

Catheter ablation as first-line treatment for paroxysmal atrial fibrillation

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Pharmacotherapy has been the mainstay of atrial fibrillation (AF) treatment. As AF progresses from paroxysmal to persistent, electrical and structural remodelling of the atria may become irreversible, rendering future rhythm-control therapies less effective. Results of earlier trials on rhythm control were disappointing and failed to establish the superiority of a rhythm-control strategy on cardiovascular outcomes, including mortality. This was attributed to populations in trials having longer established, persistent AF with potentially more advanced atrial fibrosis; and suboptimal results in sinus rhythm maintenance with the use of antiarrhythmic drugs alone. A sub-analysis of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) trial showed that achieving and maintaining sinus rhythm was associated with better outcomes than AF rhythm, but this clinical benefit appeared to be offset by the adverse effects of antiarrhythmic drugs.¹

In recent years, substantial technical and technological advancements in AF therapies have led to the development of various AF ablation modalities. AF catheter ablation now plays a key expanding role in rhythm-control strategy through the isolation of pulmonary veins using various energy sources. The latest multisocietal guidelines recommend a trial of antiarrhythmic drugs prior to consideration for catheter ablation for patients with paroxysmal AF. However, the time from AF diagnosis to ablation has been identified as a modifiable and independent factor that is associated with AF ablation outcomes. There is an increasing body of literature supporting catheter ablation as a first-line therapy. Mechanistic studies have shown that catheter ablation led to substantial reversal of the adverse structural remodelling, which may potentially alter the natural history of AF in disease progression.² Early rhythm control with catheter ablation was also associated with an increased likelihood of AF-free survival, fewer repeated procedures, fewer recurrent hospitalisations, and a reduction in the progression to persistent AF.³⁻⁵ Compared to older studies, the Early Treatment of Atrial Fibrillation for Stroke Prevention (EAST-AFNET 4) trial reported an increasing con-

temporary trend of AF catheter ablation seen in the rhythm-control arm. Catheter ablation was performed in 8% of the study population at enrolment, and up to 19.4% by 2 years.⁶

The recently published multicentre PROGRESSIVE-AF trial, which was conducted at 18 centres in Canada, built on these observations and demonstrated improvement in clinical outcomes. There is primarily a 75% reduction in progression to persistent AF after first-line ablation in relatively young patients with a median age of 58 years, with few comorbidities—other than hypertension, sleep apnoea and obesity—and presenting with symptomatic episodes of AF.⁷ The median duration of AF was 1 year from the onset of diagnosis, again targeting a selected group of patients with early-onset AF.

In this issue of the *Annals*, Fong et al. sought to evaluate the effectiveness of various ablation therapies or medical therapy largely in patients with paroxysmal AF.⁸ Relevant studies involving patients with paroxysmal AF were selected in the analyses. First-line catheter ablation as a whole was associated with reductions in AF recurrence and hospitalisations and had a similar safety profile as antiarrhythmic drugs.⁹

In this review, a total of 24 reliable and high-quality studies comprising 18 randomised controlled trials (RCTs) and 6 propensity score matched studies (PSMs) were included to generate individual patient data (IPD) network meta-analysis (NMA), in which the raw individual-level data for each study were obtained and used for synthesis. The authors reported consistent findings that all ablation modalities were superior to antiarrhythmic drugs in achieving freedom from AF or atrial tachyarrhythmia as the primary outcome. An important challenge in interpreting the results from the analyses is knowing the variability in study design and methodologic differences among the included clinical studies. The use of IPD holds several statistical advantages and serves as a rigorous statistical method known to be particularly advantageous for time-to-event analyses.¹⁰

In addition to eliminating or reducing atrial tachyarrhythmia recurrences, it is also necessary to

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understand whether first-line ablation is effective in improving important clinical endpoints such as quality of life, heart failure, stroke and mortality. Due to the small study size and low event rates in the majority of RCTs and PSMs included in the review article, the analyses were underpowered to detect any hard clinical endpoints such as stroke, all-cause mortality, and periprocedural complications.

Nonetheless, freedom of AF or atrial tachyarrhythmia remains a key clinical parameter used in predicting clinical response with AF ablation. This was particularly observed in the EAST-AFNET 4 trial as the effectiveness of this trial in improving cardiovascular outcomes at 5 years was mediated by the maintenance of sinus rhythm at the end of the follow-up period,⁶ again highlighting the important need in the prevention of AF and atrial tachyarrhythmia recurrence. It is well recognised that the use of patient-reported symptoms alone is inadequate to detect the recurrence of AF or atrial tachyarrhythmia, given that many patients may develop asymptomatic episodes after ablation. However, significant heterogeneity in AF monitoring has also been noted. Options for monitoring of underlying cardiac rhythm include Holter monitors; longer-term monitoring such as 30-day event monitors; intermittent rhythm recording with devices such as the Apple Watch or KardiaMobile; and implantable loop recorders.

The main strength of the review article by Fong et al. lies in its comparison of multiple individual AF ablation modalities relative to antiarrhythmic drugs. Network meta-analyses from this review ranked the individual AF ablation modalities in a quantitative manner based on their respective P-score. The results favour combined cryoballoon-plus-radiofrequency ablation in the long term, and laser-balloon ablation in the short term. The authors commented that cryoballoon and radiofrequency ablation were complementary and more efficacious due to significantly fewer pulmonary vein reconnections. However, this advantage in procedural efficacy was offset by a longer procedural time compared to all other ablation modalities based on NMA of procedure time. However, there are insufficient clinical data to justify the use of one ablation modality over another. Moreover, it is still important to bear in mind that such results from meta-analyses may not lead to further advancement in knowledge relating to the topic of interest when the

main findings are driven by the results of one trial. This is particularly the case when the technique of combined cryoballoon plus radiofrequency ablation was only performed in a single study.

In conclusion, the authors ensured the reliability and stability of results through layers of data analysis, including tests for publication bias and sensitivity analysis of the results. The review article provided greater evidence to support first-line ablation as a more effective and safe method for early rhythm control strategy in selected patients with paroxysmal AF. Extended and large-scale clinical trials and cost-benefit analyses are therefore required to further determine the optimal approach and timing to first-line AF ablation.

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