

New Insights On Ablation Of Persistent Atrial Fibrillation: Evidence From The SARA Trial

Felipe Bisbal MD, Lluís Mont MD PhD

Unitat de Fibril·lació Auricular (UFA), Hospital Clinic, Barcelona, Spain.

Abstract

Since Haissaguerre et al first described the pathogenic role of pulmonary vein firing as a crucial mechanism triggering atrial fibrillation, catheter ablation has been recommended as a curative treatment. Several trials have demonstrated that ablation is an effective treatment in most patients with paroxysmal atrial fibrillation and low-grade remodelled atria. In patients with persistent AF, there is substantially less evidence, mostly based on non-randomized studies, supporting this recommendation. The available scientific evidence as well as the current approaches to treating persistent AF patients are discussed in this article. Further, we describe the main findings of the SARA trial and put them into perspective.

Introduction

Since Haissaguerre et al¹ first described the pathogenic role of pulmonary vein (PV) firing as a crucial mechanism triggering atrial fibrillation (AF), catheter ablation (CA) has been recommended as treatment. However, current evidence tells us that this option is not curative in all patients.^{2,3} The role of PV in developing AF differs between patients; it becomes less relevant with more time in AF and more advanced atrial remodelling (AF begets AF), making PV ablation less effective. Several trials have demonstrated that PV isolation is an effective treatment in most patients with paroxysmal AF and low-grade remodelled atria. When ablation is applied to less selected populations such as patients with persistent or long-standing persistent AF, presence of very dilated atrium, or structural cardiomyopathy— the effectiveness drops substantially. Thus, under current guidelines ablation is a class I (level of evidence A) recommendation in patients with paroxysmal AF and resistance to at least one antiarrhythmic drug.⁴ In patients with persistent AF, there is substantially less evidence supporting this recommendation, and it is mostly based on non-randomized studies. Importantly, most of these studies include a wide range of AF patients, included under the generic term “non-paroxysmal”. Recently, we published the first randomized trial comparing CA vs. antiarrhythmic drug therapy (ADT) in the specific population fitting the current definition of persistent AF (>7 days or <7 days requiring cardioversion). The available scientific evidence as well as the current approaches to

treating persistent AF patients are discussed in this article. Further, we describe the main findings of the Study of Ablation Versus antiarrhythmic Drugs in Persistent Atrial Fibrillation (SARA) trial and put them into perspective.

Current Approaches To Treat Persistent AF

Among patients who undergo CA, outcomes are better in paroxysmal AF; this has led to extensive research to identify new ablation targets and improve success in persistent AF. Most randomized trials in paroxysmal AF are consistent in terms of population homogeneity, ablation target, and ablation endpoints, which make them comparable and provide a strong level of evidence. However, there are 3 important limitations to take into account when interpreting the results of the studies in persistent AF: (1) most compare two different ablation strategies (A vs. B) and do not assess the benefit of CA over ADT; (2) studies that compare strategies have recruited heterogeneous population (long-standing persistent, persistent + long-standing persistent, etc.) and applied different definitions of chronic or persistent AF; (3) the ablation target and the electrophysiological endpoint of the ablation strategies differ substantially, precluding consistent comparisons between studies.

Pulmonary Vein Isolation: Is It Enough In Persistent AF?

Wide antral circumferential ablation with the endpoint of electrical PV isolation is currently the cornerstone of AF ablation. Although this has been shown to be sufficient in paroxysmal AF, it seems to be less effective in persistent AF. Therefore, the role of PVs in the perpetuation of AF in patients with persistent AF remains unclear.

A recent study by Seitz et al⁵ suggests that the role of PV activity as a driver of AF decreases with time in AF and with left atrial dilatation. Those patients with “passive activation” of all PVs had greater time in AF (19.1 vs. 4.9 months, respectively; $p < 0.001$) and greater LA diameter (42.4 vs. 47.6 mm, respectively; $p < 0.001$) than those with ≥ 1 “active PV” (defined as PV CL > LAA CL). Compared to patients with PxAF, those with Pr and LS-Pr AF had a lower

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Corresponding Author:

Felipe Bisbal, MD
Arrhythmia Section,
Cardiology Department
Thorax Institute, Hospital Clinic,
Universitat de Barcelona.
C/ Villarroel, 170. 08036 Barcelona,
Catalonia – Spain.

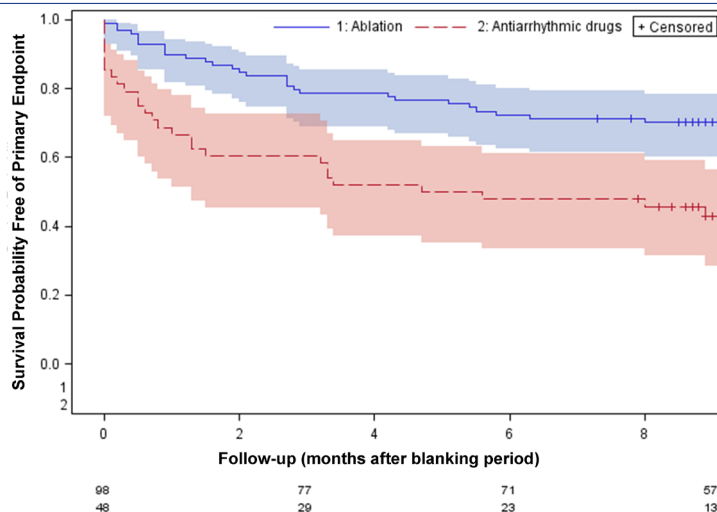


Figure 1: Survival curves for the primary endpoint (sustained episodes of AF lasting >24 hours). Reproduced with permission of Oxford Journals from Mont L et al. *Eur Heart J* 2014;35:501-507.

proportion of “active PVs” (100%, 60%, 24% and 0%, respectively; $p < 0.001$). The authors tested the hypothesis that substrate-only ablation is sufficient to treat patients without “active PVs”, and compared it to substrate+PVI in patients with ≥ 1 “active PV”. They found that the recurrence rate did not differ between groups, suggesting that the assessment of PV activity might help to decide the best ablation strategy.

On the other hand, the RASTA study⁶ failed to demonstrate a clear benefit of substrate modification beyond PVI alone in patients with PrAF. In the study by Bertaglia et al⁷, the demonstration of electrical isolation of PVs was the only factor independently associated with arrhythmia recurrence in patients with PrAF. Also, the SARA trial⁸ showed good mid-term outcome of a PVI-only strategy in patients with persistent AF, highlighting the crucial role of PVs in the perpetuation of persistent forms of AF.

Linear Ablation

Based on the concept of surgical compartmentalization of the atrium established by Cox,⁹ electrophysiologists have tried to emulate this technique by creating endocardial lines of block. Additionally, the creation of these lines eliminates atrial substrate. The most commonly performed ablation lines are located at the left atrial roof and mitral isthmus. Other less frequent lesion sets comprise posterior wall isolation, anterior lines, and septal lines.

Initial data showed a significant increase of recurrences of left atrial tachycardias, mostly macroreentrant, related to the anatomical approach and lack of confirmation of block. The inclusion of bidirectional block across the line as the endpoint of ablation has decreased the occurrence of post-AF ablation macroentries. However, the additional benefit of adding ablation lines beyond PVI is still unclear.¹⁰ On top of the questionable benefit of linear lesions, this approach might be proarrhythmogenic. It is sometimes impossible to achieve complete bidirectional block, mostly at the mitral isthmus line,¹¹ which can lead to macroreentrant tachycardias; these are usually symptomatic, persistent, and refractory to antiarrhythmic drugs. In addition, a more extensive ablation of the left atrium increases the risk of damaging contiguous extracardiac structures (phrenic nerve, esophagus, circumflex artery, etc.).

Electrogram-based ablation

The first proof of the benefit of targeting complex fractionated atrial electrograms (CFAEs) was reported by Nademanee et al.¹² The authors defined CFAEs as fractionated electrograms with ≥ 2 deflections, continuous activity, or mean cycle length < 120 ms over a period of 10 seconds and reported a high single-procedure success of CFAE ablation alone (92% freedom of AF at 1-year follow-up). This success rate has never been reproduced by other authors.

CFAE ablation has been proposed as an adjuvant strategy after PVI. Although some studies have demonstrated additional benefit over PVI alone¹³, other authors have reported no additive benefit.¹⁴

The role of fractionation during AF has been questioned. Recent studies have suggested that CFAEs represent a collision of wavefronts during AF; sites with fractionated electrograms during AF correspond in most cases to normal electrograms during sinus rhythm.¹⁵ This finding suggests the functional and passive nature of CFAEs. Fractionated electrograms during sinus rhythm also have been proposed as an ablation target. Nonetheless, limited data are currently available and further research is needed to elucidate the benefit of this strategy.¹⁶

The main limitations of electrogram-based ablation that preclude its generalization are the heterogeneity in the definition of a complex fractionated electrogram, the subjectivity in its interpretation, and the unknown pathophysiology and controversial role in AF. Some questions remain to be answered: what substrate are we targeting when ablating CFAEs? Is it an actual key substrate needed for perpetuation of AF? Is the additional benefit due to CFAE abolition or is it just the effect of debulking?

Evidence From Randomized Trials Involving Patients With Persistent AF

Robust evidence has been published in the literature supporting the superiority of ablation over AAD in patients with paroxysmal AF. In the body of evidence from the persistent AF population, one finds a great number of randomized studies comparing different ablation techniques. However, it is striking that investigators designed studies comparing ablation strategy A vs. strategy B before the key question has been answered: is ablation more effective than medical therapy in patients with persistent AF? Data providing some evidence in this regard are scarce; only a few randomized studies in patients with non-paroxysmal AF have been performed to date.

The first study, by Oral et al,¹⁴ comparing both strategies in the specific population of non-paroxysmal AF reported a superiority of CA over ADT. The study included patients with chronic AF, defined as continuous AF during at least 6 months. The mean AF duration before randomization was around 4 years, and the primary endpoint was defined as episodes of AF lasting more than 30 seconds. At the end of follow-up (1 year) the endpoint was achieved in 26% and 42% of patients in the CA and ADT arms, respectively. It is important to underline that most of the patients included in this trial met the current criteria for long-standing persistent AF, according to the guidelines¹⁷ and hence, the results may not be applicable to patients with persistent AF. Another randomized study including patients with non-paroxysmal AF, conducted by Stabile et al,⁷ compared the effectiveness of an ADT strategy vs. a combined strategy of ADT plus catheter ablation. In this series, patients with paroxysmal and persistent AF were included. The authors concluded that the combined strategy (AAD+CA) was superior to AAD alone in maintaining sinus rhythm. Of note, the study was not designed

to evaluate the effectiveness of CA alone. Additionally, data on the effect of both strategies in the subgroup of patients with persistent AF is not provided in the paper, precluding any conclusion in this specific population.

The SARA Study: What's New?

The SARA study is the first randomized trial comparing the safety and effectiveness of catheter ablation vs. antiarrhythmic drugs for the treatment of patients meeting the current definition of persistent AF. A total of 146 consecutive patients with persistent drug-refractory AF were included and randomized to CA or AAD (2:1 allocation). The most relevant exclusion criteria were presence of severe structural heart disease, significant atrial enlargement (diameter >50mm), and long-standing persistent AF (>1 year in AF). The primary endpoint was defined as sustained episodes of AF (>24 hours) occurring after a 3-month blanking period. Important secondary endpoints included any episode of AF >30 seconds, need of electrical cardioversion, and quality of life. Most patients randomized to CA received wide antral circumferential ablation, with PV isolation as procedural endpoint. Few patients received additional roof line (23%) or ablation of complex fractionated electrograms (8%). Patients allocated in the AAD arm received class Ic (44%) or class III (56%) drugs.

Outcome data was analyzed as intention-to-treat. The proportion of patients free of sustained episodes of AF at 12 months (primary endpoint) was higher in the CA group compared to ADT group (70.4% vs. 43.7%, respectively; $P=0.002$), an absolute risk reduction of 26.6% (figure 1). Also, patients in the CA group had higher probability of remaining free of any recurrence of AF or flutter (lasting >30 s) than those in the ADT group (60.2 vs. 29.2% respectively; $P<0.001$) and less need of electrical cardioversion (34.7% vs. 50%, $p=0.018$). In line with prior studies, patients with early recurrences were at higher risk of achieving the primary endpoint (OR 5.3). No significant differences in QoL scores were found between groups, using the ANCOVA analysis. The rate of complications in both groups was low (6.1% in the CA group and 4.7% in the ADT group, $p=ns$). In conclusion, CA is superior to ADT for rhythm control in patients with persistent AF.

The major criticism refers to the monitoring strategy and the use of a novel endpoint (sustained AF episodes) that had not been previously reported.¹⁸ The consensus document for the management of AF⁴ recommends a more prolonged monitoring, mainly when assessing short episodes of AF >30 secs (secondary end-point). The SARA trial aimed to be pragmatic; therefore, the "standard of care" of our environment was chosen as the most appropriate strategy for follow-up. Nonetheless, we do not believe that more extended monitoring would have had a major impact on the primary endpoint. Patients were instructed to ask for emergent ECG in case of palpitations or symptoms; therefore, most prolonged episodes (i.e., lasting > 24 hours) should have been detected. Furthermore, any impact would have affected the outcome of both groups and therefore would not substantially affect any differences between them. Regarding the selection of the primary endpoint, we considered that using a very stringent endpoint (>30 sec of documented AF) could be less clinically relevant in the context of persistent AF, particularly without using implantable monitoring systems. Therefore, a more robust endpoint was judged to be more appropriate, even if it could lead to an overestimation of the positive results. However, significant differences were also found between treatments in the secondary

endpoint (>30 seconds of AF), validating to some extent the decision to choose this endpoint.

Another important point of the study is the benefit in QoL, which was not evident in the initial publication using the ANCOVA analysis. The lack of benefit in the initial report has raised some concern.¹⁸ Recently, Wynn et al published a reanalysis of the QoL data, demonstrating a significant QoL improvement in the CA group, but not in the ADT group.¹⁹ The authors applied paired sample t-tests, which is the standard method used in most of the trials.^{20,21} This finding adds new evidence of the clinical benefit of CA.^{20,21}

Despite its limitations, this trial adds important information to the current knowledge about the role of CA in the treatment of persistent AF. It represents the first prospective, multicentre, randomized trial addressing this specific topic. In our view, one of the important observations reported in the paper is that a limited ablation procedure can obtain good results in selected patients with persistent AF (excluding patients with long-standing persistent AF or with advanced atrial remodelling). Additionally, newer data demonstrated that CA significantly improved QoL scores in the SARA trial population, while ADT did not affect the scores. Nevertheless, the results cannot be extrapolated to patients with more advanced atrial disease (severe atrial enlargement), long-standing persistent AF, or significant structural heart disease.

Clinical Perspective

Catheter ablation of paroxysmal AF is currently the standard of care in symptomatic patients after failure of medical treatment (Class I, Level of evidence A). Although several studies have demonstrated superiority of CA over ADT in patients with paroxysmal AF, the SARA study is the first multicenter, randomized controlled trial conceived to specifically evaluate patients with persistent AF. In this study, CA was demonstrated to be superior to ADT for rhythm control at mid-term follow-up, with a significant QoL improvement. Of note, the ablation approach was PVI-only in most cases, with a very low proportion of additional substrate modification. This adds evidence to the hypothesis that limited ablation may be effective in a well-selected population with persistent AF. Under the current ESC/EHRA guidelines²², the current indication for ablation of this patient population is IIa (Level of evidence B), based on the results of non-randomized trials and post-hoc analysis of randomized studies. The very recent 2014 AHA/ACC/HRS guidelines for the management of patients with atrial fibrillation²³ have incorporated the data provided by the SARA trial, increasing the level of evidence for the indication of ablation of persistent AF (level of evidence A).

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