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RESEARCH ARTICLE

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Comparing efficacy and safety in catheter ablation strategies for atrial fibrillation: a network meta-analysis

Emmanouil Charitakis^{1*} , Silvia Metelli², Lars O. Karlsson¹, Antonios P. Antoniadis³, Konstantinos D. Rizas⁴, Ioan Liuba¹, Henrik Almroth¹, Anders Hassel Jönsson¹, Jonas Schwieler⁵, Dimitrios Tsartsalis⁶, Skevos Sideris⁷, Elena Dragioti⁸, Nikolaos Fragakis³ and Anna Chaimani²

Abstract

Background: There is no consensus on the most efficient catheter ablation (CA) strategy for patients with atrial fibrillation (AF). The objective of this study was to compare the efficacy and safety of different CA strategies for AF ablation through network meta-analysis (NMA).

Methods: A systematic search of PubMed, Web of Science, and CENTRAL was performed up to October 5th, 2020. Randomized controlled trials (RCT) comparing different CA approaches were included. Efficacy was defined as arrhythmia recurrence after CA and safety as any reported complication related to the procedure during a minimum follow-up time of 6 months.

Results: In total, 67 RCTs ($n = 9871$) comparing 19 different CA strategies were included. The risk of recurrence was significantly decreased compared to pulmonary vein isolation (PVI) alone for PVI with renal denervation (RR: 0.60, CI: 0.38–0.94), PVI with ganglia-plexi ablation (RR: 0.62, CI: 0.41–0.94), PVI with additional ablation lines (RR: 0.8, CI: 0.68–0.95) and PVI in combination with bi-atrial modification (RR: 0.32, CI: 0.11–0.88). Strategies including PVI appeared superior to non-PVI strategies such as electrogram-based approaches. No significant differences in safety were observed.

Conclusions: This NMA showed that PVI in combination with additional CA strategies, such as autonomic modulation and additional lines, seem to increase the efficacy of PVI alone. These strategies can be considered in treating patients with AF, since, additionally, no differences in safety were observed. This study provides decision-makers with comprehensive and comparative evidence about the efficacy and safety of different CA strategies.

Systematic review registration: PROSPERO registry number: [CRD42020169494](https://www.crd.york.ac.uk/PROSPERO/record/CRD42020169494).

Keywords: Network meta-analysis, Atrial fibrillation, Catheter ablation, Efficacy, Safety, Antiarrhythmic drugs

Background

The main goal of treatment for atrial fibrillation (AF) is to treat symptoms and/or arrhythmia-induced heart failure. Primarily this involves pharmacological treatment and optimization of comorbidity, followed by antiarrhythmic treatment [1].

Cather ablation (CA) of AF became a treatment option after Haissaguerre's seminal study, where ectopic areas

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adjacent to the pulmonary veins were found to initiate AF and thus objectified an ablation target for the treatment of AF [2, 3]. Since then, ablation procedures for AF have become an important treatment option and the number of interventions is increasing worldwide.

The clinical problem is that the AF population is heterogeneous, and pulmonary vein isolation (PVI) alone is not the solution for all patients. As a result, different approaches or CA strategies have been suggested, but robust data are scarce, and randomized direct comparisons are rare [3, 4].

Commonly used CA strategies include linear lesions, left atrial (LA) posterior wall isolation, substrate modification, electrocardiogram (EGM)-based approaches, along with ablation of trigger sites and ganglia-plexi (GP), mainly as add-ons to PVI [3]. Yet, the efficacy of different CA ablation strategies as stand-alone or add-on to PVI has been ambiguous [4].

The objective of this study was to systematically review the efficacy and safety of all different CA strategies for the treatment of patients with paroxysmal (PAF) and non-paroxysmal AF (non-PAF). To assess treatments that have not been directly compared in previous trials, we employed a network meta-analysis (NMA). NMA is a statistical method that enables the possibility to evaluate multiple treatments in a single analysis, combining not only direct but also indirect comparisons of treatments.

Compared to a conventional meta-analysis that is limited to evaluate two interventions at a time and only compares interventions evaluated directly in head-to-head trials, the NMA provides the possibility to evaluate multiple treatments in a single analysis. This is possible by combining direct and indirect evidence (i.e., comparisons can be made even if two strategies have not been directly compared in a single study) [4, 5]. NMA is robust and has already been applied in several medical fields [6] supporting guidelines and decision-making at different levels [7].

Methods

Study design and registration

This study follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Extension Statement for NMA [8] (Additional file 1). This NMA is based on previously published data, thus it does not require ethical approval or consent to participate. The study protocol was registered on PROSPERO (registration number CRD42020169494) and has been published previously [9].

Eligibility criteria and type of interventions

Randomized controlled trials (RCTs) that included men and women with PAF and non-PAF (2) were eligible for inclusion. RCTs that included patients with prior ablation

(catheter, surgical or atrioventricular node ablation) were non-eligible.

The primary interventions of interest included CA strategies. In addition to PVI, non-PVI strategies, along with different strategies complementary to PVI, were evaluated. Table 1 contains the full list of interventions included alongside the abbreviations used.

Search strategy and study selection

A comprehensive search to identify relevant studies was performed by two investigators (EC and DT) using PubMed, the Cochrane Central Register of Controlled Trials, and the Web of Science. The search code is available in Additional file 2. The reference lists of included studies and previously published systematic reviews were searched to identify additional studies. The final search date was October 5th, 2020.

Two investigators (EC and DT) reviewed identified titles and abstracts independently, after which complete texts of eligible articles were obtained. Any disagreement between the reviewers was resolved by discussion with a third member of the investigator team (ED).

Data items and data collection

Two investigators (EC and DT) read each article and performed data abstraction independently. Any disagreements were resolved by consultation with a third reviewer (ED) [9].

Data on study characteristics were summarized (e.g., first author, publication year, trial design), patient characteristics (age, sex, type of AF, etc.), intervention-related data (fluoroscopy time, blanking period, time for follow-up, the method used for the detection of AF, etc.) and outcome measures. If articles were lacking data, the original authors were contacted for supplementation requests.

Outcomes

Primary outcomes

Efficacy Recurrence of AF or/and atrial tachycardia (AT) with a duration of ≥ 30 s recorded on implantable loop recorder, pacemaker, defibrillator, ECG, or ambulatory-ECG during a minimum follow-up of 6 months after CA.

Safety Any reported complications related to the procedure (periprocedural or occurring during the follow-up).

Secondary outcomes

All-cause mortality was evaluated from randomization and study start to the end of follow-up.

Table 1 Interventions included in NMA and their abbreviations

Interventions included in the NMA	Abbreviations of interventions included in NMA
Electrocardiogram based ablation	EGM
Ganglia plexi ablation	GP
Non-PVI lines ablation	lines
Pulmonary vein isolation	PVI
PVI and bi-atrial modification	PVI + BI-mod
PVI and combination of additional lines ablation and electrocardiogram-based ablation	PVI + comb
PVI and electrocardiogram-based ablation	PVI + EGM
PVI and ganglia plexi ablation	PVI + GP
PVI and left atrial auricle isolation	PVI + LAA
PVI and additional lines ablation	PVI + lines
PVI, posterior box isolation ± additional lines ablation	PVI + posterior ± lines
PVI and renal denervation	PVI + RDN
PVI and substrate modification	PVI + SUB-mod
PVI, superior vena cava isolation ± additional line ablation	PVI + SVC ± lines
PVI and stepwise approach	PVI + step
Isolation of some pulmonary veins	PVI partly
PVI and trigger ablation	PVI + trig
Single box isolation	Single box
Single box isolation and additional lines	Single box + lines
Antiarrhythmic drugs	AAD (used only in a sensitivity analysis)

Procedural time was defined as the time from vessel puncture to end of the procedure.

Quality assessment

The Cochrane Collaboration Risk of Bias (RoB) tool for randomized trials (RoB V.2) was used to rate the quality of the included RCTs [10]. When supplementation was not possible, the impact of missing outcome data was assessed using RoB (Additional file 3) [9, 10].

Statistical analysis and evaluation of assumptions

The fundamental assumption of transitivity (i.e., the assumption that the relative effect between two treatments can be inferred via one or more intermediate comparators) was evaluated by comparing the distribution of potential effect modifiers across the different direct comparisons in the data [11, 12].

We estimated summary risk ratios (RRs) for efficacy and safety and mean differences (MDs) for procedural time using random-effects pairwise, and network meta-analysis and the graph-theoretical approach to NMA implemented in the R package “netmeta” [13, 14]. A network diagram for each outcome was created to present the structure of the data. Finally, forest plots and league tables presenting relative effect estimates between all included strategies for the outcomes were modeled. As

many treatments included in the analyses were combinations of two or more strategies, we additionally performed a component network meta-analysis (CNMA), an extension of standard NMA that allowed deriving estimates of the effects of singular treatments, even when they have been used in combination with others [15, 16]. Specifically, to assess the individual effect of each treatment component we used an additive CNMA model in which the effect of a treatment combination is modeled as the sum of the individual treatments. Finally, we ranked the treatments for the primary outcomes using P-scores, which provide an *average degree of certainty* for a treatment to be better than the other interventions in the network [17].

Statistical heterogeneity was assessed considering the magnitude of the between-study variance (τ^2) [18]. In the NMA, the amount of heterogeneity was assumed to be the same across treatment comparisons.

Statistical incoherence (i.e., the disagreement of direct and indirect evidence) was assessed using the side-splitting method [19] and the design-by-treatment interaction model [20]. The former tests incoherence for every comparison while the latter is a global test for the entire network.

We used comparison-adjusted funnel plots for all active strategies against control (PVI) to graphically

evaluate the presence of small-study effects [5, 21], namely whether results in imprecise studies differ from those in more precise studies.

Potential sources of heterogeneity and incoherence were evaluated through subgroup analyses and network meta regressions. Subgroup analyses depended on AF detection device, re-ablation, and antiarrhythmic drugs (AADs) allowance during the follow-up, follow-up duration, type of AF included in the original studies (PAF, non-PAF, or mixed), duration of the blanking period, and year of publication. For network meta-regression we used age, sex, publication year, hypertension, structural heart disease or coronary artery disease, left atrial dimensions, duration of follow-up, and AF detection device as covariates, analyzing only those variables with non-missing values for at least 10 studies. For primary outcomes, we ran sensitivity analyses by omitting studies with high RoB, studies involving renal denervation, studies involving “only PAF patients” and the use of non-irrigational RFA-catheters. Finally, we conducted a sensitivity analysis including studies with AADs as a comparing arm in the network, and to sum up our results in fewer categories, we performed a sensitivity analysis summing the 19

categories into 6 larger ones (more details can be found in Additional files 4, 5, 6, 7, 8, 9, 10, 11, 12, 13).

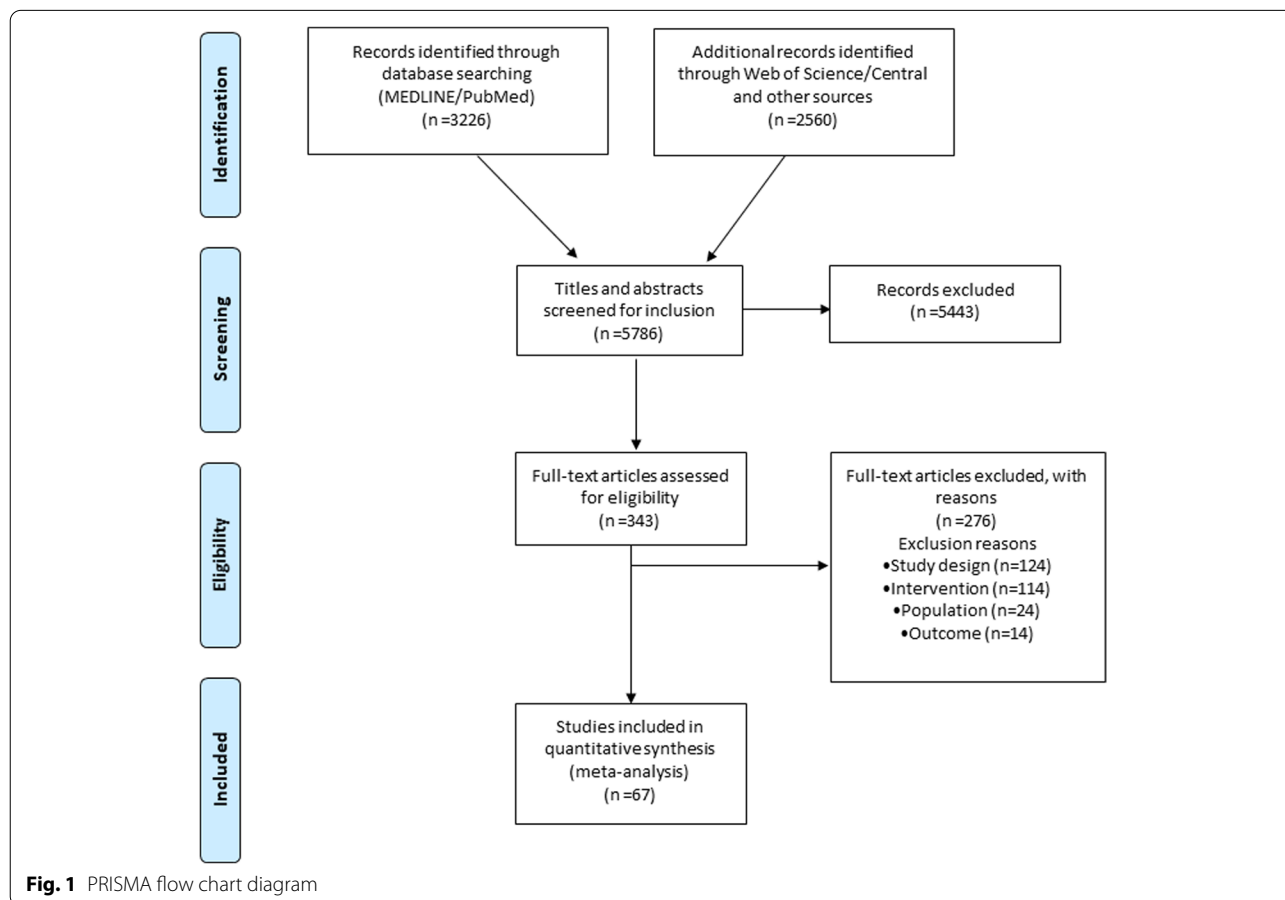
Credibility of the evidence

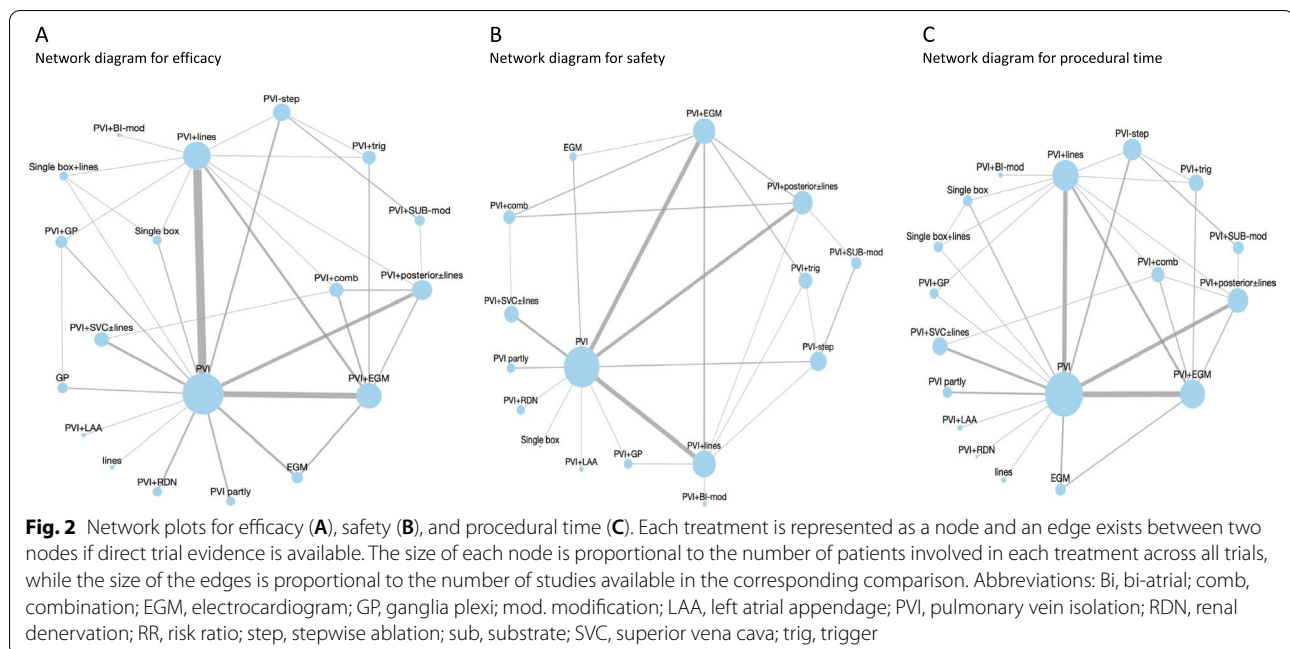
Regarding the primary outcomes, we evaluated the overall credibility of the evidence in the network using the Confidence in Network-Meta Analysis (CINeMA) tool [22]. CINeMA allows to assess and summarize the level of concern for each comparison based on the contributions of the direct comparisons to the NMA estimation (Additional file 14, Tables S1-S2).

Results

Characteristics and risk of bias of the included studies

The literature search yielded 5786 articles of which 343 were potentially eligible. Overall, 67 RCTs including 9871 patients between 2003 and 2020 ($n=9871$) comparing 19 different CA strategies were included (Fig. 1) (59 two-arm, 7 three-arm, and 1 four-arm studies). The mean age was 58 ± 3 years and the mean proportion of males was $73 \pm 9\%$. Twenty-seven RCTs (40%) included patients with only PAF, 23 (34%) only non-PAF and 17 (26%) had a mixed population (Additional file 4, Table S1) [4, 23–88].





The secondary endpoint “all-cause mortality” was not analyzed due to the large number of studies with zero events in both arms. All deviations from the original protocol are presented in the Additional file 5 in the Supplement.

Eleven (16%) RCTs included in this NMA revealed a high risk of bias when assessed by RoB V2-tool, whereas the remaining raised some concerns (Additional file 3, Table S1). The blinding of the care providers was not feasible due to the nature of the compared interventions.

Network geometries and transitivity

The network diagrams of available comparisons for each outcome are presented in Fig. 2. PVI in combination with lines (PVI+lines) vs PVI and PVI in combination with EGM (PVI+EGM) vs PVI were the most prevalent. Efficacy was reported in all studies, safety in 58 (86.5%) and procedural time in 57 (85.1%). For efficacy, at least one direct comparison was available for each strategy. For safety, no direct evidence was present for ablation lines nor PVI in combination with renal denervation (PVI+RDN), while for procedural time, no direct evidence involved GP ablation.

Studies including AADs were excluded from the main analysis due to transitivity issues. No important clinical differences in the distributions of most effect modifiers were observed (Additional file 6) in the remaining network. The transitivity assumption could not be properly evaluated for structural heart disease (SHD) and coronary artery disease (CAD) due to the small number of available data.

Relative effects and ranking of strategies

According to the NMA results, the risk for arrhythmia recurrence was significantly decreased for PVI in combination with biatrial modification (PVI+BI-mod) (RR: 0.31, CI: 0.11–0.88), PVI+RDN (RR: 0.60, CI: 0.38–0.94), PVI+GP (RR: 0.62, CI: 0.41–0.94) and PVI+lines (RR: 0.8, CI: 0.68–0.95) in comparison with PVI alone (Fig. 3a and Additional file 7 Table S1). However, PVI proved to be superior to an EGM-derived approach (RR: 1.86, CI 1.30–2.66). Interestingly, there were no significant differences in the efficacy between common CA-strategies, such as PVI+lines or PVI with posterior box (PVI+posterior±lines) and PVI+EGM (Fig. 4). Moreover, non-PVI ablation strategies, such as EGM ablation as stand-alone strategies, had significantly lower efficacy compared to most other CA strategies.

Regarding safety, no significant difference between different CA-strategies and CA-strategies compared to PVI (Fig. 3b and Additional file 7 Table S2) was evident. PVI in combination with left atrial appendage isolation (PVI+LAA), PVI+EGM, PVI+posterior±lines, and isolation of some pulmonary veins (PVI partly) appeared to have a lower risk of complications, but overall uncertainty was large, given their wide CIs. This finding might be partially explained by the limited statistical power of the model.

Only “PVI partly” was found to have significantly lower procedural time than PVI (MD: −0.68, CI: −1.09, −0.27), while PVI+GP, PVI+EGM, PVI+BI-mod, PVI with a stepwise approach (PVI+step), PVI+lines and PVI+EGM, was more time consuming when compared

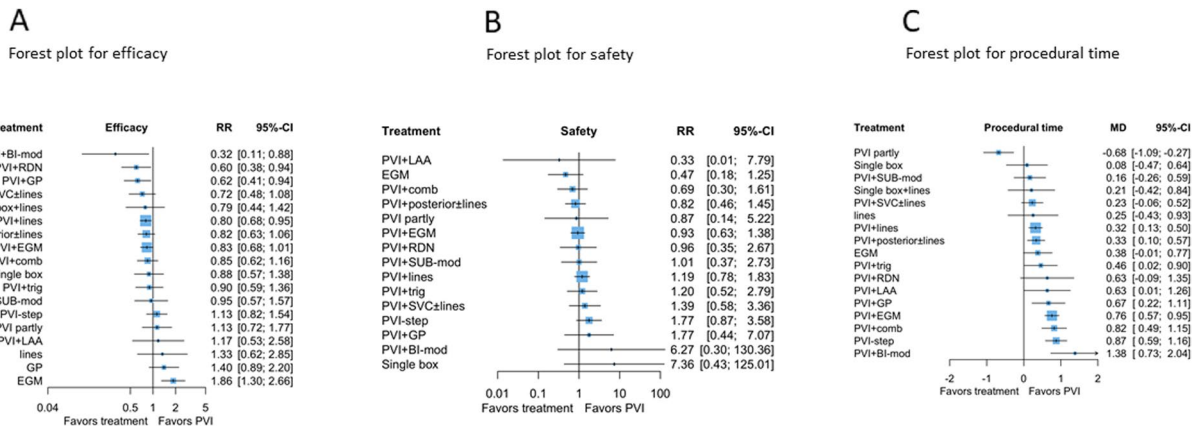


Fig. 3 Forest plots for efficacy (A), safety (B), and procedural time (C) compared with PVI showing the network meta-analysis RRs with their 95% CIs. Abbreviations: Bi, bi-atrial; comb, combination; EGM, electrocardiogram; GP, ganglia plexi; mod, modification; LAA, left atrial appendage; PVI, pulmonary vein isolation; RDN, renal denervation; RR, risk ratio; step, stepwise ablation; sub, substrate; SVC, superior vena cava; trig, trigger

	0.84	1.07	0.56	1.22	1.04	3.07	1.45	0.83	0.72	0.16	0.99	0.57	1.15	0.14		2.13
PVI	(0.55; 1.28)	(0.73; 1.58)	(0.14; 2.25)	(0.69; 2.16)	(0.37; 2.89)	(0.13; 73.31)	(0.62; 3.36)	(0.36; 1.94)	(0.30; 1.73)	(0.01; 3.32)	(0.37; 2.69)	(0.28; 1.15)	(0.19; 6.94)	(0.01; 2.31)		(0.80; 5.71)
1.25		1.28	0.67	1.46	1.24	3.66	1.72	1.00	0.86	0.19	1.18	0.68	1.38	0.16		2.55
(1.05; 1.48)		(0.80; 2.04)	(1.18; 2.57)	(0.74; 2.86)	(0.41; 3.76)	(0.15; 89.98)	(0.70; 4.25)	(0.42; 2.37)	(0.32; 2.27)	(0.01; 3.84)	(0.42; 3.36)	(0.32; 1.41)	(0.22; 8.70)	(0.01; 2.84)		(0.88; 7.39)
1.21	0.97	1.33	0.53	1.14	0.97	2.86	1.35	0.78	0.67	0.15	0.93	0.53	1.08	0.13		1.99
(0.99; 1.46)	(0.78; 1.20)	(1.13; 2.14)	(0.13; 2.14)	(0.60; 2.16)	(0.32; 2.90)	(0.12; 70.03)	(0.59; 3.09)	(0.32; 1.87)	(0.26; 1.74)	(0.01; 3.11)	(0.33; 2.61)	(0.25; 1.12)	(0.17; 6.75)	(0.01; 2.21)		(0.70; 5.63)
1.60	1.29	1.33	2.17	1.84	5.44	2.56	1.48	1.27	0.28	1.76	1.00	2.04	0.24			3.78
(1.06; 2.42)	(0.85; 1.95)	(0.85; 2.07)	(0.49; 9.54)	(0.33; 10.31)	(0.17; 1.84)	(0.52; 12.70)	(0.30; 7.22)	(0.25; 6.54)	(0.01; 7.60)	(0.33; 9.48)	(0.22; 4.57)	(0.21; 19.71)	(0.01; 5.63)			(0.70; 20.59)
1.23	0.98	1.02	0.76	0.85	2.51	1.18	0.68	0.59	0.13	0.81	0.46	0.94	0.11			1.75
(0.95; 1.59)	(0.73; 1.31)	(0.77; 1.34)	(0.47; 1.24)	(0.32; 2.75)	(0.10; 63.10)	(0.51; 2.75)	(0.26; 1.78)	(0.21; 1.65)	(0.01; 2.84)	(0.31; 2.10)	(0.20; 1.07)	(0.14; 6.20)	(0.01; 2.00)			(0.56; 5.42)
1.67	1.34	1.38	1.04	1.36	2.95	1.39	0.80	0.69	0.15	0.95	0.54	1.11	0.13			2.05
(1.07; 2.61)	(0.83; 2.16)	(0.85; 2.25)	(0.57; 1.91)	(0.81; 2.29)	(0.11; 82.74)	(0.37; 5.23)	(0.21; 3.02)	(0.18; 2.66)	(0.01; 3.77)	(0.23; 3.98)	(0.16; 1.89)	(0.14; 8.75)	(0.01; 2.65)			(0.50; 8.48)
0.85	0.68	0.71	0.53	0.70	0.51	0.27	0.23	0.05	0.32	0.08	0.38	0.38	0.04			0.70
(0.39; 1.87)	(0.31; 1.53)	(0.31; 1.59)	(0.22; 1.29)	(0.30; 1.59)	(0.21; 1.26)	(0.02; 12.57)	(0.01; 7.26)	(0.01; 6.30)	(0.00; 4.20)	(0.01; 9.01)	(0.01; 4.76)	(0.01; 14.41)	(0.00; 3.11)			(0.03; 19.30)
1.18	0.95	0.98	0.74	0.96	0.71	1.38	0.58	0.50	0.11	0.69	0.39	0.80	0.09			1.48
(0.86; 1.62)	(0.68; 1.31)	(0.73; 1.32)	(0.44; 1.22)	(0.68; 1.36)	(0.41; 1.22)	(0.59; 3.23)	(0.18; 1.83)	(0.16; 1.58)	(0.00; 2.55)	(0.20; 1.32)	(0.14; 1.68)	(0.11; 5.80)	(0.00; 1.80)			(0.41; 5.35)
1.12	0.90	0.93	0.70	0.91	0.67	1.31	0.95	0.86	0.19	1.19	1.13	1.38	0.16			2.56
(0.73; 1.70)	(0.59; 1.37)	(0.61; 1.40)	(0.39; 1.24)	(0.57; 1.46)	(0.36; 1.24)	(0.54; 3.20)	(0.58; 1.55)	(0.26; 2.90)	(0.01; 4.36)	(0.39; 3.63)	(0.39; 1.19)	(0.19; 10.04)	(0.01; 3.12)			(0.47; 9.30)
1.39	1.11	1.15	0.87	1.13	0.83	1.63	1.18	1.24	0.22	1.38	0.79	1.61	0.19			2.97
(0.93; 2.08)	(0.72; 1.72)	(0.74; 1.78)	(0.49; 1.54)	(0.71; 1.81)	(0.45; 1.52)	(0.67; 3.95)	(0.74; 1.88)	(0.70; 2.21)	(0.01; 5.23)	(0.37; 5.18)	(0.26; 2.43)	(0.22; 11.86)	(0.01; 3.67)			(0.80; 11.12)
3.16	2.54	2.62	1.97	2.58	1.90	3.71	2.68	2.83	2.28	6.22	3.55	7.23	0.85			13.38
(1.14; 8.78)	(0.93; 6.94)	(0.94; 7.34)	(0.66; 5.86)	(0.91; 7.36)	(0.62; 5.78)	(1.02; 13.47)	(0.93; 7.72)	(0.95; 8.43)	(0.76; 6.81)	(0.26; 1.16)	(0.16; 78.26)	(0.21; 245.61)	(0.01; 54.04)			(0.55; 324.31)
1.06	0.85	0.87	0.66	0.86	0.63	1.24	0.89	0.95	0.76	0.33	0.57	1.16	0.14			2.15
(0.64; 1.75)	(0.50; 1.42)	(0.52; 1.48)	(0.34; 1.26)	(0.52; 1.43)	(0.32; 1.24)	(0.49; 3.16)	(0.50; 1.59)	(0.51; 1.75)	(0.40; 1.45)	(0.11; 1.04)	(0.15; 9.05)	(0.01; 2.75)				(0.53; 8.69)
0.89	0.71	0.74	0.55	0.73	0.53	1.04	0.75	0.80	0.64	0.28	0.84	2.04	0.24			3.77
(0.65; 1.22)	(0.51; 1.00)	(0.52; 1.04)	(0.33; 0.92)	(0.50; 1.06)	(0.31; 0.92)	(0.45; 2.44)	(0.49; 1.16)	(0.51; 1.24)	(0.38; 1.06)	(0.10; 0.81)	(0.52; 1.84)	(0.30; 14.02)	(0.01; 4.44)			(1.13; 12.61)
0.88	0.71	0.73	0.55	0.72	0.53	1.04	0.75	0.79	0.64	0.28	0.84	0.99	0.12			1.85
(0.56; 1.39)	(0.44; 1.15)	(0.45; 1.20)	(0.30; 1.01)	(0.43; 1.21)	(0.28; 1.00)	(0.42; 2.57)	(0.43; 1.30)	(0.43; 1.46)	(0.35; 1.17)	(0.09; 0.85)	(0.43; 1.65)	(0.57; 1.72)	(0.00; 3.37)			(0.24; 14.34)
1.13	0.91	0.94	0.71	0.92	0.68	1.33	0.96	1.01	0.81	0.36	1.07	1.27	1.28			15.72
(0.72; 1.76)	(0.57; 1.44)	(0.58; 1.51)	(0.39; 1.29)	(0.55; 1.54)	(0.36; 1.27)	(0.54; 3.28)	(0.56; 1.64)	(0.55; 1.86)	(0.45; 1.48)	(0.12; 1.08)	(0.55; 2.10)	(0.74; 2.19)	(0.68; 2.41)			(0.78; 315.03)
1.27	1.02	1.05	0.79	1.03	0.76	1.49	1.08	1.14	0.91	0.40	1.20	1.43	1.12			2.97
(0.70; 2.29)	(0.56; 1.84)	(0.57; 1.94)	(0.39; 1.61)	(0.55; 1.96)	(0.36; 1.59)	(0.56; 3.98)	(0.56; 2.08)	(0.45; 1.86)	(0.12; 1.29)	(0.55; 2.60)	(0.73; 2.77)	(0.68; 3.01)	(0.59; 2.13)			2.97
0.75	0.60	0.62	0.47	0.61	0.45	0.88	0.64	0.67	0.54	0.24	0.71	0.84	0.66			0.59
(0.35; 1.61)	(0.28; 1.31)	(0.28; 1.36)	(0.20; 1.11)	(0.27; 1.37)	(0.19; 1.09)	(0.29; 2.63)	(0.28; 1.45)	(0.28; 1.60)	(0.23; 1.28)	(0.07; 0.85)	(0.28; 1.77)	(0.37; 1.92)	(0.35; 2.05)			0.59
0.72	0.57	0.59	0.45	0.58	0.43	0.84	0.61	0.64	0.51	0.23	0.68	0.80	0.61			0.95
(0.45; 1.12)	(0.36; 0.92)	(0.36; 0.97)	(0.26; 0.76)	(0.35; 0.98)	(0.23; 0.81)	(0.34; 2.08)	(0.35; 1.05)	(0.35; 1.18)	(0.28; 0.94)	(0.07; 0.69)	(0.34; 1.33)	(0.46; 1.39)	(0.43; 1.53)			0.95
0.54	0.43	0.45	0.34	0.44	0.32	0.63	0.46	0.48	0.39	0.17	0.51	0.61	0.48			0.72
(0.38; 0.77)	(0.29; 0.64)	(0.31; 0.65)	(0.20; 0.58)	(0.29; 0.68)	(0.18; 0.57)	(0.27; 1.50)	(0.29; 0.72)	(0.28; 0.82)	(0.23; 0.66)	(0.06; 0.50)	(0.28; 0.94)	(0.38; 0.97)	(0.34; 1.08)			0.72
																0.75
																EGM

Fig. 4 RRs for efficacy (lower triangle) and safety (upper triangle) with their 95% CIs derived from network meta-analysis of 19 AF strategies in the full network colored by certainty of evidence assessed for each comparison with CINeMA and classified in high (in green), moderate (in blue), low (in yellow) and very low (in red). Empty cells correspond to comparisons not available for the safety outcome. RRs lower than 1 favor the treatment in the column for both outcomes. Abbreviations: Bi, bi-atrial; comb, combination; EGM, electrocardiogram; GP, ganglia plexi; mod, modification; LAA, left atrial appendage; RDN, renal denervation; RR, risk ratio; step, stepwise ablation; sub, substrate; SVC, superior vena cava; trig, trigger

with stand-alone PVI (Fig. 3c and Additional file 7 Table S3).

According to the *P*-scores, the highest-ranked treatments for efficacy were PVI in combination with adjunct ablation (Additional file 7, Fig. S1).

When an additive CNMA model was employed (Additional file 8, Figs. S1-4), very small differences concerning the standard NMA model were identified, suggesting that no specific singular component is driving the total effect

of treatments used in combination. Full results and further explanation of the CNMA model used can be found in Additional file 8, Figs. S1-4.

Assessment of heterogeneity, incoherence, and small-study effects

There was evidence of moderate heterogeneity in the network ($\tau^2=0.087$) for efficacy and procedural time ($\tau^2=0.092$), while safety heterogeneity was estimated at

zero. The design-by-treatment interaction model and the side-splitting method did not suggest statistical incoherence for any outcome (Additional file 9, Tables S1-S2, Figs. S1-S3). The comparison-adjusted funnel plots appeared quite symmetrical, suggesting the absence of important small-study effects for all the outcomes (Additional file 10, Figs. S1-S3).

Subgroup, meta-regression, and sensitivity analyses

Subgroup analyses did not reveal any noteworthy differences in treatment effects for the two primary outcomes (Additional file 11, analyses 1–6). In addition, when examining the possible impact of effect modifiers with meta-regressions, all coefficients were non-significant and close to zero (Additional file 12, Table S1), with the exception for hypertension, for which a mild significant effect was observed. This is likely due to the extra variability observed in the distribution of hypertension across comparisons (Additional file 5). Still, age and presence of CAD resulted in a 44% and 80% reduction of heterogeneity, respectively.

The sensitivity analyses performed excluding studies with a high risk of bias, studies with patients with PAF, non-irrigated catheters, and the RDN technic did not result in any noteworthy change in the risk of AF recurrence or AF complications (Additional file 13, analyses 1–4).

A sensitivity analysis excluding studies with a PAF-only population (Additional file 13, analysis 3) showed that the addition of lines compared to PVI alone remained more efficient in this population (RR: 0.77, CI: 0.63–0.95). However, PVI combined with RDN lost its statistical superiority compared with PVI alone marginally (RR: 0.59, CI: 0.34–1.03). The subgroup analysis on the type of AF (Additional file 11, analysis 5) [89–99] showed that in studies with PAF-only patients none of the CA strategies outperformed PVI-alone in efficacy.

In order to sum up our results, we performed a sensitivity analysis summing the 19 categories to 6 larger ones (i.e., PVI, PVI and additional lines or substrate modification, PVI and EGM based approach, PVI and combination of substrate modification and EGM based approach, PVI and autonomic modification, and non-PVI strategies). The results of this analysis showed that PVI combined with additional lines or substrate modification, PVI and EGM based approach, and PVI and autonomic modification were more efficacious than PVI alone (RR: 0.81, CI: 0.7–0.93; RR: 0.81, CI: 0.67–0.97; RR: 0.62, CI: 0.46–0.83, respectively). PVI was more efficient than non-PVI strategies (RR: 1.47, CI: 1.18–1.83) (Additional file 13, analysis 6).

Another sensitivity analysis including AADs as comparing arm was performed. This analysis added another

11 RCTs to the 67 of the main analysis, (i.e., in total RCTs) involving 11,248 patients. In accordance with the other sensitivity analyses, this did not result in any important change in the main outcome. Additionally, it revealed that CA strategies including PVI, either as a stand-alone treatment or in combination with other complimentary ablation strategies, were associated with a statistically lower risk of recurrence when compared with ADDs (RRs range from 0.16 (CI: 0.06, 0.47) to 0.47 (CI: 0.32, 0.71) (Additional files 6 and 13).

Overall credibility of evidence

The CINeMA evaluation suggested that the confidence in the full body of evidence was low for most comparisons both in the efficacy and safety network, with the efficacy network containing a larger proportion of comparisons rated as moderate confidence. Reasons for downgrading to moderate or low certainty were mainly related to the presence of high concerns in imprecision and heterogeneity. This is generally expected in NMAs of non-pharmacological interventions. More details and the specific rules deployed for downgrading are provided in Additional file 14, Tables S1-2.

Discussion

Catheter ablation has been established as the most effective method for rhythm and symptom control in AF patients [100, 101]. Different strategies are continuously emerging to optimize ablation outcomes. Yet, a lack of agreement about the most effective CA strategy [102] is evident. To address this, we modeled a Network Meta-Analysis after scrutinizing available literature for different CA strategies. In this novel approach, 67 RCTs involving close to 10,000 patients qualified to shed light on different CA strategies with special regard to efficacy and safety.

The foremost findings of this NMA were that: a. PVI with additional sympathetic modulation and PVI with the addition of extra lines seemed to be superior compared to PVI alone, b. There were no differences in safety between different CA-strategies, c. non-PVI strategies were not associated with a better outcome when compared to strategies including PVI and d. All CA strategies that include PVI were superior to AADs with regards to efficacy.

Differences in efficacy between different CA strategies

PVI has proved to be an effective treatment strategy for AF patients to control symptoms. However, the AF population is heterogeneous and for a subset of patients, PVI alone is not sufficient.

As a result, various treatment hypotheses have evolved to different ablation strategies. The rationale for these

strategies has support from previous reports that are in clinical use. When summarized, PVI has become the cornerstone for AF ablation, but additional strategies are often used, especially in patients with non-PAF.

The value of additional ablation has been questioned, especially since the publication of the STAR AF 2 study [4], showing the lack of benefit associated with additional ablation. A possible explanation for the results could be that more extensive ablation may cause new areas of arrhythmogenesis. That is, unnecessary ablation and incomplete lines may increase the risk for AF recurrence or atrial tachycardia after the procedure [4]. However, the success of PVI as a stand-alone treatment remains limited, especially in patients with non-PAF [1]. Summarizing our results from evaluating more than 24 RCTs including PVI in combination with additional lines, PVI is a more effective therapy than AADs [101], and no less, there is support for completing this approach with additional lines to enhance the efficacy of the procedure without hampering safety. A sensitivity analysis excluding RCTs with only PAF patients confirmed that the addition of lines to PVI is more efficacious to PVI alone in this category of patients (Additional file 13, analysis 3). These findings are supported by a newly published NMA focusing only on patients with persistent AF [103]. However, in a subgroup analysis (Additional file 11, analysis 5) including only studies with a PAF population, no strategy outperformed PVI alone in efficacy. However, the number of studies in this subgroup analysis was limited, and the result can depend on the lack of power.

Isolation of the pulmonary veins has always been the focus of the CA strategies [94, 104]. Thus, it is not surprising that non-PVI strategies were not as efficient as PVI in this NMA, consistent with previous studies [4, 68, 105]. However, this NMA also showed that adding complementary therapies to PVI, such as GP ablation [52], RDN [77], or performing additional ablation [28, 85] can increase procedural efficacy.

Our results seem plausible with regards to what is known. The Cox/maze procedure is a very effective treatment option for patients with AF undergoing thoracic surgery [106]. It would therefore be reasonable that ablation with bi-atrial modification in combination with PVI is effective. However, this result should be treated with caution as there was only one small study performed before 2011 [27] that included this treatment option, thus the risk of bias is high.

Moreover, RDN and GP ablation as methods of adrenergic modulation in patients with AF have been used for more than 10 years [51, 72]. Research has shown that RDN improves AF outcome, possibly through better blood pressure control and a direct antiarrhythmic effect mediated by sympatholysis [58, 77]. Ganglia plexi

ablation as a complementary therapy to PVI can improve CA ablation's outcome by a more complete autonomic denervation and possibly by ablation of complex electrical activity areas located at the ablated parts of the left atrium [51, 52].

The results of our main analysis are also in line with a sensitivity analysis (Additional file 13, analysis 6) summing up the 19 different strategies to 6. This analysis showed that PVI with additional ablation with either additional lines, substrate modification, or by following EGM-based strategy, or by employing an autonomic modification is more efficient than PVI alone without any costs in safety.

Safety outcome

Complications are uncommon following the CA of AF. Nevertheless, they remain a major concern. The overall incidence of reported complications was <5%, with a death rate of <1%, in line with previous findings [107, 108]. This confirms that CA of AF is a relatively safe procedure, but complication rates are not trivial and should remind us of the importance of a careful selection of patients for CA of AF [109].

Additionally, the complication rates remained low regardless of the CA strategy followed. This finding is of great importance, as the choice of strategy can focus more on patient's needs than on the fear of complications of more complex procedures. It is also important to remember that most RCTs are performed by high volume academic centers, which can lead to underestimation of the complication risk, especially in more complex procedures [107, 109].

Procedural time

The procedural time is an aspect that must be taken into consideration concerning the CA of AF, especially when comparing procedures with similar efficacy. This NMA confirms that PVI in combination with supplementary therapies, in particular PVI in combination with additional lines and/or EGM approach, can be more time-consuming.

CA strategies compared with AADs

In the sensitivity analyses including also AADs as comparator arm, we identified 11 additional RCTs (78 RCTs in total) (Additional file 13, analysis 5). The results showed that regardless of the CA strategy used, except for non-PVI strategies, CA is more effective compared with ADDs. Furthermore, when PVI is combined with adjuvant ablation therapies the results are even better compared with AADs [90]. Our results are in agreement with more recent studies [100] and meta-analyses [101] comparing CA in general [110] or a specific CA strategy

with AADs [94]. Nonetheless, these results should be treated with caution due to concerns about transitivity, i.e., comparison of an invasive strategy with a drug treatment (Additional file 6).

Strengths and limitations

A major strength of this NMA is that it is the first of its kind and extent concerning this topic. With regards to the generalizability of this NMA, patients included in the original studies are assumed to have been sampled from the same theoretical population. However, efficacy is highly dependent on the monitoring strategy employed in the original studies. Thus, perceived differences, particularly between strategies tested in a small number of studies, may be driven by differences in monitoring devices, rather than the ablation strategy. Differences in the type of AF (PAF, non-PAF, or mixed), the length of the blanking period between studies, and the use of AADs after CA of AF can also add to the variability of the results. Furthermore, our long temporal period of inclusion and the different ways used for measuring outcomes (efficacy, safety, and procedural time) between studies may have an impact on the results of our analyses. Nevertheless, the additional analyses that aimed to capture these differences across studies provided similar results. In conclusion, we believe that our results can be generalized since we included RCTs with both PAF and non-PAF patients, using different ablation strategies and various energy sources, supporting applicability to real-world scenarios and clinical practice.

The strict definition of > 30 s of arrhythmia on monitoring is under much debate and can indeed be questioned as a meaningful endpoint for catheter ablation. However, this has been the endpoint used in the original RCTs. Sixteen percent of RCTs were judged to have a high risk of bias. This observation was mainly due to blinding issues, as the operator could not be blinded in the original studies, owing to the nature of the study. Further, the inclusion of RCTs with a high risk of biased data increases the risk of biased inferences. Still, the sensitivity analysis excluding these studies did not change the results. Finally, the nature of the intervention could impose heterogeneity as its efficacy may depend on unmeasurable characteristics.

Conclusions

In the present NMA, PVI in combination with additional ablation therapy such as autonomic modulation by GP ablation or RDN and additional lines seem to add efficacy when compared to PVI alone. These CA strategies could be considered to yield higher efficacy, without hampering safety. Additionally, CA seems to be superior to AADs apart from non-PVI strategies. This is the first study to

provide decision-makers with robust, comprehensive, and comparative evidence about the efficacy and safety of different CA strategies that reflect the available evidence.

Abbreviations

AAD: Antiarrhythmic drug; AF: Atrial fibrillation; AT: Atrial tachycardia; Bi: Bi-atrial; CA: Catheter ablation; CAD: Coronary artery disease; CInEMA: Confidence in Network-Meta Analysis; CNMA: Component network meta-analysis; Comb: Combination; EGM: Electrocardiogram; GP: Ganglia plexi; LAA: Left atrial appendage; MD: Mean difference; Mod: Modification; NMA: Network Meta-analysis; PAF: Paroxysmal atrial fibrillation; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; PVI: Pulmonary vein isolation; RCT: Randomized control study; RDN: Renal denervation; RoB: Risk of bias; RR: Risk ratio; SHD: Structural heart disease; Step: Stepwise; Sub: Substrate; SVC: Superior vena cava; Trig: Trigger.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12916-022-02385-2>.

Additional file 1. PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis.

Additional file 2. Search Strategy (PubMed, Cochrane central database of clinical trials, Web of Science).

Additional file 3. Risk of bias assessment, Table S1- [Risk of Bias assessment with domains (67 RCT of the main analysis)].

Additional file 4. Characteristics and list of RCTs included in the network meta-analysis, Table S1- [Characteristics of the 67 RCTs included in the network meta-analysis].

Additional file 5. Deviations from the original protocol.

Additional file 6. Evaluation of transitivity and additional transitivity boxplots for all comparisons, including also comparisons with AADs: (age distribution, male distribution, hypertension distribution, SHD distribution, CAD distribution, left atrial dimension distribution, left ventricular ejection fraction distribution).

Additional file 7. Additional results from pairwise and network meta-analysis. Tables S1-S3, Fig. S1. Table S1- [Relative risk ratios estimated from the network meta-analysis (lower triangle) and pairwise meta-analysis (upper triangle) comparing every pair of the 20 interventions with respect to efficacy.], Table S2- [Relative risk ratios estimated from the network meta-analysis (lower triangle) and pairwise meta-analysis (upper triangle) comparing every pair of the 17 interventions with respect to safety.], Table S3- [Relative risk ratios estimated from the network meta-analysis (lower triangle) and pairwise meta-analysis (upper triangle) comparing every pair of the 18 interventions with respect to procedural time.], Fig. S1- [*P*-scores for the two primary outcomes].

Additional file 8. Results from component network meta-analysis.

Figures S1-S4. Figure S1- [Network plots from CNMA model for efficacy (a), safety (b) and procedural time (c). Each treatment is represented as a node and an edge exists between two nodes if direct trial evidence is available. The size of each node is proportional to the number of patients involved in each treatment across all trials, while the size of the edges is proportional to the number of studies available in the corresponding comparison]. Figure S2- [Component network forest plots of relative risk ratios for efficacy]. Figure S3- [Component network forest plots of relative risk ratios for safety]. Figure S4- [Component network forest plots of relative risk ratios for procedural time].

Additional file 9. Evaluation of inconsistency. Tables S1-S2, Figures S1-S3. Table S1- [Design-by-treatment interaction test, with global *p*-value, Q statistic and degrees of freedom for each outcome]. Table S2- [Results of the inconsistency net-split approach for all outcomes. For each comparison the direct and indirect estimates are provided along with the respective *z*-values and *p*-values of differences. *P*-values < 0.10 indicate significant

disagreement between direct and indirect evidence (in red)). Figure S1- [Forest plots of the net-split approach separating direct and indirect evidence for efficacy]. Figure S2- [Forest plots of the net-split approach separating direct and indirect evidence for safety]. Figure S3- [Forest plots of the net-split approach separating direct and indirect evidence for procedural time].

Additional file 10. Investigation of small-study effects. Figures S1-S3. Figure S1- [Comparison-adjusted funnel plot for efficacy]. Figure S2- [Comparison-adjusted funnel plot for safety]. Figure S3- [Comparison-adjusted funnel plot for procedural time].

Additional file 11. Subgroup analyses. 1 Depending on AF detection device. 2 Depending on AAD or reablation allowance during the follow-up. 3 Depending on follow-up duration. 4 Depending on publication year. 5. Subgroup analysis on the type of AF included in the original studies (PAF, non-PAF, and mixed). 6 Subgroup analysis depending on the blanking period (cut-off 8 weeks).

Additional file 12. Meta-regression. Table S1- [Meta-regression coefficients, alongside Credible Intervals and percentage reduction in heterogeneity for efficacy outcome].

Additional file 13. Sensitivity analyses. 1 Excluding high risk of bias RCTs (57 RCTs left). 2 Excluding RCTs with Renal Denervation (RDN) treatment (64 RCTs left). 3 Excluding RCTs with only PAF patients (42 RCTs left). 4 Excluding catheter 8mm, 8mm plus 3.5mm irrigated, 8mm and 4mm irrigated (55 RCTs left). 5 INCLUDING RCTs with antiarrhythmic drugs (AADs) as control arm (78 total RCTs). 6. Sensitivity analysis with reduced categories.

Additional file 14. Overall quality of the evidence with CINeMA assessment. Tables S1-S2. Table S1- [Confidence rating for efficacy using CINeMA]. Table S2- [Confidence rating for safety using CINeMA].

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Authors' contributions

Study design, EC, AC, SM, and ED; methodology, E.C., S.M., and A.C.; data curation, E.C., D.T., S.M., A.C., and E.D.; formal analysis, S.M. and A.C.; validation, A.C.; E.C.; L.O.K., and N.F.; writing—original draft, E.C., S.M., and H.A. writing—review and editing, E.C., S.M., L.O.K., A.H.J., I.L., H.A., A.P.A., N.F., S.S., J.S., D.T., E.D., K.R., and A.C. All authors commented on different versions of the article. The authors read and approved the final manuscript.

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Availability of data and materials

All data analyzed in this study are available in this published article and supplementary material. The references of articles included in this network meta-analysis are presented on the reference list and the background data of the original studies in the Supplementary Material.

Declarations

Ethics approval and consent to participate

Not applicable. This study is a network meta-analysis, of previously collected data, thus additional ethical approval was not required.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

- Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5):373–498.
- Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998;339(10):659–66.
- Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. *Heart Rhythm*. 2017;14(10):e445–94.
- Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med*. 2015;372(19):1812–22.
- Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med*. 2013;159(2):130–7.
- Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet*. 2007;369(9557):201–7.
- Gupta D, Potter T, Disher T, Eaton K, Goldstein L, Patel L, Grima D, Velleca M, Costa G. Comparative effectiveness of catheter ablation devices in the treatment of atrial fibrillation: a network meta-analysis. *J Comp Eff Res*. 2020;9(2):115–26.
- Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
- Charitakis E, Karlsson LO, Rizas K, Almroth H, Hassel Jonsson A, Schweiler J, Sideris S, Tsartsalis D, Dragioti E, Chaimani A. Comparing efficacy and safety in catheter ablation strategies for atrial fibrillation: protocol of a network meta-analysis of randomised controlled trials. *BMJ Open*. 2020;10(11):e041819.
- Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:4898.
- Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. *BMC Med*. 2013;11:159.
- Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods*. 2012;3(2):80–97.

13. Rucker G. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods*. 2012;3(4):312–24.
14. netmeta: Network Meta-Analysis using Frequentist Methods. <https://github.com/guido-s/netmeta> <http://meta-analysis-with-r.org>.
15. Rucker G, Petropoulou M, Schwarzer G. Network meta-analysis of multi-component interventions. *Biom J*. 2020;62(3):808–21.
16. Welton NJ, Caldwell DM, Adamopoulos E, Vedhara K. Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. *Am J Epidemiol*. 2009;169(9):1158–65.
17. Rucker G, Schwarzer G. Resolve conflicting rankings of outcomes in network meta-analysis: partial ordering of treatments. *Res Synth Methods*. 2017;8(4):526–36.
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–60.
19. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med*. 2010;29(7–8):932–44.
20. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods*. 2012;3(2):98–110.
21. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS ONE*. 2013;8(10):e76654.
22. Papakonstantinou T, Nikolakopoulou A, Higgins JPT, Egger M, Salanti G. CINeMA: software for semiautomated assessment of the confidence in the results of network meta-analysis. *Campbell Syst Rev*. 2020;16(1):e1080.
23. Ammar-Busch S, Bourier F, Reents T, Semmler V, Telishevska M, Kathan S, Hofmann M, Hessling G, Deisenhofer I. Ablation of complex fractionated electrograms with or without ADDitional LINEar lesions for persistent atrial fibrillation (The ADLINE Trial). *J Cardiovasc Electrophysiol*. 2017;28(6):636–41.
24. Arbelo E, Guiu E, Ramos P, Bisbal F, Borrás R, Andreu D, Tolosana JM, Berrueto A, Brugada J, Mont L. Benefit of left atrial roof linear ablation in paroxysmal atrial fibrillation: a prospective, randomized study. *J Am Heart Assoc*. 2014;3(5):e000877.
25. Atienza F, Almendral J, Ormaetxe JM, Moya A, Martínez-Alday JD, Hernández-Madrid A, Castellanos E, Arribas F, Arias MA, Tercedor L, et al. Comparison of radiofrequency catheter ablation of drivers and circumferential pulmonary vein isolation in atrial fibrillation: a non-inferiority randomized multicenter RADAR-AF trial. *J Am Coll Cardiol*. 2014;64(23):2455–67.
26. Bassiouny M, Saliba W, Hussein A, Rickard J, Diab M, Aman W, Dresing T, Callahan Tt, Bhargava M, Martin DO, et al. Randomized study of persistent atrial fibrillation ablation: ablate in sinus rhythm versus ablate complex-fractionated atrial electrograms in atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2016;9(2):e003596.
27. Calo L, Lamberti F, Loricchio ML, De Ruvo E, Colivicchi F, Bianconi L, Pandozi C, Santini M. Left atrial ablation versus biatrial ablation for persistent and permanent atrial fibrillation: a prospective and randomized study. *J Am Coll Cardiol*. 2006;47(12):2504–12.
28. Chauhan VS, Verma A, Nayyar S, Timmerman N, Tomlinson G, Porta-Sanchez A, Gizurarson S, Haldar S, Suszko A, Ragot D, et al. Focal source and trigger mapping in atrial fibrillation: randomized controlled trial evaluating a novel adjunctive ablation strategy. *Heart Rhythm*. 2020;17(5 Pt A):683–91.
29. Chen M, Yang B, Chen H, Ju W, Zhang F, Tse HF, Cao K. Randomized comparison between pulmonary vein antral isolation versus complex fractionated electrogram ablation for paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. 2011;22(9):973–81.
30. Chilukuri K, Scherr D, Dalal D, Cheng A, Spragg D, Nazarian S, Barcelon BD, Marine JE, Calkins H, Henrikson CA. Conventional pulmonary vein isolation compared with the “box isolation” method: a randomized clinical trial. *J Interv Card Electrophysiol*. 2011;32(2):137–46.
31. Corrado A, Bonso A, Madalosso M, Rossillo A, Themistoclakis S, Di Biase L, Natale A, Raviele A. Impact of systematic isolation of superior vena cava in addition to pulmonary vein antrum isolation on the outcome of paroxysmal, persistent, and permanent atrial fibrillation ablation: results from a randomized study. *J Cardiovasc Electrophysiol*. 2010;21(1):1–5.
32. Da Costa A, Levallois M, Romeyer-Bouchard C, Bisch L, Gate-Martinet A, Isaac K. Remote-controlled magnetic pulmonary vein isolation combined with superior vena cava isolation for paroxysmal atrial fibrillation: a prospective randomized study. *Arch Cardiovasc Dis*. 2015;108(3):163–71.
33. Deisenhofer I, Estner H, Reents T, Fichtner S, Bauer A, Wu J, Kolb C, Zrenner B, Schmitt C, Hessling G. Does electrogram guided substrate ablation add to the success of pulmonary vein isolation in patients with paroxysmal atrial fibrillation? A prospective, randomized study. *J Cardiovasc Electrophysiol*. 2009;20(5):514–21.
34. Di Biase L, Elayi CS, Fahmy TS, Martin DO, Ching CK, Barrett C, Bai R, Patel D, Khaykin Y, Hongo R, et al. Atrial fibrillation ablation strategies for paroxysmal patients: randomized comparison between different techniques. *Circ Arrhythm Electrophysiol*. 2009;2(2):113–9.
35. Dixit S, Gerstenfeld EP, Ratcliffe SJ, Cooper JM, Russo AM, Kimmel SE, Callans DJ, Lin D, Verdino RJ, Patel VV, et al. Single procedure efficacy of isolating all versus arrhythmogenic pulmonary veins on long-term control of atrial fibrillation: a prospective randomized study. *Heart Rhythm*. 2008;5(2):174–81.
36. Dixit S, Marchlinski FE, Lin D, Callans DJ, Bala R, Riley MP, Garcia FC, Hutchinson MD, Ratcliffe SJ, Cooper JM, et al. Randomized ablation strategies for the treatment of persistent atrial fibrillation: RASTA study. *Circ Arrhythm Electrophysiol*. 2012;5(2):287–94.
37. Dong JZ, Sang CH, Yu RH, Long DY, Tang RB, Jiang CX, Ning M, Liu N, Liu XP, Du X, et al. Prospective randomized comparison between a fixed “2C3L” approach vs. stepwise approach for catheter ablation of persistent atrial fibrillation. *Europace*. 2015;17(12):1798–806.
38. Elayi CS, Verma A, Di Biase L, Ching CK, Patel D, Barrett C, Martin D, Rong B, Fahmy TS, Khaykin Y, et al. Ablation for longstanding permanent atrial fibrillation: results from a randomized study comparing three different strategies. *Heart Rhythm*. 2008;5(12):1658–64.
39. Estner HL, Hessling G, Biegler R, Schrieck J, Fichtner S, Wu J, Jilek C, Zrenner B, Ndrepepa G, Schmitt C, et al. Complex fractionated atrial electrogram or linear ablation in patients with persistent atrial fibrillation—a prospective randomized study. *Pacing Clin Electrophysiol*. 2011;34(8):939–48.
40. Fassini G, Riva S, Chiodelli R, Trevisi N, Berti M, Carbuicchio C, Maccabelli G, Giraldi F, Bella PD. Left mitral isthmus ablation associated with PV Isolation: long-term results of a prospective randomized study. *J Cardiovasc Electrophysiol*. 2005;16(11):1150–6.
41. Faustino M, Pizzi C, Agricola T, Xhyheri B, Costa GM, Flacco ME, Capasso L, Cicolini G, Di Girolamo E, Leonzio L, et al. Stepwise ablation approach versus pulmonary vein isolation in patients with paroxysmal atrial fibrillation: randomized controlled trial. *Heart Rhythm*. 2015;12(9):1907–15.
42. Fichtner S, Hessling G, Ammar S, Reents T, Estner HL, Jilek C, Kathan S, Buchner M, Dillier R, Deisenhofer I. A prospective randomized study comparing isolation of the arrhythmogenic vein versus all veins in paroxysmal atrial fibrillation. *Clin Cardiol*. 2013;36(7):422–6.
43. Fink T, Schluter M, Heeger CH, Lemes C, Maurer T, Reissmann B, Riedl J, Rottner L, Santoro F, Schmidt B, et al. Stand-alone pulmonary vein isolation versus pulmonary vein isolation with additional substrate modification as index ablation procedures in patients with persistent and long-standing persistent atrial fibrillation: the randomized Alster-Lost-AF Trial (Ablation at St. Georg Hospital for long-standing persistent atrial fibrillation). *Circ Arrhythm Electrophysiol*. 2017;10(7):e005114.
44. Gaita F, Caponi D, Scaglione M, Montefusco A, Corleto A, Di Monte F, Coin D, Di Donna P, Giustetto C. Long-term clinical results of 2 different ablation strategies in patients with paroxysmal and persistent atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2008;1(4):269–75.
45. Gavin AR, Singleton CB, Bowyer J, McGavigan AD. Pulmonary venous isolation versus additional substrate modification as treatment for paroxysmal atrial fibrillation. *J Interv Cardiac Electrophysiol*. 2012;33(1):101–7.
46. Haissaguerre M, Sanders P, Hocini M, Hsu LF, Shah DC, Scavee C, Takahashi Y, Rotter M, Pasquie JL, Garrigue S, et al. Changes in atrial fibrillation cycle length and inducibility during catheter ablation and their relation to outcome. *Circulation*. 2004;109(24):3007–13.
47. Han SW, Shin SY, Im SI, Na JO, Choi CU, Kim SH, Kim JW, Kim EJ, Rha SW, Park CG, et al. Does the amount of atrial mass reduction improve clinical outcomes after radiofrequency catheter ablation for long-standing persistent atrial fibrillation? Comparison between linear ablation and defragmentation. *Int J Cardiol*. 2014;171(1):37–43.

48. Hocini M, Jais P, Sanders P, Takahashi Y, Rotter M, Rostock T, Hsu LF, Sacher F, Reuter S, Clemency J, et al. Techniques, evaluation, and consequences of linear block at the left atrial roof in paroxysmal atrial fibrillation: a prospective randomized study. *Circulation*. 2005;112(24):3688–96.
49. Kang KW, Pak HN, Park J, Park JG, Uhm JS, Joung B, Lee MH, Hwang C. Additional linear ablation from the superior vena cava to right atrial septum after pulmonary vein isolation improves the clinical outcome in patients with paroxysmal atrial fibrillation: prospective randomized study. *Europace*. 2014;16(12):1738–45.
50. Katritsis DG, Ellenbogen KA, Panagiotakos DB, Giazitzoglou E, Karabinos I, Papadopoulos A, Zambartas C, Anagnostopoulos CE. Ablation of superior pulmonary veins compared to ablation of all four pulmonary veins. *J Cardiovasc Electrophysiol*. 2004;15(6):641–5.
51. Katritsis DG, Giazitzoglou E, Zografos T, Pokushalov E, Po SS, Camm AJ. Rapid pulmonary vein isolation combined with autonomic ganglia modification: a randomized study. *Heart Rhythm*. 2011;8(5):672–8.
52. Katritsis DG, Pokushalov E, Romanov A, Giazitzoglou E, Siontis GC, Po SS, Camm AJ, Ioannidis JP. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. *J Am Coll Cardiol*. 2013;62(24):2318–25.
53. Khaykin Y, Skanes A, Champagne J, Themistoclakis S, Gula L, Rossillo A, Bonso A, Raviele A, Morillo CA, Verma A, et al. A randomized controlled trial of the efficacy and safety of electroanatomic circumferential pulmonary vein ablation supplemented by ablation of complex fractionated atrial electrograms versus potential-guided pulmonary vein antrum isolation guided by intracardiac ultrasound. *Circ Arrhythm Electrophysiol*. 2009;2(5):481–7.
54. Kim JS, Shin SY, Na JO, Choi CU, Kim SH, Kim JW, Kim EJ, Rha SW, Park CG, Seo HS, et al. Does isolation of the left atrial posterior wall improve clinical outcomes after radiofrequency catheter ablation for persistent atrial fibrillation?: A prospective randomized clinical trial. *Int J Cardiol*. 2015;181:277–83.
55. Kim TH, Uhm JS, Kim JY, Joung B, Lee MH, Pak HN. Does additional electrogram-guided ablation after linear ablation reduce recurrence after catheter ablation for longstanding persistent atrial fibrillation? A prospective randomized study. *J Am Heart Assoc*. 2017;6(2):e004811.
56. Kim TH, Park J, Park JK, Uhm JS, Joung B, Hwang C, Lee MH, Pak HN. Linear ablation in addition to circumferential pulmonary vein isolation (Dallas lesion set) does not improve clinical outcome in patients with paroxysmal atrial fibrillation: a prospective randomized study. *Europace*. 2015;17(3):388–95.
57. Kircher S, Arya A, Altmann D, Rolf S, Bollmann A, Sommer P, Dagres N, Richter S, Breithardt OA, Dinov B, et al. Individually tailored vs. standardized substrate modification during radiofrequency catheter ablation for atrial fibrillation: a randomized study. *Europace*. 2018;20(11):1766–75.
58. Kiuchi MG, Chen S, Hoye NA, Purerfellner H. Pulmonary vein isolation combined with spironolactone or renal sympathetic denervation in patients with chronic kidney disease, uncontrolled hypertension, paroxysmal atrial fibrillation, and a pacemaker. *J Interv Card Electrophysiol*. 2018;51(1):51–9.
59. Lee KN, Choi JJ, Kim YG, Oh SK, Kim DH, Lee DI, Roh SY, Ahn JH, Shim J, Park SW, et al. Comparison between linear and focal ablation of complex fractionated atrial electrograms in patients with non-paroxysmal atrial fibrillation: a prospective randomized trial. *Europace*. 2019;21(4):598–606.
60. Lee KN, Roh SY, Baek YS, Park HS, Ahn J, Kim DH, Lee DI, Shim J, Choi JJ, Park SW, et al. Long-term clinical comparison of procedural end points after pulmonary vein isolation in paroxysmal atrial fibrillation: elimination of nonpulmonary vein triggers versus noninducibility. *Circ Arrhythm Electrophysiol*. 2018;11(2):e005019.
61. Lee JM, Shim J, Park J, Yu HT, Kim TH, Park JK, Uhm JS, Kim JB, Joung B, Lee MH, et al. The electrical isolation of the left atrial posterior wall in catheter ablation of persistent atrial fibrillation. *JACC Clin Electrophysiol*. 2019;5(11):1253–61.
62. Lim TW, Koay CH, See VA, McCall R, Chik W, Zecchin R, Byth K, Seow SC, Thomas L, Ross DL, et al. Single-ring posterior left atrial (box) isolation results in a different mode of recurrence compared with wide antral pulmonary vein isolation on long-term follow-up: longer atrial fibrillation-free survival time but similar survival time free of any atrial arrhythmia. *Circ Arrhythm Electrophysiol*. 2012;5(5):968–77.
63. Lin YJ, Chang SL, Lo LW, Hu YF, Suenari K, Li CH, Chao TF, Chung FP, Liao JN, Hartono B, et al. A prospective, randomized comparison of modified pulmonary vein isolation versus conventional pulmonary vein isolation in patients with paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. 2012;23(11):1155–62.
64. Liu X, Dong J, Mavrakis HE, Hu F, Long D, Fang D, Yu R, Tang R, Hao P, Lu C, et al. Achievement of pulmonary vein isolation in patients undergoing circumferential pulmonary vein ablation: a randomized comparison between two different isolation approaches. *J Cardiovasc Electrophysiol*. 2006;17(12):1263–70.
65. Mamchur SE, Mamchur IN, Khomenko EA, Bokhan NS, Scherbinina DA. “Electrical exclusion” of a critical myocardial mass by extended pulmonary vein antrum isolation for persistent atrial fibrillation treatment. *Interv Med Appl Sci*. 2014;6(1):31–9.
66. Mun HS, Joung B, Shim J, Hwang HJ, Kim JY, Lee MH, Pak HN. Does additional linear ablation after circumferential pulmonary vein isolation improve clinical outcome in patients with paroxysmal atrial fibrillation? Prospective randomised study. *Heart*. 2012;98(6):480–4.
67. Nuhric JM, Steven D, Berner I, Rostock T, Hoffmann B, Servatius H, Sultan A, Luker J, Treszl A, Wegscheider K, et al. Impact of biatrial defragmentation in patients with paroxysmal atrial fibrillation: results from a randomized prospective study. *Heart Rhythm*. 2014;11(9):1536–42.
68. Oral H, Chugh A, Good E, Igic P, Elmouchi D, Tschopp DR, Reich SS, Bogun F, Pelosi F Jr, Morady F. Randomized comparison of encircling and nonencircling left atrial ablation for chronic atrial fibrillation. *Heart Rhythm*. 2005;2(11):1165–72.
69. Oral H, Scharf C, Chugh A, Hall B, Cheung P, Good E, Veerareddy S, Pelosi F Jr, Morady F. Catheter ablation for paroxysmal atrial fibrillation: segmental pulmonary vein ostial ablation versus left atrial ablation. *Circulation*. 2003;108(19):2355–60.
70. Pappone C, Manguso F, Vicedomini G, Gugliotta F, Santinelli O, Ferro A, Gulletta S, Sala S, Sora N, Paglino G, et al. Prevention of iatrogenic atrial tachycardia after ablation of atrial fibrillation: a prospective randomized study comparing circumferential pulmonary vein ablation with a modified approach. *Circulation*. 2004;110(19):3036–42.
71. Pappone C, Ciconte G, Vicedomini G, Mangual JO, Li W, Conti M, Giannelli L, Lipartiti F, McSpadden L, Ryu K, et al. Clinical outcome of electrophysiologically guided ablation for nonparoxysmal atrial fibrillation using a novel real-time 3-dimensional mapping technique: results from a prospective randomized trial. *Circ Arrhythm Electrophysiol*. 2018;11(3):e005904.
72. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Baranova V, Turov A, Shirokova N, Karaskov A, Mittal S, Steinberg JS. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. *J Am Coll Cardiol*. 2012;60(13):1163–70.
73. Pokushalov E, Romanov A, Katritsis DG, Artyomenko S, Shirokova N, Karaskov A, Mittal S, Steinberg JS. Ganglionated plexus ablation vs linear ablation in patients undergoing pulmonary vein isolation for persistent/long-standing persistent atrial fibrillation: a randomized comparison. *Heart Rhythm*. 2013;10(9):1280–6.
74. Pontoppidan J, Nielsen JC, Poulsen SH, Jensen HK, Walfridsson H, Pedersen AK, Hansen PS. Prophylactic cavotricuspid isthmus block during atrial fibrillation ablation in patients without atrial flutter: a randomized controlled trial. *Heart*. 2009;95(12):994–9.
75. Romanov A, Pokushalov E, Artemenko S, Yakubov A, Stenin I, Kretov E, Krestianinov O, Grazhdankin I, Risteski D, Karaskov A, et al. Does left atrial appendage closure improve the success of pulmonary vein isolation? Results of a randomized clinical trial. *J Interv Card Electrophysiol*. 2015;44(1):9–16.
76. Sawhney N, Anousheh R, Chen W, Feld GK. Circumferential pulmonary vein ablation with additional linear ablation results in an increased incidence of left atrial flutter compared with segmental pulmonary vein isolation as an initial approach to ablation of paroxysmal atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2010;3(3):243–8.
77. Steinberg JS, Shabanov V, Ponomarev D, Losik D, Ivanickiy E, Kropotkin E, Polyakov K, Ptaszynski P, Keweloh B, Yao CJ, et al. Effect of renal denervation and catheter ablation vs catheter ablation alone on atrial fibrillation recurrence among patients with paroxysmal atrial fibrillation

- and hypertension: the ERADICATE-AF randomized clinical trial. *JAMA*. 2020;323(3):248–55.
78. Verma A, Mantovan R, Macle L, De Martino G, Chen J, Morillo CA, Novak P, Calzolari V, Guerra PG, Nair G, et al. Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF): a randomized, multicentre, international trial. *Eur Heart J*. 2010;31(11):1344–56.
 79. Verma A, Patel D, Fany T, Martin DO, Burkhardt JD, Elayi SC, Lakkireddy D, Wazni O, Cummings J, Schweikert RA, et al. Efficacy of adjuvant anterior left atrial ablation during intracardiac echocardiography-guided pulmonary vein antrum isolation for atrial fibrillation. *J Cardiovasc Electrophysiol*. 2007;18(2):151–6.
 80. Vogler J, Willems S, Sultan A, Schreiber D, Luker J, Servatius H, Schaffer B, Moser J, Hoffmann BA, Steven D. Pulmonary vein isolation versus defragmentation: the CHASE-AF clinical trial. *J Am Coll Cardiol*. 2015;66(24):2743–52.
 81. Wang XH, Li Z, Mao JL, He B. A novel individualized substrate modification approach for the treatment of long-standing persistent atrial fibrillation: preliminary results. *Int J Cardiol*. 2014;175(1):162–8.
 82. Wang YL, Liu X, Tan HW, Zhou L, Jiang WF, Gu J, Liu YG. Evaluation of linear lesions in the left and right atrium in ablation of long-standing atrial fibrillation. *Pacing Clin Electrophysiol*. 2013;36(10):1202–10.
 83. Wang XH, Liu X, Sun YM, Shi HF, Zhou L, Gu JN. Pulmonary vein isolation combined with superior vena cava isolation for atrial fibrillation ablation: a prospective randomized study. *Europace*. 2008;10(5):600–5.
 84. Willems S, Klemm H, Rostock T, Brandstrup B, Ventura R, Steven D, Risius T, Lutomsky B, Meinertz T. Substrate modification combined with pulmonary vein isolation improves outcome of catheter ablation in patients with persistent atrial fibrillation: a prospective randomized comparison. *Eur Heart J*. 2006;27(23):2871–8.
 85. Wong KC, Paisey JR, Sopher M, Balasubramaniam R, Jones M, Qureshi N, Hayes CR, Ginks MR, Rajappan K, Bashir Y, et al. No benefit of complex fractionated atrial electrogram ablation in addition to circumferential pulmonary vein ablation and linear ablation: benefit of complex ablation study. *Circ Arrhythm Electrophysiol*. 2015;8(6):1316–24.
 86. Wynn GJ, Panikker S, Morgan M, Hall M, Waktare J, Markides V, Hussain W, Salukhe T, Modi S, Jarman J, et al. Biatrial linear ablation in sustained nonpermanent AF: results of the substrate modification with ablation and antiarrhythmic drugs in nonpermanent atrial fibrillation (SMAN-PAF) trial. *Heart Rhythm*. 2016;13(2):399–406.
 87. Yang B, Jiang C, Lin Y, Yang G, Chu H, Cai H, Lu F, Zhan X, Xu J, Wang X, et al. STABLE-SR (Electrophysiological substrate ablation in the left atrium during sinus rhythm) for the treatment of nonparoxysmal atrial fibrillation: a prospective, multicenter randomized clinical trial. *Circ Arrhythm Electrophysiol*. 2017;10(11):e005405.
 88. Yu HT, Shim J, Park J, Kim IS, Kim TH, Uhm JS, Joung B, Lee MH, Kim YH, Pak HN. Pulmonary vein isolation alone versus additional linear ablation in patients with persistent atrial fibrillation converted to paroxysmal type with antiarrhythmic drug therapy: a multicenter, prospective, randomized study. *Circ Arrhythm Electrophysiol*. 2017;10(6):e004915.
 89. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Konstad O, Pehrson S, Englund A, Hartikainen J, Mortensen LS, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med*. 2012;367(17):1587–95.
 90. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, Reddy M, Jais P, Themistoclakis S, Dello Russo A, et al. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. *Circulation*. 2016;133(17):1637–44.
 91. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, McDonagh TA, Underwood SR, Markides V, Wong T. A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol*. 2013;61(18):1894–903.
 92. Krittayaphong R, Raunggrattanaamporn O, Bhuripanyo K, Sriratanasathavorn C, Pooranawattanakul S, Punlee K, Kangkagate C. A randomized clinical trial of the efficacy of radiofrequency catheter ablation and amiodarone in the treatment of symptomatic atrial fibrillation. *J Med Assoc Thai*. 2003;86(Suppl 1):S8–16.
 93. Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi F Jr, Bates ER, Lehmann MH, Vicedomini G, Augello G, et al. Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med*. 2006;354(9):934–41.
 94. Packer DL, Kowal RC, Whealan KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol*. 2013;61(16):1713–23.
 95. Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, Paglino G, Mazzone P, Sora N, Greiss I, et al. A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. *J Am Coll Cardiol*. 2006;48(11):2340–7.
 96. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, Sugumar H, Lockwood SM, Stokes MB, Pathik B, et al. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. *J Am Coll Cardiol*. 2017;70(16):1949–61.
 97. Sohara H, Ohe T, Okumura K, Naito S, Hirao K, Shoda M, Kobayashi Y, Yamauchi Y, Yamaguchi Y, Kuwahara T, et al. HotBalloon ablation of the pulmonary veins for paroxysmal AF: a multicenter randomized trial in Japan. *J Am Coll Cardiol*. 2016;68(25):2747–57.
 98. Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G, Turco P, Pascotto P, Fazzari M, Vitale DF. Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). *Eur Heart J*. 2006;27(2):216–21.
 99. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, Bash D, Schweikert R, Brachmann J, Gunther J, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA*. 2005;293(21):2634–40.
 100. Andrade JG, Wells GA, Deyell MW, Bennett M, Essebag V, Champagne J, Roux JF, Yung D, Skanes A, Khaykin Y, et al. Cryoablation or drug therapy for initial treatment of atrial fibrillation. *N Engl J Med*. 2021;384(4):305–15.
 101. Asad ZUA, Yousif A, Khan MS, Al-Khatib SM, Stavarakis S. Catheter ablation versus medical therapy for atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2019;12(9):e007414.
 102. Kirchhof P, Calkins H. Catheter ablation in patients with persistent atrial fibrillation. *Eur Heart J*. 2017;38(1):20–6.
 103. Sagnetto A, Ballatore A, Gaita F, Scaglione M, De Ponti R, De Ferrari GM, Anselmino M. Comparative efficacy and safety of different catheter ablation strategies for persistent atrial fibrillation: a network meta-analysis of randomized clinical trials. *Eur Heart J Qual Care Clin Outcomes*. 2021;qcab066. <https://doi.org/10.1093/ehjqcco/qcab066>.
 104. Nattel S, Guasch E, Savelieva I, Cosio FG, Valverde I, Halperin JL, Conroy JM, Al-Khatib SM, Hess PL, Kirchhof P, et al. Early management of atrial fibrillation to prevent cardiovascular complications. *Eur Heart J*. 2014;35(22):1448–56.
 105. Sau A, Howard JP, Al-Aidarous S, Ferreira-Martins J, Al-Khayatt B, Lim PB, Kanagaratnam P, Whinnett ZI, Peters NS, Sikkil MB, et al. Meta-analysis of randomized controlled trials of atrial fibrillation ablation with pulmonary vein isolation versus without. *JACC Clin Electrophysiol*. 2019;5(8):968–76.
 106. Raanani E, Albage A, David TE, Yau TM, Armstrong S. The efficacy of the Cox/maze procedure combined with mitral valve surgery: a matched control study. *Eur J Cardiothorac Surg*. 2001;19(4):438–42.
 107. Loring Z, Holmes DN, Matsouka RA, Curtis AB, Day JD, Desai N, Ellenbogen KA, Feld GK, Fonarow GC, Frankel DS, et al. Procedural patterns and safety of atrial fibrillation ablation: findings from get with the guidelines-atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2020;13(9):e007944.
 108. Arbelo E, Brugada J, Blomstrom-Lundqvist C, Laroche C, Kautzner J, Pokushalov E, Raatikainen P, Efremidis M, Hindricks G, Barrera A, et al. Contemporary management of patients undergoing atrial fibrillation ablation: in-hospital and 1-year follow-up findings from the ESC-EHRA atrial fibrillation ablation long-term registry. *Eur Heart J*. 2017;38(17):1303–16.
 109. Tripathi B, Arora S, Kumar V, Abdelrahman M, Lahewala S, Dave M, Shah M, Tan B, Savani S, Badheka A, et al. Temporal trends of in-hospital complications associated with catheter ablation of atrial fibrillation in the United States: an update from Nationwide Inpatient Sample database (2011–2014). *J Cardiovasc Electrophysiol*. 2018;29(5):715–24.
 110. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnsen TD, Poole JE, Noseworthy PA, Rosenberg YD, Jeffries N, Mitchell LB, et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA*. 2019;321(13):1261–74.

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