Received: 16 February 2022 | Revised: 5 March 2022 | Accepted: 7 March 2022

DOI: 10.1002/joa3.12696

ORIGINAL ARTICLE

Journal of Arrhythmia Open Access WILEY

Two years after pulmonary vein isolation guided by ablation index—a multicenter study

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Abstract

Background: The use of the Ablation Index (AI) software for paroxysmal atrial fibrillation (AF) has been associated with higher acute effectiveness and higher 1-year arrhythmia freedom. There is, however, a lack of data concerning longer follow-up. We aim to evaluate the 2-year outcomes after a standardized AI-guided pulmonary vein isolation (PVI).

Methods: Prospective, multicenter study of consecutive patients referred for paroxysmal AF ablation from January 2018 to July 2019. PVI was guided by a tailored AI value (≥500 for anterior segment, ≥450 for the roof segments and inferior segments, and 400 for the posterior wall) and an ILD ≤6 mm. The primary endpoints were acute and long-term effectiveness.

Results: The study included 218 (842 PV) patients (61% males, median age of 60 [IQR 49–68] years) with paroxysmal AF. First-pass isolation was obtained in 93% of the patients, with an acute reconnection occurring in 10.6% of the patients (3.2% of the PV) following adenosine trial. After a median follow-up of 26 (IQR 20–30) months, freedom from any documented atrial arrhythmia was 83.4%, off-AAD. The rate of adverse events was 1.4%. Although procedural parameters differ across centers ($p < 0.001$), the acute ($p = 0.56$) and long-term effectiveness ($p = 0.83$) were consistent between centers.

Conclusions: Patients with paroxysmal AF submitted to an AI-guided PVI workflow presented high arrhythmia freedom at 2-years of follow-up.

KEYWORDS
ablation index, pulmonary vein isolation, standardized workflow, tailored ablation, two years follow-up

1 | INTRODUCTION

Catheter ablation for atrial fibrillation (AF) has become a first-line treatment for symptomatic patients refractory to antiarrhythmic drugs, with pulmonary vein isolation (PVI) being the cornerstone in paroxysmal AF ablation.[1] Long-standing electric isolation of the pulmonary vein (PV) is associated with long-term success.[2–4] However, despite the introduction of the contact-force (CF) sensing

technology, PV reconnection remained a concern with most clinical recurrences of AF following AF ablation being related to the recovery of conduction from the PV.[2–7]

Recently, studies using the Ablation Index (AI) software (Biosense Webster), have demonstrated a lower acute PV reconnection and higher atrial arrhythmia freedom at 1-year of follow-up.[8–13] Despite higher effectiveness being achieved in these studies, they were all limited to 1-year follow-up. Therefore, there is a lack of data regarding longer outcomes after AI-guided PVI.

This prospective, multicenter study aimed to evaluate if a tailored AI with contiguous inter-lesion distance (ILD) ≤6 mm remains effective at 2 years of follow-up.

2 | METHODS

2.1 | Study design and setting

Prospective, multicenter study of consecutive patients referred for paroxysmal AF ablation from January 2018 to July 2019 in four tertiary hospitals. All centers perform more than 150 AF ablations per year. Acute reconnection (after adenosine trial) and 2-year arrhythmia recurrence rate were assessed.

All patients provided written informed consent and the study was approved by the local institutional ethics committee.

2.2 | Patient eligibility criteria

Paroxysmal AF patients aged ≥18 years who were refractory or intolerant to anti-arrhythmic drug (AAD) therapy were considered eligible for inclusion in this study. Paroxysmal AF was defined as terminating spontaneously or cardioverted within 7 days, according to the 2020 ESC Guidelines for the Management of Atrial Fibrillation developed in collaboration with EACTS (terminating spontaneously or cardioverted within 7 days).[1]

Exclusion criteria included a history of previous AF ablation, contraindication to anticoagulation, and the presence of intracardiac thrombus detected prior to the ablation procedure.

2.3 | Procedure details

The presence of intracardiac thrombus was excluded prior to the procedure by either computed tomographic or transesophageal echocardiography. All procedures were conducted under general anesthesia and patients interrupted AAD at least 5 days before the procedure. All patients were under oral anticoagulation for at least 2 months prior to the procedure. In patients under vitamin K antagonists, anticoagulation was continued in the peri-procedural period with an international normalized within 2.0–3.0 range. In patients taking non-VKA, the last drug dose was omitted. During the procedure, unfractionated heparin was administered immediately after the transeptal puncture and adjusted as needed for a target-activated clotting time above 300 s. No esophageal probe was used. Anatomical mapping data was collected using a 3D mapping system (Biosense Webster), and respiratory data was excluded (ACCURESP™ Module, Biosense Webster). The left atrium (LA) anatomy was constructed with the circular mapping catheter (LASSO® NAV eco, Biosense Webster).

Ostial circumferential ablation was performed, consisting of an anatomic point-by-point encirclement using a THERMOCOOL SMARTTOUCH® irrigated tip contact force-sensing RF ablation catheter (Biosense Webster, Inc.) in a power-control mode with temperature limited to 43°C and saline flow rate of 17 ml/min (15 ml/min when a THERMOCOOL SMARTTOUCH® SF was used above 30 W). Automated lesion tagging (CARTO VISITAG™ Module with Ablation Index, Biosense Webster, Inc.) was used to mark the location of each lesion, with the lesion tag display size of 3 mm. The VISITAG™ settings were as follows: stability minimum time 6 s, maximum range 3 mm; force over time: time 30% and minimum contact force 5 g. These VISITAG™ settings were similar to the ones used in earlier published work from which AI targets were derived.[9] The radiofrequency (RF) lesions were contiguous with an inter-lesion distance (ILD) ≤6 mm as confirmed by the overlap of adjacent VISITAg™ lesions.[12] The power setting was 25-50 W depending upon the region of the LA being targeted: AI target values were ≥ 500 for the anterior segment, ≥ 450 for the roof segments and inferior segments and 400 for the posterior wall. These target values were rounded up from the values validated in previous studies and according to the theoretical LA wall thickness.[8,9,14,15] High-power short-duration (HPSD) ablation was defined as the delivery of 40 W in the posterior wall and 50 W elsewhere.

No additional ablation beyond PVI was performed, except cavotricuspid isthmus (CTI) ablation in every case with previous or procedural documentation of typical flutter. Atrial fibrillation that persisted after PVI was terminated with electrical cardioversion.

After PVI, a bidirectional block was confirmed by demonstrating entry and exit block with a 20-pole circular mapping catheter (LASSO® NAV Eco, Biosense Webster, Inc) placed sequentially in each of the PVs. Intravenous adenosine was administered to unmask sites of dormant conduction. The initial dose was 12 mg which was titrated until at least one blocked P wave or a 3-s pause was observed.[16] Each encirclement was divided into eight segments as depicted in Figure S-1. Further ablation was performed at sites of overt or unmasked reconnection to re-isolate the PVs. Administration of further adenosine bolus after re-ablation was required to confirm successful re-isolation.

Bipolar voltage mapping was carried out during sinus rhythm in all patients. The criteria for an adequate LA map was >500 points. Myocardial regions were considered “abnormal” and “dense scar” when bipolar voltages were 0.2–0.5 mV and <0.2 mV, respectively.

Know history of thyroid disease was defined as previous history of thyroiditis, thyroidectomy, or ongoing medical treatment for hypothyroidism or hyperthyroidism, independently of the levels of FT_4.

2.4 | Study endpoints

Primary endpoints focused on acute and long-term effectiveness. The former was defined by the percentage of patients with first-pass isolation

after PV encirclement and after the administration of adenosine. The long-term effectiveness was the freedom of any atrial arrhythmia documentation of at least 30 s of duration and irrespective of symptoms, after the 3-month blanking period and during the follow-up.[17]

The secondary endpoint was safety. Safety was defined as any of the following events occurring within the first month after the index AF ablation: death, major bleeding as defined by the International Society on Thrombosis and Hemostasis,[18] occurrence of a thromboembolic event, atrio-esophageal fistula, phrenic nerve palsy, PV stenosis, pericarditis, and vascular access complications.

2.5 | Follow-up

After the index procedure, patients were evaluated before hospital discharge, as well as at 3, 6, 12, 18, and 24, and 36 months after the procedure. Transthoracic echocardiography and 24-hour Holter monitoring were performed before discharge. Information collected during follow-up included a 12-lead electrocardiogram (ECG) and a 24-hour Holter monitoring at each appointment. A 7-day Holter monitoring was performed at least once a year. At discharge, AAD was interrupted (beta-blockers were allowed). The first 3 months post-procedure were considered a blanking period and recurrences in this period were not considered. The anticoagulation strategy after the first 3 months was based on the CHA_2DS_2Vasc score.

2.6 | Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 25 (IBM, Armonk, New York) software. Categorical variables are expressed in frequencies and percentages and continuous variables are expressed as mean ± standard deviation or median and interquartile range (IQR) for variables with or without normal distribution, respectively. The X^2 test was used to assess for differences between categorical variables and the Student's *t*-test or the Wilcoxon test were used to compare continuous variables with or without normal distribution, respectively. The Kolmogorov–Smirnov test was used to test for normality of distribution of continuous variables. ANOVA test was used to evaluate if study endpoints were consistent among the four different centers. Kaplan–Meier curve was performed to illustrate freedom from atrial arrhythmia recurrence during follow-up. Cox regression was used to identify predictors of atrial arrhythmia recurrence during follow-up. Statistical significance was accepted for p values <0.05.

3 | RESULTS

Of the initial 230 patients included in this study, 12 were lost during follow-up. The final study sample included 218 patients (61% males, median age of 60 [IQR 49–68] years), corresponding to a total of 842 PV evaluated. Only 6 patients (3%) presented a left ventricular ejection fraction (LVEF) inferior to 45%. The vast majority of the patients (80%) were on AAD, namely amiodarone which was present in approximately one-third of the patients. The main baseline characteristics are detailed in Table 1.

3.1 | Procedural characteristics

Procedural data is detailed in Table 2 and ablation lesion data analysis in Table S-1. PVI was obtained in all cases and 25% of the patients also performed a CTI line, with bidirectional block achieved in all of them. Low voltage areas beyond PV were present in 12% of the patients. There was no significant difference concerning the utilization of an HPSD strategy between centers ($p = 0.34$).

3.2 | Acute and long-term effectiveness

The overall first-pass isolation was 93%. Acute reconnection after adenosine trial occurred in 10.6% of the patients and 3.2% in the PV (Table 2).

Median follow-up was 26 (IQR 20–30) months. Overall, single-procedure freedom from atrial arrhythmia after the 3-month blanking period and off-AAD was 83.4%. (Table 2 & Figure 1) Recurrence occurred in 36 patients during follow-up—right atrial flutter in 1 patient, left atrial tachycardia in 10 patients, paroxysmal AF in 19 patients and persistent AF in 6 patients. During follow-up 24 (94 PV) patients performed another AF ablation procedure. The mean time to repeat ablation was 18 ± 10 months. Among patients with repeated ablation, reconnection occurred in 13 PV (14%). Fourteen patients (58%) did not have any PV reconnected. There were no predictors of recurrence during follow-up (Table S-2).

TABLE 1 Baseline characteristics

	Overall($n = 218$)
Male, *n* (%)	133 (61)
Age, years (median, Q1–Q3)	60 (49–68)
BMI, kg/m^2 (median, Q1–Q3)	27.3 (24.9–29.7)
Hypertension, *n* (%)	133 (61)
Diabetes mellitus, *n* (%)	24 (11)
Stroke history, *n* (%)	17 (8)
Congestive heart failure, *n* (%)	13 (6)
Sleep apnea, *n* (%)	20 (9)
Thyroid disease, *n* (%)	39 (18)
Clearance of creatinine (ml/min)	94 (74–120)
Antiarrhythmic drug therapy, *n* (%)	174 (80)
Amiodarone therapy, *n* (%)	76 (35)
CHA_2DS_2VASc score (median, Q1–Q3)	2 (1–3)
First AF episode to PVI, months (median, Q1–Q3)	36 (15–67)
LVEF, % (median, Q1–Q3)	60 (58–65)
LA diameter (mm), % (median, Q1–Q3)	41 (37–45)

Abbreviations: AF, atrial fibrillation; BMI, body mass index; LA, left atrium; LVEF, left ventricle ejection fraction.

TABLE 2 Procedure data and study endpoints

	All patients ($n = 218$)	Center 1 ($n = 71$)	Center 2 ($n = 63$)	Center 3 ($n = 48$)	Center 4 ($n = 36$)	p value
CTI line, *n* (%)	55 (25)	25 (35)	15 (24)	10 (21)	5 (14)	0.07
Low-voltage áreas, *n* (%)	26 (12)	10 (15)	5 (8)	3 (7)	8 (22)	0.09
HPSD strategy, *n* (%)	24 (11)	10 (14)	6 (10)	5 (10)	3 (8)	0.34
Median PV ablation time (min)	26 (22–31)	26 (22–310	28 (25–31)	22 (19–26)	33 (30–43)	<0.001
Median overall procedure time (min)	94 (75–115)	85 (70–100)	100 (90–115)	87 (75–108)	128 (120–140)	<0.001
Median fluoroscopy time, min	4.5 (3.0–6.3)	3 (2.3–4.5)	5.1 (3.6–6.1)	7.0 (6–9.5)	5.3 (3–8.2)	<0.001
First-pass isolation, *n* (%)	203 (93)	63 (89)	60 (95)	46 (96)	24 (94)	0.46
Acute reconnection, *n* (%)	23 (10.6)	7 (10.6)	9 (14.3)	2 (4.2)	5 (13.9)	0.56
PV acute reconnection, *n* (%)	27/842 (3.2)	7/260 (2.7)	11/250 (4.4)	4/192 (2.1)	5/140 (3.6)	0.72
Arrhyhmia recurrence during follow-up, *n* (%)	36 (16.6)	14 (19.7)	9 (14.3)	8 (16.7)	5 (13.9)	0.83
Complications, *n* (%)	3 (1.4)	2 (2.8)	1 (1.6)	0 (0)	0 (0)	0.75

Abbreviations: CTI, cavotricuspid isthmus; HPSD, high-power short-duration; PV, pulmonary vein.

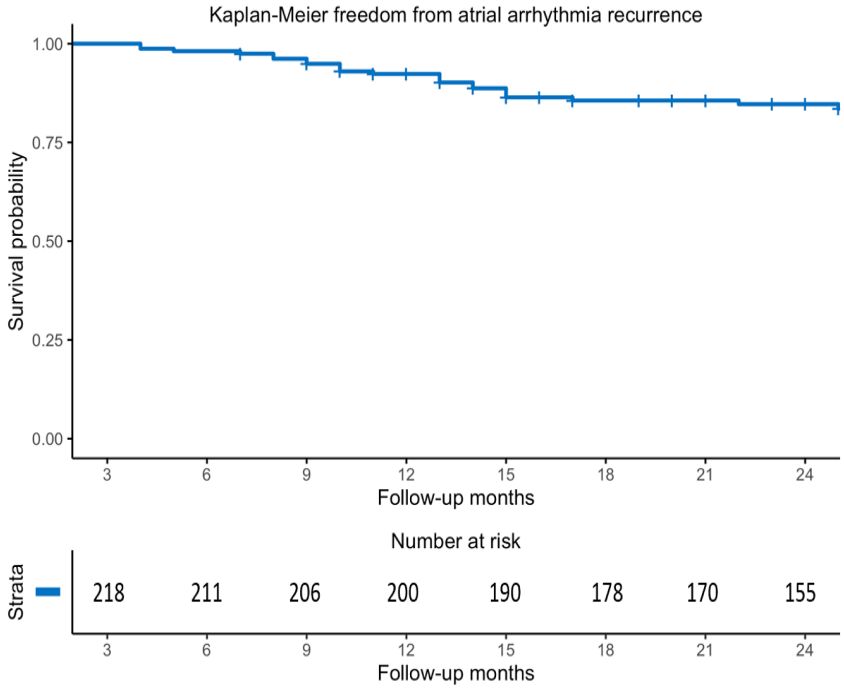

FIGURE 1 Freedom from recurrence of atrial arrhythmia following PVI workflow guided by the ablation index software (83.4%, off-AAD at 2 years of follow-up)

3.3 | Safety

There were three cases of major complications (1.4%)—two femoral hematoma (managed conservatively but with prolonged hospitalization) and 1 patient who had a phrenic nerve palsy (full recovery during the first 6 months).

3.4 | Reproducibility among centers

There was a significant deviation ($p < 0.001$) regarding the procedure, radiofrequency, and fluoroscopy median times across centers (Figure 2A & Table 2). However, there were no significant differences regarding the primary endpoint, with similar acute and long-term effectiveness across centers (Figure 2B & Table 2).

4 | DISCUSSION

To our knowledge, this study presents the longest follow-up after PVI guided by the AI software. This multicenter, prospective study suggests that a standardized AI-guided workflow (1) was associated with lower acute PV reconnection; (2) had effectiveness sustained over 2 years of follow-up, and (3) presented a low rate of adverse events.

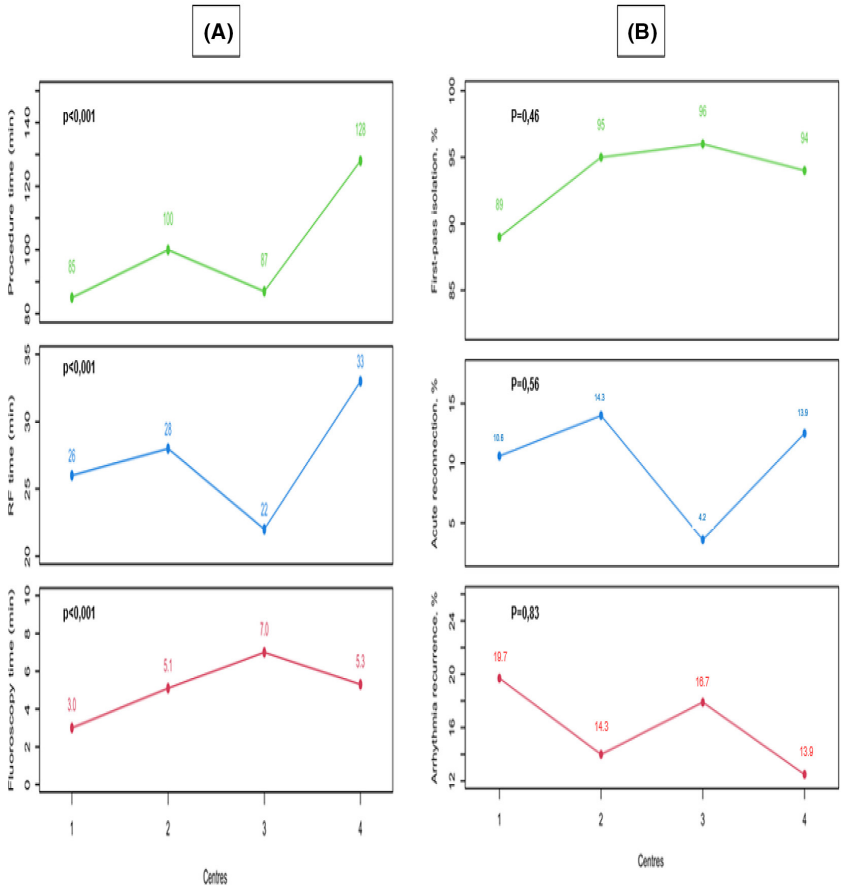

FIGURE 2 Reproducibility among the centers regarding (A) procedural, radiofrequency, and fluoroscopy times and (B) acute and long-term effectiveness

Despite CF-sensing technology had improved acute effectiveness, PV reconnection remains a problem.[5,7,19,20] Recently, studies using the AI software reported lower rates of PV acute reconnection,[9,10,12,21–23] in line with the results obtained in this study. We have chosen a more tailored approach taking three aspects into consideration. First, the majority of the acute reconnections normally occur in the superior veins given their ticker walls.[14,21,24,25] Second, there is still a considerable rate of late reconnection occurring in the inferior segment of the PV,[20,26] reason why we choose to achieve a 450 AI value in this segment. Third, the thickness in the anterior segments/appendage ridge is increased, requiring a higher AI value. Ostial ablation may also have contributed to the low PV acute reconnection rate, eliminating some epicardial connection between the right-sided PV and the right atrium,[27] as well as the contiguous RF lesion with an ILD≤6 mm avoiding the presence of gaps.[28–30]

Freedom from atrial arrhythmia at 1-year after AI-guided PVI, ranging from 78% to more than 90%[10,22,31–34] with a lower rate of PV reconnection at repeat study.[9,21] Our results provide the longest outcome following PVI guided by the AI software. Importantly, it confirms the effectiveness of the AI software and suggests that these tailored lesions result in higher arrhythmia freedom over 2 years of follow-up. While in EFFICAS I study[5] 65% of the patients had at least 1 gap and a sub-analysis of the FIRE AND ICE[33] showed that approximately only 20% of the patients had all PV isolated, our approach allowed that more than half of the patients had all their PV isolated at 18 months after the index procedure.[21,22,35] There is still, however, the scope for improvement.

Atrial fibrillation ablation is associated with a 6.3% major complication rate and with in-hospital mortality of around 0.5%.[17] In the present study, the complication rate was 1.4%. Although the low rate of adverse events may be explained by the low-risk profile of the patients included in this study (all of them with paroxysmal AF with a median CHA2DS2VASc of 2) and to the experience and volume of the centers included in this study, it might also be attributable to the standardized workflow as well.[36] Our data corroborate the safety profile of an AI-guided workflow for PVI, as other studies using AI also reported lower rates of complications related to paroxysmal AF ablation.[10,22,33,34]

Globally, PV ablation time, procedural time, and fluoroscopy time were shorter than described in other studies, despite a low percentage of patients subjected to a HPSD strategy.[12,22,37] Also, likewise observed in the VISTAX trial,[22] the data was still variable among the different centers. However, importantly and opposite to the results of the VISTAX trial, our study suggests that following a standardized approach will result in similar acute and long-term outcomes. This probably reflects the experience of the centers included in this study, while the VISTAX trial (which included 15 centers) had some results outliers to the overall mean reported. The operators of the centers included in this study were all experienced users of CF catheters and therefore generalizing our results to other centers requires further investigation.

In summary, this standardized approach allows a low rate of acute PV reconnection but also sustained high freedom from atrial arrhythmia over 26 months of follow-up. It also suggests that following an AI-guided PVI workflow will result in similar acute and long-term effectiveness. Further studies are required to validate the reproducibility of the outcomes across centers.

4.1 | Limitation

We acknowledge some limitations in our work. First, this was an observational, non-randomized study. Therefore, the next step should be evaluating this tailored approach versus a control group. However, our main goal was to assess the effectiveness of this approach concerning PV acute reconnection and provide long-term outcome data. Second, the study was not powered for reproducibility. Therefore, as stated above, despite our study suggests that following this standardized tailored approach results in a similar outcome, further research is required. Third, we recognize that the use of systematic monitoring using implantable loop recorder could have documented a higher rate of asymptomatic atrial arrhythmia. To minimize the underestimation of the true recurrence, a 7-day Holter monitoring was performed at least once a year.

5 | CONCLUSION

The use of a tailored PVI guided by the AI in paroxysmal AF ablation led to a low acute PV reconnection and high freedom of arrhythmia recurrence at 2 years of follow-up.

CONFLICT OF INTEREST

P.A.S has received speaker fees from Biosense Webster, Boston Scientific, Medtronic, and Abbott. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ETHICS STATEMENT

The study was approved by the local institutional ethics committee.

PATIENT CONSENT STATEMENT

All patients provided written informed consent.

CLINICAL TRIAL REGISTRATION

N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Sousa PA, Puga L, Adão L, Primo J, Khoueiry Z, Lebreiro A, Two years after pulmonary vein isolation guided by ablation index—a multicenter study. J Arrhythmia. 2022;38:346–352. https://doi.org/10.1002/joa3.12696