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EDITORIAL
Arrhythmias

Ablation of persistent atrial fibrillation: never say never again

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This editorial refers to 'Catheter ablation for persistent atrial fibrillation: patterns of recurrence and impact on quality of life and health care utilization', by R. Crowley *et al.*, https://doi.org/10.1093/eurheartj/ehae291.

Graphical Abstract

Trial	Population	Trial Arms	N	% Persistent AF	12-month post ablation burden Ablation versus AAD	Healthcare utilization	QoL at 12 months
CABANA[7]	▪ Age ≥ 65 years or age < 65 years with ≥1 stroke risk factors ▪ ≥2 episodes of paroxysmal AF or ≥1 episodes of persistent AF in <6 months prior	Catheter ablation VS Antiarrhythmic drugs (AADs)	1108	47.3% persistent AF 10.3% longstanding persistent AF	Paroxysmal AF: 2% AF burden in ablation vs 8% AF burden in AADs Persistent AF: 9% AF burden in ablation vs 20% AF burden in AADs	Not reported	↑ 31 point AFEQT score
EAST-AFNET 4[11,12]	▪ Early AF (diagnosed ≤12 months prior) ▪ ≥ 75 years and prior stroke or TIA or had 2 stroke risk factors	Early Rhythm control VS Usual care (8% of patients underwent ablation)	2789	26.6%	AF recurrence: Paroxysmal AF: 6% usual care vs 2% early rhythm control Persistent AF: 11% usual care vs 10% early rhythm control	Not reported	↑ 2.3 point EQ-5D score
CAPLA[5]	▪ Symptomatic Persistent AF ▪ Refractory to ≥1 AADs	Pulmonary vein isolation (PVI)+ posterior wall isolation VS PVI only	338	78.6% persistent AF 21.4% longstanding persistent AF	63% of patients had paroxysmal AF after ablation 0.9% AF burden in paroxysmal AF patients 27.4% AF burden in persistent AF patients	78.9% persistent VS 46.4% paroxysmal AF underwent a hospitalization, cardioversion, repeat ablation, of AADs	↑ 15.1 point AFEQT score

*Atrial fibrillation, AF; Antiarrhythmic drugs, AADs; Pulmonary vein isolation, PVI; Atrial Fibrillation Effect on Quality of Life, AFEQT; EuroQol 5-dimensions, EQ-5D.

Trials assessing post-rhythm control therapy AF burden in paroxysmal and persistent patients.

Persistent atrial fibrillation (AF) is a marker of more severe atrial electrical and anatomical remodelling presenting as atrial cardiomyopathy and characterized by atrial fibrosis, dilation, and abundant non-pulmonary vein triggers.[1] Compared with paroxysmal AF, persistent AF is associated with a higher risk of thromboembolism [meta-analysis, relative risk (RR) 1.4, 95% confidence interval (CI) 1.3–1.7] and

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mortality (meta-analysis, RR 1.2, 95% CI 1.1–1.4), as well as poorer quality of life and higher healthcare resource utilization.[2] Rhythm control of persistent AF is challenging, with maintenance of sinus rhythm in <50% of persistent AF patients.[3] Extensive ablation strategies, including pulmonary vein antral isolation and pulmonary vein isolation (PVI) with posterior wall isolation, failed to reduce AF recurrences.[4] However, a change in pattern of AF with a reduction of AF burden may potentially improve outcome and quality of life, and reduce healthcare utilization.

In the current issue of the *European Heart Journal*, a substudy of the Catheter Ablation of Persistent Atrial Fibrillation: A Multicenter Randomized Trial of Pulmonary Vein Isolation vs. PVI with Posterior Left Atrial Wall Isolation (CAPLA) randomized trial ($n = 333$) was performed to assess potential changes in the clinical pattern of AF (paroxysmal or persistent AF) following PVI with or without posterior wall isolation.[5] The present subanalysis followed patients with antiarrhythmic drug-(AAD) refractory persistent AF for 12 months post-ablation to determine the incidence of paroxysmal or persistent AF from monitoring with cardiac implantable electronic devices (CIEDs; 15.9%), twice daily single-lead ECG (70.3%), or Holter monitoring (13.8%).[5] AF recurred in 154 (46.2%) patients at 12 months post-ablation, of which 63% of patients had only paroxysmal AF episodes and 37% of patients had at least one episode of persistent AF (*Graphical Abstract*).[5] As a consequence, AF burden was greater among patients who had at least one episode of persistent AF (27.4%) compared with patients who only had episodes of paroxysmal AF (0.9%; $P < .001$).[5] Lower left ventricular ejection fraction [LVEF; odds ratio (OR) 1.1, 95% CI 1.0–1.1] and higher left atrial (LA) volume index (OR 1.0, 95% CI 1.0–1.1) were associated with recurrence of persistent AF after multivariable logistic regression.[5] In addition, there was a greater magnitude of improvement in quality of life and a reduction in healthcare resource utilization among patients with paroxysmal AF recurrence than those with at least one persistent AF episode.[5]

The authors should be applauded for recognizing the potential incremental improvement in the clinical AF pattern following catheter ablation in the challenging persistent AF population. Although PVI with and without pulmonary wall isolation did not result in sinus rhythm being sustained, the potential reduction in AF burden to a paroxysmal pattern of AF is encouraging. Paroxysmal AF may be easier to manage,[6] and was associated with reduced healthcare utilization. The results of the CAPLA substudy build on the growing body of evidence that suggests that rhythm control therapy and especially catheter ablation reduces AF burden and interrupts progression of AF, also in persistent AF. In the CABANA trial ($n = 2204$), patients randomized to catheter ablation had statistically significantly lower AF burden after 5 years of follow-up compared with those receiving drug therapy (6% vs. 14% in ablation vs. AAD patients, respectively; $P < .001$).[7] Among persistent and long-standing persistent AF patients in CABANA (57.6%), catheter ablation was also associated with lower AF burden compared with AADs (*Graphical Abstract*; 9% vs. 20%, respectively).[7] Similarly, the CIRCA-DOSE trial, which compared cryoballoon and radiofrequency ablation, resulted in a >98% reduction in AF burden following catheter ablation.[8] In line with that study, the EARLY-AF trial showed that early ablation, compared with AADs, in paroxysmal AF patients was associated with a lower incidence of progression to persistent AF [hazard ratio (HR) 0.3, 95% CI 0.1–0.7] and recurrent atrial tachycardia (HR 0.5, 95% CI 0.4–0.7).[9] Further, the EAST-AFNET 4 trial indicated that potential reductions in burden with early rhythm control therapy translated to fewer clinical events, including cardiovascular death, stroke, and hospitalization for worsening heart failure and acute coronary disease (HR 0.8, 95% CI 0.7–0.9).[10] Also EAST-AFNET 4 included a subgroup of patients with, albeit early, persistent AF ($n = 743$, 27%), of which sinus rhythm was achieved in 71% of early rhythm control patients compared with 37% of usual care patients.[10,11]

Further, although the CAPLA substudy included persistent AF patients, the present results align with results from CIRCA-DOSE showing that reduction of AF burden is associated with less healthcare resource utilization.[5,8,12]

Thus, there is mounting evidence for early intervention to reverse AF progression. Now, the results of the present CAPLA subanalysis suggest that this is also the case in patients with persistent AF who failed on AAD therapy, i.e. patients who undergo ablation later in the trajectory of AF. What these data clearly show is that persistent AF is not one entity and that the atrial cardiomyopathy is still 'modifiable' in a selection of patients. These results warrant the question of how to identify persistent AF patients with an atrial cardiomyopathy susceptible to successful AF ablation with the aim of reducing AF burden and improving healthcare utilization before the ablation.

To determine the true clinical pattern, phenotype, and atrial cardiomyopathy of AF, clinicians predominantly categorize patients depending on the pattern of AF. To improve selection of patients undergoing ablation, especially those with persistent AF, it seems necessary to consider not only the ECG but also other more reliable markers taking into account the severity of atrial cardiomyopathy when referring patients for rhythm control therapy including AF ablation.[1] Increasing evidence supports LA dilation as a determinant for AF recurrence and thus severity of atrial cardiomyopathy. LA dilation has consistently been identified as a determinant of AF progression, worse outcomes, and AF recurrence.[13] In line with this, in the CAPLA subanalysis, a high LA volume index in addition to a low LVEF were associated with a higher risk of persistent AF recurrence as compared with recurrence of paroxysmal AF.[5] Chollet *et al.* conducted a prospective cohort ($n = 476$) to compare the association between the clinical pattern of AF and LA volume with the outcome of AF recurrence at 12 months. Investigators concluded that the combination of persistent AF (adjusted HR 1.4, 95% CI 1.0–1.8) and LA volume index ≥42 mL/m^2 (adjusted HR 1.7, 95% CI 1.1–2.0) best predicted post-ablation AF recurrences.[14] However, model performance statistics such as Harrell's C statistic or the Akaike or Bayesian information criterion were not conducted to determine which model or determinant (e.g. persistent AF only, LA volume index only, or both) would best predict the outcome.[14] The importance of LA dimensions in the prediction of AF recurrences was also recently confirmed in a meta-analysis of 21 studies ($n = 3822$) which showed that patients with AF recurrences had higher LA volumes or LA volume indices (OR 1.0, 95% CI 1.0–1.1).[15] In the future, imaging techniques on the association between atrial sizes and, if possible, severity of atrial cardiomyopathy together with AF patterns of AF could contribute to improve selection of persistent AF patients for ablation.

Although the CAPLA substudy contributes to the innovative concept that outcome after ablation of persistent AF may be ranked according to pattern of recurrent AF, a few limitations should be noted. Fewer AF episodes were detected in the 14% of patients followed with Holter monitoring compared with other monitoring modalities. In addition, 75% of patients with a persistent AF recurrence and 40% of patients with paroxysmal AF recurrences used AADs during follow-up; thus, the magnitude of the effect from AADs is unclear. Also, follow-up duration is only 12 months. Finally, it is unclear if frequent or continuous monitoring was used to diagnose patients with persistent AF at baseline, as single intermittent monitoring is inconsistent and often not correlated with the AF burden and clinical pattern of AF.[8]

Nevertheless, the present subanalysis of the CAPLA trial highlights the need for better identification of patients with persistent AF who

are suitable for AF ablation with the aim of decreasing AF burden, improving symptom burden, and reducing morbidities and mortality associated with AF. The arbitrary measurement of the clinical pattern of AF, however, may be inconsistent and not truly reflect the extent of the atrial cardiomyopathy. Therefore, other more reliable criteria on the atrial substrate and the severity of the atrial cardiomyopathy may be more relevant discriminators to determine treatment responders and guide decisions for referral for ablation in patients classified with persistent AF.

Declarations

Disclosure of Interest

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