Editorial

FIRE or ICE for paroxysmal atrial fibrillation?—perspectives from the largest randomized evaluation of cryoballoon and radiofrequency ablation to date

Konstantinos C. Siontis[1], Peter A. Noseworthy[2]

[1]Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI, USA; [2]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

Correspondence to: Dr. Peter A. Noseworthy, MD. Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, 200 1st Street SW, Rochester, MN, USA. Email: Noseworthy.Peter@mayo.edu.

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For patients with symptomatic paroxysmal atrial fibrillation (PAF), radiofrequency (RF) catheter ablation is now a common procedure worldwide and its cornerstone is the point-by-point electrical isolation of the pulmonary veins (PVI) (1). While short-term symptom improvement is frequently the case after a single ablation procedure (2), the sustained success of the procedure depends largely on the completeness of the isolation. Most patients with recurrent arrhythmia have evidence of electrical reconnection between the PVI and the atrial tissue (3). Performing complete and lasting PVI requires meticulous point-by-point delivery of RF ablation which can be tedious and is prone to incomplete lesion sets. To overcome this limitation and improve the efficiency of the procedure, a balloon-based catheter technology was developed with which a single circumferential isolation lesion can be delivered to the pulmonary vein antra via a catheter-guided cryotherapy balloon. This approach showed promising results and favorable learning curves in early feasibility studies (4,5) and in the Sustained Treatment of Paroxysmal Atrial Fibrillation (STOP AF) trial, the first randomized comparison of cryoballoon ablation versus antiarrhythmic drug therapy (6). In STOP AF, all four PVs were successfully isolated in 97.6% of patients and 12-month freedom from recurrent arrhythmia was ~70%. Results of randomized comparisons with the control group being treated with conventional RF ablation emerged shortly thereafter. In the Cryo *vs.* RF trial, 237 patients were randomized to first-generation cryoballoon ablation, RF ablation, or a combination of the two (7). The 1-year success rate (freedom from atrial arrhythmia after single procedure) was significantly higher in the cryoballoon group compared to the RF group (67% *vs.* 47%, P<0.001), while the combined approach was not significantly better than cryoballoon ablation alone. In the FreezeAF trial of 315 patients with PAF, cryoballoon ablation was non-inferior to RF and 6-month procedural success was about 63% for both groups after a single procedure (8).

Following these encouraging early results, cryoballoon ablation begun being utilized as an alternative to RF ablation, while more definitive data on the comparative performance of the two techniques was awaited. Establishing such definitive evidence was the goal of the FIRE AND ICE trial (9) which was designed to address the question: is cryoballoon ablation non-inferior to the conventional point-by-point RF ablation in terms of efficacy and safety? A total of 762 patients with drug-refractory, symptomatic PAF from 16 centers in eight European countries were enrolled and 750 patients were randomized 1:1 to the two techniques between 2012 and 2015. None of the included patients had undergone a prior ablation procedure. Patients were followed at regular clinic visits and arrhythmia surveillance was performed with 24-hr ambulatory ECG at

each clinic visit, weekly transtelephonic ECG transmissions, and based on symptoms. For efficacy, the primary endpoint was a composite of documented recurrent AF (duration >30 seconds), atrial flutter or tachycardia, prescription of antiarrhythmic drugs (class I or III), or repeat ablation. A blanking period of 90 days was implemented for the primary endpoint, as early recurrences after ablation do not predict long-term outcome. The primary safety endpoint was a composite of death from any cause, stroke or transient ischemic attack from any cause, and other serious adverse events.

Procedures were shorter in the cryoballoon group (mean 124.4 *vs.* 140.9 minutes) but utilized more fluoroscopy (mean 21.7 *vs.* 16.6 minutes). Acute procedural success (complete PVI) was high in both the cryoballoon and RF ablation groups (98.9% and 97.9% of all PVIs in the respective groups). Patients were followed for a mean of 1.5 years. After the 90-day blanking period, in intention-to-treat analysis the primary efficacy endpoint occurred in 138 patients in the cryoballoon group and 143 patients in the RF group leading to an estimated hazard ratio of 0.96 (95% confidence interval 0.76–1.22) with P<0.0001 for non-inferiority. The effect estimate was similar in a per-protocol analysis. The primary safety endpoint occurred in 40 patients in the cryoballoon group and 51 patients in the RF group (hazard ratio 0.78, 95% confidence interval 0.52–1.18, P=0.24). There was a trend towards more groin-site complications in the RF group (4.3% *vs.* 1.9%) and more phrenic nerve injury in the cryoballoon group (2.7% *vs.* 0% at the time of discharge). There were no differences between the two groups in the frequency of cerebrovascular events, cardiac tamponade, atrio-esophageal fistula, or pulmonary vein stenosis, all of which were rare or did not occur at all during this study.

The FIRE AND ICE trial is the largest randomized comparison of cryoballoon versus RF ablation in PAF to-date and indicates that the two approaches have overall comparable efficacy and safety profiles. So, if the two interventions appear equivalent, how does one choose the one over the other? The current state of the evidence would suggest that the main tangible difference between the two approaches is the simplicity and shorter procedure duration with cryoballoon. This alone may be sufficient reason for many providers and patients to favor cryoballoon as a first-line approach to PAF ablation, but additional factors can facilitate the selection of the optimal strategy. For example, the acute and long-term outcomes of cryoballoon ablation may be impacted by the anatomy of the PVI and their spatial interaction with the balloon (10,11). Thus, patients with unfavorable pulmonary vein anatomy for cryoballoon ablation may be better served by RF ablation. The secondary endpoints reported in a subsequent analysis of the FIRE AND ICE trial also offer potentially useful insights on the comparative performance of the two interventions (12). In comparison to RF ablation, cryoballoon ablation was associated with a lower risk of re-ablation (11.8% *vs.* 17.6%; P=0.03), direct-current cardioversion (3.2% *vs.* 6.4%; P=0.04), all-cause re-hospitalization (32.6% *vs.* 41.5%; P=0.01), and cardiovascular re-hospitalization (23.8% *vs.* 35.9%; P<0.01). However, this was an unblinded trial, thus any endpoints related to follow-up therapeutic interventions should be interpreted cautiously, as the decision to treat a patient one particular way or another may have been biased by knowledge of their assigned randomized treatment. Also, unlike the primary analysis, these secondary comparisons included events within the 90-day blanking period. Curiously, despite these significant differences in repeat procedures, cardioversions and hospitalizations between the two arms, all quality of life measures improved to similar extents throughout the 30 months of follow-up.

Cryoballoon ablation was generally safe in the FIRE AND ICE trial. Serious adverse events were uncommon and the majority of them pertained to phrenic nerve injury, which may be regarded as the Achilles heel of cryoballoon ablation and occurred in 10 (2.7%) of patients. In 9 of these 10 patients, the phrenic nerve palsy resolved within 12 months post-ablation. This is consistent with previous observations where phrenic nerve palsy was shown to be typically a transient phenomenon (13). Interestingly, a trend towards more post-ablation atrial flutters/tachycardias was noted in the RF group, which may be a suggestion of more incomplete PVIs or tissue heterogeneity along the ablation line in that group.

One of the criticisms of the FIRE AND ICE trial is that it utilized various different catheters, which may not reflect the most contemporary practice patterns: two different generations of cryoballoon (first-generation Arctic Front® and second-generation Arctic Front Advance®) and three generations of RF catheters (ThermoCool®, ThermoCool® SF, and ThermoCool SmartTouch®). The second-generation of the cryoballoon has a larger surface area of coolant distribution, while the first-generation cryoballoon distributes the refrigerant to an equatorial belt on the balloon's surface. This difference in the width of the freezing zone may be associated with differences

in the durability of the PVI and prior investigations have suggested superior freedom from recurrent AF with the second-generation cryoballoon (14). With regards to RF catheter technology, contact-force sensing is becoming an integral component of RF ablation procedures and it has been shown to improve long-term outcomes when the technology is properly employed (15). Thus, one could argue that the exclusive use of the second-generation cryoballoon and the contact-force sensing RF catheter could have led to different conclusions regarding the comparative effectiveness of the two interventions. Even though small observational studies have suggested that the second-generation cryoballoon and the contact-force sensing RF catheter may have similar long-term effects (16), results from a randomized comparison are lacking.

The theoretical advantage of the cryoballoon approach, i.e. the more complete and durable PVI that may lead to fewer AF recurrences, was not corroborated in this randomized trial, in the FreezeAF trial (8), or in any of the preceding observational studies (16). This may be due to several factors, some of which remain unknown. All operators in the FIRE AND ICE trial have extensive experience with RF ablation, thus results of RF ablation could represent ideal outcomes compared to real world settings outside of a clinical trial. However, the counterargument is that this could very well be the case also for the cryoballoon ablation arm as well. Regardless of operator expertise, it should be recognized that RF ablation is an established technique that has been used and refined for over two decades, whereas cryoballoon ablation is relatively new and may not have yet reached its maximum potential in terms of optimizing patient selection, catheter performance, application of cryo-lesions, and post-ablation care.

Several questions remain and should be the focus of future research, such as the role of cryoballoon ablation in persistent AF for PVI with or without additional targets; a randomized comparison of the second-generation cryoballoon with the contact-force sensing RF catheter; the assessment of the cost-effectiveness of the most contemporary cryoballoon and RF ablation technologies; and the development of strategies to minimize the risk of phrenic nerve injury, which will be critical for the more widespread adoption of cryoballoon ablation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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