Heart, Lung and Circulation (2025) **34**, 25–33
1443-9506/24/$36.00
https://doi.org/10.1016/j.hlc.2024.10.014

REVIEW

Radiofrequency and Cryoablation as Energy Sources in the Cox-Maze Procedure: A Meta-Analysis of Rhythm Outcomes

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Received 17 November 2023; received in revised form 21 October 2024; accepted 22 October 2024; online published-ahead-of-print 14 December 2024

Aim Cox-maze IV is the most effective surgical procedure for atrial fibrillation (AF) treatment to date; however, few studies have compared the outcomes of the different energy sources applied to achieve transmurality. This study aimed to analyse the impact of the different energy sources on Cox-maze IV results in terms of sinus rhythm restoration.

Method A systematic review and meta-analysis was conducted by including studies reporting rhythm outcomes on biatrial Cox-maze AF ablation with bipolar radio-frequency (BRF), cryoenergy (Cryo), or both (BRF+Cryo). The primary endpoints were the early and late rhythm outcomes of AF ablation using the different energy sources. Late AF recurrences were evaluated through timepoint analysis, and freedom from AF from Kaplan-derived data. Sixty articles including 8,293 patients were selected (3,364 patients Cryo, 1,937 BRF, and 2,992 BRF+Cryo).

Results At 6 months, AF incidence was significantly lower in the Cryo group at 6.73%; it was 25.52% in the BRF and 16.79% in the BRF+Cryo groups (p=0.0112). At the 4-year timepoint, AF incidence was lower in the Cryo group compared with the BRF and BRF+Cryo: 6.14% vs 51.59% vs 16.09%, respectively (p=0.0392). Freedom from AF was 76.7%±2.2%, 60.9%±2.2%, and 66.3%±1.6% for Cryo, BRF, and BRF+Cryo at 4 years, respectively (p<0.001). At meta-regression, mean left atrial diameter was positively associated with higher AF recurrences (OR 1.04, 95% CI 1.01–1.08; p=0.0159).

Conclusion When performing this procedure, cryoablation seems to be associated with improved rhythm outcomes when compared with bipolar radiofrequency ablation.

Keywords Atrial fibrillation ablation • Energy source • Cox-maze • Meta-analysis

Introduction

The cut-and-sew Cox-maze III operation, first performed by Dr James Cox in 1991, is still considered the gold standard for the treatment of atrial fibrillation (AF). The main goal is to effectively ablate focal atrial triggers originating at the level of the four pulmonary veins and interrupt macro-re-entrant circuits perpetuating AF without hampering the sinus activity and atrio-ventricular conduction [1]. Hence, the effectiveness of the Cox-maze procedure is mainly related to the

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creation of transmural lesions without disrupting atrial function and damaging the surrounding tissues. Although the original Cox-maze III cut-and-sew technique is still considered to be the most effective approach [2], it is perceived to be technically demanding and prone to important postoperative complications, which limit wide use of this procedure [3].

The introduction of physical energy sources in AF surgery has led to the latest evolution of the Cox-maze operation, the so-called Cox-maze IV [1]. In this procedure, the cut-and-sew lesions have been replaced by ablation lines, thus significantly reducing surgical invasiveness and procedural time. Although different energy sources have been tested over the years, only cryoablation (Cryo) and bipolar radiofrequency (BPF) energy sources have succeeded in producing reliable and durable transmural lesions. Bipolar radiofrequency is a hyperthermic energy determining cellular apoptosis by inducing protein denaturation, while Cryo freezes the tissue until it reaches cellular damage temperatures of around –60 °C. In both cases, the efficacy of such energy sources in transmural lesion creation can be limited if the atrial tissue is significantly remodelled and thick [4]. Cryoablation works well for creating lesions around the mitral region and near coronary arteries, especially where thick atrioventricular tissue limits the effectiveness of standard BRF clamps. It is particularly advantageous in minimally invasive procedures as it avoids the need for additional dissection. However, Cryo takes more time to create linear ablations compared with BRF. Using both Cryo and BRF together could help balance the benefits of each, reducing the risk of coronary thrombosis and stenosis typically associated with RF energy [5].

Despite articles reporting optimal outcomes of the Cox-maze IV [6,7], few studies have directly addressed clinical outcomes of patients who underwent Cox-maze IV procedures performed with different subsets of energy sources [8–10]. This systematic review analysed the effect of the energy sources used for the Cox-maze IV AF ablation in terms of AF recurrence.

Methods

Protocol and Registration

This review was registered with the PROSPERO register of systematic reviews (ID: CRD42022384218). There was no individual patient involvement in this study because it involved analysis of previously published data; as such, research ethics board approval and patient consent were not required. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Search Strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. The PRISMA flow diagram is presented in Supplementary Figure S1. Pubmed, ScienceDirect, Ovid EMBASE, SciELO, DOAJ, and Cochrane databases were searched until December 2022 for publications reporting rhythm outcomes of patients undergoing biatrial Cox-maze surgery with BRF, cryoenergy, or both. The search strategy can be seen in Supplementary Table S1. In addition, the bibliographies of all studies and reviews were searched to identify further articles (i.e., "backward snowballing"). Studies were independently screened for inclusion by two authors (M.B. and F.R.). In case of disagreement, a consensus was reached with the aid of a third author (L.D.B).

Inclusion and Exclusion Criteria for Study Selection

Only studies reporting outcomes of patients undergoing biatrial Cox-maze AF ablation with BRF, Cryo, or both were included. Studies were excluded if uni-/mono-polar RF was used or if surgical ablation was performed through a left-maze or any other reduced lesion ablation scheme [1]. Papers with <10 patients were excluded. Case reports, reviews, and comments were also excluded. The study period was assessed in case of multiple publications from the same institution. In case of overlap, the largest sample size study was included.

Data Extraction

Data were extracted on Microsoft Office 365 Excel software (Microsoft, Redmond, WA, USA). Categorical variables were expressed as frequency, while continuous variables were reported as mean with standard deviation. Data on study period, study centre, country, type of energy source, and sample size were retrieved. The patient characteristics, postoperative and follow-up outcomes were evaluated.

Individual patient data (IPD) were retrieved from the Kaplan–Meier graphs when available. Data extraction was performed as described by Liu et al. [12] as a two-step approach. In the first step, Kaplan–Meier curves were digitised using a dedicated software (WebPlotDigitizer, https://apps.automeris.io/wpd/) and, using mouse clicks to select the points of the curve, raw data (time and freedom from AF probability) were extracted from each Kaplan–Meier curve. Digitised Kaplan–Meier curves were checked graphically with the original ones. The curves were also assessed using the root mean square error, along with the mean and maximum absolute errors. In the analysis, a root mean square error of ≤ 0.05, mean absolute error of ≤ 0.02, and maximum absolute error of ≤ 0.05 demonstrated that the extracted data points were accurately captured and suitable for further analysis. Kaplan–Meier data from different studies were stored together in the study database. In the second step, the data coordinates were processed based on the raw data coordinates from the first stage in conjunction with the numbers at risk at given timepoints and/or total number of patients, and IPD were reconstructed based on the R package "IPDfromKM". Finally, the reconstructed IPD from all the studies with available IPD were merged to create the study data set and analysed altogether.

Critical Appraisal

The Newcastle–Ottawa Quality Assessment Scale for cohort studies and the Cochrane Collaboration's risk of bias tool (RoB I) were used for critical appraisal of the quality of included non-randomised studies [13] and for randomised controlled trials (RCTs) [14], respectively.

Outcomes of Interest

The primary endpoints were the early (AF at discharge) and late rhythm outcomes of AF ablation using the different energy sources to perform the lesions: Cryo, BRF, or the combination of both (i.e., BRF+Cryo). Late AF rhythm outcomes were evaluated using two different methods, as the included papers did not express AF recurrence homogeneously: 1) a timepoint analysis evaluated the number of patients with AF, when papers reported the rhythm outcome by timepoints; 2) the freedom from AF was analysed if a Kaplan–Meier curve reporting this outcome was available. The paper's definition of freedom from AF was used for each included study. Secondary endpoints included postoperative cerebrovascular accident (CVA), postoperative permanent pacemaker (PPM) implant, 30-day mortality, late CVA, late PPM, and late mortality.

Statistical Analysis

The pooled event rate (PER) was used for the timepoint analysis of AF and postoperative outcomes. A random intercept logistic regression model (generalised linear mixed effect model) was used and between-study variance was estimated with the maximum-likelihood estimator. For late outcomes and AF incidence rate, to account for the studies' different follow-up times, Poisson regression modelling was used, assuming a constant event rate. The total person-time of follow-up was calculated from the total number of events and mean follow-up time. A log transformation to model the overall incidence rate (IR) was used. All results were calculated with a 95% confidence interval (CI).

Hypothesis testing for equivalence was set at the two-tailed 0.05 level. Heterogeneity was based on the Cochran Q test, with I^2 values. In case of high heterogeneity (I^2>50%), a sensitivity study was carried out through a leave-one-out analysis (LOO), and its results were displayed as a variation range of the estimates. Individual patient data were represented through Kaplan–Meier curves with the outcome expressed as percent (%)±standard error (SE), and groups were compared with the log-rank test. A 4-year landmark analysis was performed to establish the significance of the curves. A univariable meta-regression was performed to further analyse the rhythm outcome at different timepoints according to the type of energy source. Univariable and multivariable meta-regression of the patients' characteristics were performed on the AF incidence rate. Univariable predictors were selected for inclusion within the multivariate model if p<0.05. Results were expressed as odds ratio (OR), 95% CI, and p-value. All analyses were performed using R, version 4.2.2 (R Project for Statistical Computing, Vienna, Austria) and RStudio version 2022.12.0+353, using the R packages "meta", "IPDfromKM", "survival", "survminer", and "jskm".

Results

Study Selection and Characteristics

An outline of the systematic review process is presented in Supplementary Figure S1. The literature search identified 1,067 potentially eligible studies. Nine additional articles were identified through backward snowballing. After removal of duplicates, 582 studies were screened. Among these, 197 full-text articles were assessed for eligibility. Sixty articles (Supplementary References) met the inclusion criteria, with a total of 8,293 participants: 3,364 in the Cryo group, 1,937 in the BRF group, and 2,992 in the BRF+Cryo group. The studies were published from the period 2001–2022, and the sample size ranged 14–807 participants. Details of the individual studies are shown in Supplementary Table S2. The studies included six RCTs, seven propensity-matched studies, one inverse-probability of treatment weighting study, and 46 non-adjusted observational studies. A critical appraisal of the non-randomised and randomised included studies is provided in Supplementary Tables S3 and S4, respectively. There was one study with a Newcastle–Ottawa Quality Assessment Scale score <6, indicating poor study appraisal. The baseline patients' characteristics are shown in Supplementary Table S5, while concomitant procedures are listed in Supplementary Table S6. The three groups were found to be significantly different for the prevalence of male sex, diabetes, hypertension, re-intervention, type of AF, left atrial diameter, and the concomitant procedures performed. The overall mean follow-up was 32.4±24.2 months.

Meta-Analysis of the Primary Outcomes

At the timepoint analysis, Cryo presented a significantly lower AF PER compared with BRF both at 3 and 6 months (p=0.020 and p=0.0124, respectively). These outcomes were confirmed at 3 and 4 years (p=0.0359 and p=0.0215, respectively). Cryo had also a lower AF PER than BRF+Cryo (6.73%, 95% CI 3.59–12.25 vs 16.79%, 95% CI 12.01–22.99; p=0.0086, respectively) at 6 months, while the Cryo group maintained a trend towards lower AF PER beyond this timepoint when compared with BPR+Cryo. Moreover, the BRF group also showed a significantly higher AF PER at 4 years when compared with the BRF+Cryo group (51.39%, 95% CI 20.40–81.69 vs 16.09%, 95% CI 10.97–22.97; p=0.0262). Sensitivity analysis through LOO did not report any important variation for any of the estimated outcomes. Most of the outcomes showed a high level of heterogeneity and were further analysed through meta-regression. The rhythm outcomes are summarised in Table 1.

Eighteen papers displayed a survival freedom from AF (Kaplan–Meier curve) (sensitivity analysis in Supplementary Table S7). Freedom from AF at 1 year for Cryo, BRF, and

Table 1 **Meta-analysis of the main outcome.**

Outcome	Studies, n	Patients, n	Effect (95% CI)	Comparison p-value	Heterogeneity: I^2, p-value	LOO effect variation
AF at 3 months	13	749	15.94% (8.95–26.78)	C vs R, **0.0200**	75.2%, <0.0001	14%–19%
Cryo	7	348	12.90% (6.88–22.91)	C vs C+R, 0.8037	62.5%, 0.0138	11%–15%
BRF	3	249	30.67% (19.48–44.71)	R vs C+R, 0.3106	81.2%, 0.0050	26%–38%
Cryo+RF	3	152	9.38% (0.66–61.63)	C vs R vs C+R, *0.0524*	78.9%, 0.0087	3%–30%
AF at 6 months	30	3,120	12.59% (8.30–18.65)	C vs R, **0.0124**	86.0%, <0.0001	12%–14%
Cryo	13	1,058	6.73% (3.59–12.25)	C vs C+R, **0.0086**	75.9%, <0.0001	6%–8%
BRF	7	712	25.52% (10.93–44.88)	R vs C+R, 0.3451	94.0%, <0.0001	17%–31%
Cryo+BRF	10	1,329	16.79% (12.01–22.99)	C vs R vs C+R, **0.0112**	65.4%, 0.0020	15%–18%
AF at 1 year	38	4,694	14.50% (11.28–18.44)	C vs R, 0.1072	85.3%, <0.0001	14%–15%
Cryo	17	2,071	11.28% (8.09–15.51)	C vs C+R, *0.0860*	73.6%, <0.0001	10%–13%
BRF	10	1,038	19.80% (10.74–33.61)	R vs C+R, 0.4595	90.6%, <0.0001	17%–22%
Cryo+BRF	11	1,585	15.66% (12.88–18.92)	C vs R vs C+R, 0.1352	62.5%, 0.0029	15%–16%
AF at 2 years	20	2,365	19.20% (12.86–27.68)	C vs R, 0.2178	89.2%, <0.0001	17%–22%
Cryo	8	701	12.91% (5.74–24.52)	C vs C+R, 0.1679	58.1%, 0.0193	11%–18%
BRF	5	491	26.75% (10.60–52.94)	R vs C+R, 0.7288	94.6%, <0.0001	17%–30%
Cryo+BRF	7	1,173	22.81% (16.37–30.85)	C vs R vs C+R, 0.3319	90.9%, <0.0001	21%–25%
AF at 3 years	17	1,951	21.76% (14.95–30.57)	C vs R, **0.0359**	85.8.3%, <0.0001	20%–24%
Cryo	7	605	16.02% (7.85–29.94)	C vs C+R, 0.3854	88.8%, <0.0001	13%–21%
BRF	2	112	56.50% (20.77–86.55)	R vs C+R, *0.0577*	95.3%, <0.0001	30%–80%
Cryo+BRF	8	1,234	21.42% (18.28–24.93)	C vs R vs C+R, 0.1103	52.9%, 0.0377	20%–22%
AF at 4 years	11	1,140	15.72% (7.74–29.32)	C vs R, **0.0215**	71.0%, 0.0002	13%–20%
Cryo	4	469	6.14% (0.98–30.13)	C vs C+R, 0.2766	0.0%, 0.7805	-
BRF	2	78	51.39% (20.40–81.69)	R vs C+R, **0.0262**	87.5%, 0.0046	31%–77%
Cryo+BRF	5	593	16.09% (10.97–22.97)	C vs R vs C+R, **0.0392**	70.8%, 0.0083	14%–21%

Bold denotes p<0.05; italics denote p<0.1 and p>0.05.

Abbreviations: AF, atrial fibrillation; BRF or R, bipolar radiofrequency; CI, confidence interval; Cryo or C, cryoablation; LOO, leave-one-out analysis; mth, month.

BRF+Cryo was 91.1%±1.3% vs 88.6%±1.3% vs 85.5%±1.0%, respectively, and at 4 years it was 76.7%±2.2% vs 60.9%±2.2% vs 66.3%±1.6%, respectively (log-rank p<0.0001), as shown in Figure 1. Overall, Cryo was found to have higher freedom from AF with respect to BRF (log-rank p<0.0001) and BRF+Cryo (log-rank p<0.0001), while no significant difference was found between BRF and BRF+Cryo (log-rank p=0.450). In view of the latest timepoint analysis and the considerable decrease in patients in the analysis at the latest follow-up, a 4-year landmark analysis was conducted. Cryo was still characterised by a significantly higher survival freedom from AF compared with BRF (log-rank p<0.001) and BRF+Cryo (log-rank p<0.001), while no differences were seen between BRF and BRF+Cryo (log-rank p=0.178), as seen in Figure 2.

Meta-Analysis of the Secondary Outcomes

Bipolar radiofrequency reported a lower PER of postoperative PPM compared with BRF+Cryo (1.06%, 95% CI 0.60–1.86 vs 3.91%, 95% CI 2.07–7.27, respectively; p=0.0025), and a lower late mortality IR compared with BRF+Cryo (0.06%/month, 95% CI 0.02–0.12 vs 0.22%/month, 95% CI 0.12–0.41, respectively; p=0.0084). There were no other significant differences among the three groups regarding the secondary outcomes, particularly including AF at discharge. Sensitivity analysis did not report any significant variation in the estimated outcomes. The secondary outcomes are summarised in Supplementary Table S8.

Meta-Regression Analysis

The meta-regression of the primary outcomes found that BRF was associated with a higher rate of AF recurrence at 6 months (p=0.0025), 1 year (p=0.0294), 3 years (p=0.039), and 4 years (p=0.0047) with respect to Cryo. Similarly, Cryo had a significantly lower rate of patients with AF recurrence compared with BRF+Cryo at the 6-month timepoint (p=0.0333), while no significant differences were reported beyond this timepoint. No other differences were noted within the meta-regression (Table 2).

In the entire cohort, a higher left ventricular ejection fraction (LVEF) was a protective factor for AF relapse (p=0.0458), while the mean left atrial (LA) diameter was found to be a risk factor for arrhythmia recurrence (p=0.0017) on univariable meta-regression. Only LA diameter proved to be significant on multivariable meta-regression (OR 1.04, 95% CI 1.01–1.08; p=0.0159).

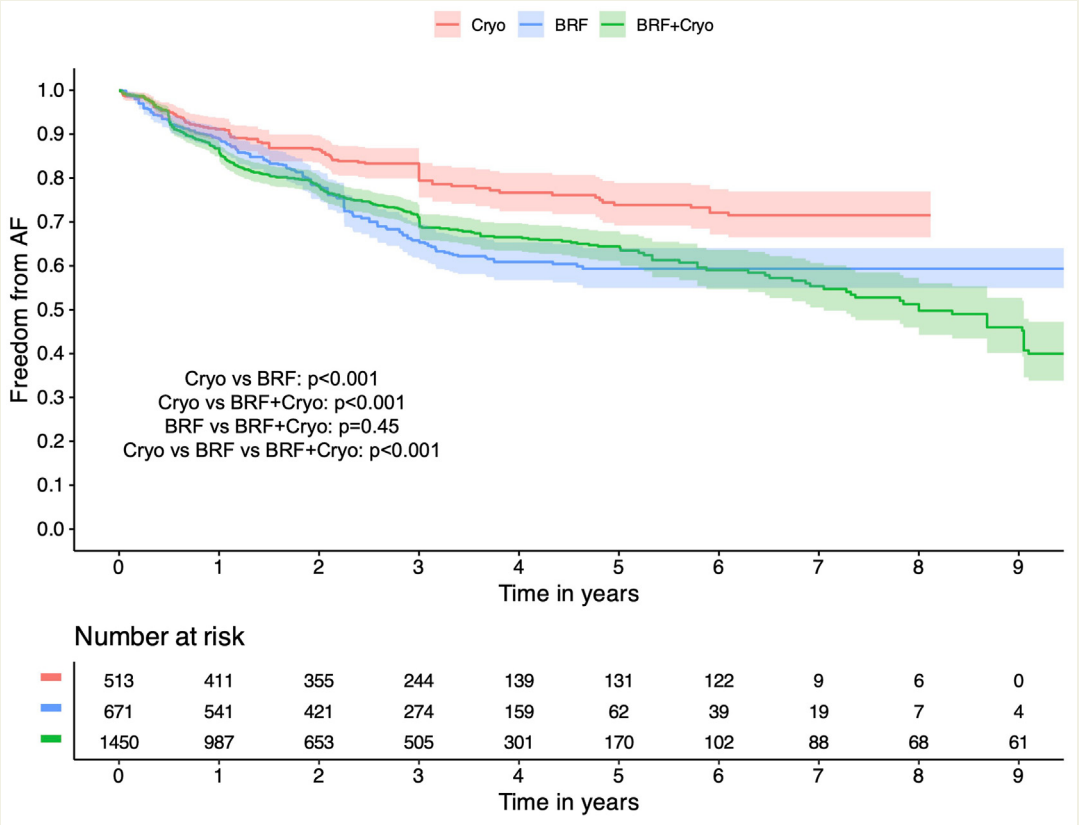

Figure 1 Freedom from atrial fibrillation among the different energy sources. p-values represent pairwise group comparison through the log-rank test.
Abbreviations: AF, atrial fibrillation; BRF, bipolar radiofrequency; Cryo, cryoablation.

When the Cryoenergy subgroup was considered, mean LA diameter was identified as a risk factor for higher AF IR, with an increase of 6% for each millimetre of LA diameter (p=0.0436). In this group, higher LVEF and lone ablation were protective factors reducing AF IR at follow-up (OR 0.90, 95% CI 0.83–0.97; p=0.0074 and OR 0.89, 95% CI 0.81–0.98; p=0.0218, respectively). However, only LVEF remained significant at multivariable meta-regression (p=0.0218).

In the BRF subgroup, a history of cerebrovascular accidents (p=0.0356) and LA diameter (p=0.0016) were found to be predictive factors increasing the risk of AF, while LAA occlusion was a protective factor (p=0.0038) for AF recurrence at follow-up; all of them maintained their significance at multivariable analysis (OR 1.13, 95% CI 1.07–1.19, p<0.0001; OR 1.02, 95% CI 1.01–1.05, p=0.0496; OR 0.92, 95% CI 0.88–0.97, p=0.0004, respectively).

In the BRF+Cryo group, concomitant interventions on the tricuspid valve (OR 1.01, 95% CI 1.00–1.03; p=0.0188), aorta (OR 1.17, 95% CI 1.02–1.34; p=0.0260), and two or more concomitant procedures (OR 1.02, 95% CI 1.00–1.04; p=0.0492 and OR 1.05, 95% CI 1.04–1.06; p<0.0001, respectively) were associated with higher AF recurrence. Multivariable analysis could not be performed as the number of parameters to be estimated was larger than the number of observations.

Univariable and multivariable meta-regressions are summarised in Supplementary Table S9 and Table 3.

Discussion

The efficacy of AF ablation devices relies on the capability of performing continuous transmural lesions, thus determining a complete conduction block interrupting the propagation of activation waves and macro-micro re-entrant circuits. On the other hand, safety is related to the possibility of effectively controlling thermal spread, thus avoiding collateral damage of the surrounding structures [4].

Radiofrequency produces thermal injury by a high-frequency alternating current that physically causes heating. Myocardial cell proteins are thus denatured and irreversibly dried [15]. Bipolar RF demonstrated a high safety and effective profile in producing reliable transmural lesions (effectiveness) with very limited energy spread (safety), which is different from unipolar RF [16,17]. For this reason,

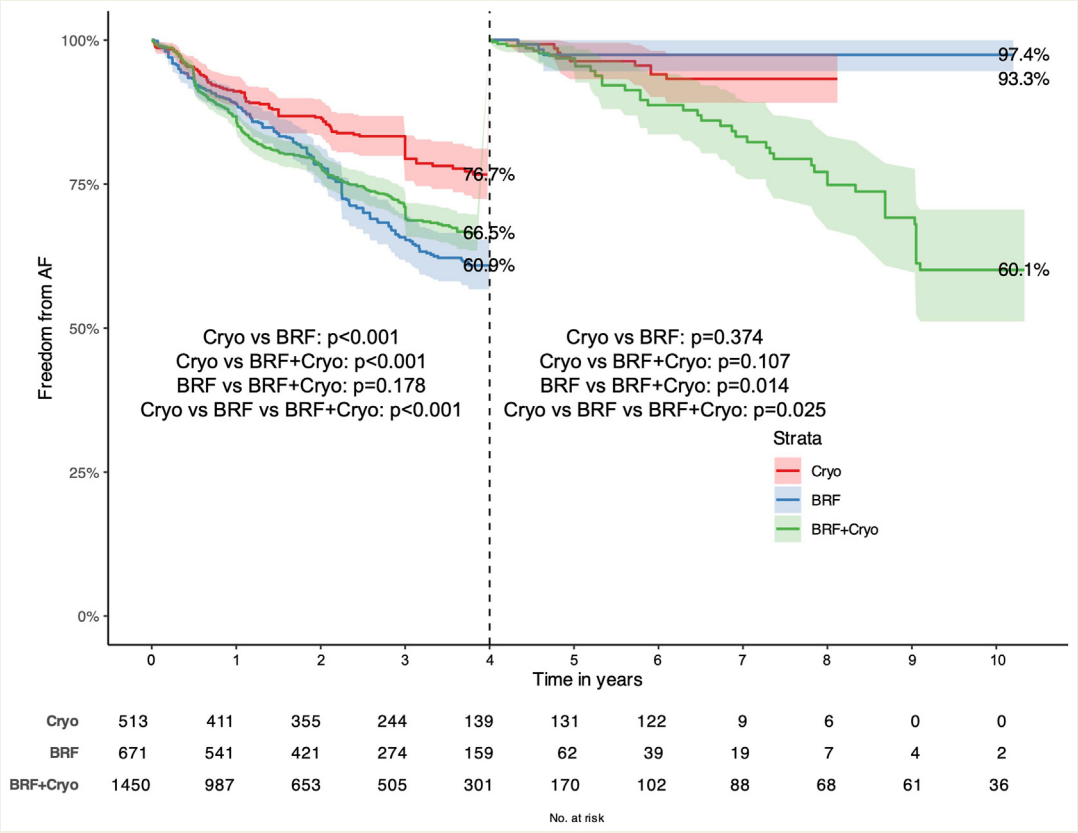

Figure 2 Landmark analysis of the freedom from atrial fibrillation among the different energy sources. The cutoff point was set at 4-years follow-up. p-values represent pairwise group comparison through the log-rank test.
Abbreviations: AF, atrial fibrillation; BRF, bipolar radiofrequency; Cryo, cryoablation.

studies employing unipolar RF were excluded from this analysis.

Cryoablation acts by direct physical injury using thermal cooling able to induce molecular-based cell death [18]. A refrigerated gas in a fluid state (nitrous oxide or argon) is pressurised to the inner lumen of the probe, where it is converted from liquid to gas and cools the tissue by energy absorption [19]. Due to the preservation of fibrous tissue and collagen, Cryo is considered one of the safest energy sources [4]. Concerns about safety have been dispelled by unequivocally demonstrating that no damages occur when used in proximity to coronary arteries (right coronary artery, cavotricuspid isthmus; circumflex artery, mitral annular lesion) and when directly applied to produce the coronary sinus ablation line. Cryoablation is often regarded as a safer option, since cooling the coronary arteries does not directly lead to coagulative necrosis. Cryoablation has been shown not to increase the risk of coronary lesion in the ablation territories during follow-up [20]. However, despite this advantage, damage to the major coronary branch in the atrioventricular groove has been documented with all types of ablation energy, including Cryo [21]. Moreover, Cryo was associated with higher atrial contractility restoration rate (48.8% vs 32.2%) and superior LVEF (59.1%±6.3% vs 53.1%±11.5%) than BRF [9].

Both BRF and Cryo are the most frequently recommended energy sources for AF ablation. However, studies directly comparing these technologies are scant and conclusions are far from univocal. Ad and colleagues [8] reported significantly higher restoration rates to sinus rhythm without antiarrhythmic drugs in the lone cryoablation group compared with BRF+Cryo at 6, 36, and 60 months. On the other hand, Kim et al. [9] did not find significant rhythm outcome differences between Cryo and BRF, even if the latter had higher AF rates at 1 year. Nevertheless, cryoablation was associated with a higher atrial contractility restoration rate and better LVEF than BRF ablation. Similarly, in the study by Vural et al., the maintenance rate of sinus rhythm was similar between BRF and Cryo [10].

Considering the ongoing debate regarding the optimal energy source, this meta-analysis aimed to compare the incidence of AF recurrence when Cryo, BRF, or a combination of both were used for AF ablation in patients undergoing the Cox-maze IV procedure. Early rhythm outcomes defined as AF at discharge were not found to differ among the three groups (p=0.6620). At the timepoint analysis, AF

Table 2 Meta-regression of the primary outcomes by energy source.

Outcome	OR (95% CI)	p-value
AF at 3 months (Cryo=Ref)		
BRF	3.41 (0.86–13.63)	*0.0821*
Cryo+BRF	1.25 (0.30–5.20)	0.7550
AF at 6 months (Cryo=Ref)		
BRF	4.82 (1.74–13.34)	**0.0025**
Cryo+BRF	2.70 (1.08–6.74)	**0.0333**
AF at 1 year (Cryo=Ref)		
BRF	2.06 (1.07–3.96)	**0.0294**
Cryo+BRF	1.45 (0.77–2.72)	0.2467
AF at 2 years (Cryo=Ref)		
BRF	2.37 (0.75–7.48)	0.1430
Cryo+BRF	1.82 (0.64–5.18)	0.2606
AF at 3 years (Cryo=Ref)		
BRF	6.23 (1.80–21.62)	**0.0039**
Cryo+BRF	1.31 (0.59–2.92)	0.5050
AF at 4 years (Cryo=Ref)		
BRF	12.04 (2.15–67.6)	**0.0047**
Cryo+BRF	2.08 (0.56–7.69)	0.2705

Bold denotes $p<0.05$; italics denote $p<0.1$ and $p>0.05$.
Abbreviations: AF, atrial fibrillation; BRF, bipolar radiofrequency; CI, confidence interval; Cryo, cryoablation; OR, odds ratio; Ref, reference.

incidence was lower in most of the observations for Cryo compared with lone BRF, with high rates of heterogeneity; this was confirmed at the meta-regression, which further analysed the outcomes addressing potential sources of heterogeneity. Reconstructed Kaplan–Meier curves for freedom from AF depicted an evident difference between the groups, with more favourable outcomes in the Cryo group when compared with BRF ($p<0.0001$) and BRF+Cryo ($p<0.0001$). These findings were confirmed at the 4-year landmark analysis ($p<0.001$ and $p<0.001$, respectively). Thus, Cryo showed a valuable advantage, at least over BRF alone, in the primary outcomes. Moreover, cryoablation showed a lower AF recurrence rate regardless of the presence of a larger LA mean diameter in this group when compared with the other groups (BRF and BRF+Cryo). As confirmed by the literature [22], LA diameter was identified in the meta-regression analysis as an independent predictor of AF recurrence.

Conversely, the differences were more subtle in the comparison between Cryo and BRF+Cryo. An advantage for Cryo was observed ($p=0.0086$) when compared with BRF+Cryo only at the 6-month timepoint, which was confirmed at meta-regression ($p=0.0333$). The choice between the two techniques may be more related to the complexity of the surgery. Cryoablation is a more time-consuming procedure considering the freezing and defrosting time to perform multiple lesions. Moreover, the tissue remains frozen for several minutes before returning to a pliable state, potentially prolonging the procedural time. Hence, a combination of the two energy sources may represent a valuable option in case of complex surgery, although more expensive in terms of costs.

At the 4-year timepoint, BRF+Cryo showed significantly lower AF rates when compared with BRF ($p=0.0262$); however, this finding was not confirmed with survival freedom AF curve analysis. A possible explanation of such contrasting findings may lie in the reduced number of studies reporting the outcomes with survival curves, thus affecting the reliability of the analysis, particularly for the BPR group.

Several factors have been suggested to negatively influence the efficacy of BRF ablation. Despite bipolar clamping devices being demonstrated to be effective in the creation of transmural lesions, adipose epicardial tissue, technical features of the clamp (irregular contact pressure between the jaws of the clamp), and anatomical aspects may hamper BPR ablation itself. Devices presenting a hinged opening/closure structure have a reduced contact pressure, reducing the efficacy of the ablation at the tip of the jaws [23]. Moreover, BPR clamps are limited in the completion of mitral and tricuspid isthmus lesions: the tip of the endocardial jaw cannot reach the mitral and tricuspid annulus, leaving a gap that may determine onset of postoperative arrhythmias, eventually jeopardising the efficacy of the procedure [24].

Interestingly, this meta-regression analysis confirmed that rhythm outcomes are negatively influenced by larger atrial sizes ($p=0.0017$). A severely dilated LA is considered an independent predictor for AF recurrences, as well as a risk factor for early mortality and thromboembolic events [25]. Outcomes of Cryo and BRF+Cryo were shown to be influenced by the presence and number of concomitant procedures. Lone ablations were associated with better rhythm outcomes in the Cryo group ($p=0.0218$), while concomitant procedures negatively affected rhythm outcomes in the BRF+Cryo group. However, these results could not be confirmed with the multivariable analysis.

Strengths and Limitations

It is believed that this is the first meta-analysis comparing BRF and Cryo rhythm outcomes after Cox-maze, which were investigated through different analyses to be as thorough as possible and include the maximal number of studies. To avoid lesion set influence, only biatrial Cox-maze studies were included, while studies using unipolar RF were excluded.

This meta-analysis had some limitations. First, the three groups significantly differed in many baseline characteristics and the concomitant procedures performed. This may have influenced the final analysis of the rhythm outcomes together with high rates of heterogeneity. The freedom from AF analysis suffered from important limitations: data could only be retrieved for a third of the included papers (18 of 60) and, despite the elevated precision, it was constructed from indirectly derived data. The results were obtained from Kaplan–Meier-derived IPD, not from real IPD. With this technique it was not possible to analyse predictors of the

Table 3 Multivariable meta-regression of atrial fibrillation incidence rate by patients' baseline demographics and concomitant surgical procedures.

Variable	Overall – OR (95% CI) p-value	Cryoablation – OR (95% CI) p-value	Bipolar radiofrequency – OR (95% CI) p-value	BRF+Cryo – OR (95% CI) p-value
History of CVA %			**1.13 (1.07–1.19), <0.0001**	N/A
Mean LVEF	0.96 (0.91–1.01), 0.1320	**0.85 (0.74–0.98), 0.0218**		
Mean LA diameter	**1.04 (1.01–1.08), 0.0159**	0.96 (0.88–1.05), 0.3854	**1.02 (1.01–1.05), 0.0496**	
Lone ablation %		0.92 (0.80–1.06), 0.2425		
LAA occlusion %			**0.92 (0.88–0.97), 0.0004**	

Bold denotes $p<0.05$; italics denote $p<0.1$ and $p>0.05$.

Abbreviations: BRF, bipolar radiofrequency; CI, confidence interval; Cryo, cryoablation; CVA, cerebrovascular accident; LA, left atrial; LAA, left atrial appendage; LVEF, left ventricular ejection fraction; N/A, not applicable; OR, odds ratio.

rhythm outcome, as individual patient data were lacking. Finally, the multivariable meta-regression was limited by the number of observations regarding the BRF+Cryo group.

Conclusions

Independent from the energy source, the Cox-maze IV proved to be a powerful tool in the surgeon's hands for patients undergoing AF ablation, with low rates of postoperative and late CVA, PPM, and mortality when correctly performed. Cryoablation was associated with better rhythm outcomes when compared with radiofrequency ablation. However, these results need to be confirmed by powerful, prospective RCTs.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

C.M. reports a consulting fee for Estech, Corcym. S.B. reports a consulting fee for AtriCure Inc., Artivion, Medtronic Inc.

Appendices

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2024.10.014

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