

Persistent atrial fibrillation: Time to stop comparing apples with oranges & take a step in the right direction towards optimal profiling of patients to tailor therapy.

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Short Title: Persistent AF: Optimal patient profiling to tailor therapy

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Conflicts of Interest: none

Words: 603

We have read with interest the study by *Vogel* and colleagues showing no benefit of full-defragmentation vs. pulmonary vein isolation (PVI) in patients undergoing catheter ablation of persistent atrial fibrillation (AF)[1].

We believe that there are some aspects deserving reflection, which may account for the observed lack of benefit of the full-defragmentation strategy and may lead to the failure of other strategies under evaluation.

This study clearly illustrates that the population of patients with persistent AF is highly heterogeneous: 52 out of 205 patients (25.4%) in the initial cohort reverted to sinus rhythm while receiving PVI, and thus were classified by the authors as having PV-dependent AF. However, we cannot rule out that even among the remaining patients (not going back to sinus rhythm after PVI), some of them might also be presenting with PV-dependent AF, as after induction of AF from PV-foci, AF may self-perpetuate in the atria even after PVI[2]. In such patients, direct-current cardioversion after successful PVI would likely be enough to allow long-term persistence of sinus rhythm, and this seemed to be the case in the vast majority of patients in the PVI-only group (75% among those receiving a single ablation procedure). Logically, there would be no benefit of additional defragmentation in that sub-set of patients, as may have occurred in some patients belonging to the full-defragmentation group. The key is to try and identify such patients prospectively.

On the other-hand, there was a second subset of patients where triggers/drivers of AF were not exclusively located to the PVs. In these patients, full-defragmentation can theoretically be of interest. However, based on the positive results observed in the PVI-only group it seems that patients with non-PV dependent AF were significantly under-represented in this CHASE-AF-cohort. Accordingly, as the authors

acknowledge, in this population left atrial size was smaller than in most persistent AF studies and “short-duration persistent AF” was the rule, with most episodes lasting for less than a year, and time since diagnosis being less than 5 to 6 years. Atrial dilation and AF duration are known to be associated higher relapse rate, and thus likely to associate with a more resistant persistent-AF phenotype[3, 4] due to structural and electrical atrial remodeling which is non-PV dependent.

Therefore, this study illustrates that persistent AF seems to comprise two completely different patient populations: PV-dependent and non-PV-dependent AF. Until we are able to clearly identify them, research on the best approach to ablate persistent AF is clearly compromised and all results will be very difficult to interpret.

The current classification for AF based on symptom/episode duration is clearly subjective and insufficient, and this study proves it associates poorly with the underlying pathophysiologic mechanisms. What is required is a more comprehensive AF classification scheme taking into account multiple cardiovascular risk factors including hypertension, diabetes, structural heart disease, lipid profile, body mass index, as well as specific electrophysiological (e.g surface ECG parameters, endocardial voltage & electrogram features), and structural phenotypes (e.g. left atrial pressure/compliance[5], MRI fibrosis[6] if validated across multiple centres, low voltage area in atrial tissue on mapping, mitral valve disease, left ventricular function) to facilitate stratification of AF phenotypes and identify key factors determining therapeutic approaches, analogous to the CHA₂DS₂-VAsc scoring system. Without such a systematic approach we will continue to compare “*apples with oranges*” and fail to assess the true impact of different catheter-based and drug interventions, compromising our efforts to halt the progression of this epidemic.

International registries of outcomes incorporating agreed clinical, structural and electrophysiological data and documented procedural approaches would be a step in the right direction to develop such a scoring system to predict clinical response to ablation.

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