Pulmonary Vein Antrum Isolation in Patients With Paroxysmal Atrial Fibrillation
More Than a Decade of Follow-Up

Yalçın Gökoğlan, MD; Sanghamitra Mohanty, MD, MS, FHR; Mahmut F. Güneş, MD; Chintan Trivedi, MD, MPH; Pasquale Santangeli, MD; Carola Gianni, MD; Issa K. Asfour, BS; Rong Bai, MD, FHR; J. David Burkhardt, MD, FHR; Rodney Horton, MD, FHR; Javier Sanchez, MD; Steven Hao, MD; Richard Hongo, MD; Salwa Beheiry, RN; Luigi Di Biase, MD, PhD, FHR; Andrea Natale, MD, FHR, FESC

Background—We report the outcome of pulmonary vein (PV) antrum isolation in paroxysmal atrial fibrillation (AF) patients over more than a decade of follow-up.

Methods and Results—A total of 513 paroxysmal AF patients (age 54±11 years, 73% males) undergoing catheter ablation at our institutions were included in this analysis. PV antrum isolation extended to the posterior wall between PVs plus empirical isolation of the superior vena cava was performed in all. Non-PV triggers were targeted during repeat procedure(s). Follow-up was performed quarterly for the first year and every 6 to 9 months thereafter. The outcome of this study was freedom from recurrent AF/atrial tachycardia. At 12 years, single-procedure arrhythmia-free survival was achieved in 58.7% of patients. Overall, the rate of recurrent arrhythmia (AF/atrial tachycardia) was 21% at 1 year, 11% between 1 and 3 years, 4% between 3 and 6 years, and 5.3% between 6 and 12 years. Repeat procedure was performed in 74% of patients. Reconnection in the PV antrum was found in 31% of patients after a single procedure and in no patients after 2 procedures. Non-PV triggers were found and targeted in all patients presenting with recurrent arrhythmia after ≥2 procedures. At 12 years, after multiple procedures, freedom from recurrent AF/atrial tachycardia was achieved in 87%.

Conclusions—In patients with paroxysmal AF undergoing extended PV antrum isolation, the rate of late recurrence is lower than what previously reported with segmental or less extensive antral isolation. However, over more than a decade of follow-up, nearly 14% of patients developed recurrence because of new non-PV triggers. (Circ Arrhythm Electrophysiol. 2016;9:e003660. DOI: 10.1161/CIRCEP.115.003660.)

Key Words: atrial fibrillation ▼ non-PV triggers ▼ paroxysmal AF ▼ pulmonary vein isolation ▼ recurrence

Atrial fibrillation (AF) is the most common sustained arrhythmia associated with a variety of adverse outcomes, including death, stroke, heart failure, reduced quality of life, and increased rate of hospitalizations.1 Because the initial observation of pulmonary veins (PV) triggering AF was described by Haissaguerre et al2 in 1998, significant advances have been made in the catheter-based treatment of AF. Today, pulmonary vein antrum isolation (PVAI) is the cornerstone of catheter-based therapies in symptomatic, drug-resistant paroxysmal AF (PAF) patients.

See Editorial by Kumar and Michaud

Long-term arrhythmia-free survival after AF ablation is important and highly desirable because this would have beneficial effects on patient prognosis, clinical decision-making process, and economic policies. Long-term success is defined as freedom from AF/atrial flutter (AFL)/atrial tachycardia (AT) recurrences after the 3-month blanking period through a minimum of 36-month follow-up from the date of the ablation procedure in the absence of Class I and III antiarrhythmic drug (AAD) therapy according to the latest guidelines.3 Several published reports have provided information on the outcomes of AF ablation.4-20 A meta-analysis evaluating studies reporting >3 years of outcome after catheter ablation (CA) found that nearly 80% multiprocedure success rates can be achieved in patients with PAF.21 Few series have reported long-term outcomes of AF ablation over 5 years.4-6,10-12,16 However, data on long-term follow-up of PVAI are limited, which would provide valuable information regarding the efficacy and safety of CA and necessity of repeat procedures. Therefore, we sought to assess the outcome of PVAI in patients with PAF over a follow-up period of more than a decade.

Received October 8, 2015; accepted March 1, 2016.

For the author affiliations, please see the Appendix section.

Correspondence to Andrea Natale, MD, Texas Cardiac Arrhythmia Institute, St David’s Medical Center, 3000 N IH-35, Suite 720, Austin, TX 78705.

E-mail dr.natale@gmail.com

© 2016 American Heart Association, Inc.

Circ Arrhythm Electrophysiol is available at http://circep.ahajournals.org

DOI: 10.1161/CIRCEP.115.003660
WHAT IS KNOWN

- Pulmonary vein antrum isolation (PVAI) for paroxysmal atrial fibrillation (PAF) at \( \geq 3 \) years of follow-up has the reported success rate of up to 80% off antiarrhythmic drugs after multiple procedures.
- Relapse of AF in the presence of permanent PV isolation reflects dynamic alterations in the underlying substrates.
- Non-PV triggers initiating AF can be identified in up to one third of unselected patients referred for catheter ablation for paroxysmal AF and elimination of those increases the success rate of AF ablation.

WHAT THE STUDY ADDS

- In the absence of PV reconnection, very late recurrences were exclusively attributable to new non-PV triggers and ablation of those sites during repeat procedures yielded substantially higher cumulative long-term success.
- Occurrence of recurrent AF after being arrhythmia-free for several years suggested that the evolution of the cardiac substrate facilitating origin of the non-PV triggers can happen even after establishment of sinus rhythm by earlier procedures, especially in elderly patients, females and subjects with genetic predisposition.
- Thus, patients should be educated about the need for long-term close rhythm surveillance because of the possibility of AF recurrence consequent upon cardiac substrate changes as they age.

Methods

Study Population

Five hundred and thirteen (513) consecutive patients who underwent their primary ablation for PAF between 2000 and 2002 were included in this study and prospectively followed up for 12 years. Each patient who underwent radiofrequency (RF) CA provided written informed consent before the procedure. The outcome data were extracted from an Institutional Review Board–approved prospective registry. All patients were symptomatic and drug resistant. AF was classified as paroxysmal if episodes terminated spontaneously in \(< 7 \) days.

Until 2005, transesophageal echocardiogram was done immediately after the ablation to exclude the presence of thrombus in the left atrium for patients who presented in AF on the day of the study. After 2005, as uninterrupted warfarin approach was routinely used in our practice, transesophageal echocardiogram was performed in patients presenting with AF if they had subtherapeutic international normalized ratio within 3 weeks.

Ablation Procedure

Institutional protocol for standard mapping and ablation procedure was followed by all physicians as described in earlier publications from our group.22 Briefly, all AADs were discontinued 4 to 5 half-lives before ablation, whereas amidarone was stopped at least 4 months before the procedure. Early in the practice, warfarin was discontinued before the procedure, and patients were bridged with low molecular weight heparin. This anticoagulation strategy continued until 2005 when uninterrupted warfarin approach was adapted. PVAI was performed guided by circular mapping catheter and intracardiac echocardiography (ICE) using 8-mm nonirrigated or 4-mm cooled-tip catheter, and open irrigation was used for procedures after 2006. The electric isolation of PV was extended to the posterior wall contained between the pulmonary veins. Complete ablation of all PV potentials rather than decrease in the amplitudes was the end point and confirmed by entrance or exit block. With the 8-mm-tip catheter, RF energy was set at 30 W and 55°C, and power was titrated upward every 5 s from 30 to 70 W while monitoring for microbubble formation. Each lesion typically lasted 30 to 50 seconds. A temperature probe was routinely placed in the esophagus. RF applications were limited to 20 seconds at a single location over esophagus and immediately halted if the temperature reached 39°C or rapidly rose. The protocol with the 4-mm cooled-tip catheter has been described in an earlier publication from our group.23 Briefly, RF energy was delivered using an average power of 35±7 W to maintain a target temperature of 35–40°C; power was titrated down whenever microbubbles formed. Energy was delivered for 40 to 60 s at each site and no >20 s at left atrial (LA) sites close to the esophagus and was terminated automatically if there was a rise in impedance.23 With the open-irrigation catheter, initially a temperature of 45°C and maximum power of 50 W was used.24 However, after observation of high incidence of steam pops and pericardial effusion at higher power in a randomized trial, the maximum temperature and power were changed to 42°C and 45 W, respectively.25,26

The superior vena cava (SVC) was also mapped and isolated circumferentially in all patients. Briefly, the circular mapping catheter, guided by ICE, was positioned at the SVC–right atrial junction, which is marked by the lower border of the pulmonary artery. Isolation of the SVC was then performed at that level.27

During repeat procedures, in addition to ablation of sites showing recovery of conduction, high-dose isoproterenol challenge (≤30 μg/min) was used to disclose non-PV triggers which were targeted using additional RF energy. Initially, non-PV triggers were defined as firings from the posterior wall of left atrium, crista terminalis, coronary sinus (CS), ligament of Marshall, and interatrial septum. From 2007 onwards, left atrial appendage (LAA) was recognized as an additional site of initiation of AF. Furthermore, early in the practice, only sustained non-PV triggers (>30 s) were targeted for ablation, but starting from 2008, nonsustained drivers, including premature atrial contractions from ectopic sites, were ablated as non-PV triggers.

Follow-Up

All patients were hospitalized overnight with continuous rhythm monitoring and usually discharged the day after the procedure. They were discharged on their previously ineffective AADs, which were continued during the blanking period (12 weeks); amiodarone was never used. AADs were discontinued after the blanking period in all patients if they were in sinus rhythm. Recurrence was defined as episodes of AF/AFL/AT lasting >30 s off AADs.

Follow-up visits were performed in the outpatient clinic at 3, 6, 9, and 12 months after ablation and every 6 months thereafter. An ECG and Holter recording (48-hour Holter until 2006 and 7-days Holter from 2007 onwards) were obtained routinely at each follow-up visit in the first year. In addition, patients were given an event recorder for the first 5 months and asked to record when they experienced symptoms as well as 3 times per week even if they were asymptomatic. After the first year, arrhythmia monitoring was performed during each office visit (at least annually). In addition to routine clinical assessment, all patients were asked to perform pulse checks twice daily and report any pulse irregularity or increase in heart rate at rest. Referring care providers were also contacted on a regular basis (every 6–9 months) to document recurrences. Repeat ablation procedure was offered to all patients with recurrent arrhythmia. Recurrence of any atrial tachyarrhythmia (AF/AFL/AT) after 3 months of blanking period was the study end point. The study design is presented in Figure 1.

Statistical Analysis

Continuous data are reported as mean±standard deviation (or median and interquartile range for skewed distributions) and as
absolute frequencies and percentages if categorical. Long-term arrhythmia-free survival over time was assessed by the Kaplan–Meier method. Patients who remained event-free at the end of the study period of the first procedure were censored for single procedure outcome. Patients remaining arrhythmia-free at the end of 12-year follow-up after repeat ablations were censored for Kaplan–Meier analysis of multiple procedure outcomes. To identify the predictors of recurrence, multivariate Cox regression analysis was used, and all the variables were entered into the model if significant association was observed in the univariate analysis or if there was some clinical relevance of the variable with the recurrence. All tests were 2-sided, and a P value <0.05 was considered statistically significant. Statistical analyses were performed using SAS 9.2 (SAS Institute Inc, Cary, NC) and IBM SPSS Statistics 22.0 (IBM SPSS Inc, Chicago, IL).

Results

Patient Characteristics
Baseline characteristics of the patients are shown in Table 1. The average age of the study population was 54.4±10.6 years with 374 (73%) male patients. Overall, 180 (35%) patients had hypertension and 41 (8%) had type II diabetes mellitus. The average body mass index was 28.0±5.2, and average left atrial diameter was 4.3±0.6 cm (Table 1). Additionally, comparison of baseline clinical characteristics by recurrence status has been provided in Table 2.

Index Procedure and Follow-Up
PVAI and isolation of the posterior wall between the PVs and of the SVC was achieved in all patients. The average RF time was 57.1±24.3 minutes, whereas the mean procedure time was 137.3±55.5 minutes. No major procedural complications occurred. There were 3 (0.6%) groin hematoma and 2 (0.4%) minor pericardial effusions.

After index procedure, recurrent arrhythmia (AF/AT) was observed in 108 (21%) patients at 1 year, 56 (11%) patients between 1 and 3 years, 21 (4%) patients between 3 and 6 years, and 27 (5.3%) patients between 6 and 12 years. Out of 212 patients with recurrence, 86 (40.8%) patients had recurrence of AF, 116 (55%) patients had recurrence of AFL, 4 (1.9%) patients had recurrence of both AF and AFL, and 6 (2.8%) patients had recurrence of AT. Overall, recurrence-free survival was achieved in 301 (58.7%) patients after the single procedure (Figure 2).

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Patients (N=513)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>374 (73%)</td>
</tr>
<tr>
<td>Age</td>
<td>54.4±10.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.0±5.2</td>
</tr>
<tr>
<td>BMI ≥30 kg/m²</td>
<td>176 (34.3)</td>
</tr>
<tr>
<td>Duration of AF</td>
<td>48 (24, 80.5)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>180 (35.1)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>41 (8.0)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>228 (44.4)</td>
</tr>
<tr>
<td>CAD</td>
<td>85 (16.6)</td>
</tr>
<tr>
<td>History of Stroke/TIA</td>
<td>13 (2.5)</td>
</tr>
<tr>
<td>COPD</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>37 (7.2)</td>
</tr>
<tr>
<td><strong>Preprocedure echo parameters</strong></td>
<td></td>
</tr>
<tr>
<td>LAD, cm</td>
<td>4.3±0.6</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>54.4±7.6</td>
</tr>
<tr>
<td><strong>Procedural parameters</strong></td>
<td></td>
</tr>
<tr>
<td>Procedure time, min</td>
<td>137.3±55.5</td>
</tr>
<tr>
<td>Fluoroscopic time, min</td>
<td>43.7±21.5</td>
</tr>
<tr>
<td>Radiofrequency time, min</td>
<td>57.1±24.3</td>
</tr>
<tr>
<td>Presence of scar</td>
<td>125 (24.4%)</td>
</tr>
<tr>
<td>Cardioversion during the procedure</td>
<td>64 (12.5%)</td>
</tr>
<tr>
<td>Baseline INR</td>
<td>1.9±0.5</td>
</tr>
</tbody>
</table>

Values are reported as mean±SD or n (%). AF indicates atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; INR, international normalized ratio; and TIA, transient ischemic attack.
Overall, after multiple procedures and 12 years of follow-up, freedom from AF/AT was achieved in 446 (86.9%) patients.

A further analysis was performed to examine the distribution of failure time for patients who were arrhythmia-free at 2 years. A total of 419 patients were in sinus rhythm for 2 years after ≥1 procedures. Of the 419 patients, 361 (86%) remained arrhythmia-free at the end of 12-year follow-up and 58 patients experienced recurrence; 6 (10%) failed between 4 and 5 years, 20 (34%) between 6 and 8 years, and 32 (55%) had recurrence between 9 and 12 years (Figure 3). In these 58 patients, new sites for non-PV triggers were identified from LAA (73%), CS (58%), and interatrial septum (13%) with no PV and posterior wall reconnection and were targeted for ablation (Figures 4 and 5).

Predictors of Recurrence
Multivariable analysis of recurrence-free survival was performed with the Cox proportional hazard model for the variables which had statistically significant association in the univariate analysis (Table 3). In the multivariable analysis, the only predictors of recurrence were LA diameter (hazard ratio [HR] =1.32; 95% confidence interval [CI] 1.06–1.66; P=0.014), female sex (HR =1.72; 95% CI 1.30–2.28; P<0.001), age ≥65 years (HR =2.25; 95% CI 1.63–3.10; P<0.001), and obesity (body mass index ≥30; HR =1.34; 95% CI 1.02–1.77; P=0.037). A subanalysis exploring relation of obesity (body mass index ≥30) showed significant predictive association with outcome at 2 years (HR =1.39; 95% CI 1.01–1.93; P=0.04), whereas it did not show significance at long-term outcome (HR =1.27; 95% CI 0.75–2.13; P=0.38).

Discussion
This prospective study was designed to evaluate the effectiveness of PVAI plus isolation of SVC guided by ICE and circular mapping catheter in terms of arrhythmia-free survival at more than a decade of follow-up. To the best of our knowledge, this study has the longest follow-up duration for patients who underwent CA of PAF.

Our major findings are as follows: (1) single procedure success rate was 59% off AADs at the end of the follow-up period, which improved to 87% after repeat ablation(s); (2) PVAI plus isolation of SVC guided by ICE and circular mapping catheter was a safe and effective approach to achieve long-term arrhythmia-free survival; (3) after 1 or 2 procedures, majority of patients remained arrhythmia-free for 2 years, and recurrences were mostly observed 5 to 10 years thereafter. Moreover, PV reconnection was not detected in any of the recurrent cases after 2 procedures, whereas non-PV triggers were found in all; (4) predictors of recurrence were age, left atrial size, female sex, and obesity; (5) late recurrences were always because of triggers identified at new non-PV sites.

Among study results addressing the long-term outcomes of ablation efficacy in PAF patients, there is a wide disparity because of differences in patient characteristics, ablation techniques, success definitions, monitoring approaches, and follow-up frequencies.

### Table 2. Comparison of Baseline Clinical Characteristics Based on Recurrence Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Recurrence (N=301)</th>
<th>Recurrence (N=212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>238 (79.1)</td>
<td>136 (64.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>51.9±10.8</td>
<td>58.0±9.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.9±5.3</td>
<td>28.2±5.2</td>
<td>0.55</td>
</tr>
<tr>
<td>BMI ≥30 kg/m²</td>
<td>92 (30.6)</td>
<td>84 (39.6)</td>
<td>0.036</td>
</tr>
<tr>
<td>Duration of AF</td>
<td>40.5 (24.7)</td>
<td>48 (21.0, 83.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>105 (34.9)</td>
<td>75 (35.4)</td>
<td>0.91</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22 (7.3)</td>
<td>19 (9.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>127 (42.2)</td>
<td>101 (47.6)</td>
<td>0.22</td>
</tr>
<tr>
<td>CAD</td>
<td>49 (16.3)</td>
<td>36 (17.0)</td>
<td>0.83</td>
</tr>
<tr>
<td>History of stroke/TIA</td>
<td>9 (3.0)</td>
<td>4 (1.9)</td>
<td>0.43</td>
</tr>
<tr>
<td>COPD</td>
<td>7 (2.3)</td>
<td>1 (0.5)</td>
<td>0.15</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>24 (8.0)</td>
<td>13 (6.1)</td>
<td>0.43</td>
</tr>
<tr>
<td>Preprocedure echo parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD, cm</td>
<td>4.25±0.6</td>
<td>4.38±0.6</td>
<td>0.02</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>54.2±7.4</td>
<td>54.7±7.8</td>
<td>0.49</td>
</tr>
<tr>
<td>Procedural parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure time, min</td>
<td>134.3±35.9</td>
<td>141.4±74.0</td>
<td>0.15</td>
</tr>
<tr>
<td>Fluoroscopic time, min</td>
<td>43.9±21.9</td>
<td>43.4±21.2</td>
<td>0.80</td>
</tr>
<tr>
<td>Radiofrequency time, min</td>
<td>56.1±22.1</td>
<td>58.5±27.1</td>
<td>0.27</td>
</tr>
<tr>
<td>Presence of scar</td>
<td>68 (22.6)</td>
<td>57 (26.9)</td>
<td>0.26</td>
</tr>
<tr>
<td>Cardioversion during the procedure</td>
<td>35 (11.6)</td>
<td>29 (13.7)</td>
<td>0.49</td>
</tr>
<tr>
<td>Baseline INR</td>
<td>1.9±0.6</td>
<td>1.9±0.5</td>
<td>1.00</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LAD, left atrium diameter; LVEF, left ventricular ejection fraction; INR, international normalized ratio; and TIA, transient ischemic attack.

Repeat Procedures and Follow-Up
Repeat procedure was offered to all patients (n=212) with recurrence and performed in 156 (73.6%) patients (mean 1.4±0.6 procedure/patient). During the second ablation procedure, reconnection of the pulmonary vein was detected in 48 (31%) patients, whereas non-PV triggers were detected in the remaining 108 (69%; Figure 3). The non-PV foci were mapped to LAA (10%), CS (59%), interatrial septum (17%), crista terminalis (22%), and SVC (13%). In the remaining patients, the site of origin was undetermined, and empirical lesions were deployed that included left septal line, CS ablation, mitral isthmus line, and more recently LAA isolation. Out of the 156 patients who underwent reablation, 118 patients (75.6%) required 2 ablation procedures, 32 (20.1%) patients required 3 procedures, and 6 (3.8%) patients required 4 ablation procedures. PV reconnection was not noted in any patient after the second procedure.
Ouyang et al demonstrated a 46.6% success rate off AADs with index procedure, improving to 79.5% arrhythmia-free survival rate off AADs with repeat ablation(s) in 161 patients with PAF at a median period of 4.8-year follow-up. Medi et al evaluated 100 patients and documented 82% multiprocedure success rate, including patients using AADs at a mean of 39±10 months after last RF procedure. Sawhney et al followed 71 patients over 5 years and reported overall success rate of 56% at 5 years after the index ablation, which improved to 84% with multiple procedures. The difference in the overall success rate as observed in our study is most likely because of our extensive PV AI approach compared with circumferential PV isolation performed in these trials. Previous studies have reported significantly better outcome with PV AI guided by circular mapping catheter over 3D mapping–guided circumferential PV isolation. Also, in a meta-analysis by Proietti et al, wide-antral approach encompassing the part of the posterior wall in between the PVs was observed to be more effective than ostial PV isolation in achieving freedom from arrhythmia. For Shah et al, the recurrence rate at 1, 2, 3, 4, and 5 years of follow-up were 8.7%, 5.8%, 8.8%, 13%, and 25.5%. This was a retrospective study of mixed PAF (86%) and non-PAF cohort. Although majority of patients had PAF, inclusion of non-PAF patients might have contributed to higher late recurrence. Additionally, at the second procedure, their patients received PV reisolation plus 2 linear lesions (roof and isthmus line). This ablation approach is known to be associated with suboptimal outcomes; recently published randomized trials have demonstrated no additional benefit of linear ablations in terms of arrhythmia recurrence when performed in conjunction with PV isolation.

Our ablation approach targeting non-PV triggers along with PVAI appeared to yield higher long-term success rate, which is in agreement with findings from earlier studies. Superiority of PV AI and isolation of SVC guided by ICE and circular mapping catheter over the other ablation techniques have already been demonstrated in multiple trials. Herein, we showed the durability of this approach in maintaining sinus rhythm over more than a decade of follow-up.
Time distribution of arrhythmia recurrences in the present study was an interesting and novel observation. Majority of our patients remained free of AF off AAD for at least 2 years after the initial or the second procedure, which is consistent with the findings of Tzou et al. The 419 patients who remained arrhythmia-free after 1 or 2 procedures mostly experienced arrhythmia recurrence 5 to 10 years after being in sinus rhythm for 4 years and underwent redo ablations. Of note, PV reconnection was not detected in a single patient during the third and fourth procedure, whereas new non-PV arrhythmogenic foci mostly located in the LAA and CS region were identified in all having late recurrences. Relapse of AF in the presence of permanent PV isolation reflects dynamic alterations in the underlying substrates. Our finding of recurrent events happening in the latter part of the follow-up period after being AF-free for years and the recurrences being exclusively attributable to non-PV triggers is of utmost importance because it suggests that the evolution of the cardiac substrate is possibly not affected by elimination of AF in the first place and thus contests the age-old hypothesis of AF begetting AF.

Possibly, other risk factors, such as age, sex, genetic predisposition, left atrial size, and comorbidities, such as hypertension, obesity, sleep apnea, structural heart disease, and left ventricular dysfunction, play causal role in modifying the substrate even after establishment of sinus rhythm by earlier procedures. Additionally, our past experience and findings from this study reinforce the crucial role of non-PV triggers in the maintenance of AF and strongly suggest the importance of effective ablation of these ectopic foci. In the early 2000, because of stringent definition of non-PV triggers and limited use of mapping to locate trigger points, many of those ectopic foci typically remained unidentified, especially the LAA which was not a widely recognized site of AF initiation back then. For the same reason, most of the non-PV triggers from LAA were not ascertained during the second procedure, and many of those patients were labeled as permanent failures. Years later, during repeat ablation for late arrhythmia recurrence, new LAA sites were revealed with isoproterenol challenge to be the major source of arrhythmia, and ablation of those improved the procedure outcome significantly.
We observed age and sex to be the strongest independent predictors of late recurrence in our study population. Aging process of the heart and remodeling of the atrium contribute to development of ectopic triggers at non-PV sites. Moreover, non-PV triggers are known to be highly prevalent in females, which explain higher rate of AF recurrences after PVI in women. The findings from these published trials are in accordance with the results of our study documenting the role of non-PV triggers for late recurrences. Obesity and left atrial size were also found to be independent predictors of late AF recurrence in our population as has been shown by several prior publications. In this context, it is worth mentioning that the Aggressive Risk Factor Reduction Study-Implication for AF (ARREST-AF) study has reported improved long-term success of AF ablation in a majorly PAF population from a single center after aggressive risk factor reduction and efficient weight management. However, this was not a randomized study, and more than half of the patients experiencing recurrence in our series were not obese. Additionally, our findings showed high body mass index to be an independent predictor of early recurrence only and not late recurrence. Based on our findings, high-risk patients should be educated about the possible evolution of the substrate over time and long-term close rhythm surveillance for timely determination of the need for reinitiation of anticoagulation therapy.

In contrast to previous reports, PV reconnection was not found to be the major mechanism of arrhythmia recurrence in our study. This differential observation can be attributed to the use of higher power and our standard practice of high-dose isoproterenol challenge to reveal PV reconnection at the end of the procedure, which confirms PV isolation and minimizes the likelihood of recovery of conduction in future. Of note, our main indication for repeat ablations was not AF as reported in earlier studies. AFL (54.5%) was the major cause rather than AF (40.8%) in this trial.

Our result has strong clinical relevance because the study included a relatively large number of subjects compared with other published trials and was composed of only PAF patients thus minimizing heterogeneity. Additionally, it had the longest duration of follow-up after CA of AF.

Limitations
Certain limitation in our study needs to be acknowledged. The definition of arrhythmia-free survival depended on symptom-based or intermittent rhythm monitoring data. A substantial portion of patients might have remained unrecognized because of asymptomatic episodes falling outside the monitoring periods.

Conclusions
Patients with PAF benefitted significantly from extended PVI in terms of arrhythmia-free survival off AAD at long-term follow-up. All late recurrences, in the absence of PV reconnection, were as a result of new non-PV triggers, and ablation of those sites during repeat procedures yielded substantially higher cumulative success after more than a decade.

Appendix
From the Texas Cardiac Arrhythmia Institute, St David’s Medical Center, Austin (Y.G., S.M., M.F.G., C.T., C.G., I.K.A., R.B., J.D.B., R.H., J.S., L.D.B., A.N.); Department of Cardiology, Gulhane Military Academy of Medicine, Ankara, Turkey (Y.G.); Department of Cardiology, Turgut Ozal University Faculty of Medicine, Alparslan, Turkey (M.F.G.); Electrophysiology Section, Cardiovascular Division, Hospital of the University of Pennsylvania, Philadelphia (P.S.); Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy (C.G.); Royal College of Surgeons in Ireland, Medical University of Bahrain, Bahrain (I.K.A.); Beijing Anzhen Hospital, Capital Medical University, Beijing, China (R.B.); Electrophysiology and Arrhythmia Services, California Pacific Medical Center, San Francisco (S.H., R.H., S.B., A.N.); Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY (L.D.B.); Interventional Electrophysiology, Scripps Clinic, La Jolla, CA (A.N.); Metro Health Medical Center, Case Western Reserve University School of Medicine, Cleveland, OH (A.N.); Division of Cardiology, Stanford University, Stanford, CA (A.N.); and Dell Medical School, University of Texas, Austin (A.N.).

Disclosures
Dr Di Biase is a consultant for Hansen Medical, St Jude Medical and Biosense Webster, Atricure, and EpiEP. Dr Natale received honoraria from Boston Scientific, Biosense Webster, Janssen, St Jude Medical, Biotronik, and Medtronic. The other authors report no conflicts.
Long-Term Outcome of PVAI in Paroxysmal AF Patients

References


2716. doi: 10.1161/01.CIR.0000070541.83326.15.


Corrado A, Bonso A, Madalosso M, Rossillo A, Themistoclakis S, Di Biase L, Natale A, Raviele A. Impact of systematic isolation of superior vena cava in addition to pulmonary vein antrum isolation on the outcome of paroxysmal, persistent, and permanent atrial fibrillation ablation: re-

Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation be-


Themistoclakis S, Schweikert RA, Saliba WL, Bonso A, Rosillo A, Bader G, Wazni O, Burkhardt DJ, Raviele A, Natale A. Clinical predic-


Manganello S, Ancelminio M, Amellone C, Pelissero E, Giuggia M, Trapani G, Giordano B, Senatore G, Gaia T. Symptomatic and asymp-


ijcard.2011.06.094.

Sotomi Y, Inoue K, Ino N, Kimura R, Toyoshima Y, Masuda I, Iwakura K, Fujii K. Incidence and risk factors for very late recurrence of atrial fibrilla-

Pathak RK, Middendorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, Kuhlman JM, Abhayaratna WP, Sanders P. Aggressive risk factor reduction study for atrial fibril-
Jacc.2014.09.028.


Elayi CS, Di Biase L, Bai R, Burkhardt JD, Mohanty P, Santageli P, Sanchez J, Horton R, Galllinghouse GJ, Horton, B, Beheiry S, Beheiry S, Natale A. Administration of isoproterenol and adenosine to guide sup-


Pulmonary Vein Antrum Isolation in Patients With Paroxysmal Atrial Fibrillation: More Than a Decade of Follow-Up

Yalçin Gökoglan, Sanghamitra Mohanty, Mahmut F. Günes, Chintan Trivedi, Pasquale Santangeli, Carola Gianni, Issa K. Asfour, Rong Bai, J. David Burkhardt, Rodney Horton, Javier Sanchez, Steven Hao, Richard Hongo, Salwa Beheiry, Luigi Di Biase and Andrea Natale

Circ Arrhythm Electrophysiol. 2016;9:
doi: 10.1161/CIRCEP.115.003660

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/9/5/e003660

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Arrhythmia and Electrophysiology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Arrhythmia and Electrophysiology is online at:
http://circep.ahajournals.org//subscriptions/