ORIGINAL ARTICLE

Pulsed Field or Conventional Thermal Ablation for Paroxysmal Atrial Fibrillation

Vivek Y. Reddy, M.D., Edward P. Gerstenfeld, M.D., Andrea Natale, M.D., William Whang, M.D., Frank A. Cuoco, M.D., Chinmay Patel, M.D., Stavros E. Mountantonakis, M.D., Douglas N. Gibson, M.D., John D. Harding, M.D., Christopher R. Ellis, M.D., Kenneth A. Ellenbogen, M.D., David B. DeLurgio, M.D., Jose Osorio, M.D., Anitha B. Achyutha, M.Tech., M.S.E., Christopher W. Schneider, M.Eng., Andrew S. Mugglin, Ph.D., Elizabeth M. Albrecht, Ph.D., Kenneth M. Stein, M.D., John W. Lehmann, M.D., M.P.H., and Moussa Mansour, M.D., for the ADVENT Investigators*

ABSTRACT

BACKGROUND

Catheter-based pulmonary vein isolation is an effective treatment for paroxysmal atrial fibrillation. Pulsed field ablation, which delivers microsecond high-voltage electrical fields, may limit damage to tissues outside the myocardium. The efficacy and safety of pulsed field ablation as compared with conventional thermal ablation are not known.

METHODS

In this randomized, single-blind, noninferiority trial, we assigned patients with drug-refractory paroxysmal atrial fibrillation in a 1:1 ratio to undergo pulsed field ablation or conventional radiofrequency or cryoballoon ablation. The primary efficacy end point was freedom from a composite of initial procedural failure, documented atrial tachyarrhythmia after a 3-month blanking period, antiarrhythmic drug use, cardioversion, or repeat ablation. The primary safety end point included acute and chronic device- and procedure-related serious adverse events.

RESULTS

A total of 305 patients were assigned to undergo pulsed field ablation, and 302 were assigned to undergo thermal ablation. At 1 year, the primary efficacy end point was met (i.e., no events occurred) in 204 patients (estimated probability, 73.3%) who underwent pulsed field ablation and 194 patients (estimated probability, 71.3%) who underwent thermal ablation (between-group difference, 2.0 percentage points; 95% Bayesian credible interval, −5.2 to 9.2; posterior probability of noninferiority, >0.999). Primary safety end-point events occurred in 6 patients (estimated incidence, 2.1%) who underwent pulsed field ablation and 4 patients (estimated incidence, 1.5%) who underwent thermal ablation (between-group difference, 0.6 percentage points; 95% Bayesian credible interval, −1.5 to 2.8; posterior probability of noninferiority, >0.999).

CONCLUSIONS

Among patients with paroxysmal atrial fibrillation receiving a catheter-based therapy, pulsed field ablation was noninferior to conventional thermal ablation with respect to freedom from a composite of initial procedural failure, documented atrial tachyarrhythmia after a 3-month blanking period, antiarrhythmic drug use, cardioversion, or repeat ablation and with respect to device- and procedure-related serious adverse events at 1 year. (Funded by Farapulse–Boston Scientific; ADVENT ClinicalTrials.gov number, NCT04612244.)

The authors' affiliations are listed in the Appendix. Dr. Reddy can be contacted at vivek.reddy@mountsinai.org or at the Helmsley Electrophysiology Center, Icahn School of Medicine at Mount Sinai, 1190 5th Ave., Guggenheim Pavillon, Suite 280, New York, NY 10029.

*A complete list of the ADVENT investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Catheter-based ablation is an effective treatment for patients with drug-refractory paroxysmal atrial fibrillation.[1,2] The procedure is typically performed with the use of radiofrequency or cryothermal energy that heats or freezes tissue, respectively, to electrically isolate the pulmonary veins, which harbor triggers of atrial fibrillation.[3] However, tissue-indiscriminate effects of thermal ablation may extend beyond the myocardium to adjacent tissues. Thus, potential complications of thermal ablation include atrioesophageal fistula (in 0.02 to 0.1% of cases), hemidiaphragmatic paralysis (in up to 0.4%), and pulmonary vein stenosis (in <1%).[3]

Pulsed field ablation is a largely nonthermal energy approach that involves the use of microsecond-scale, high-voltage electrical fields to cause irreversible electroporation and destabilization of cell membranes, a process that culminates in cellular necrosis.[4,5] Preclinical and clinical studies have shown that pulsed field ablation has a degree of ablative specificity that allows myocardial tissue to be preferentially ablated with limited effects on adjacent tissues such as the esophagus, phrenic nerve, and pulmonary vein tissue.[6-16]

Previous nonrandomized, single-center clinical studies have shown favorable safety and effectiveness when pulsed field ablation is used for atrial fibrillation.[17-27] The ADVENT Trial was designed to compare pulsed field ablation with conventional thermal ablation (either radiofrequency or cryoballoon ablation) in the treatment of drug-refractory paroxysmal atrial fibrillation.

Methods

Trial Design

The ADVENT trial was a multicenter, randomized, noninferiority, single-blind, pivotal trial with blinded end-point adjudication. The trial protocol was described previously[28] and is available with the full text of this article at NEJM.org. The trial was funded by the manufacturer of the pulsed field ablation system, Farapulse (later acquired by Boston Scientific). The trial was approved by the Food and Drug Administration (since the ablation catheter that we used is an investigational device) and by the institutional review board at each center and was conducted in accordance with the principles of the Declaration of Helsinki. The trial was designed by the sponsor with input from the first author. An independent data and safety monitoring board oversaw patient safety and trial conduct, and a clinical-events committee adjudicated all clinically significant outcome events. Independent blinded core laboratories were used for assessments of rhythm monitoring, imaging of the pulmonary veins, and magnetic resonance imaging (MRI) of the brain.

The sponsor collected and monitored the trial data and performed outcome analyses according to the statistical analysis plan, available with the protocol. The first author had full access to all the data and analyses. All drafts of this manuscript were written by the first author, with review and edits by the other authors. The sponsor provided input, but the first author had final authority over manuscript content. The authors attest to the accuracy and completeness of the data and to the fidelity of the trial to the protocol.

A Quick Take is available at NEJM.org

Patients

After providing written informed consent, adults 75 years of age or younger with symptomatic paroxysmal atrial fibrillation that was refractory to at least one antiarrhythmic drug (class I, II, III, or IV) were enrolled. A full description of the inclusion and exclusion criteria is provided in the Supplementary Appendix (available at NEJM.org). After treatment of one to three roll-in patients per center to ensure operator familiarity with the investigational pulsed field ablation catheter, all the subsequent patients were randomly assigned in a 1:1 ratio to undergo either pulsed field ablation or thermal ablation. Randomization was stratified according to site with the use of permuted blocks of randomly varying block sizes. Each center was limited to either radiofrequency ablation or cryoballoon ablation for the control group undergoing thermal ablation, with each thermal method planned to constitute approximately 50% of the control group. Patients who underwent radiofrequency ablation or cryoballoon ablation were aggregated into the group undergoing thermal ablation because the two catheter-based therapies result in similar outcomes.[29-31]

Interventions

Patients were unaware of their procedure assignments. The multielectrode pentaspline pulsed

field ablation catheter was delivered over the wire to each pulmonary vein with the use of a deflectable sheath (see the Supplementary Appendix for additional details).[28] Pulsed field energy was delivered to achieve pulmonary vein isolation (Fig. S1 in the Supplementary Appendix). For radiofrequency ablation, a commercially available saline-irrigated, contact force–sensing catheter was used; for cryoballoon ablation, the balloon catheter was advanced to each vein for ablation (additional details are provided in the Supplementary Appendix). Esophageal-management strategies such as temperature monitoring, cooling, or deviation were permitted for thermal ablation but were discouraged for pulsed field ablation. For all the ablation methods, the procedural end point was entrance conduction block of all treated pulmonary veins after a 20-minute observation period.

FOLLOW-UP

After discharge, oral anticoagulation was continued according to standard guidelines, and class I or III antiarrhythmic drugs (with the exception of amiodarone) were permitted during the initial 3-month blanking period. Patients were followed for 1 year with telephone calls at 7, 30, and 60 days and office visits at 3, 6, and 12 months. For arrhythmia detection, 72-hour Holter monitoring was performed at 6 and 12 months, and trans-telephonic electrocardiographic (ECG) recordings were obtained weekly after the blanking period and for any symptoms. Follow-up testing included a 3-month cardiac computed tomographic or MRI scan to assess the anatomical features of the pulmonary veins. In a subgroup of patients, brain MRI was performed within 48 hours after the ablation procedure to assess for silent cerebral lesions.

END POINTS

The primary efficacy end point was freedom from a composite of initial procedural failure to achieve pulmonary vein isolation with the use of the randomly assigned treatment method only, documented atrial tachyarrhythmia lasting 30 seconds or longer after the 3-month blanking period, the use of class I or III antiarrhythmic drugs or cardioversion after the 3-month blanking period, the use of amiodarone at any time, or repeat ablation at any time during the 1-year follow-up period. The primary safety end point was a composite of prespecified device- and procedure-related serious adverse events within 7 days after the procedure (a detailed description is provided in the Supplementary Appendix). Atrioesophageal fistula and pulmonary vein stenosis were included as serious adverse events regardless of the timing of occurrence.

The secondary safety end point was the change in the aggregate pulmonary vein cross-sectional area between baseline and 3 months. The secondary efficacy end point was the same as the primary efficacy end point but tested for the superiority of pulsed field ablation as compared with thermal ablation. Additional end points are described in the Supplementary Appendix.

STATISTICAL ANALYSIS

The trial was designed with the use of Bayesian statistical methods, with noninformative prior distributions. The sample size was determined adaptively through a Goldilocks design[32]; at specified enrollment milestones (350, 450, 550, 650, and 750 patients), the predictive probability that noninferiority would eventually be shown for each primary end point determined whether enrollment should stop, either for a high probability of trial success or for futility. Data from 550 patients met stopping criteria; by this time point, 607 patients had undergone randomization (see the Supplementary Appendix for additional details). All end points were analyzed in the modified intention-to-treat population, which was defined as all the patients who underwent randomization and in whom energy was delivered with the use of a trial ablation catheter.

The primary safety hypothesis was that pulsed field ablation would be noninferior to thermal ablation with respect to the percentage of patients with at least one primary safety end-point event, with an absolute margin of 8 percentage points. The primary efficacy hypothesis was that pulsed field ablation would be noninferior to thermal ablation with respect to the probability of 1-year treatment success, with an absolute margin of 15 percentage points. (The rationale for the safety and effectiveness margins is provided in the Supplementary Appendix.) Both hypotheses were tested with the use of a noninformative beta prior distribution with parameters (0.5 and 0.5) that was updated on the basis of observed 1-year binary outcomes; patients whose data had been

censored were included in the analysis by the use of multiple imputation. Alternative prior distributions were also studied (see the Supplementary Appendix). Trial success was defined by posterior probabilities of noninferiority for safety and efficacy exceeding 0.966 and 0.956, respectively. For between-group differences in the secondary safety end point of the aggregate pulmonary vein cross-sectional area, the within-patient changes between baseline and 3 months were compared with the use of a Bayesian version of a t-test with noninformative priors. Results that are presented here have not undergone a Bayesian multiplicity adjustment.

Other end points without formal hypothesis testing are summarized with descriptive statistics and 95% Bayesian credible intervals. The widths of these intervals have not been adjusted for multiplicity. Assessments of whether patients were aware of the procedure assignments were performed at the time of the index procedure and at 1-year follow-up. Statistical analyses were performed with the use of SAS software (SAS Institute) and R software (R Foundation).

RESULTS

PATIENTS

From March 1, 2021, to June 3, 2022, a total of 706 patients with paroxysmal atrial fibrillation were enrolled in the trial. A total of 687 patients underwent catheter ablation at 30 centers by 65 operators. Once the roll-in phase (which included 80 patients) was completed, the remaining 607 patients (modified intention-to-treat population) were randomly assigned in a 1:1 ratio to undergo pulsed field ablation (305 patients) or conventional thermal ablation (302 patients; 167 patients were assigned to undergo radiofrequency ablation and 135 to undergo cryoballoon ablation) (Fig. 1, Fig. S2, and Tables S1 and S2). The baseline characteristics of the patients appeared to be balanced between the two groups (Table 1 and Tables S3 and S4).

At the 1-year follow-up, 16 of 299 patients (5.4%) who underwent pulsed field ablation and 22 of 292 patients (7.5%) who underwent thermal ablation were taking class I or III antiarrhythmic drugs (Table S5). Overall adherence to trial follow-up visits was more than 99% among patients in both groups, with 92.8% of the modified intention-to-treat cohort having known 12-month outcomes (Table S6). Adherence to rhythm monitoring was 67.5% for weekly event monitoring, 89.3% for electrocardiography, and 81.3% for 72-hour Holter monitoring (Fig. S3 and Table S7). Before hospital discharge, 237 of 287 patients (82.6%) who were assigned to undergo pulsed field ablation and 236 of 283 patients (83.4%) who were assigned to undergo thermal ablation remained unaware to their trial-group assignment (Tables S8 and S9).

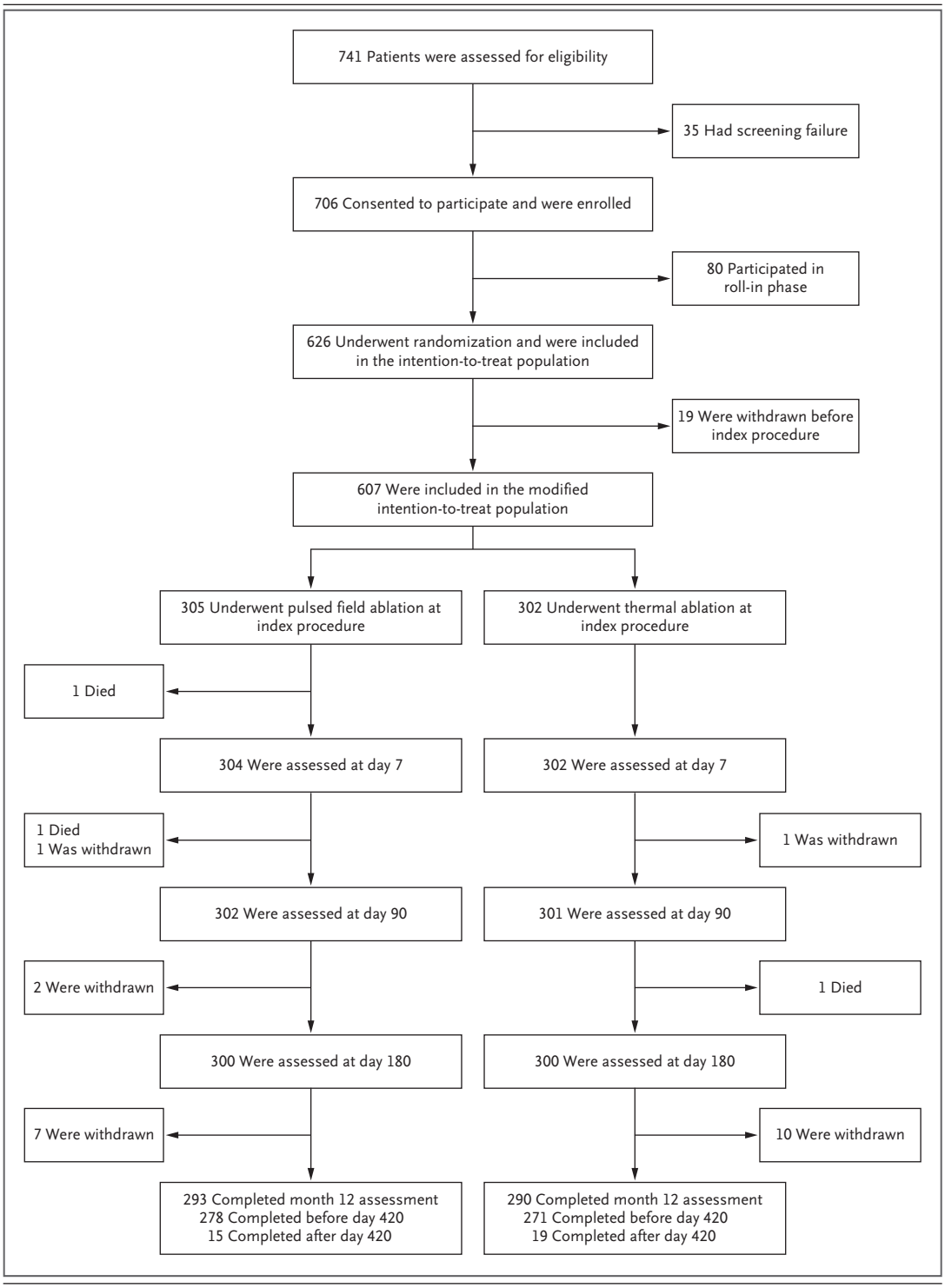
TREATMENT CHARACTERISTICS

The mean (±SD) total procedure time was 105.8±29.4 minutes for patients who underwent pulsed field ablation and 123.1±42.1 minutes for patients who underwent thermal ablation. The mean fluoroscopy time was 21.1±11.0 minutes for patients who underwent pulsed field ablation and 13.9±12.8 for patients who underwent thermal ablation (Fig. S4 and Table S10). The overall success of pulmonary vein isolation during the index procedure was 99.6% with pulsed field ablation and 99.8% with thermal ablation (Tables S11, S12, and S13). Electrical reconnection of the pulmonary veins during the 20-minute waiting period occurred in 53 of 1208 pulmonary veins (4.4%) treated with pulsed field ablation and 65 of 1182 pulmonary veins (5.5%) treated with thermal ablation.

Cavotricuspid isthmus ablation with the use of radiofrequency energy to treat atrial flutter was performed in 70 patients (23.0%) who underwent pulsed field ablation and 86 patients (28.5%) who underwent thermal ablation, with bidirectional block achieved in all cases. Additional ablation outside the pulmonary veins was performed in 5 patients (1.6%) who underwent pulsed field ablation and 16 patients (5.3%) who underwent thermal ablation.

END POINTS

Of the 305 patients who underwent pulsed field ablation, 204 had treatment success with respect to the primary efficacy end point (i.e., they were free of the composite of events) at 1 year, 80 had treatment failure, and 21 had censored data. Of the 302 patients who underwent thermal ablation, 194 had treatment success, 85 had treatment failure, and 23 had censored data. The estimated probability of treatment success was 73.3% for



pulsed field ablation and 71.3% for thermal ablation, with a between-group difference of 2.0 percentage points (95% Bayesian credible interval, –5.2 to 9.2) (Table 2 and Fig. 2). Pulsed field ablation met the criterion for noninferiority as compared with thermal ablation, with a poste-

Figure 1 (facing page). Screening, Randomization, and Follow-up.

Of the 741 patients screened for participation in the trial, 35 were classified as having screening failure: 27 patients (77%) did not meet eligibility criteria, 4 (11%) had an insurance denial, 2 (6%) declined to consent to participate, 1 (3%) was not enrolled owing to lack of availability of sponsor personnel support, and 1 (3%) was not enrolled because the trial enrollment cap had been met. Of the 626 patients comprising the intention-to-treat population, 19 were withdrawn before insertion of the ablation catheter into the body (8 who were assigned to undergo pulsed field ablation and 11 who were assigned to undergo thermal ablation [7 who were assigned to undergo cryoballoon ablation and 4 who were assigned to undergo radiofrequency ablation]), resulting in 607 patients being included in the modified intention-to-treat analysis; these patients had an ablation catheter inserted and received energy delivery. Of these 607 patients, 583 (96.0%) completed the trial, with 12 patients from each group prematurely exiting the trial.

rior probability of more than 0.999 (Fig. S5); results for analyses that used alternative priors are provided in Table S14. Device- or procedure-related serious adverse events (primary safety end point) occurred in 6 patients who underwent pulsed field ablation and 4 patients who underwent thermal ablation (estimated incidence, 2.1% vs. 1.5% [posterior means]; difference, 0.6 percentage points; 95% Bayesian credible interval, –1.5 to 2.8) (Tables 2 and 3 and Table S15); these findings met the criterion for noninferiority, with a posterior probability of more than 0.999 (Fig. S6).

The mean change in the cross-sectional area of the pulmonary veins (secondary safety end point) was –0.18 cm^2 (0.9%) with pulsed field ablation and –1.18 cm^2 (12.0%) with thermal ablation (Table 2), which met the criterion for superiority (posterior probability, >0.999). Among the patients who underwent thermal ablation, the mean change was –1.86 cm^2 (19.5%) with radiofrequency ablation and –0.39 cm^2 (3.3%) with cryoballoon ablation. No patients in either trial group had symptoms of pulmonary vein stenosis. The superiority of pulsed field ablation as compared with thermal ablation (secondary efficacy end point) had a posterior probability of 0.708 (Fig. S7). The probability of treatment success appeared to be similar among patients who underwent radiofrequency ablation and those who underwent cryoballoon ablation (95% Bayesian credible interval of the between-group difference, –14.1 to 6.4%) (Fig. S8).

Outcomes in the two groups also appeared to be similar when alternative definitions of treatment success that allowed for repeat ablation or continued use of class I or III antiarrhythmic drugs were considered (Table 2). Catheter ablation resulted in improvement in patient quality of life, without apparent between-group differences (Table 2). Repeat ablation was performed for clinical recurrence in 14 patients (4.6%) who initially underwent pulsed field ablation and 20 patients who underwent thermal ablation (6.6%). The durability of pulmonary vein isolation in patients who underwent a repeat ablation procedure was 64.8% per vein (28.6% per patient) with pulsed field ablation and 64.9% per vein (26.3% per patient) with thermal ablation.

Two patients who underwent pulsed field ablation had pericardial tamponade, one of whom underwent emergency sternotomy and lengthy resuscitation leading to multiorgan failure and death on day 10. In the brain MRI substudy that examined cerebral lesions after ablation, 3 of 33 patients who underwent pulsed field ablation and 0 of 37 patients who underwent thermal ablation had asymptomatic ischemic phenomena detected by MRI (Table 2). The single procedure-related clinical stroke occurred in a patient who underwent radiofrequency ablation (Table 3). Persistent phrenic-nerve injury occurred in 2 patients who underwent cryoballoon ablation (Table S16). A full list of adverse events is provided in Tables S17 and S18.

DISCUSSION

The ADVENT trial was a randomized, single-blind, noninferiority trial to determine whether pulsed field ablation is noninferior to conventional thermal ablation (radiofrequency ablation or cryoballoon ablation) for the treatment of patients with paroxysmal atrial fibrillation in whom medical therapy had failed. Among patients with paroxysmal atrial fibrillation receiving a catheter-based therapy, pulsed field ablation was noninferior to conventional thermal ablation with respect to the primary end point of freedom from a composite of initial procedural failure, documented atrial tachyar-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Pulsed Field Ablation (N=305)	Thermal Ablation (N=302)†
Age — yr	62.4±8.7	62.5±8.5
Sex — no. (%)		
Male	202 (66.2)	195 (64.6)
Female	103 (33.8)	107 (35.4)
Body-mass index‡	28.3±4.6	29.0±4.8
Race or ethnic group — no. (%)§		
American Indian or Alaska Native	0	1 (0.3)
Asian	6 (2.0)	5 (1.7)
Black	4 (1.3)	11 (3.6)
Native Hawaiian or other Pacific Islander	1 (0.3)	2 (0.7)
White	286 (93.8)	272 (90.1)
Unknown or declined to disclose	8 (2.6)	11 (3.6)
CHA_2DS_2-VASc score¶	1.7±1.2	1.7±1.2
Concomitant clinical conditions — no. (%)		
Coronary artery disease	32 (10.5)	51 (16.9)
Congestive heart failure: NYHA class I or II	59 (19.3)	59 (19.5)
Diabetes	33 (10.8)	32 (10.6)
Dyslipidemia	133 (43.6)	141 (46.7)
Hypertension	174 (57.0)	159 (52.6)
Sleep apnea	81 (26.6)	88 (29.1)
Previous stroke or TIA	12 (3.9)	15 (5.0)
Years since first diagnosis of paroxysmal atrial fibrillation	3.8±6.2	3.3±4.5
Any antiarrhythmic drug at baseline — no. (%)‖	301 (98.7)	300 (99.3)
Class I	115 (37.7)	101 (33.4)
Class II**	174 (57.0)	201 (66.6)
Class III	70 (23.0)	72 (23.8)
Class IV	79 (25.9)	66 (21.9)
Any anticoagulant — no. (%)	305 (100)	301 (99.7)
Nonwarfarin oral anticoagulant	303 (99.3)	300 (99.3)
Vitamin K antagonist	2 (0.7)	1 (0.3)

* Plus–minus values are means ±SD. NYHA denotes New York Heart Association, and TIA transient ischemic attack.
† The characteristics of the patients according to thermal-ablation method (radiofrequency ablation or cryoballoon ablation) are provided in Table S3 in the Supplementary Appendix.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Race or ethnic group was reported by the patient.
¶ CHA_2DS_2-VASc scores (an assessment of the risk of stroke among patients with atrial fibrillation) range from 0 to 9, with higher scores indicating a higher risk of stroke.
‖ Details of preablation treatment with antiarrhythmic drugs are provided in Table S4.
** The 95% Bayesian credible interval of the between-group difference did not include zero.

rhythmia after a 3-month blanking period, antiarrhythmic drug use, cardioversion, or repeat ablation and with respect to the primary safety end point of device- and procedure-related serious adverse events at 1 year.

In the ADVENT trial, the specific pulsed field

technology that was studied was the pentaspline pulsed field ablation catheter, which uses a waveform and dose strategy similar to that currently being used in clinical practice in Europe.[23,27,33-35] The population that was enrolled in the trial was also representative of patients with paroxysmal atrial fibrillation who present for treatment (Tables S19 and S20). The overall incidence of primary safety end-point events appeared low in both groups, but one procedure-related death occurred in a patient who underwent pulsed field ablation. This complication occurred as a result of catheter manipulation and was not related to the delivery of pulsed field energy. Such complications may become less frequent with greater operator familiarity with the technology. Indeed, in the initial postapproval European experience in the observational MANIFEST-PF study of the pulsed field ablation catheter, the incidence of pericardial tamponade seemed to decrease with increasing operator experience, and death occurred in 1 of 1758 patients (0.06%).[23]

In our trial, clinically significant pulmonary vein stenosis was not observed in either trial group. However, cardiac imaging showed that narrowing of the pulmonary vein ostia occurred to a greater extent with thermal ablation (primarily radiofrequency ablation) than with pulsed field ablation (Table 2). This finding is consistent with those of a previous nonrandomized comparative clinical study that showed frequent narrowing of the pulmonary veins, and occasionally pulmonary vein stenosis, with radiofrequency ablation but no instances of pulmonary vein stenosis or narrowing with pulsed field ablation.[16] On the basis of MRI studies, the mechanism appears to be related to the qualitatively different reparative process of pulsed field ablation, in which less chronic fibrosis occurs than with thermal ablation.[36]

To limit the possibility of other complications related to thermal ablation, including esophageal fistula and phrenic-nerve palsy, operators routinely used mitigation strategies such as esophageal deviation or temperature monitoring, as well as phrenic-nerve pacing during right pulmonary vein ablation (Table S21). Nonetheless, persistent phrenic-nerve paralysis occurred in two patients who underwent conventional thermal ablation (both treated with cryoballoon ablation). In contrast, no special maneuvers were used during pulsed field ablation, and no complications that appeared to be related to the energy delivered were observed. These findings are consistent with those of the observational MANIFEST-PF study of pulsed field ablation, in which no esophageal complications occurred (0 of 1758 patients), transient phrenic-nerve paralysis occurred in 8 of 1758 patients (0.46%), and persistent phrenic-nerve palsy occurred in 1 of 1568 patients (0.06%).[23,27]

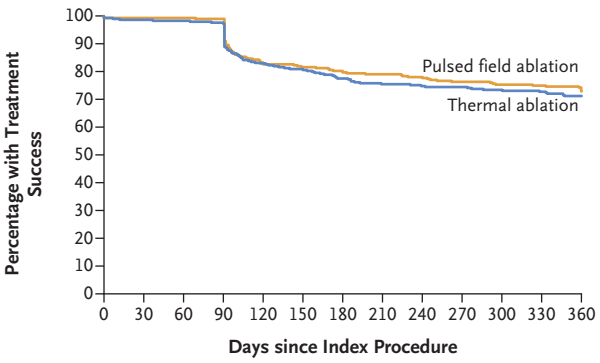
From a technical perspective, pulsed field ablation was associated with shorter procedure times than thermal ablation but required a longer duration of fluoroscopy. The difference in fluoroscopy time is probably related to the ubiquitous use of nonfluoroscopic electroanatomical mapping systems with radiofrequency ablation. Operator experience has been shown to reduce fluoroscopy exposure during pulsed field ablation,[33] and with the incorporation of these mapping systems into future pulsed field ablation platforms,[22-26] fluoroscopy use may be further decreased.

Pulsed field ablation was noninferior to thermal ablation with respect to efficacy. This finding is consistent with those of previous retrospective nonrandomized, single-center studies comparing pulsed field ablation with radiofrequency ablation or cryoballoon ablation.[34,35] In our trial, all the operators (except those at one center) had no previous clinical experience with the pulsed field ablation system but were considered to be expert operators with the thermal methods. Although operators were not as experienced with the use of pulsed field ablation, efficacy appeared similar to that of procedures completed with thermal ablation. Furthermore, observational data suggest that with improved operator technique and incorporation of ancillary methods such as electroanatomical mapping or intracardiac echocardiography into the procedures, the effectiveness of pulsed field ablation may improve further.[27]

Our trial has several limitations. Some episodes of asymptomatic recurrence of atrial fibrillation may have been missed because continuous invasive monitoring was not used. However, in contrast to the results of other recent trials, our results represent single-procedure outcomes in which treatment success did not allow the use of class I or III antiarrhythmic drugs, and patients underwent follow-up ECG monitoring and 72-hour

Table 2. Primary, Secondary, and Other End Points.*

End Point	Pulsed Field Ablation (N=305)	Thermal Ablation (N=302)	Difference (95% BCI)	Posterior Probabilities	
				Noninferiority	Superiority
Primary and secondary efficacy end point†					
Treatment success — no. (%)	204 (73.3)	194 (71.3)	2.0 (−5.2 to 9.2)‡	>0.999§	0.708¶
Reason for treatment failure — no. (%)					
Initial procedural failure with the use of the assigned treatment method	2 (0.8)	2 (0.8)	0.0 (−1.5 to 1.5)‡		
Recurrent atrial arrhythmia lasting ≥30 sec after the 3-mo blanking period	51 (17.2)	48 (16.4)	0.7 (−5.2 to 6.7)‡		
Cardioversion after the 3-mo blanking period	1 (0.5)	0 (0.2)	0.3 (−0.6 to 1.5)‡		
Use of class I or III antiarrhythmic drugs after the 3-mo blanking period	24 (8.1)	27 (9.2)	−1.1 (−5.6 to 3.4)‡		
Amiodarone use at any time	1 (0.5)	7 (2.5)	−2.0 (−4.2 to −0.2)‡		
Repeat ablation at any time	1 (0.5)	1 (0.5)	0.0 (−1.2 to 1.2)‡		
Other prespecified efficacy end points — no. (%)					
Treatment success allowing repeat ablation	204 (73.3)	194 (71.3)	2.0 (−5.2 to 9.2)‡		
Treatment success allowing the use of class I or III antiarrhythmic drugs	219 (78.5)	208 (76.3)	2.3 (−4.4 to 9.0)‡		
Quality-of-life assessments — mean (95% BCI)					
Change from baseline to 1 yr in the AFEQT score‖	30.1 (27.7 to 32.5)	27.7 (25.2 to 30.3)	2.3 (−1.2 to 5.9)		
Change from baseline to 1 yr in the EQ-5D score**	0.05 (0.03 to 0.06)	0.04 (0.03 to 0.06)	0.01 (−0.02 to 0.03)		
Change from baseline to 1 yr in the EQ-VAS score††	7.9 (6.5 to 9.4)	6.8 (5.1 to 8.4)	1.2 (−1.0 to 3.4)		
Primary safety end point: device- or procedure-related serious adverse events — no. (%)‡‡	6 (2.1)	4 (1.5)	0.6 (−1.5 to 2.8)‡	>0.999	
Secondary safety end point: change in the cross-sectional area of the pulmonary veins§§					
Mean absolute difference (95% CI) — cm^2	−0.18 (−0.37 to 0.00)	−1.18 (−1.39 to −0.97)	1.00 (0.72 to 1.28)		>0.999
Mean relative difference (95% CI) — %	−0.9 (−3.0 to 1.1)	−12.0 (−14.2 to −9.7)	11.0 (8.0 to 14.1)‡		
SCE or SCL on MRI of the brain — no./total no. (%)¶¶					
Data as adjudicated by the centers	6/34 (18)	4/37 (11)			
Data as adjudicated by the core laboratory	3/33 (9)‖‖	0/37			



No. at Risk					
Pulsed field ablation	301	298	238	228	176
Thermal ablation	296	292	228	219	150
Treatment Success (%)					
Pulsed field ablation	99.3	99.0	79.7	76.4	73.1
Thermal ablation	98.7	97.3	77.5	74.5	71.3

Figure 2. Efficacy Outcomes of Pulsed Field Ablation as Compared with Thermal Ablation.

Shown are the Kaplan–Meier survival curves for freedom from a composite of initial procedural failure to isolate the pulmonary veins with the use of the randomly assigned treatment method only, atrial tachyarrhythmia (atrial fibrillation, atrial flutter, or atrial tachycardia) lasting 30 seconds or more after the 3-month blanking period, the use of class I or III antiarrhythmic drugs or cardioversion after the 3-month blanking period, the use of amiodarone at any time, or repeat ablation at any time. Shown are the two primary cohorts, patients who underwent pulsed field ablation and those who underwent thermal ablation. The latter group includes patients who underwent radiofrequency ablation and those who underwent cryoballoon ablation.

Holter monitoring.[24,29,37-39] Follow-up was limited to 1 year, so comparative longer-term outcomes are unknown. However, recurrence of symptomatic atrial fibrillation appeared infrequent between years 2 to 5 in a recent single-center study involving patients with paroxysmal atrial fibrillation who were followed for 5 years.[40] Our trial evaluated a single pulsed field ablation catheter technology in patients with paroxysmal atrial fibrillation only, so the outcomes are not generalizable to other pulsed field ablation systems or to patients with nonparoxysmal atrial fibrillation.

The ADVENT trial showed that among patients with paroxysmal atrial fibrillation receiving a catheter-based therapy, pulsed field ablation was noninferior to conventional thermal ablation with respect to the primary efficacy end point of freedom from a composite of initial procedural failure, documented atrial tachyarrhythmia after a 3-month blanking period, anti-

* All data are derived from the modified intention-to-treat population. Unless otherwise specified, percentages represent the probability of a patient having the condition, estimated as the mean of the posterior distribution, after inclusion of censored observations through multiple imputation. BCI denotes Bayesian credible interval.

† The primary efficacy end point was freedom from a composite of initial procedural failure to isolate the pulmonary veins with the use of the randomly assigned treatment method only, atrial tachyarrhythmia (atrial fibrillation, atrial flutter, or atrial tachycardia) lasting 30 seconds or more after the 3-month blanking period, the use of class I or III antiarrhythmic drugs or cardioversion after the 3-month blanking period, the use of amiodarone at any time during the 1-year follow-up period, with assessment for the noninferiority of pulsed field ablation as compared with thermal ablation. The secondary efficacy end point was the same as the primary efficacy end point but was tested for the superiority of pulsed field ablation as compared with thermal ablation.

‡ The difference is expressed in percentage points.

§ The posterior distribution of the between-group difference in the population proportions is depicted in Fig. S5.

¶ The posterior distribution of the between-group difference in the population proportions is depicted in Fig. S7.

‖ The Atrial Fibrillation Effect on Quality-of-Life (AFEQT) survey is a disease-specific health-related quality-of-life survey. Scores range from 0 to 100, with higher scores indicating a better quality of life.

** The EuroQol 5-Dimension (EQ-5D) survey is a generic health-related quality-of-life survey. Scores range from 0.0 to 1.0, with higher scores indicating a better quality of life.

†† The EuroQol Visual Analogue Scale (EQ-VAS) is a vertical visual-analogue scale on which patients provide a global assessment of their health. Scores range from 0 to 100, with higher values indicating a better quality of life.

‡‡ The point estimates were calculated as the means of the posterior distributions. Details regarding these safety end-point events are provided in Table S15 and S17. A comprehensive list of all the adverse events is provided in Table S18.

§§ This end point was defined as the paired difference in the computed aggregate pulmonary vein cross-sectional area between baseline and 3 months. These data include 259 patients who underwent pulsed field ablation and 255 patients who underwent thermal ablation.

¶¶ Silent cerebral events (SCEs) are positive on diffusion-weighted imaging (DWI) but not on fluid-attenuated inversion recovery (FLAIR), whereas silent cerebral lesions (SCLs) are positive on both DWI and FLAIR.

‖‖ One MRI scan that was reviewed by the center was not reviewed by the core laboratory because the scan was performed on a 3-Tesla scanner.

Table 3. Serious and Nonserious Adverse Events.*

Event	Serious Adverse Events†		Serious or Nonserious Adverse Events‡	
	Pulsed Field Ablation (N=305)	Thermal Ablation (N=302)	Pulsed Field Ablation (N=305)	Thermal Ablation (N=302)
	number of patients (percent)			
Any event	6 (2.0)§	4 (1.3)	7 (2.3)§	6 (2.0)
Death	1 (0.3)	0	1 (0.3)	0
Myocardial infarction	0	0	0	0
Persistent phrenic-nerve palsy	0	0	0	2 (0.7)
Stroke	0	1 (0.3)	0	1 (0.3)
TIA	1 (0.3)	0	1 (0.3)	0
Systemic thromboembolism	0	0	0	0
Cardiac tamponade or perforation	2 (0.7)	0	2 (0.7)	0
Pericarditis	1 (0.3)	0	2 (0.7)	0
Pulmonary edema	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Vascular-access complication	1 (0.3)	2 (0.7)	1 (0.3)	2 (0.7)
Heart block	0	0	0	0
Gastric motility or pyloric spasm	0	0	0	0
Pulmonary vein stenosis	0	0	0	0
Atrioesophageal fistula	0	0	0	0

* All data are derived from the modified intention-to-treat population. Details regarding these adverse events are provided in Table S15.
† The primary safety end point was a composite of prespecified device- and procedure-related serious adverse events within 7 days after the procedure. Atrioesophageal fistula and pulmonary vein stenosis were included as serious adverse events regardless of the timing of occurrence.
‡ These events include all device- or procedure-related adverse events that were prespecified in the primary safety end point but without regard to the seriousness categorization of the event.
§ One patient who had a cardiac tamponade subsequently died; accordingly, the individual components add to more than the total number of patients with any event.

arrhythmic drug use, cardioversion, or repeat ablation and with respect to the primary safety end point of device- and procedure-related serious adverse events at 1 year.

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APPENDIX

The authors' affiliations are as follows: the Helmsley Electrophysiology Center, Icahn School of Medicine at Mount Sinai (V.Y.R., W.W.), and Lenox Hill Hospital, Northwell Health (S.E.M.) — both in New York; the University of California, San Francisco, San Francisco (E.P.G.), Scripps Clinic and Prebys Cardiovascular Institute, San Diego (D.N.G.), and Boston Scientific, Menlo Park (A.B.A., C.W.S.) — all in California; Texas Cardiac Arrhythmia Institute, St. David's Medical Center, Austin (A.N.); Case Western Reserve University, Cleveland (A.N.); Trident Medical Center, Charleston, SC (F.A.C.); University of Pittsburgh Medical Center Pinnacle, Harrisburg (C.P.), and Doylestown Hospital, Doylestown (J.D.H.) — both in Pennsylvania; Vanderbilt University Medical Center, Nashville (C.R.E.); Virginia Commonwealth University, Richmond (K.A.E.); Emory University Hospital, Atlanta (D.B.D.); Grandview Medical Center, Birmingham, AL (J.O.); Paradigm Biostatistics, Anoka (A.S.M.), and Boston Scientific, St. Paul (E.M.A., K.M.S.) — both in Minnesota; Lehmann Consulting, Naples, FL (J.W.L.); and Massachusetts General Hospital, Boston (M.M.).

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