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COMPREHENSIVE REVIEWS

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Systematic review and network meta-analysis of atrial fibrillation percutaneous catheter ablation technologies using randomized controlled trials

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Abstract

Aims: We sought out to make comparisons between all atrial fibrillation (AF) catheter ablation technologies using randomized controlled trial data. Our comparisons were freedom from AF, procedural duration, and fluoroscopy duration.

Methods: Searches were made of EMBASE, MEDLINE, and CENTRAL databases, and studies were selected which had cryoballoon, conventional radiofrequency (RF), multipolar RF catheters, and laser technology as an arm in the study and were identified as randomized controlled trials (RCTs). These studies were analyzed for direct comparisons using conventional meta-analysis and a combination of indirect and direct comparisons via a network meta-analysis (NMA).

Results: With respect to freedom from AF both direct comparisons and NMA did not demonstrate any significant difference. However in analysis of procedural and fluoroscopy duration (minutes) for the pulmonary vein ablation catheter (PVAC), both conventional analysis and NMA revealed significantly shorter procedure times, RF vs PVAC (conventional: 61.99 [38.03-85.94], P <.00001; NMA: 54.76 [36.64-72.88], P < .0001) and fluoroscopy times, RF vs PVAC (conventional: 12.96 [6.40-19.53], P = .0001; NMA: 8.89 [3.27-14.51], P < .01). The procedural duration was also shorter for the cryoballoon with NMA, RF vs CRYO (20.56 [3.47-37.65], P = .02).

Discussion: Our analysis demonstrated that while there was no difference in the efficacy of the individual catheter technologies, there are significant differences in the procedural duration for the PVAC and the cryoballoon. While they may seem an attractive solution for high-volume centers, further RCTs of next-generation technologies should be examined.

KEYWORDS

atrial fibrillation, catheter ablation, network meta-analysis, systematic review

1 | INTRODUCTION

The global age-adjusted prevalence of atrial fibrillation (AF) in the Global Burden of Disease 2010 was 596 per 100 000 men and 373 per 100 000 women.[1] In the European Union the projections from a current estimated prevalence of 8.8 million to 18 million in 2060[2] present important challenges in the coming decades, particularly when considering mortality rates between 0.8 and 0.9 per 100 000 and age-adjusted disability life years between 37 and 54 per 100 000. This increase could be a result of aging populations and improving the ability to be able to treat chronic cardiac diseases.[3] Symptoms can often be disabling leading to high rates of hospital admission for AF and heart failure, and while the condition is often refractory to drug therapy with respect to rhythm control, there remain low levels of catheter ablation being performed (4.4%).[4]

Focal ectopic triggers for AF were identified in pulmonary veins and were subsequently successfully ablated with radiofrequency (RF) energy (pulmonary vein isolation—PVI) in seminal work done by Haïssaguerre et al in 1998.[5] Following this, RF ablation for AF was then suggested as a treatment alternative, which has gained adoption in the European and American guidelines.[6,7]

Despite this, point-by-point circumferential RF ablation is fraught with technical difficulty, long procedure, and fluoroscopy times (though advancements have been made with contact force (CF) technology, and 3D mapping systems[8,9]) and significant complications.[10-12] Advances in ablation technology have brought newer catheter technologies and different energy sources. Methods utilizing RF energy but delivered via multiple poles have been explored. The pulmonary vein ablation catheter (PVAC) has been a widely used catheter for this technique.[13] More advanced catheters have attempted to combine electroanatomic mapping capabilities with delivering RF energy such as the HD Mesh Ablator and nMARQ catheters.[14,15] Cyroenergy delivered via cooled nitrous oxide in a balloon catheter with fluoroscopic guidance has proved a popular and safe alternative energy source.[16] More recently, laser energy delivered via a compliant balloon and guided endoscopically has been explored.[17]

The development of new catheters dedicated for AF ablation with single-shot capability should provide alternatives for shorter procedure times, shorter learning curves, fewer complications, and more reproducible results.[18] However, to date, most of the comparisons have used standard point-by-point RF as the comparator, and there have been few head-to-head trials comparing the more recent techniques. A network meta-analysis (NMA) could provide further insight into this matter.

2 | METHODS

2.1 | Study selection

Searches were performed on the MEDLINE (via PubMED), EMBASE (via HDAS), and CENTRAL (via Cochrane's website) databases from November 2016 to January 2018. The search parameters used were (["catheter ablation" AND "atrial fibrillation"] OR "pulmonary vein isolation") AND ("radiofrequency ablation" OR "cryoballoon" OR "cryotherapy" OR "laser" OR "mesh" OR "nmarq") AND ("randomized" OR "randomised"). The search protocol was undertaken by two independent reviewers (PJ and KK) who evaluated all abstracts and titles to identify potential studies that they then assessed the full texts of.

We then reviewed the references for all the full-text articles we selected and contacted authors of papers as well as conference abstract authors for additional information via email. For our inclusion criteria, we selected studies performed on humans only that compared two (or more) different catheter types for treatment of AF (paroxysmal or permanent) with a follow-up period of more than 3 months with and endpoint of freedom from AF or atrial tachycardia (AT). All trials had to be randomized controlled trials.

Studies were also excluded if there was any evidence of patients recruited who had previous ablations. The differences between the patient populations had to be only the type of catheter used. If the primary endpoint was not that of freedom from AF/AT, but data on that was provided, the study was included.

We collected data on how the AF/AT recurrence was demonstrated, occurrences within the blanking period, and monitoring methods. We also collected data on the fluoroscopy duration and procedural duration as well as the success of PVI and complications.

Data on the patient samples included in each study was collected to compare patient sample populations. These included the percentage of patients with paroxysmal atrial fibrillation (PAF), duration of AF, left ventricular ejection fraction percentage (LVEF%), left atrial diameter (LAD) (mm), hypertension, diabetes status, evidence of coronary artery disease, and structural heart disease.

Both the HD Mesh Ablator and nMARQ catheters are now no longer in use. Safety concerns regarding the nMARQ catheter have been raised with respect to esophageal ulceration and fistula formation with one study reporting two fatal outcomes.[19,20] The initial randomized trial comparing the HD Mesh Ablation catheter with cryoablation was terminated early as the HD Mesh Ablator did not achieve PVI in any of the procedures that had been performed.[21]

2.2 | Bias assessment and quality of evidence

Two independent reviewers (KK and NP) assessed each selected paper individually for the risk of bias according to the Cochrane Collaboration tool for the risk of bias assessment. Population, intervention, and comparison data was well defined throughout all the studies. Where there was a discrepancy between the individual bias assessors, a third reviewer (RP) was bought in to adjudicate. Assessment of the quality of the evidence was assessed in five domains: study limitations, indirectness, inconsistency, imprecision, and publication bias. This was performed using the online "Confidence In Network Meta-Analysis" approach (CINeMA).[22]

2.3 | Statistical analysis

NMA was performed to compare the treatments Laser, Cryoballoon, PVAC, and RF. Indirect comparisons were made using RF as a common comparator. All analysis was done using the frequentist method using the R package "netmeta" in R version 3.4.3. The statistical method for network analysis was done via the graph-theoretical method as set out by Rücker et al.[23] The meta-analytic network is analogized to an electrical network, where observed variances are interpreted as resistances and weighted effects as current. Direct comparisons are made as parallel connections, where the weights are combined as the sum of the inverse variances (conductance). Indirect comparisons are made as a connection in series where the variances are combined as the sum of the variances (resistance) in series.

Overall heterogeneity is measured with the I^2 statistic, a value of greater than 50% was given as significant heterogeneity. In this case, the random-effects model was used and the fixed effects model if less than 50%. Summary statistics for event-free survival were given as the odds ratio (OR), and differences between cohorts for continuous variables were as weighted mean difference (MD). Treatment outcome rankings when a significant difference was observed is given as the P-Score statistic which is a surrogate for the "Surface Under the Cumulative Ranking curve" (SURCRA) in Bayesian NMA methods.

For analysis of baseline characteristics and procedural outcomes, data given in articles varied by per-protocol population and intention to treat population. Thus, pooled data had combinations of both populations. However, for the endpoint of the efficacy outcome, analysis of the on-treatment population of patients was used.

A direct conventional pairwise meta-analysis will also be performed for all comparisons and outcomes via the software packaged RevMan 5. As with the frequentist NMA in between-study heterogeneity as measured with the I^2 statistic is regarded as significant if greater than 50% and a random-effects model was applied.[24]

3 | RESULTS

3.1 | Search results

Out of 620 titles and abstracts obtained from the systematic search of the three databases used, 600 were excluded due to being duplicate studies of those selected or not suitable for analysis for several reasons (not randomized controlled trials (64), incorrect patient population (47), incorrect comparison, and appropriate endpoint not available) (Figure 1). We selected 20 studies for full-text analysis and review of their reference lists. Twelve were selected from these as following full-text analysis; some were found not to be randomized controlled trials or randomization is not explicitly identified and one other did not have a full-text article published more than 2 years after the conference abstract.[17,25-34] Two studies excluded were of the MACPAF trial on HD Mesh ablator vs cryoballoon as the study was interrupted early. Detailed full-text assessment of two other studies demonstrated that they did not satisfy the correct endpoints for analysis. We obtained two more studies from looking at the reference lists[35,36] (Figure 1).

3.2 | Baseline characteristics

Characteristics of the patient cohorts for the individual trials are summarized in Supporting Information Table S1. There were no significant differences between the pooled catheter cohorts compared with the RF cohort for any of the reported characteristics other than the average duration of AF before recruitment. The patients in the laser catheter pooled cohort had, on average, a much shorter duration of symptoms before recruitment (MD: −11.99 [−12.63 to −11.36], $P < .001$) (Table 1).

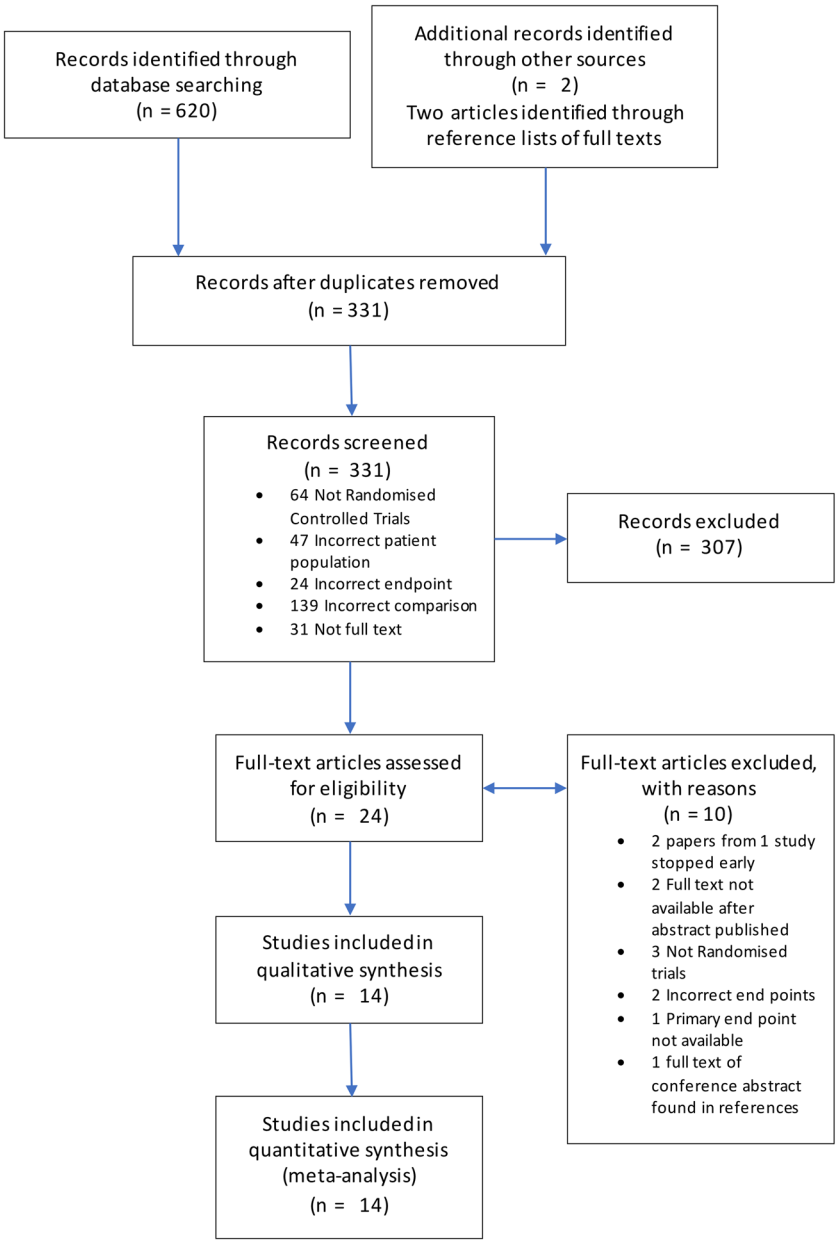
There was overall heterogeneity of greater than 50% in the average age of participants (57.59%), average LVEF% (65.22%), and average LAD (52.73%). However, overall, as there are minimal differences between the patient cohorts, one can conclude minimal transitivity between the studies. The majority of the studies had patient cohorts of 100% PAF. One study was done solely on persistent AF patients[33]; three other studies had mixtures of both persistent and paroxysmal AF patients[28,29,34] (Supporting Information Table S1).

3.3 | Evidence quality and bias assessment

The bias assessment revealed significant variability in the risks between the individual trials (Supporting Information Table S4). A consistent observation was that there was high bias throughout all studies in the blinding of participants and personnel, this being inevitable due to blinding of the operator being impossible. There is considerable variability in the categories of random sequence generation, allocation concealment, blinding of outcome assessment, and attrition bias, largely due to the appropriate information not being available in the published texts. All the trials included were reported to be randomized controlled trials despite the sequence allocation being unclear in six studies.[17,25,28,29,34,37] As a result, the level of evidence as set out by the center of evidence-based medicine would be 1A-.[38]

Supporting Information Table S5 demonstrates the GRADE report for the outcomes for freedom from AF. Although there was high imprecision, there was low heterogeneity and incoherence. We attributed an overall moderate level of confidence to the outcomes observed in this analysis. Supporting Information Table S6 provides the GRADE report for the outcomes for the procedural duration. There were some concerns with respect to imprecision, incoherence, and heterogeneity. However, overall confidence in the comparisons was moderate to high. Finally, Supporting Information Table S7 demonstrates the report for fluoroscopy duration. There were some concerns with imprecision and incoherence and there were major concerns with incoherence. The suggestion here that there are significant differences between direct and indirect comparisons.

FIGURE 1 Search strategy



Thus, we have graded this observation with a low to moderate confidence rating.

3.4 | Procedural characteristics

All studies employing the point-by-point RF technology used electroanatomic mapping technologies, either CARTO or NavX systems. Three studies also employed intracardiac echocardiography to guide transseptal puncture and ensure correct catheter positioning,[17,35,36] transoesophageal echocardiography was used to guide transseptal puncture in one study[28]; these data are available in Supporting Information Table S2.

Additional catheter types were used to complete PVI in some cryoablation arms; the cryocatheter in four arms,[26-28,34] an additional balloon in two arms,[26,27] and a standard RF catheter in one study arm.[26] An RF catheter was also used to touch up PVAC lesions in one trial.[34] Pulmonary vein isolation was confirmed using a circular mapping catheter in all point-by-point RF techniques.

With respect to additional substrates, Pérez-Castellano et al[36] comparing RF and Cryo included repetitive focal ectopics and cavotricuspid isthmus (CTI) ablation in both arms. Dukkipati et al[17] included linear lesions, complex fractionated electrograms (CFAE), and CTI ablation was included in the RF arm and CTI ablation in the laser arm. Schmidt et al[33] did also include additional substrate ablation in the RF arm, but it was not specified (Supporting Information Table S2).

TABLE 1 Baseline characteristics per comparison, RR and WMD given with confidence intervals

Catheter compared to RF	Average PAF, %	RR PAF	*P*-value PAF		
Cryo	96.77	1.000 (0.995, 1.005)	.980	Total patients	2516
Laser	71.43	1.000 (0.989, 1.012)	1.000	Total studies	14
PVAC	88.43	1.000 (0.984, 1.015)	.952	I^2	0
RF	92.04	…			
	Average age	**WMD age**	***P*-value age**		
Cryo	59.23	−1.200 (−3.573, 1.174)	.322	Total patients	2151
Laser	61.43	−0.432 (−3.766, 2.902)	.800	Total studies	12
PVAC	58.77	−1.298 (−3.609, 1.014)	.271	I^2	57.59
RF	60.45	…			
	Average men, %	**RR men**	***P*-value men**		
Cryo	64.24	0.997 (0.925, 1.075)	.940	Total patients	2516
Laser	66.43	1.039 (0.912, 1.185)	.563	Total studies	14
PVAC	60.42	0.953 (0.851, 1.067)	.401	I^2	39.71
RF	63.30	…			
	Average duration, mo	**WMD duration**	***P*-value duration**		
Cryo	59.70	−3.007 (−11.052, 5.038)	.464	Total patients	1526
Laser	24.57	−11.994 (−12.627, −11.361)	<.001	Total studies	7
PVAC	88.60	−0.345 (−13.746, 13.057)	.960	I^2	7.76
RF	53.36	…			
	Average LVEF, %	**WMD LVEF**	***P*-value LVEF**		
Cryo	59.80	0.600 (−3.81, 5.01)	.790	Total patients	876
Laser	60.71	0.222 (−2.77, 3.214)	.884	Total studies	6
PVAC	61.83	−1.06 (−3.91, 1.790)	.466	I^2	65.22
RF	61.60	…			
	Average LAD, mm	**WMD LAD**	***P*-value LAD**		
Cryo	41.13	−0.415 (−1.716, 0.885)	.828	Total patients	1957
Laser	40.00	0.000 (−2.277, 2.277)	1.000	Total studies	10
PVAC	39.97	0.043 (−1.197, 1.282)	.848	I^2	52.73
RF	40.45	…			
	Average HTN, %	**RR HTN**	***P*-value HTN**		
Cryo	53.01	0.955 (0.873, 1.045)	.317	Total patients	2396
Laser	62.61	0.991 (0.866, 1.135)	.901	Total studies	13
PVAC	41.42	1.170 (0.952, 1.438)	.137	I^2	0
RF	53.46	…			
	Average DM, %	**RR DM**	***P*-value DM**		
Cryo	9.32	1.284 (0.882, 1.869)	.192	Total patients	2166
Laser	13.45	1.338 (0.810, 2.210)	.255	Total studies	10

TABLE 1 (Continued)

	Average DM, %	RR DM	*P*-value DM		
PVAC	7.62	1.336 (0.605, 2.948)	.474	I^2	9.66
RF	7.47	…			
	Average CAD, %	**RR CAD**	***P*-value CAD**		
Cryo	9.10	0.891 (0.642, 1.237)	.492	Total patients	2018
Laser	21.43	1.130 (0.789, 1.619)	.504	Total studies	9
PVAC	7.58	1.151 (0.460, 2.878)	.764	I^2	0
RF	12.03	…			
	Average SHD, %	**RR SHD**	***P*-value SHD**		
Cryo	5.08	0.807 (0.533, 1.220)	.309	Total patients	1733
PVAC	3.99	1.190 (0.471, 3.009)	.713	Total studies	9
RF	6.03	…		I^2	0

Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; PAF, paroxysmal atrial fibrillation; PVAC, pulmonary vein ablation catheter; RF, radiofrequency; RR, relative risk; SHD, structural heart disease; WMD, weighted mean difference.

3.5 | Meta-analysis

3.5.1 | Freedom from AF

AF lasting more than 30 seconds on a Holter monitor was the predominant measure of relapse in the majority of trials. In conjunction with this, the use of antiarrhythmic drugs (AAD) and redo procedures were also determined as relapse.[17,26,28,30,37] One study used the criteria of AF for greater than 60 seconds on a Holter monitor.[17] However, in two studies, implantable loop recorders or pacemakers were used to determine AF burden with the monitors being triggered if there was irregularity over a 2 minutes period.[32,36] Three studies included other atrial arrhythmias in the relapse definition.[30,31,37] Bittner et al[29] also included symptomatic AF recorded by the patient as a definition for relapse (Supporting Information Table S3).

A 3-month blanking period was adopted for most studies other than two, which used a 1-month period.[29,35] In two studies, AADs were discontinued after ablation,[25,26] two other studies only allowed beta-blockers,[27,32] and one study discontinued amiodarone after 1 month[30] (Supporting Information Table S3). Recurrences within the blanking periods were considered relapses.

The follow-up period for the majority of trials was 12 months, however, there were two that had variable follow-up periods.[29,35] Two trials included outcomes for one or more ablations performed within the follow-up period,[25,27] however, Luik et al included single procedure only outcomes. These studies were excluded from some subgroup analyses described below.

The relationship between all trials used in the analysis is depicted in the network graph (Figure 2). The individual pooled rates of freedom from AF for each of the catheter technologies (given as percentage) is as follows—OR: Cryo 50 (46-53), RF 55 (52-57), PVAC 56 (51-61), Laser 64 (58-70).

The overall comparison of freedom from AF at any follow-up period for one or more procedures was not significantly different for any catheter type when using RF as a common comparator (OR: PVAC 0.91 [0.66-1.28], Laser 1.05 [0.72-1.51], and Cryo 1.04 [0.84-1.29], I^2 = 21%) (Figure 3A), this was reflected when other catheter types were used as common comparators. On direct comparison done via conventional frequentist meta-analysis, there was no difference found in the freedom from AF at any follow-up duration for comparisons between RF and Cryo, RF and PVAC, and RF and Laser (Figure 3B). Additionally, no significant differences were found when considering studies with the 12-month follow-up (Supporting Information Figure S1).

Furthermore, when data for only single procedures was included no significant difference was found between the individual catheters

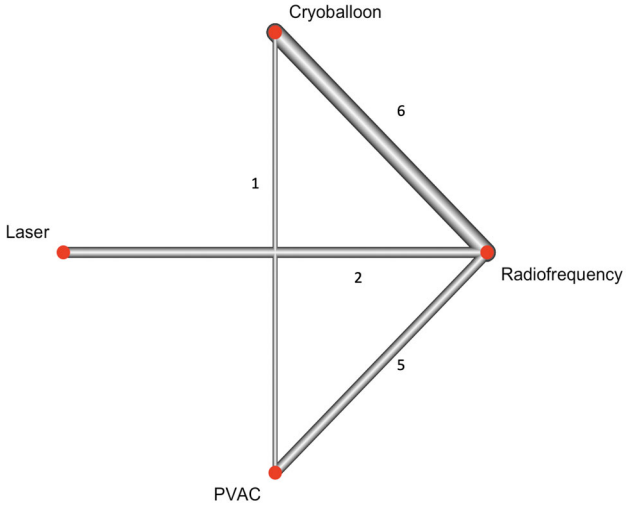


FIGURE 2 Network plot—number of studies on each arm

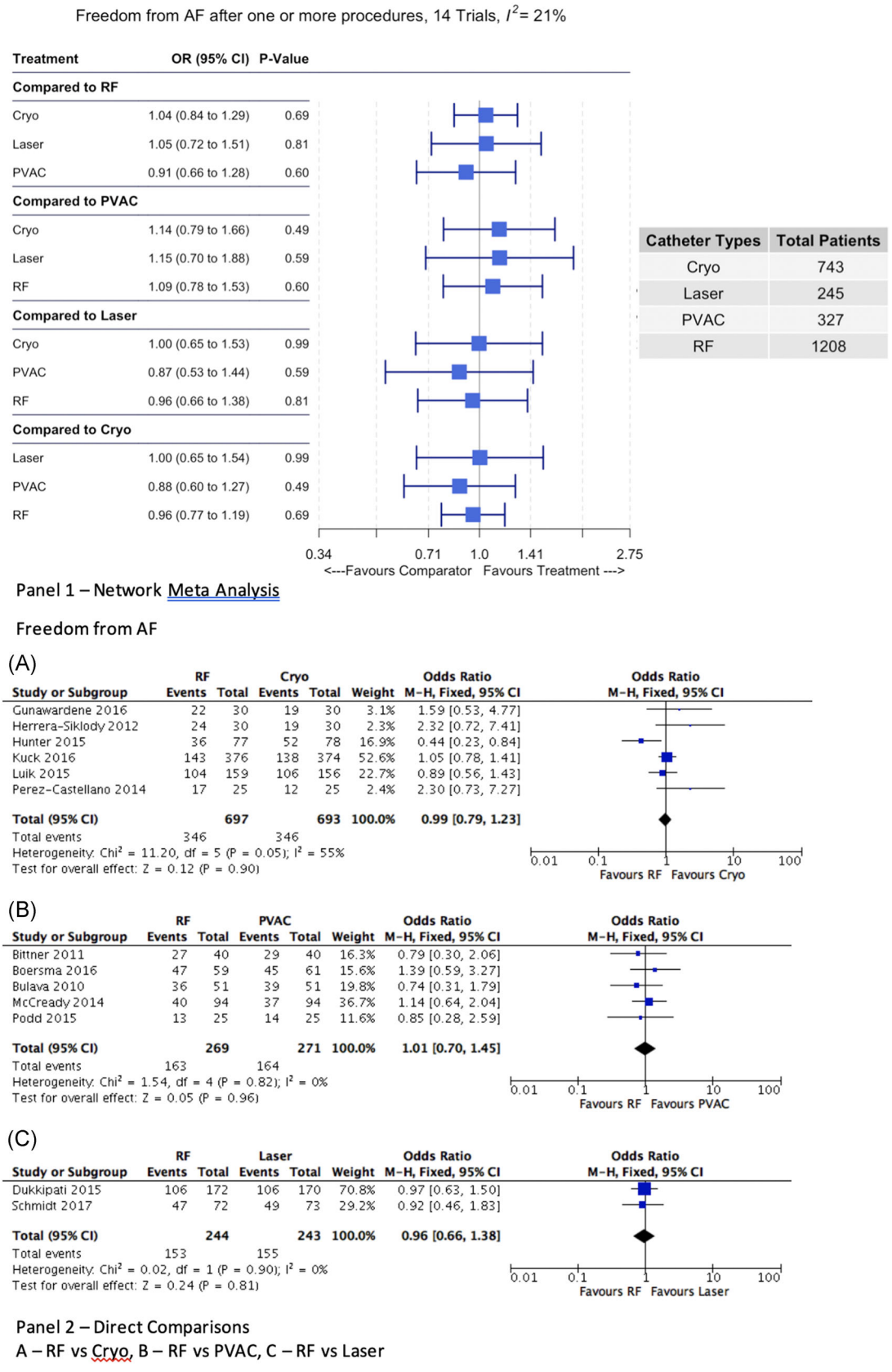


FIGURE 3 Freedom from AF—multiple procedures, any follow-up duration. 95% CI, 95% confidence interval; AF, atrial fibrillation; OR, odds ratio; PVAC, pulmonary vein ablation catheter; RF, radiofrequency

at 12-month follow-up (OR: PVAC 0.80 [0.54-1.18], Laser 0.98 [0.68-1.42], Cryo 1.02 [0.82-1.26], I^2 = 30%) (Supporting Information Figure S2A). There were no differences found when only direct comparisons were examined (Supporting Information Figure S2B). No significant differences were noted when considering studies with any follow-up period (Supporting Information Figure S3). It is worth noting here that the confidence intervals for PVAC and Laser are relatively large with respect to those for RF comparisons.

3.5.2 | Procedure duration and fluoroscopy

For procedural duration we did note some significant differences with the PVAC catheter being significantly superior to all catheters when used as a common comparator (MD: Cryo 34.20 minutes [11.30-57.10], Laser 80.14 minutes [44.30-115.97], RF 54.76 minutes [36.64-72.88], I^2 = 91%) (Figure 4A) and this is reflected when other catheters were used as comparators. Interestingly it is also noted that the cryoballoon has a shorter procedure duration than RF and Laser (MD: Laser 45.94 minutes [10.52-81.26], PVAC −34.20 minutes [−57.10 to −11.30], RF 20.56 minutes [3.47-37.65], I^2 = 91%) (Figure 4A).

Direct comparisons for procedural duration reflected the results from the NMA with the composite PVAC duration being significantly shorter than RF (MD: RF vs PVAC 61.99 minutes [38.03-85.94], P < .00001). Interestingly the difference between the cryoablation and RF was found not to be significant when only direct comparisons were taken into account (MD: RF vs Cryo 11.56 minutes [−22.90 to 46.01], P = .51) (Figure 4B).

Fluoroscopy duration is significantly shorter in the PVAC pooled cohort vs other catheters as evidenced when using PVAC as a common comparator (MD: Cryo 8.58 minutes [1.43-15.73], Laser −13.31 minutes [2.32-24.29], RF 8.89 minutes [3.27-14.51], I^2 = 91%). This again is reflected when other comparators are used (Figure 5A).

With fluoroscopy duration direct comparisons noted a significantly reduced fluoroscopy time when RF was compared with Cryo (MD: RF vs Cryo −3.68 minutes [−5.99 to −1.37], P = .002), which is not reflected in the NMA comparison. Additionally, the RF procedure duration when compared with the Laser catheter had a significantly reduced fluoroscopy time (MD: RF vs Laser −9.73 minutes [−17.65 to −1.80], P = .02). The direct comparison between RF and PVAC reflects the conclusion that PVAC has a significantly reduced fluoroscopy time (MD: RF vs PVAC 12.96 minutes [6.40-19.53], P = .0001) (Figure 5B).

Only two studies reported fluoroscopy radiation dose so meta-analysis was not performed for this outcome. In Malmborg et al,[34] the dose for the PVAC catheter was 4245 ± 2170 μGy/m^2, which was significantly more than that for the cryoballoon 3174 ± 1780 μGy/m^2 (P = .007). Luik et al[27] also reported outcomes as median and interquartile ranges with cryoballoon median at 61.5 Gy/cm^2 (36.0-95.5), which is significantly more than the dose for the RF arm 50 Gy/cm^2 (IQR not reported) (P = .012).

P-score values were given for these analyses, as some observations were statistically significant. The rankings for procedural durations reflected the results in the sense that PVAC had the shortest time followed by the cryoballoon and then RF and laser. For fluoroscopy duration, PVAC again had the shortest duration and was thus ranked the highest, note RF was ranked higher than the cryoballoon.

3.5.3 | Complications

Due to the inconsistent method of reporting of complications, a meta-analysis was not performed on these data. However, data is represented in Table 2. However, there appears to be a higher frequency of phrenic nerve injuries, transient or otherwise, in cryo-catheter and laser populations.

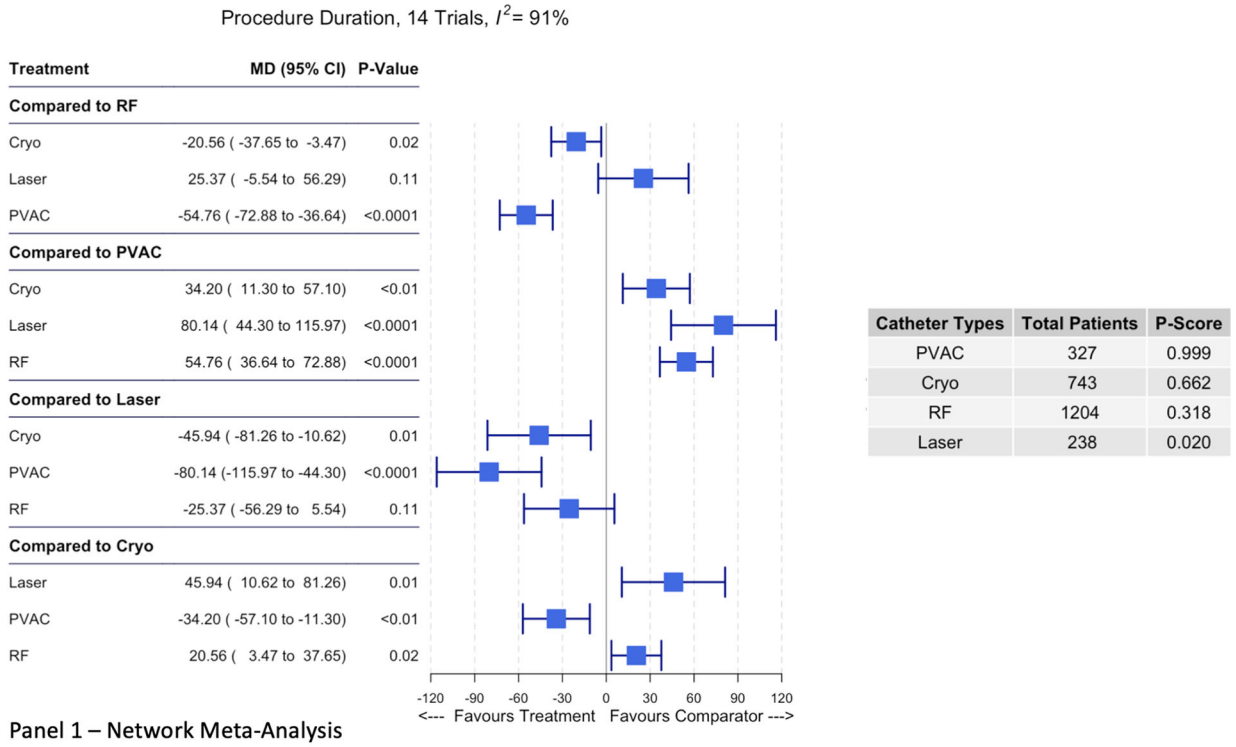
It is important to note that studies did not consistently report tamponade requiring drainage and simple effusions separately.[17,37] One episode of tamponade requiring drainage was reported in the RF arm of the Hunter et al[26] study. In the McCready et al[31] study, three patients in the RF arm developed tamponade during the procedure requiring drainage, and two declined a further procedure due to this. One patient in the Podd et al[32] study under the PVAC arm required a drain for tamponade requiring an overnight stay in the hospital.

3.5.4 | Secondary analyses

Overall differences in PVI were not significant, however, due to some anomalous results of PVI in some of the studies, secondary analysis were conducted to exclude those with PVI < 95% or were not reported. These were conducted for single and multiple procedures and variable and 12-month follow-up duration. No significant differences were found in any of these analyses (Supporting Information Figures S4-S7).

4 | DISCUSSION

This is the first NMA that compares the three different single-shot ablation technologies using only RCTs. As such, it gives us a comprehensive review of the catheter technologies at the highest level of evidence (Level 1A-). It is evident from the analysis that there are no significant differences in the efficacies of the individual catheter technologies. A previous NMA, including also observational studies, has suggested that PVAC and conventional RF are more efficacious than the cryoballoon catheter.[39] There is only one study directly comparing cryoballoon and PVAC, which demonstrated no difference in efficacy.[34] The pertinent differences gleaned from this study, however, suggest that there are significant differences in the procedural duration in both cryoballoon and PVAC pooled groups and also a significant difference in the fluoroscopy duration for PVAC.

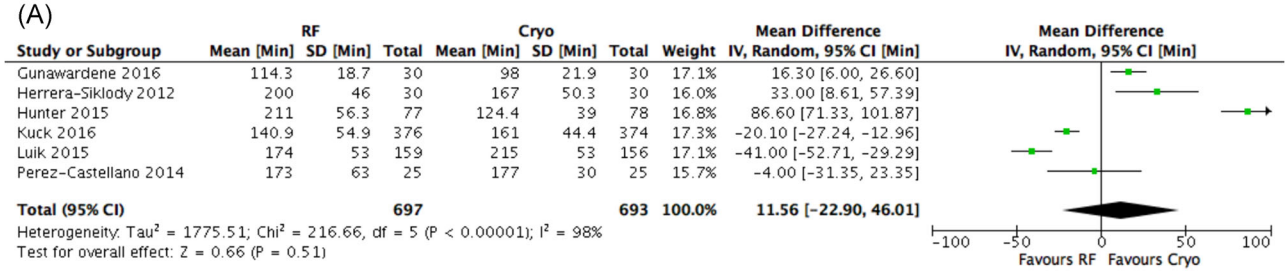


Catheter Types	Total Patients	P-Score
PVAC	327	0.999
Cryo	743	0.662
RF	1204	0.318
Laser	238	0.020

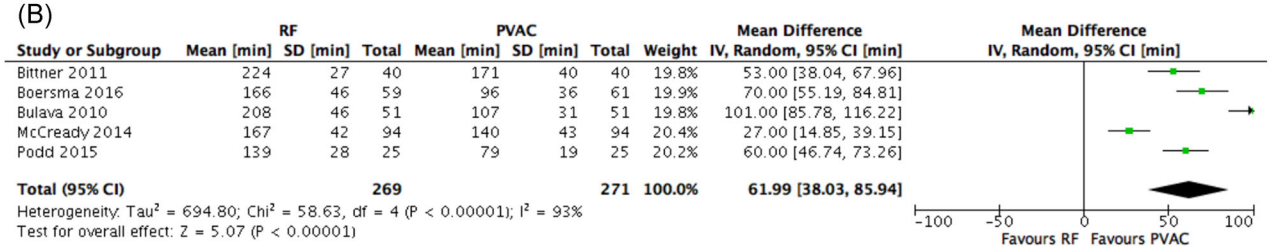
Panel 1 – Network Meta-Analysis

Procedure Duration

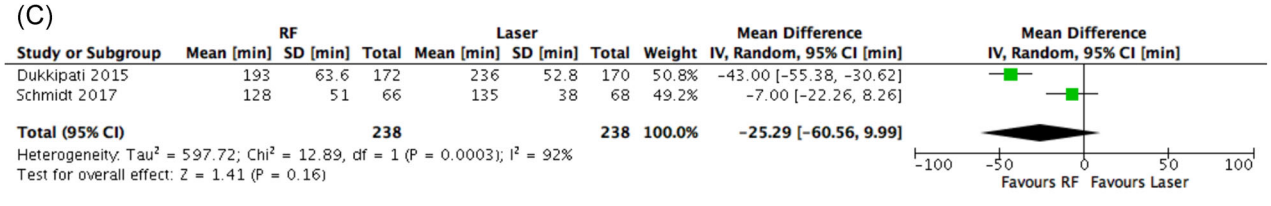
(A)



(B)

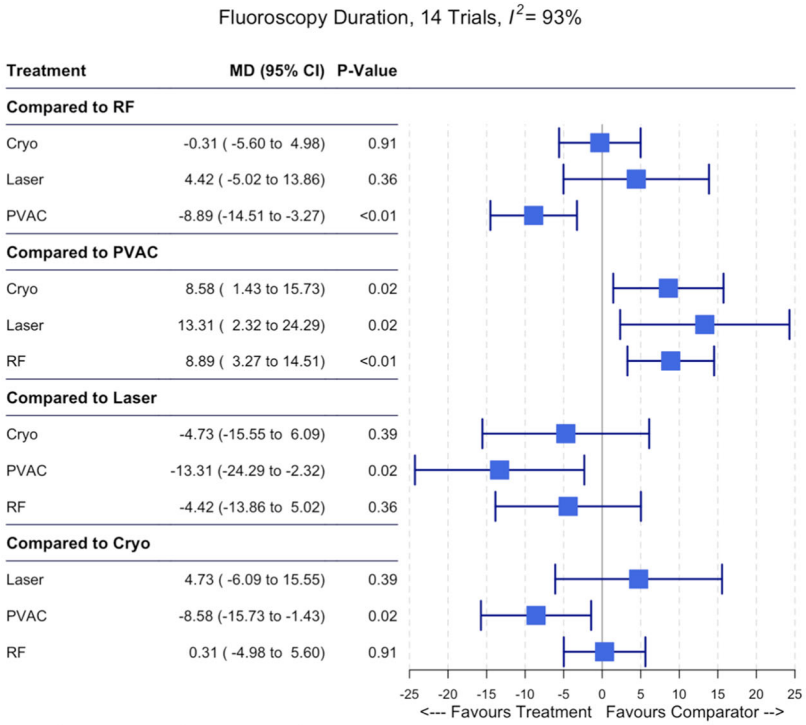


(C)



Panel 2 – Direct Comparisons
A – RF vs Cryo, B – RF vs PVAC, C – RF vs Laser

FIGURE 4 Procedural duration. 95% CI, 95% confidence interval; OR, odds ratio; PVAC, pulmonary vein ablation catheter; RF, radiofrequency



Catheter Types	Total Patients	P-Score
PVAC	327	1.000
RF	1204	0.666
Cryo	743	0.251
Laser	238	0.083

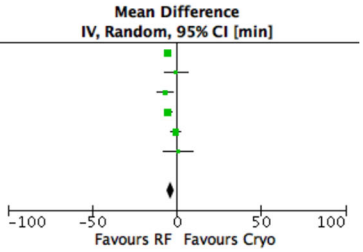
Panel 1 – Network Meta-Analysis

Fluoroscopy Duration

(A)

Study or Subgroup	RF Mean [min]	RF SD [min]	RF Total	Cryo Mean [min]	Cryo SD [min]	Cryo Total	Weight	Mean Difference IV, Random, 95% CI [min]
Gunawardene 2016	10	4.3	30	15.4	3.9	30	26.2%	-5.40 [-7.48, -3.32]
Herrera-Siklody 2012	37	16.2	30	37.3	11.8	30	7.9%	-0.30 [-7.47, 6.87]
Hunter 2015	28.7	15.9	77	35.7	15.9	78	13.0%	-7.00 [-12.01, -1.99]
Kuck 2016	16.6	17.8	376	21.7	13.9	374	25.1%	-5.10 [-7.39, -2.81]
Luik 2015	24	15	159	24.5	10	156	22.3%	-0.50 [-3.31, 2.31]
Perez-Castellano 2014	45	16	25	44	16	25	5.6%	1.00 [-7.87, 9.87]
Total (95% CI)			**697**			**693**	**100.0%**	**-3.68 [-5.99, -1.37]**

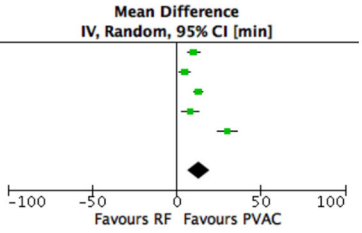
Heterogeneity: Tau² = 4.18; Chi² = 12.18, df = 5 (P = 0.03); I² = 59%
Test for overall effect: Z = 3.12 (P = 0.002)



(B)

Study or Subgroup	RF Mean [min]	RF SD [min]	RF Total	PVAC Mean [min]	PVAC SD [min]	PVAC Total	Weight	Mean Difference IV, Random, 95% CI [min]
Bittner 2011	35	9	40	25	8	40	20.3%	10.00 [6.27, 13.73]
Boersma 2016	27	9	59	22	9	61	20.7%	5.00 [1.78, 8.22]
Bulava 2010	28	8	51	15	5	51	21.1%	13.00 [10.41, 15.59]
McCready 2014	42	20	94	34	16	94	19.2%	8.00 [2.82, 13.18]
Podd 2015	51	12	25	21	8	25	18.7%	30.00 [24.35, 35.65]
Total (95% CI)			**269**			**271**	**100.0%**	**12.96 [6.40, 19.53]**

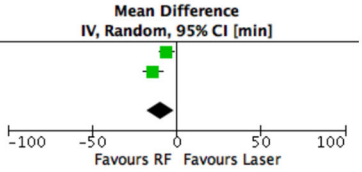
Heterogeneity: Tau² = 51.57; Chi² = 60.41, df = 4 (P < 0.00001); I² = 93%
Test for overall effect: Z = 3.87 (P = 0.0001)



(C)

Study or Subgroup	RF Mean [min]	RF SD [min]	RF Total	Laser Mean [min]	Laser SD [min]	Laser Total	Weight	Mean Difference IV, Random, 95% CI [min]
Dukkipati 2015	29.7	21	172	35.6	18.2	170	52.8%	-5.90 [-10.06, -1.74]
Schmidt 2017	32	16	66	46	17	68	47.2%	-14.00 [-19.59, -8.41]
Total (95% CI)			**238**			**238**	**100.0%**	**-9.73 [-17.65, -1.80]**

Heterogeneity: Tau² = 26.48; Chi² = 5.19, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 2.41 (P = 0.02)



Panel 2 – Direct Comparisons
A – RF vs Cryo, B – RF vs PVAC, C – RF vs Laser

FIGURE 5 Fluoroscopy duration. 95% CI, 95% confidence interval; OR, odds ratio; PVAC, pulmonary vein ablation catheter; RF, radiofrequency

TABLE 2 Complications—data given as n (%)

Name and year of study	Vascular complications		Phrenic nerve palsy		Tamponade/Effusion		PV stenosis		Stroke	
RF vs Cryo	RF	Cryo	RF	Cryo	RF	Cryo	RF	Cryo	RF	Cryo
Gunawardene et al 2018[25]	4 (13.3)	5 (16.7)	0	1 (3.3)	0	0	Not investigated		0	0
Hunter et al 2015[26]	1 (1.3)	0	0	4 (5.1)	2 (2.6)	0	1 (1.3)	0	0	0
Kuck et al 2016[37]	16 (4.3)	7 (1.9)	0	13 (3.5)	5 (1.3)	1 (0.3)	0	0	2 (0.5)	2 (0.5)
Luik et al 2015[27]	5 (3.1)	8 (5.1)	0	9 (5.8)	0	0	0	0	0	0
Pérez-Castellano et al 2014[36]	1 (4)	0	0	4 (16)	0	0	Not investigated		0	0
Herrera Siklódy et al 2012[28]	0	2 (6.7)	0	2 (6.7)	0	0	Not investigated		0	0
RF vs PVAC	RF	PVAC	RF	PVAC	RF	PVAC	RF	PVAC	RF	PVAC
Bittner et al 2011[29]	1 (2.5)	0	0	0	0	0	0	0	0	0
Boersma et al 2016[30]	Not reported		0	0	0	0	2 (3.4)	0	0	0
Bulava et al 2010[35]	0	0	0	0	0	0	Not investigated		0	0
McCready et al 2014[31]	0	1 (1.1)	0	0	3 (3.2)	0	0	2 (2.1)	0	2 (2.1)
Podd et al 2015[32]	0	0	0	0	0	1 (4)	Not investigated		0	0
RF vs Laser	RF	Laser	RF	Laser	RF	Laser	RF	Laser	RF	Laser
Dukkipati et al 2015[17]	Not reported		1 (0.6)	6 (3.5)	3 (1.7)	2 (1.2)	5 (2.9)	0	1 (0.6)	2 (1.2)
Schmidt et al 2017[33]	2 (3)	1 (1.5)	0	1 (1.5)	0	0	Not investigated		0	2 (2.9)
Cryo vs PVAC	Cryo	PVAC	Cryo	PVAC	Cryo	PVAC	Cryo	PVAC	Cryo	PVAC
Malmborg et al 2013[34]	2 (4)	1 (1.8)	0	0	0	0	0	0	0	0

Abbreviations: PVAC, pulmonary vein ablation catheter; RF, radiofrequency.

No studies comparing the nMARQ and HD Mesh Ablator catheters were included.

4.1 | Freedom from AF

Not all studies included in the analysis had a total follow-up period of 12 months. Despite this, there were no significant differences noted in the freedom from AF in any of the catheter types when the shorter duration studies were excluded. A previous NMA using observational data suggested that PVAC was more efficacious than conventional RF,[39] however, this signal was lost when only randomized data was included which reflects our conclusion. However, when comparing cryoballoon with conventional RF this meta-analysis noted no significant difference between the technologies when comparing randomized evidence. This difference from the previous study is likely driven by the data from Cryo vs RF[26] and FIRE and ICE.[37]

4.2 | Procedure and fluoroscopy duration

Part of the rationale behind introducing single-shot techniques was that they may herald shorter procedure and fluoroscopy times.[40] This was observed in the direct and pooled direct and indirect comparisons between point-by-point RF and PVAC approaches. However, the differences in procedural duration when comparing cryoablation with RF was not significant when direct comparisons were made and only just became significant when indirect comparisons were taken into account. Furthermore, the fluoroscopy duration when comparing cryoablation with RF was significantly longer although this signal was lost when combined with indirect comparisons (likely to be driven by indirect evidence coming from the results of the PVAC vs first-generation cryoballoon (Arctic Front) comparisons. Importantly, of the studies included only one used the second-generation cryoballoon (Arctic Front Advance) exclusively,[25] and two used a combination of first and second-generation balloons[27,41] of which the data was impossible to delineate.

The use of electroanatomic mapping strategies and, in some situations, intracardiac echocardiography, and the advent of CF technology for RF ablation reduced the need for prolonged fluoroscopy time.[8,42,43] In fact, in recent times, some centers and operators have even gone as far as being able to provide for zero-fluoro procedures.[44] In this context, contemporary RF techniques may confer an advantage of lower exposure to fluoroscopy over single-shot technologies.

4.3 | Complications

Though meta-analysis was not possible in the comparison between cryoablation and other catheter techniques, it is generally considered

to be a safer technique with complication rates as low as 2% with the advent of the second-generation balloon catheter.[45] A rare but observed severe complication in RF ablation is atrio-esophageal fistula formation.[46] None of the trials included in this study encountered such a complication, but observational evidence suggests that this is much rarer in cryoablation strategies.[47]

Reports of significantly increased asymptomatic cerebroembolic events (ACE) in multiple observational studies comparing cryoballoon, PVAC, and standard RF led to concern over the PVAC technology.[48,49] Following this, the use of the catheter technology dropped off significantly in clinical practice. However, changes to the ablation protocol (procedures performed under uninterrupted therapeutic oral anticoagulants; intraprocedural target ACT > 350 seconds; loading the catheter into the introducer submerged in saline before sheath insertion to reduce air ingress; deactivation of either the distal or proximal electrode to avoid electrode overlap and phased RF interaction) led to the dramatic reduction in ACE.[50] This concern was further eased with the development of an updated version of the catheter, the PVAC Gold. Two trials to date have provided conflicting data on the ACE rate in the PVAC Gold catheter, with one having rates comparable to standard RF[51] and another similar to the previous PVAC iteration.[52] None of the trials included in our study used the PVAC Gold catheter.

Tamponade was not observed in any of the cryoablation patients in the study included and observational evidence suggests that the rate is significantly lower than that found in RF ablation.[53] Overall, cryoablation tends to have fewer complications compared with other catheters with the caveat that there is an increased frequency of phrenic nerve palsy, however, this can be mitigated with pacing of the phrenic nerve during energy application.[54]

4.4 | Limitations

The lack of a large amount of randomized controlled trials comparing different ablation catheter technologies leads to this meta-analysis having a lower statistical power compared to that of those that have included observational studies. However, we acknowledge that from the start, we wanted to use the highest quality data available only. Furthermore, the presence of the FIRE and ICE trial data may skew the data due to its comparatively large number of patients.

Our review includes results from the first-generation cryoballoon, which are known to be inferior to the currently available technology. Newer cryoballoons have been developed, which may have significantly shorter procedural duration with comparable success rates, and allowing determination of time-to-isolation in more patients.[55,56] Additionally, the discontinuation of the PVAC catheter and the subsequent introduction of PVAC Gold makes the generalizability of the conclusions to real-world practice difficult. This, plus the development of new catheter types such as the Heliostar RF balloon,[57] means that these updated technologies should be included in further comparisons.

Since the majority of the trials included were published, the use of CF technology has become ever more prevalent. Only one trial included in our review exclusively used a CF catheter, and two others mentioned some use (Supporting Information Table S2). Fluoroscopy time and RF time were significantly less and freedom from AF was significantly greater in a randomized comparison of CF to non-CF catheters.[58] Furthermore, advances have been made from the use of force-time integrals for a lesion quality-surrogate marker to incorporating RF power, CF, and time into a nonlinear algorithm called Ablation Index (AI).[59] Utilization of AI has been found to associate with lower rates of acute PVI reconnection and better rates of freedom from AF at 12 months.[60] AI or similar algorithms were not used in any of the included studies in our review. A NMA including RCTs and observational studies comparing standard catheters, CF catheters AI systems, and first- and second-generation cryoballoon, demonstrated better freedom from AF at 12 months with the RF guided by AI technology.[61] However, this conclusion was driven by observational data.[62-64] Further randomized comparisons should be made to provide an updated and higher level of evidence analysis. When more trials comparing the new technologies become available, an update for this review will be conducted.

As there is evidence that the combination of indirect comparisons with direct comparisons in the meta-analysis may alter the statistical signal, further evaluation with a Bayesian network model may provide additional support to the NMA approach.[65]

5 | CONCLUSIONS

This NMA suggests that efficacy of the newer technologies is comparable to that of point-by-point RF. Procedural times with PVAC and cryoballoon ablation are significantly shorter, which may support the use of these techniques in high-volume centers, and centers with waiting lists for AF ablation procedures. Further randomized analyses the comparing latest generation cryoballoon, PVAC Gold and AI-guided RF ablation should be conducted to evaluate if this conclusion still stands.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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