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The Efficacy and Safety of Hybrid Ablations for Atrial Fibrillation

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ABSTRACT

OBJECTIVES This study sought to comprehensively determine the procedural safety and midterm efficacy of hybrid ablations.

BACKGROUND Hybrid ablation of atrial fibrillation (AF) (thoracoscopic ablation followed by catheter ablation) has been used for patients with nonparoxysmal AF; however, accurate data regarding efficacy and safety are still limited.

METHODS Patients with nonparoxysmal AF underwent thoracoscopic, off-pump ablation using the COBRA Fusion radiofrequency system (Estech) followed by a catheter ablation 3 months afterward. The safety of the procedure was assessed using sequential brain magnetic resonance and neuropsychological examinations at baseline (1 day before), postoperatively (2-4 days for brain magnetic resonance imaging or 1 month for neuropsychological examination), and at 9 months after the surgical procedure. Implantable loop recorders were used to detect arrhythmia recurrence. Arrhythmia-free survival (the primary efficacy endpoint) was defined as no episodes of AF or atrial tachycardia while off antiarrhythmic drugs, redo ablations or cardioversions.

RESULTS Fifty-nine patients (age: 62.5 ± 10.5 years) were enrolled, 37 (62.7%) were men, and the mean follow-up was 30.3 ± 10.8 months. Thoracoscopic ablation was successfully performed in 55 (93.2%) patients. On baseline magnetic resonance imaging, chronic ischemic brain lesions were present in 60% of patients. New ischemic lesions on postoperative magnetic resonance imaging were present in 44.4%. Major postoperative cognitive dysfunction was present in 27.0% and 17.6% at 1 and 9 months postoperatively, respectively. The probability of arrhythmia-free survival was 54.0% (95% CI: 41.3-66.8) at 1 year and 43.8% (95% CI: 30.7-57.0) at 2 years.

CONCLUSIONS The thoracoscopic ablation is associated with a high risk of silent cerebral ischemia. The midterm efficacy of hybrid ablations is moderate. (J Am Coll Cardiol EP 2021;■:■–■) © 2021 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drug

AF = atrial fibrillation

AT = atrial tachycardia

bMRI = brain magnetic resonance imaging

CA = catheter ablation

CTI = cavotricuspid isthmus

DWI = diffusion-weighted images

ECG = electrocardiogram

EP = electrophysiology

FLAIR = fluid-attenuated inversion recovery

ILR = implantable loop recorder

LA = left atrium

LAA = left atrial appendage

LMWH = low-molecular-weight heparin

MRI = magnetic resonance imaging

OAC = oral anticoagulation

PeAF = persistent atrial fibrillation

POCD = postoperative cognitive dysfunction

PV = pulmonary vein

Despite the rapid evolution in treatment, patients with nonparoxysmal atrial fibrillation (AF) still have unsatisfactory outcomes. Modification of the arrhythmogenic substrate during Cox maze surgery, with a division of both atria into segments, represents an aggressive but efficient treatment for such patients (1). However, because of its invasiveness (ie, on-pump cardiac surgery), it cannot be used for the general AF population. Therefore, over the last decade, surgical treatment of AF has shifted from open heart surgery toward minimally invasive procedures (1). To ensure (and complete) thoracoscopic lesions and to ablate structures that are difficult for surgeons to ablate, the initial procedure is often followed by percutaneous electrophysiology (EP) study and catheter ablation (CA), the combination of which is called a hybrid ablation.

The degree of AF freedom described after hybrid ablation was high, as reported in previous studies; however, with only a few exceptions, all studies used 1-day or 7-day Holter monitoring (2,3). Implantable loop recorders (ILRs) can detect AF or atrial tachycardia (AT) recurrences more effectively compared to routine Holter monitoring and can, therefore, more accurately establish the effect of the procedure. Thoracoscopic ablation, compared to catheter ablation, seems to carry a higher risk of complications, including the most serious, that is, stroke. Apart from a clinically manifest stroke, silent brain embolizations can occur during ablations, which can lead to cognitive decline. In contrast to catheter ablation studies, to our knowledge, no study has addressed the risk of silent stroke during thoracoscopic ablations and changes in cognitive functions after an ablation.

The goal of the present study was to assess the efficacy and safety of hybrid ablation using highly sensitive methods, such as contiguous ILR electrocardiogram (ECG) recordings, brain magnetic resonance imaging (bMRI), and cognitive function examinations.

METHODS

TRIAL DESIGN. The efficacy and safety of hybrid ablations for AF, assessed using implantable ECG recorders, sequential magnetic resonance imaging, and neuropsychological examination (NCT02832206), was an investigator-initiated, single-center, single-arm, prospective study. The study was initiated and conducted at Charles University and the Kralovske Vinohrady University Hospital, Prague, Czech Republic. Database management and primary analyses were performed at the Institute for Biostatistics and Analyses, Masaryk University, Brno, Czech Republic. The multicenter ethics committee at the Kralovske Vinohrady University Hospital approved the protocol, and all patients signed informed content before enrollment. The Data Safety and Monitoring Board (see Supplemental Appendix) received a list of clinical complications for all patients on an annual basis.

PATIENTS. Patients with symptomatic, drug-resistant, nonparoxysmal AF were enrolled in this prospective observational study. Before enrollment, patients underwent cardiology examination, including echocardiography, a computed tomography-coronary angiogram (or coronary angiography), spirometry, and chest x-ray. Full inclusion and exclusion criteria are shown in the Supplemental Appendix.

THORACOSCOPIC CARDIAC SURGERY. Surgical ablations were performed using a thoracoscopic, right-sided, off-pump, epicardial approach. The goal was to create a circumferential lesion anterior to the pulmonary veins (PVs) to isolate all the PVs together with the posterior aspect of the left atrium (LA) (ie, a box lesion set). This continuous lesion was created using a versapolar (unipolar/bipolar) linear radiofrequency COBRA Fusion 150 ablation catheter (Estech, an AtriCure Company, San Ramon, California). A graphical representation of the surgical ablation procedure is shown in Supplemental Figure 1. Three or 4 ablation cycles were performed in both modes (ie, bipolar and unipolar) with a temperature-controlled energy application setting of 70 °C and a duration of 60 seconds per cycle. If the patient remained in AF, direct current cardioversion was performed. Our surgical technique was previously published in detail (4). The ablation, done through the right chest, was then followed by a left-sided thoracoscopic occlusion of the left atrial appendage (LAA), using the AtriClip Pro device (AtriCure, IncMason, Ohio). The ligament of Marshall was dissected by electrocoagulation under a direct left-sided thoracoscopic view. Oral anticoagulation (OAC) was stopped before surgery and switched to low-molecular-weight heparin (LMWH). Intravenous heparin was given to all patients before the ablation and continued while patients were in the intensive care unit. OAC was restarted before discharge. The anticoagulation protocol is described in detail in the Supplemental Appendix.

EP AND CA. The staged EP study and CA were performed approximately 2 to 3 months after the surgery ablation. The goal of the EP study was to verify (and complete, if needed) the box lesion, to create a prophylactic mitral isthmus line, and to ablate the cavotricuspid isthmus (CTI). The EP study was done with patients under mild sedation; a detailed methodology of the EP study has been published elsewhere and is also described in detail in the Supplemental Appendix (5).

PATIENT FOLLOW-UP AND EFFICACY ASSESSMENT. Sinus rhythm maintenance was evaluated using implantable ECG recorders (Reveal LinQ, Medtronic, Minneapolis, Minnesota) in all patients. Implantation of the ILR occurred before discharge from cardiac surgery. The programming of the ILR for AF/AT detection was standardized for all patients. Follow-up visits were performed at 30, 90, 180, 270, and 360 days after the EP procedure, which was considered the index procedure, and then every 6 months thereafter. All visits consisted of a clinical evaluation, a medical history, anticoagulation assessment, assessments of antiarrhythmic and other pharmaceutical treatments, and an examination of the ILR. (Remote interrogation of the ILR was not used.) Antiarrhythmic drugs (AADs) were withdrawn during the first 3 (or maximum 6) months after CA; however, AADs could be restarted based on a reoccurrence of arrhythmia, and this decision was left to the discretion of the treating physician. Cessation of OAC was assessed individually at the follow-up visits for each patient and was based on the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥ 65 or ≥ 75, diabetes, prior cardioembolic event, female gender, or vascular disease) risk score and the efficacy of the ablation. Rhythm assessment was based on the ILR findings at each visit. The success of ablation was divided into the following categories.

PRIMARY EFFICACY ENDPOINT. SR OFF (arrhythmia-free survival) presents the primary efficacy endpoint of the study and is defined as absence of any AF or AT episodes for the whole observational period and the absence of AAD reinitiation, reablation, or electrical cardioversion.

SECONDARY EFFICACY ENDPOINTS. SR ON is defined as a reoccurrence of either AT or AF with a need of AAD reinitiation, cardioversion, or reablation, but without further episodes of AF or AT after the mentioned antiarrhythmic measure(s) were instituted. Rhythm control survival is defined the presence of repeated self-terminated paroxysms of AF or AT despite the reintroduction of AADs, a reablation, or electrical cardioversions; nonetheless, it is an absence of a continuous (permanent) form of AF or AT. Rate control survival is defined as progression to

TABLE 1 Baseline Clinical Characteristics

Baseline characteristics	
Age, y	62.5 ± 10.5
Sex	
Male	37 (62.7)
Female	22 (37.3)
Weight, kg	92.3 ± 18.3
Height, cm	172.6 ± 8.8
Arrhythmia history	
AF type	
Persistent	31 (52.5)
LS persistent	28 (47.5)
AF duration, months	34.2 ± 39.7
History of electrical cardioversion	48 (81.3)
History of catheter ablation	8 (13.6)
Pacemaker	0 (0.0)
ICD	1 (1.7)
History of AADs	43 (72.9)
If yes: amiodaron	32 (74.4)
Baseline ECG (admission to hospital): sinus rhythm	8 (13.6)
Clinical history	
Coronary artery disease	6 (10.2)
Hypertension	39 (66.1)
Episode of heart failure	21 (35.6)
NYHA class	2.0 ± 0.6
Diabetes mellitus	15 (25.4)
COPD	2 (3.4)
Thyropathy	11 (18.6)
Renal insufficiency	0 (0.0)
Cardioembolic event	1 (1.7)
Bleeding complication	2 (3.4)
CHA_2DS_2VASc score	2.3 ± 1.3
Medical therapy before surgery	
Beta blocker	37 (62.7)
ACE inhibitor/sartan	32 (54.2)
Calcium-channel blocker	12 (20.3)
Amiodarone	18 (30.5)
Propafenone	6 (10.2)
Digoxin	9 (15.3)
Antithrombotic treatment before surgery	
Warfarin	29 (49.2)
DOAC	31 (52.5)
Aspirin	1 (1.7)
Clopidogrel	0 (0.0)
Echocardiography	
Left atrium diameter, mm	46.0 ± 5.6
Left ventricle size (LVEDd), mm	52.6 ± 5.8
Ejection fraction of LV, %	53.9 ± 10.7
Mitral regurgitation	
No	9 (15.3)
Mild	39 (66.1)
Modern	11 (18.6)
Severe	0 (0.0)

Continued on the next page

TABLE 1 Continued

Preoperative laboratory test results	
Hemoglobin, g/L	140 ± 15
Platelets, $\times 10^9$/L	216 ± 51
Creatinine, μmol/L	93 ± 18
Urea, mmol/L	5.7 ± 1.7
ALT, μkat/L	0.58 ± 0.19
AST, μkat/L	0.52 ± 0.16
NT-proBNP, pmol/L	1,027 ± 803

Values are mean ± SD or n (%).

AAD = antiarrhythmic drug; ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ALT = alanine aminotransferase; AST = aspartate aminotransferase; COPD = chronic obstructive pulmonary disease; DOAC = direct oral anticoagulation; ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; LS = long-standing; LV = left ventricle; LVEDd = Left ventricular end-diastolic dimension; NT-proBNP = NYHA = New York Heart Association.

permanent AF despite all aforementioned measures; that is, the patient required a rate control strategy.

SAFETY ASSESSMENT. A standard clinical examination was done during and at the end of the hospital stay for the surgical ablation. Death, stroke, or transient ischemic attack; conversion to a sternotomy; bleeding with a need for reexploration; and all other complications significantly affecting the length of hospital stay or leading to disability were considered to be major complications. Furthermore, 3 bMRIs, as well as neuropsychological examinations, were done during the study: at baseline (ie, 1 day before surgery), postoperatively (2-4 days after surgery for the bMRI and 1 month after surgery for the neuropsychological examination), and late (6 months after the EP or 9 months after the thoracoscopic procedure).

bMRI PROTOCOL. All bMRI examinations were performed using the same diagnostic 1.5-T MRI whole-body equipment (Signa HDx 1.5-T, GE Healthcare, Milwaukee, Wisconsin) consisting of a high-definition, 8-channel, high-resolution brain array. For baseline and late follow-up MRI examinations, the following protocol was used: axial and turbo spin-echo T_2-weighted images (slice thickness: 4 mm), axial T_2 fluid-attenuated inversion recovery (FLAIR) (slice thickness: 4.5 mm), sagittal spin-echo T_1-weighted image (slice thickness: 4 mm), axial gradient recalled echo T2 (GRE T_2*) (slice thickness: 5 mm), and axial diffusion-weighted image (DWI) (b = 0; b = 1,000; apparent diffusion coefficient (ADC) map; slice thickness: 5 mm). For the early postoperative MRI, the following abbreviated MRI protocol was used: axial T_2 FLAIR (slice thickness: 4.5 mm), axial DWI (b = 0; b = 1,000; ADC map; slice thickness: 5 mm). On the initial bMRI, the following were assessed:

- the presence of acute/subacute ischemia,
- the signs of chronic territorial infarction, and
- the signs of chronic small vessel disease.

On early postoperative MRI, the presence of hyperacute/acute ischemic lesions was evaluated; moreover, acute ischemic lesions were classified according to size (<5, 5-10, 10-30, and >30 mm). On the late follow-up MRI, the following signs were evaluated:

- development of previously detected acute/hyperacute brain ischemia,
- new acute ischemic lesions, and
- progression of chronic ischemic lesions/brain affection.

Diagnostic MRI criteria for acute/subacute ischemia were as follows: a hyperintense lesion on DWI (b = 1,000) corresponding with a hypointense lesion on the ADC map with or without a hyperintense lesion on FLAIR.

NEUROPSYCHOLOGICAL EXAMINATIONS. Neuropsychological testing comprised 13 subtests of 7 tests administered by trained clinical neuropsychologists. The results are given as the number of correct answers or the time taken to complete the test. The individual subtests are described in detail in Supplemental Table 1. Absolute test scores were reversed for timed tasks; that is, decreased test scores reflected cognitive decline for all tests. In addition to the neuropsychological tests, patients were also administered the Mini-Mental State Examination to exclude pre-existing cognitive impairment at baseline. The results of the neuropsychological examinations were expressed as postoperative cognitive dysfunction (POCD). Test scores were analyzed to identify POCD using the reliable change index described by Rasmussen (6); for details, see the Supplemental Appendix **and** Supplemental Table 1, as well as the AF population already described by Medi (7). POCD was considered present as either major (severe deterioration in ≥2 subtests) or minor (less severe deterioration in ≥4 subtests) relative to baseline functioning.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD, and categorical variables are expressed as absolute and relative frequencies. Kaplan-Meier estimates were used for visualization of AF freedom (SR OFF, SR ON, and rhythm control). The use of OAC and AADs during the follow-up is shown as the proportion of patients using these drugs over time. It is based on the current disease-free survival method—in this case, using drugs corresponds to a

remission. These states are changeable as drug treatment is stopped or reinitiated. All statistical analyses were done using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, New York) and R 3.6.1 (R Core Team) with the R package currentSurvival. Logistic regression was used to assess the relation between POCD and the clinical and MRI variables.

RESULTS

PATIENT BASELINE CHARACTERISTICS. From March 2017 to June 2019, 59 patients were enrolled and underwent thoracoscopic surgery; 37 (62.7%) were men, with a mean age of 62.5 ± 10.5 years. Thirty-one (52.5%) had persistent AF (PeAF), and 28 (47.5%) had long-standing PeAF. Twenty-one (35.6%) had a history of heart failure. The baseline characteristics of all enrolled patients, including medication before enrollment, are shown in Table 1.

SURGICAL PROCEDURE. The surgical procedure was performed on 59 patients; surgical characteristics, including the major and minor complications, are shown in Table 2. The ablation, using the COBRA Fusion device, was completed in 55 (93.2%) patients. In 4 (6.8%) patients, it was not completed because of pericardial adhesions or anatomic anomalies (3 patients) or atypical bronchial anatomy that made selective pulmonary ventilation impossible (1 patient). Those 4 patients underwent CA only. Occlusion of the LAA was successfully performed, using the AtriClip PRO device, in 54 (91.5%) patients. In 5 patients, LAA occlusion was not done because of pericardial adhesions or anomalies (n = 2), inability to provide selective ventilation (n = 1), or hemodynamic instability (n = 1); in 1 patient, who was atypically young (24 years), the appendage was intentionally left unoccluded. The majority of patients (49 [83.1%]) were discharged on AADs, and AADs were kept up to the EP procedure.

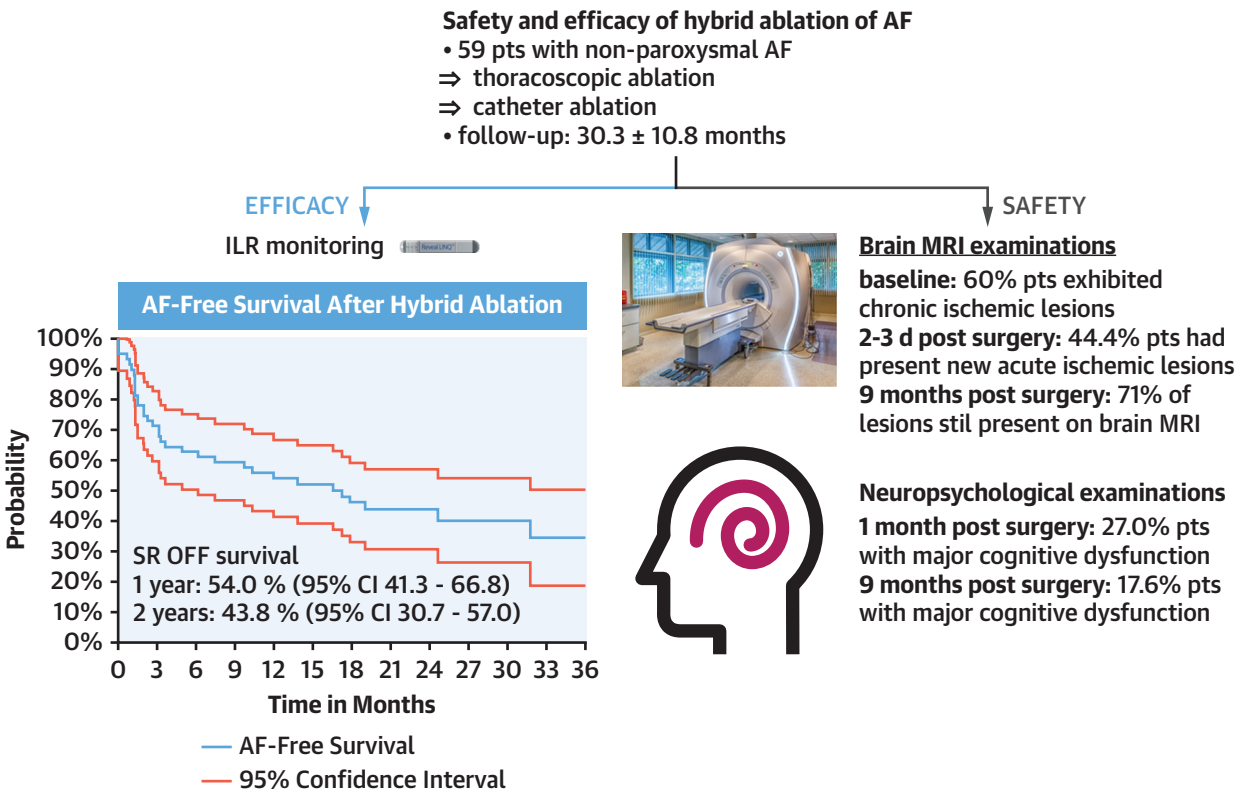
Significant complications occurred in 9 (15.3%) patients. (The list of all complications is shown in Table 2). There were no perioperative deaths and no conversions to sternotomy. One patient (1.7%) had a perioperative stroke; however, his status was almost completely resolved before discharge, and he had no residual disability or subsequent outpatient issues. Bleeding with a need for surgical revision from a small thoracotomy was required in 3 (5.1%) patients. After surgical revision, 1 patient developed pneumonia and impaired renal function that required temporary hemodialysis. Despite these complications, the patient was successfully discharged without sequelae. An atypical complication occurred in 1 patient a few days after the surgery: this patient had an acute abdominal accident requiring abdominal surgery; the cause was a bowel volvulus. In 1 patient, a pacemaker was implanted because of sick sinus syndrome after SR restoration.

TABLE 2 Surgical Procedural Characteristics

Procedural (operative) data	
Length of surgery, minutes	171 ± 35
Sinus rhythm at the beginning of surgery	9 (15.3)
Sinus rhythm at the end of surgery	44 (74.6)
Spontaneous version to SR	13 (22.0)
Electric cardioversion	34 (57.6)
If yes	
Successful	24 (70.6)
Unsuccessful	10 (29.4)
Entrance block confirmed	18 (30.5)
Exit block confirmed	22 (37.3)
Ablation of Marshall ligament	19 (32.2)
Preoperative LAA velocity, m/s	37.9 ± 14.6
Preoperative occlusion of the LAA	54 (91.5)
Postoperative data until discharge	
Length of hospital stay, days	
Mean ± SD	7.2 ± 6.3
Median (interquartile range)	6 (5-6)
Rhythm at discharge	
Sinus rhythm	26 (44.1)
Atrial fibrillation	29 (49.2)
Atrial flutter	3 (5.1)
Other	1 (1.7)
AADs at discharge	
Any	49 (83.1)
Amiodarone	44 (74.6)
Propafenone	4 (6.8)
Other	1 (1.7)
Number of patients with major complications	9 (15.3)
Major complications	
Stroke/transient ischemic attack	1 (1.7)
Conversion to sternotomy	0 (0.0)
Bleeding with a need for reexploration	3 (5.1)
Renal insufficiency with need for hemodialysis	1 (1.7)
Reintubation (respiratory failure)	1 (1.7)
Death	0 (0.0)
Pneumothorax	2 (3.4)
Pleural effusion with puncture	1 (1.7)
Pneumonia	2 (3.4)
Phrenic nerve paresis	1 (1.7)
Postpericardiotomy syndrome	1 (1.7)
Other (ileus, bowel volvulus)	1 (1.7)
Sum (events)	14
Drainage loss/24 h, mL*	606 ± 423
Drainage loss total, mL*	844 ± 660
Minor postoperative complication	
Pacemaker implantation	1 (1.7)

Values are mean ± SD or n (%) unless otherwise indicated. *Expresses the amount of drained serosanguineous fluid (not the blood loss).
AAD = antiarrhythmic drug; LAA = left atrial appendage.

CENTRAL ILLUSTRATION The Summary of the Results



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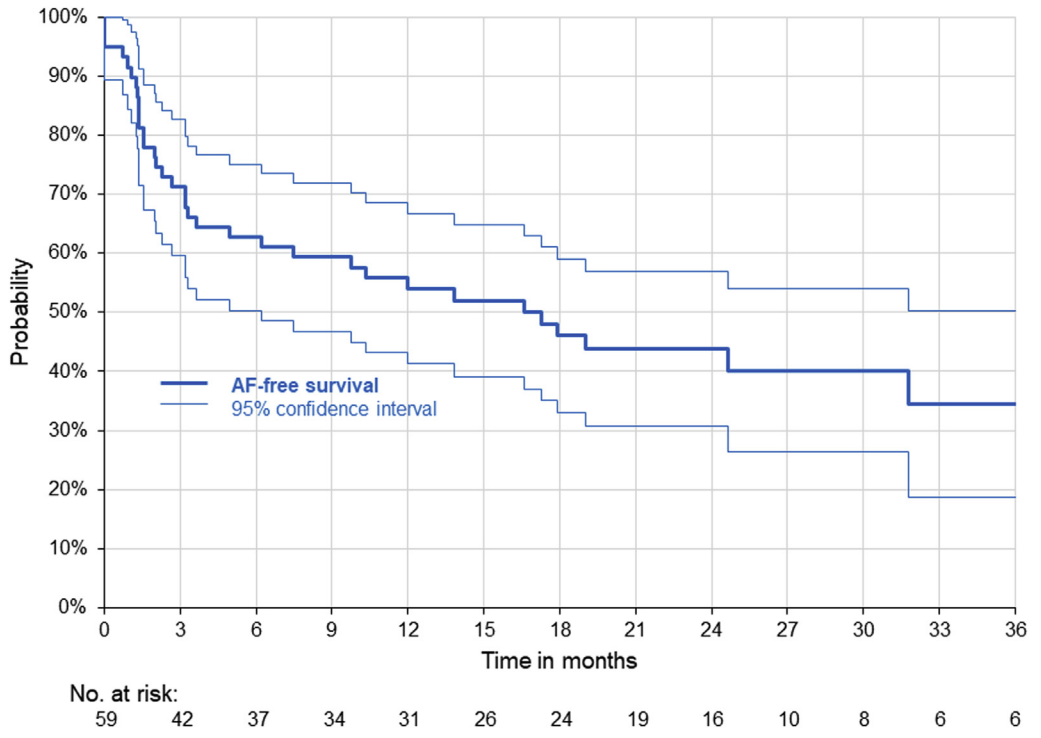
Kaplan-Meier estimates of SR OFF survival, the incidence of silent strokes, and neuropsychological dysfunction. AF = atrial fibrillation; ILR = implantable loop recorder; MRI = magnetic resonance imaging; SR = sinus rhythm.

EP PROCEDURE AND CA. The EP procedure was performed on all 59 patients. Procedural and periprocedural data from the EP procedure and ablations are shown in Supplemental Table 2. A transesophageal echocardiography was done before the CA to exclude the thrombus in the stump of the LAA and again after the occlusion and to evaluate the success of the occlusion. No thrombi were present in the stump of the LAA or in the LAA, and the LAA occlusions were considered satisfactory in all patients in whom the LAA was occluded. The box lesion (ie, all PVs and posterior wall isolation) was found to be complete in 12 (20.3%) patients. The mean number of gaps was 2.4 ± 0.9 in the remaining 47 patients. The box lesion was completed using CA in 50 (84.7%) patients. The mitral isthmus line was ablated in 53 (89.8%) and the CTI line in 51 (86.4%) patients. SR was present at discharge in 56 (94.9%) patients. No periprocedural complications occurred during the EP procedure.

RHYTHM OUTCOME. The first 3 months after the EP procedure were considered to be a blanking period, and the rhythm follow-ups were started after that. The mean follow-up was 30.3 ± 10.8 months—in aggregate, 149 patient-years. The probability of SR OFF (arrhythmia-free) survival was 54.0% (95% CI: 41.3%-66.8%) at 1 year and 43.8% (95% CI: 30.7%-57.0%) at 2 years. Kaplan-Meier estimates of AF freedom are shown in the **Central Illustration, Figure 1 and Table 3**. Patients with a recurrence of arrhythmia but with SR maintenance due to a repeat procedure or pharmacotherapy were reported as the SR ON group and are shown in **Figure 2 and Table 3**. The probability of SR ON survival was 84.6% (95% CI: 75.4%-93.9%) at 1 year and 72.3% (95% CI: 60.3%-84.4%) at 2 years. Redo ablations were done in 8 (13.6%) patients during the follow-up; all reablations were indicated because of the presence of regular AT (perimitral, CTI flutter, or focal AT). The

FIGURE 1 Kaplan-Meier Estimates of AF-Free Survival as Assessed Using Implantable Loop Recorder Analyses



AF = atrial fibrillation.

ATs typically occurred later during the follow-up (6-18 months). Cardioversions were done in 12 (20.3%) patients during the follow-up. The indication was regular AT in 3 patients (with an ablation performed later) and AF in 9 patients. The distribution of cardioversion was relatively consistent during the follow-up. The use of AADs during the follow-up is shown in Supplemental Figure 2. The majority of patients were discharged on AADs (46 [78%]) after the EP procedure, and AADs were stopped in all patients within 3 to 6 months after CA. AADs were reinitiated in 16 (27.1%) patients during the follow-up, and at the last available control, 15 (25.4%) patients were on antiarrhythmic medication. The probability of rhythm control survival was 91.5% (95% CI: 84.4%-98.6%) at 1 year and 87.8% (95% CI: 79.2%-96.3%) at 2 years (**Figure 3, Table 3**). AF/AT burden during each of the follow-up visits of these patients is shown in Supplemental Table 3. The use of OAC is shown in Supplemental Figure 3. All patients were discharged on OAC after the ablation procedure. In patients with lower CHA_2DS_2VASc scores but without an AF/AT reoccurrence, OAC was stopped after 6 months of follow-up. Similarly, as with AADs, OAC could be reinitiated later during follow-up in patients with an AF/AT reoccurrence.

RESULTS OF bMRI EXAMINATIONS. The baseline MRI examination was done in 55 patients (3 reported claustrophobia, and 1 refused even the initial MRI); an additional 10 patients refused the early postoperative MRI examination. Thus, 45 patients (26 men, aged 64.3 ± 8.5 years) were eventually included in the MRI evaluations. All of them underwent a baseline and a postoperative MRI, and 39 of them also underwent an MRI later in the follow-up. On the baseline MRI examination, chronic ischemic lesions were found in 60.0% of patients. Moreover, in 3 patients, a small acute solitary ischemic lesion, sized <10 mm, was found.

On the early postoperative MRI, new acute ischemic lesions were detected in 20 (44.4%) patients. Ischemic lesions were mostly multiple; the mean number was 10 ± 11 lesions/patient (median: 6 lesions). Seventy-nine percent of all lesions were small (<5 mm), 13% of lesions were between 5 and 10 mm, and 6% were 10 to 30 mm. Territorial ischemia of >30 mm was found in only 2 patients. One patient with acute ischemic lesions had a

TABLE 3 Probability of SR OFF, SR ON, Rhythm Control Survival, the Use of AADs and OAC During Follow-Up

Rhythm Outcome	SR OFF Survival, % (95% CI)	SR ON Survival, % (95% CI)	Rhythm Control Survival, % (95% CI)	AAD Use, % (95% CI)	OAC Use, % (95% CI)
6 months (37-57-57)*	62.7 (50.4-75.1)	96.6 (92.0-100.0)	96.6 (92.0-100.0)	30.5 (18.6-42.4)	86.4 (76.3-94.9)
1 y (31-48-52)*	54.0 (41.3-66.8)	84.6 (75.4- 93.9)	91.5 (84.4-98.6)	23.6 (13.6-35.4)	49.1 (35.6-62.7)
2 y (16-30-37)*	43.8 (30.7-57.0)	72.3 (60.3-84.4)	87.8 (79.-96.3)	27.4 (14.1-41.4)	41.8 (29.4-55.0)
3 y (6-14-20)*	34.4 (18.6-50.2)	59.2 (43.9-74.6)	87.8 (79.-96.3)	29.0 (12.5-45.5)	46.7 (29.6-65.5)

*The number of patients at risk is shown in parentheses: the first number is the number at risk for SR OFF survival, the second number is the number at risk for the SR ON survival, and the third number is the number at risk for rhythm control survival).

AAD = antiarrhythmic drug; OAC = oral anticoagulation; SR = sinus rhythm.

stroke; the remaining 19 patients were asymptomatic. Acute ischemic lesions were mostly situated in the cerebral hemispheres. No association was found among the number of new lesions with electrical cardioversion, length of surgery, or number of ablations.

Regarding the late follow-up MRI, the acute ischemic lesions had disappeared entirely in 29% of patients. (No residual gliosis or cavitation was detected.) In 53% of patients, some lesions had disappeared, while some were still present as residual spots of gliosis or small cavitations. A typical example of an MRI finding is shown in Supplemental Figure 4.

NEUROPSYCHOLOGICAL EXAMINATION. Both baseline and early postoperative neuropsychological examination was conducted on 37 patients (age: 62.4 ± 10.9 years; years of education: 13.6 ± 2.6) with normal cognitive status based on the Mini-Mental State Examination (mean score: 27.9 ± 2.3). The initial preoperative neuropsychological examination was done in 55 patients; however, 18 patients refused the early postoperative examination. Thirty-four patients also underwent a 6-month follow-up examination. Major POCD was seen in 10 of 37 patients (27.0%), and minor POCD was seen in 11 of 37 patients (29.7%) 1 month after surgery. Major POCD was present in 6 of 34 patients (17.6%), and minor POCD was seen in 12 of 34 (35.3%) patients at the follow-up examination 6 months after EP (Supplemental Table 4). Impairment was detected across the entire range of tests in patients, reflecting a generalized deficit on multiple tests in most patients; however, in some patients, an improvement was also noted. In a logistic regression, no association was found between the development of POCD and important clinical variables or MRI findings.

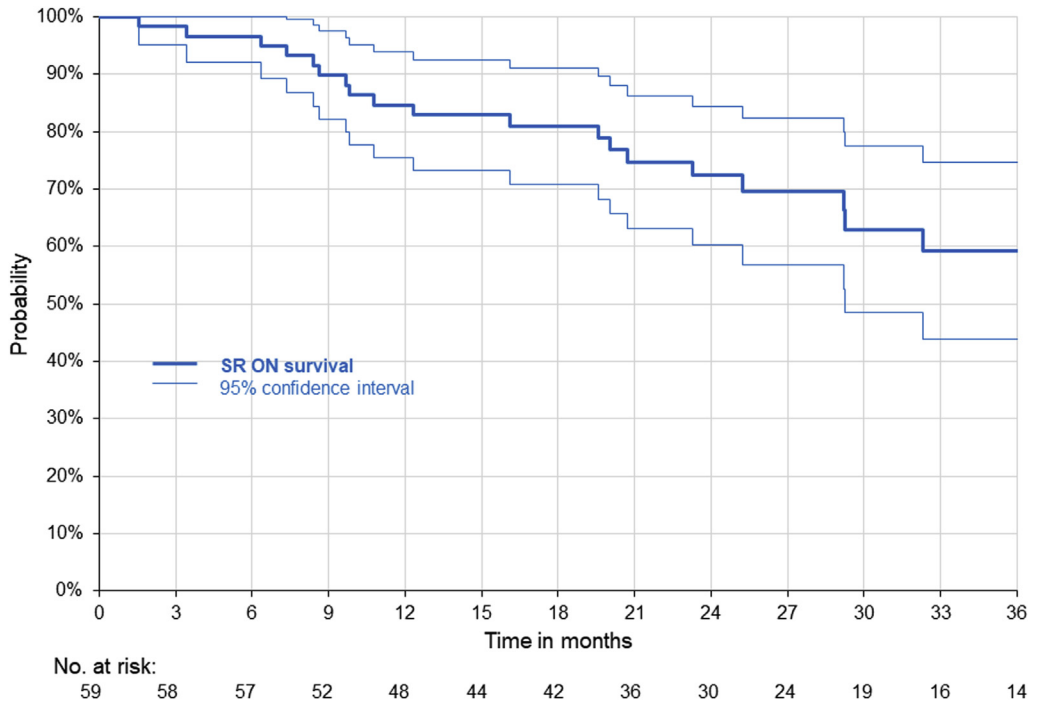
DISCUSSION

SAFETY: THE INCIDENCE OF SILENT BRAIN EMBOLIC LESIONS. Various invasive cardiac procedures can lead to silent microembolisms, called silent strokes. Performing a CA without discontinuing warfarin (or a direct OAC) reduces periprocedural stroke/transient ischemic attack occurrence compared to bridging with LWMH (8). In a recent large study on CA, silent strokes were reported in 13.8% of patients on direct OAC and 9.6% on warfarin (9). Importantly, only a temporary decrease in anticoagulation levels was associated with a higher risk of silent strokes (10).

So far, to our knowledge, no single study has assessed silent stroke rates during thoracoscopic ablations. Other cardiac surgery procedures are associated with a high risk of silent stroke: new brain ischemic lesions were detected in 45% of patients after surgical aortic valve replacement (11). However, aortic cardiac surgery is quite different in nature compared to thoracoscopic ablations, and a comparison of these data is difficult. Despite the absence of direct comparisons, thoracoscopic ablation using the COBRA catheter seems to be associated with a higher number of silent strokes than CA. Although thoracoscopic ablation is done epicardially, the ablated lesions are transmural for the vast majority of the ablated circumference. Bridging to LWMH before surgery, reduced anticoagulation before and immediately after surgery, atrial stunning after cardioversion, and general anesthesia could all increase the prothrombotic milieu.

Spontaneous silent strokes are often seen in patients with AF, even without CA, and seem to be related to cognitive decline (12). Verma et al (13) reported new silent brain lesions in only 1.7% of patients after CA; however, preexisting cerebral lesions (seen on MRIs before CA) were present in 60% of AF patients (all on OAC). This finding is very similar to that seen in our cohort. Therefore, it is difficult to conclude whether the possible adverse effect of thoracoscopic ablation could be outweighed by the positive effect of SR maintenance. However, the high number of silent brain lesions definitively presents a caveat.

FIGURE 2 **Probability of SR ON Survival**



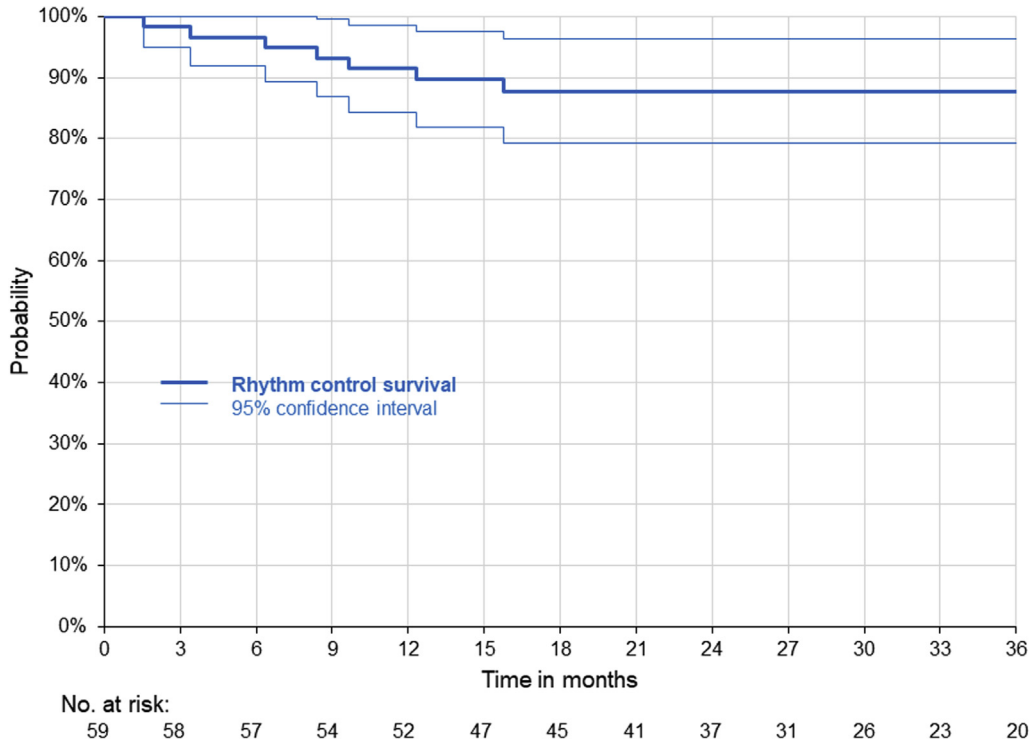
Data are shown as Kaplan-Meier estimates. SR = sinus rhythm.

In our cohort, major POCD was present in 27.0% and 17.6% at 1 and 9 months after the thoracoscopic procedure, respectively. Studies using cognitive function examinations after CA have shown mixed results. Medi et al (7) studied the prevalence of POCD using the same neuropsychological examinations after CA performed under general anesthesia and anticoagulation bridging. In a population with PeAF, POCD was present in 27% 2 days after and 20% 90 days after CA. On the other hand, Jin et al (14) described an improvement in cognitive function o1ne year after CA for AF performed under mild sedation without OAC interruption, which was especially evident in patients with impaired cognitive function before the ablation (14). The etiology of POCD is clearly multifactorial. Surgical procedures leading to brain emboli, general anesthesia, and patient susceptibility are all likely to increase the vulnerability to POCD. The higher early prevalence of POCD may reflect the reversible effects of anesthesia, while late cognitive impairment might reflect a direct intraprocedural cerebral insult.

EFFICACY OF HYBRID ABLATION PROCEDURES: SINUS RHYTHM MAINTENANCE. In our cohort, the probability of complete AF-free survival was 54.0% at 1 year; with the help of an additional procedure or AADs, the probability of SR maintenance was 84.6% at 1 year.

According to a metaanalysis of observational trials assessing the midterm efficacy of hybrid ablations in patients with nonparoxysmal AF, SR maintenance was present in 70.7% of patients at 1 year (15). Importantly, 1-day or 7-day Holter ECG monitoring was used in almost all hybrid ablation studies. In the recently published CONVERGE trial, the 1-year AF-free survival was achieved in 67.7% of AF patients after hybrid ablation (16). However, arrhythmia freedom was defined as freedom from AF or AT absent class I/III AADs, except for AADs that had previously failed, and ECG monitoring was done using 2 24-hour Holter recordings at 6 and 12 months. This endpoint definition is more comparable to the SR ON definition used in our study. Furthermore, the AF/AT freedom absent all class I/III AADs in the CONVERGE trial was 53.5%, which was similar to the SR OFF survival in our study. Bisleri et al (2) studied 45 patients with longstanding PeAF after hybrid ablations performed using methods similar to ours (ie, COBRA ablation catheter and rhythm monitoring using ILR) (2). At the mean follow-up of 28.4 months, 88.9% of

FIGURE 3 **Probability of Rhythm Control Survival**



Data are shown as Kaplan-Meier estimates.

patients were AF free. However, AF-free survival was the absence of AF-episodes lasting >5 minutes and an overall AF burden of <0.5%. The definition used in our study was much stricter, which can, in part, explain the better results described by Bisleri et al. Gersak et al (3) studied 43 patients with nonparoxysmal AF after hybrid ablation with ILR monitoring with an efficacy of 88% at 1 year. However, in that study, the endpoint definition was closer to our SR ON definition, which makes the results similar to ours.

In our previous study of 75 patients with nonparoxysmal AF, the quality of life increased significantly in patients with complete AF freedom and patients with only AF paroxysms after ablation, but it remained unchanged in patients with continuous AF after ablation (17). This indicates that bridging continuous AF to paroxysmal AF can represent a significant improvement. Although rhythm monitoring by ILR is very sensitive, reasonable rhythm control (defined as SR ON), which was present in the vast majority of our patients, might better reflect the clinical significance of the procedure.

STUDY LIMITATIONS. The present study was completed without a control group. It is known that nonparoxysmal AF is rarely a self-limiting disease that will undergo spontaneous conversion to SR. Although the absence of a control group was a limitation, the high rate of rhythm control could not have been achieved without the ablation treatment. However, only the presence of a CA control group could directly compare the risk of silent brain ischemia during the ablation procedures.

CONCLUSIONS

In nonparoxysmal AF patients, the probability of complete AF-free survival after a hybrid ablation was 54.0% and 43.8% at 1 and 2 years, respectively. With the help of an additional procedure or AADs, the SR maintenance probability was 84.6% and 72.3% at 1 and 2 years, respectively. Immediately after thoracoscopic ablation, 44.4% of patients had new ischemic brain lesions (seen on MRI), and 17.6% of patients had measurable POCD 9 months after the procedure.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: For patients with nonparoxysmal AF, the probability of SR maintenance after hybrid ablation with additional procedures or antiarrhythmic agents was 84.6% and 72.3% at 1 and 2 years, respectively. However, 44.4% of patients had acute ischemic lesions during the early postoperative period, and 17.6% of patients showed POCD late into the follow-up.

TRANSLATIONAL OUTLOOK: Despite its efficacy, this risk should be considered when deciding which patients are best suited for hybrid ablations.

REFERENCES

1. Je HG, Shuman DJ, Ad N. A systematic review of minimally invasive surgical treatment for atrial fibrillation: a comparison of the Cox-Maze procedure, beating-heart epicardial ablation, and the hybrid procedure on safety and efficacy. Eur J Cardiothorac Surg 2015;48(4):531–40.

2. Bisleri G, Rosati F, Bontempi L, et al. Hybrid approach for the treatment of long-standing persistent atrial fibrillation: electrophysiological findings and clinical results. Eur J Cardiothorac Surg 2013;44(5):919–23.

3. Gersak B, Pernat A, Robic B, et al. Low rate of atrial fibrillation recurrence verified by implantable loop recorder monitoring following a convergent epicardial and endocardial ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2012; 23(10):1059–66.

4. Budera P, Osmancik P, Herman D, et al. Risk of intraatrial thrombi after thoracoscopic ablation in absence of heparin and appendage closure. Ann Thorac Surg 2017;104(3):790–6.

5. Osmancik P, Budera P, Zdarska J, et al. Electrophysiological findings after surgical thoracoscopic atrial fibrillation ablation. Heart Rhythm 2016;13(6):1246–52.

6. Rasmussen LS, Larsen K, Houx P, et al. The assessment of postoperative cognitive function. Acta Anaesthesiol Scand 2001;45(3):275–89.

7. Medi C, Evered L, Silbert B, et al. Subtle postprocedural cognitive dysfunction after atrial fibrillation ablation. J Am Coll Cardiol 2013;62(6):531–9.

8. Liu XH, Gao XF, Chen CF, et al. Thromboembolism and bleeding risk in atrial fibrillation ablation with uninterrupted anticoagulation between new oral anticoagulants and vitamin K antagonists: insights from an updated meta-analysis. J Thromb Thrombolysis 2019;50(1):201–10.

9. Hohnloser SH, Camm J, Cappato R, et al. Uninterrupted edoxaban vs. vitamin K antagonists for ablation of atrial fibrillation: the ELIMINATE-AF trial. Eur Heart J 2019;40(36):3013–21.

10. Di Biase L, Gaita F, Toso E, et al. Does periprocedural anticoagulation management of atrial fibrillation affect the prevalence of silent thromboembolic lesion detected by diffusion cerebral magnetic resonance imaging in patients undergoing radiofrequency atrial fibrillation ablation with open irrigated catheters? Results from a prospective multicenter study. Heart Rhythm 2014;11(5): 791–8.

11. Abdul-Jawad Altisent O, Ferreira-Gonzalez I, Marsal JR, et al. Neurological damage after transcatheter aortic valve implantation compared with surgical aortic valve replacement in intermediate risk patients. Clin Res Cardiol 2016; 105(6):508–17.

12. Madhavan M, Graff-Radford J, Piccini JP, et al. Cognitive dysfunction in atrial fibrillation. Nat Rev Cardiol 2018;15(12):744–56.

13. Verma A, Debruyne P, Nardi S, et al. Evaluation and reduction of asymptomatic cerebral embolism in ablation of atrial fibrillation, but high prevalence of chronic silent infarction: results of the evaluation of reduction of asymptomatic cerebral embolism trial. Circ Arrhythm Electrophysiol 2013; 6(5):835–42.

14. Jin MN, Kim TH, Kang KW, et al. Atrial fibrillation catheter ablation improves 1-year follow-up cognitive function, especially in patients with impaired cognitive function. Circ Arrhythm Electrophysiol 2019;12(7):e007197.

15. van der Heijden CAJ, Vroomen M, Luermans JG, et al. Hybrid versus catheter ablation in patients with persistent and longstanding persistent atrial fibrillation: a systematic review and meta-analysis. Eur J Cardiothorac Surg 2019; 56(3):433–43.

16. DeLurgio DB, Crossen KJ, Gill J, et al. Hybrid convergent procedure for the treatment of persistent and long-standing persistent atrial fibrillation: results of CONVERGE clinical trial. Circ Arrhythm Electrophysiol 2020;13(12): e009288.

17. Osmancik P, Budera P, Talavera D, et al. Improvement in the quality of life of patients with persistent or long-standing persistent atrial fibrillation after hybrid ablation. J Interv Card Electrophysiol 2020;57(3):435–42.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.