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EDITORIAL

Moving catheter ablation forward from paroxysmal to persistent atrial fibrillation: progress, limitations, and surprises of the SARA trial

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This editorial refers to 'Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA Study)'†, by L. Mont *et al.*, on page 501

Over the past decade, eight randomized studies have compared the efficacy of catheter ablation and antiarrhythmic drug therapy for rhythm control in patients with atrial fibrillation (AF).[1] Most studies investigated patients with paroxysmal AF after failure of one or more antiarrhythmic drug.[1] All studies showed superiority of catheter ablation over antiarrhythmic drug treatment with respect to rhythm outcome.[1] In addition, two prospective randomized multicentre trials were recently reported comparing catheter ablation with antiarrhythmic drugs for the treatment of paroxysmal AF as first-line therapy.[2,3] In the MANTRA-PAF study, the total burden of AF during follow-up, which was the primary endpoint of the study, was not significantly different between the ablation arm and the drug arm of the study. However, at 24-month follow-up, AF burden was significantly lower in the ablation group and the overall number of AF recurrences was also significantly lower in the ablation group.[2] The RAAFT 2 trial still awaits peer-reviewed publication; however, the data reported indicate a significantly higher efficacy of catheter ablation.[3] The difference between treatment groups in these studies was smaller than seen in other randomized trials, however. These outcomes are not surprising in therapy-naïve patients. In addition, only a few randomized studies have focused on the efficacy of catheter ablation in comparison with antiarrhythmic drug treatment in patients with persistent AF.[1] The few studies available were quite heterogeneous with respect to the patients included and mainly investigated patients with 'non-paroxysmal' or 'chronic' AF, i.e. patients with persistent and longstanding persistent AF. In other randomized studies, $< 25\%$ of patients had persistent arrhythmia.[4,5] Therefore, the role of catheter ablation in patients with persistent AF could not be resolved in these two studies.

Mont *et al.* have now presented the results of the SARA trial.[6] In this trial, 146 patients with persistent AF refractory to at least one antiarrhythmic drug were randomized to catheter ablation or antiarrhythmic drug treatment in a 2:1 fashion. Patients with longstanding AF, severely reduced left ventricular ejection fraction, and a significantly enlarged left atrium were excluded from the study. During 9 months of follow-up (after a 3-month blanking period), more patients in the ablation group were free from documented AF recurrence lasting >24 h and also had fewer documented shorter AF episodes of > 30 s duration. In addition, patients treated with catheter ablation required fewer cardioversions during follow-up.

What are the strong aspects of the SARA trial?

The robust prospective, multicentre, randomized design of the study providing the best scientific framework available needs to be emphasized. Data were analysed in a blinded fashion by an independent adjudication board—all well done. To the best of our knowledge no previous study has approached the same scientific question to this degree. Thus, data are new and add to existing knowledge. The results provide further evidence that catheter ablation is superior to antiarrhythmic drugs in patients with persistent AF that have failed a previous course of antiarrhythmic drug treatment. However, although formally in persistent AF, the patients included in the trial were relatively young, and had only slightly enlarged left

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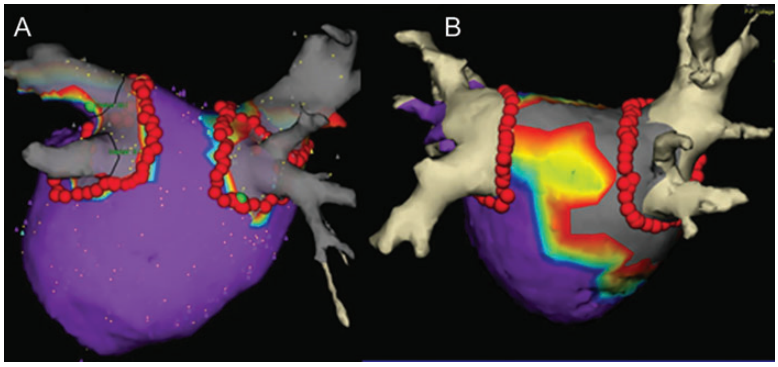

Figure 1 Not all patients with persistent atrial fibrillation (AF) are the same: voltage maps from two patients with persistent AF taken during catheter ablation of AF. The purple area represents normal voltage, suggesting normal atrial myocardium, while the green, yellow, and red zones demark areas with reduced voltage and abnormal conduction properties. Grey demarks scarred tissue which is electrically unexcitable. Both patients present with the same AF 'ECG phenotype', i.e. persistent AF. However, patient A shows no intense atrial remodelling as compared with patient B showing extensive scars and low voltage areas along the roof and the posterior wall of the left atrium. The red tags demark circumferential ablation lines for isolation of the pulmonary veins.

atria, normal left ventricular function, and no severe structural heart disease. The spectrum of patients with persistent AF is very wide ranging, from patients with no or only minor cardiovascular disease to patients with severe cardiovascular disease and advanced atrial remodelling (*Figure 1*). Although there is no clear correlation of AF ECG phenotype (i.e. paroxysmal, persistent, and longstanding persistent AF) and co-morbidities with the extent of atrial remodelling,[7] it seems that the patients treated in the SARA trial had less advanced remodelling. It is important to note that the results of the current study were obtained in a selected subgroup of patients with persistent AF and cannot be extrapolated to patients with persistent AF and advanced atrial remodelling, especially not to those with longstanding persistent AF, atrial enlargement, or substantial co-morbidities.

Another important result of the study is the remarkably low complication rate in both treatment arms. Besides the fact that patients were treated in very experienced hands, the low incidence of complications is also in line with the assumption that the patients included in the SARA trial represent the 'healthy' spectrum of patients with AF because such patients are known to be at lower risk for procedure-related complications.[8]

What are the weak aspects and limitations of the SARA trial?

First of all it needs to be emphasized that the trial was terminated prematurely due to a patient inclusion rate lower than expected. The study was terminated after inclusion of 149 patients, whereas the study protocol foresaw inclusion of a total of 208 patients. Not all patients randomized to ablative intervention actually received this therapy and some were lost to follow-up. This reduced sample size and incomplete treatment in the ablation group certainly affected the statistical power of the study. However, the most striking limitations of the trial are (i) the primary study endpoint and (ii) the low intensity of follow-up. The EHRA HRS Consensus Documents recommend that every documented recurrence of AF or atrial tachycardia lasting longer than 30 s should be reported as the primary outcome parameter.[1,9] It is difficult to understand why the authors selected AF recurrence of $>$ 24 h as the primary endpoint. The authors argument that the endpoint chosen was considered 'more robust' in the light of the low intensity of rhythm monitoring during follow-up is not fully convincing. It would have been better to apply the recommended and generally accepted primary endpoint of AF recurrence lasting $>$30 s and to work with a more intense follow-up. With just two 24-h Holter recordings scheduled during 1-year follow-up, it is very likely that a significant number of symptomatic and asymptomatic AF recurrences have not been documented.

According to systematic studies that compared the detection of AF recurrences after catheter ablation in relation to monitoring intensity, up to 50% of all recurrences may have been missed.[10] Thus, the recurrence rates reported should significantly underestimate the true recurrence rates in both arms of the study and overestimate the treatment efficacy. Another limiting factor of the study is the high crossover rate from the ablation arm to the drug arm: 35 patients (36%) in the ablation arm received new antiarrhythmic drugs after randomization. In most of these patients, antiarrhythmic drugs were added without a documentation of AF, and were simply guided by symptoms such as palpitations. In some cases, the patients remained on antiarrhythmic drugs established before ablation, thus precluding a chance to establish true recurrence rates after ablation off antiarrhythmic therapy. Thus, the crossovers happened in a significant number of patients that did not reach a single study endpoint—which is a quite unusual workflow.

What are the surprising findings of the SARA trial?

In this respect, two issues are striking: first, quality of life was assessed with a disease-specific questionnaire and there was no positive effect of catheter ablation on quality of life. The assumption of the authors

of the SARA trial that statistical issues, i.e. the premature termination of the trial, are likely to explain this finding may be too superficial. All previous randomized studies that have assessed the effects of catheter ablation on quality of life reported significant benefits for mental or physical scores or even both.[1,2] However, all these studies included patients with paroxysmal AF only, and it may be that symptomatic benefits are more pronounced in paroxysmal AF patients as compared with patients with persistent AF. The lack of symptomatic improvement is a surprising but important observation of the SARA trial since the indication for catheter ablation currently is mainly based on symptoms, with the expectation that symptoms improve after ablation. That only limited methods and details of the quality of life survey are provided also renders the interpretation of these data difficult. Further studies on the impact of catheter ablation on quality of life in patients with persistent AF are necessary.

Another surprise is the extremely low re-hospitalization rate during follow-up of only 2% in the ablation arm and 6% in the drug arm. Since hospitalizations of AF patients are mainly driven by symptoms and/or heart failure, the low re-hospitalization rate despite a significant AF recurrence rate observed may indicate (i) an only moderately impaired quality of life at baseline and (ii) as discussed above a rather healthy patient population with persistent AF unlikely to develop heart failure symptoms. However, the extremely low re-hospitalization rate observed may also be indicative for some gaps in the completeness of follow-up.

What is the perspective on catheter ablation of persistent atrial fibrillation after the SARA trial?

Nevertheless, despite these issues, SARA is the first prospective, randomized, multicentre study attempting to investigate this specific patient population. Despite all the limitations of the SARA trial discussed above, the study is an important piece of clinical science and helps to better understand the role of catheter ablation of persistent AF. Further studies in the same field are clearly needed to fill the knowledge gaps that remain open. Current guidelines recommend catheter ablation of symptomatic persistent AF after failed antiarrhythmic drug therapy as a class IIa level of evidence B indication. However, what is the benefit of ablation if symptoms do not improve? Is there any?

These issues and the limited number of patients enrolled in the study stop short of a change in the recommendations for persistent AF ablation. Because of the significant methodological limitations, the SARA trial should be considered hypothesis-generating rather than conclusive in the field of catheter ablation of persistent AF. Additional information from the currently ongoing CABANA and EAST trials with significantly larger study populations will hopefully answer the remaining questions, including longer term efficacy outcomes and impact of underlying disease on treatment effects, and clarify the effect of ablation on symptom relief and other quality of life outcome measures.

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