A Randomized Trial of Circumferential Pulmonary Vein Ablation Versus Antiarrhythmic Drug Therapy in Paroxysmal Atrial Fibrillation

The APAF Study

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OBJECTIVES

We compared ablation strategy with antiarrhythmic drug therapy (ADT) in patients with paroxysmal atrial fibrillation (PAF).

BACKGROUND

Atrial fibrillation (AF) ablation strategy is superior to ADT in patients with an initial history of PAF, but its role in patients with a long history of AF as compared with ADT remains a challenge.

METHODS

One hundred ninety-eight patients (age, 56 ± 10 years) with PAF of 6 ± 5 years’ duration (mean AF episodes 3.4/month) who had failed ADT were randomized to AF ablation by circumferential pulmonary vein ablation (CPVA) or to the maximum tolerable doses of another ADT, which included flecainide, sotalol, and amiodarone. Crossover to CPVA was allowed after 3 months of ADT.

RESULTS

By Kaplan-Meier analysis, 86% of patients in the CPVA group and 22% of those in the ADT group who did not require a second ADT were free from recurrent atrial tachyarrhythmias (AT) (p < 0.001); a repeat ablation was performed in 9% of patients in the CPVA group for recurrent AF (6%) or atrial tachycardia (3%). At 1 year, 93% and 35% of the CPVA and ADT groups, respectively, were AT-free. Ejection fraction, hypertension, and age independently predicted AF recurrences in the ADT group. Circumferential pulmonary vein ablation was associated with fewer cardiovascular hospitalizations (p < 0.01). One transient ischemic attack and 1 pericardial effusion occurred in the CPVA group; side effects of ADT were observed in 23 patients.

CONCLUSIONS

Circumferential pulmonary vein ablation is more successful than ADT for prevention of PAF with few complications. Atrial fibrillation ablation warrants consideration in selected patients in whom ADT had already failed and maintenance of sinus rhythm is desired. (A Controlled Randomized Trial of CPVA Versus Antiarrhythmic Drug Therapy in for Paroxysmal AF: APAF/01; http://clinicaltrials.gov/ct/show; NCT00340314) (J Am Coll Cardiol 2006;48: 2340–7) © 2006 by the American College of Cardiology Foundation

Currently, antiarrhythmic drug therapy (ADT) is considered as first line therapy to prevent recurrent and symptomatic atrial fibrillation (AF), but antiarrhythmic drugs (AADS) are frequently ineffective and may be associated with serious adverse effects (1–3). Atrial fibrillation ablation has been demonstrated to be effective in patients with AF and may be a realistic alternative to chronic ADT (4–10). Recently, it has been reported in 3 randomized trials the striking superiority of AF ablation strategy over ADT (11–13). The first study by Wazni et al. (11) was a pilot study that confined the analysis to untreated patients with an initial history of paroxysmal AF (PAF), who represent only a minority of the wide AF population. In another randomized study, Stabile et al. (12) reported that ablation therapy combined with ADT was superior to ADT alone in patients with paroxysmal or persistent AF. Recently, we demonstrated that circumferential pulmonary vein ablation (CPVA) is more effective than amiodarone in maintaining sinus rhythm (SR) at 1 year, even in patients with permanent AF (13). Whether CPVA alone is superior to ADT in patients with PAF is still unknown. Thus, we conducted a randomized controlled trial (the APAF [Ablation for Paroxysmal Atrial Fibrillation] trial) to determine whether CPVA was superior to ADT for maintaining SR at 1 year in patients with a long history of PAF.

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Abbreviations and Acronyms
AAD = antiarrhythmic drug
ADT = antiarrhythmic drug therapy
AF = atrial fibrillation
AT = atrial tachyarrhythmia
CPVA = circumferential pulmonary vein ablation
EF = ejection fraction
PAF = paroxysmal atrial fibrillation
SR = sinus rhythm

METHODS

Study design. This study was designed to compare the relative efficacy of CPVA and ADT in the treatment of patients with PAF who have already failed AADs. Patients were randomized to another 3 widely used AADs (amiodarone, flecainide, or sotalol, either as single drugs or in combination) at the maximum tolerable doses (Fig. 1). All consecutive patients with PAF referred to our electrophysiology lab at the San Raffaele University Hospital starting from January 2005 were screened for inclusion and exclusion criteria (Table 1). At time of enrollment, patients were randomized to 1 of 2 treatment arms: CPVA or long-term ADT (Fig. 1). The 198th patient was enrolled on May 11, 2005. All patients signed a written informed consent, which was first approved by the institutional ethics and review board committees of the San Raffaele University Hospital.

CPVA therapy. The details of the CPVA procedure have been previously described (4,5,14,15). Left atrial geometry was constructed with either CARTO (Biosense-Webster, Inc., St. Paul, Minnesota) (Fig. 2). Radiofrequency applications were done with either an 8-mm standard catheter (Navi-Star, Biosense-Webster or Livewire TC, St. Jude Medical, St. Paul, Minnesota) or an irrigated tip catheter (3.5-mm Cool-Path, St. Jude Medical or Thermo-Cool Navi-Star, Biosense-Webster); radiofrequency settings were assessed as previously described (15). Ablation at the cavotricuspid isthmus was performed in all patients. To reduce the probability of early recurrences of AF that could interfere with the reverse remodeling process, patients were treated with ADT for 6 weeks after catheter ablation; thereafter, a 12-month follow-up started (Fig. 1). If there was a recurrence of atrial tachyarrhythmias (AT) (including both AF and atrial tachycardia) beyond the first 6 weeks after the ablation, then a re-do procedure could be performed if the patient wished to proceed.

ADT. Oral flecainide was given at an initial dose of 100 mg every 12 h, oral sotalol at an initial dose of 80 mg every 8 h, and oral amiodarone at an initial loading of 600 mg/day for the first week, 400 mg/day for the next week, after which a daily maintenance dose of 200 mg a day was given. The maximum tolerable dosage (up to 300 mg/day for flecainide and 320 mg/day for sotalol) was based on the clinical response and/or the occurrence of side effects. Doses of each drug were reduced if intolerable adverse reactions occurred, and treatment was stopped if they persisted. Even with AF

Table 1. Exclusion and Inclusion Criteria

Inclusion criteria
Age >18 or <70 yrs
Creatinine concentration <1.5 mg/dl
AF history >6 months
AF burden >2 episodes/month in the last 6 months*

Exclusion criteria
AF secondary to transient or correctable abnormality
Intra-atrial thrombus, tumor precluding catheter insertion
Left ventricular ejection fraction <35%
HF symptoms > NYHA functional class II
Prior ADT therapy with amiodarone, flecainide, and sotalol
Contraindication to beta-blocking therapy
Patients with rheumatic mitral valve disease
Unstable angina or acute or prior myocardial infarction (<6 months)
Wolff-Parkinson-White syndrome
Renal or hepatic failure
Implanted device (pacemaker or cardioverter-defibrillator)
Wolff-Parkinson-White syndrome
Renal or hepatic failure
Implanted device (pacemaker or cardioverter-defibrillator)

Diamond Bar, California) or NavX (Endocardial Solutions Inc., St. Paul, Minnesota) (Fig. 2). Radiofrequency applications were done with either an 8-mm standard catheter (Navi-Star, Biosense-Webster or Livewire TC, St. Jude Medical, St. Paul, Minnesota) or an irrigated tip catheter (3.5-mm Cool-Path, St. Jude Medical or Thermo-Cool Navi-Star, Biosense-Webster); radiofrequency settings were 60 to 100 W, 50 to 65°C and 25 to 40 W, 35 to 40°C, respectively. Completeness across mitral isthmus lines was assessed as previously described (15). Ablation at the cavotricuspid isthmus to prevent isthmsus-dependent atrial flutter was performed in all patients. To reduce the probability of early recurrences of AF that could interfere with the reverse remodeling process, patients were treated with ADT for 6 weeks after catheter ablation; thereafter, a 12-month follow-up started (Fig. 1). If there was a recurrence of atrial tachyarrhythmias (AT) (including both AF and atrial tachycardia) beyond the first 6 weeks after the ablation, then a re-do procedure could be performed if the patient wished to proceed.

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recurrences, the patient could be maintained on the same drug and dose regimen if the investigator determined that an acceptable clinical response was achieved based on the duration and/or frequency of previous arrhythmia recurrences. In case of failure of the first assigned drug at the maximum tolerable dosage, the choice of a second drug trial was left to the primary physician, to be chosen from the other 2 antiarrhythmic agents or a combination of 2 of the 3 agents used in this study; the minimum period after which the second ADT trial was considered unsuccessful was set at 3 months. After 2 trials of ADT, patients could be considered for crossover to CPVA (Fig. 1).

Anticoagulant therapy. All patients were anticoagulated with warfarin to maintain an international normalized ratio of 2.0 to 3.0. Anticoagulation was discontinued if SR was maintained for >6 weeks without any episodes of symptomatic or asymptomatic AF and in the absence of concurrent indications.

Follow-up. All patients were seen in an outpatient clinic during the initial screening period before randomization and at 3, 6, and 12 months after randomization. At each visit, 12-lead electrocardiogram (ECG), 48-h Holter monitoring, and a transthoracic echocardiogram were obtained. Three months after randomization, thyroid function tests, hepatic panel, and serum chemical measurements were obtained. Chest X-ray and potential corneal deposits were also evaluated in patients receiving long-term amiodarone therapy. All patients were provided with an event monitor (Life Watch, Buffalo Grove, Illinois) and were asked to record their rhythm 1 to 3 times daily and whenever they experienced symptoms suggestive of AT. All 1-min rhythm tracings and echocardiograms were interpreted by 2 physicians blinded to the patient randomized arm. In the event of disagreement, the final interpretation was left to one of the authors, who were unaware of which group the patient belonged. An arrhythmia had to last >5 s. Rhythm transmissions were available from all patients for 94 ± 2% days of follow-up.

End point. The primary end point of this study was freedom from documented recurrent AT during a 12-month follow-up in patients who underwent CPVA and in those receiving ADT. The end point was reached with the first episode of AT, and cases with a second ADT or repeat ablation procedure were considered failures. Recurrence of AT was defined as AT that lasted at least 30 s (5).

Monthly rhythm analysis according to different mapping systems and different catheters as well as number of hospitalizations and complications in both groups were also analyzed.

Statistical analysis. Based on a conservative assumption that SR would be maintained at 1 year in at least 75% of patients in the CPVA group (4,5) and 50% of patients in the control group (16), a minimum of 85 patients was required in each group at a power of 90% to reach a 2-tailed alpha of 0.05. Considering the possibility of drop-outs, we planned to increase the number of patients by 15% for each group. Data are expressed as mean values ± SD and analyzed using the intention-to-treat method. Continuous variables were compared by independent samples t test after checking with Levene’s test for equality of variances and with the paired samples t test, when appropriate. Categorical variables were analyzed by chi-square test. Multivariate Cox regression...
Table 2. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CPVA Group (n = 99)</th>
<th>ADT Group (n = 99)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>55 ± 10</td>
<td>57 ± 10</td>
<td>0.24</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>69/30</td>
<td>64/35</td>
<td>0.54</td>
</tr>
<tr>
<td>AF episode/month</td>
<td>6 ± 4</td>
<td>6 ± 6</td>
<td>0.81</td>
</tr>
<tr>
<td>Duration of AF (yrs)</td>
<td>6 ± 4</td>
<td>6 ± 6</td>
<td>0.81</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>40 ± 6</td>
<td>38 ± 6</td>
<td>0.25</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5.1%</td>
<td>4%</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>17%</td>
<td>21%</td>
<td>0.59</td>
</tr>
<tr>
<td>Hypertension</td>
<td>56%</td>
<td>57%</td>
<td>1.00</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>60 ± 8</td>
<td>61 ± 6</td>
<td>0.49</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>3%</td>
<td>1%</td>
<td>0.22</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>2%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>No. of previously ineffective</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
<td>0.63</td>
</tr>
<tr>
<td>antiarrhythmic drugs</td>
<td></td>
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</tbody>
</table>

CPVA = circumferential pulmonary vein ablation; LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

Analysis was performed to determine the clinical predictors of freedom from recurrent AF. Observed event-free survival curves for both groups—presented as Kaplan-Meier plots—were compared among them by 2-sample log-rank tests. A value of p < 0.05 indicated statistical significance. SPSS 14.0.2 (SPSS Inc., Chicago, Illinois) was used for the statistical analysis. The prevalence of SR and AT during follow-up were also reported and compared on a monthly basis. One rhythm recording in AT in a given month was sufficient to classify the patient as having suffered from AT in that month.

RESULTS

Study population. Among 334 screened patients, 198 were enrolled in the study and underwent randomization (Fig. 1). The most frequent reasons for the failure to enroll screened patients were previous ADT over the last 24 months with amiodarone (46 patients), flecainide (35 patients), and sotalol (25 patients) or combination of them (22 patients). Characteristics of the 2 randomized groups are shown in Table 2. Most enrolled patients had received previous treatment with propafenone, disopyramide, and quinidine as single agents (140 patients) or in combination of digoxin and verapamil (58 patients).

Ablation group. Circumferential pulmonary vein ablation was performed in 99 patients with a mean of 35 ± 12 min of radiofrequency energy. The mean CPVA procedure time was 81 ± 31 min. Inferior vena cava-tricuspid annulus isthmus bidirectional block was successfully achieved in all patients. We performed CPVA by 8-mm catheter in 50 patients, and irrigated tip catheters were used in 49 patients. Six weeks after the procedure, no patients in the ablation group were on AAD therapy. During follow-up, 85 patients remained free from AT and discontinued ADT; warfarin was also stopped in all but 3 having a mechanical mitral valve. Recurrent symptomatic AF was documented by transtelephonic ECG monitoring in 11 patients at the end of the blanking period; 5 were controlled by continuing ADT (flecainide in 4, sotalol in 1), whereas 6 required a repeat ablation session (Fig. 3A). At this time, recovery of conduction was documented in 5 left superior pulmonary veins, 4 right superior pulmonary veins, 2 left inferior pulmonary veins, and 1 left inferior pulmonary vein. After a touch-up of the previous ablation lines, 5 patients stopped having AF (mean post-repeat ablation follow-up 6 months). The use of an irrigated tip catheter had a better outcome than those ablated with an 8-mm catheter (p = 0.03). After ablation, asymptomatic AF was observed in 3 patients who otherwise also reported symptomatic AF recurrences. In the CPVA group, the left atrial size was smaller at 12 months after (36 ± 6 mm) than before (40 ± 6 mm) ablation (p < 0.01).

No serious complications were observed in any patient who underwent CPVA. Shortly after the procedure with an 8-mm catheter, 1 patient with a mild apical hypertrophic cardiomyopathy developed a spell transient ischemic attack, which resolved within a few seconds. Another patient who performed CPVA by the irrigated-tip catheter had a very small pericardial effusion not due to cardiac perforation, which otherwise did not require pericardiocentesis. Three patients in the CPVA group developed post-ablation atrial tachycardia requiring activation mapping and ablation (Fig. 3A). All patients underwent successful ablation after the index procedure, and no further ATs were detected after 5, 7, and 8 months of follow-up, respectively.

ADT group. Of the 99 patients randomized to ADT, only 24 had their AF suppressed by a single AAD (amiodarone: n = 12 of 33; flecainide: n = 7 of 33; sotalol: n = 5 of 33) (Fig. 3B) during the 12 months of follow-up. Of the 75 patients with AF recurrences, 20 (27%) had asymptomatic episodes; 49 were placed on combination therapy of 200 mg of flecainide and 200 mg of amiodarone daily and 26 on 200 mg of flecainide and 240 mg of sotalol; 11 patients were subsequently free from AF with the combination of flecainide and amiodarone; 22 patients still had AF on combination therapy although the arrhythmia was less frequent and of short duration (amiodarone plus flecainide: n = 16; flecainide plus sotalol: n = 6); the other 42 patients (7, 20, and 15 patients of the 3 subgroups, respectively) crossed over to CPVA (Fig. 3B). Overall, amiodarone was given to 61 patients as a single drug (33 patients) or in combination (28 patients). Amiodarone was as effective as flecainide and sotalol (35%, 19%, and 11%, respectively, p = 0.11). No change in atrial size was noted in patients who remained in SR in the ADT group.

Significant adverse events leading to permanent drug withdrawal occurred in 23 patients. Pro-arrhythmia developed in 3 patients in the flecainide group (hypotensive wide QRS tachycardia in 2 patients and 1:1 atrial flutter in 1); thyroid dysfunction occurred in 7 patients in the amiodarone group requiring drug discontinuation; and sexual impairment in 11 patients in the sotalol group.
Primary end point. By Kaplan-Meier analysis, 86% of patients randomized to CPVA were AT-free at the end of follow-up as compared with the 22% of patients randomized to ADT \((p < 0.001)\) (Fig. 3A); time 0 started at the end of the 6-week blanking period.

Follow-up. Among the 99 patients in the ADT group, 42 underwent CPVA after a mean of 5.8 months. At a mean of 6.2 months of follow-up after crossover, 36 were free of recurrent AF in the absence of ADT, whereas AF was present in 6 (14%).

Hospital admissions. Among patients assigned to CPVA, 9 summed up 24 hospital admissions for cardiovascular causes, including repeat procedures. In the ADT group, 167 cardiovascular event-related hospital admissions occurred, not including the hospitalizations for crossover to CPVA \((p < 0.001)\). Monthly rhythm analysis in the NavX versus CARTO subgroups showed sinus rhythm in 95% and 87% at 1 year, respectively \((p = 0.08)\) (Fig. 4B), and in the 8-mm versus irrigated tip catheter groups 95% and 78% at 1 year, respectively \((p = 0.03)\) (Fig. 4C). By monthly rhythm analysis that took into account also the outcome of the second procedure and for patients controlled with combined therapy in ADT group, 93% of CPVA patients were free from atrial arrhythmias as compared with the 35% in the ADT group (Fig. 4D).

Predictors of freedom from PAF. Among the clinical parameters of age, gender, duration of AF (years), left atrial size, left ventricular ejection fraction (EF), whether or not structural heart disease was present, and treatment assignment, CPVA was independently associated with SR maintenance \((hazard ratio 0.13, 95\% confidence interval 0.07 to 0.23, p < 0.001)\). Further analysis revealed that EF \((hazard ratio 1.08, 95\% confidence interval 1.03 to 1.13, p = 0.003)\), hypertension \((hazard ratio 2.31, 95\% confidence interval 1.34 to 3.97, p = 0.003)\), and AF duration \((hazard ratio 1.03, 95\% confidence interval 1.01 to 1.11, p = 0.015)\) were independent predictors of drug failure in the ADT group. No independent predictors of AF recurrences were found in the ablation group.

**DISCUSSION**

Main findings. The results of the present study demonstrate that a single CPVA procedure is more effective than ADT in preventing AF relapses in selected patients with PAF. Ablation strategy resulted in maintenance of SR at 1
year without the need for continuing ADT in 86% of patients as documented by intensive daily transtelephonic monitoring, whereas only 22% of patients in the ADT group remained in SR at 1 year. Maintenance of SR after ablation was associated with a reverse left atrial remodeling and with fewer adverse events and hospital admissions due to cardiovascular causes.

**AF ablation strategy versus ADT: efficacy to prevent PAF.** Fueled by dissatisfaction with pharmacologic therapy and the explosive development in catheter-based technologies, AF ablation has matured from a purely investigational technique to a preferred effective approach for treating AF (4–13). Currently, there are few studies comparing ablation strategy with ADT in patients with PAF (4,11–13). We first reported in a non-randomized observational study the striking superiority of AF ablation over ADT, which persisted up to 3 years after ablation (4). We also reported that AF ablation was associated with significantly lower mortality and adverse events compared with ADT in the long term (4). In the first pilot randomized study by Wazni et al. (11), who compared AF ablation with ADT, the authors, for the first time, suggested that a strategy of using first-line pulmonary vein isolation among patients with initial episodes of PAF may be superior to initial ADT at 1-year follow-up because 87% of ablated patients were AF-free compared with 37% of patients who received ADT. A more recent randomized trial by Stabile et al. (12) also suggests that AF ablation combined with ADT is superior to ADT alone in preventing AF recurrences in patients with paroxysmal or persistent AF in whom ADT has already failed. The results of the present study demonstrate a striking superiority of the ablation strategy over ADT. Ablation was about 2.5 times more effective than amiodarone (86% vs. 35%, respectively) in preventing AF recurrences in relatively young patients with PAF of long duration in the absence of major complications. During a 12-month follow-up by using an intense transtelephonic monitoring, asymptomatic AF post-ablation was detected only in 3 patients in addition to symptomatic AF recurrences, similarly to those reported by Oral et al. (17); on the contrary, asymptomatic episodes were recorded in many patients (27%) in the ADT group. The reports of these trials taken together indicate that AF ablation strategy indeed warrants consideration as first-line therapy in selected patients in whom maintenance of SR is
desired. In the present study, the rate of AF recurrence in the ADT group was higher than that reported in previous studies but similar to that recently reported by Stabile et al. (12), and this in all probability was due to the same intensive monitoring strategy performed in both studies. Consistent with prior reports of the effect of CPVA on left atrial size (18,19), there was a significant decrease in left atrial size after CPVA. This is an important issue in patients with increased left atrial dimensions because this can further prevent atrial dilatation and disease progression. On the other hand, no left atrial remodeling was observed in the group of patients assigned to ADT.

**AF ablation strategy versus ADT: complications. ABLATION STRATEGY.** The efficacy of AF ablation strategy is superior to ADT, but the main concern and limitation of any ablative procedure is the potential occurrence of major complications. Unlike ADT, previous studies have shown that complications of CPVA typically result in only acute and not long-term morbidity with no case of death (4,5,12–15,18). In the present study, a few transient complications occurred in the CPVA group. Patients who underwent CPVA by using tip-irrigated catheters were less likely to have AF recurrences than those ablated with an 8-mm catheter. By introducing the modified CPVA approach that includes additional posterior lines, the incidence of AT has been lowered to 3.9% (15); in this study, we corroborate the findings of others that CPVA is well tolerated, but its chronic administration frequently is associated with side effects, which in some cases may be serious and may require drug discontinuation. Amiodarone is well tolerated, but its chronic administration frequently is associated with drug toxicity, as observed in 7 patients in our series, which may further aggregate episodes of PAF. In addition, the drug may induce pulmonary toxicity, but our study was relatively short (1 year), and did not address the potential for this serious adverse effect.

Overall, in the present study, 23 patients (23%) discontinued ADT because of adverse events, and these data compare well to the 11% to 28% reported in the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management), CTAF (Canadian Trial of Atrial Fibrillation), and PIAF (Rhythm or Rate Control in Atrial Fibrillation Pharmacological Intervention in Atrial Fibrillation Randomized Trial) studies (2,20,21). Thus, although more than one-third of patients can be maintained in SR with 1 or more AAD, there is serious concern about the life-long use of these drugs to suppress AF. Proarrhythmic effects leading to hemodynamic instability were observed in 3 patients in the flecainide group (hypotensive wide QRS tachycardia in 2 and 1:1 atrial flutter in 1). Sexual dysfunction may be an important limitation especially in young patients, and in our series this complication occurred in 11 young patients during sotalol therapy.

**Study limitations.** The ablation procedures were performed in a single highly specialized center with extensive experience in CPVA in patients most of whom were relatively young and healthy subjects. Therefore, these results cannot be generalized or applied to all AF patient populations. Although ablation was more effective than ADT at 1 year, maintenance of benefit and incidence of adverse events over a much longer follow-up as compared with ADT remain unknown. Indeed, most patients will require ADT for many years, even decades, and thus would be subject to longer potential adverse effects of the drugs. It is possible that this “early” end point biases our results toward ADT, for which longer-term adverse effects are a concern. Finally, although every effort was made to avoid potential bias excluding patients with previous treatment with amiodarone, flecainide, and sotalol, we cannot completely exclude that in this study some patients also had received these drugs over the past years. Even recognizing the limitations of the study, we believe that our results challenge the notion that multiple and different AADs should be used life-long in patients with a long history of PAF.

**Conclusions.** Among selected patients with a long history of PAF, a single CPVA is more effective than ADT with 3 AADs widely used as single agents or in combination. However, before translating the results of this study into clinical practice, further multicenter randomized trials in older patients with more extensive heart disease with longer follow-up are required. Nevertheless, the results of our study suggest that AF ablation strategy warrants consideration in selected patients in whom ADT has already failed and maintenance of SR is desired.

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