# Effectiveness of hybrid therapy versus radiofrequency ablation alone in decreasing recurrence after ablation of atrial fibrillation

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**Introduction**
Atrial fibrillation (AF) represents an important public health problem. Catheter ablation has emerged as effective therapy. Recurrence after ablation is still around 20–40%. The long-term use of anti-arrhythmic drugs (AAD) after AF ablation has been traditionally reported to reduce late AF recurrences; but has never been supported by randomised trials.
**Objective**
To test if routine continuation of the previously unsuccessful AAD beyond blanking period reduces AF recurrence at one year after AF ablation.
**Patients and method**
This randomised controlled clinical trial was conducted between January 2013 and January 2015 in Critical Care Medicine Department – Cairo University. Patients with symptomatic, drug refractory AF were enrolled. All patients underwent pulmonary vein isolation ± left atrial ablation according to AF type. The previously unsuccessful AAD was continued for at least 3 months after ablation, after which patients were randomised to either continue or stop that drug. Patients were regularly followed up for at least additional 9 months. The primary endpoint was reduction of AF recurrence. Secondary endpoints included identification of predictors of recurrence and rate of complications.
**Results**
Thirty-one patients with paroxysmal (80.6%) and persistent (19.4%) AF were enrolled. Pulmonary vein isolation was achieved in all patients. Seventeen patients were randomized to continue AAD (54.8%) beyond blanking period. After 12 months, there was no statistically significant difference of AF recurrence between the two groups (35.3% vs. 21.4%, $P$=0.46). The same was observed for paroxysmal AF patients (30.8% vs. 8.3%, $P$=0.32). Persistent AF and early AF recurrence were associated with late recurrence. Only 2 patients had major complications.
**Conclusion**
Routine continuation of previously unsuccessful AAD did not reduce AF recurrence, over a period of 12 months. Persistent AF and recurrence during blanking period were associated with later recurrence.

**Keywords:**
ablation, atrial fibrillation, hybrid therapy, recurrence

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## Introduction

Atrial fibrillation (AF) represents an important public health problem. Patients with AF have an increased long-term risk of stroke, heart failure, and all-cause mortality [1–4]. Furthermore, patients with AF describe a considerably impaired quality of life that is independent of the severity of the disease [5]. Restoration and maintenance of normal sinus rhythm following treatment directly correlates with improved quality of life in these patients [5,6]. Although antiarrhythmic drugs (AADs) are generally used as first-line therapy to treat patients with AF, effectiveness remains inconsistent. AADs are also associated with cumulative adverse effects over time [1]. Catheter ablation has emerged as effective therapy for AF, especially when AADs fail. Several guidelines recommend performing AF ablation after failure of at least one class Ic or class III AAD, in both symptomatic paroxysmal and persistent AF [1,7–10].

The use of AAD after AF ablation, especially long-term use, is still a matter of question. It has been repeatedly shown that short-term use of AAD over blanking period after ablation reduces the morbidity associated with early recurrence of atrial arrhythmias;



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however, it has no effect on later recurrence [11,12]. Accordingly, it is acceptable now to keep patients on AAD for a short period after ablation [8]. The evidence for long-term use of AAD after ablation is not as solid. Although several studies showed that catheter ablation success rate increases on average from 55–60 to 70–75% with the use of AADs that were ineffective before catheter ablation, most of these studies are not randomized trials [12].

Thus, we conducted this randomized controlled trial to see if routine continuation of the previously unsuccessful AAD beyond blanking period reduces AF recurrence at 1 year after AF ablation.

## Patients and methods

This randomized controlled clinical trial was conducted between January 2013 and January 2015 in Critical Care Medicine Department, Cairo University. Consecutive patients with symptomatic paroxysmal or persistent AF who failed at least one class Ic or class III AAD were enrolled. We excluded patients with long-lasting persistent AF, congestive heart failure, left atrial (LA) diameter equals to or more than 5.5 cm, uncontrolled thyrotoxicosis or ischemic heart disease, redoablation, and those who preferred not to try medical treatment first. Our primary endpoint was to evaluate whether routine continuation of the previously unsuccessful AAD beyond the blanking period minimizes AF recurrence after the first ablation procedure. Secondary endpoints included identification of possible predictors of AF recurrence and incidence of procedure-related complications.

The study was approved by our local institutional research board. All patients provided informed written consent before the study.

Demographic and clinical data were recorded for all patients. HATCH score was calculated for patients with PAF only (HATCH is an acronym for Hypertension '1 point', Age above 75 years '1 point', TIA or stroke '2 points', COPD '1 point', and Heart failure '2 points'. A score >5 has a 50% chance of progressing to persistent AF over the following year) [13].

Ablation was done on therapeutic anticoagulation (international normalized ratio=2–3). However, according to operator preference, warfarin was discontinued before the procedure in some patients and bridging anticoagulation using low-molecular-weight heparin was used instead. In either case, anticoagulation was started 4–6 h after procedure, provided there was adequate hemostasis.

Absence of LA thrombus was confirmed by either transesophageal echocardiogram or computed tomography of LA with contrast done in the week before the procedure. The presence of common pulmonary vein (PV) ostia (left or right), middle PV (left or right), roof PV, or any other uncommon PV anatomical variation was considered variant LA anatomy.

In our study, AAD was not interrupted and were continued for at least 3 months after the procedure (the blanking period). Continuation of AAD beyond blanking period was dependent on the randomization process.

### The procedure

On the day of the procedure, all patients provided informed written consent.

Surface ECG and bipolar endocardial electrograms were stored continuously using multichannel polygraph (LabSystem PRO, Bard Electrophysiology or EP WorkMate; St Jude Medical Inc., St Paul, Minnesota, USA) for further analysis. Bipolar recordings were filtered from 30 to 500 Hz. Arterial blood pressure and oxygen saturation were continuously monitored. Most patients had the procedure done under conscious sedation and local anesthesia. Some patients with persistent AF, in whom extensive ablation was anticipated, received general anesthesia.

In all cases, trans-septal puncture was guided by fluoroscopy and multipolar catheter placed in coronary sinus. In addition, aortic root was marked by either HIS catheter or pigtail catheter placed retrogradely at the aortic root. One or two 8 Fr long sheaths were then placed in LA through the puncture.

Following trans-septal puncture, weight-adjusted unfractionated heparin was administered to achieve an ACT of 300–350. It was then repeated every 15–30 min, and unfractionated heparin was given accordingly to achieve that target.

Using the 3D navigation system (CARTO3; Biosense Webster, Diamond Bar, California, USA or EnSite Velocity; St Jude Medical Inc.), LA shell was reconstructed with special attention to careful delineation of PV ostia. A fully expanded 10-pole (electrode width 1 mm, interelectrode distance 8 mm) or 20-pole (electrode width is 1 mm, interelectrode distance is 2.6–2 mm) circular mapping catheter (Lasso

2515; Biosense Webster) was then placed as proximal as possible in PV ostia, and the vein was isolated by either circumferential or segmental ostial ablation. In all cases, demonstration of entrance block into the vein was a mandatory endpoint.

After isolating all veins that demonstrated pulmonary vein potentials, veins were rechecked at least 20 min later for gaps, and if there had been any, they were closed. According to operator's discretion, adenosine was sometimes given to unmask dormant conduction into PV, which, when found, was ablated. In those cases, adenosine was given at a dose that produced complete atrioventricular block (usually 12–15 mg) [14]. Of note, if the patient remained in AF at the end of procedure, he/she was electrically cardioverted, and all veins were rechecked in sinus rhythm. In patients with persistent AF, further LA ablation for substrate modification was always performed. However, the technique varied among operators. Some operators performed roof and lateral mitral isthmus lines, with demonstration of bidirectional block as a strict endpoint. Others performed ablation of manually identified complex fractionated atrial electrograms (CFAE). In the latter case, areas targeted for ablation were those with low amplitude (<0.15 mV) and fractionated atrial electrograms (composed of two or more deflections) or baseline perturbation with continuous deflections, lasting at least 10 s.

The other CFAE targets were areas with very short AF cycle length (≤120 ms) over a 10-s period [15]. Occasionally both linear and CFAE ablation techniques were used in the same patient.

Ablation was done using standard 3.5-mm irrigated-tip catheter. The energy delivered was 25 W on the posterior wall of LA and 30–35 W elsewhere. Ablation catheter was continuously irrigated using heparinized saline at background rate of 2 ml/min that increases to 17 ml/min during RF application. At the end of procedure, protamine was given, at operator's discretion, to reverse the effect of heparin. Procedure time (from skin puncture to removal of sheaths) and fluoroscopy time were recorded.

#### Arrhythmia monitoring and randomization

All patients were instructed to continue the same AAD used before ablation, for a minimum of 3 months (blanking period), and to have a 12-lead ECG done for any attack of palpitation during that period. If the attack was too short to be recorded, a 24–48-h Holter monitoring was done. At the end of blanking period, all patients had at least 12-lead ECG. Those who did not experience any palpitations in the blanking period had at least 24-h Holter monitoring. Patients were then randomized to either continue or stop antiarrhythmic medication for the following 9 months. Randomization was done using sealed envelope system, in which pieces of paper containing group allocation were sealed in opaque envelopes and at the time of randomization, a single envelope is picked for each patient to determine his/her allocation in the study groups. Patient recruitment for the study continued until the targeted sample size of each study group was reached. Again, patients were instructed to have a 12-lead ECG done whenever they experience palpitations, and 24–48-h Holter monitoring if the attack had been too short to be captured on 12-lead ECG. At the end of the ninth month, all patients without documented AF recurrence after the blanking period had a 12-lead ECG and at least 24-h Holter monitoring. In our study, AF recurrence was defined as documented AF/atrial tachycardia episode longer than 30 s with or without symptoms. In each follow-up visit, patients were examined for complications related to ablation such as thromboembolism, PV stenosis, phrenic nerve injury, and atrioesophageal fistula. Complications were defined according to the recommendations of the 2012 expert consensus statement on catheter and surgical ablation of AF [8].

#### Statistical analysis

Statistical analysis was done using statistical package for social sciences software, release 16.0.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were described using mean±SD if they were normally distributed, and median and interquartile range if data were skewed. Categorical variables were described using frequencies and percentages. Bivariate analysis of categorical variables was done using $\chi^2$-test with Yates Continuity correction for 2×2 tables. Whenever cell frequency was less than 5, Fisher's exact test was used. Comparing two groups of quantitative variable was done using independent-sample Student's *t*-test for parametric data, and Mann–Whitney test for nonparametric ones. The correlation between two quantitative variables was explored using Pearson's test for parametric data and Spearman's test for nonparametric one. In all cases, the two-sided significance was always taken as *P* value, and a *P* value less than 0.05 was considered statistically significant.

## Results

Our study included 31 consecutive patients who underwent their first radiofrequency ablation for paroxysmal or persistent AF between January 2013 and January 2014, in Critical Care Medicine

Department, Cairo University. In all cases, pulmonary vein isolation (PVI) confirmed by entrance block was a standard target. Additional ablation for persistent AF was left at operator's discretion. All patients were followed up for a minimum of 12 months. According to study protocol, patients were randomized at the end of the 3-month blanking period to either stop or continue AAD. Our primary endpoint was to study whether routine continuation of the previously unsuccessful antiarrhythmic medication reduces AF recurrence after ablation.

Characteristics of study population and study groups are listed in Table 1.

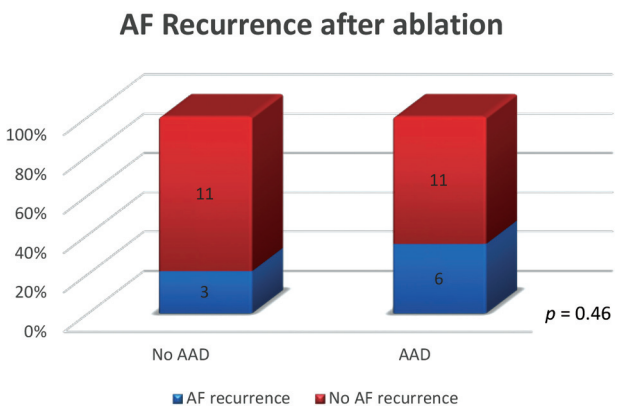
The AAD used in group 1 were propafenone ($n$=2), flecainide ($n$=8), and amiodarone ($n$=4). In group 2, the AAD used were propafenone ($n$=1), flecainide ($n$=9), amiodarone ($n$=6), and sotalol ($n$=1).

### Effect on atrial fibrillation recurrence

Our study showed that routine continuation of the ADD used before ablation beyond blanking period did not reduce AF recurrence after first ablation, over the follow-up period of 12 months (Fig. 1). AF recurred in three (21.4%) of 14 patients who stopped AAD compared with six (35.3%) of 17 patients who did not. This difference is statistically insignificant ($P$=0.46). All recurrences were in the form of AF except for one patient in group 1 whose recurrence was in the form of atrial tachycardia/atrial flutter.

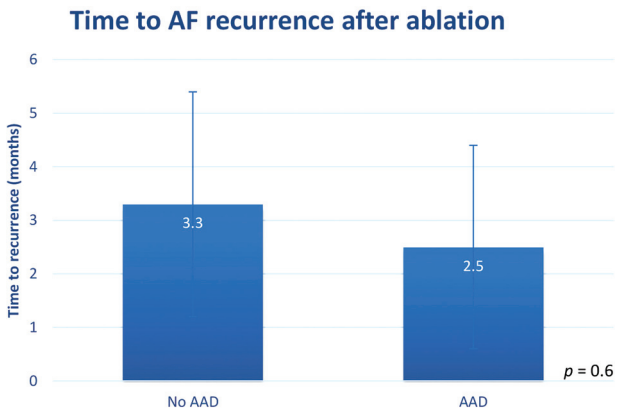
It was also found that routine continuation of AAD did not prolong the time to AF recurrence after ablation (Fig. 2). The time to recurrence in patients who stopped AAD was 3.3±2.1 months compared with 2.5±1.9 months in patients who continued on them ($P$=0.6) (Fig. 2).

**Figure 1**




Effect of routine continuation of antiarrhythmic drug (AAD) on atrial fibrillation (AF) recurrence after ablation.

**Figure 2**




Effect of antiarrhythmic drug (AAD) continuation on time to atrial fibrillation (AF) recurrence after ablation.

**Table 1 Characteristics of study population and study groups**

| | All ($n$=31) [$n$ (%)] | Group 1 (no AAD) ($n$=14) [$n$ (%)] | Group 2 (AAD) ($n$=17) [$n$ (%)] | $P$ |
|---|---|---|---|---|
| Age (years) | 61.7±13.9 | 65.2±9.2 | 58.7±16.6 | 0.18 |
| Sex (male) | 15 (48.4) | 8 (57.1) | 7 (41.2) | 0.6 |
| Hypertension | 15 (48.4) | 5 (35.7) | 10 (58.8) | 0.36 |
| DM | 2 (6.5) | 1 (7.1) | 1 (5.9) | 1 |
| Prior stroke/TIA | 2 (6.5) | 0 | 2 (11.8) | 0.49 |
| LVEF (%) | 63.7±7.1 | 63.6±8.4 | 63.8±6 | 0.94 |
| LAD (cm) | 3.8±0.6 | 3.7±0.5 | 3.9±0.7 | 0.45 |
| AF duration (years) | 3±2.3 | 3±2.5 | 3±2.1 | 0.96 |
| AADs before ablation (count) | 1.5±0.6 | 1.3±0.6 | 1.6±0.6 | 0.18 |
| COPD | 3 (9.7) | 3 (21.4) | 0 (0) | 0.08 |
| CAD | 1 (3.2) | 0 (0) | 1 (5.9) | 1 |
| AF type: PAF | 25 (80.6) | 12 (85.7) | 13 (76.5) | 0.66 |
| Persistent | 6 (19.4) | 2 (14.3) | 4 (23.5) | |
| HATCH score (for PAF patients) | 1±1.3 | 1.2±1.5 | 0.9±1 | 0.54 |

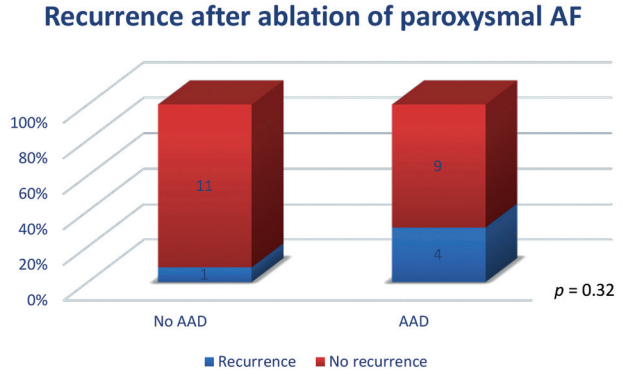
AAD, antiarrhythmic drug; AF, atrial fibrillation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HATCH: Hypertension, Age, TIA/Stroke, COPD, and Heart failure; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; PAF, paroxysmal atrial fibrillation; TIA, transient ischemic attack.

The same result was obtained when analyzing patients with PAF only. In addition, routine continuation of AAD did not convey any added benefit (Fig. 3). Of 12 patients with PAF who stopped AAD, one (8.3%) had recurrence whereas four (30.8%) of 13 patients with PAF on AAD experienced recurrence ($P$=0.32).

### Predictors of recurrence

Several clinical and procedural variables were analyzed aiming at identifying possible predictors of AF recurrence after ablation. Of the clinical variables, only two were seen prevalent in the AF recurrence group (Table 2).

**Figure 3**




Effect of antiarrhythmic drug on atrial fibrillation (AF) recurrence following ablation of paroxysmal AF.

**Table 2 Possible clinical predictors of atrial fibrillation recurrence after ablation**

| | Recurrence ($n$=9) [$n$ (%)] | No recurrence ($n$=22) [$n$ (%)] | $P$ |
|---|---|---|---|
| Age (years) | 60.8±13.2 | 62±14.5 | 0.83 |
| Sex (male) | 2 (22.2) | 13 (59.1) | 0.11 |
| Hypertension | 3 (33.3) | 12 (54.5) | 0.43 |
| DM | 1 (11.1) | 1 (4.5) | 0.5 |
| Prior stroke/TIA | 0 | 2 (9.1) | 1.0 |
| COPD | 1 (11.1) | 2 (9.1) | 1.0 |
| CAD | 0 | 1 (4.5) | 1.0 |
| AF type (PAF) | 5 (55.6) | 20 (90.9) | 0.04 |
| AF duration (years) | 2.5±2.1 | 3.2±2.3 | 0.42 |
| HATCH score (for PAF patients only) | 0.4±0.5 | 1.2±1.3 | 0.24 |
| AADs before ablation | 1.3±0.5 | 1.5±0.7 | 0.51 |
| Recurrence in blanking period | 6 (67) | 5 (23) | 0.04 |
| AAD continuation after ablation | 6 (67) | 11 (50) | 0.46 |
| LA diameter (cm) | 3.7±0.5 | 3.9±0.6 | 0.5 |
| Ejection fraction (%) | 63.4±3.7 | 63.8±8.1 | 0.91 |
| Abnormal LA anatomy | 4 (44.4) | 8 (36.4) | 0.7 |

AAD, antiarrhythmic drug; AF, atrial fibrillation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HATCH, Hypertension, Age, TIA/Stroke, COPD, and Heart failure; LA, left atrium; PAF, paroxysmal atrial fibrillation; TIA, transient ischemic attack.

Patients with persistent AF were more likely to have AF recurrence (4/6, 66.7%) than those with paroxysmal AF (5/25, 20%) ($P$=0.04) (Fig. 4).

Recurrence in blanking period was also found to precede most cases of later recurrence (Fig. 5).

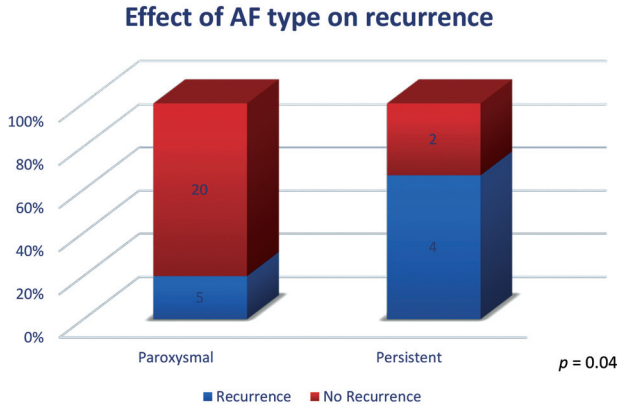
On the contrary, our study did not show any of the procedure variables to have an effect on recurrence after ablation (Table 3).

### Frequency of complications

In our study, two (6.4%) of 31 patients had major complications (Table 4).

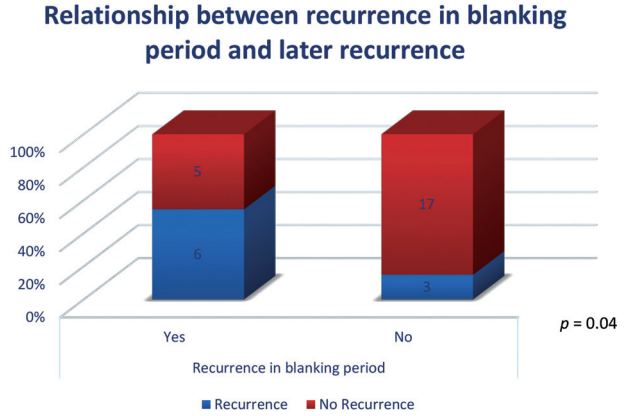
One patient had major groin bleeding that prolonged his hospital stay for 3 days. Bleeding was controlled by manual compression, vascular ultrasound showed no aneurysms, and finally, the patient was discharged without blood transfusion.

**Figure 4**




Relationship between atrial fibrillation (AF) type and recurrence after ablation. AAD, antiarrhythmic drug.

**Figure 5**




Relationship between recurrence in blanking period and later recurrence.

**Table 3 Possible procedural predictors of atrial fibrillation recurrence after ablation**

| | Recurrence (*n*=9) | No recurrence (*n*=22) | *P* |
|---|---|---|---|
| Procedure variables | | | |
| Navigation system used (CARTO3/EnSite Velocity) | 8/1 | 17/5 | 0.64 |
| Circular mapping catheter used (20 poles/10 poles) | 9/0 | 18/4 | 0.3 |
| Patients with PVPs in all PVs [*n* (%)] | 6 (66.7) | 13 (59.1) | 1.0 |
| PVI confirmation by adenosine [*n* (%)] | 2 (22.2) | 5 (22.7) | 1.0 |
| Total procedure duration (min) | 165.8±50.3 | 174.7±53.6 | 0.67 |
| Total fluoroscopy time (min) | 38.5±24.7 | 60.6±32.5 | 0.08 |

PV, pulmonary vein; PVI, pulmonary vein isolation; PVP, pulmonary vein potential.

**Table 4 Complications associated with radiofrequency ablation of atrial fibrillation**

| Complications | Frequency (%) |
|---|---|
| Major groin bleeding | 1 (3.2) |
| Pericardial tamponade | 1 (3.2) |
| Phrenic nerve injury | 0 (0) |
| Entrapment of circular mapping catheter | 0 (0) |
| Atrioesophageal fistula | 0 (0) |
| Stroke | 0 (0) |
| Symptomatic pulmonary vein stenosis | 0 (0) |

The other patient had pericardial tamponade that was attributed to perforation of LA roof. Pericardial drain was inserted and heparin was reversed with protamine. Patient required repeated pericardiocentesis with retransfusion of the aspirated blood. Eventually, bleeding was controlled.

## Discussion

Early data from nonrandomized trials suggested that routine continuation of AAD beyond blanking period reduces long-term AF recurrence [12]. However, very few randomized trials addressed this question. Turco *et al.* [16] randomized 107 patients with drug refractory, or intolerant, paroxysmal or persistent AF to either ablation alone (*n*=53) or ablation plus long-term AAD, mostly amiodarone (*n*=54). Patients were followed up for 12 months, with standard ECG, ambulatory ECG, and a weekly transtelephonic 30-s ECG. They found no statistically significant difference of AF recurrence at the end of follow-up period (34 vs. 30% respectively, *P*=0.63). This observation was consistent in both paroxysmal AF (29 vs. 34%, *P*=0.71) and persistent AF (41 vs. 24%, *P*=0.17). However, among patients with AF recurrence, the incidence of asymptomatic recurrence was higher in those on AAD (63 vs. 28%, *P*=0.04). They hypothesized this to be because of placebo effect, slower mean ventricular rate, or lesser RR variability.

Few years later, Pokushalov *et al.* [17] showed that the efficacy of AAD after initial failed ablation of paroxysmal AF is significantly inferior to redoablation. In their study, they randomized 154 patients with symptomatic AF recurrence after initial ablation of paroxysmal AF to either redoablation (*n*=77) or medical treatment with AAD (*n*=77). The AADs used were mainly (79% of patients) class Ic drugs (propafenone and flecainide), and in most patients (88%), it was the one they used unsuccessfully before the first ablation. None of those patients was on Amiodarone. All patients received implantable loop recorders that were implanted during the first ablation and were followed up for 3 years. At the end of follow-up period, 58% of the reablation group were free of AF without AAD, compared with only 12% of the AAD group (*P*<0.01). Moreover, progression from paroxysmal to persistent AF was less likely to occur in reablation group than in AAD group (4 vs. 23%, respectively, *P*<0.01)

The results of our study were in line with those of Turco and Pokushalov. We found that routine continuation of the previously unsuccessful AAD beyond blanking period did not reduce the incidence of AF recurrence after ablation. After 12 months of follow-up, AF recurrence was seen in 21.4% of patients off AAD (3/14) and 35.3% of those on AAD (6/17) (*P*=0.46). The time to AF recurrence was not affected either. The mean time to recurrence was 3.3±2.1 months in patients off AAD and 2.5±1.9 in the other group (*P*=0.6). Similar result was obtained when looking only at patients with paroxysmal AF. Recurrence without AAD occurred in 8.3% (1/12) compared with 30.8% (4/13) of patients with PAF on AAD (*P*=0.32).

There is a possible explanation why the previously perceived improvement of AF recurrence by long-term use of AAD after ablation was not supported by results of randomized controlled trials. There are many important aspects of an AF ablation trial that can affect long-term freedom of AF, and until the release of the HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of AF in 2007, there had been no standardization in the design of such trials [8,18]. Among these are the frequency and intensity of arrhythmia monitoring, and the variable definitions of procedural success. Some studies defined success as freedom from symptomatic AF during follow-up,

whereas others have defined success as freedom from both symptomatic and asymptomatic AF [8]. Turco *et al.* [16] showed that long-term use of AAD did not significantly reduce AF recurrence, but was more likely associated with asymptomatic recurrence. This could explain how AADs improve the outcome of studies defining success as absence of symptomatic AF, whereas not affecting studies that included asymptomatic recurrences.

### Predictors of recurrence

#### *Preprocedural variables*

Several studies have investigated the predictors of AF recurrence following ablation, as it would help the proper selection of patients with the aim of reducing unnecessary procedures, minimizing complications, and reducing healthcare costs [19]. Clinical, procedural, and postprocedural variables were considered. The systematic review by Balk *et al.* [20] is an extensive effort in this regard. Authors searched for relevant studies in MEDLINE and Cochrane Central Trials Registry databases between 2000 and 2008 with the aim of identifying the most significant preprocedural patients characteristics associated with AF recurrence. Because eligible studies were highly heterogeneous regarding ablation technique and definition of AF recurrence, neither AF type, sex, age (between 40 and 70 years old), ejection fraction, LA diameter, structural heart disease, hypertension nor AF symptom duration alone independently predicted AF recurrence. Nevertheless, meta-analysis of univariable AF recurrence rates by AF type in 31 studies found that nonparoxysmal AF predicted AF recurrence compared with paroxysmal AF (risk ratio=1.59; 95% confidence interval: 1.38–1.82; $P<0.01$).

A later meta-analysis by D'Ascenzo *et al.* [21] pooled the data of 4357 PAF, 1083 persistent AF, and 1777 patients with long-standing AF and found that patients with persistent AF had the highest risk of recurrence after the first ablation (odds ratio=1.78; 99% confidence interval: 1.14–2.77). However, a trend toward nonsignificance was present in patients with more than one procedure. Other predictors of AF recurrence were recurrence within 30 days, valvular AF, and LA diameter more than 50 mm.

Our study showed similar results, as patients with persistent AF had significantly higher recurrence rate at the end of follow-up period than those with paroxysmal AF (66.7 vs. 20%, $P=0.04$).

The poorer outcome of ablation of persistent AF is probably the reflection of more LA fibrosis and accordingly the need for more extensive ablation, beyond PVI, targeting substrate modification such as linear and CFAE ablation [1,8]. Currently, there is no consensus on the best strategy for persistent AF ablation, and even when more extensive ablation is performed, outcome is less favorable than that for paroxysmal AF.

### Procedural variables

Ablation strategies that target PVs or PV antrum are the cornerstone for most AF ablation procedures, and whenever PVs are targeted, electrical isolation should be the goal [8]. This recommendation is supported by the repeated demonstration that AF recurrence is strongly related to PV reconnection [22–26]. Several intraprocedural predictors of durable PVI, and accordingly long-term ablation success, have been investigated. Isoproterenol infusion and burst pacing have varying ability to identify non-PV triggers of AF post-PVI; however, neither has allowed for dependable prediction of either acute or chronic PV reconnection [27,28].

Adenosine was found to be able to transiently unmask dormant conduction into significant proportion of PVs immediately after electrical isolation [29,30]. However, targeting these potentials yielded conflicting long-term results. Whereas some studies [31–33] showed improvement of success rate of paroxysmal AF ablation from 60 to 73% at 6 months of follow-up [31] and from 62.3 to 76.4% at 16 months [33]. Miyazaki *et al.* [34] showed that not only did elimination of ATP-dependent transient reconnection not improve success after AF ablation, but its presence was a predictor of an inferior long-term outcome, and thus, concluded that ATP-provoked conduction is a marker of inadequate ablation rather than a target to improve outcome. These different results could be attributed in part to different patient populations. Miyazaki *et al.* [34] compared contemporaneous groups of patients, whereas studies that showed improved outcomes compared sequential population (i.e. they compared their results with those of a prior group of patients ablated using similar approaches). The observed improvement in the latter case is likely owing to an increase in overall technical proficiency rather than an effect of further ablation of veins demonstrating transient reconnection [27]. McLellan *et al.* [35] performed a meta-analysis of six studies including 544 patients and suggested that routine adenosine testing was associated with an improvement in freedom from AF after PVI. Paradoxically, acute adenosine-induced PV reconnection may portend a greater likelihood of AF recurrence despite additional ablation [35]. Randomized controlled trials are required to determine the role of

adenosine testing after PVI. To resolve this conflict, the Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination study is an ongoing randomized clinical trial assessing the effect of adenosine-guided PVI in preventing AF recurrences compared with conventional PVI [36].

In our study, we found that elimination of adenosine-provoked PV reconnection did not improve success rate. There is statistically insignificant difference in AF recurrence between the group of patients who received adenosine (2/7; 28.6%) and those who did not (7/24; 29.2%) ($P$=1.0).

We also looked at the effect of some technological aspect of ablation procedure on recurrence. It is common now to use one of the two popular 3D electroanatomic mapping system; CARTO3 (Biosense Webster) or EnSite Velocity (St. Jude Medical Inc.) which were validated in several trials [37–40]. In experimental and controlled environment, both systems have slightly different spatial accuracy; however, this difference is below a clinically relevant threshold [41]. Khaykin *et al.* [42] retrospectively analyzed AF recurrence rates after PVAI guided by CARTO XP (but not CARTO3), EnSite NavX, or fluoroscopy alone without 3D mapping system. Authors found no statistically significant difference of early or late AF recurrence among the three approaches. To our knowledge, there has been no studies comparing AF recurrence rate after ablation guided by CARTO3 system versus EnSite Velocity.

In this work, we found that AF recurrence rate was not affected by the use of either CARTO3 or EnSite Velocity systems (8/25 vs. 1/6 respectively, $P$=0.64). This finding supports Bourier *et al.* [41] conclusion that the difference of spatial accuracy between these two mapping systems has little clinical relevance.

#### Postprocedural variables

Recurrence of AF is common in the first few months after ablation regardless of the catheter technique and technology used [8,43,44]. Compared with the immediate preablation period, the frequency of recurrent AF during the first days after ablation is variable, and in about 15% of patients, the episodes may even become more frequent than before ablation [45]. Although early recurrence of AF carries an independent risk of treatment failure [8,21], up to 60% of patients experiencing this event within the first month after ablation will not have any further arrhythmias during long-term follow-up [8,45]. In a study using 3 months of continuous automatic ECG loop recordings, 85% of the patients who did not experience AF within the first 2 weeks after PVI were complete responders at 12 months [46]. In contrast, time of recurrence within the first 3 months after ablation was not significantly associated with procedural success or failure [46].

Consistent with the published data, our study showed that 35% ($n$=11) of patients had early recurrence in the first 3 months after ablation; however, 45.5% of them ($n$=5) never had later recurrence and were considered to have successful ablation at the end of follow-up. A significant proportion of patients who had late recurrence experienced early recurrence (6/9, 66.7%) compared with those who were free of AF at the end of study (5/22, 22.7%) ($P$=0.04). Accordingly, early AF recurrence does not necessarily mean procedure failure; however, those patients are at higher risk of late recurrence and should be monitored carefully.

#### Complications

Catheter ablation of AF is one of the most complex interventional electrophysiological procedures [8]. It is therefore to be expected that the risk associated with AF ablation is higher than for ablation of most other cardiac arrhythmias. The 2010 updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human AF analyzed voluntarily submitted surveys from 182 centers around the world and reported an overall risk of major complications of 4.5% [47]. Cardiac tamponade, vascular complications, and transient ischemic attack accounted for 77.6% of all complications. It must be recognized that the data were from voluntary surveys and likely underestimated the true complication rates. Gupta *et al.* [48] published their systematic review on complications of catheter ablation of AF. They pooled the data of 83 236 patients from 192 studies and reported an overall acute complication rate of 2.9%, with vascular complications, pericardial effusion/tamponade, and stroke/transient ischemic attack occupying the first three places on the list. They also observed that between 2007 and 2012, complications were significantly lower than those during 2000–2006 (2.6 vs. 4.0%; $P$=0.03), which reflects advancements in catheter technology and techniques, as well as increased experience [48]. The reduction of overall complication rate between the 2010 worldwide survey and Gupta and colleagues systematic review could be explained by, in addition to technological and technical improvements, publication bias in which there is a tendency to publish articles demonstrating low complication rate. Moreover, this systematic review included only studies larger than 100

patients in size and ignored case reports and small series which, according to authors, may underestimate the true incidence of rare adverse events by selectively reporting these events in often very specific patient subgroups, and thus confounding the analysis of overall complication rate. This is probably why the complication rate in our study (2/31, 6.4%) is perceived to be higher than those reported in those studies, where it could be, in fact, closer to the real-life complication rate. Interestingly, the pilot study of ESC-EURObservational Research Programme on Atrial Fibrillation Ablation reported an overall complication rate of around 7.3%, which is closer to the one reported in our study [49].

### Limitations

The technique of PVI, whether segmental ostial isolation or wide area circumferential pulmonary vein ablation, was left to the operator's discretion. Although circumferential pulmonary vein ablation is suggested to be superior for minimizing AF recurrences [50,51], it is also more proarrhythmic [52]. Up till now, there is no consensus preference for one technique over the other, as long as PVI has been achieved. A large randomized clinical trial is currently ongoing to test which of those techniques results in better AF control [53].

Detection of AF recurrence in our study had been mainly 'signaled' by symptoms. Asymptomatic patients had at least 24-h Holter monitoring at the end of follow-up period. Although some asymptomatic recurrences had been detected, more rigorous monitoring protocols (e.g. 1-week event recorder or implantable loop recorder) could have detected even more episodes of AF recurrences. However, the success rate of AF ablation in our study is similar to that reported in large surveys and systematic reviews over similar follow-up periods, making it unlikely for more extensive monitoring to significantly alter our follow-up results.

The rate of AF recurrence and its predictors have been analyzed using univariate analysis. A larger study would allow for detection of smaller difference in recurrence rates and to use multivariate analysis for more accurate identification of predictors.

## Conclusion

In our study, routine continuation of previously unsuccessful antiarrhythmic medication did not reduce AF recurrence, nor prolonged time to recurrence, over a follow-up period of 12 months. Persistent AF and recurrence during blanking period are predictors of later recurrence.

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### Conflicts of interest

There are no conflicts of interest.

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