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Pulsed Field vs Conventional Thermal Ablation for Paroxysmal Atrial Fibrillation

Recurrent Atrial Arrhythmia Burden

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ABSTRACT

BACKGROUND The ADVENT randomized trial revealed no significant difference in 1-year freedom from atrial arrhythmias (AA) between thermal (radiofrequency/cryoballoon) and pulsed field ablation (PFA). However, recent studies indicate that the postablation AA burden is a better predictor of clinical outcomes than the dichotomous endpoint of 30-second AA recurrence.

OBJECTIVES The goal of this study was to determine: 1) the impact of postablation AA burden on outcomes; and 2) the effect of ablation modality on AA burden.

METHODS In ADVENT, symptomatic drug-refractory patients with paroxysmal atrial fibrillation underwent PFA or thermal ablation. Postablation transtelephonic electrocardiogram monitor recordings were collected weekly or for symptoms, and 72-hour Holters were at 6 and 12 months. AA burden was calculated from percentage AA on Holters and transtelephonic electrocardiogram monitors. Quality-of-life assessments were at baseline and 12 months.

RESULTS From 593 randomized patients (299 PFA, 294 thermal), using aggregate PFA/thermal data, an AA burden exceeding 0.1% was associated with a significantly reduced quality of life and an increase in clinical interventions: redo ablation, cardioversion, and hospitalization. There were more patients with residual AA burden $<$0.1% with PFA than thermal ablation (OR: 1.5; 95% CI: 1.0-2.3; $P = 0.04$). Evaluation of outcomes by baseline demographics revealed that patients with prior failed class I/III antiarrhythmic drugs had less residual AA burden after PFA compared to thermal ablation (OR: 2.5; 95% CI: 1.4-4.3; $P = 0.002$); patients receiving only class II/IV antiarrhythmic drugs pre-ablation had no difference in AA burden between ablation groups.

CONCLUSIONS Compared with thermal ablation, PFA more often resulted in an AA burden less than the clinically significant threshold of 0.1% burden. (The FARAPULSE ADVENT PIVOTAL Trial PFA System vs SOC Ablation for Paroxysmal Atrial Fibrillation [ADVENT]; NCT04612244) (J Am Coll Cardiol 2024;84:61-74) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AA = atrial arrhythmia

AAD = antiarrhythmic drug

AF = atrial fibrillation

AFEQT = Atrial Fibrillation Effect on QualiTy-of-Life

PFA = pulsed field ablation

PV = pulmonary vein

PVI = pulmonary vein isolation

TTM = transtelephonic electrocardiogram monitor

Over the past 2.5 decades, catheter ablation for atrial fibrillation (AF) has typically been performed using either radiofrequency or cryothermal energy, which heats or freezes tissue, respectively, to electrically isolate the pulmonary veins (PVs) that harbor the triggers for AF.[1] However, tissue-indiscriminate thermal effects can extend beyond the target myocardium to affect adjacent nontarget tissues. This can result in infrequent, but potentially serious, complications such as phrenic nerve injury resulting in diaphragmatic paralysis, PV stenosis, or most dangerously, damage to the esophagus, which can result in atrioesophageal fistula culminating in death.[1,2]

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Unlike thermal ablation, pulsed field ablation (PFA) is a largely nonthermal energy modality using microsecond-scale, high-voltage electrical fields to irreversibly electroporate tissue.[3,4] Preclinical and clinical studies have demonstrated that PFA destabilizes cell membranes to cause cellular necrosis, with sufficient ablative tissue preferentiality such that myocardial tissue is ablated with limited effect on adjacent structures such as the esophagus, phrenic nerve, and PV tissue.[5-15] Nonrandomized single-arm clinical studies demonstrated favorable safety and effectiveness of PFA for AF ablation.[16-27] Most recently, the ADVENT (FARAPULSE ADVENT PIVOTAL Trial PFA System vs SOC Ablation for Paroxysmal Atrial Fibrillation; NCT04612244) trial randomized 607 patients with drug-resistant paroxysmal AF to either PFA using a pentaspline catheter or conventional thermal ablation using either point-by-point radiofrequency or cryoballoon ablation catheters.[28,29] This trial demonstrated that, relative to thermal ablation, PFA was superior in efficiency and noninferior for safety. PFA also met the criterion for noninferiority for treatment success, primarily driven by the "traditional" endpoint of 1-year freedom from atrial arrhythmia (AA) recurrence lasting at least 30 seconds over 1-year follow-up; however, the criterion for superiority of effectiveness was not met.[29]

On the other hand, recent studies in patients with cardiac implanted electronic devices (such as pacemakers and defibrillators) have demonstrated that AA burden is a good predictor of clinically meaningful outcomes.[30,31] Indeed, studies have also demonstrated that postablation AA burden is a better indicator of improvements in patient quality of life and clinical outcomes—including reduced health care utilization—than the dichotomous endpoint of 30-second AA recurrence.[32,33] Accordingly, in this secondary analysis of the ADVENT trial, we studied: 1) the impact of postablation AA burden on outcomes including quality-of-life and health care utilization—redo ablation, electrical cardioversion, or hospitalization; and 2) the effect of ablation modality on postablation AA burden.

METHODS

The ADVENT trial was a prospective, multicenter, randomized, blinded, noninferiority safety and effectiveness pivotal study comparing a novel pentaspline PFA catheter with standard-of-care ablation using either force-sensing radiofrequency ablation or cryoballoon ablation for the treatment of paroxysmal AF.[28,29] This study was performed in accordance with the U.S. Code of Federal Regulations, Good Clinical Practice, and ethical principles consistent with the Declaration of Helsinki. Institutional Review Board approval was obtained at all investigational sites. Informed written consent was obtained from all trial participants before enrollment and randomization.

ABLATION PROCEDURE. Detailed ablation procedures have been published previously.[28,29] Briefly, patients with symptomatic paroxysmal AF resistant or intolerant to at least 1 antiarrhythmic drug (AAD) (class I-IV) were enrolled. Patients were randomized 1:1 to PFA or thermal ablation to electrically isolate the PVs (**Central Illustration**). Each center used *either* radiofrequency or cryoballoon ablation, but not both, as their thermal control arm. Anticoagulation was administered based on standard of care. Sedation or general anesthesia was used according to institutional protocol. Intravenous heparin was administered before or immediately after transseptal puncture, with procedural activated clotting times maintained at a minimum of 300 seconds.

PULSED FIELD ABLATION. Subjects randomized to PFA underwent pulmonary vein isolation (PVI) using

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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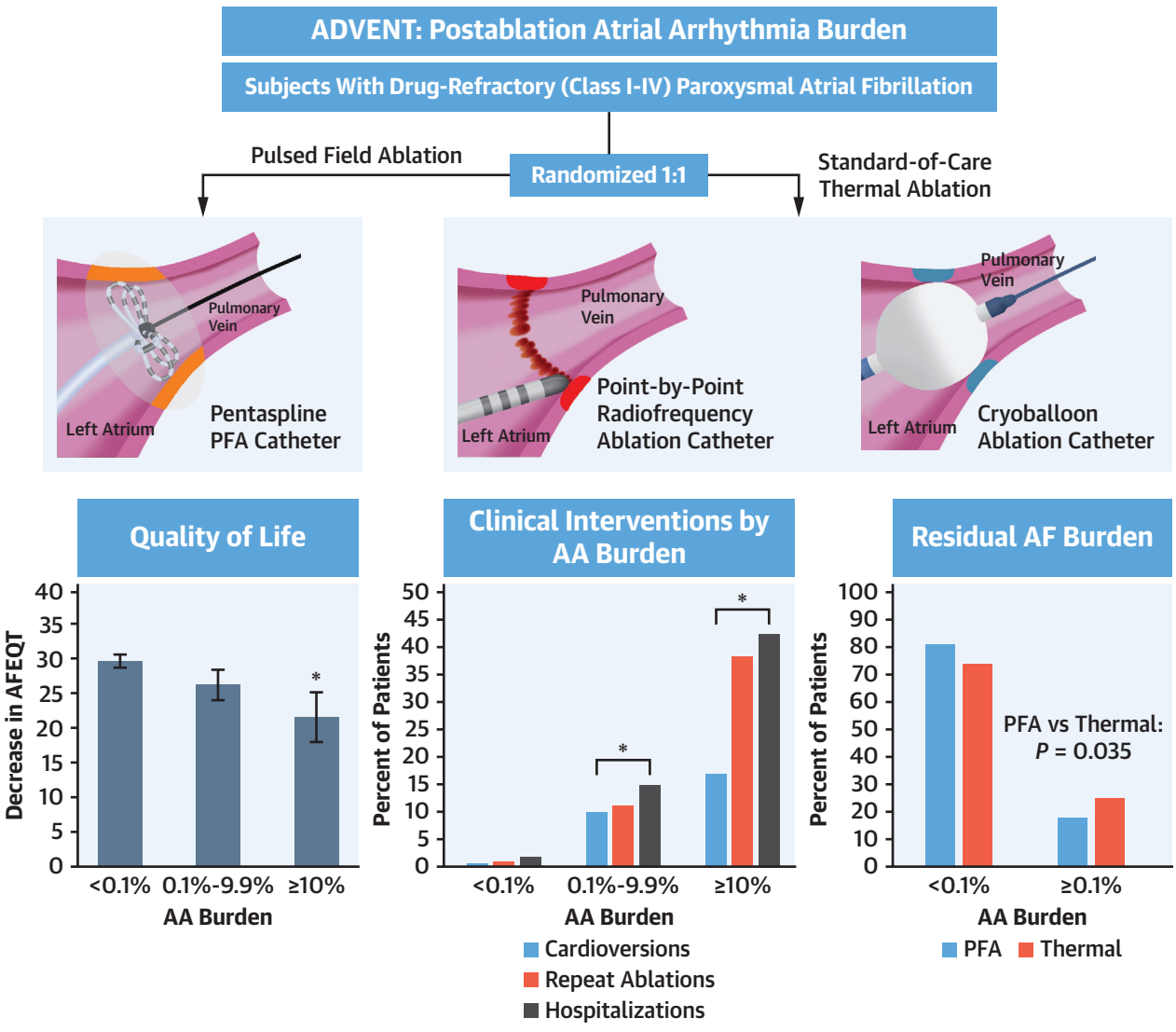
CENTRAL ILLUSTRATION **Postablation Atrial Arrhythmia Burden and Outcomes in the FARAPULSE ADVENT PIVOTAL Trial PFA System vs SOC Ablation for Paroxysmal Atrial Fibrillation**



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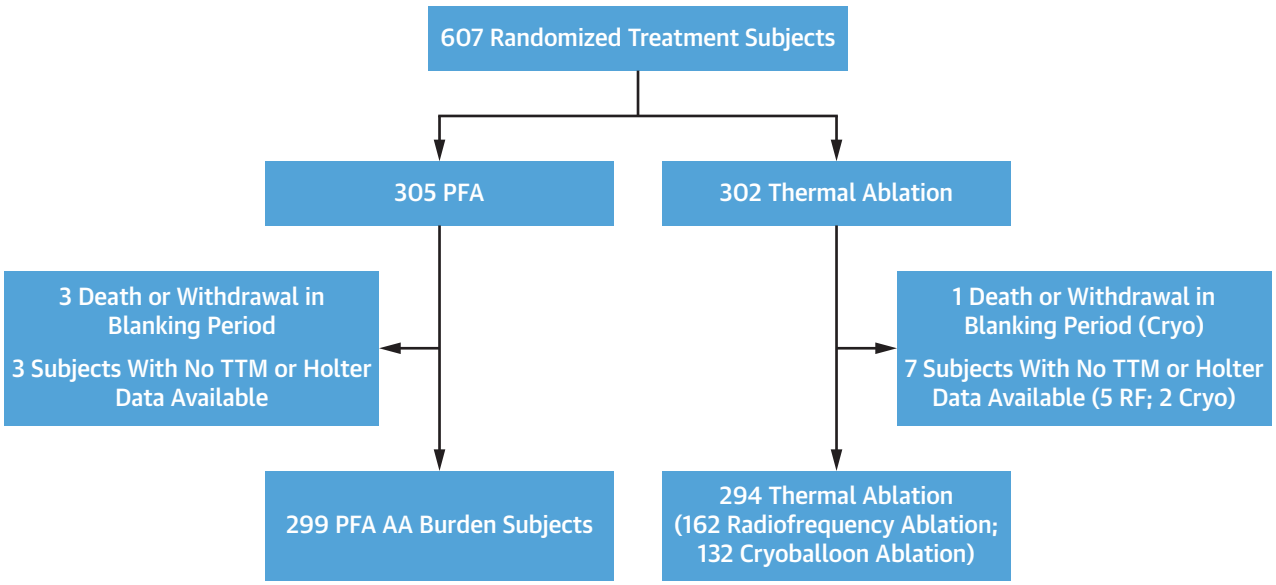
The randomization of the patient population is shown in the top panel—to either pulsed field ablation or to conventional thermal ablation (either with radiofrequency energy or cryothermy). When the aggregate (all patients in both groups) postablation atrial arrhythmia burden was analyzed, patients with a residual burden <0.1% fared best: better quality of life (bottom left), and fewest clinical interventions: cardioversions, repeat ablation procedures, and hospitalizations (bottom middle). Thus, a postablation residual atrial arrhythmia burden cutoff of <0.1% is optimal for both patient well-being and clinical resource utilization. When comparing between ablation groups, on the one hand, most patients in both cohorts fared well with a residual atrial arrhythmia burden <0.1%. On the other hand, as compared with thermal ablation, the pulsed field ablation group had statistically significantly more patients with this optimal residual atrial arrhythmia burden of <0.1%. *Significantly different from <0.1%. AA = atrial arrhythmia; AF = atrial fibrillation; AFEQT = Atrial Fibrillation Effect on QualiTy-of-Life survey; PFA = pulsed field ablation.

the pentaspline PFA catheter (Farawave, Boston Scientific Inc), a deflectable sheath (Faradrive, Boston Scientific Inc), and a dedicated PFA generator (Farastar, Boston Scientific Inc). The PFA protocol has previously been described.[28] Briefly, a minimum of 8 applications were delivered to each PV at 1,800, 1,900, or 2,000 volts using the PFA generator. Per protocol, intracardiac echocardiography was used during PFA to monitor catheter positioning. Esophageal management strategies (eg, temperature

FIGURE 1 Consort Diagram



Shown is the patient flow for this secondary AA burden analysis of ADVENT. AA = atrial arrhythmia; cryo = cryoablation; PFA = pulsed field ablation; RF = radiofrequency; TTM = transtelephonic electrocardiogram monitor.

monitoring, mechanical deviation, cooling) during PFA procedures was discouraged. Following PVI, entrance block was confirmed after a 20-minute waiting period. Additional applications were delivered per operator preference if the PV was not isolated.

THERMAL ABLATION. PVI with thermal ablation was performed with commercially available devices. Radiofrequency ablation was performed with a conventional saline-irrigated force-sensing catheter in conjunction with an electroanatomical mapping system. Radiofrequency applications were delivered (typically 25-50 W) to create a circumferential lesion set to isolate the PVs, either individually or as ipsilateral pairs. Esophageal protection was used based on institution protocols. Cryoballoon ablation was performed with a clinically available ablation catheter with lesions typically delivered for 2 to 4 minutes per lesion. Monitoring PV potentials during cryoballoon ablation was optionally used to guide lesions. After the 20-minute protocol-mandated waiting period, PVI was confirmed by assessing for entrance block.

STUDY FOLLOW-UP. Patients were followed for 1 year. Arrhythmia detection was performed using two 72-hour Holter monitors at 6 and 12 months, and transtelephonic electrocardiogram monitors weekly after the 3-month blanking period and for any symptoms. The Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) questionnaire was performed at baseline and 12 months.

AA BURDEN ANALYSIS. AA burden was calculated using the intermittent monitoring strategies used in this study. Total AA burden is estimated per patient as the greater of 2 calculated values: 1) the percentage of AA over the total duration of Holter data available; or 2) the percentage of weeks of transtelephonic electrocardiogram monitors (TTMs) with AA over total number of weeks with TTMs recorded.[33,34] Outcomes were compared across ablation modalities and AA burden levels were correlated to patient quality of life and the need for clinical interventions during follow-up (redo ablations, cardioversions, and hospitalizations). For this analysis, AA burden is grouped by <0.1%, 0.1% to 9.9%, and ≥10%. To avoid bias from our data set affecting analysis design, the 0.1% AA burden cutoff was selected based on prior literature and clinical relevance of maximum AF episode durations, see the Supplemental Material. A lower threshold of 0.1% was chosen based on previous literature from CIRCA-DOSE (Cryoballoon vs Irrigated Radiofrequency Catheter Ablation: Double Short vs Standard Exposure Duration) demonstrating this threshold to be significantly correlated to patient-oriented clinical outcomes, such as quality of life and health care utilization,[32] and the LINQ AF (LINQ Atrial Fibrillation) study, which used <0.1% burden to

indicate subclinical AF.[35] In two 72-hour Holters, 0.1% AA burden corresponds to 8.6 minutes of AA or 1.4 minutes of arrhythmia per day. Notably, 82 patients (36 PFA, 46 Thermal) were treatment failures and received AADs (including amiodarone) during ADVENT, for inclusiveness their data are included in the analysis.

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD. Categorical variables were summarized as count (%). Quality of life is reported as the change from baseline to 12 months and was tested using differences of least squares means in a linear mixed model adjusting for the baseline AFEQT score. Comparisons of clinical interventions and ablation modality across AA burden groups were performed using chi-squared tests. For the subgroup analysis, interaction terms were calculated using logistic regression to model AA burden (treated as a dichotomous variable) as a function of ablation modality and baseline demographics of interest (including the interaction of baseline modality and baseline demographics). Statistical analyses were performed using SAS version 9.4 (SAS Institute). All analyses were performed post hoc and $P < 0.05$ was considered significant.

RESULTS

PATIENT POPULATION. In ADVENT, symptomatic drug-refractory paroxysmal AF patients were randomized 1:1 to PFA or thermal ablation (radiofrequency or cryothermy). In total, 607 patients were enrolled in the ADVENT trial, of whom 593 patients (97.7%) were included in this subanalysis. Four patients were excluded because of death or withdrawal in the blanking period, and 10 patients had no TTM or Holter data available. The randomized cohort included 299 patients receiving PFA and 294 receiving thermal ablation, with the latter relatively evenly split between radiofrequency (n = 162) and cryothermal (n = 132) ablation (Figure 1). The baseline demographics for the PFA and thermal ablation groups are shown in Table 1. This paroxysmal AF cohort was relatively young with a mean age of 62.4 years and was largely Caucasian with 34% women. The mean CHA_2DS_2-VASc score was 1.7 ± 1.2, and the most common comorbidity, at 54%, was hypertension. Virtually all patients had received a class I-IV antiarrhythmic drug to treat the AF, with ~60% receiving a membrane active antiarrhythmic drug (class I or III); most patients (99%) were taking a nonwarfarin oral anticoagulant. There were no clinical differences between groups at baseline. Mean follow-up for all 593 patients was 378 ± 40 days.

TABLE 1 Patient Demographics

	All (N = 593)	PFA (n = 299)	Thermal (n = 294)	*P* Value
Age, y	62.4 ± 8.6	62.4 ± 8.7	62.5 ± 8.6	0.86
Female	204 (34.4)	100 (33.4)	104 (35.4)	0.62
BMI	28.6 ± 4.7	28.3 ± 4.5	28.9 ± 4.8	0.10
Comorbidities				
CAD	82 (13.8)	32 (10.7)	50 (17.0)	0.03
Congestive HF (NYHA functional class I or II)	115 (19.4)	57 (19.1)	58 (19.7)	0.84
Diabetes	61 (10.3)	31 (10.4)	30 (10.2)	0.95
Dyslipidemia	266 (44.9)	130 (43.5)	136 (46.3)	0.50
Hypertension	322 (54.3)	170 (56.9)	152 (51.7)	0.21
Sleep apnea	165 (27.8)	79 (26.4)	86 (29.3)	0.44
Stroke/TIA	27 (4.6)	12 (4.0)	15 (5.1)	0.52
CHA_2DS_2-VASc	1.7 ± 1.2	1.7 ± 1.2	1.7 ± 1.2	0.94
LA diameter, mm	39.2 ± 5.7	38.8 ± 5.6	39.6 ± 5.8	0.082
LVEF, %	60.1 ± 6.0	60.5 ± 5.9	59.7 ± 6.1	0.11
Years since AF diagnosis	3.6 ± 5.5	3.8 ± 6.3	3.3 ± 4.5	0.27
No. failed AADs	1.5 ± 0.7	1.5 ± 0.7	1.5 ± 0.7	0.88
Any AAD at baseline	587 (99.0)	295 (98.7)	292 (99.3)	0.42
Class I	212 (35.8)	114 (38.1)	98 (33.3)	0.22
Class II	364 (61.4)	170 (56.9)	194 (66.0)	0.022
Class III	140 (23.6)	69 (23.1)	71 (24.1)	0.76
Class IV	142 (23.9)	78 (26.1)	64 (21.8)	0.22
Any anticoagulant at baseline	592 (99.8)	299 (100.0)	293 (99.7)	0.31
NOAC	589 (99.3)	297 (99.3)	292 (99.3)	0.99
VKA	3 (0.5)	2 (0.7)	1 (0.3)	0.57

Values are mean ± SD or n (%).

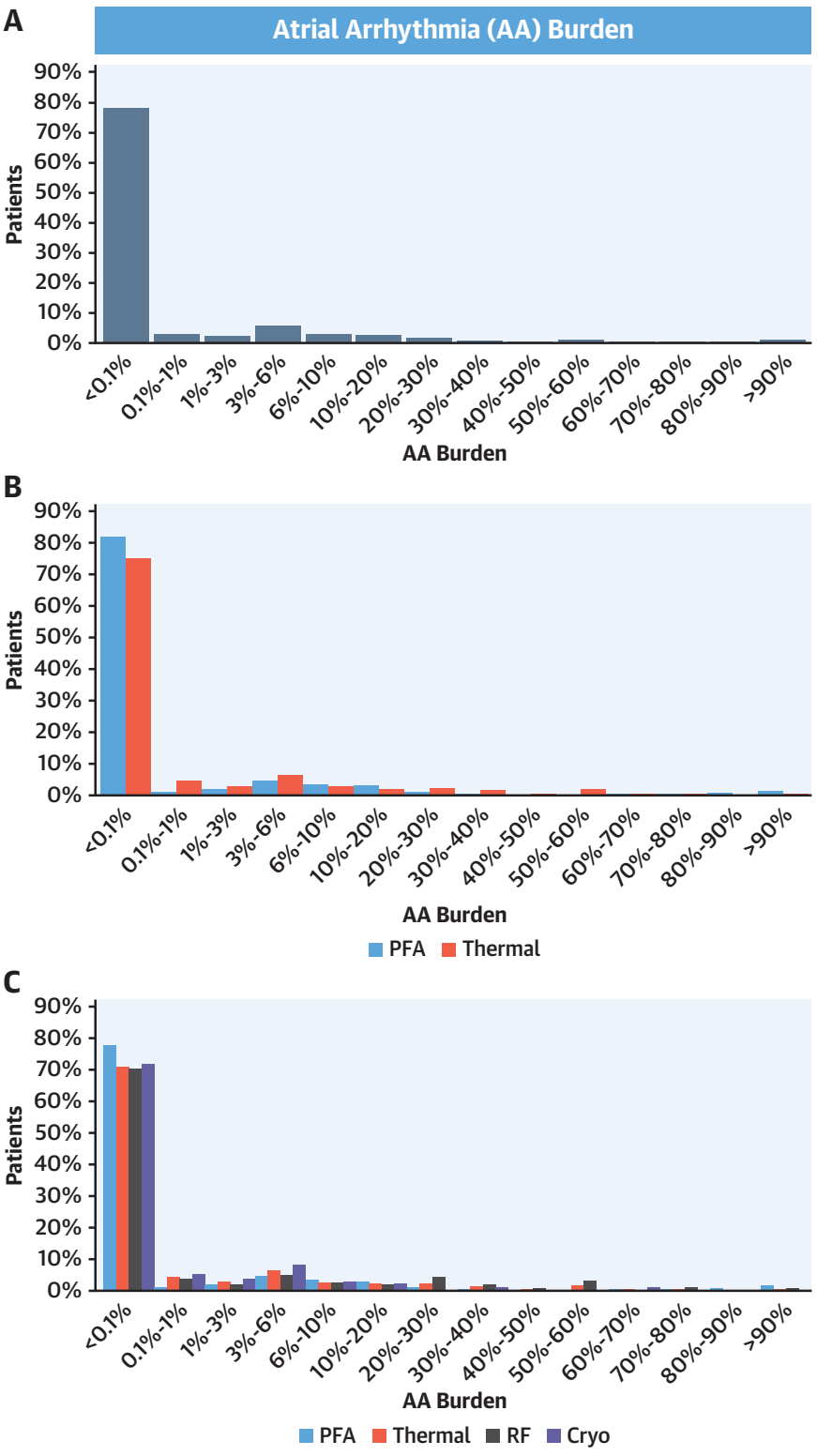
AAD = antiarrythmic drug; AF = atrial fibrillation; BMI = body mass index; CAD = coronary artery disease; HF = heart failure; LA = left atrium; LVEF = left ventricular ejection fraction; NOAC = non-warfarin oral anticoagulation; PFA = pulsed field ablation; TIA = transient ischemic attack; VKA = vitamin K antagonist.

AA BURDEN SUMMARY. As previously reported, the overall compliance for weekly TTMs and 72-hour Holter monitoring was 67.5% and 81.3%, respectively.[29] The AA burden analysis included an average of 27 weeks of TTM from 589 patients, and 61,841 hours of Holter recordings (an average of 114.7 hours per patient) from 539 patients. For this analysis, TTM identified a higher residual AA burden in 143 patients (n = 58 PFA; n = 85 thermal ablation), and Holter monitoring identified a higher residual AA burden for the remaining 450 patients (n = 241 PFA; n = 209 thermal ablation).

In Figure 2A, the 1-year postablation AA burden is shown with data aggregated between all ablation arms. The vast majority of patients (n = 465 [78.4%]) had a residual AA burden of <0.1%, translating on average to <1.4 minutes of AA per day. Only a minority (n = 47 [7.9%]) of the aggregate patient population had a residual AA burden exceeding 10%.

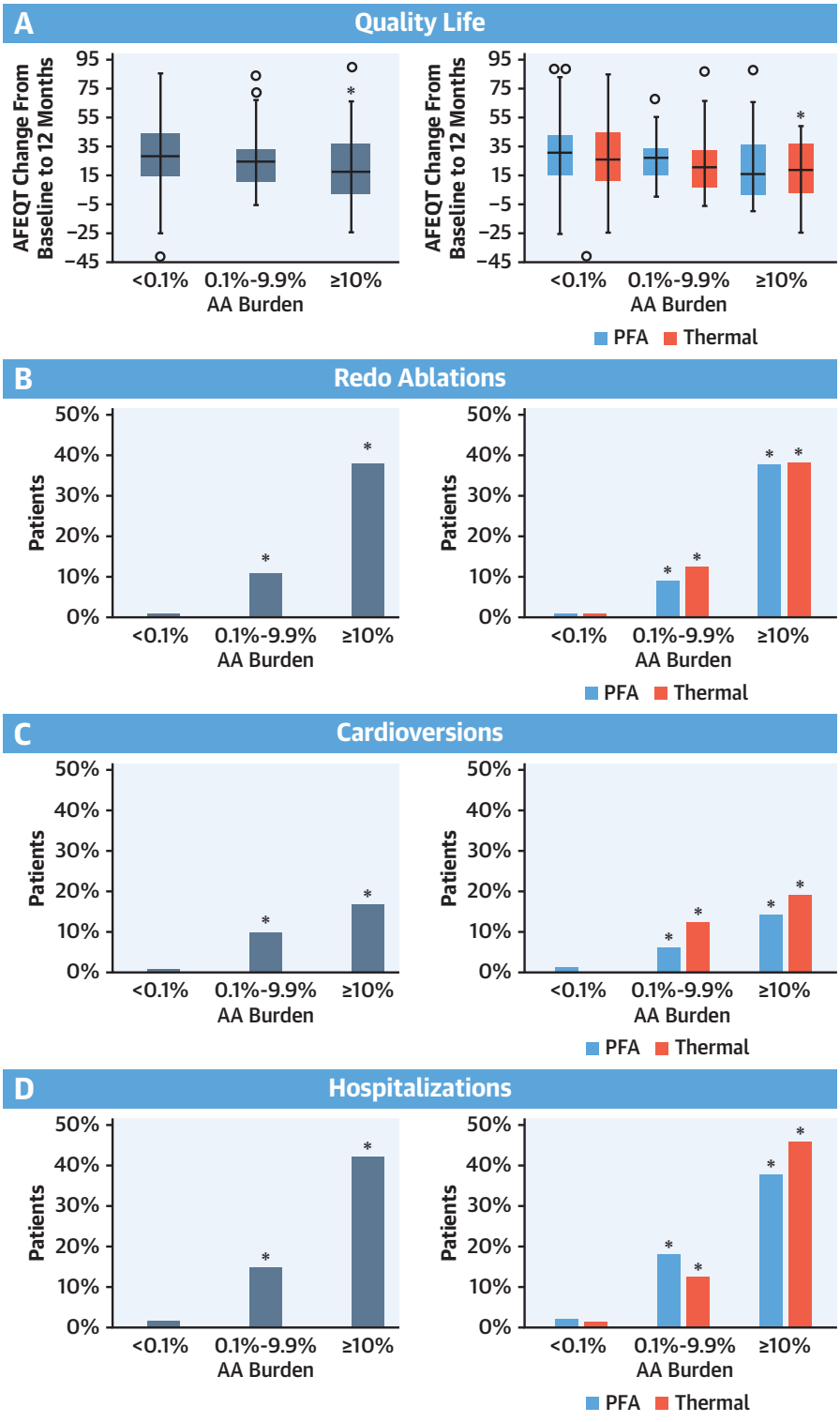
AA BURDEN, QUALITY OF LIFE, AND CLINICAL INTERVENTIONS. Among the patients included in the AA burden subanalysis, the AFEQT quality-of-life assessments administered at baseline and 12 months

FIGURE 2 **Postablation AA Burden Distribution**



Shown are the distribution of postablation postblanking AA burden data for the aggregate cohort (A), and the 2 randomized groups, PFA and thermal ablation (B), and the full breakdown by ablation modality (C). Abbreviations as in Figure 1.

FIGURE 3 **Impact of AA Burden on Quality of Life and Clinical Interventions**



The postablation AA burden was grouped into 3 categories, <0.1%, 0.1%-9.9% and ≥10%, and assessed for (A) the baseline-to-12-month improvement in quality of life as assessed by the Atrial Fibrillation Effect on QualiTy-of-Life survey, (B) the need for repeat ablation, (C) postablation cardioversion, and (D) hospitalization after the 3-month blanking period. The outcomes were calculated for both aggregated data of the full cohort (left graphs) and the data separated by the randomized groups, PFA, or thermal ablation (right graphs). Abbreviations as in Figure 1.

TABLE 2 Atrial Arrhythmia Burden by Ablation Modality and Antiarrhythmic Drugs

	PFA	Thermal	*P* Value	Cryo	RF
No. with burden data	299	294	0.035	132	162
<0.1% AA burden	245 (81.9)	220 (74.8)		100 (75.8)	120 (74.1)
≥0.1% AA burden	54 (18.1)	74 (25.2)		32 (24.2)	42 (25.9)
Class I/III failures			0.001		
<0.1% AA burden	142 (86.1)	112 (71.3)		53 (74.6)	59 (68.6)
≥0.1% AA burden	23 (13.9)	45 (28.7)		18 (25.4)	27 (31.4)
Class II/IV failures			0.70		
<0.1% AA burden	103 (76.9)	108 (78.8)		47 (77.0)	61 (80.3)
≥0.1% AA burden	31 (23.1)	29 (21.2)		14 (23.0)	15 (19.7)

Values are n (%) unless otherwise indicated. Comparisons between PFA and thermal performed using a chi-squared test.

Cryo = cryothermy; RF = radiofrequency ablation; other abbreviations as in Table 1.

of follow-up were available from 287 PFA patients and 282 thermal patients. The aggregate data were grouped by AA burden in those with <0.1%, 0.1%-9.9%, and ≥10% postablation burden over 1-year follow-up. Overall, there were significant improvements in quality of life, regardless of residual AA burden. When comparing subjects with <0.1% AA burden, the increase in quality of life was significantly greater than compared with those with ≥10% AA burden (30.1 ± 21.6 vs 21.9 ± 24.4; $P < 0.001$) (**Figure 3A**). This association between residual AA burden and quality of life was also observed for both: 1) the 2 randomized groups, PFA and thermal ablation; and 2) the individual thermal modalities, radiofrequency and cryothermy (Supplemental Figure 1).

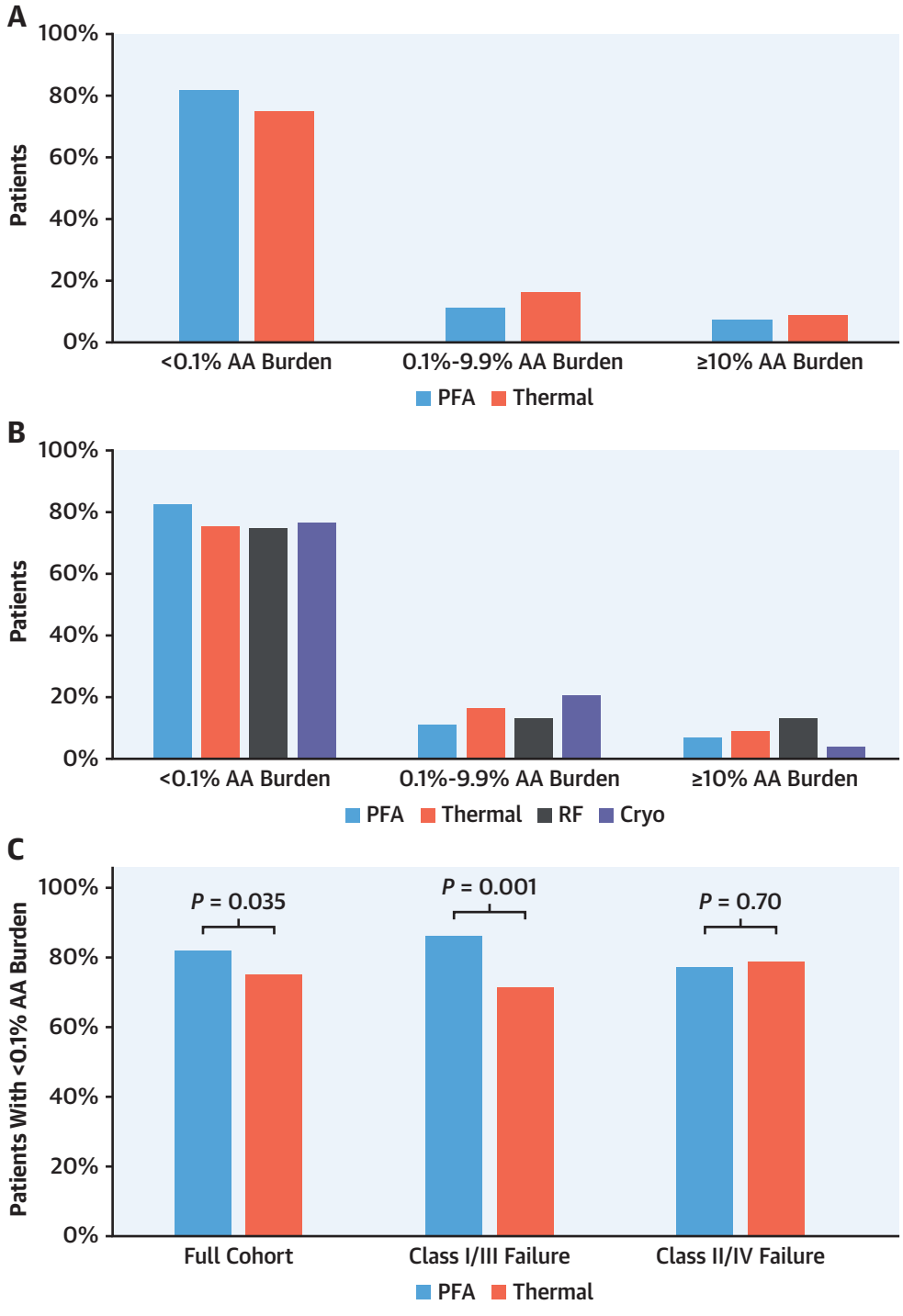
Similarly, the impact of the postablation AA burden on clinical interventions—redo catheter ablation, electrical cardioversion, or hospitalization—during the 1-year follow-up after the 3-month blanking period was assessed. As shown in **Figures 3B to 3D**, there were very few such clinical interventions in follow-up for the cohort of patients with <0.1% residual AA burden over 1 year: 0.86%, 0.65%, and 1.72% underwent redo ablation, cardioversion, or hospitalization, respectively. On the other hand, both the 0.1% to 9.9% and the ≥10% AA burden cohorts experienced significantly greater frequency of clinical interventions over follow-up: indeed, for the latter, 38.3%, 17.0%, and 42.6% underwent redo ablation, cardioversion, or hospitalization, respectively (in comparison to <0.1% AA burden, the *P* values were <0.001 for all 3 interventions). Compared with patients experiencing ≤0.1% AA burden over 1 year, patients with >0.1% AA burden experienced increased risks for redo ablation (relative risk [RR]: 24.5; 95% CI: 8.7-68.8), cardioversion (RR: 19.4; 95% CI: 5.7-65.5), and hospitalization (RR: 14.5; 95% CI: 6.90-30.8). Again, these associations between AA burden and these 3 clinical interventions were observed for both: 1) the 2 randomized groups, PFA and thermal ablation (**Figure 3B to D**); and 2) the individual thermal modalities, radiofrequency and cryothermy (Supplemental Figure 1).

Taken together, and consistent with prior studies,[32,33] these data indicate that a residual postablation AA burden during 1-year follow-up exceeding 0.1% is an important threshold value—above which one can expect a significantly worse quality of life and an increase in the need for clinical interventions: redo ablation, cardioversion, and hospitalization.

ABLATION MODALITY AND AA BURDEN. This threshold value of 0.1% was used to compare postablation AA burden outcomes at 1 year as a function of the ablation modality. As shown in **Table 2** and **Figure 4A**, there was a greater percentage of patients with residual AA burden <0.1% with PFA (n = 245 of 299 [81.9%]) than with thermal ablation (n = 220 of 294 [74.8%]; $P = 0.035$). Indeed, in comparing the randomized ablation modalities, patients treated with PFA were more likely to have a residual AA burden <0.1% over the 1-year follow-up compared with thermal ablation (OR: 1.5; 95% CI: 1.0-2.3; $P = 0.036$) (Supplemental Table 1). As expected, higher AAD use occurred in patients with higher burden (>0.1% burden) but there were no differences between treatment groups (Supplemental Table 2). This difference in residual AA burden was also present when comparing PFA with the individual thermal ablation modalities, radiofrequency or cryothermy (**Table 2**, **Figure 4B**). Finally, to account for data missingness, this analysis was repeated with the subset of patients with either both Holter monitors available (n = 377) or who completed ≥36 weeks of TTM (n = 104); despite the expected decrease in statistical power, the primary conclusions were consistent (Supplemental Table 3).

The difference in postablation AA burden between PFA and thermal ablation was evaluated as a function of baseline demographics: age, sex, body mass index, sleep apnea, heart failure, hypertension, timing of AF diagnosis, and prior failed AADs. As shown in **Figure 5** and Supplemental Figure 2, the only variable to demonstrate a statistically significant difference in AA burden to <0.1% over 1 year was the type of prior failed AAD(s) (P for interaction = 0.012): patients with prior failed class I/III AADs pre-ablation were more likely to have an AA burden <0.1% with PFA compared with thermal ablation (86.0% vs 71.3%; OR: 2.5; 95% CI: 1.4-4.3; $P = 0.002$) (Supplemental Table 1). In contrast,

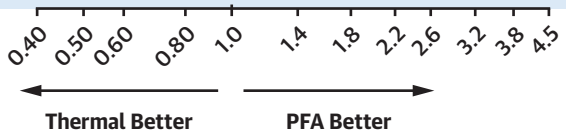
FIGURE 4 **Differences in Postablation AA Burden by Ablation Modality**



The postablation AA burden was grouped into 3 categories, <0.1%, 0.1%-9.9%, and ≥10%, and compared either between the 2 randomized groups, PFA and thermal ablation (A), or across all ablation modalities (B). The percentage of patients with a postablation residual AA burden <0.1% is shown for the randomized groups, both the full cohort, and based on drug history before catheter ablation (C). Abbreviations as in Figure 1.

FIGURE 5 Forest Plot of Comparative AA Burden Outcomes by Subgroups

Variable	N PFA	N Thermal	Interaction *P* Value	OR for Zero AA Burden (Log Scale)	OR (95% CI)
Treatment Group	299	294	0.04*		1.5 (1.0-2.3)
Age <60 y	99	97	0.39		2.0 (1.0-4.1)
Age ≥60 y	200	197			1.4 (0.8-2.2)
Female	100	104	0.57		1.3 (0.7-2.5)
Male	199	190			1.7 (1.0-2.8)
BMI <30 kg/m^2	200	181	0.35		1.8 (1.0-2.9)
BMI ≥30 kg/m^2	99	113			1.2 (0.6-2.2)
No Sleep Apnea	220	208	0.34		1.3 (0.8-2.1)
Sleep Apnea	79	86			2.1 (1.0-4.4)
Heart Failure	57	58	0.65		1.2 (0.5-3.3)
No Heart Failure	242	236			1.6 (1.0-2.5)
Hypertension	170	152	0.10		1.2 (0.7-1.9)
No Hypertension	129	142			2.3 (1.2-4.4)
AF Diagnosis <3 y Before Ablation	196	191	0.28		1.8 (1.1-3.1)
AF Diagnosis ≥3 y Before Ablation	103	103			1.2 (0.6-2.2)
Class I/III AAD Failure	165	157	0.01		2.5 (1.4-4.3)
Class II/IV AAD Failure	134	137			0.9 (0.5-1.6)
1 Failed AAD at Baseline	182	175	0.16		1.2 (0.7-2.0)
≥2 Failed AADs at Baseline	117	119			2.1 (1.1-4.0)



The forest plot shows the ORs, CIs, and interaction *P* values for the impact of patient baseline demographics and ablation modality on postablation AA burden. **P* value for treatment group. AAD = antiarrythmic drug; AF = atrial fibrillation; BMI = body mass index; other abbreviations as in Figure 1.

patients with only prior failed class II/IV AADs preablation had no difference in AA burden between ablation groups (76.9% vs 78.8%; OR: 0.9; 95% CI: 0.5-1.6; $P = 0.70$) (Figure 4C). In addition, see Supplemental Table 3 for analysis of AAD history by ablation modality.

DISCUSSION

The following are the main findings in this secondary analysis of the ADVENT randomized trial: 1) a postablation residual AA burden of <0.1% over 1-year follow-up is associated with the greatest improvement in quality of life; 2) this residual AA burden of <0.1% is also associated with the fewest clinical interventions—redo ablation, electrical cardioversion, or hospitalization—and a ≥10% residual AA burden is associated with the largest increase in such interventions; 3) patients in *both* randomized arms of the trial, PFA and thermal ablation, did quite well, with 78.4% expressing a 1-year postablation AA burden <0.1%; 4) the 1-year postablation AA burden is less for PFA than thermal ablation; and 5) in subgroup analyses, patients in whom class I/III AADs failed preablation demonstrated the greatest differential in residual AA burden between PFA and thermal ablation (OR: 2.5). These results indicate the potential for improved effectiveness of PFA over thermal ablation in this post hoc analysis of the randomized study.

For nearly 2 decades, clinical trials of AF ablation have used a strict definition of a single 30-second AA recurrence as a primary endpoint and indicator of

therapeutic failure.[2,36] This guideline has enabled relative comparisons across studies and technologies, albeit needing to consider differences in study design, rhythm monitoring, etc. However, this endpoint lacks clinical significance and significantly underestimates the effectiveness of ablation therapies.[30,37] The recent 2023 American College of Cardiology/American Heart Association/American College of Clinical Pharmacy/Heart Rhythm Society guidelines on the management of AF acknowledge this oversimplification of the historical 30-second endpoint, and its limitation in capturing patient-oriented outcomes.[1]

On the other hand, there are increasing data that postablation AA burden is a better indicator of clinical success. The gold standard to capturing postablation AA burden data is an implanted device such as an insertable cardiac monitor, as used in the randomized CIRCA-DOSE trial comparing radiofrequency with cryothermal ablation to treat paroxysmal AF.[38] In a secondary analysis of the CIRCA-DOSE trial, compared with patients experiencing ≤0.1% postablation AA burden, patients with >0.1% AA burden required greater health care utilization—including a 2.4-fold increased risk for emergency department consultation, a 6.8-fold increased risk of hospitalization, a 9.1-fold increased risk for cardioversion, and a 21.8-fold increased risk for repeat ablation.[32]

Because of the practical complexities of using implanted cardiac devices to determine AA burden, intermittent monitoring strategies have also been used to determine AA burden.[33,34] In the single-arm PULSED-AF (Pulsed Field Ablation to Irreversibly Electroporate Tissue and Treat AF) study of a circular PFA catheter, postablation AA burden was estimated based on intermittent monitoring strategies: TTMs (weekly and for symptoms) and 24-hour Holter monitoring at 6 and 12 months. As described previously, lower levels of post-PFA AA burden translated to improved quality of life and reduced health care utilization, with the best outcomes observed for AA burden <10%.[33] Although we discuss them evenly here, it should be noted that continuous monitoring is a more sensitive measure of AA burden and may better bridge the divide between clinical trials and clinical practice; however, this and previous burden analyses suggest that there is value in reconsidering clinical trials in terms of burden rather than relying on the strict 30-second definition of failure.[33]

These prior studies have demonstrated that a postablation AA burden <0.1% translates to optimal improvements in quality of life and freedom from clinical interventions/health care utilization. In the current analysis, the impact of the aggregate postablation AA burden on quality of life and clinical interventions was evaluated. These analyses demonstrated that a 0.1% AA burden threshold translated to a combination of the best improvement in quality of life and fewest required clinical interventions: cardioversion, redo ablation, or hospitalization. This threshold was relevant for not just the aggregate cohort, but also for the individual randomized groups: PFA and thermal ablation.

As previously reported for ADVENT, the primary endpoint of treatment success, which incorporated the "traditional" dichotomous endpoint of 30-second AA recurrence, was 73.3% with pentaspline PFA and 71.3% with thermal ablation (between-group difference: 2.0%; 95% Bayesian credible interval: −5.2 to 9.2); thus, although PFA met the criteria for noninferiority (posterior probability > 99.9%), it did not meet the criteria for superiority (posterior probability = 70.8%).[29] The first-in-human trials with this PFA technology predicted that this arm should demonstrate superiority, but its absence was not completely surprising given that virtually all of the operators were using the pentaspline PFA catheter for the first time in this trial (and conversely, possessed years/decades of experience with thermal ablation). On the other hand, when these data were further analyzed in the current study using the more clinically relevant endpoint of <0.1% residual AA burden, there was a clear difference: the PFA patients were 1.5 times more likely than the thermal patients to have a postablation AA burden below the 0.1% threshold. The present effect would translate to 1 of 14 patients having a better outcome with PFA, which we feel represents not only a statistical but also a clinically significant difference. In addition, the potential effects of operator experience on safety and efficacy should be considered. In ADVENT, most operators were highly experienced with thermal ablation, yet only 1 operator had prior clinical experience with the pentaspline catheter, suggesting that the relative effectiveness and safety of PFA may be expected to increase as operators accrue experience with this novel, now available technology. Furthermore, there is the potential that this difference between groups could in fact be larger among electrophysiologists just entering this field without years of experience with thermal ablation, and this difference might grow as experience with PFA increases.

This between-group difference was also present when comparing PFA with the individual ablative modalities of the thermal arm, radiofrequency and cryothermal ablation. Although assignment to these energy modalities in the thermal arm was not

randomized, it *was* assigned by center, which should minimize bias. And certainly, consistent with other comparative studies, such as FIRE AND ICE (Comparative Study of Two Ablation Procedures in Patients With Atrial Fibrillation), CIRCA-DOSE, and RACE-AF (Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation) (the latter 2 trials including insertable cardiac monitors), it is quite plausible that residual AA burden outcomes would indeed be equivalent between the 2 thermal modalities.[38-40]

Analyses of subgroups demonstrated that the benefit of PFA over thermal ablation for residual AA burden was present regardless of age; sex; body mass index; presence of sleep apnea, heart failure, or hypertension; timing of AF diagnosis; or the number of prior failed AADs. In the subgroup of patients with a history of class I or III AAD use, PFA was more likely than thermal ablation to result in a postablation AA burden of <0.1% (OR: 2.5). One interpretation of this is that patients further along in AF disease progression (since a class I/III AAD had already been attempted) might fare best with PFA. Of course, AAD failure and PVI response could also indicate some underling pathology of AF or AAD selection bias of treating physicians. Hopefully, future research can delve deeper into describing the current landscape of AAD usage and progression in patients with AF, as well as the question of whether patients' AAD history is relevant to the effectiveness of PVI.

Together with the recent literature, these results also suggest that AF ablation clinical trials should transition away from the arbitrary endpoint of 30-second AA recurrence to the more clinically meaningful endpoint of residual AA burden—using a threshold of 0.1% burden. And importantly, although insertable cardiac monitors would provide the highest-quality data, it seems clear that actionable AA burden data can be derived from a combination of weekly TTMs and episodic continuous Holter monitoring. Of note, most of the available data (including from ADVENT) were obtained from a population of patients with *paroxysmal* AF. It is unclear whether it would be appropriate to apply this same 0.1% threshold to a *persistent* AF population, or whether this might be an overly strict metric; additional studies in patients with persistent AF undergoing ablation are warranted.

STUDY LIMITATIONS. First, it is important to recognize that outcomes by AA burden was not a prespecified analysis but is instead a post hoc analysis. On the other hand, any potential bias is mitigated by the fact that this is an obvious analysis to perform after the aforementioned recent studies of the importance of AA burden on quality of life and health care utilization (largely published after the ADVENT trial commenced enrollment).[31-33,37] Second, AA burden was not derived from continuous implantable monitoring, but rather from weekly TTMs and episodic 72-hour Holter monitoring. In addition, this AA burden calculation relies on an intermittent monitoring strategy and only considers 1 time point during follow-up (1 year). Further studies are needed to understand the relation between burden over time based on ablation treatment modalities and clinical outcomes. But as described previously, clinically relevant AA burden data can nonetheless be derived from intermittent monitoring. Third, preablation AA burden data were not collected in this study; accordingly, we cannot directly confirm the magnitude of reduction in AA burden by catheter ablation. However, there is a wealth of data indicating that catheter ablation in paroxysmal AF results in an ~99% reduction in AA burden.[32,40,41] Last, although patients were blinded to the ablation modality, treating physicians were not blinded, which could potentially bias referral for clinical interventions.

CONCLUSIONS

In the randomized ADVENT trial of paroxysmal AF, PFA resulted in significantly more patients with a postablation residual AA burden below the clinically meaningful threshold of 0.1% compared with thermal ablation—either radiofrequency or cryoballoon ablation. Future comparative trials should incorporate AA burden into the primary effectiveness endpoint.

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KEY WORDS arrhythmia burden, atrial fibrillation, pulsed field ablation

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

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