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ORIGINAL ARTICLE

Marshall-Plan Ablation Strategy Versus Pulmonary Vein Isolation in Persistent AF: A Randomized Controlled Trial

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BACKGROUND: Beyond pulmonary vein (PV) isolation, the optimal ablation strategy for persistent atrial fibrillation (AF) remains poorly defined. The purpose of this study was to compare 2 ablation strategies in the treatment of patients with persistent AF: a comprehensive ablation strategy based on anatomic considerations versus PV isolation alone.

METHODS: The Marshall-Plan trial is a prospective, randomized, parallel-group, controlled clinical trial of superiority conducted at the Bordeaux University Hospital. Consecutive patients with symptomatic, documented persistent AF were included and randomized into 2 arms: Marshall-Plan consisting of PV isolation with additional ablation including vein of Marshall ethanol infusion, and lines of block at the mitral, dome, and cavotricuspid isthmuses versus PV isolation alone. The main outcome was the 1-year freedom from any arrhythmia (atrial fibrillation/atrial tachycardia >30 seconds) after a single ablation procedure with or without any antiarrhythmic medication at 12 months.

RESULTS: A total of 120 patients were included (age 65±8 years; 21 women). Two patients were excluded from analysis. All PVs were successfully isolated in both groups. In the Marshall-Plan group, vein of Marshall ethanol infusion was completed in 57 (97%) patients. Conduction block across linear lesions was obtained in 93%, 92%, and 93% of the mitral, dome, and cavotricuspid isthmuses, respectively. The full lesion set was successfully completed in 52 (88%) patients in the Marshall-Plan group and 59 (100%) patients in the PV isolation group. At 12 months, freedom from recurrence of atrial arrhythmia >30 seconds after 1 ablation procedure, with or without antiarrhythmic medication, had occurred in 51 of the 59 (86.4%) patients assigned to the Marshall-Plan approach, and 39 of the 59 (66.1%) patients assigned to PV isolation only (P=0.012).

CONCLUSIONS: In this prospective randomized controlled trial, the Marshall-Plan strategy was significantly superior to a PV isolation strategy at 12 months.

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Key Words: cardiac arrhythmia ■ ethanol ■ heart ■ human ■ pulmonary veins ■ tachycardia ■ therapeutics

Catheter ablation is an established treatment strategy for patients with drug-refractory atrial fibrillation (AF). Patient selection and indications for catheter ablation are well defined in the latest guidelines[1]; however, beyond pulmonary vein (PV) isolation, the optimal ablation strategy for persistent AF remains controversial.

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WHAT IS KNOWN?

- Beyond pulmonary vein isolation, the optimal ablation strategy for persistent AF remains controversial with no clear recommendation.
- Linear ablation or ethanol infusion in the vein of Marshall have already been evaluated but never combined in a comprehensive ablation strategy that adds systematically to pulmonary vein isolation vein of Marshall ethanol infusion and 3 lines of block at the mitral, dome, and cavotricuspid isthmuses (Marshall-Plan).

WHAT THE STUDY ADDS

- In this randomized controlled trial, catheter ablation of patients with persistent AF following the Marshall-Plan ablation strategy is associated with a higher rate of freedom from any arrhythmia (atrial fibrillation/atrial tachycardia >30 seconds) after a single procedure at 12 months.
- The Marshall-Plan ablation strategy preserves atrial function and is not associated with an increased rate of procedure-related adverse events.

Nonstandard Abbreviations and Acronyms

AA	atrial arrhythmia
AF	atrial fibrillation
AT	atrial tachycardia
CS	coronary sinus
LA	left atrial
PV	pulmonary vein
SR	sinus rhythm
VOM	vein of Marshall

We have previously reported encouraging clinical results of a comprehensive strategy strictly guided by anatomic principles that consists of (1) ethanol infusion in the vein of Marshall (VOM); (2) PV isolation; and (3) a linear ablation set to close the 3 main anatomic isthmuses. To date, we have not demonstrated its superiority to the current standard of care: PV isolation.[2,3]

The Marshall-Plan randomized controlled study aimed to determine whether the addition of systematic VOM ethanol infusion and empirical linear ablation to PV isolation improves outcomes in patients undergoing first-time catheter ablation for persistent AF.

METHODS

Trial Design

The Marshall-Plan trial is a prospective, randomized, parallel-group, controlled clinical trial of superiority conducted at the Bordeaux University Hospital. The designed population consisted of patients suffering from symptomatic persistent AF. The patients were randomly assigned to 2 arms: PV isolation only or the 3-step Marshall-Plan lesion set.

All patients provided written and oral consent to participate in the study. The study protocol was approved by the institutional clinical research committee and by the French national ethics committee. Trial registration: ClinicalTrials.gov NCT04206982. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Selection

All patients aged >18 years with a documented episode of symptomatic, persistent or long-standing persistent AF were candidates for enrollment into the study. Persistent AF was defined to last for a minimum of 1 week to a maximum of 1 year, and long-standing persistent AF to last >1 year. Main exclusion criteria were hypertrophic cardiomyopathy, prior left atrial (LA) ablation, and history of heart surgery with atrial incision (see Supplemental Methods for a detailed list of the exclusion criteria).

Randomization

The randomization list was created by a statistician from the University Hospital of Bordeaux before the start of the research project. The numbers of participants in the 2 treatment groups were balanced, with a 1:1 ratio. A confidential document describing the preparation of the randomization list was kept within the Methodology and Data Management Center.

Ablation

Radiofrequency ablation of AF was performed under conscious sedation using the CARTO-3 mapping system (Biosense Webster, Diamond Bar, CA). Preprocedural computed tomography imaging was systematically acquired to rule out intracardiac thrombus and subsequently used for merging with the electroanatomic map. Transseptal puncture was performed using fluoroscopic landmarkS after a bolus of unfractionated heparin, with a target activated clotting time of 300 to 400 seconds. Three catheters were placed in heart cavities: (1) a steerable decapolar catheter in the CS; (2) an irrigated-tip ablation catheter (ThermoCool SmartTouch SF, Biosense Webster); and (3) a multipolar mapping catheter (PentaRay NAV or OctaRay NAV, Biosense Webster). A steerable long sheath was systematically used to improve catheter contact and stability. The ablation technique was point-by-point using power-control mode and irrigation between 8 and 20 mL/min. For each ablation point, radiofrequency current was delivered for 10 to 30 seconds with a power of 20 to 25 W in the CS, 30 to 50 W posteriorly, and 40 to 50 W at other sites.

Real-time automated display of each radiofrequency application (VisiTag) was systematic, using the following parameters:

- Contact and stability parameters: catheter stability ≤2 mm during 4 seconds; minimum force of 8 g for 70% of the radiofrequency application. Ablation index was then monitored to adjust application duration with the aim of: 400 to 450 at the posterior wall and 550 to 600 at the anterior wall.

Ablation Strategy 1: PV Isolation Only

The goal was to perform a wide PV disconnection at the antral level to isolate ipsilateral PVs in the same circle. The end point was the demonstration of complete entrance and exit block at each PV encirclement. If AF or atrial tachycardia (AT) persisted after PV isolation, an electrical cardioversion was used to restore sinus rhythm (SR) and validate the end point.

A voltage map was acquired at the end of the procedure in SR.

Ablation strategy 2: Marshall-Plan Lesion Set (Figure 1)

First Step: VOM Ethanolization

After coronary sinus (CS) cannulation (steerable sheath, left internal mammary artery catheter), contrast was injected to localize the VOM. A preloaded angioplasty balloon (Mini Trek, length 6–8 mm, nominal diameter 2–3.5 mm; Abbott) with an angioplasty guidewire (Hi-Torque Whisper MS; Abbott, Chicago, IL) was advanced into the VOM near its ostium. A total of 10 mL of 96% ethanol was infused (3 separate 1-minute injections). Ethanol infusion was considered successful if repeat angiograms between the 3 injections demonstrated: (1) complete occlusion of the vessel by the angioplasty balloon without contrast leakage back into the CS; (2) stability of the angioplasty balloon; (3) visualization of the distal VOM arborization; and (4) absence or limited dissection of the VOM.

Second Step: PV Isolation

Wide antral PV isolation was performed using the same principle as for the group PV isolation only. Of note, ablation was performed also in the low-voltage induced by VOM ethanol infusion.

Third Step: Atrial Lines Completion

Ablation was performed in AF if SR had not been reached during steps 1 and 2, and completed in SR if necessary. Three lines were systematically attempted: (1) roof line between the

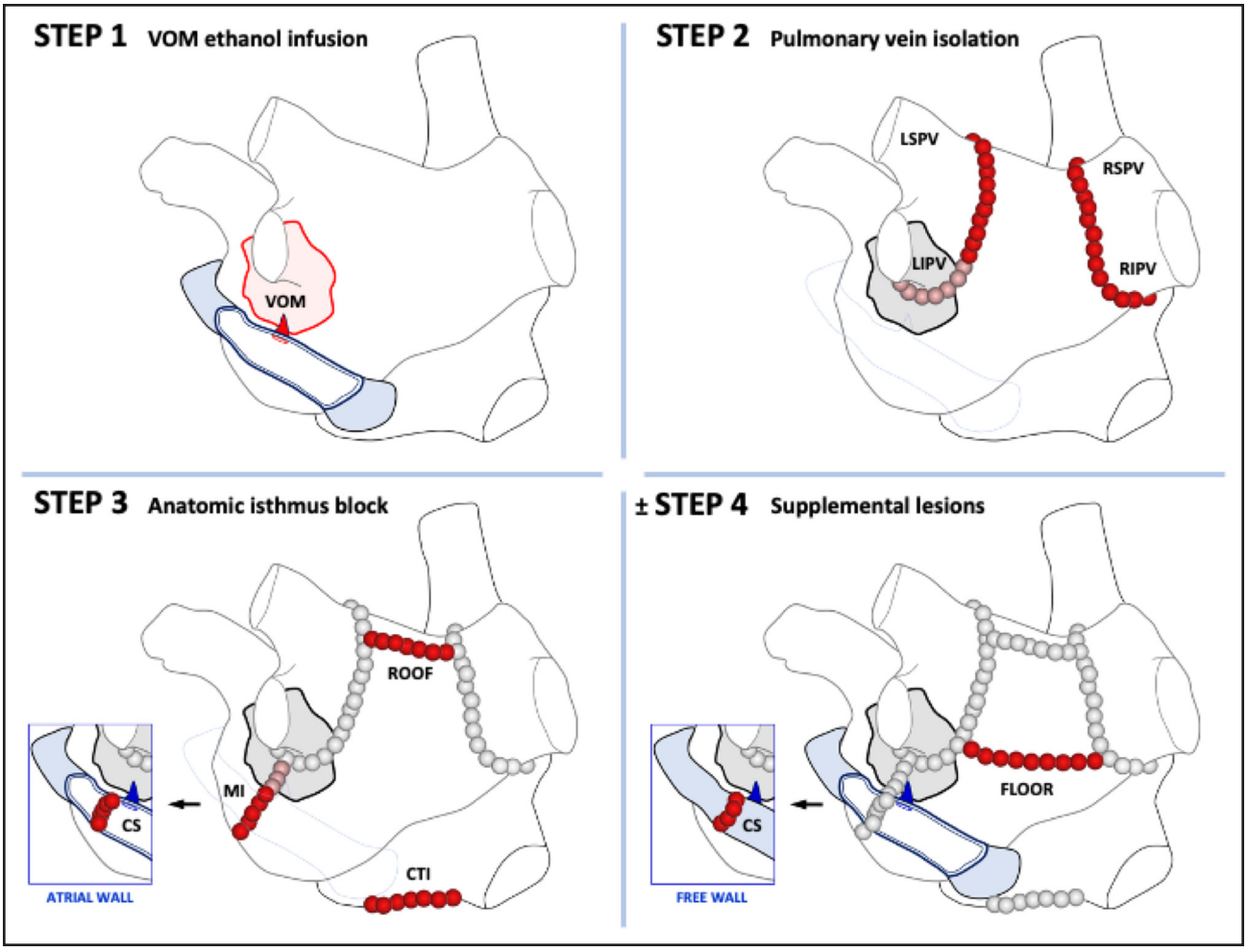

Figure 1. Marshall-Plan lesion set.
The figure shows the 3 systematic step plus 1 supplemental step in case of gap in the left atrial (LA) lines of the Marshall-Plan ablation strategy. Step 1: ethanol infusion in the vein of Marshall (VOM); Step 2: pulmonary vein (PV) isolation. The ablation points represented in light red indicate that radiofrequency application overlapping with ethanol-induced low voltage area were reduced in time. Step 3: linear lesion completion at the mitral, dome, and cavotricuspid isthmuses. It includes systematic coronary sinus (CS) ablation at the atrial aspect at the level of the endocardial line. Supplemental step: if the mitral line is not blocked after step 3, ablation at the CS free wall is performed if required. If the roof line is not blocked after step 3, creation of a floor line is performed between the lowest part of the PV encirclements.

upper part of the PV encirclements; (2) mitral line between the mitral annulus and the left inferior PV, with systematic ablation of the atrial aspect of the CS in front of the endocardial line (including the low-voltage induced by VOM ethanol infusion); (3) cavotricuspid isthmus line between tricuspid annulus and inferior vena cava.

At the end of these 3 steps, if AF was still present, an electrical cardioversion was performed to restore SR and to assess PV isolation and lines block.

Lines of block were confirmed by a high-density map of the left atrium during 600 ms pacing from the LA appendage. Block across the mitral line was defined by: (1) homogeneous proximal-to-distal activation of the CS catheter, and (2) septal-to-lateral activation of the LA posterior wall.[4] Block across the roof line was defined by strict upward activation of the posterior wall.[5] Block across the cavotricuspid isthmus line was defined by pacing maneuvers as previously described.[6]

In case of residual conduction across the mitral line, more ablation at the atrial aspect or eventually at the CS free wall was performed depending on the exact location of the gap as identified by CS mapping during LA appendage pacing. In case of residual conduction across the roof line an alternative floor line was attempted between the lowest part of the PV encirclements. Block across the floor line was defined by 2 changes in CS and LA appendage activation while pacing with the ablation catheter below and then above this line: (1) an increase in the CS activation delay becoming greater than the LA appendage activation delay, and (2) a modification of the CS activation sequence from a bracket pattern to a proximal-distal pattern.[5] The term dome transection was used to describe a conduction block across the anatomic isthmus between the 2 sets of PVs.[5]

Postprocedure management

Patients were followed up for 12 months after ablation. Their baseline antiarrhythmic medication was maintained for 1 month and then systematically interrupted. Follow-up visits were performed at 3, 6, 9, and 12 months. At each visit, patients had a physical examination, and a 12-lead electrocardiogram. Cardiovascular medication and occurrence of adverse events were collected. In addition, a transthoracic echocardiography was performed at day 1 post-ablation and at the 3-, and 12-month visits. The echocardiography performed at day 1 post-ablation, in SR, was considered as the baseline function. Patients were given a transtelephonic monitor (KardiaMobile, AliveCor) for the 12-month follow-up period. They were requested to transmit every week a 30 seconds electrocardiogram recording. Participants were also instructed to record and transmit any symptomatic arrhythmia episode. All rhythm strips were sent to a centralized database at the University Hospital of Bordeaux (blinded core laboratory) and reviewed by arrhythmia specialists. Atrial arrhythmia (AA) burden was calculated using the intermittent monitoring strategies used in this study. As described recently, total AA burden was estimated per patient as the greater of 2 calculated values: (1) the percentage of AA over the total duration of Holter data available; (2) the percentage of weeks of transtelephonic electrocardiogram monitors (TTMs) with the AA over total number of weeks with TTMs recorded.[7,8] AA burden was grouped by <0.1%, 0.1% to 9.9%, and ≥10%. Outcomes were compared between ablation strategies in all patients.

Study Outcomes

The primary outcome was to compare the 1-year freedom from any arrhythmia (AF/AT >30 seconds) between the Marshall-Plan strategy and the PV isolation strategy after a single ablation procedure after a 3-month blanking period with or without any antiarrhythmic medication. Main secondary outcomes included freedom from any arrhythmia (AF/AT >30 seconds) after 1 or 2 procedures, freedom from any arrhythmia (AF/AT >30 seconds) without the use antiarrhythmic drug, procedure time, incidence of per and peri-procedural severe complications and evolution of atrial function (see Supplemental Methods for detailed definitions of the secondary end points).

Statistical Analysis

Sample Size Calculation

Based on previous studies, a 1-year recurrence rate of 50% in the PV isolation arm was expected. Based on our preliminary studies, a 1-year recurrence rate of around 25% in the Marshall-Plan arm was estimated. Thus, with a 5% α risk and an 80% power (ie, 20% β risk) using a χ^2 test, we calculated that we needed to include 57 patients in each arm. Based on a 5% loss of follow-up, 60 patients were included in each arm, meaning 120 patients in total.

Table 1. Baseline Patients Characteristics (n=120)

Characteristics	Marshall-Plan (n=60)	PV isolation (n=60)	*P* value
Demographics			
Age, y	66±8	65±8	0.21
Sex			0.47
F	12 (20%)	9 (15%)	
M	48 (80%)	51 (85%)	
CHA_2DS_2-Vasc score	2±1	2±1	0.04
Hypertension	36 (60%)	25 (42%)	0.04
Diabetes	9 (15%)	3 (5%)	0.07
Previous stroke	5 (8.3%)	2 (3.3%)	0.44
History of amiodarone	54 (90%)	49 (82%)	0.19
LVEF, %	51±12	56±10	0.12
SHD	6 (10%)	6 (10%)	0.99
AF characteristics			
Maximum AF length, m	10±18	7±6	0.86
Current AF length, m	9±19	6±7	0.77
Long-standing AF >1 y	11 (18%)	11 (18%)	1.00
History of DCC	1±1	1±1	0.32
Rhythm at inclusion			0.19
AF	32 (53%)	39 (65%)	
SR	28 (47%)	21 (35%)	
Left atrial volume, mL	187±53	192±53	0.31

Values are given as mean±SD or n (%). AF indicates atrial fibrillation; DCC, direct current cardioversion; LVEF, left ventricular ejection fraction; m, month; PV, pulmonary vein; SHD, structural heart disease; SR, sinus rhythm; and y, year.

The intention to treat principle was applied to this study, however we used a modified intention to treat based on the advice of the scientific council. Two patients were removed from the analysis (1 in each arm): 1 patient in the PV isolation arm was wrongly included (unknown prior left heart surgery) and 1 patient in the Marshall-Plan arm had to cancel the procedure due to unrelated health problem (Hyperthyroidism diagnosed after randomization).

Continuous variables are presented as mean±SD when following a normal distribution and as median (interquartile range) otherwise. Categorical variables are presented as proportions and percentages. Continuous variables were compared using independent-sample parametric (unpaired Student *t* test) or nonparametric tests (Mann-Whitney *U* test) depending on data normality. Categorical variables were compared using Fisher exact or χ^2 tests, as appropriate.

Survival curves (ie, time to event) for AF recurrence were generated according to the study's arm using the Kaplan-Meier method and compared using the log-rank test.

To estimate transthoracic echocardiography features differentiation (ie, EF and A-wave velocity) between arm, visit time (ie, V0: day 1, V1: 3 months, V2: 12 months) and cardiac rhythm before procedure (ie, Sinusal versus AF) we fitted a random slope and intercept linear mixed model for longitudinal data. Model assumptions were systematically checked through normalized residual assessment. Finally, we compared the occurrence of adverse event between arms using Fisher exact test or χ^2 test depending on the conditions.

RESULTS

Patients Characteristics

A total of 120 patients were enrolled between January 2020 and November 2022 and randomly assigned to the Marshall-Plan lesion set (60 patients) and PV isolation only (60 patients). There were no differences in baseline characteristics except for hypertension and CHA_2DS_2-VASc score, which was higher in the Marshall-Plan group (Table 1). A majority of patients were in AF at the outset of the procedure (60%), with no difference between groups for the longest continuous AF episode (10±18 months versus 7±6 months for Marshall-Plan and PV isolation, respectively; *P*=0.86). Twenty-two patients (18%) were in AF for > 1 year at inclusion. Two patients were wrongly included with a nonrespected eligibility criteria: 1 patient in the PV isolation group had a history of atrial surgery, and 1

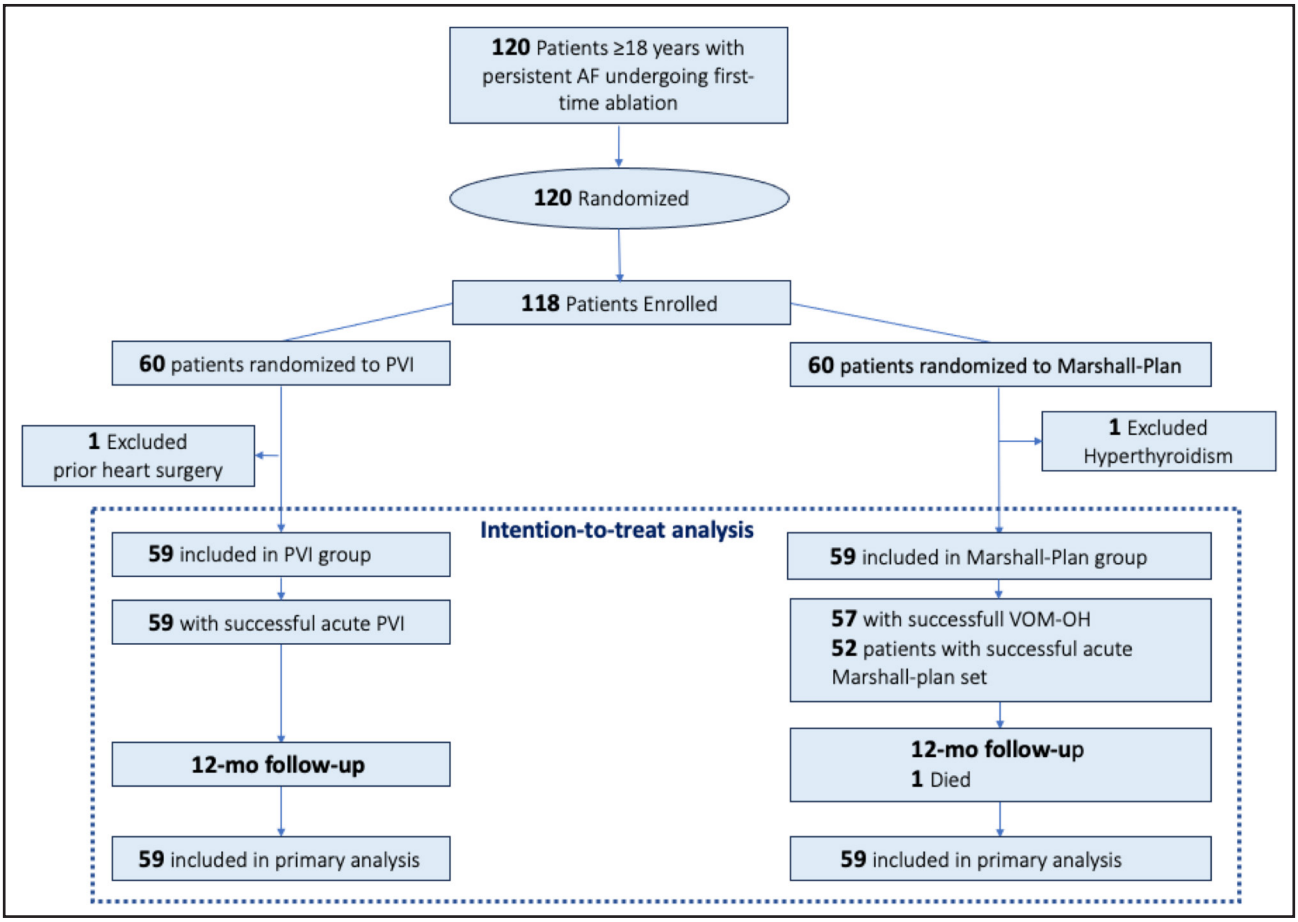

Figure 2. Study flowchart.
Consecutive patients with symptomatic documented persistent atrial fibrillation (AF) were included and randomized in 2 arms: Marshall-Plan vs pulmonary vein (PV) isolation.

patient in the Marshall-Plan group had hyperthyroidism identified before ablation. These 2 patients were excluded from the analysis (Figure 2).

Procedural Outcomes

Complete PV isolation was achieved for both groups in all patients. Mean radiofrequency time for PV isolation was significantly shorter in the Marshall-Plan group compared with the PV isolation group (23±8 versus 29±8 minutes; $P<0.01$), mainly due to a shorter time to isolate the left PV in the Marshall-Plan group after VOM ethanol infusion (9.5±4.3 versus 13.0±3.7; $P<0.01$). The rate of first-pass PV isolation was 83% (10/59) in the PV isolation group and 80% (12/59) in the Marshall-Plan group ($P=0.81$).

In the Marshall-Plan group VOM ethanol infusion could be completed in 57 patients (97%). Cases with failed VOM ethanol infusion were due to nonidentification of the VOM in 1 patient and CS dissection in the second patient. The mean ethanol infusion was 10±2 mL. The mean time required for VOM ethanol infusion was 23±15 minutes, with fluoroscopy times and doses of 6.3±6.8 minutes and 13.2±18.9 mGy/cm^2, respectively. Linear lesions were attempted in 56 (95%) patients. The mitral line was successfully blocked in 55 (93%) patients with a mean radiofrequency time of 7±6 minutes, including systematic CS ablation (4±3 minutes). In 3 (5%) patients, supplemental radiofrequency applications at the free wall of the CS were required to obtain complete mitral line block. The roof line was successfully blocked in 30 (51%, 4.5±1.4 minutes) patients. Creation of a floor line was required in the remaining 26 (44%, 4.8±2.7 minutes) patients due to residual epicardial gaps, but failed in 2 patients. Therefore, dome transection was finally obtained in 54 (92%, 6.3±3.4 minutes) patients. Complete block at the cavotricuspid isthmus was obtained in 55 (93%, 5.9+4.5 minutes) patients. Linear ablation was not attempted in 3 patients: the 2 patients with failed VOM ethanol infusion underwent only PV isolation; 1 patient was discovered per procedure to have extensive silent areas in both atria and was later diagnosed with a severe laminopathy.

Overall, the complete Marshall-Plan lesion set (including VOM ethanol infusion, PV isolation and the 3 lines of block) was achieved in 52 (88%) patients. Acute AF termination was observed in 1 patient of the Marshall-Plan group and 3 patients of the PV isolation group ($P=0.62$). All of these terminations were directly into SR.

Total procedure time, radiofrequency time, and X-ray time were longer for the Marshall-Plan group compared with the PV isolation group (respectively: 157±53 versus 125±31 minutes, 36.8±16.0 versus 29.6±8.1 minutes, 21±6 versus 11±6 minutes; $P<0.001$).

The main procedural results are summarized in Table 2.

Clinical Outcomes

Overall compliance for weekly TTMs and Holter monitoring was 85.3% and 86.9%, respectively.

Primary Outcome

At 12 months, freedom from recurrence of any AA (AF/AT) lasting longer than 30 seconds after 1 ablation procedure, with or without the use of antiarrhythmic medication, had

Table 2. Procedural Characteristics (n=118)

	Marshall-Plan (n=59)	PV isolation (n=59)	*P* value
Rhythm in EP laboratory			0.19
AF	32 (54%)	39 (66%)	
SR	27 (46%)	20 (34%)	
LAA cycle length (if AF; ms)	206±138	176±26	0.88
LA volume, mL	182±52	192±53	0.22
PVI	59	59	1.00
Total RF LPV, min	9.5±4.3	13.0±3.7	0.001
Total RF RPV, min	13.4±5.1	15.8±5.5	0.012
Total RF PVs, min	23±8	29±8	0.001
VOM-OH	57 (97%)	…	…
OH volume, mL	10±2	…	…
Time for OH, min	22.5±15.4	…	…
X-ray time for OH, min	6.3±6±8	…	…
Mitral isthmus line attempt	56 (95%)	…	…
Mitral isthmus block (% per attempt; %total)	55 (98%; 93%)	…	…
RF mitral line, min	7.2±6.2	…	…
Posterior wall line attempt	56 (95%)	…	…
Posterior wall block (% per attempt; %total)	54 (96%; 92%)	…	…
Roof line block (% per attempt; %total)	30 (54%; 51%)	…	…
RF roof line, min	6.3±4.4	…	…
Floor line attempt	26 (46%)	…	…
Floor line block (% per attempt; %total)	24 (92%; 43%)	…	…
RF floor line, min	4.8±2.6	…	…
CTI line attempt	56 (95%)	…	…
CTI line block(% per attempt; %total)	55 (93%; 98%)	…	…
RF CTI line, min	5.9±4.5	…	…
Ablation set complete	52 (88%)	59 (100%)	0.058
Total procedure time, min	157±53	125±31	0.001
Total RF time, min	36.8±16.0	29.6±8.1	0.001
Total X-ray time, min	21±16	11±6	0.001

Values are given as mean±SD or n (%). AF indicates atrial fibrillation; CTI, cavotricuspid isthmus; EP, electrophysiology; LA, left atrium; LAA, left atrial appendage; PV, pulmonary veins; PVI, pulmonary veins isolation; RF, radiofrequency; RPV, right pulmonary veins; SR, sinus rhythm; and VOM-OH, vein of Marshall ethanol infusion.

occurred in 39 of the 59 (66.1%) patients assigned to PV isolation only, and 51 of the 59 (86.4%) patients assigned to the Marshall-Plan approach. The rate of the primary outcome was significantly higher in the group receiving the Marshall-Plan approach (*P*=0.012; Figure 3, Table 3).

Secondary Outcomes

The rate of freedom from any AA after a single ablation procedure, without the use of antiarrhythmic medication, was significantly higher in the group receiving the Marshall-Plan approach (*P*=0.022). The rate of freedom from any AA after 1 or 2 ablation procedures, without the use of antiarrhythmic medication, was significantly higher in the of the group receiving the Marshall-Plan approach (*P*=0.011; Figure 3; Table 3).

Repeat Ablation Procedures

During the 12-month follow-up, 11 of the 29 patients with clinical recurrence underwent a second ablation procedure. The ablation set was found complete in all patients assigned to the PV isolation group (7 patients) while it was incomplete in the patients assigned to the Marshall-Plan group (4 patients). Among the latter, all PVs were found isolated. Electrical gaps were identified across the linear lesions (mitral line in 3 patients, roof line in 2 patients, and cavotricuspid isthmus line in 3 patients). The main mode of arrhythmia recurrence was persistent AF in both groups (Marshall-Plan: 6 [76%] patients; PV isolation: 14 patients [70%]; *P*=0.67; Figure 4). No significant difference in arrhythmia burden was observed

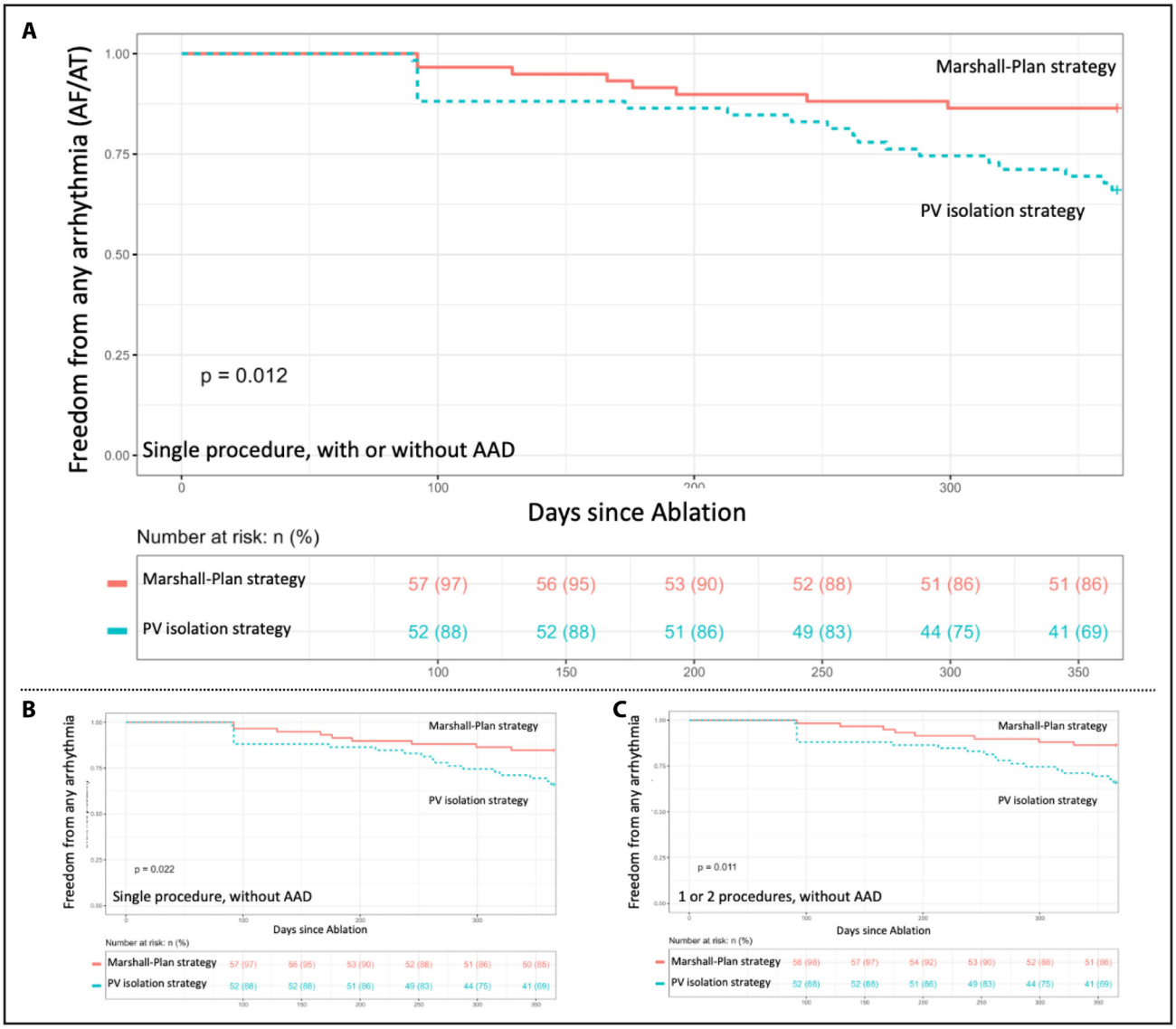

Figure 3. Freedom from atrial fibrillation.
The graph shows Kaplan-Meier estimates of freedom from any documented arrhythmias (atrial fibrillation [AF]/atrial tachycardia [AT] >30 seconds). **A**, After a single ablation procedure with or without antiarrhythmic medication at 12 months. **B**, After a single ablation procedures without antiarrhythmic medication at 12 months. **C**, After 1 or 2 ablation procedures without antiarrhythmic medication at 12 months. There were significant differences between groups in favor of the Marshall-Plan strategy (*P*=0.012, *P*=0.022, and *P*=0.011, respectively).

Table 3. Major Efficacy Outcomes

	n (%)			
	Marshall-Plan (n=59)	PV isolation (n=59)	Absolute difference	*P* value
Primary outcome				
Freedom from any arrhythmias (AF/AT), after a single ablation procedure with or without antiarrhythmic medication at 12 mo	51 (86.4)	39 (66.1)	+12 (+20.3)	0.012
Secondary outcomes				
Freedom from any arrhythmias (AF/AT), after a single ablation procedure without antiarrhythmic medication at 12 mo	50 (84.7)	39 (66.1)	+11 (+18.6)	0.022
Freedom from any arrhythmias (AF/AT), after 1 or 2 ablation procedures without antiarrhythmic medication at 12 mo	51 (86.4)	39 (66.1)	+12 (+20.3)	0.011
Freedom from any arrhythmias (AF/AT), after 1 or 2 ablation procedures with or without antiarrhythmic medication at 12 mo	52 (88.1)	39 (66.1)	+13 (+22.0)	0.005

AF indicates atrial fibrillation; AT, atrial tachycardia; and PV, pulmonary veins.

between groups (Marshall-Plan 35±29% versus PV isolation 29±27%; *P*=0.32; Supplemental Methods).

Atrial Function

For both groups, a significant improvement in A-wave velocity was observed in SR patients during the first 3 months post-ablation and maintained at 12 months: 49±17 cm/s at baseline versus 67±16 cm/s at 12 months (*P*<0.001) in the PV isolation group versus 47±21 cm/s at 3 months versus 61±20 cm/s at 12 months (*P*<0.001) in the Marshall-Plan group. This improvement was mainly observed among patients in AF at inclusion compared with patients in SR. No significant difference was observed between patients assigned to the Marshall-Plan approach or PV isolation (Figure 5; Supplemental Methods).

Adverse Events

Peri-procedural adverse events occurring in patients who underwent an ablation procedure are shown in Table 4. Major procedure-related adverse events did not differ significantly between the 2 groups (Marshall-Plan 1.7% versus PV isolation 1.7%; *P*=1.0). In the PV isolation group 1 patient developed an oesophago-pericardial fistula associated with mediastinitis. The patient benefited from early surgical management with oesophagus repair and interposition of an intercostal muscle flap, and had no sequelae. In the Marshall-Plan group 1 patient had a severe groin hematoma requiring radioembolization and blood transfusion. Otherwise, most complications were pericarditis defined as chest pain and limited pericardial effusion, with no significant differences observed between arms. One patient died during follow-up in

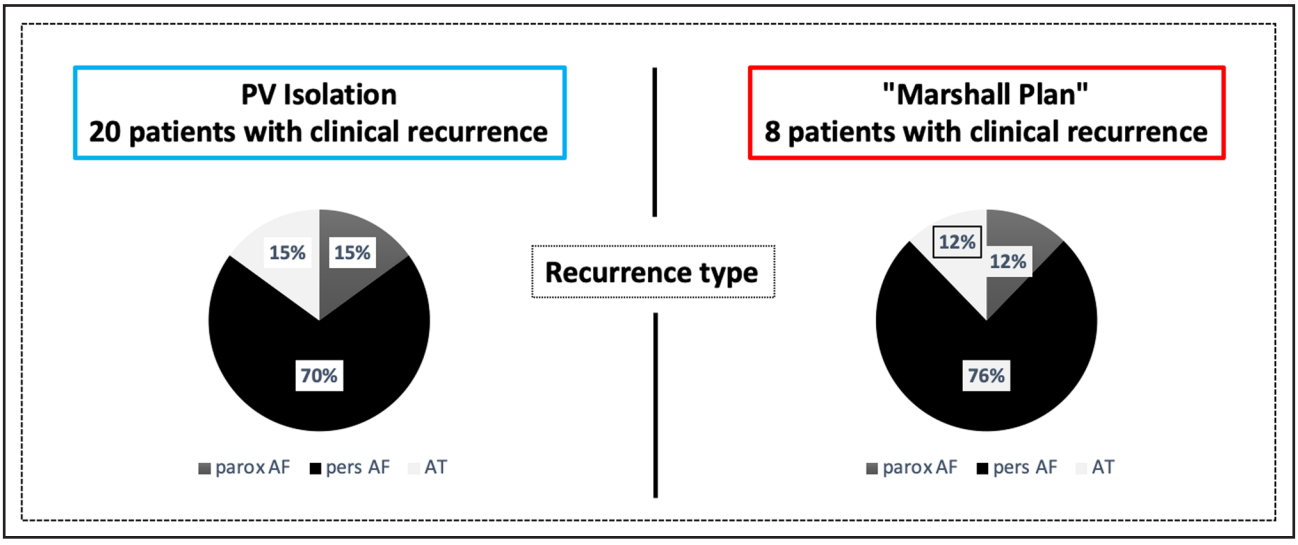

Figure 4. Mode of arrhythmia recurrence during follow-up.
Distribution of the mode of arrhythmia recurrence in both group. AF indicates atrial fibrillation; AT, atrial tachycardia; Parox AF, paroxysmal AF; and pers AF, persistent AF.

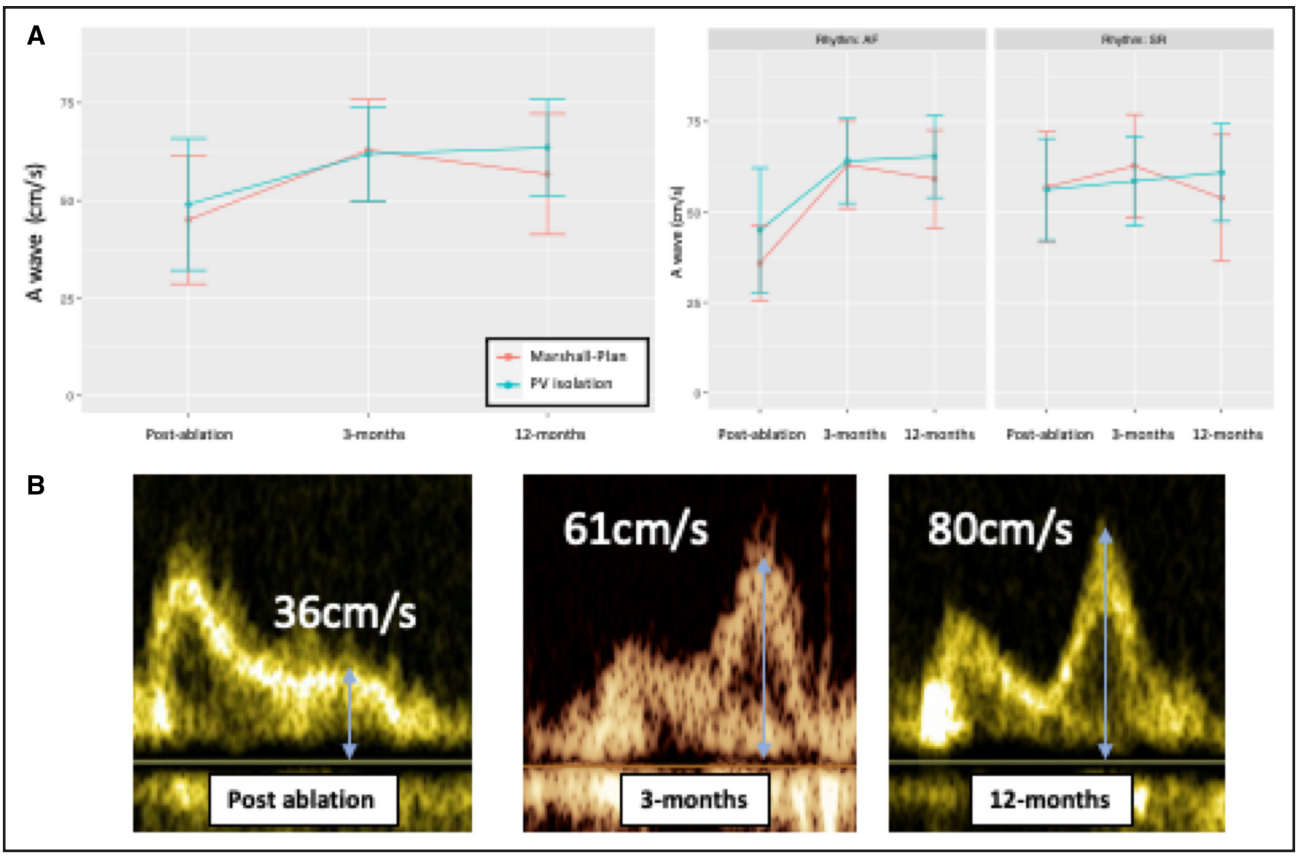

Figure 5. Evolution of the left atrial function after ablation.
A, A-wave velocity (cm/s) at post-ablation, 3- and 12-month for all the patients included in the Marshall-Plan group (blue line) and pulmonary vein (PV) isolation (red line; mean±SD). Right panel: A-wave velocity (cm/s) at post ablation, 3- and 12-month for patients in atrial fibrillation (AF) at the beginning of the procedure (mean±SD) and for patients in sinus rhythm (SR) at the beginning of the procedure (mean±SD) included in the Marshall-Plan group (blue line) and PV isolation (red line). **B**, Transmitral flow velocity assessment for a patient from the Marshall-Plan group and in AF at inclusion. Note the evolution of the A-wave velocity from 36 cm/s at day 1 post-ablation to 80 cm/s at 12-month post-ablation.

relation to a severe laminopathy diagnosed after the index procedure.

DISCUSSION

In this prospective randomized trial, we compared 2 approaches to ablation of persistent AF. The main findings are: (1) we found a significant improvement in the rate of SR maintenance with the Marshall-Plan strategy, despite a good success rate with PV isolation alone, (2) total procedure time was significantly longer in the Marshall-Plan group, (3) there were no significant differences in procedure-related adverse events between the 2 arms, and (4) the evolution of LA contractile function after ablation was similar in both groups.

The characteristics of our study population were similar to those of other comparable trials, and representative of patients with persistent AF.[9–11] Nearly 20% of participants had long-standing persistent AF, 41% were in constant AF for >6 months at inclusion, and those included in SR had generally undergone previous electrical cardioversion for worsening symptoms. However, our PV isolation group had a higher rate of freedom from any arrhythmia than the 1 reported in these trials. The durability of PV isolation certainly plays a major role, and recent studies using a strict combination of higher power settings and tissue-contact criteria report comparable success rates at 12 months.[12,13] To support this hypothesis, all 8 patients from the PV isolation group who benefited from a redo procedure had all 4 PVs isolated. Of note, the principal mode of arrhythmia recurrence was persistent AF with no difference between groups, as reflected by a high burden of arrhythmia (AF/AT) in patients with clinical recurrence (Marshall-Plan 35±29% versus PV isolation 29±27%; *P*=0.32). The common idea that an ablation strategy based on anatomic lines would promote recurrence in AT in case of reconduction through these lines was not supported by our results. Strategies based on per-procedure AF termination with substrate modification are more likely to favor such type of recurrence, while strategies based only on linear ablation did not demonstrate more AT recurrences.[9,14–16] The main hypothesis to explain why anatomic strategies decrease AF recurrence is that, by closing the 3 main isthmuses

Table 4. Procedural Adverse Events

	Marshall-Plan (n=59)	PV isolation (n=59)	Total (N=118)	*P* value
Major complications	1*	1*	2*	1.0
Oesophageal fistulae	0	1	1	1.0
Severe Groin hematoma	1	0	1	1.0
Stroke/TIA/arterial embolism	0	0	0	1.0
Phrenic nerve palsy	0	0	0	1.0
Tamponade	0	0	0	1.0
Internal bleeding	0	0	0	1.0
Minor complications	12*	5*	17*	0.11
Femoral AV fistula	1	0	1	1.0
Femoral pseudoaneurysm	0	0	0	1.0
Pericarditis	6	1	7	0.12
Hyperthermia	1	3	4	0.62
Sepsis	0	0	0	1.0
Nausea	2	1	3	1.0
Dyspnea	2	0	2	0.50

*Total numbers or major and minor complication. AV indicates arterioveinous; and TIA, transient ischemic attack.

that account for the vast majority of macroreentrant AT, it will prevent the simpler reentrant mechanisms that bridge initiation of AF to its permanent state.[17,18]

From this respect, the Marshall-Plan ablation strategy has been developed with a triple aim: (1) to target clear anatomic structures considered critical to the fibrillatory process, (2) to prevent the main anatomic reentrant arrhythmias, and (3) to respect the natural physiological activation of the atria by using rationally placed linear lesions. Using a rigorous prospective, randomized, 2-arm methodology (Marshall-Plan versus PV isolation only), the present study outperformed our earlier results with 86% of patients free from any arrhythmia at 12 months.[2] We attribute this improvement to a better understanding of the critical determinants that ameliorate each step of the strategy. VOM ethanol infusion is certainly a key element as it has demonstrated its importance for mitral block durability.[19,20] With the gain of experience, we have improved success for VOM ethanol infusion while decreasing vein dissection that can affect the size of the lesion.[21,22] The identification of epicardial structures hindering lesion transmurality was although critical and led us to: (1) systematically ablate the CS at the mitral line level, and (2) to create a floor line rather than debulk the dome in case of failed roof line.[4,5] Keeping these determinants in mind, we can hypothesize that the disappointing results of previous studies based on a purely anatomic strategy might have been related to the insufficient durability of the linear lesions.[9] The VENUS randomized controlled trial (Vein of Marshall Ethanol for Untreated Persistent AF) was the first study to evaluate the role of VOM ethanol infusion in the treatment of persistent AF. The main result of the trial was a demonstration of an improved outcome in patients treated with additional VOM ethanol infusion.[23] However, in the trial, VOM ethanol infusion was added to a relatively wide range of atrial lesions beyond PV isolation. This heterogeneity may account for the overall success rate that was slightly under expectation. The same group reported, in an ancillary study, that the best outcome was found among patients with mitral line block.[24] These results suggest that not only VOM ethanol infusion is important, but also effective lines of block. More recently, the multicentric prospective PROMPT-AF trial (Pulmonary Veins Isolation With Optimized Linear Ablation Versus Pulmonary Veins Isolation Alone for Persistent Atrial Fibrillation) has demonstrated the superiority of a similar approach (PV isolation+VOM ethanol infusion+linear ablation) against PV isolation.[16] This important result reinforces the interest in the anatomic approach.

The Marshall-Plan group had significantly longer procedure time and fluoroscopy exposure than the PV isolation group. The strict methodology used for the Marshall-Plan certainly accounted for this additional time, but also contributed to the high rate of SR maintenance. This additional time needs to be compared with the 1 required for similar procedures reported before the description of VOM ethanol infusion.[25,26]

The overall rate of adverse events was not significantly different between groups. We have observed slightly more pericarditis among patients treated with the Marshall-Plan strategy. It occurs generally at day 1 or 2 post-procedure and ceases within few days with nonsteroid antiinflammatory drug.[21] Of note, the rate of major complications was low in this trial (1.7%) and did not differ between groups. As previously reported, VOM ethanol infusion does not significantly alter the overall safety of the procedure.[21] Unfortunately, 1 patient in the PV isolation group had an oesophago-pericardial fistula complicated with mediastinitis. The patient benefited from an early surgical management and had a favorable outcome. This severe complication occurred despite use of the recommended ablation parameters (power of 40 W, max contact force <15 g, max duration on the posterior wall <10 seconds and max ablation index <400 with no consecutive lesions). To date, no clear recommendations have emerged from the latest international expert consensus regarding the use of temperature probe.[27] To this respect, the growing use of pulse field ablation will certainly help to achieve this lesion set more rapidly and safely in the future.

Regarding LA function, our analysis of A-wave velocity showed no significant alteration in all patients, and rather an improvement in those who were in AF at inclusion. These results were observed at 3 months, and maintained at 12 months for both groups. Bi-atrial activation sequence is subjected to individual variations. However, the natural wavefront collisions are remarkably stable

and observed at 3 sites: septal aspect of the cavotricuspid isthmus, lower part of the dome and mitral isthmus. Therefore, in contrast with previous substrate ablation, by placing the linear lesions at these natural collision sites, the Marshall-Plan set respects the physiological activation of the atria and does not deteriorate LA function.[28,29]

LIMITATIONS

Some important limitations of this trial should be considered. First, our trial was monocentric and requires validation by more operators from different centers. Second, the follow-up period was limited to 12 months and conducted without implantable devices for surveillance. We are currently running a randomized, multicentric trial with 24 months follow-up and a larger study population that should overcome these limitations. The inclusion period was longer than expected due to the COVID-19 pandemic.

CONCLUSIONS

In patients undergoing first-time catheter ablation for persistent AF, the Marshall-Plan strategy significantly improved freedom from any AA at 12 months compared with PV isolation only. These findings support the addition of systematic VOM ethanol infusion and empirical linear ablation at the 3 main isthmuses to PV isolation in the treatment of persistent AF.

ARTICLE INFORMATION

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Supplemental Material

Supplemental Methods
Figures S1–S3

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