)	31.9±6.5	NR	47.0±7.5	53.4±9.4
Pappone 2004	Both	PVI + PWI	280	12	Recurrent AF	ECG and Holter monitor	6 weeks	56.6±8.0	127 (45.4)	NR	86.4±25.2	39.5±3.7	NR
		PVI	280					56.4±6.5	142 (50.7)	NR	86.4±21.6	39.5±3.8	NR
Mun 2012	Paroxysmal	PVI + PWI	52	12	AF/AT > 30 s	ECG and Holter monitor	3 months	54.3±10.6	11 (21.2)	NR	NR	40.7±5.4	63.7±6.6
		PVI	52					54.9±12.7	15 (28.8)	NR	NR	39.3±5.2	64.7±7.6
Kim 2015[24]	Paroxysmal	PVI + PWI	50	12	AF/AT > 30 s	ECG and Holter monitor	3 months	57.7±10.2	15 (30.0)	NR	NR	41.0±6.8	64.9±6.8
		PVI	50					55.3±12.4		NR	NR	40.1±6.4	64.4±7.3
Kim 2015[28]	Persistent	PVI + PWI	60	16.3	Documented AF/AFL	ECG and Holter monitor	Unspecified	56.2±11.9	14 (23.3)	24.4±2.8	NR	42.3±6.4	64.5±8.5
		PVI	60					58.3±9.6	19 (31.7)	24.4±4.1	NR	42.1±5.1	62.9±8.1
Yu 2017	Persistent	PVI + PWI	54	12	AF/AT > 30 s	ECG and Holter monitor	3 months	59.3±8.9	13 (24.1)	251±3.2	41.7±36.7	42.7±5.7	62.9±7.7
		PVI	59					61.4±11.1	15 (25.4)	24.9±3.1	43.7±50.8	42.6±5.3	61.2±10.5
Lee 2019	Persistent	PVI + PWI	102	16	AF/AT > 30 s	ECG and Holter monitor	3 months	58.9±10.5	14 (13.7)	NR	44.0±44.6	45.0±5.3	59.2±9.0
		PVI	105					58.6±11.0	19 (20.0)	NR	33.1±31.4	44.5±6.7	58.8±9.5
Pak 2020	Persistent	PVI + PWI	57	23.8	AF/AT > 30 s	ECG and Holter monitor	3 months	58.6±11.4	15 (26.3)	NR	24 (12 – 60)	41.4±6.1	59.1±11.5
		PVI	57					61.6±7.8	17 (29.8)	NR	21 (9 – 71)	42.7±6.1	61.9±8.1
Aryana 2021	Persistent	PVI + PWI	55	12	AF/AT/AFL > 30 s	ECG and mobile telemetry	3 months	67.0±8.0	20 (36.4)	30.0±8.0	NR	44.0±4.0	60.0±7.0
		PVI	55					70.0±9.0	22 (40.0)	29.0±6.0	NR	44.0±5.0	61.0±8.0

Table 1 (continued)

Study	Class of AF	Trial Arm	*n*	Duration of Follow Up (months)	Definition of AAR	Rhythm Monitoring	Blanking Period	Age	*n* Female (%)	BMI (kg/m^2)	AF Duration (months)	LA diameter (mm)	LVEF (%)
Kim 2022	Both	PVI + PWI	75	17	AF/AT > 30 s	ECG and Holter monitor	3 months	60.0±9.9	22 (29.3)	24.2 (22.3 – 26.3)	48 (30 – 84)	41.7±7.1	64 (61 – 67)
		PVI	75					59.1±9.9	13 (17.3)	25.0 (23.5 – 27.0)	72 (29 – 120)	41.0±5.8	63 (60 – 67)
Ahn 2022	Persistent	PVI + PWI	50	12	AF/AT/AFL > 30 s	ECG and Holter monitor	3 months	65.1±8.6	11 (22.0)	26.4±3.7	58.0±43.5	48.1±7.4	57.6±9.4
		PVI	50					65.9±8.8	5 (10.0)	25.8±2.7	54.3±43.1	48.5±8.1	58.5±8.4
Kistler 2022	Persistent	PVI + PWI	170	12	AF/AT/AFL > 30 s	ECG, Holter monitor, and/or implantable devices	3 months	66 (59 – 71)	39 (22.9)	29.1 (26.3 – 32.8)	5 (2 – 8)	46±6	56 (45 – 60)
		PVI	168					66 (58 – 72)	40 (23.8)	28.6 (26.0 – 33.1)	5 (2 – 8)	44±7	55 (45 – 60)
Dixit 2012	Persistent	PVI + enPV	50	12	AF/AT > 30 s	ECG	6 weeks	57.0±10.0	8 (16.0)	NR	44.0±44.0	47.0±6.0	57.0±10.0
		PVI	55					59.0±8.0	7 (12.7)	NR	56.0±65.0	48.0±7.0	56.0±9.0
Wang 2008	Paroxysmal	PVI + SVCI	52	4	AT > 30 s	ECG and Holter monitor	1 month	65.4±8.9	22 (42.3)	NR	44.4±24.3	36.5±2.7	62.4±4.6
		PVI	54					66.6±8.8	26 (48.1)	NR	42.9±24.2	36.9±2.5	62.1±4.0
Corrado 2010	Both	PVI + SVCI	134	12	AF > 30 s	ECG and Holter monitor	8 weeks	55±10	35 (26.1)	NR	78±60	45±8	54±6
		PVI	160					57±9	42 (26.3)	NR	85.2±48	46±6	53±7
Da Costa 2015	Paroxysmal	PVI + SVCI	51	15	Documented AF/AT/AFL	ECG and Holter monitor	2 months	55±10	11 (21.6)	NR	NR	42±7	63±7
		PVI	49					58±9	10 (20.4)	NR	NR	39±6	64±7
Arbelo 2014	Paroxysmal	PVI + Linear	59	12	AF/AT/AFL > 30 s	Holter monitor	3 months	55±11	17 (28.8)	NR	59±59	41±6	62±7
		PVI	61					55±12	19 (31.1)	NR	60±56	41±6	62±5
Fassini 2005	Both	PVI + Linear	95	12	Documented AF	ECG and Holter monitor	Unspecified	54±10	22 (23.2)	NR	NR	43.7	55.3
		PVI	92					57±8	15 (16.3)	NR	NR	41.5	56.8
Gaita 2008	Both	PVI + Linear	137	36	AF/AFL > 30 s	ECG and Holter monitor	2 months	56.0±9.9	30 (22)	NR	58.8±45.6	47±6	NR
		PVI	67					53.3±9.0	12 (18)	NR	68.4±54	45±7	NR
Gavin 2012	Paroxysmal	PVI + Linear	20	18	Documented AF	ECG and Holter monitor	3 months	67 (47 – 73)	5 (25)	NR	NR	41.1 (31 – 55)	64.8 (53-79)
		PVI	22					68 (44 – 73)	7 (31.8)	NR	NR	40.6 (28 – 55)	63.5 (51-85)
Hocini 2005	Paroxysmal	PVI + Linear	45	12	Documented atrial arrhythmia	Cardiac monitor	Unspecified	54±10	8 (18)	NR	70±61	41±6	67±8
		PVI	45					55±8	11 (24)	NR	56±44	41±6	67±11
Kang 2014	Paroxysmal	PVI + Linear	100	12	AF/AT > 30 s	ECG and Holter monitor	3 months	57.9±11.5	25 (25)	NR	NR	40.1±5.7	64.6±9.4
		PVI	100					55.7±11.9	26 (26)	NR	NR	39.5±6.2	63.4±9.9
Mun 2012	Paroxysmal	PVI + Linear	52	12	AF/AT > 30 s	ECG and Holter monitor	3 months	58.3±10.8	11 (21.2)	NR	NR	40.4±4.3	63.8±7.6
		PVI	52					54.9±12.7	15 (28.8)	NR	NR	39.3±5.2	64.7±6.0

Table 1 (continued)

Study	Class of AF	Trial Arm	*n*	Duration of Follow Up (months)	Definition of AAR	Rhythm Monitoring	Blanking Period	Age	*n* Female (%)	BMI (kg/m^2)	AF Duration (months)	LA diameter (mm)	LVEF (%)
Sawhney 2010	Paroxysmal	PVI + Linear	33	24	Documented atrial arrhythmia	Mobile telemetry	90 days	58.6±9.6	8 (24)	NR	72.0±68.4	37.0±4.0	61.1±4.3
		PVI	33					55.2±11.7	10 (30)	NR	62.4±60	36.0±3.0	61.8±5.8
Sheikh 2006	Paroxysmal	PVI + Linear	50	9	Documented AF	ECG and Holter monitor	Unspecified	61±10	21 (42)	NR	NR	41.2±6.5	53±14
		PVI	50					60±12	16 (32)	NR	NR	40.2±7.1	54±12
Verma 2015	Persistent	PVI + Linear	259	18	AF > 30 s	ECG and Holter monitor	3 months	61±9	63 (24)	NR	43.2±50.4	46±6	57±10
		PVI	67					58±10	15 (22)	NR	51.6±75.6	44±6	55±11
Willems 2006	Persistent	PVI + Linear	32	16	AF/AFL > 30 s	Tele-ECG	Unspecified	58.3±11.8	NR	NR	7 (1 – 18)	47±6	NR
		PVI	30					60.1±9.3	NR	NR	7 (2 – 17)	48±4	NR
Wynn 2016	Both	PVI + Linear	66	12	AF/AT > 30 s	ECG and Holter monitor	3 months	61.9±11.4	25 (38)	28.6±8.0	5.5±3.9	43±6	61.5±12.6
		PVI	64					61.8±9.7	17 (27)	29.2±9.3	5.5±4.2	43±6	60.5±11.0
DeLurgio 2020	Persistent	PVI + Hybrid	102	12	AF/AT/AFL > 30 s	ECG and Holter monitor	3 months	63.7±9.6	22 (22)	32.9±5.9	52.8±57.6	44±6	55.3±7.8
		PVI	51					65.1±6.7	24 (47)	35.1±7.1	54.0±56.4	43±6	55.7±6.1
Jan 2018	Paroxysmal	PVI + Hybrid	24	36	Documented AF/AT/AFL	ILR	3 months	58.8±6.3	8 (33)	30.6±5.9	49.2±42.0	NR	65.6±6.2
		PVI	26					59.5±10.8	5 (19)	29.0±3.5	62.4±44.4	NR	63.3±7.0
Di Biase 2009	Paroxysmal	PVI + CFAE	34	12	AF/AT > 60 s	Event recorder and Holter monitor	2 months	58.4±7.5	4 (12)	NR	63.6±60	44±6	54.6±6.0
		PVI	35					57.0±8.1	6 (17)	NR	63.6±68.4	43±6	55±8
Dixit 2012	Persistent	PVI + CFAE	51	12	AF/AT > 30 s	ECG	6 weeks	60.0±9.0	5 (10)	NR	43±40	49±8	56±14
		PVI	55					59.0±8.0	7 (12.7)	NR	56.0±65.0	48.0±7.0	56.0±9.0
Elayi 2008	Persistent	PVI + CFAE	49	16	AF/AT > 60 s	ECG, event recorder, Holter monitor	2 months	59.2±11.5	17 (35)	NR	75.6±30	46.2±6.4	55
		PVI	95					59.1±10.2	32 (33.7)	NR	73.1±40.7	45.0±6.9	54
Hwang 2021	Persistent	PVI + CFAE	25	12	AF/AT > 30 s	Event recorder and Holter monitor	3 months	58.8±9.3	5 (20)	25.9±3.0	21.4±26.2	49±4	59.4±11.4
		PVI	25					57.9±9.8	2 (8)	27.6±3.7	27.1±19.2	50±6	57.9±10.0
Oral 2004	Paroxysmal	PVI + CFAE	30	6	Documented AF	Event monitor	6 weeks	56±9	4 (13.3)	NR	72±48	44±6	58±7
		PVI	70					54.4±10.4	16 (22.9)	NR	84±81.6	43±7	55.6±10.5
Oral 2009	Persistent	PVI + CFAE	50	10	AT > 30s	Event monitor	Unspecified	62±8	9 (18)	NR	60±48	46±6	54±9
		PVI	69					58.6±9.3	14 (20.3)	NR	64.8±57.6	45.6±6.1	53.3±11.4
Verma 2015	Persistent	PVI + CFAE	263	18	AF > 30 s	ECG and Holter monitor	3 months	60±9	50 (19)	NR	50.4±60	44±6	57±10
		PVI	67					58±10	15 (22)	NR	51.6±75.6	44±6	55±11

Table 1 (continued)

Study	Class of AF	Trial Arm	*n*	Duration of Follow Up (months)	Definition of AAR	Rhythm Monitoring	Blanking Period	Age	*n* Female (%)	BMI (kg/m^2)	AF Duration (months)	LA diameter (mm)	LVEF (%)
Vogler 2015	Persistent	PVI + CFAE	75	12	AA > 30 s	ECG and Holter monitor	3 months	61.1±10.9	15 (20)	27.5±3.2	64.4±61.2	43.7±5.2	59.8±7.1
		PVI	78					63.0±9.6	22 (28.2)	27.2±4.7	52.1±47.7	44.5±6.6	60.0±7.1
Masuda 2022	Paroxysmal	PVI + LVA	30	25	AF/AT > 30 s	ECG and event monitor	3 months	75.3±7.2	21 (70)	22.3±3.5	4 (2 – 14)	40±6	64±14
		PVI	368					68.4±11.5	154 (41.8)	23.6±3.8	NR	37.1±5.9	65.9±9.1
Yang 2022	Persistent	PVI + LVA	134	18	AF/AT > 30 s	ECG and event monitor	3 months	60.6±9.4	46 (33.8)	27.8±4.9	6 (2.0 – 15.5)	41.4±5.9	61.3±9.2
		PVI	142					60.4±9.6	43 (30.3)	25.8±4.5	6 (1.0 – 12.0)	42.5±5.3	62.1±6.8
Marrouche 2022	Persistent	PVI + MRI-f	421	15	AF/AT/AFL > 30 s	ECG and event monitor	90 days	62 (57 – 68)	89 (21.1)	NR	NR	NR	NR
		PVI	422					63 (57 – 69)	89 (21.1)	NR	NR	NR	NR

Abbreviations: millimeters (mm), seconds (s), not reported (NR), atrial arrhythmia recurrence (AAR), atrial fibrillation (AF), atrial arrhythmia (AA), atrial tachyarrhythmia (AT), Atrial flutter (AFL), implantable loop recorder (ILR), body mass index (BMI), left atrium (LA), left ventricular ejection fraction (LFEV), pulmonary vein isolation (PVI), left atrial ganglionic plexus ablation (GP), renal denervation (RD), vein of Marshall ethanol infusion (VMEI), posterior wall isolation (PWI), empiric non-PV trigger (mitral annulus, fossa ovalis, eustachian ridge, crista terminalis, and superior vena cava) ablation (enPV), superior vena cava isolation (SVCI), complex fractionated electrograms (CFAE), left atrial low voltage areas (LVA), and left atrial fibrosis on magnetic resonance imaging (MRI-f)

Fig. 2), and there was moderate interstudy heterogeneity ($I^2 = 46.89$). The interstudy heterogeneity was sensitive to the exclusion of Kiuchi et al. [9] (OR 0.45; $p < 0.001$; $I^2 = 0.00$). Meta-regression analysis for left atrial diameter was not done because only 3 trials reported this data; however, studies that were published more recently were significantly correlated with a lesser reduction in AAR with adjunctive RD ($R^2 = 1.00$; correlation coefficient 0.19; 95% CI 0.00 to 0.38; $p = 0.05$).

3.1.3 Vein of marshall ethanol infusion

One VMEI study was identified that included 343 participants. Adjunctive VMEI was associated with a statistically significant 36.8% relative reduction in AAR compared to PVI alone (OR 0.63; 95% CI 0.41 to 0.97; $p = 0.04$; Fig. 2).

3.2 Linear ablation

Twelve linear ablation studies were identified that included 1,610 participants. Adjunctive linear ablation did not show a statistically significant change in AAR compared to PVI alone (OR 0.68; 95% CI 0.41 to 1.14; $p = 0.14$; Fig. 2), and there was severe interstudy heterogeneity ($I^2 = 77.49$). Neither the overall effect estimate nor the interstudy heterogeneity were sensitive to the exclusion of any study. Meta-regression analysis did not show any significant correlation between left atrial diameter and AAR ($R^2 = 0.00$; correlation coefficient -0.10; 95% CI -0.28 to 0.08; $p = 0.27$; Fig. S1B); however, studies that were published more recently were significantly correlated with a lesser reduction in AAR with adjunctive linear ablation ($R^2 = 0.34$; correlation coefficient 0.12; 95% CI 0.01 to 0.23; $p = 0.03$).

3.3 Non-pulmonary vein trigger elimination

Fifteen studies (11 PWI, 1 enPV, and 3 SVCI) were identified that included 2,647 participants. Adjunctive non-PV trigger ablation did not show a statistically significant change in AAR compared to PVI alone (OR 0.86; 95% CI 0.68 to 1.08; $p = 0.20$; Fig. 2), and there was moderate interstudy heterogeneity ($I^2 = 35.65$).

3.3.1 Posterior wall isolation

Eleven PWI studies were identified that included 2,016 participants. Adjunctive PWI did not show a statistically significant reduction in AAR compared to PVI alone (OR 0.83; 95% CI 0.62 to 1.11; $p = 0.21$; Fig. 2), and there was moderate interstudy heterogeneity ($I^2 = 43.75$).

Table 2 Cochrane Risk of Bias Assessment Results

	Random Sequence Generation	Allocation Concealment	Blinding of Participants And Personnel	Blinding of Outcome Assessment	Incomplete Data	Selective Reporting
Berger 2019	+	?	-	-	+	+
Katritsis 2011	?	?	-	-	+	+
Katritsis 2013	+	+	-	-	+	+
Kiuchi 2016	?	?	+	+	+	+
Kiuchi 2018	?	?	+	+	+	+
Pokushalov 2012	+	+	+	+	+	+
Steinberg 2020	+	+	+	-	+	+
Valderrabano 2020	+	+	+	+	-	+
Arbelo 2014	+	+	+	+	+	+
Fassini 2005	?	?	-	-	+	+
Gaita 2008	+	+	+	-	+	+
Gavin 2012	+	+	-	-	+	+
Hocini 2005	?	?	-	-	+	+
Kang 2014	?	?	-	-	+	+
Mun 2012	?	?	-	-	+	+
Sawhney 2010	?	?	-	-	+	+
Sheikh 2006	?	?	-	-	+	+
Verma 2015	+	?	+	-	+	+
Willems 2006	+	?	-	-	+	+
Wynn 2016	+	?	+	-	+	+
Ahn 2022	+	?	-	-	+	+
Aryana 2021	?	?	+	-	+	+
Kim 2015[28]	+	?	-	-	+	+
Kim 2015[24]	+	?	-	-	+	+
Kim 2022	+	+	+	-	+	+
Kistler 2023	+	?	+	-	+	+
Wang 2008	+	+	+	+	+	+
Corrado 2010	+	?	-	-	+	+
Da Costa 2015	?	?	-	-	+	+
Lee 2019	?	?	-	-	+	+
Pak 2020	+	+	?	-	+	+
Pappone 2004	+	+	?	+	+	+
Yu 2017	?	?	-	-	+	+
Dixit 2012	?	?	-	-	+	+
DeLurgio 2020	?	?	-	?	+	+
Jan 2018	?	?	-	-	+	+
Di Biase 2009	+	?	-	-	+	+
Elayi 2008	+	?	-	-	+	+
Hwang 2021	+	?	-	-	+	+
Oral 2004	?	?	-	-	+	+
Oral 2009	?	?	-	-	+	+
Vogler 2015	?	?	-	-	-	+
Huo 2022	Unable to assess	Unable to assess	Unable to assess	Unable to assess	Unable to assess	Unable to assess
Masuda 2022	?	?	-	-	+	+
Yang 2022	+	+	+	-	-	+
Marrouche 2022	+	?	+	-	+	+

Green indicates low risk, yellow indicates moderate risk, and red indicates high risk of bias

Neither the overall effect estimate nor the interstudy heterogeneity were sensitive to the exclusion of any study. Meta-regression analysis did not show any significant correlation between left atrial diameter and AAR ($R^2 = 0.00$; correlation coefficient -0.09; 95% CI -0.21 to 0.03; $p = 0.14$; Fig. S1C) or between year of publication and AAR ($R^2 = 0.00$; correlation coefficient -0.02; 95% CI -0.07 to 0.04; $p = 0.59$).

3.3.2 Empiric non-pulmonary vein trigger ablation

One enPV study was identified that included 105 participants. Adjunctive enPV did not show a statistically significant reduction in AAR compared to PVI alone (OR 0.70; 95% CI 0.32 to 1.51; $p = 0.36$; Fig. 2).

3.3.3 Superior vena cava isolation

Three SVCI studies were identified that included 526 participants. Adjunctive SVCI did not show a statistically significant reduction in AAR compared to PVI alone (OR 1.08; 95% CI 0.70 to 1.69; $p = 0.73$; Fig. 2), and there was mild interstudy heterogeneity ($I^2 = 9.55$). Neither the overall effect estimate nor the interstudy heterogeneity were sensitive to the exclusion of any study.

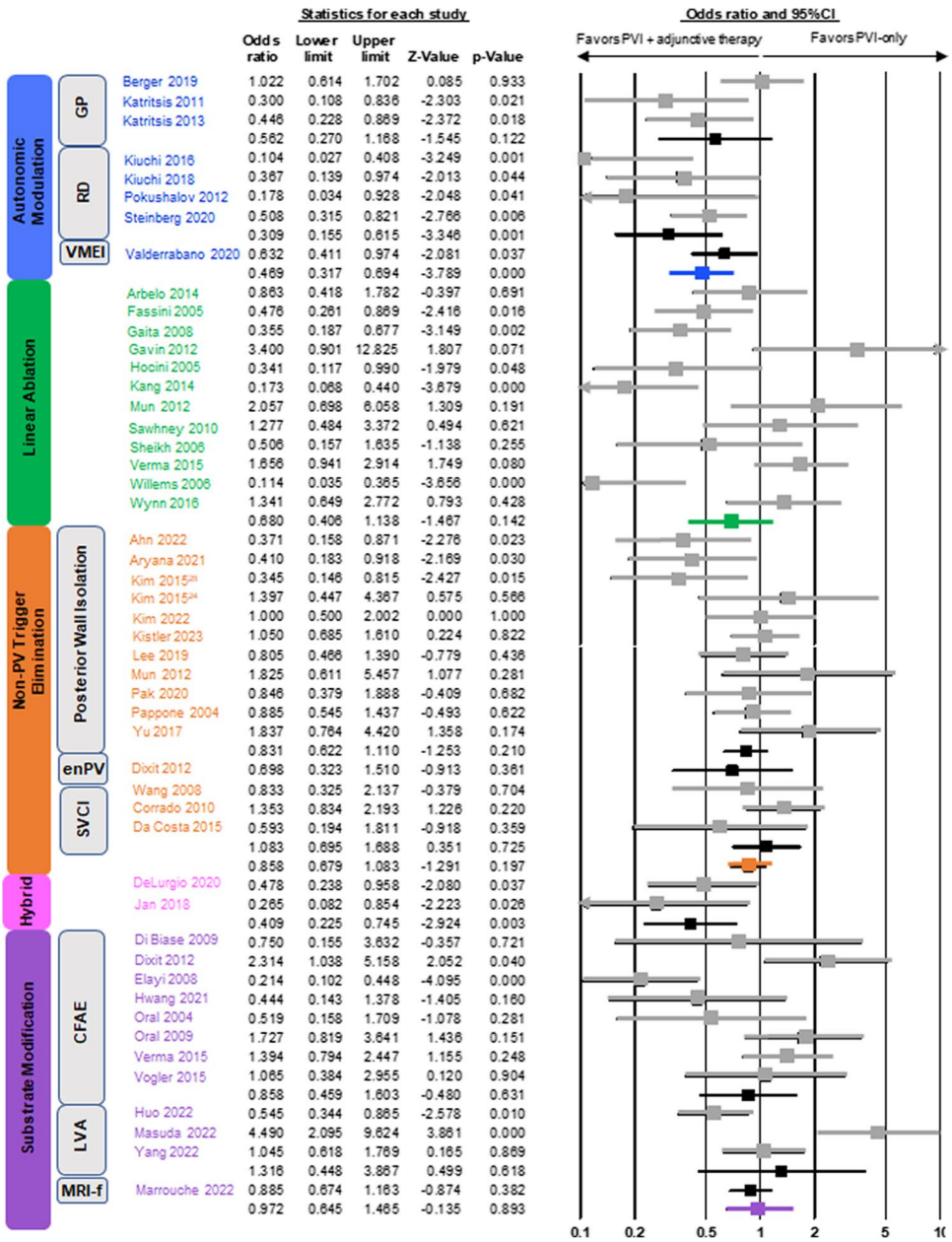

Fig. 2 Atrial Arrhythmia Recurrence in PVI Plus Adjunctive Therapy vs PVI Alone. This forest plot depicts the odds ratios and 95% confidence intervals of atrial arrhythmia recurrence between pulmonary vein isolation (PVI) plus an adjunctive therapy and PVI alone. The results are stratified by adjunctive strategy. Hybrid ablation refers to convergent epicardial and endocardial ablation. Abbreviations: Left atrial ganglionic plexus ablation (GP), renal denervation (RD), vein of Marshall ethanol infusion (VMEI), pulmonary vein (PV), empiric non-PV trigger (mitral annulus, fossa ovalis, eustachian ridge, crista terminalis, and superior vena cava) ablation (enPV), superior vena cava isolation (SVCI), ablation of complex fractionated electrograms (CFAE), ablation of left atrial low voltage areas (LVA), and ablation of left atrial fibrosis on magnetic resonance imaging (MRI-f)

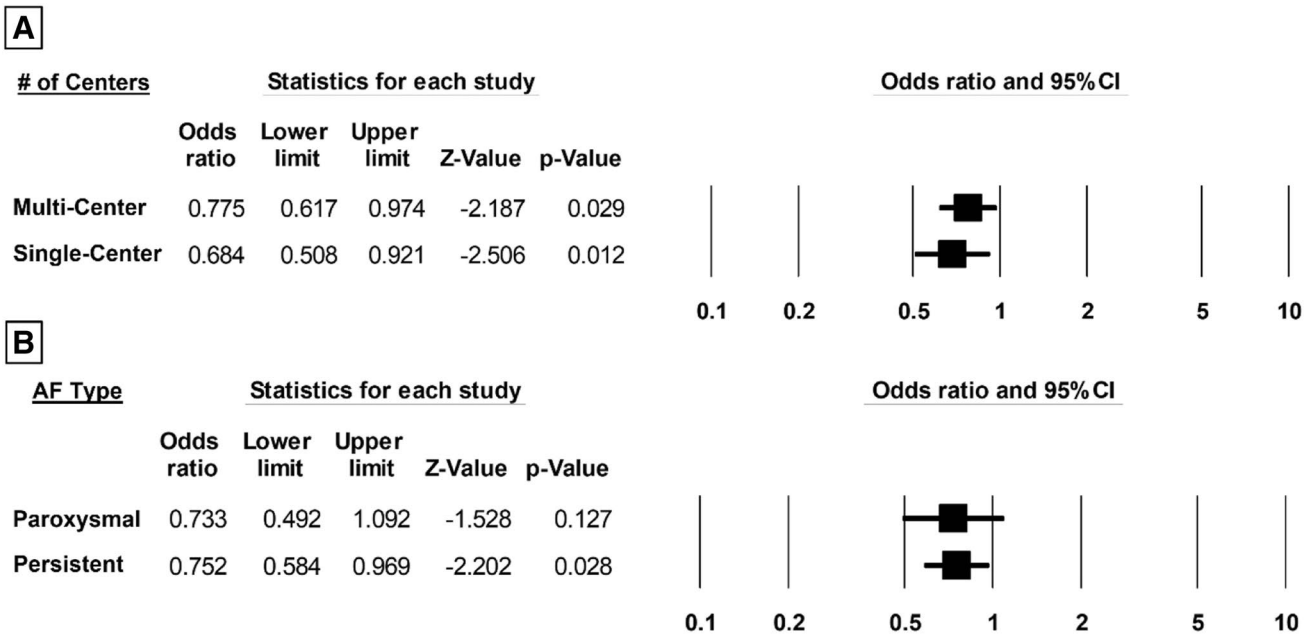

Fig. 3 Subgroup Analysis by Number of Centers and Classification of Atrial Fibrillation. This forest plot depicts the odds ratios and 95% confidence intervals of atrial arrhythmia recurrence between pulmonary vein isolation (PVI) plus an adjunctive therapy and PVI alone. Panel **A**: Subgroup analysis performed by number of centers used to enroll patients in the trials (single-center vs multi-center). Panel **B**: Subgroup analysis performed by classification of atrial fibrillation (paroxysmal vs persistent). Abbreviations: atrial fibrillation (AF)

3.4 Hybrid ablation

Two studies were identified that included 199 participants. Adjunctive epicardial PVI was associated with a statistically significant 59.1% relative reduction in AAR compared to PVI alone (OR 0.41; 95% CI 0.23 to 0.75; $p = 0.003$; Fig. 2), and there was no interstudy heterogeneity ($I^2 = 0.00$).

3.5 Substrate modification

Twelve studies (8 CFAE, 3 LVA, and 1 MRI-f) were identified that included 2,791 participants. Adjunctive substrate modification did not show a statistically significant reduction in AAR compared to PVI alone (OR 0.97; 95% CI 0.65 to 1.47; $p = 0.89$; Fig. 2), and there was severe interstudy heterogeneity ($I^2 = 77.72$).

3.5.1 Ablation of complex fractionated atrial electrograms

Eight CFAE studies were identified that included 971 participants. Adjunctive CFAE did not show a statistically significant reduction in AAR compared to PVI alone (OR 0.86; 95% CI 0.46 to 1.60; $p = 0.63$; Fig. 2), and there was severe interstudy heterogeneity ($I^2 = 74.55$). The overall effect estimate was not sensitive to the exclusion of any study, however the interstudy heterogeneity decreased from severe to moderate after the exclusion of Elayi et al. [42] (OR 1.18; $p = 0.43$; $I^2 = 32.77$). Meta-regression analysis did not show any significant correlation between left atrial diameter and AAR ($R^2 = 0.00$; correlation coefficient 0.05; 95% CI -0.29 to 0.38; $p = 0.79$; Fig. S1A) or between year of publication and AAR ($R^2 = 0.00$; correlation coefficient 0.03; 95% CI -0.11 to 0.16; $p = 0.71$).

3.5.2 Low voltage area ablation

Three LVA studies was identified that included 977 participants. Adjunctive LVA ablation did not show a statistically significant reduction in AAR compared to PVI alone (OR 1.32; 95% CI 0.45 to 3.87; $p = 0.62$; Fig. 2).

3.5.3 Ablation of magnetic resonance imaging-guided left atrial fibrosis

One MRI-f study was identified that included 843 participants. Compared to PVI alone, adjunctive MRI-f did not show a statistically significant reduction in AAR compared to PVI alone (OR 0.89; 95% CI 0.67 to 1.16; $p = 0.38$; Fig. 2).

3.6 Complications

When analyzing by strategy, there was no statistically significant difference in composite of complications for adjunctive autonomic modulation, linear ablation, non-PV trigger elimination, or substrate modification when compared to PVI alone. However, adjunctive epicardial PVI was associated with a statistically significant increase in complications compared to PVI alone (OR 9.61; 95% CI 1.39 to 71.72; $p = 0.04$).

3.7 Subgroup analysis

All 46 RCTs included in this meta-analysis were grouped according to whether they were single-center or multi-center studies. Subgroup analysis showed that the odds of finding effectiveness with adjunctive therapy compared to PVI alone was not significantly different among single-center RCTs (OR 0.68; 95% CI 0.51 to 0.92; p = 0.01) compared with multi-center RCTs (OR 0.78; 95% CI 0.62 to 0.97; $p = 0.03$; Fig. 3A). There was not a clinically meaningful difference in the odds of finding effectiveness with adjunctive therapy compared to PVI alone in trials evaluating patients with persistent AF (OR 0.75, 95% CI 0.58 to 0.97, $p = 0.03$) or paroxysmal AF (OR 0.73, 95% CI 0.49 to 1.09, $p = 0.13$; Fig. 3B).

4 Discussion

This meta-analysis demonstrated that of adjunctive strategies studied, only PVI plus autonomic modulation and PVI plus epicardial PVI (convergent hybrid ablation) promoted a significant reduction in AAR compared to PVI alone. Collectively, the number of centers and classification of atrial fibrillation did not meaningfully influence effectiveness of adjunctive therapy.

Meta-analyses of studies evaluating adjunctive therapies to PVI such as CFAE ablation [49–54], PWI [55–57], GP ablation [58, 59], and RD [60–63] have been conducted. Wu et al. [51] analyzed 11 studies comparing PVI plus CFAE ablation to PVI alone and found that additional CFAE ablation resulted in a significant reduction in AAR. Salih et al. [56] evaluated 6 studies comparing PVI plus PWI to PVI alone and found adjunctive PWI was associated with a significant reduction in both AF recurrence and AAR. Recently, Rackley et al. [59] evaluated 5 RCTs comparing PVI plus GP ablation to PVI alone and found that adjunctive GP ablation significantly reduced AAR. Lastly, Atti et al. [63] conducted a meta-analysis on studies that compared PVI plus RD to PVI alone and found that adjunctive RD significantly decreased the risk of AF recurrence.

Importantly, these analyses either included nonrandomized and observational studies [51, 56, 53] or studies that did not directly compare PVI alone to PVI plus a single adjunctive therapy [59]. To date, there are no meta-analyses that have strictly evaluated RCTs comparing PVI alone to PVI plus adjunctive therapy stratified by class of strategy (i.e. autonomic modulation, substrate modification, non-PV trigger ablation, linear ablation, or hybrid ablation). Whereas Wu et al. [51] and Salih et al. [56] found a significant reduction in AAR for adjunctive CFAE and PWI, respectively, the present meta-analysis did not reveal this significance after incorporating data from the latest RCTs such as STABLE-SR-II [45], DECAAF II [48], CAPLA [31], Ahn et al. [27], and Kim et al. [29]

Autonomic dysfunction and cardiac hyperinnervation play a significant role in the pathogenesis of AF [64]. It is well recognized that PVI by catheter ablation disrupts several of the major intrinsic cardiac autonomic ganglia located on the epicardial PV-atrium interface [1, 65–68], a process which may be critical for suppression of AF. In fact, GP ablation alone has demonstrated comparable arrhythmia-free survival to PVI with less ablation time in several small trials [4, 69–71]. After exclusion of the AFACT trial, adjunctive GP ablation was associated with a reduction in AAR in the present analysis similar to prior studies [59]. Further study is needed to identify the optimal method to detect and target epicardial GP. The AFACT trial, which evaluated surgical epicardial ablation, failed to show a benefit to adjunctive GP ablation [3]. It is possible that epicardial PVI more effectively targets autonomic GP, attenuating the benefit of additional anatomic GP ablation [72]. Interestingly, this concept may explain the success of the convergent hybrid approach. Currently, there are 3 ongoing RCTs evaluating adjunctive epicardial PVI [73–75] that will help further clarify the risk benefit ratio of this therapy.

The ligament of Marshall is an epicardial vestigial fold which contains the vein of Marshall, Marshall bundle, and autonomic neural fibers connecting the thoracic and intrinsic cardiac autonomic ganglia. VMEI has been shown to eliminate parasympathetic responses to high-frequency stimulation suggesting it can result in neuronal damage and autonomic modulation/LA denervation [76]. Additional RCTs should be conducted to determine if the success of VMEI [10] for treatment of AF can be reproduced. The Marshall Bundle complex which encircles the vein of Marshall has also been implicated in focal and re-entrant atrial tachycardias which may serve as triggers for AF. Thus, VMEI may also result in non-PV trigger elimination. In addition to GP ablation, VMEI, and RD, additional research should consider alternative methods for autonomic modulation as an adjunctive therapy to PVI including non-invasive therapies such as tragus nerve stimulation [77–80].

There are several limitations to consider. First, measurement of AAR in the trials studied was not uniform across all trials. The method of AAR detection can influence treatment efficacy estimates. Furthermore, no studies evaluated AAR burden, which may be a more important endpoint to consider when evaluating the success of AF ablation and classification of AF prior to ablation [81]. However, measurement of AAR was uniform for each individual trial, thus allowing for comparison of PVI to PVI plus adjunctive therapy in this meta-analysis. Second, there was significant heterogeneity across all trials. We attempted to address this by conducting sensitivity analyses. In the case of adjunctive GP ablation and RD, these analyses did identify trials, which after removal, resulted in reduction of heterogeneity. For example, the GP ablation analysis was sensitive to the exclusion of AFACT trial [3], which evaluated thoracoscopic epicardial PVI. Third, there were a limited number of RCTs for certain adjunctive therapies. Hybrid ablation had only 2 trials while enPV and MRI-f had only 1 trial each. Importantly, there were fewer studies for the adjunctive strategies associated with AAR reduction (autonomic modulation and hybrid ablation) compared to those which did not improve AAR. Thus, caution should be taken in interpreting results, and future studies are needed to clarify the potential benefit of adjunctive autonomic modulation and epicardial PVI. Lastly, focal impulse and rotor modification (FIRM) was not included in the present study as there was only 1 RCT which met inclusion criteria. However, observational data for this strategy has suggested that there is no significant adjunctive benefit [82].

5 Conclusion

Autonomic modulation and hybrid ablation may improve the effectiveness of PVI. Future work should be done to evaluate strategies minimizing additional ablation of the LA, as this can be proarrhythmic and impair atrial mechanics [83] and in the case of epicardial ablation, increase procedural complication risk. Future studies should also evaluate AAR utilizing long-term continuous cardiac monitoring to allow for calculation of AF burden as well as frequency and duration of AF episodes, which may be more clinically meaningful endpoints.

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Data availability Any inquires regarding the data can be submitted to the corresponding author and it will be addressed accordingly.

Declarations

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