Comparative efficacy and safety of different catheter ablation strategies for persistent atrial fibrillation: a network meta-analysis of randomized clinical trials

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Abstract

Aims. Whereas pulmonary vein isolation (PVI) is the universally agreed target in catheter ablation of paroxysmal AF, an ideal ablation set in persistent AF patients remains questioned. Aim of the present study is to conduct a network meta-analysis (NMA) of available randomized controlled clinical trials (RCTs) comparing different ablation strategies in persistent AF patients.

Methods and Results. NMA was performed in a frequentist framework with the different ablation strategies constituting the competitive arms of interest. Primary efficacy endpoint was recurrences of atrial tachyarrhythmia (AF, atrial flutter and/or organized atrial tachycardia). Secondary endpoints included major peri-procedural complications, procedure and fluoroscopy duration. PubMED/MEDLINE and EMBASE databases were searched through June 2020. 2548 records were screened and 57 full-text articles assessed. Eventually 24 RCTs were included, encompassing 3,245 patients (median follow-up 15 months, IQR 12-18). Compared to PVI alone, PVI plus linear lesions in the left atrium and elimination of extra-PV sources was the only strategy associated with a reduced risk of arrhythmia recurrence (RR 0.49, 95% CI 0.27-0.88). Most treatment arms were associated with longer procedural time compared with PVI, however, major peri-procedural complications and fluoroscopy time did not differ.

Conclusion. A comprehensive strategy including PVI, linear lesions in the left atrium and elimination of extra-PV sources (constrained by a heterogeneous definition across studies) associated with reduced risk of recurrent atrial tachyarrhythmias compared to PVI alone. All investigated treatments arms yielded similar safety profiles. Further research should rely on enhanced substrate-based approach definitions to solve one of the most evident knowledge gaps in interventional electrophysiology.

Keywords: atrial fibrillation; persistent; catheter ablation; strategies

Introduction

Atrial fibrillation (AF) catheter ablation is recommended to improve symptoms and quality of life in patients in whom pharmacologic therapy has failed, and as first line treatment, in patients with heart failure[1].

Ablation target in paroxysmal AF ablation is well defined, with pulmonary vein isolation (PVI) being the established approach. Conversely, an ideal ablation set in case of persistent AF is lacking[2]. In fact, the need of additional ablation lesions in this subset of patients is questioned[3]. The underlying rationale is that due to the wider atrial remodeling[4], mechanisms other than the sole pulmonary vein (PV) triggers are likely implied in onset and maintenance of the arrhythmia. In this scenario extra PV trigger ablation[5], substrate-modification by creation of lines of block[6], elimination of complex fractionated atrial electrograms (CFAE)[7] or low voltage areas (LVA)[8] seem intriguing; a role for ganglionic plexi[9] and rotor[10] ablation has also been advocated. As a matter of fact, despite doubts on effectiveness[11], several randomized clinical trials (RCTs) have been published on alternative ablation targets, other than PVI, in persistent AF procedures.

Few meta-analyses have compared the alternative ablation lesion sets with conventional PVI in persistent AF patients, leading to conflicting results. While a potential benefit of additional ablation lesions occasionally emerged[12], other analyses did not register any statistically significant improvement on long term arrhythmic outcomes in patients treated with additional ablation strategies compared to PVI[13,14]. Notably, a meta-regression on 58 studies (randomized and observational)[15] suggested that lines of block and CFAE ablation improve intraprocedural AF termination but not arrhythmia-free long-term outcomes, while posterior wall isolation and left atrial (LA) appendage isolation, which frequently embody extra-PV sources, relate to improved long-term rhythm outcomes.

Network meta-analysis (NMA) is a recent development in the statistical field, which extends principles of meta-analysis to the evaluation of multiple treatments in a single analysis,

overcoming the main limitation of classical pairwise approaches comparing only two interventions at a time[16].

Driven by one of the most evident knowledge gaps in interventional electrophysiology, aim of the present study was to conduct a NMA on available RCTs to compare different ablation strategies in persistent AF patients and identify the most effective and safe ablation strategy.

Methods

Literature search and study selection

PubMED, MEDLINE and EMBASE databases were searched for relevant articles using the following search strategy: ((((((atrial fibrillation OR af OR afib)) AND (persistent OR long-standing OR chronic OR non-paroxysmal OR longstanding OR nonparoxysmal OR non paroxysmal OR long standing)) AND (ablation OR catheter ablation OR afca)) AND (clinical trial OR random*))). MESH terms and publication type labels were avoided, in order not to miss studies that could have not already been indexed when the search was performed. Search ended in June 2020. Results were screened by three independent authors (A.B., A.S. and M.A.) through title and abstract, divergences were solved by consensus. Non-English language studies, abstracts and unpublished data were excluded. Inclusion criteria were:

- RCTs in patients undergoing percutaneous catheter ablation for non-paroxysmal atrial fibrillation;
- presence of at least two arms in the protocol of each study, comparing different strategy of ablation;
- presence of at least 10 patients with non-paroxysmal AF for each study arm;
- indication of number of recurrences or patients free from atrial arrhythmia at the end of follow-up;
- randomization to different ablation strategies before the procedure (to ensure adherence to the transitivity principle, studies focusing on a certain subgroup of AF patients as, for example, those without restoration of sinus rhythm after PVI, were excluded).

Risk of bias assessment was performed at the study level using the Cochrane bias risk assessment tool (RoB2)[17]. Studies were classified as low-risk if all domains were low risk; if one or two domains presented some concerns, studies were classified as intermediate risk; if three domains presented some concerns or one domain was high-risk, studies were deemed at

high risk for bias. Results were reported according to Cochrane recommendation[18] and the specific PRISMA statement[19].

Data collection, competitive arms and study endpoint

The following study-level data were collected: general characteristics, patient population, ablation strategies, follow-up duration, major inclusion and exclusion criteria, primary and secondary end-points, and sponsor (Supplementary Table S1).

Stroke risk evaluation was based on the CHA2DS2-VASc score [congestive heart failure history; hypertension history; age $\geqslant$ 75 years old – 2 points; diabetes mellitus history; stroke/transient ischemic attack/thromboembolism history – 2 points; vascular disease history (prior myocardial infarction, peripheral artery disease or aortic plaque); age 65-74 years old; sex category – female, 1 point][20,21].

The different ablation strategies constituted the competitive arms of interest and were described according to a modular scheme, categorized in predetermined singular ablation approaches, as follows: pulmonary vein isolation [PVI], ablation lines [LIN], complex fractionated atrial electrogram ablation [CFAE], ganglionic plexi ablation [ganglionic], extra PV sources ablation [extraPV], posterior wall box isolation [BOX], low voltage area ablation [LVA]. A stepwise ablation strategy [stepwise] was also considered as a separate ablation strategy. In more details LIN included LA roof line, LA posterior wall line, mitral isthmus line, LA anterior line and LA septal line. ExtraPV sources were thoroughly searched for in the atria (and superior vena cava) during isoprotenerol infusion; presence was registered when a repetitive regular activity emerged (study specific details in Table S1, Supplementary Material).

For the purpose of this analysis, cavo-tricuspid isthmus (CTI) ablation was not included as a competitive arm of interest. Nevertheless, whenever part of the study protocol, it was reported in Table S1 (Supplementary Material).

Primary efficacy endpoint of the present analysis was the number of recurrences of any atrial arrhythmia (AF, atrial flutter and/or organized atrial tachycardia) at the longest follow-up period for which event counts were available. Secondary endpoints included safety (peri-procedural major complications: please refer to Supplementary Table S2 for study-specific definitions), as well as procedure and fluoroscopy duration.

Statistical analysis

Pooled estimates of baseline characteristics of study populations were calculated by meta-analysis of mean values for continuous variables and percentage for categorical variables with the corresponding 95% CI, using a generic random-effect inverse variance model. Follow-up duration was summarized as median values between the studies with the corresponding interquartile range (IQR). In case of binary endpoint, comparison between the competitive arms was performed in terms of risk ratio (RR), while mean difference (MD) was used as summary measure in case of continuous outcome. For each contrast, RR, its standard error and the corresponding 95%CI were calculated (detailed summary of study-level outcome data used for the NMA of primary and secondary endpoints are reported in the Supplementary Table S3 and Table S2-5, respectively; the R code used is indicated in the Appendix). NMA was performed in a frequentist framework, using a random-effect model accounting for correlations induced by multi-arm trials (the used statistical package automatically accounts for within-study correlation by reweighting comparisons of each multi-arm study). The competitive arm characterized by PVI-only ablation strategy was used as the reference group. Cochran's Q statistics and I^2 statistics was used to evaluate heterogeneity/inconsistency across the network. In particular, the Q statistic was decomposed in a within-design Q statistic (representing heterogeneity in studies comparing the same treatment arms) and a between-design Q statistic (which incorporates the concept of design inconsistency). To assess the inconsistency in a

random-effect model, the between-design Q statistic was calculated based on a full design-by-treatment interaction random effects model, as proposed by Higgins[22]. Publication bias was assessed by comparison-adjusted funnel plot[23] and Egger's test[24]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) method was used to evaluate the certainty of the network meta-analysis evidence[25]. Sensitivity analyses was also performed after excluding studies with a high risk of bias. Treatment ranking was assessed by p-scores[26], the frequentist analogues of Surface Under the Cumulative RAnking curve (SUCRA) values in the Bayesian framework, which measure the extent of certainty that a treatment is better than another, averaged over all competing treatments. Analyses were performed using the R version 4.0.0; in particular, NMA was performed with the R package *netmeta* (version 1.2)[27].

Results

Out of 57 eligible studies, 24 were finally included in the analysis (Figure 1). A detailed description of the selection process, including references and reasons for exclusion is found in the Supplementary Appendix.

Table 1 reports treatment arm, sample size and bibliographic references for each of the 24 included RCTs. Main characteristics of each study are reported in the Supplementary Appendix (Table S1).

The included studies encompassed 3,245 patients, with a median follow-up of 15 (IQR 12-18) months. Table 2 reports summarized baseline characteristics of studies included in this review. Pooled mean age was 58.1 (95%CI 57.7-58.4) years, with a 3:1 male-to-female pooled ratio (males 79%, 95%CI 77-80%). Hypertension was a frequent concurrent comorbid condition (52%, 95%CI 50-54%). Diabetic patients accounted for a pooled mean 10% of the included patients (95%CI 9-12%), while baseline heart failure was present in 5% of the patients (95%CI 4-6%; pooled mean left ventricular ejection fraction [LVEF] 56.7%, 95%CI 56.4-57.0%). 8% of the patients had ischemic heart disease (95%CI 7-9%) and 4% had history of previous thromboembolic events (95%CI 3-5%). Pooled mean LA antero-posterior diameter was 45.2 mm (95%CI 44.9-45.4 mm). The pooled mean CHA_2DS_2-VASc score was 1.8 (95% CI 1.6-1.9). Pooled mean AF history was 4.1 years (95%CI 3.9-4.3), while pooled mean duration of persistent episodes was 8.9 months (95%CI 8.7-9.1 months). Three of the included studies were deemed at high risk of bias, since three out of the five RoB2 assessed domains presented alarms (Figure 2).

Primary outcome analysis

All included studies reported recurrences of atrial tachyarrhythmias (Supplementary Table S3). Figure 3 graphically represents the network of treatment arms included in the primary outcome

analysis. 14 treatment arms (graph nodes) were encompassed, with 17 different designs and 28 pairwise comparisons. 2 studies[11,28] were multi-arm studies. The most frequent design was PVI+LIN vs PVI (5 studies reported this pairwise comparison).

Compared to PVI alone (Figure 4), PVI+LIN+extraPV was the only strategy reducing the risk of atrial arrhythmia recurrence during follow-up (RR 0.49, 95%CI 0.27-0.88). Table 3 is the NMA league table for the primary outcome, providing pairwise comparison between the investigated treatment arms. We found that standalone ganglionic plexi ablation was the least likely to achieve the best results if compared to most of the other treatments. GRADE assessment of each pairwise comparison is reported under the RR estimate to evaluate certainty: GRADE assessment of comparisons including PVI resulted, on average, higher.

Figure 5 reports treatment arm ranking according to p-score values. Of note, ablation strategies based on a single approach (LIN, PVI, CFAE, ganglionic) achieved the lowest rankings.

Some degree of heterogeneity/inconsistency across the network (I^2 = 68%) was found; within-design heterogeneity was significant (Q statistics: 18.46, p-value 0.010), while no between-design inconsistency was detected (Q statistics: 9.11, p-value 0.168). Further decomposition of the within-design Q statistics indicates the PVI+LIN vs PVI design as the culprit of the observed heterogeneity (p-value 0.015). Funnel plot analysis (Supplementary Figure S1) and Egger test did not indicate potential publication bias (p-value 0.837).

A sensitivity analysis, excluding the three studies deemed at high risk of bias, yielded unvaried results, with the PVI+LIN+extraPV arm consistently remaining the only ablation strategy achieving improved arrhythmia freedom compared to PVI alone (Supplementary Figure S2).

Supplementary Figure S3 illustrates the direct evidence plot showing the proportion of direct evidence available for network comparisons contributing both direct and indirect evidence.

Secondary outcomes analysis

15 out of the 24 included studies provided details concerning major peri-procedural complications (Supplementary Table S2). 10 treatment arms (graph nodes) were encompassed, with 11 different designs and 17 pairwise comparisons. No significant differences emerged between the different treatment arms.

No heterogeneity/inconsistency was found for this outcome (I^2 = 0%; within-design Q statistic 2.00, p-value 0.734; between-design Q statistic 0.38, p-value 0.944). Forest plot, with PVI alone ablation strategy as reference, and NMA league table, providing pairwise comparison between the included treatment arms, are reported in Supplementary Appendix (Supplementary Figure S4 and Supplementary Table S4, respectively).

15 and 17 out of the 24 included studies reported data on procedure and fluoroscopy time, respectively (Supplementary Table S5). 12 treatment arms (graph nodes) were encompassed for both outcomes, with 13 and 14 different designs and 17 and 19 pairwise comparisons for procedure and fluoroscopy time, respectively. Compared to PVI alone, a significant increase in mean procedure duration was observed for all treatment arms, except ganglionic plexi ablation (Supplementary Figure S5). Fluoroscopy time, however, did not significantly differ between the different strategies (Supplementary Figure S6).

Discussion

The main findings of the present study on catheter ablation of persistent AF can be summarized as follows: 1) a comprehensive ablation set including PVI, lines of block in the LA, and elimination of extra-PV sources is the only strategy, compared to PVI alone, associated with a reduced risk of recurrent atrial tachyarrhythmias; 2) strategies involving single approaches show the least likelihood of being the ideal treatment; 3) the investigated treatment arms have similar safety profiles, not exposing, compared to PVI alone, to an increase of peri-procedural complications or longer fluoroscopy times.

It is widely acknowledged that AF catheter ablation outcomes are suboptimal in patients with persistent AF, if compared to paroxysmal AF[1,2]. Anatomical, electrical and mechanical remodeling, induced both by the arrhythmia itself ('AF begets AF')[29] and by the eventual underlying heart disease, are within the most likely reasons. At least hypothetically, thus, the arrhythmia may result in less "PV trigger" and more "substrate" dependent. In addition, non-PV triggers, which can be found in 10-33% of unselected patients undergoing AF catheter ablation, more easily act as arrhythmia initiators in the context of an altered atrial substrate[30]. However, despite several adjunctive ablation approaches have been proposed and tested, a definitive conclusion regarding the potential additional benefit compared to PVI alone has not been reached. In fact, the latest consensus document on AF catheter ablation recommends PVI isolation as the cornerstone approach in every procedure (class I recommendation), suggesting only a marginal role for adjunctive ablation approaches (class IIb recommendation)[2].

The present NMA, to our knowledge the first of its kind, holds the advantage of being able to gather evidence both from direct and indirect comparisons, allowing ranking of different ablation strategies in similar settings. The similar inclusion criteria of the included studies (please refer to Table S1) guarantee the satisfaction of the transitivity assumption, one of the most important statistical assumptions underlying a network meta-analysis. In this sense, our

choice of excluding studies in which patients were randomized after PVI and/or included in the study only if the PVI was not able to restore sinus rhythm (refer to Supplementary Material) was driven by the fact that, including these studies with a selected subgroup of persistent AF patients, would have violated the transitivity principle. In addition, NMA, as suggested by previous literature[31,32], has been used to compare non independent treatments (e.g. PVI and PVI+LIN+extraPV both include PVI). The finding that an approach including PVI, linear lines of block and elimination of non-PV triggers represents the best transcatheter treatment option for persistent AF supports the rationale that a comprehensive ablation strategy targeting all postulated components of AF induction and maintenance (PV/non-PV triggers and susceptible atrial substrate) is needed. Previous meta-analysis, albeit not designed as network meta-analysis, suggested PVI alone might be inferior to a more comprehensive ablation scheme in persistent AF patients: Sau et al.[15], in a recent meta-regression, suggested that linear blocks and CFAE ablation did not relate to improved long-term freedom from arrhythmia recurrences, while posterior wall isolation and LA appendage isolation were associated with fewer long-term arrhythmia recurrences. Similarly, Romero et al.[12] reported that LA appendage isolation, in addition to PVI, improved long-term freedom from atrial arrhythmia recurrence, without increasing acute periprocedural complications or the risk of stroke. Conversely, other meta-analysis did not register significant benefits for CFAE ablation and linear blocks[14], as well as for ganglionated plexi ablation[13]. Overall, the main difference of these analyses is that they limit their focus to a single alternative ablation approach, while the present work, assesses the effect of comprehensive strategies, including more than one strategy in addition to PVI.

Similar indications supporting the benefit of a comprehensive ablation scheme originate, indirectly, from cohorts of patients who have, for other reasons, modified LA substrate and eliminated ectopic sources. During heart transplantation, for example, the recipients receive a complete (“cut and sew”) electrical isolation of the PV/posterior LA wall and venae cavae,

similar to the target of the PVI+LIN+extraPV ablation strategy. In a recent observational study on more than 350 heart transplantation patients followed for 10 years, despite a high comorbidity burden, persistent AF incidence was extremely low (0.3%)[33]. Interestingly, the four ablation strategies yielding the lowest p-scores consisted in single approaches (PVI, LIN, CFAE, and ganglionic ablation alone, not in combination).

Given the mean duration of AF episodes of 8.9 months (95% CI 8.7-9.1), present findings are mainly generalizable to persistent AF cases with at least about 9-month episode duration. It cannot be excluded that less complex strategies, as PVI alone, may be sufficient in AF cases with less than 6-month duration, particularly in case of short diagnosis-to-ablation time[34].

Importantly all investigated strategies did not result in an increased risk of major peri-procedural complications. The sole potential trade-off is that more comprehensive treatment arms require longer procedural times, however, without increasing fluoroscopy exposure to the patient, most likely associated with the wide use in this setting of three-dimensional electro-anatomical mapping systems[35].

Limitations

First, the modular definition of the treatment arms is a forced but necessary simplification of the broad spectrum of ablation protocols: in particular, the same ablation approach can refer to non-identical interventions in different studies (for example, in the extraPV approach different sources can be targeted; similarly, PVI can be performed by ostial or wide antral isolation, as well as linear lesions may include different combination of ablation lines). In this regard, the hot-spot of heterogeneity identified in studies comparing PVI vs PVI+LIN, the most frequent design in the included RCTs, might be explained both by the heterogeneous definition of the lines, and the challenge of obtaining continuous and transmural lesions, requiring validation by differential pacing. Moreover, we cannot exclude that the modular and simplified classification of the treatment arms may, at least partly, reduce the validity of the transitivity assumption. Second, definition of persistent AF can be heterogeneous, as it reflects guidelines indication contemporary to the specific study. Anyhow, mean duration of persistent AF episodes (8.9 months) strongly suggests inclusion of "true" persistent AF patients[1]. Third, outcome assessment during follow-up, anti-arrhythmic drugs management and blanking period definition vary across studies. However, the use of a random effect model was chosen to cope with the anticipated heterogeneity within studies. Fourth, the lack of specification of recurrence type (AF, atrial flutter and/or organized atrial tachycardia) in most of the studies prevented subtype-specific analysis and, consequently, assessment of any potential pro-arrhythmic effect (iatrogenic atrial flutter and/or organized atrial tachycardia) of the different treatment arms. Finally, albeit the period range of the included studies is wide (2005-2019), the nature of NMA (where the single studies are head-to-head comparisons) limits the possible impact of technological advancement on overall results, being the time-dependent benefit comparable for all ablation strategies.

Conclusion

In this network meta-analysis of catheter ablation strategies in persistent AF patients, a comprehensive strategy including PVI, linear lesion in the LA and elimination of extra-PV triggers was the only approach, compared to PVI alone, associated to reduced risk of recurrent atrial tachyarrhythmias. All investigated treatments arms yielded similar safety profiles, not differing concerning peri-procedural complications. Further research should rely on enhanced substrate-based definitions, going beyond the actual heterogeneous definitions of extra-pulmonary vein sources, to definitely solve one of the most evident knowledge gaps in interventional electrophysiology.

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None.

Ethics

Not applicable.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary data to this article are available online. Including:

Additional Results

R code

Online Figures S1-S6

Online Tables S1-S5

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Figure Legends

Figure 1. Flow diagram of study selection.

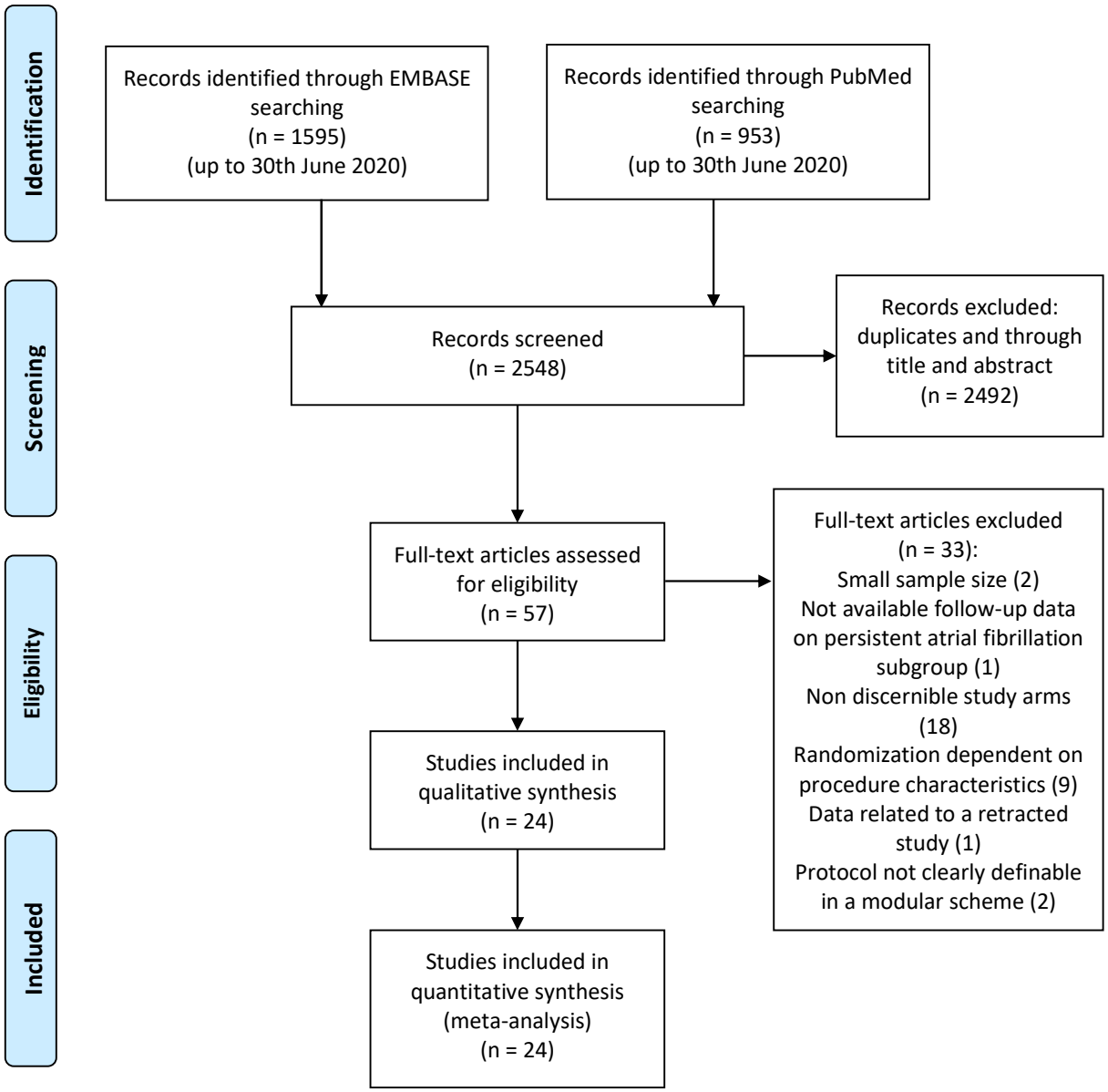


Figure 2. Risk of bias assessment of the included studies using Cochrane Risk of Bias 2 tool (RoB2).

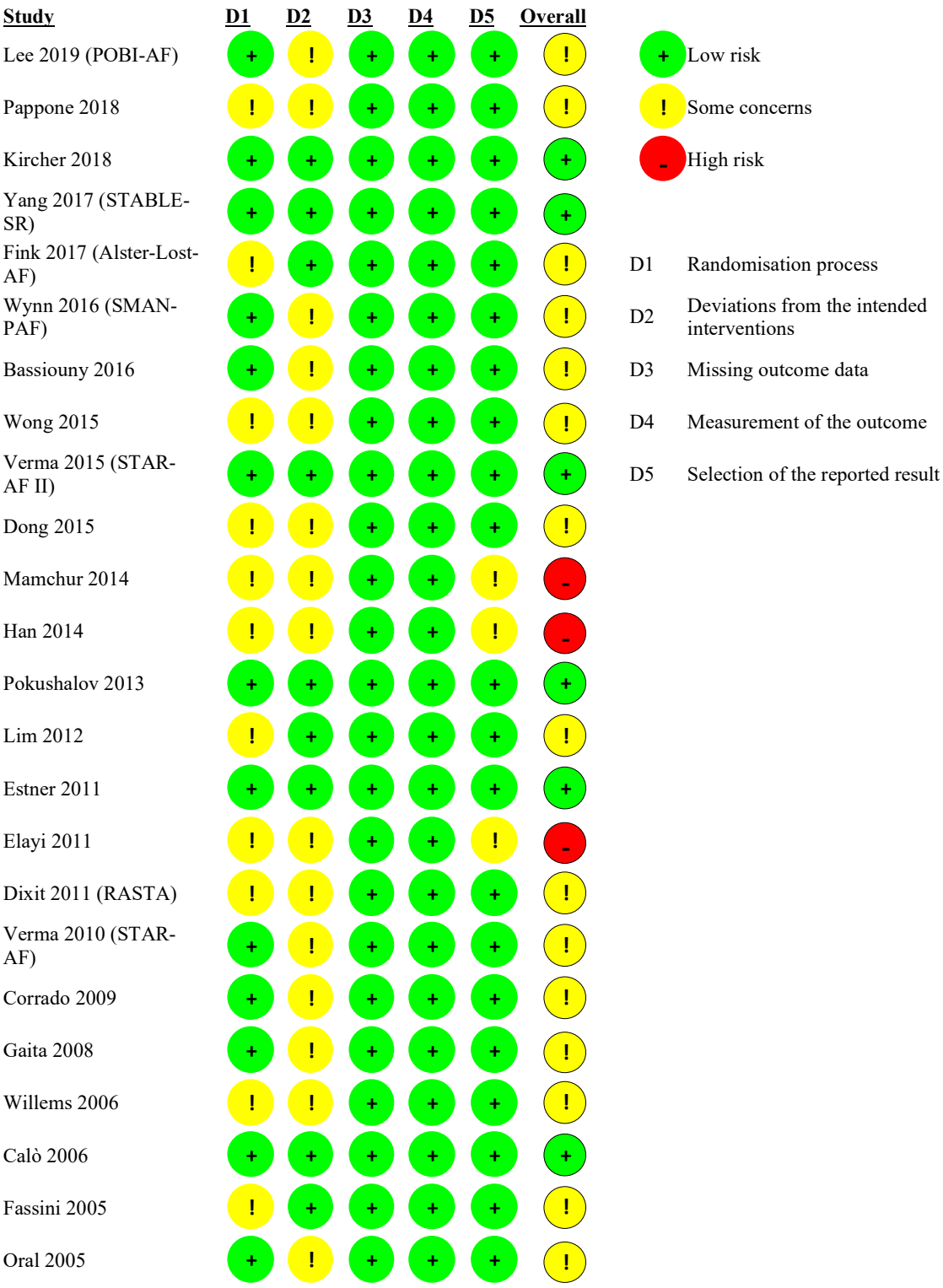
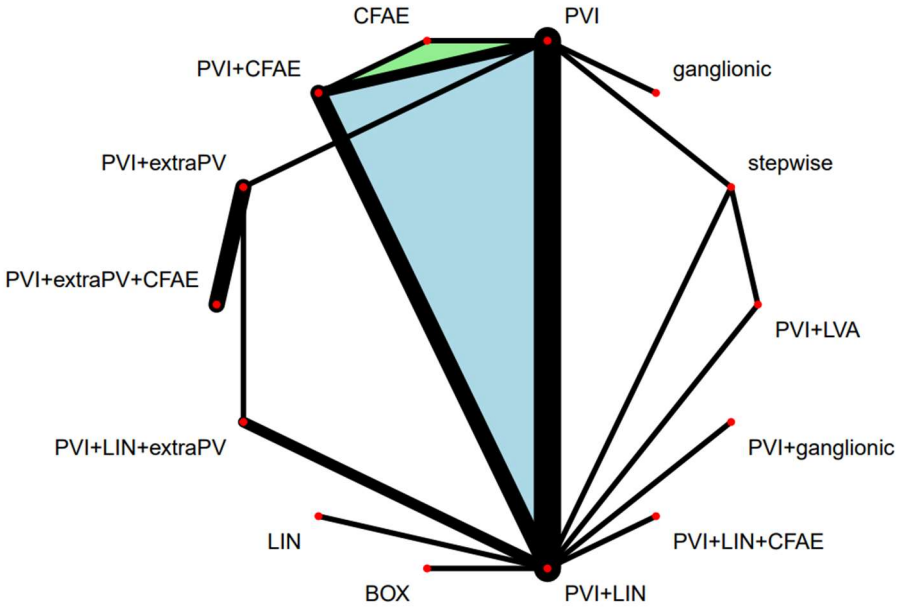


Figure 3. Network plot for comparison of primary outcome (arrhythmia recurrences). Each node represents an ablation strategy. The width of the lines connecting two nodes is proportional to the number of studies providing a direct comparison between the two strategies. Shaded areas connect comparisons involved in multi-arm studies**.**



BOX: posterior wall box isolation; CFAE: complex fractionated atrial electrogram ablation; extraPV: extra pulmonary veins AF triggers ablation; ganglionic: ganglionic plexi ablation; LIN: ablation lines; LVA: low voltage area ablation; PVI: pulmonary vein isolation; stepwise: stepwise ablation strategy.

Figure 4 (Representative figure). Network meta-analysis forest plot for primary outcome (arrhythmia recurrences) comparing different ablation strategies with PVI.

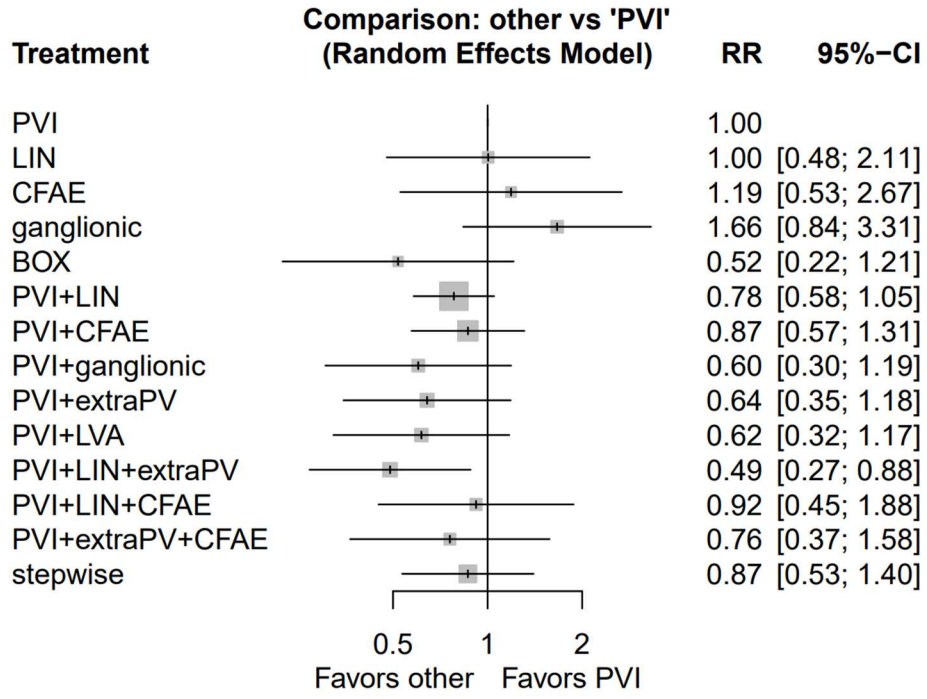


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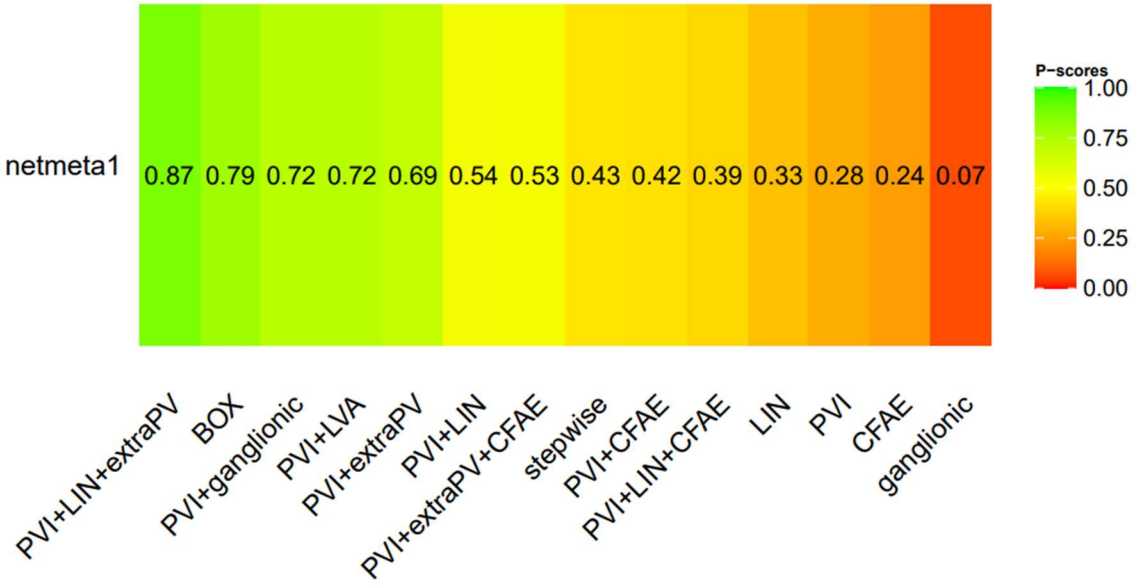
Figure 5. Treatment ranking based on p-score (probability of being ranked the best treatment) analysis.



BOX: posterior wall box isolation; CFAE: complex fractionated atrial electrogram ablation; extraPV: extra pulmonary veins AF triggers ablation; ganglionic: ganglionic plexi ablation; LIN: ablation lines; LVA: low voltage area ablation; PVI: pulmonary vein isolation; stepwise: stepwise ablation strategy.

Tables

Table 1. Studies included, treatment arms and number of patients for each arm.

Study	Treatment Group 1	Treatment Group 2	Treatment Group 3	N1	N2	N3
Lee 2019 (POBI-AF)[36]	PVI+extraPV	PVI+LIN+extraPV		105	102	
Pappone 2018[37]	PVI+LIN	PVI+LIN+extraPV		40	41	
Kircher 2018[8]	PVI+LIN	PVI+LVA		25	36	
Yang 2017 (STABLE-SR)[38]	PVI+LVA	stepwise		114	114	
Fink 2017 (Alster-Lost-AF)[39]	PVI	stepwise		61	57	
Wynn 2016 (SMAN-PAF)[40]	PVI	PVI+LIN		39	40	
Bassiouny 2016[41]	PVI+extraPV	PVI+extraPV+CFAE		46	44	
Wong 2015[7]	PVI+LIN	PVI+LIN+CFAE		65	65	
Verma 2015 (STAR-AF II)[11*]	PVI	PVI+CFAE	PVI+LIN	67	263	259
Dong 2015[42]	PVI+LIN	stepwise		73	73	
Mamchur 2014[43]	PVI	ganglionic		83	37	
Han 2014[44]	PVI+LIN	PVI+CFAE		60	59	
Pokushalov 2013[9]	PVI+LIN	PVI+ganglionic		132	132	
Lim 2012[45]	PVI+LIN	BOX		44	41	
Estner 2011[46]	PVI+LIN	PVI+CFAE		59	57	
Elayi 2011[47]	PVI+extraPV	PVI+extraPV+CFAE		48	50	
Dixit 2011 (RASTA)[48]	PVI+extraPV	PVI+extraPV+CFAE		105	51	
Verma 2010 (STAR-AF)[28]	PVI	CFAE	PVI+CFAE	11	13	12
Corrado 2009[49]	PVI	PVI+extraPV		87	73	
Gaita 2008[50]	PVI	PVI+LIN		26	53	
Willems 2006[51]	PVI	PVI+LIN		30	32	
Calò 2006[52]	PVI+LIN	PVI+LIN+extraPV		41	39	
Fassini 2005[53]	PVI	PVI+LIN		29	32	
Oral 2005[54]	PVI+LIN	LIN		40	40	

* 40 patients were eventually not included in the outcome analysis.

BOX: posterior wall box isolation; CFAE: complex fractionated atrial electrogram ablation; extraPV: extra pulmonary veins AF triggers ablation; ganglionic: ganglionic plexi ablation; LIN:

ablation lines; LVA: low voltage area ablation; N1, N2 and N3: number of patients in treatment group 1, 2 and 3, respectively; PVI: pulmonary vein isolation; stepwise: stepwise ablation strategy.

Table 2. Pooled baseline clinical features of the meta-analytic population.

Baseline characteristics	Pooled mean/proportion (95%CI)
Age [years]	58.1 (57.7-58.4)
Males	79% (77-80%)
Hypertension	52% (50-54%)
Diabetes	10% (9-12%)
Heart failure	5% (4-6%)
LVEF [%]	56.7 (56.4-57.0)
Ischemic heart disease	8% (7-9%)
Previous thromboembolic events	4% (3-5%)
Left atrial antero-posterior diameter [mm]	45.2 (44.9-45.4)
CHA_2DS_2-VASc score	1.8 (1.6-1.9)
AF history [years]	4.1 (3.9-4.3)
Duration of persistent episodes [months]	8.9 (8.7-9.1)

CHA2DS2-VASc score: congestive heart failure history; hypertension history; age ⩾ 75 years old – 2 points; diabetes mellitus history; stroke/transient ischemic attack/thromboembolism history – 2 points; vascular disease history (prior myocardial infarction, peripheral artery disease or aortic plaque); age 65-74 years old; sex category – female 1 point[20,21]; LVEF: left ventricular ejection fraction.

Table 3. League table for the pairwise comparison of the primary outcome (arrhythmia recurrences) according to the network meta-analysis. Reported estimates (RR with corresponding 95%CI) refer to the comparison between treatment in the column and treatment in the row. For each pairwise comparison, GRADE evaluation is reported under the relative risk estimate.

PVI	1.00 (0.48-2.11) *Low*	1.19 (0.53-2.67) *Low*	1.66 (0.84-3.31) *Moderate*	0.52 (0.22-1.21) *Low*	0.78 (0.58-1.05) *High*	0.87 (0.57-1.31) *High*	0.60 (0.30-1.19) *Low*	0.64 (0.35-1.18) *Moderate*	0.62 (0.32-1.17) *Low*	0.49 (0.27-0.88) *Moderate*	0.92 (0.45-1.88) *Low*	0.76 (0.37-1.58) *Low*	0.87 (0.53-1.40) *Moderate*
1.00 (0.47-2.09) *Low*	LIN	1.18 (0.40-3.52) *Low*	1.66 (0.60-4.57) *Low*	0.52 (0.18-1.47) *Low*	0.78 (0.39-1.54) *Moderate*	0.86 (0.40-1.86) *Low*	0.60 (0.24-1.50) *Low*	0.64 (0.25-1.62) *Low*	0.61 (0.25-1.53) *Low*	0.49 (0.20-1.17) *Low*	0.92 (0.36-2.35) *Low*	0.76 (0.27-2.08) *Low*	0.86 (0.38-1.97) *Low*
0.84 (0.37-1.90) *Low*	0.85 (0.28-2.52) *Low*	CFAE	1.40 (0.48-4.06) *Low*	0.44 (0.14-1.40) *Low*	0.66 (0.28-1.54) *Low*	0.73 (0.30-1.76) *Low*	0.51 (0.18-1.45) *Low*	0.54 (0.20-1.49) *Low*	0.52 (0.19-1.45) *Low*	0.41 (0.15-1.12) *Moderate*	0.77 (0.27-2.26) *Low*	0.64 (0.22-1.90) *Low*	0.73 (0.29-1.86) *Low*
0.60 (0.30-1.20) *Moderate*	0.60 (0.22-1.66) *Low*	0.71 (0.25-2.07) *Low*	ganglionic	0.31 (0.10-0.93) *Moderate*	0.47 (0.22-0.99) *Moderate*	0.52 (0.23-1.16) *Low*	0.36 (0.14-0.95) *Moderate*	0.39 (0.15-0.97) *Moderate*	0.37 (0.14-0.95) *Moderate*	0.29 (0.12-0.73) *Moderate*	0.55 (0.20-1.49) *Low*	0.46 (0.17-1.24) *Low*	0.52 (0.22-1.20) *Low*
1.93 (0.83-4.50) *Low*	1.94 (0.68-5.51) *Low*	2.29 (0.71-7.33) *Low*	3.21 (1.08-9.55) *Moderate*	BOX	1.51 (0.68-3.33) *Moderate*	1.67 (0.70-3.98) *Low*	1.16 (0.43-3.16) *Low*	1.24 (0.45-3.41) *Low*	1.19 (0.44-3.22) *Low*	0.94 (0.36-2.48) *Low*	1.77 (0.63-4.94) *Low*	1.46 (0.49-4.34) *Low*	1.67 (0.67-4.18) *Low*
1.28 (0.95-1.72) *High*	1.29 (0.65-2.54) *Moderate*	1.52 (0.65-3.56) *Low*	2.13 (1.01-4.51) *Moderate*	0.66 (0.30-1.47) *Moderate*	PVI+LIN	1.11 (0.78-1.58) *High*	0.77 (0.42-1.42) *Moderate*	0.82 (0.44-1.54) *Low*	0.79 (0.43-1.45) *Moderate*	0.63 (0.36-1.09) *Moderate*	1.18 (0.61-2.26) *Moderate*	0.97 (0.46-2.05) *Low*	1.11 (0.70-1.76) *Moderate*
1.15 (0.76-1.75) *High*	1.16 (0.54-2.51) *Low*	1.37 (0.57-3.30) *Low*	1.92 (0.86-4.29) *Low*	0.60 (0.25-1.43) *Low*	0.90 (0.63-1.29) *High*	PVI+CFAE	0.69 (0.34-1.41) *Low*	0.74 (0.37-1.50) *Low*	0.71 (0.35-1.43) *Low*	0.57 (0.29-1.08) *Moderate*	1.06 (0.51-2.23) *Low*	0.88 (0.39-1.97) *Low*	1.00 (0.57-1.77) *Low*
1.66 (0.84-3.28) *Low*	1.67 (0.67-4.18) *Low*	1.97 (0.69-5.63) *Low*	2.77 (1.05-7.28) *Moderate*	0.86 (0.32-2.35) *Low*	1.30 (0.70-2.40) *Moderate*	1.44 (0.71-2.93) *Low*	PVI+ganglionic	1.07 (0.44-2.57) *Low*	1.02 (0.43-2.42) *Low*	0.81 (0.36-1.86) *Low*	1.53 (0.62-3.74) *Low*	1.26 (0.48-3.31) *Low*	1.44 (0.67-3.10) *Low*
1.56 (0.84-2.87) *Moderate*	1.56 (0.62-3.96) *Low*	1.85 (0.67-5.09) *Low*	2.59 (1.03-6.52) *Moderate*	0.81 (0.29-2.23) *Low*	1.22 (0.65-2.28) *Low*	1.35 (0.67-2.73) *Low*	0.94 (0.39-2.26) *Low*	PVI+extraPV	0.96 (0.41-2.27) *Low*	0.76 (0.42-1.40) *Moderate*	1.43 (0.58-3.54) *Low*	1.18 (0.79-1.76) *Moderate*	1.35 (0.63-2.86) *Low*
1.62 (0.85-3.10) *Low*	1.63 (0.65-4.07) *Low*	1.93 (0.69-5.39) *Low*	2.70 (1.05-6.94) *Moderate*	0.84 (0.31-2.29) *Low*	1.27 (0.69-2.33) *Moderate*	1.41 (0.70-2.82) *Low*	0.98 (0.41-2.32) *Low*	1.04 (0.44-2.47) *Low*	PVI+LVA	0.80 (0.35-1.80) *Low*	1.49 (0.61-3.64) *Low*	1.23 (0.48-3.18) *Low*	1.41 (0.79-2.51) *Moderate*
2.04 (1.13-3.69) *Moderate*	2.05 (0.85-4.94) *Low*	2.43 (0.90-6.57) *Moderate*	3.40 (1.37-8.42) *Moderate*	1.06 (0.40-2.79) *Low*	1.60 (0.92-2.78) *Moderate*	1.77 (0.92-3.39) *Moderate*	1.23 (0.54-2.81) *Low*	1.31 (0.72-2.40) *Moderate*	1.26 (0.56-2.84) *Low*	PVI+LIN+extraPV	1.88 (0.80-4.41) *Low*	1.55 (0.75-3.20) *Low*	1.77 (0.87-3.59) *Low*
1.09 (0.53-2.22) *Low*	1.09 (0.43-2.81) *Low*	1.29 (0.44-3.77) *Low*	1.81 (0.67-4.88) *Low*	0.56 (0.20-1.58) *Low*	0.85 (0.44-1.63) *Moderate*	0.94 (0.45-1.98) *Low*	0.65 (0.27-1.60) *Low*	0.70 (0.28-1.73) *Low*	0.67 (0.28-1.63) *Low*	0.53 (0.23-1.25) *Low*	PVI+LIN+CFAE	0.83 (0.31-2.22) *Low*	0.94 (0.42-2.09) *Low*
1.32 (0.63-2.74) *Low*	1.32 (0.48-3.64) *Low*	1.57 (0.53-4.65) *Low*	2.19 (0.80-5.99) *Low*	0.68 (0.23-2.03) *Low*	1.03 (0.49-2.17) *Low*	1.14 (0.51-2.57) *Low*	0.79 (0.30-2.08) *Low*	0.85 (0.57-1.26) *Moderate*	0.81 (0.31-2.09) *Low*	0.65 (0.31-1.33) *Low*	1.21 (0.45-3.26) *Low*	PVI+extraPV+CFAE	1.14 (0.49-2.68) *Low*
1.16 (0.71-1.87) *Moderate*	1.16 (0.51-2.65) *Low*	1.37 (0.54-3.50) *Low*	1.92 (0.83-4.45) *Low*	0.60 (0.24-1.50) *Low*	0.90 (0.57-1.43) *Moderate*	1.00 (0.57-1.77) *Low*	0.70 (0.32-1.50) *Low*	0.74 (0.35-1.58) *Low*	0.71 (0.40-1.27) *Moderate*	0.57 (0.28-1.15) *Low*	1.06 (0.48-2.36) *Low*	0.88 (0.37-2.06) *Low*	stepwise

BOX: posterior wall box isolation; CFAE: complex fractionated atrial electrogram ablation; extraPV: extra pulmonary veins AF triggers ablation; ganglionic: ganglionic plexi ablation; LIN: ablation lines; LVA: low voltage area ablation; PVI: pulmonary vein isolation; stepwise: stepwise ablation strategy