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ORIGINAL ARTICLE

No Effect of Continued Antiarrhythmic Drug Treatment on Top of Optimized Pulmonary Vein Isolation in Patients With Persistent Atrial Fibrillation: Results From the POWDER-AF2 Trial

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BACKGROUND: In patients with persistent atrial fibrillation (PersAF), catheter ablation aiming for pulmonary vein isolation (PVI) is associated with moderate clinical effectiveness. We investigated the benefit of continuing previously ineffective class 1C or 3 antiarrhythmic drug therapy (ADT) in the setting of a standardized PVI-only ablation strategy.

METHODS: In this multicenter, randomized controlled study, patients with PersAF (≥7 days and <12 months) despite ADT were prospectively randomized 1:1 to PVI with ADT continued versus discontinued beyond the blanking period (ADT ON versus ADT OFF). Standardized catheter ablation was performed aiming for durable isolation with stable, contiguous, and optimized radio frequency applications encircling the pulmonary veins (CLOSE protocol). Clinical visits and 1-to-7-day Holter were performed at 3, 6, and 12 months. The primary end point was any documented atrial tachyarrhythmia lasting >30 seconds beyond 3 months. Prospectively defined secondary end points included repeat ablations, unscheduled arrhythmia-related visits, and quality of life among groups.

RESULTS: Of 200 PersAF patients, 98 were assigned to ADT OFF and 102 to ADT ON. The longest atrial fibrillation episode qualifying for PersAF was 28 (10–90) versus 30 (11–90) days. Clinical characteristics and procedural characteristics were similar. Recurrence of atrial tachyarrhythmia was comparable in both groups (20% OFF versus 21.2% ON). No differences were observed in repeat ablations and unscheduled arrhythmia-related visits. Marked improvement in quality of life was observed in both groups.

CONCLUSIONS: In patients with PersAF, there is no benefit in continuing previously ineffective ADT beyond the blanking period after catheter ablation. The high success rate of PVI-only might be explained by the high rate of durable isolation after optimized PVI and the early stage of PersAF (POWDER-AF2).

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03437356.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: antiarrhythmia agents ■ atrial fibrillation ■ catheter ablation ■ pulmonary veins ■ treatment outcome

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Early rhythm control through antiarrhythmic drug therapy (ADT) or catheter ablation (CA) represents the preferred treatment strategy in patients with atrial fibrillation (AF).[1] In patients with persistent AF (PersAF), CA aiming for pulmonary vein isolation (PVI) is associated with moderate clinical effectiveness

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WHAT IS KNOWN?

- Catheter ablation is a well-established treatment for persistent atrial fibrillation. However, it has shown moderate clinical effectiveness.

WHAT THE STUDY ADDS

- Comparable recurrence rates: the study findings show that continuing or discontinuing antiarrhythmic drug treatment postablation results in comparable rates of atrial tachyarrhythmia recurrence, challenging the notion that prolonged drug therapy is necessary.
- No difference in quality of life: importantly, this research reveals that quality of life significantly improves in both groups, indicating that discontinuing ineffective antiarrhythmic drug therapy does not negatively impact patients' well-being.
- Potential shift in treatment paradigm: the study's conclusion, indicating high freedom of atrial fibrillation irrespective of antiarrhythmic drug therapy, suggests a potential shift in the treatment paradigm for persistent atrial fibrillation toward a more streamlined pulmonary vein isolation-only approach.
- Early-stage persistent atrial fibrillation consideration: the study highlights that the high success rate of pulmonary vein isolation-only may be attributed to the early stage of persistent atrial fibrillation, shedding light on the importance of tailoring treatments based on the disease's progression.

Nonstandard Abbreviations and Acronyms

ADT	antiarrhythmic drug therapy
AF	atrial fibrillation
ATA	atrial tachyarrhythmia
CA	catheter ablation
LA	left atrial
PersAF	persistent atrial fibrillation
PVI	pulmonary vein isolation
QOL	quality of life

with most studies reporting a 50%-to-60% single-procedure freedom from atrial tachyarrhythmia (ATA) at 1 year.[2–9] PVI-only remains the preferred CA strategy given the lack of evidence that adjunctive ablation improves outcome.[3–9]

Continuation of previously ineffective ADT is a widely applied and intuitive approach to improve clinical outcomes after CA.[10,11] A study in paroxysmal patients with AF showed that ADT improved outcome after PVI[12] with efficacy of previously failing ADT attributed to suppression of slow conduction in the case of pulmonary vein reconnection[13] or suppression of residual nonpulmonary vein ectopy.

In the present multicenter study, we evaluated the incremental benefit of continuing previously ineffective ADT after PVI for PersAF, considered a substrate-mediated rather than trigger-driven arrhythmia.[14] We opted for a strategy aiming to deliver stable, contiguous, and optimized radiofrequency applications encircling the veins (CLOSE). Prior work from our group together with European and US multicenter studies in paroxysmal AF has demonstrated that this strategy is associated with excellent freedom from ATA[15–19] and durable pulmonary vein isolation.[20–22] To better understand which PersAF patients may benefit from PVI-only, we prospectively collected various parameters to stage the severity of PersAF.[8]

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

This was a multicenter, prospective, randomized, controlled, open-label trial. The study was investigator initiated in the St Jan Hospital (Bruges, Belgium) and conducted in 9 centers across 5 European countries.

Patients planned for first-time ablation of PersAF (defined as any prior episode ≥7 days)[8] were locally screened for inclusion. Inclusion criteria were symptomatic PersAF resistant to ongoing or prior ADT (failed class IC or III ADT) and at least 1 episode of PersAF in the last year. Exclusion criteria included, but were not limited to, unwillingness or unsuitability to restart or continue ADT, any prior AF episode lasting ≥12 months, any recurrence of AF <3 days after cardioversion, left atrial (LA) size>50 mm, the presence of advanced structural heart disease, life expectancy<12 months, or any other contraindication for CA.

The trial was conducted in accordance with the Helsinki Declaration, was approved by the respective Ethics Committees and National Competent Authorities, and was registered with ClinicalTrials.gov and the EU Clinical Trials Register before study commencement (ClinicalTrials.gov identifier: NCT03437356; EudraCT number: 2018-002103-33). Written informed consent was obtained from all participants before inclusion. Enrollment was completed on May 31, 2021, and follow-up was finalized on May 30, 2022.

Randomization, Ablation, and Study Treatment

At the time of procedural planning, enrolled patients were randomly assigned (block randomization with center stratification) to continue (ADT ON group) or discontinue previously ineffective ADT (ADT OFF group) after the 3-month blanking period up to 1 year after ablation. In the ADT ON group, ADT was continued after verifying for correct dosage according to the European Society of Cardiology guidelines on the treatment of AF.[8] If not already the case, β-blocking agents were added to Class 1C ADT. In the case of preprocedural use of amiodarone, ADT was switched to conventional class 1C or sotalol. In the ADT OFF group, all antiarrhythmic medications were

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discontinued after the 3-month blanking period with the exception of β-blocking agents if these were given for other indications (eg, hypertension, ischemic heart disease).

All patients underwent CLOSE-guided PVI-only adhering to strict ablation index (>400 at the posterior wall, >300 in the setting of esophageal temperature rise >38.5 °C, and >550 at the anterior wall) and intertag distance <6 mm criteria.[15] Use of anesthesia and ultrasound for groin or transseptal puncture were at the discretion of the operator. A contact-force sensing catheter (Thermocool ST, Biosense, Inc.) and a three-dimensional mapping system (CARTO, Biosense, Inc.) were used in all patients. LA, high-density (>300 points) voltage mapping was performed in sinus rhythm before or after PVI (patients in AF were cardioverted). Irrigated radio frequency was applied using 35 to 45 W in the power-controlled mode. The end point of the procedure was the isolation of the pulmonary veins (confirmed during sinus rhythm with a circular mapping catheter and pacing maneuvers if required). Cavo-tricuspid isthmus ablation was performed in patients with documented typical atrial flutter. Patients were discharged from the hospital the day after the CA procedure, and oral anticoagulation was continued for at least 3 months. Cardioversions were allowed during the blanking period.

Patient Follow-Up

Study visits were scheduled before randomization and at 3, 6, and 12 months after CA. Each visit consisted of a detailed history, a physical examination, a 12-lead electrocardiography, and confirmation of ADT compliance and dosage. Holter monitoring was performed at 6- (24 hours) and 12-month visits (48 hours up to 7 days according to the standard of care in each center). At each visit, the patients completed questionnaires about quality of life (QOL, Short Form 36 Health Survey, and AF Symptom Checklist). Patients were encouraged to register all arrhythmia-related symptoms and have an electrocardiography taken during symptoms. In the case of a documented recurrence, a repeat ablation was recommended.

Primary and Secondary Outcomes

The prespecified primary end point of the trial was any documented ATA (AF, atrial flutter, or atrial tachycardia) lasting >30 seconds between 3 and 12 months of follow-up. Secondary end points included primary adverse events, the number of repeat ablations, and the number of unscheduled arrhythmia-related health care provider visits. Additional secondary end points included the impact on QOL and predictors of recurrence in the overall population. For the latter purpose, we collected prespecified procedural and patient characteristics with emphasis on structural and temporal parameters for better phenotyping PersAF (LA diameter, presence, and area of low-voltage zone [>1 cm^2, <0.5 mV], longest continuous AF episode, history of paroxysmal AF, time from first diagnosis to CA, the number of cardioversions, and rhythm at the time of the procedure).

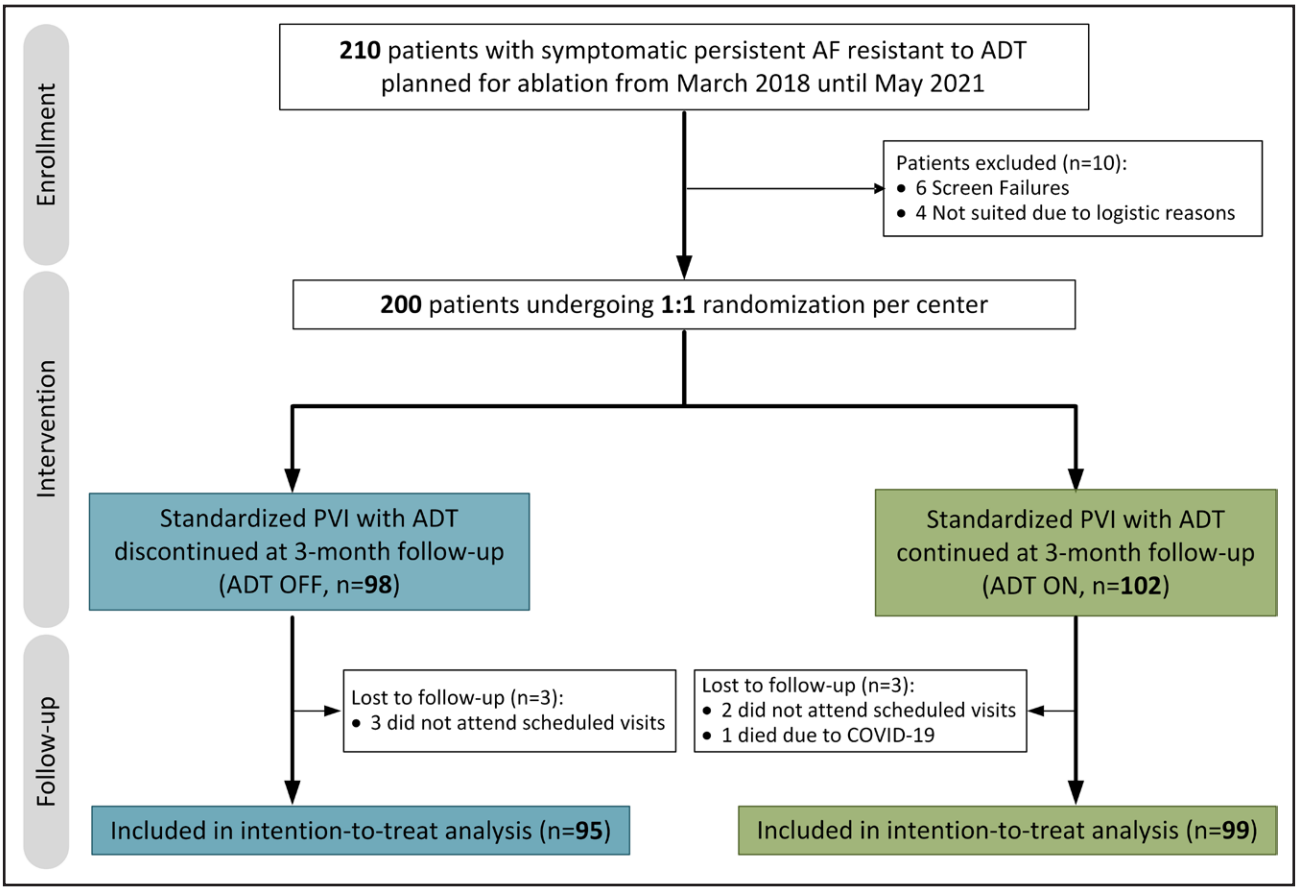

Figure 1. Consort flowchart.
ADT indicates antiarrhythmic drug therapy; AF, atrial fibrillation; and PVI, pulmonary vein isolation.

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Data Collection and Verification

Local personnel (study nurses or investigators) from each site were responsible for recording all data from the study on paper case report forms and uploading the case report forms to the study website. All case report forms underwent manual inspection for data integrity. In the case of inconsistencies or missing data, the relevant center was contacted with a request for verification or addition of data. Patient safety was monitored by the local investigator at each site. Any adverse event and serious adverse event required notification of the principal investigating center within 7 days and within 24 hours, respectively.

Sample Size Calculation

A minimum of 186 patients (80% power and alpha 0.05) needed to be randomized in the study (93 in each arm) to determine an absolute reduction of 20% in the anticipated recurrence of ATA of 50% after a single PVI procedure (ADT OFF). Given a projected dropout rate of 5% to 10%, up to 200 patients were anticipated for inclusion.

Statistics

Continuous data are reported as means (±SD) or medians (interquartile range). The Shapiro-Wilk test was used to test for normality. Accordingly, comparisons between groups were performed using the Student *t* test or Mann-Whitney *U* test where appropriate. Categorical data were reported as proportions or percentages, and comparisons between groups were performed using the χ^2 test or the Fisher exact test. The Kaplan-Meier survival curves with Log-rank statistic test were used to compare time to the first documented ATA recurrence (lost to follow-up and death were censored). A Cox regression model was used to assess possible predictors of recurrence and interaction with ADT and presented in a Forest plot. Log-minus-log plots were used to evaluate the proportional hazards assumption. Clinical characteristics were assessed to predict recurrence in Cox proportional hazard analysis, and clinically relevant variables with *P* value<0.2 in univariate analysis were included in the multivariable analysis. QOL (physical and mental components) was based on SF-36v2 and scored using factor scoring coefficients from Farivar et al.[23] The symptom frequency score and the symptom severity score based on the AF Symptom Checklist were scored according to the guideline provided by Bubien et al.[24] Except for the Kaplan-Meier survival curve and the Cox regression model, the analysis was performed in accordance to the modified intention-to-treat principle excluding patients who were lost to follow-up or died before completing the 12-month follow-up visit. Statistical tests were 2-tailed, and $P \leq 0.05$ was considered statistically significant. Analyses were conducted using SPSS, version 28.0 (IBM Corporation, Armonk, NY).

RESULTS

Study Population

After initial screening by research staff at 9 participating hospitals, 200 patients were randomized 1:1 to PVI with ADT discontinued at 3 months (98 patients in the ADT OFF group) and PVI with ADT continued

Table 1. Clinical, AF, and Procedural Characteristics

Clinical characteristics	Overall (n=200)	ADT OFF (n=98)	ADT ON (n=102)	*P* value
Persistent AF, n (%)	200 (100)	98 (100)	102 (100)	1.000
EHRA score; median, IQR	2 (2–3)	2 (2–3)	2 (2–3)	0.983
Age, y; mean±SD	65±9	65±9	65±8	0.936
Male sex, n (%)	139 (70)	66 (67)	73 (72)	0.517
BMI, kg/m²; mean±SD	28.0±3.8	27.6±3.6	28.3±3.9	0.188
Left atrial diameter, mm; median, IQR	43 (40–46)	43 (40–46)	43 (40–47)	0.729
Structural heart disease, n (%)	28 (14)	12 (12)	16 (16)	0.483
Congestive heart failure, n (%)	31 (16)	15 (15)	16 (16)	0.941
Hypertension, n (%)	125 (63)	59 (60)	66 (65)	0.511
Diabetes, n (%)	20 (10)	12 (12)	8 (8)	0.300
Stroke/TIA, n (%)	19 (10)	9 (9)	10 (10)	0.881
CHA2DS2-VASc score; median, IQR	2 (1–3)	2 (1–3)	2 (1–3)	0.643
Time from initial diagnosis to CA, mo; median, IQR	24 (7–60)	21 (7–56)	24 (8–72)	0.397
Longest AF episode, d; median, IQR*	30 (10–90)	29 (10–90)	30 (11–90)	0.832
Prior paroxysmal AF, n (%)	101 (51)	51 (52)	50 (49)	0.669
Longest AF episode in last year before CA, n (%)	174 (87)	86 (88)	93 (91)	0.430
Prior cardioversion, n (%)	166 (83)	81 (83)	85 (83)	0.898
Number of cardioversions; median, IQR	1 (1–2)	1 (1–2)	2 (1–2)	0.299
Patients with 1 ECV, n (%)	76 (38)	42 (43)	34 (33)	0.165
Patients with ≥2 ECVs, n (%)	91 (46)	39 (40)	52 (51)	0.112
Sinus rhythm at the time of CA, n (%)	106 (53)	51 (52)	55 (54)	0.790
General anesthesia during procedure, n (%)	168 (84)	83 (85)	85 (83)	0.793
Presence of low-voltage zone, n (%)†	58/183 (32)	34/89 (38)	29/94 (26)	0.296
Surface of low-voltage zone, %; median, IQR	18 (8–43)	20 (8–40)	18 (9–49)	0.190
Procedural time, min; median, IQR	111 (88–130)	111 (87–129)	110 (90–132)	0.663
Primary adverse events, n (%)	6 (3)	3 (3)	3 (3)	1.000
Vascular, n (%)	5 (3)	3 (3)	2 (2)	
Tamponade, n (%)	1 (1)	0 (0)	1 (1)	

ADT indicates antiarrhythmic drug therapy; AF, atrial fibrillation; BMI, body mass index; CA, catheter ablation; ECV, electric cardioversion; EHRA, European Heart Rhythm Association; IQR, interquartile range; LVZ, low-voltage zone; and TIA, transient ischemic attack.

*Data on the longest AF episode was not available in 19 patients and could not be retrieved.

†Voltage mapping was performed in 183 patients. Of 58 patients with LVZ, the area of LVZ was measured in 42 patients.

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at 3 months (102 patients in the ADT ON group; Figure 1). In each group, 3 patients were lost to follow-up (5 patients did not attend their scheduled visits and 1 patient died due to COVID-19). Patients were followed up for a median of 370 (interquartile range, 363–381) days after the CA procedure. Endoscopic investigation in 59 (30%) patients 2 to 3 weeks after CA revealed no ulceration.

Clinical, AF, and Procedural Parameters

Results are depicted in Table 1. All patients had symptomatic PersAF (median European Heart Rhythm Association score of 2) with a mean age of 65 years, a median LA diameter of 43 mm, and a median $CHADS_2VAS_c$ of 2 with 38% having a score of 3 or more. The median time from initial diagnosis of AF to CA was 30 months. The longest episode of PersAF was 30 (10–90) days and occurred in the year preceding CA in 87% of patients. In 51% of patients, there was a previous history of paroxysmal AF. The median number of prior electric cardioversions was 1. At the time of CA, 54% of patients presented with sinus rhythm. Mapping (performed in 183 patients) revealed a low-voltage zone in 58 cases (32%). In those latter patients, the median low-voltage zone area was 18% (8%–43%). All the above parameters were similar between the ADT OFF and ON groups (Table 1). Subtypes of AF as a function of rhythm at the time of the procedure and the number of cardioversions are graphically depicted in Figure 2.

ADT at Randomization and During Follow-Up

The ADT regimen before CA, during the 3-month blanking period, and at 6- and 12-month postablation is illustrated in Figure 3. At baseline, the proportion of patients taking Class 1C agents, sotalol, or amiodarone was evenly distributed and comparable between the ADT OFF and ON groups. During the blanking period, ADT was continued as a standard of care with a shift from amiodarone to predominantly Class 1C agents in both groups. At 6 and 12 months, 89% and 88% of patients were not taking Class 1C/3 drugs in the ADT OFF group. Conversely, in the ADT ON group, at 6 and 12 months, 87% and 87% of the patients were taking class 1C/3 ADT. Overall, 13 (12.8%) patients assigned to the ADT ON group discontinued ADT due to noncompliance (n=4) or adverse events (fatigue, n=3; tachycardia, n=2; exercise intolerance, n=1; and other adverse events suspected by patients, n=3). In the ADT OFF group, 12 (12.6%) patients restarted ADT due to recurrence after the blanking period. The median daily dosage of flecainide, propafenone, and sotalol at the 12-month follow-up was 150 (100–200), 450 (450–600), and 160 (80–160) mg, respectively. β-blocking drugs were used in 40 of 98 (40.8%) and 42 of 102

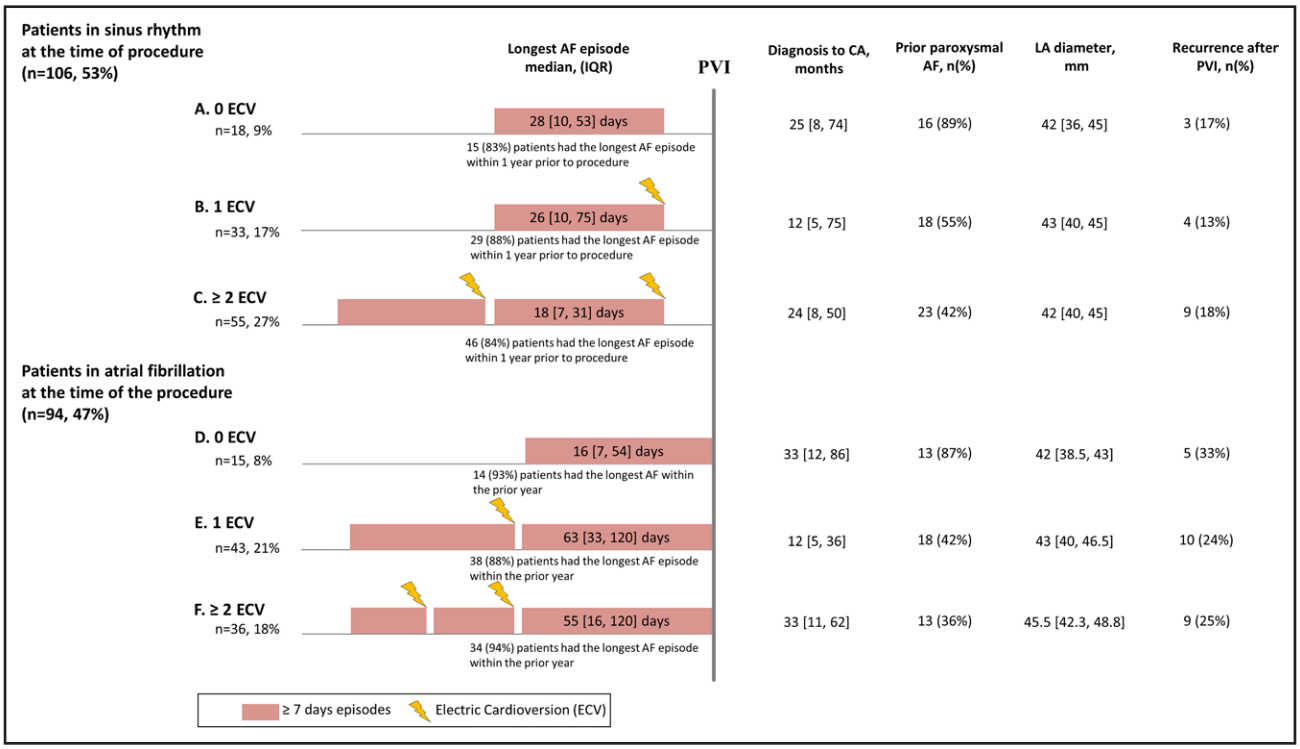

Figure 2. Subtypes of persistent atrial fibrillation (AF) according to rhythm at the time of ablation and number of prior cardioversions.
CA indicates catheter ablation; ECV, electric cardioversion; IQR, interquartile range; LA, left atrial; and PVI, pulmonary vein isolation.

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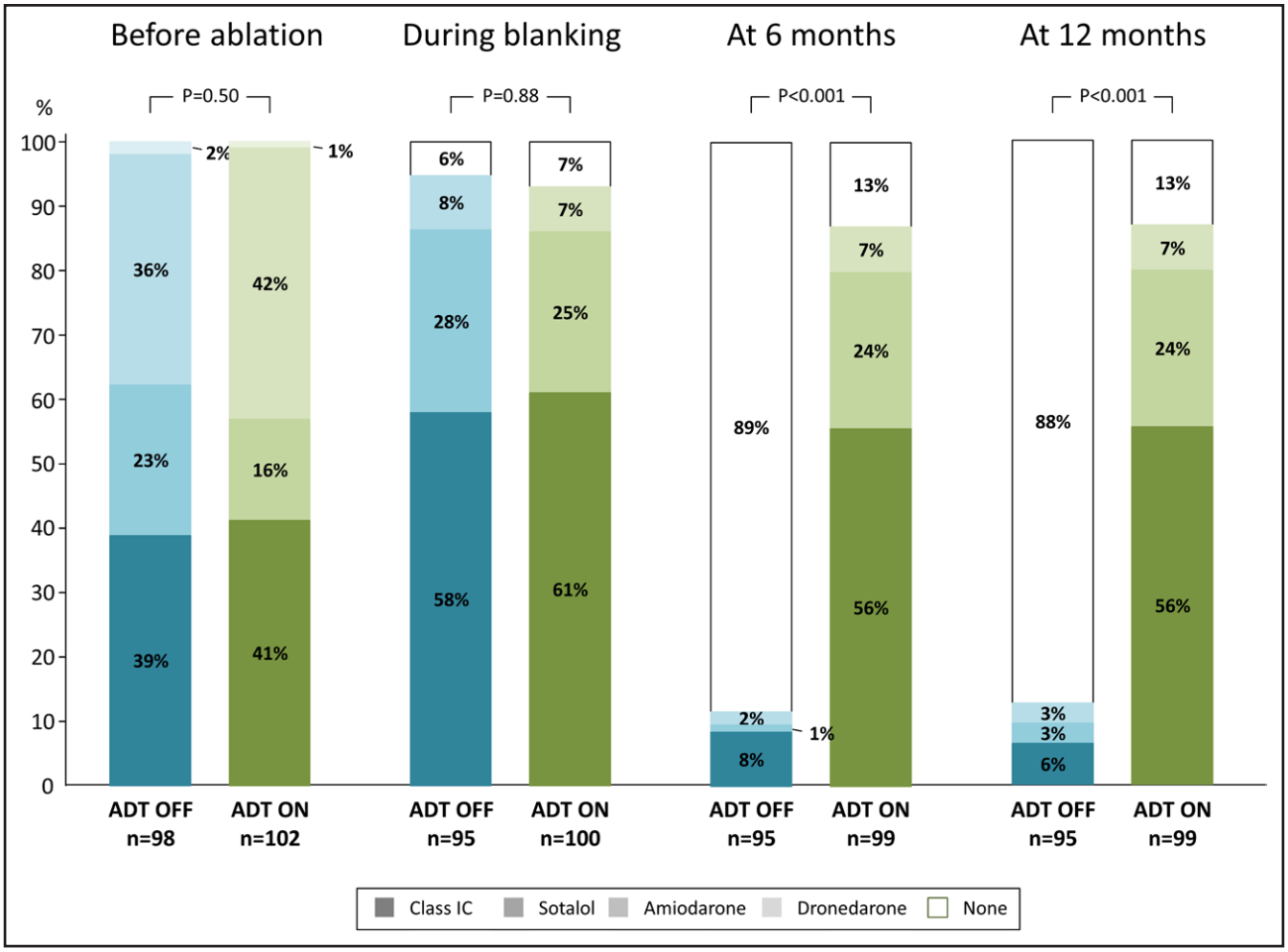

Figure 3. Antiarrhythmic drug therapy (ADT) before ablation and during follow-up.

(41.2%) patients in the ADT OFF and ADT ON groups, respectively.

Primary Outcome

In total, 194 patients completed the last patient visit and were available for analysis of the primary end point. Throughout the 9-month follow-up, 19 of 95 (20%) patients in the ADT OFF group and 21 of 99 (21.2%) patients in the ADT ON group had a documented ATA recurrence (P=0.835). The time to the first documented incidence of ATA was plotted using the Kaplan-Meier method (Figure 4). The observed neutral effect of ADT after CA was consistent among all subgroups (Figure 5). Although not statistically significant (P=0.06), sex represented the parameter displaying the greatest disparity in outcome, among all variables.

Repeat Ablation, Unscheduled Health Care Visits, and QOL

There was no difference in repeat ablations (11.5% versus 6%; hazard ratio, 0.46 [95% CI, 0.17–1.25]; P=0.127) and unscheduled visits (18.8% versus 14%; hazard ratio, 0.74 [95% CI, 0.37–1.49]; P=0.399) in ADT OFF versus ADT ON groups. We found no statistically significant differences in physical or mental component scores, symptom frequency scores, and symptom severity scores between the ADT OFF and ADT ON groups at baseline, at 6 months, or 12 months (Figure 6). In both groups, QOL after PVI improved significantly after CA (P<0.001).

Predictors of Recurrence After CA

In Table 2, we compared parameters between patients without (n=154) versus with (n=40) recurrence after CA. In univariate analysis (Mann-Whitney U test and χ^2 test), only stroke was found to predict outcome after CA. In a multivariable predictive model, including variables with a P value of <0.2 from the univariable analysis, no parameter was found to predict outcome after CA. Parameters aiming to stage PersAF were not predictive of recurrence except for a tendency toward a worse outcome when patients presented in AF at the time of ablation (26% recurrence versus 15% recurrence in patients with sinus rhythm, P=0.086, Figure 2).

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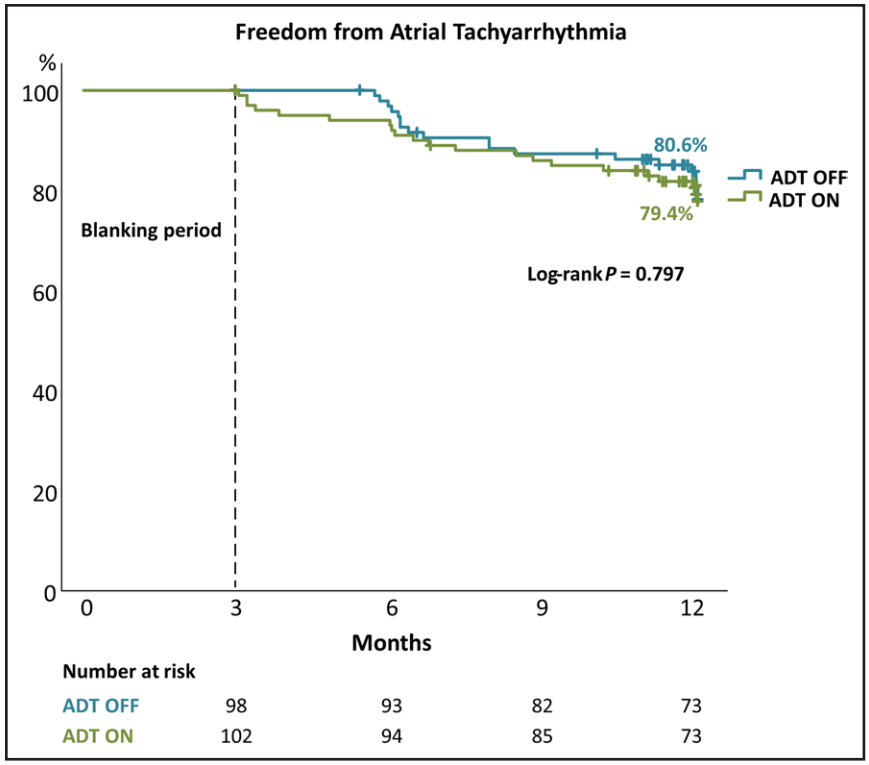

Figure 4. Primary end point of recurrence.
ADT indicates antiarrhythmic drug therapy.

DISCUSSION

Main Findings

In patients with early-stage PersAF, there is no benefit in continuing previously ineffective ADT beyond the blanking period after CA.

Irrespective of ADT, optimized PVI aiming for durable isolation is associated with high rates of freedom from recurrent ATA, marked improvement in QOL, and a low number of repeat ablations.

Among a wide set of parameters aiming to stage the severity of PersAF, only presenting rhythm at baseline was associated with the outcome.

The Effect of Continued ADT on Outcome After CA Beyond the Blanking Period

In real-world clinical practice, ADT is often continued or restarted beyond the blanking period after CA, out of fear of reexperiencing AF recurrence, actual AF recurrence, or the presence of atrial extrasystoles.(10-11) This intuitive approach is supported by observational studies reporting better outcomes after CA when ADT is continued or recommenced[10,11,25] and by the randomized, controlled POWDER AF study, which demonstrated superior outcomes with ADT after CA of paroxysmal AF.[12]

In the present contemporary cohort of PersAF patients, we observed no benefit of continuing previously ineffective ADT (class 1C agents and sotalol) after CA beyond the blanking period. We confirmed that ADT is safe and well tolerated when appropriately dosed[8] but failed to demonstrate any impact on freedom from ATA, QOL, or likelihood of repeat ablation. Several potential explanations may be put forward to explain the discrepancy with prior studies. First, PersAF in contrast to paroxysmal AF may represent a predominantly substrate-mediated rather than trigger-driven arrhythmia, thus rendering it less sensitive to the trigger-suppressing effect of membrane-active ADT. Second, one can postulate that the superior durability of lesion sets using contiguous lesions mitigates the previously described beneficial effect of ADT on residual gap conduction.[13] Third, it has been shown that the Class III effect of sotalol is reduced in remodeled atria.[26] Fourth, it is possible that part of the described benefit of ADT in prior studies may be attributable to the use of amiodarone in ≈20% of patients.[11,25] Finally, the observed difference might be due to the difference in the study designs. In the current study, patients were randomized preprocedure, while, in POWDER AF 1, only patients who were free from ATA (and taking ADT during the blanking period) were randomized. As such, this may have led to the inclusion of more ADT-sensitive patients.

Clinical Effectiveness of PVI-Only in PersAF

In the present study, single-procedure freedom from ATA off ADT nears 80%, comparable to success rates in contemporary studies using intermittent Holter monitoring after PVI in paroxysmal AF patients.[15,17–19] Traditionally, PersAF patients have represented a more challenging cohort, however, with more modest success rates (in the

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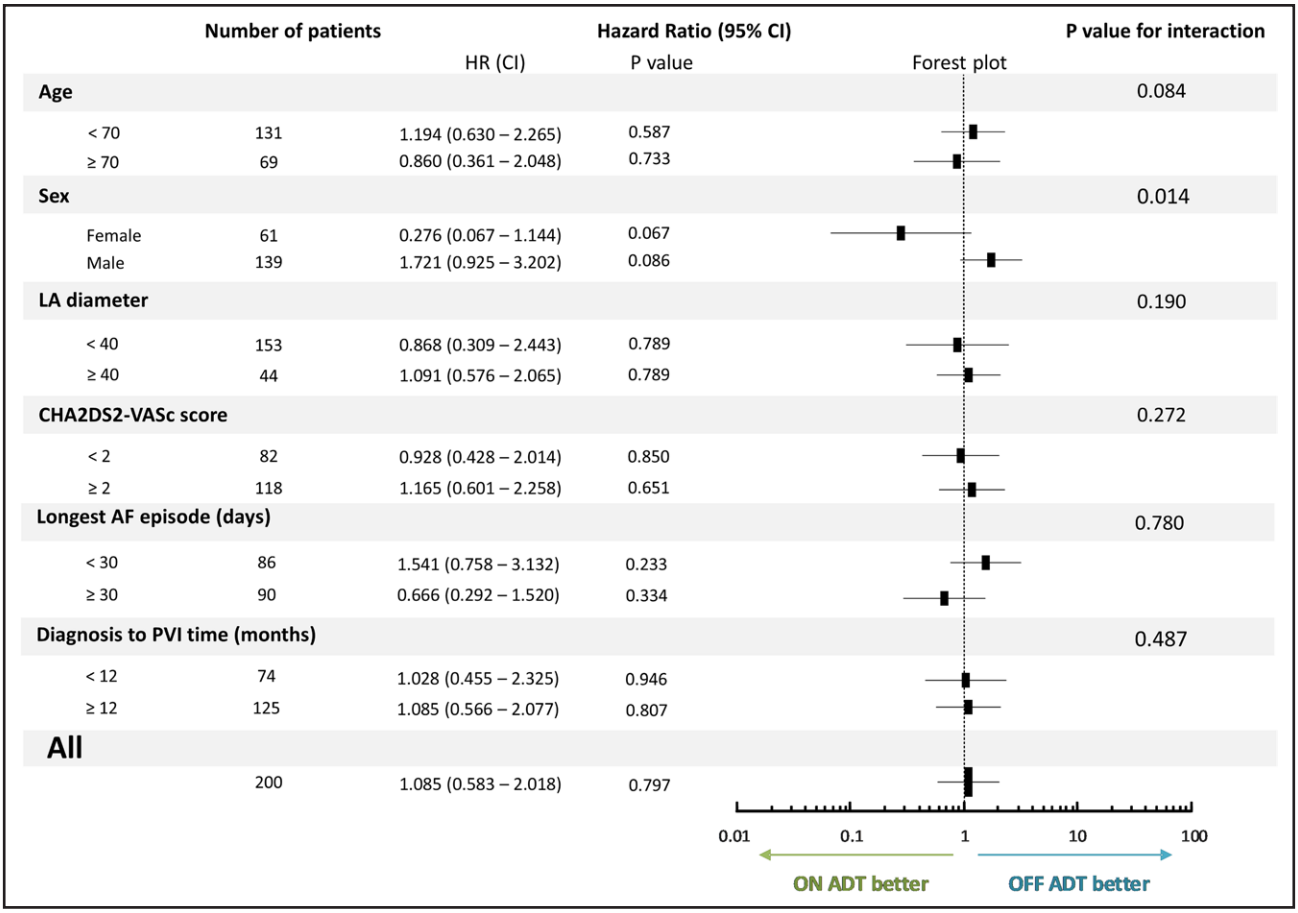

Figure 5. Forest plot displaying subgroup analysis of the primary end point.
ADT indicates antiarrhythmic drug therapy; AF, atrial fibrillation; HR, hazard ratio; LA, left atrial; and PVI, pulmonary vein isolation.

range of 50%–67% at 1 year) demonstrated post-PVI alone in large-scale trials.[2–7]

It is tempting to speculate that the high success rate observed in the present study is due to the increased likelihood of durable isolation after CLOSE-guided ablation, as demonstrated in paroxysmal AF[18,20–22] and PersAF patients.[27] Caution is required, however, when comparing the efficacy of CA in PersAF patients between trials. Despite a similar definition of PersAF (>7 days) and a similar LA diameter (43 mm), participants in POWDER AF2 were likely referred early in the course of the disease (due to symptoms and in line with EASTAFNET4).[1] Early AF is evidenced by a relatively short diagnosis-to-ablation time and duration of the longest continuous AF episode (29–30 days), as well as the presence of sinus rhythm in half of the patients at the time of the procedure. In comparison, patients in STAR AF2 were predominantly in continuous AF for >6 months preprocedure with 79% of patients presenting in AF on the day of the procedure.[3] The relatively limited incidence (32%) and area of low-voltage zone (18%) seen in this study are suggestive of limited remodeling in early-stage PersAF. In line with the results presented here, a subanalysis of the DECAAF II and STABLE-SR-II trials revealed high success rates after PVI-only in PersAF patients without evidence of atrial fibrosis (up to 84% in the absence of LA low voltage or delayed enhancement).[5,7] Patients with recurrence of AF within 3 days post-cardioversion and those with an LA diameter>50 mm were excluded. This coupled with more benign clinical characteristics including a low rate of heart failure, a body mass index in the overweight rather than obese range, and a relatively low CHA2DS2-VASc score of 2 likely enriched the patient population to one less likely to derive additional benefit from ADT after an effective and durable PVI procedure.

Clinical Implications

Although ADT has a beneficial effect when taken in the early blanking period,[28] the findings of POWDER AF2 do not support a strategy of continued ADT therapy postablation in the setting of early PersAF. They also suggest that repeat ablation rather than restarting ADT is a more valid option to achieve early rhythm control.[1] It remains to be seen how treatment with amiodarone may affect outcomes after CA of PersAF with or without atrial remodeling. Also, it remains to be proven how continued ADT might affect the outcome in patients who had an apparent failure of

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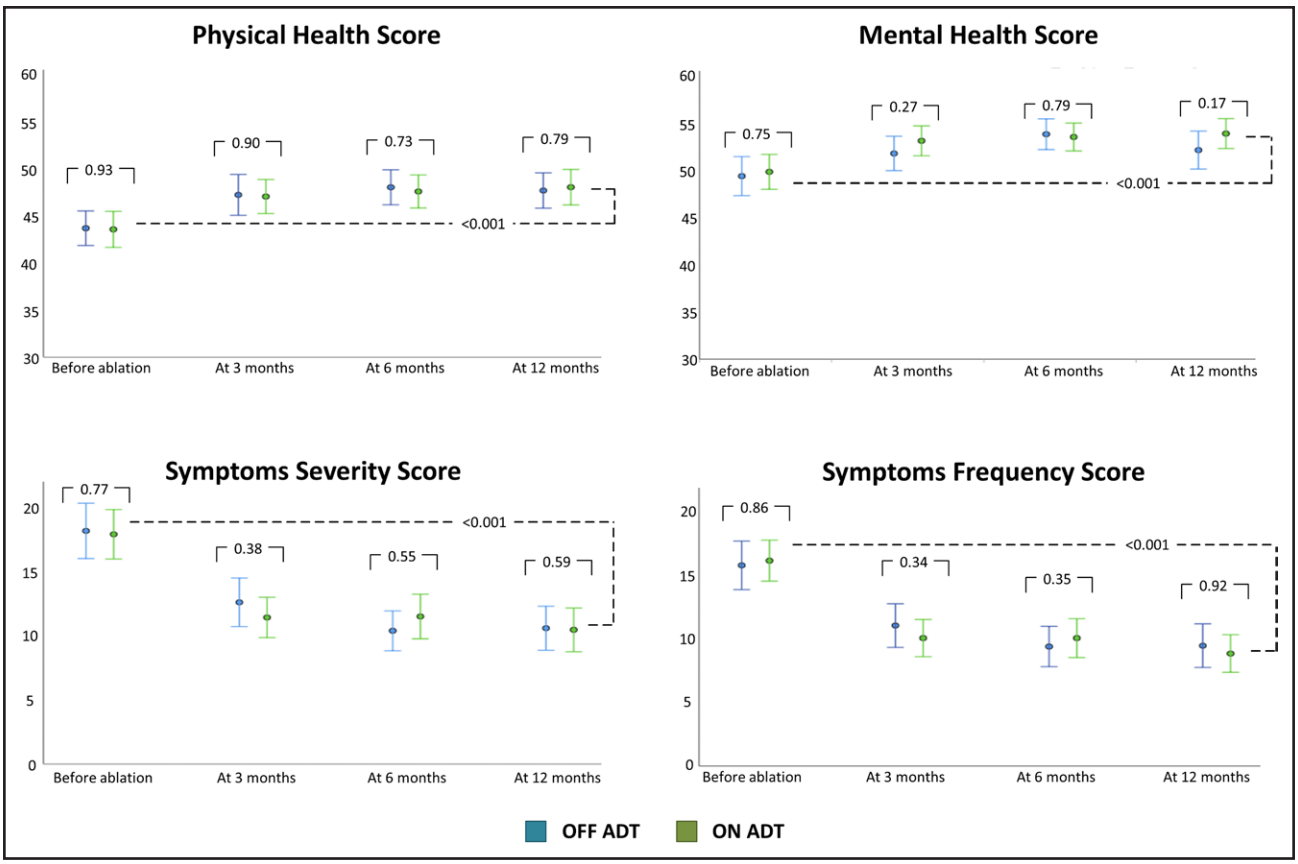

Figure 6. Impact of catheter ablation on quality of life.
ADT indicates antiarrhythmic drug therapy.

ADT before CA (according to the study protocol) but with a marked reduction of AF burden in response to ADT.

POWDER AF2 confirms that PVI is a safe, first-line therapy for early-stage PersAF, a population that is expected to grow in the setting of early detection and timely referral. This study also fuels the ongoing debate about the classification of PersAF.[8] Evidently, the traditional 7-day classification does not cover the wide range of underlying subtypes present in this heterogeneous population. These subtypes are likely to vary among studies depending on ablation protocol, procedural end points, or anticipated outcome. Parameters including the duration of continuous AF episodes, rhythm at the time of CA, and the number of prior cardioversions may correct for or identify selection bias. In this study, the presence of AF at baseline correlated with poor outcomes after CA. Further parameters to refine the classification of PersAF could include the longest duration of sinus rhythm after cardioversion, rhythm at the time of enrollment, and size of the low-voltage area.

Limitations

We are unable to provide data on the screening of persistent AF patients selected for CA, which would be helpful in the assessment of the relevance of the results in the population of persistent AF, as the collection and analysis of screening logs were not part of the study protocol due to logistic reasons. This was an open-label study. Despite meeting the sample size calculation, a type II error is still possible due to the relatively small sample size. Cardiac rhythm recordings about the primary outcome were not evaluated by an adjudication committee. As we did not perform continuous electrocardiography monitoring but rather planned 12-lead electrocardiographies, 3-day Holter monitors, and symptom-driven monitoring, it is possible that, even in patients with a history of PersAF, asymptomatic and transient recurrences were missed, likely contributing to the high success rates in comparison to other studies. Predictor analysis suffers from bias relating to unknown variables. The effect of amiodarone was not studied. Due to favorable baseline characteristics, the population of PersAF patients recruited may have been less likely to derive a benefit from ADT in addition to durable PVI. We did not specify electrocardiography characteristics of AF before antiarrhythmic therapy or CA. Determination of AF cycle length, coarse/fine AF, and f-wave amplitude, might be of additional value in the phenotyping of persistent AF. Figure 2 is a simplified way of phenotyping persistent AF based on clinical and temporal AF parameters. Other parameters such as LA anatomy, voltage, biomarkers, AF cycle length, refractory period, genetics, and stretch are needed to further

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Table 2. Predictors of Recurrence

Clinical characteristics	Overall (n=194)	No recurrence (n=154)	Recurrence (n=40)	Univariable prediction of recurrence			Multivariable prediction of recurrence		
				HR	95% CI	*P* value	HR	95% CI	*P* value
Persistent AF, n (%)	194 (100)	154 (100)	40 (100)	…	…	…			
ADT ON, n (%)	99 (51)	78 (51)	21 (53)	1.085	0.583–2.018	0.797			
EHRA; median, IQR	2 (2–3)	2 (2–3)	2 (2–3)	1.100	0.624–0.939	0.741			
Age, y; mean±SD	65±8	65±8	66±9	1.022	0.984–1.061	0.257			
Male sex, n (%)	133 (69)	104 (68)	29 (73)	1.226	0.612–2.454	0.566			
BMI, kg/m^2; mean±SD	28.0±3.8	28.2±4.0	27.2±3.3	0.942	0.865–1.025	0.164	0.945	0.857–1.042	0.258
Left atrial diameter, mm; median, IQR	43 (40–46)	43 (40–46)	43 (39–47)	0.992	0.943–1.043	0.755			
Structural heart disease, n (%)	27 (14)	19 (12)	8 (20)	1.693	0.780–3.675	0.183			
Congestive heart failure, n (%)	30 (16)	25 (16)	5 (13)	0.728	0.285–1.859	0.507			
Hypertension, n (%)	122 (63)	98 (64)	24 (60)	0.886	0.470–1.668	0.707			
Diabetes, n (%)	19 (10)	17 (11)	2 (5)	0.505	0.122–2.093	0.346			
Stroke/TIA, n (%)	19 (10)	11 (7)	8 (20)	2.410	1.110–5.231	0.026	1.845	0.752–4.528	0.181
CHA2DS2-VASc score, median (IQR)	2 (1–3)	2 (1–3)	2 (1–4)	1.153	0.957–1.388	0.134	1.106	0.901–1.358	0.337
Time from initial diagnosis to CA, mo; median, IQR	24 (7–60)	24 (7–59)	26 (9–72)	1.001	0.997–1.005	0.653			
Longest AF episode, d; median, IQR*	30 (10–90)	30 (10–90)	26 (10–75)	1.000	0.995–1.004	0.875			
Prior paroxysmal AF, n (%)	98 (51)	81 (54)	17 (43)	0.688	0.368–1.289	0.244			
Longest AF episode in last year before CA, n (%)	174 (90)	137 (89)	37 (93)	0.959	0.376–2.447	0.930			
Prior cardioversion, n (%)	160 (83)	128 (83)	32 (80)	0.844	0.389–1.832	0.668			
Number of cardioversions; median, IQR	1 (1–2)	1 (1–2)	1 (1–2)	0.984	0.793–1.221	0.882			
Patients with 1 ECV, n (%)	72 (37%)	58 (38%)	14 (35%)	0.926	0.484–1.774	0.817			
Patients with ≥2 ECVs, n (%)	87 (45%)	69 (45%)	18 (45%)	0.968	0.519–1.804	0.918			
Sinus rhythm at the time of CA, n (%)	100 (52)	84 (55)	16 (40)	0.563	0.299–1.060	0.075			
General anesthesia during procedure, n (%)	163 (84)	130 (84)	33 (83)	0.932	0.412–2.109	0.866			
Presence of low-voltage zone, n (%)	57/177 (32)	43/142 (30)	14/35 (40)	1.618	0.822–3.183	0.164	0.599	0.303–1.184	0.140
Surface of low-voltage zone, %	18 (8–43)	12 (8–39)	31 (11–53)	1.013	0.989–1.037	0.295			
Procedural time, min; median, IQR	110 (88–130)	110 (86–128)	112 (90–144)	1.002	0.992–1.012	0.684			
Primary adverse events, n (%)	6 (3)	5 (3)	1 (3)	0.833	0.114–6.063	0.857			

ADT indicates antiarrhythmic drug therapy; AF, atrial fibrillation; BMI, body mass index; CA, catheter ablation; ECV, electric cardioversion; EHRA, European Heart Rhythm Association; HR, hazard ratio; IQR, interquartile range; and TIA, transient ischemic attack.

*Data on the longest AF episode was not available in 19 patients and could not be retrieved.

improve the phenotyping of persistent AF. Finally, we did not collect information about the type of recurrence of ATA (duration and paroxysmal versus persistent).

Conclusions

The use of previously ineffective ADT beyond the blanking period did not improve outcomes in patients with persistent AF undergoing first-time CA. In the patients studied with early-stage persistent AF, high success rates were achievable with a strategy of PVI-only, focused on optimized, contiguous lesion sets.

ARTICLE INFORMATION

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Disclosures

None.

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