Prevalence and outcome of early recurrence of atrial tachyarrhythmias in the Cryoballoon vs Irrigated Radiofrequency Catheter Ablation (CIRCA-DOSE) study

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BACKGROUND Early recurrence of atrial tachyarrhythmia (ERAT) is common after pulmonary vein isolation (PVI) and has been associated with an increased risk of late atrial fibrillation (AF) recurrence.

OBJECTIVE The purpose of this study was to determine the incidence and outcomes of patients experiencing ERAT after PVI using advanced-generation ablation technologies.

METHODS This is a prespecified substudy of the CIRCA-DOSE (Cryoballoon vs Irrigated Radiofrequency Catheter Ablation: Double-Short vs Standard Exposure Duration) trial, a prospective, randomized, multicenter study comparing PVI with contact force–guided radiofrequency ablation to secondary-generation cryoballoon ablation for paroxysmal AF. All study patients received an implantable cardiac monitor to allow continuous rhythm monitoring. ERAT was defined as any recurrent atrial tachyarrhythmia within the first 90 days after AF ablation.

RESULTS ERAT occurred in 61% of the 346 patients at a median of 12 days (range 1–90 days) after ablation. ERAF was a significant predictor of late recurrence (60.1% with ERAF vs 25.9% without ERAF; P < .001). Receiver operating curve analyses revealed a strong correlation between ERAT timing and burden and late recurrence. Multivariate analysis identified ERAT timing (hazard ratio [HR] 2.90; 95% confidence interval [CI] 1.41–5.95; P = .004) and burden (HR 1.05 per 1% ERAF burden; 95% CI 1.04–1.07; P < .001) as strong independent predictors of late recurrence. Incidence rate, timing, burden, and prognostic significance of ER did not differ between the study groups.

CONCLUSION ERAT remains common after PVI despite use of advanced-generation ablation technologies. Early AF recurrence beyond 3 weeks after ablation is associated with increased risk of late recurrence.

KEYWORDS Atrial fibrillation; Atrial fibrillation burden; CIRCA-DOSE; Early recurrence of atrial fibrillation; Implantable cardiac monitor

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Introduction
Early recurrence of atrial fibrillation (ER), which has been defined as any recurrence of symptomatic or asymptomatic atrial fibrillation (AF) within the first 3 months following an ablation procedure, is a relatively common occurrence.

The immediate postablation period is characterized by a multitude of electrical and physical changes, including direct mechanical injury, atrial inflammation, and autonomic nervous system alterations, all of which predispose to AF recurrence through alterations in atrial myocardial conduction and refractoriness. These transient proarhythmic processes usually subside at some point within 3 months after the procedure, such that many have considered the first 3 months after AF ablation to be a “blanking” period, wherein recurrences are not considered a treatment failure, as they may not predict long-term recurrence. However, approximately one-half of the patients with ER will continue to experience atrial tachyarrhythmias during further follow-up, suggesting a need to identify characteristics of an early clinical course that better predict true longer-term outcome.

There is limited comparative data regarding the prevalence and impact of ER following advanced-generation catheter ablation technologies (contact force–guided radiofrequency [RF] ablation and advanced-generation cryoballoon-based ablation). Moreover, previous studies examining the significance of ER timing have been limited by a reliance on noninvasive intermittent monitoring.

A fundamental strength of the CIRCA-DOSE (Cryoballoon vs Irrigated Radiofrequency Catheter Ablation: Double-Short vs Standard Exposure Duration) study was the use of continuous cardiac rhythm monitoring, which allows us to precisely define the timing of early and late arrhythmia recurrence.

We sought to determine the prevalence and clinical impact of ER using contemporary advanced-generation AF ablation technologies, as well as to use the continuous monitoring data available in this study to provide empirical evidence to redefine a more clinically predictive postprocedure blanking period. The current report is a prespecified subanalysis of the multicenter prospective randomized CIRCA-DOSE study.

Methods
Study design
The CIRCA-DOSE study (ClinicalTrials.gov Identifier: NCT01913522) was a multicenter, prospective, parallel-group, single-blinded randomized clinical trial, with blinded endpoint ascertainment conducted at 8 clinical centers in Canada. Details of the protocol have been reported previously. The study was approved by the Institutional Ethics and Review Board of each participating center. The steering committee was responsible for the study design, conduct, and reporting. Data monitoring, collection, and primary data analysis were performed by the Montreal Health Innovations Coordinating Centre (MHICC) and the steering committee.

In brief, 346 patients with symptomatic paroxysmal AF and failure of at least one class I or III antiarrhythmic drug were randomized in a 1:1:1 ratio to (1) contact force–guided radiofrequency (CF-RF) ablation; (2) short (2-minute) cryoballoon ablation (CRYO-2); or (3) standard (4-minute) cryoballoon ablation (CRYO-4). Patients were blinded to their randomization assignment.

Arrhythmia monitoring on follow-up
As part of the study protocol, all enrolled patients underwent insertion of an implantable cardiac monitor (ICM) (Reveal LINQ, Medtronic, Minneapolis, MN) a minimum of 30 days before the index ablation procedure. Arrhythmia monitoring included automatic daily transmissions from the ICM and patient-triggered symptomatic arrhythmia episodes. All patients were followed for 12 months following the index ablation with clinical visits, including a resting 12-lead electrocardiogram (ECG) and 24-hour ambulatory Holter at 3, 6, and 12 months. All ICM transmissions were analyzed by an independent adjudication committee that was blinded with regard to clinical characteristics and the type of ablation procedure. Antiarrhythmic drugs (except amiodarone) were allowed during the 3-month blanking period but were discontinued 5 half-lives before the end of the blanking period. All patients were followed for 1 year after the index ablation procedure.

Endpoints and outcomes
Early recurrence of atrial tachyarrhythmia (ERAT) was defined as any atrial tachyarrhythmia (AF, atrial flutter [AFL], or atrial tachycardia [AT]) occurring within the first 90 days after the index ablation procedure. Late recurrence (LR) was defined as the time to first recurrence of symptomatic or asymptomatic atrial tachyarrhythmia documented by 12-lead ECG, ECG rhythm strips, 24-hour ambulatory ECG (Holter), or ICM between days 91 and 365 postablation, or a repeat ablation procedure between days 0 and 365 postablation (the primary endpoint for the CIRCA-DOSE trial). An atrial tachyarrhythmia qualified as an arrhythmia episode if it lasted ≥30 seconds (on surface ECG rhythm strips, 24-hour ambulatory Holter monitor) or ≥120 seconds on ICM (the minimum programmable episode interval). Secondary arrhythmia endpoints included time to first recurrence of symptomatic atrial tachyarrhythmia between 91 and 365 days after ablation, and arrhythmia burden (percent time in AF).

Statistical analysis
Categorical variables were analyzed using the Fisher exact test or χ² test where indicated. Continuous variables were tested for normal distribution and analyzed using the Student t test, Mann-Whitney U test, analysis of variance, or Kruskal-Wallis test where indicated. Differences in AF or AFL/AT burden were assessed using the Kruskal-Wallis test. Survival free from recurrent AF or AFL/AT was evaluated by the Kaplan-Meier method and compared by the Mantel-Cox test. Hazard ratios (HRs) were evaluated by the Cox-Mantel-Haenszel method. Univariable and multivariable
analyses were performed using logistic regression and Cox proportional methods. Variables with $P < .1$ at univariate analysis were entered into the multivariate regression model. Receiver operator characteristic (ROC) curve analysis was performed to assess the correlation between ERAT episode timing and LR, as well as ERAT burden and LR. The value with the greatest discriminatory potential was selected based on Youden Index. All statistical tests were 2-sided, with a significance level of .05. Statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC), Stata 14.1 (StataCorp, College Station, TX), and GraphPad Prism 9.0 (GraphPad Software, San Diego, CA).

Results

A total of 211 of the 346 patients (60.9%) enrolled in the CIRCA-DOSE study experienced ER. Patients with ER had a significantly higher preablation AF burden (13.4% vs 5.3%; $P < .001$) and were more likely to have experienced acute pulmonary vein reconnection during the index ablation procedure (33.6% vs 21.5%; $P = .01$). Baseline characteristics were otherwise similar between patients with and those without ER (Table 1).

ERATs

Median time between the index ablation procedure and the first ER episode was 12 days (interquartile range [IQR] 89 days; range 1–90 days) (Figure 1A). Symptomatic ER occurred in 55 of 211 individuals (26.1%) with ER, with a median time between ablation to the first symptomatic ER episode of 11 days (IQR 25; range 1–365 days). Symptomatic ER occurred in 55 of 211 individuals (26.1%) with ER, with a median time between ablation to the first symptomatic ER episode of 11 days (IQR 25; range 1–365 days) (Figure 1B). There was no difference in symptomatic or asymptomatic ER among the 3 randomized groups (Supplemental Figure S1).

ER and LR

At 12 months after a single ablation procedure, recurrence of any atrial tachyarrhythmia after the blanking period (60.5% vs 24.6%; $P < .001$; HR 2.93; 95% confidence interval [CI] 2.15–3.99) and recurrence of symptomatic AT after the blanking period (31.6% vs 6.7%; $P < .0001$; HR 3.47; 95% CI 2.22–5.42) was significantly greater in patients with ER than in those without ER (Figure 2). Median time from ablation to any late atrial tachyarrhythmia was significantly shorter in patients with ER (5.8 months; IQR 3.3–12.0; range 3.03–17.3 vs 11.9 months; IQR 10.5–12.4; range 3.2–17.1; $P < .0001$) (Supplemental Table 1). AF burden from 91–365 days postablation was significantly greater in the group with ER than in the group without ER (1.90%; 95% CI 1.15%–2.65 vs 0.14%; 95% CI 0.01%–0.06%; $P < .0001$). Patients with ER were more likely to undergo per-protocol redo ablation procedures compared to patients without (23.7% vs 3.0%; $P < .001$). When stratified by the presence or absence of ER, there was no difference in LR among the 3 randomized groups (Supplemental Figure S2).

<table>
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<th>Table 1 Baseline characteristics</th>
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<td>EQSD score</td>
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<td>AFEQ score</td>
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Values are given as mean ± SD, n (%), or median (interquartile range) unless otherwise indicated.

AAD = antiarrhythmic drug; AF = atrial fibrillation; AFEQ = Atrial Fibrillation Effect on Quality of Life; BMI = body mass index; CIRCA-DOSE = Cryoballoon vs Irrigated Radiofrequency Catheter Ablation: Double-Short vs Standard Exposure Duration; COPD = chronic obstructive pulmonary disease; EQSD = EuroQol-5 Dimension; ER = early recurrence; LA = left atrial; LVEF = left ventricular ejection fraction; PV = pulmonary vein; TIA = transient ischemic attack.

ER timing and LR

The distribution of the 6575 ER episodes recorded throughout the 90-day period following the index ablation procedure is shown in Figure 3. Of these episodes, 3165 (48.1%) occurred between 0 and 30 days postablation; 1864 (18.7%) occurred between 31 and 60 days postablation; and 1546 (19%) occurred between 61 and 90 days postablation. Most episodes (6139 [93.4%]) were asymptomatic.

A total of 625 ER episodes occurred in patients without LR, whereas 5950 occurred in patients with LR of AT. ER episodes occurring in patients without LR of AT occurred at a median of 10.0 days (IQR 5.0–19.0), whereas ER episodes occurring in patients with LR of AT occurred later (median 35.0 days; IQR 17.0–61.0). ER episodes occurred in the first postablation month in 85% (534/625) of those without LR compared to 44% (2631/5950) of those with LR.

The 1-year freedom from recurrent atrial tachyarrhythmia after a single ablation procedure was 74.1% in the absence of ER, 59.9% in patients with first ER during the first month, and only...
27.8% in patients with first ER during the second and third months \((P < .001)\). ER episodes in the first, second, and third month of blanking were associated with 4.9, 26.8, and 63.4 times higher likelihood of LR. A similar trend was also observed for symptomatic ER, although the difference did not reach statistical significance \((P = .06)\) given the small number of events.

ROC analysis of all 6575 ER episodes as predictors of LR identified an area under the curve (AUC) of 0.79 (95% CI 0.77–0.81; \(P < .0001\)). The point on the ROC curve associated with the greatest discriminatory potential was 19.5 days (Youden index 0.47; sensitivity 70.7%; specificity 76.3%). A cutoff of 38 days was associated with 90% specificity for predicting LR, and 95% specificity could be reached at 52 days (Figure 4 and Supplemental Table 2).

**ER burden and LR**

Median ER burden was 0.03% (IQR 0.00%–1.02%; range 0%–81.7%). ER burden was significantly increased in individuals with LR (0.00%; IQR 0.00%–0.08%; range 0%–12.7%) vs 0.58% (IQR 0.01–3.92%; range 0.00%–81.7%; \(P < .001\)).

ROC analysis for ER burden during the blanking period identified an AUC of 0.77 (95% CI 0.71–0.82; \(P < .001\)). The point on the ROC curve associated with the greatest discriminatory potential was an ER burden of 0.46% (Youden index 0.46; sensitivity 56.1%; specificity 90.1%). A cutoff of 1.05% days was associated with 95% specificity for predicting LR (Figure 5 and Supplemental Table 2).
Figure 3  **Left:** Distribution early recurrence (ER) episodes recorded throughout the 90-day period blanking period. A total of 625 ER episodes occurred in patients without late recurrence (LR), whereas 5950 episodes occurred in patients with LR. **Right:** ER episodes occurring in patients without LR occurred at a median of 10.0 days (interquartile range [IQR] 5.0–19.0), whereas ER episodes occurring in patients with late recurrence of atrial tachyarrhythmia occurred later (median 35.0 days; IQR 17.0–61.0). ERAT = early recurrence of atrial tachyarrhythmia.

Figure 4  **Left:** Receiver operator characteristic (ROC) analysis assessing the optimal cutoff of early recurrence timing to predict late recurrence of atrial tachyarrhythmia. Area under the curve 0.79 (95% confidence interval 0.77–0.81; *P* < .0001). **Right:** The point on the ROC curve associated with the greatest discriminatory potential was 19.5 days (Youden index 0.47), although improved specificity was observed at 40 days (90% specificity) and 60 days postablation (96% specificity). ERAT = early recurrence of atrial tachyarrhythmia; LR = late recurrence.
ER by subtype of atrial arrhythmia

AF accounted for the vast majority of ERAT episodes (78.5%), with only 21.5% of all episodes being secondary to AFL/AT. Similar to early AF recurrence, 42.9% of early AFL/AT occurred during the first month and 57.1% during the second and third months after the index ablation. Mean delay until the first recurrence of AFL/AT was similar compared to early AF recurrence ($P = .10$). Supplemental Figure S3 shows the frequency distribution by subtypes of early atrial tachyarrhythmias during the first 3 months. The subtype of atrial arrhythmia did not affect the risk of late AF recurrence ($P = .92$). Recurrence of AFL/AT during the second or third month after the index ablation procedure significantly increased the risk of LR compared to arrhythmia recurrence during the first month (61.5% vs 38.5%; $P < .001$). Separate ROC analysis for early recurrence of AFL/AT showed comparable AUCs and the same predictive value as ROC analysis for early AF recurrence (Supplemental Figure S3) (AFL/AT: $AUC = 0.79$; 95% CI 0.74–0.83 vs AF: $AUC = 0.76$; 95% CI 0.74–0.78; $P = .35$). The point on the ROC curve associated with the greatest discriminatory potential was 17.5 days (Youden index 0.58; sensitivity 79%; specificity 79%), which was comparable to the predictive timing of early AF recurrence. In the case of recurrent AFL/AF, a cutoff of 64 days and 73 days was associated with 90% and 95% specificity, respectively, for predicting LR.

ER by randomized group

The proportion of patients with any form of ER ($P = .95$), median ER burden ($P = .60$), and median delay between the index ablation procedure and the first ER episode ($P = .90$) did not differ between randomized groups. Symptomatic ER occurred more frequently in the CRYO-2 group ($P = .01$); however, the prognostic significance of ER and the proportion of redo procedures was similar among the 3 study groups ($P = .76$). ROC analysis of ER episode timing and ER burden showed similar results in all 3 study groups.

Multivariable predictors for LR

The results of multivariate analysis are given in Table 2. Early recurrence of AF and ER burden were independently

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AF = atrial fibrillation; CI = confidence interval; ER = early recurrence of atrial fibrillation; HR = hazard ratio.
associated with late atrial tachyarrhythmia recurrence and redo ablation procedures.

**Discussion**

The CIRCA-DOSE trial was a prospective, randomized, single-blinded multicenter study with blinded endpoint adjudication comparing the efficacy and safety of contemporary advanced-generation ablation technologies for pulmonary vein isolation (PVI). This prespecified substudy is the first to provide a prospective comparison of the incidence, burden, and clinical importance of ERAT between advanced-generation ablation technologies, using continuous rhythm monitoring.

Key findings of this study include the following. (1) ERAT remains common despite the use of contemporary advanced-generation ablation technologies, occurring in up to 61% of patients. (2) ERAT incidence, timing, burden, and prognostic significance were independent of the ablation technology, with similar findings for contact force–enhanced RF ablation and second-generation cryoballoon ablation. (3) The majority of ER episodes were asymptomatic and occurred within the first month after ablation. (4) ERAT episodes during the second or third month after ablation were more prognostically significant and more likely to be symptomatic. (5) ERAT timing and ER burden were powerful predictors for late AF recurrence after PVI. (6) ERAT episodes occurring later than 38 days postablation were associated with >90% specificity for predicting LR. (7) ER burden ≥0.5% was associated with >90% specificity for predicting LR.

In accordance with previous studies, we confirmed the importance of ER as a powerful independent predictor for long-term procedural success. Previous studies reported variable incidences of ERAT, ranging from 16%–65% depending on the type of ambulatory rhythm monitoring used. However, these previous studies likely underestimated the true incidence of ERAT given their reliance on symptoms and/or noninvasive rhythm monitoring (eg, Holter or transtelephonic monitor recordings), which have limited sensitivity for detecting arrhythmia recurrence. A key strength of the present study is the use of ICMs for prospective, continuous monitoring of ER, which facilitated detection of all arrhythmia episodes including brief asymptomatic episodes. Notably, a minority of ERAT episodes in our series were symptomatic, with nearly 75% of individuals with documented ERAT remaining asymptomatic. As such, although the incidence of ER in the CIRCA-DOSE trial is among the highest reported, it most likely accurately approximates the true incidence of ERAT following catheter ablation.

ERAT timing and ER burden are independently linked to LR of atrial tachyarrhythmia. Atrial tachyarrhythmia recurrence during the second or third month after ablation significantly increased the risk of LR compared to episodes within the first month after PVI. These observations also may reflect the changing pathophysiological mechanisms whereby inflammation and electrophysiological remodeling is the most likely mechanism for ERAT within the first few weeks after ablation, with PV reconnection or nonpulmonary vein triggers becoming relatively more important later after ablation.

The current study is consistent with previous observations; however, the use of continuous cardiac monitoring has allowed us to better quantify the extent and significance of ERAT. Specifically, the majority of ERAT episodes in patients without LR were concentrated within the first postablation month (85%), whereas the majority of ERAT episodes in those with LR occurred after the first postablation month (66%). Although ROC analysis identified 19.5 days (sensitivity 70.7%; specificity 76.3%) as the interval with the greatest discriminatory potential, a more clinically useful cutoff would give greater weight to specificity than sensitivity. A blanking period of 5–7 weeks would improve the discriminative ability, predicting LR with >90% sensitivity and >95% specificity.

In addition, the use of continuous cardiac monitoring has allowed us to accurately quantify ER burden. We demonstrated that the quantitative ER burden is related to the long-term outcome after PVI. In our study, ER burden was a sensitive independent predictor of LR. The concept of AF burden during the blanking period as a predictor of LR was previously suggested by a large-scale retrospective study. While important, the main limitations preventing the clinical use of ER burden to predict treatment failure are (1) the recognition that the relative prognostic importance of ER burden varies depending on the timing of assessment; and (2) the need for continuous cardiac monitoring, as commonly used noninvasive rhythm monitoring is unable to accurately quantify AF burden. With respect to the former, ER burden assessed in the first postablation month was less likely to predict later recurrence; however, the same ER burden assessed in the second or third postablation month was much more likely to predict treatment failure. As such, ER burden may be less clinically useful when used in conjunction with the patient’s symptom burden for individualized clinical decisions. Instead, ERAT timing may be a more pragmatic method to assess the need for early reintervention when used in conjunction with the patient’s symptom burden.

**Redefining the blanking period**

Given the growing evidence base, there is clearly a need to redefine the postablation “blanking period” in order to better inform clinical decision-making in patients and to improve patient outcomes. Similar to previous studies, our data challenge the concept of the standard 90-day blanking period post-PVI. Whereas recent publications have used noninvasive rhythm monitoring to suggest that the postablation blanking period could be truncated to 23–50 days, our data using continuous cardiac monitoring suggest that >90% specificity for predicting LR can be observed more than 5 weeks postablation.

**Study limitations**

The CIRCA-DOSE trial enrolled patients with paroxysmal AF, and the ablation strategy was limited to PVI. Our results
cannot be generalized to patients with persistent AF or those undergoing more extensive ablation beyond PVI. In addition, most early and late recurrences observed in CIRCA-DOSE were asymptomatic and detected on continuous cardiac monitoring. However, symptomatic and asymptomatic ER were predictive of symptomatic and asymptomatic LR of atrial tachyarrhythmia, suggesting the findings are generalizable to the clinical realm. Despite the predictive value of ERAT timing and burden, asymptomatic ER and LR alone should not be the sole parameter to guide clinical management, including reinterventions in the absence of tachycardiomypathy. The primary goal of PVI is improvement of symptoms and quality of life. Thus, any therapeutic strategy for rhythm control should be based on the individual symptom status. Lastly, the CIRCA-DOSE trial was designed to evaluate LR of atrial tachyarrhythmias and was not specifically powered for the evaluation of ERAT. However, the observed ERAT prevalence exceeded the prespecified event rates for LR used in the index power calculation, suggesting that the current analysis was adequately powered to evaluate differences in the randomized ablation technologies.

Conclusion
ER remains common after PVI despite use of advanced-generation ablation technologies. The incidence of ER is independent of ablation technology, showing similar results for cryoablation or contact force–enhanced RF ablation. This predefined substudy of the CIRCA-DOSE trial provides empirical evidence in support of shortening the postablation blanking period to 5 weeks.

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2021.06.1172.

References