To burn or to freeze: a burning question yet to be resolved

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This editorial refers to ‘Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial’, by K.-H. Kuck et al. on page 2858.

Recently, the FIRE AND ICE Trial comparing cryoballoon ablation and radiofrequency catheter ablation (RFCA) in patients with symptomatic, drug-refractory paroxysmal atrial fibrillation (AF) was reported.1 This was a randomized controlled non-inferiority trial with the primary efficacy endpoint of time to first documented recurrent AF or atrial tachycardia (AT), prescription of antiarrhythmic drugs (AADs), or repeat ablation after a 90-day blanking period.2 After a mean follow-up of 1.5 years, non-inferiority of cryoballoon ablation was confirmed; the two treatments did not differ with respect to either efficacy or overall safety (a composite of all-cause death, all-cause cerebrovascular events, and serious treatment-related adverse events).1 In the current issue of the journal, the authors publish some of the secondary endpoints from the FIRE AND ICE trial,3 namely all-cause and cardiovascular rehospitalizations, repeat ablations, direct current cardioversions, and quality of life. These are indeed important endpoints to report, addressing both the healthcare burden of an intervention and the patients’ perception of success.

Cryoballoon ablation performed significantly better in reducing all-cause and cardiovascular rehospitalizations, including repeat ablations and direct current cardioversions, whereas there was no difference in improving quality of life. However, these findings raise some questions. For cardiovascular rehospitalizations, AF/AT recurrence was the main event driving the difference between groups. Why were these marked differences not accompanied by any alterations in the primary efficacy endpoint of arrhythmia control between the two groups? The primary efficacy endpoint was a composite endpoint that also included AT/AF recurrence/AAD prescriptions that did not result in rehospitalizations or repeat ablations. This analysis takes into account only those AT/AF recurrences that resulted in rehospitalizations. Therefore, one can infer that patients after RFCA are more symptomatic, requiring more cardioversions or repeat ablation compared with simple AAD prescription. However, it is important to note that this study also included events occurring in the blanking period. Considering the time-to-event curves and plots depicting events during follow-up, the difference in direct current cardioversions between groups was probably not significant beyond the blanking period. Similarly, for both all-cause and cardiovascular rehospitalizations, a larger difference in events occurred during the blanking period (Figure 1). Do the differences between groups mainly reflect a difference during the first 90 days? This might be explained by a heightened inflammatory response after RFCA, with consequent more frequent early recurrences, which did not appear to influence later clinical outcomes in this cohort. Another explanation could be a lower prevalence of persistent pulmonary vein (PV) isolation in this group. On one hand, operators in the participating centres were more familiar with cryoballoon ablation, and contact force was employed only in one-third of RFCA procedures. Moreover, there was no direction regarding maintenance of a contact force range, and power was delivered up to 30 W in the posterior wall and roof and 40 W in the anterior aspect of the PVs, without any mention of contact force-guided power titration. Lastly, no drug challenge (adenosine or isoproterenol) was employed after ablation—which has been proven useful with RFCA.4 It is also important to highlight that the study protocol specified that arrhythmia-related events during the blanking period would not be counted towards the primary endpoints.3 Therefore, this being an unblinded study, a potential bias may have affected the results as regards the decision on the type of intervention (AAD, cardioversion, or repeat ablation).

Another puzzling result is the difference in major bleeding events between groups. It is not easy to find a plausible explanation for it, and no clear definition for major bleeding is given. It does not appear to be related to a different rate in cardiac tamponades, also considering that adverse events occurring during the index hospitalization (such as cardiac perforation-related tamponades) should not be included in this analysis. In the original FIRE AND ICE trial, it was noted that a higher number of groin complications occurred in the
RFCA group. The authors explained it by the double femoral puncture, compared with the single puncture required for cryoballoon ablation. First, it is important to note that the use of ultrasound to guide access would have prevented this complication to begin with. Moreover, it is hard to believe that a bigger sheath did not lead to a similar rate of haematoma/psuedoaneurysm, unless some other confounding factor was not taken into account (for example, a difference in the prevalence of uninterrupted anticoagulation or obese people between the two groups). Thus, this may be just a random effect as it lacks plausibility. Finally, other major bleeding events that are not treatment related (such as intracranial or gastrointestinal hemorrhage), should not be considered.

After all, this is an analysis of secondary endpoints, not all of which were pre-specified. While hypothesis-generating, post-hoc analysis of data from a randomized trial principally should not be considered conclusive and need to be further tested by a trial specifically set up to test this hypothesis.

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References
A 21-year-old male was referred to our hospital with chief complaint of palpitations and exercise-induced dyspnoea for half a year. Physical examination indicated a diastolic murmur at the apex and electrocardiogram and Holter demonstrated persistent atrial fibrillation (Panel A). Transthoracic echocardiography and transoesophageal echocardiography revealed a membranous structure in the left atrium (LA) (Panel B, arrow). Three dimensionally reconstructed CT distinguished that the membrane at the left side of the interatrial septum separated the LA into two parts (Panel C, arrow), with a posterior superior accessory chamber (AC) receiving drainage from the four pulmonary veins (PVs), and the main left atrial chamber (MC) containing the LA appendage (MC). A diagnosis was cor triatriatum sinister (CTS) with persistent atrial fibrillation was made and the patient underwent surgical operation under cardiopulmonary bypass. Following pericardiotomy, electrophysiological mapping of the right atrium, PVs, posterior and anterior wall of LA and left atrial appendage was performed (Panel D). Mapping of the right and left PV antra and posterior wall of LA revealed the presence of complex fractionated electrograms (Panel E, arrow) in contrast to very regular organized electrical activity in the right atrium and left atrial appendage (Panel F, arrow). Both antra of the PVs were then isolated using the AtriCure bipolar radiofrequency (RF) ablation clamp (AtriCure, Inc., USA) (Panel G). After cardioplegia had been achieved, the membrane separating the LA into two chambers was resected (Panel H). Ablation of the posterior wall of LA with a box lesion set, left atrial appendage ablation, and mitral isthmus ablation were performed using the AtriCure RF ablation clamp and additionally, the left atrial appendage was surgically ligated. After rewarming, the cardiac rhythm was noted to be sinus rhythm (Panel I). Retesting of the PVs and linear ablation lesion sets confirmed isolation and bidirectional block across all lines. Pathological examination of the resected membrane revealed heterogeneous myocardial hypertrophy and fibrous tissue (Panel J). There was no recurrence of atrial fibrillation during a 3-month follow-up period.

Cor triatriatum sinister is a rare congenital cardiac anomaly in which a fibromuscular membrane subdivides the LA into two chambers. The prevalence of cor triatriatum is estimated to be ~0.1% in children with congenital heart disease and CTS presenting with atrial fibrillation is even more rare. Mapping prior to ablation in this case indicated that atrial fibrillation originated from the right and left PV antra and posterior wall of LA based on presence of complex fractionated electrical activity in these regions. One potential mechanism may be structural remodelling due to elevated blood pressure within the AC leading to electrical remodelling and maintenance of atrial fibrillation. In this case, resection of the intra-atrial membrane and surgical ablation were performed for optimal resolution of CTS with atrial fibrillation.