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Brugada Syndrome Ablation for the Prevention of Ventricular Fibrillation Episodes (BRAVE)

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ABSTRACT

BACKGROUND Catheter ablation has emerged as a promising treatment to prevent ventricular fibrillation (VF) in Brugada syndrome (BrS). However, evidence from a prospective, randomized clinical trial is lacking.

OBJECTIVE The Brugada Syndrome Ablation for the Prevention of Ventricular Fibrillation Episodes trial is a prospective, multicenter, 2-arm, randomized (1:1), open-label clinical study designed to evaluate the efficacy and safety of ablation therapy in patients with symptomatic BrS.

METHODS We enrolled patients with symptomatic BrS with an implantable cardioverter-defibrillator. Patients were randomized to ablation therapy or control groups. Ablation targeted arrhythmogenic areas identified through electroanatomical mapping, predominantly at the right ventricular epicardium. The primary outcome was the first occurrence of VF or death. One interim analysis was planned after 50 patients were randomized.

RESULTS Of 67 patients screened, 52 were randomized (25 to ablation, 25 to control, 2 withdrawals), and 15 declined randomizations but remained in a registry (10 chose ablation, 5 opted against ablation). After 3 years of follow-up, the ablation group had significantly fewer VF events than the control group (hazard ratio, 0.288; $P = .0184$). At the interim analysis, the Data Safety Monitoring Board recommended early trial termination. Among all ablation recipients (including crossovers and registry participants), 83% remained VF free after a single procedure and 90% after a repeat ablation. Complications of ablation included 1 hemopericardium without a long-term sequel.

CONCLUSION Epicardial substrate ablation significantly reduces VF recurrence in patients with symptomatic BrS with implantable cardioverter-defibrillators and seems safe, supporting its potential role as a first-line therapy to prevent recurrent VF in patients with symptomatic BrS.

KEYWORDS Brugada syndrome; Ablation; Ventricular fibrillation; Implantable cardioverter-defibrillator; Sudden death

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Introduction

Brugada syndrome (BrS) is a leading cause of sudden cardiac death in otherwise healthy individuals with no overt structural heart disease, primarily owing to ventricular fibrillation (VF).[1,2] An implantable cardioverter-defibrillator (ICD) has been the cornerstone treatment for patients with symptomatic BrS,[3] whereas quinidine is the only antiarrhythmic agent with documented efficacy.[4] However, both treatment options have limitations. The ICD effectively terminates VF episodes but does not prevent them, and patients may have traumatic experiences from frequent ICD shocks. In addition, long-term ICD therapy carries unwanted effects.[5–8] Clinicians often face challenges in suppressing recurrent VF episodes and managing arrhythmic storms that lead to repeated ICD discharges.[7] Quinidine is unavailable in many countries and may cause intolerable side effects during prolonged use.[9,10]

Catheter ablation of arrhythmic substrate areas on the anterior right ventricular outflow tract and right ventricular epicardium emerged over a decade ago as a promising therapeutic modality to prevent VF occurrences in BrS.[11] Since then, epicardial substrate ablation has been increasingly performed in patients with symptomatic BrS. Recently, 2 large observational studies with long-term follow-up further supported the efficacy of catheter ablation for symptomatic BrS. However, these studies were observational and did not use a prospective randomized controlled trial design.[12–14]

In 2017, we initiated the Brugada Syndrome Ablation for the Prevention of Ventricular Fibrillation Episodes (BRAVE) trial (ClinicalTrials.gov, NCT0270441), a prospective, multicenter, 2-arm, randomized, open-label clinical trial aimed at evaluating the effectiveness and safety of epicardial ablation therapy in symptomatic BrS who had initially received an ICD. During an interim analysis, the Data Safety Monitoring Board (DSMB) recommended stopping the trial owing to clear evidence that ablation significantly reduces VF recurrences. Herein, we present the findings of the BRAVE study.

Abbreviations

BRAVE: Brugada Syndrome Ablation for the Prevention of Ventricular Fibrillation Episodes

BrS: Brugada syndrome

CI: confidence interval

DSMB: Data Safety Monitoring Board

ECG: electrocardiogram

EPS: electrophysiologic study

ER: early repolarization

HR: hazard ratio

ICD: implantable cardioverter-defibrillator

PVC: premature ventricular contraction

VT/VF: ventricular tachycardia/ventricular fibrillation

Methods

Study design

We conducted a multicenter, open-label, prospective, 2-arm, randomized (1:1) trial comparing the effectiveness of ablation therapy in patients with BrS initially treated with an ICD. All participating sites (see Appendix) secured approval for the study from their respective institutional review board. Our study was conducted in the accordance with the Declaration of Helsinki and Consolidated Standards of Reporting Trials guidelines. Data monitoring was performed at the Center of Excellence in Arrhythmia Research at Chulalongkorn University, Bangkok, Thailand.

Study population

We enrolled patients with symptomatic BrS. BrS was diagnosed in accordance with the latest consensus statement by Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society.[15] Symptomatic BrS was defined by the presence of a type 1 BrS electrocardiogram (ECG) pattern with or without sodium channel blocker challenge, along with 1 or more of the following: (1) aborted cardiac arrest, (2) documented VF episodes, (3) agonal respiration during sleep with difficulty arousing, (4) unexplained syncope with malignant characteristics, or (5) seizures suspected to be of arrhythmic origin. Additional inclusion criteria were (1) previous ICD implantation within the last 5 years, or if the ICD was implanted more than 5 years ago, at least 1 appropriate shock within the last 5 years; (2) patient consent to participate in the study; and (3) absence of structural heart disease, confirmed by cardiac imaging (echocardiogram, computed tomography, or magnetic resonance imaging) and coronary angiogram or significant comorbidities. Exclusion criteria were (1) age younger than 16 or older than 70 years, (2) coexisting BrS and long QT syndrome, and (3) any medical or psychological conditions precluding fitness for ablation.

Study protocol

Randomization

Patients were randomly assigned in a 1:1 ratio to undergo catheter ablation (ablation group) or no ablation (control group) (Figure 1). Randomization was blocked and stratified by the participating centers to avoid imbalances in treatment allocation. Patients in the control arm who experienced frequent ICD discharges could cross over to undergo ablation.

Electrophysiologic studies, mapping of VF substrates, and ablation protocol

All patients, randomized to the ablation arm, underwent comprehensive electrophysiologic studies (EPSs). For patients with frequent premature ventricular contractions (PVCs) documented as VF triggers, mapping was performed to identify the site of earliest activation relative to the QRS onset. PVCs with Purkinje potentials preceding spontaneous ventricular activation were considered Purkinje originated. Substrate mapping used electroanatomical mapping with the CARTO system (Biosense Webster, Irvine, California) during sinus rhythm. Both endocardial and epicardial mapping was performed. Abnormal electrograms were defined by (1) low voltage ($\leq$ 1 mV), (2) split or fractionated signals with $\geq$ 2 components separated by > 20 ms isoelectric intervals, and (3) long duration (> 80 ms) or late potentials.

Programmed ventricular stimulation for ventricular tachycardia (VT) and VF induction (2–3 cycle lengths: 600, 500,

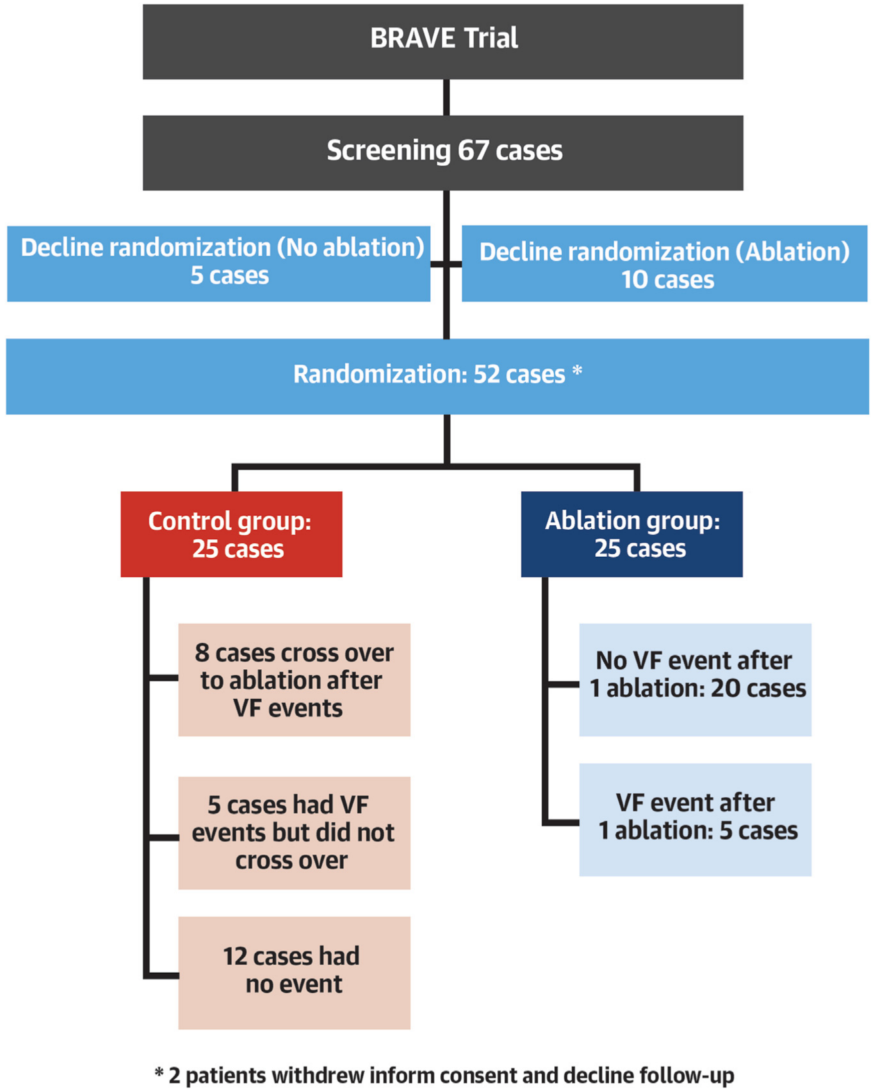


Figure 1
Flow chart illustrating the randomized controlled trial design, patient inclusion criteria, and allocation after randomization. BRAVE = Brugada Syndrome Ablation for the Prevention of Ventricular Fibrillation Episodes; VF = ventricular fibrillation.

400 ms) with up to triple stimuli was performed at baseline and repeated after ablation. Ablation targets included PVCs initiating VF (VF triggers) and/or VF substrates (areas with abnormal electrograms). Irrigated-tip, contact-force catheters were used, applying 20–50 W of radiofrequency energy guided by voltage reduction and elimination of mid-late fractionated electrograms. Intravenous or intrapericardial corticosteroids were administered at the end of the procedure.

The ablation endpoint included the elimination of any PVCs identified as VF triggers and ablation of all VF substrates, with elimination of all abnormal fractionated electrograms. Ajmaline was used to unmask arrhythmogenic substrates, as discussed elsewhere,[16] with repeat doses administered if remapping exceeded 10 minutes.

Noninducibility of sustained VT/VF was not a mandatory endpoint, although additional ablation was performed at the operator's discretion if sustained arrhythmias (≥ 10 seconds) remained inducible.

Clinical endpoints

Patients were followed every 3 months, including ICD interrogation and assessment of VT/VF events. We recommend that all centers to program ICD, according to the 2015 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society/Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia expert consensus guidelines: a single detection zone (≥ 200 bpm) with prolonged tachycardia detection to 12 seconds, therapy consisting of 1 or 2 bursts anti-tachycardia pacing using at least 8 stimuli at 84%–88% of the tachycardia cycle length, followed by shock therapy at maximum output.[17] Ajmaline challenges were done 3 months after ablation only in patients with no Brugada ECG pattern. At each follow-up, ECGs with V1–V3 leads placed in the second to fourth intercostal spaces were recorded.

The primary endpoint was the time from randomization to the first VT/VF episode detected by ICD interrogation or death, whichever occurred first. Secondary endpoints included normalization of the Brugada ECG pattern and noninducibility of VT/VF. Complications from EPSs, ablation, or adverse effects from ICDs (eg, inappropriate ICD discharges) were reported. All VF episodes and ICD discharges were adjudicated by independent electrophysiologists who were blinded to the randomization group.

Statistical analysis

Randomized groups were compared for differences in baseline characteristics using the Wilcoxon-rank sum test for continuous variables and based on Fisher's exact test for categorical variables. Factors significantly different between the groups were included as covariates in subsequent analyses. Event rates between the 2 treatment arms were analyzed using (1) Kaplan-Meier methods to calculate survival curves, (2) log-rank tests to compare survival curves, and (3) Cox proportional hazards regression to compare survival curves while adjusting for covariates that differed significantly between treatment arms.

The time to be censored for the composite endpoint (VT/VF or death) was the date of the first event. If participants did not experience an event, they were censored at their last follow-up date

Interim analysis

One interim analysis was planned after 50 patients had been randomized with early stopping rules for futility and efficacy, comparing the ablation and control groups using a group sequential design. The interim analysis was based on the observed annual event rates in the ablation and control groups. The decision rule for terminating the study was based on demonstrating a significant difference in hazard rates between the 2 groups. In particular, the null hypothesis of no difference in hazard rates was rejected if the type I error was 5% and the study achieved 80% power.

Results

The BRAVE study was temporarily halted during the coronavirus disease 2019 pandemic from 2020 to 2022, resulting in slower patient accrual. Nonetheless, the trial reached its milestone for the first interim analysis after randomizing 50 patients. The DSMB reviewed this analysis and recommended stopping the trial in December 2024 owing to a significant difference in hazard rates between the 2 groups.

Patients

A total of 67 patients were screened for eligibility (Figure 1). Fifteen declined randomizations; 10 opted for catheter ablation outside the study, whereas 5 chose no treatment; all 15 remained under follow-up at the arrhythmia clinic as part of the BRAVE Registry. The remaining 52 patients (51 males) were randomized as follows: 27 to the ablation group and 25 to the control group. Two patients (1 female and 1 male) in the ablation group withdrew their consent immediately after randomization, opting out of both ablation and follow-up; these 2 patients were excluded from analysis.

Baseline demographics and clinical characteristics of randomized patients were well balanced (Table 1). The cohort was predominantly young, with a mean age of 43 years and only 10% older than 65 years. All participants were symptomatic: 45 patients had survived VF/cardiac arrest, and 5 had experienced syncope suspected to be arrhythmogenic in origin. In addition, 38 patients (76%) had experienced ICD shocks within 6 months before randomization. Of these, 45 (90%) demonstrated a spontaneous type 1 BrS ECG pattern and thus did not require ajmaline challenge at baseline, whereas 5 showed this pattern only after an ajmaline challenge. In addition, 15 patients (30%) exhibited combined Brugada and spontaneous early repolarization (ER) ECG patterns (Figure 2).

Table 1 Demographics and baseline characteristics

Characteristics	Group: RF ablation group (n = 25)	Group: Control group (n = 25)	*P* value
Age, y			
Mean (SD)	43 ± 14	44 ± 13	.90
Median (Q1, Q3)	43.0 (32.0, 51.0)	44.0 (35.0, 50.0)	
How long the AICD was implanted, n (%)			
≤2 y	10 (40)	11 (44)	1.00
>2 y	15 (60)	14 (56)	
Status case, n (%)			
Symptomatic Brugada defined VF or SCA	24 (96)	21 (84)	.35
Symptomatic Brugada defined syncope	1 (4)	4 (16)	
Concomitant ER			
ER on inferior lead only, n (%)	5 (20)	4 (16)	1.00
ER on lateral lead only, n (%)	2 (8)	2 (8)	1.00
ER inferolateral leads	1 (4)	1 (4)	1.00
Brugada marker on ECG, n (%)			
Yes, spontaneous ECG	24 (96)	21 (84)	.35
Yes, only on drug test ECG	1 (4)	4 (16)	
SCN5A testing	n = 23	n = 22	
SCN5A positive, n (%)	2 (13)	4 (18)	.41
VF episodes on ICD, n (%)			
No episode	8 (32)	8 (32)	
1–4 episodes	5 (20)	7 (28)	
5–9 episodes	6 (24)	3 (12)	
10–20 episodes	6 (24)	3 (12)	.18
>20 episodes	0 (0)	4 (16)	

AICD = automated implantable cardioverter-defibrillator; ECG = electrocardiogram; ER = early repolarization; ICD = implantable cardioverter-defibrillator; Q1 = first quartile; Q3 = third quartile; RF = radiofrequency; SCA = sudden cardiac arrest; SD = standard deviation of a sample; VF = ventricular fibrillation.

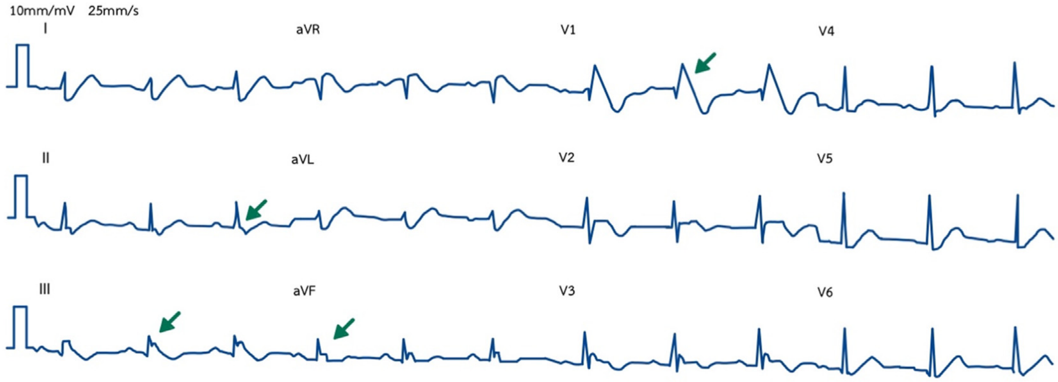


Figure 2
Electrocardiogram from a patient exhibiting overlapping Brugada and early repolarization patterns. Arrows indicate the classic type 1 Brugada electrocardiogram pattern in lead V1 and augmented J-waves characteristic of early repolarization in the inferior leads (II, III, and aVF).

Interim analysis findings

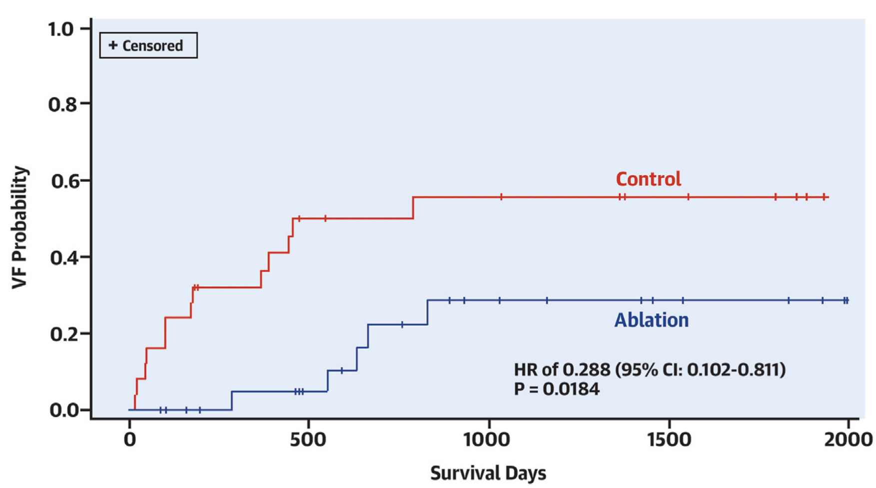
The follow-up durations are comparable between the 2 groups: the follow-up time was 1056 ± 138 for the ablation group vs 1259 ± 173 for the control group (P = .77). During follow-up, a total of 18 patients experienced at least 1 VF events: 5 (20%) in the ablation group and 13 (52%) in the control group.

The rate of recurrent VF was lower in the ablation group than the control group (hazard ratio [HR], 0.288; 95% confidence interval, 0.102–0.811; Cox proportional hazard P = .0184; Figure 3). This result met the prespecified interim analysis stopping criterion (HR, <0.342) at a type I error of 0.05 and 80% power. Consequently, the DSMB recommended stopping the trial in December 2024 based on the superior outcomes observed in the ablation group. After trial termination, we promptly informed all study participants of the results and offered ablation treatment to patients initially assigned to the control group.

For the 15 patients who entered the BRAVE Registry but declined randomization, 10 underwent ablation. Of these, 9 remained free from VF recurrence (1 patient required a second ablation), and 1 patient was lost to follow-up but reportedly remains alive. Among the 5 patients who declined both randomization and ablation, 2 experienced VF events (one had a single event, the other had 2 events), whereas the remaining 3 patients had no VF episodes.

Adverse events

No deaths occurred. The only major complication from ablation therapy was a hemopericardium in 1 patient; this resolved without prolonged hospitalization or long-term sequelae. Four inappropriate ICD discharges were observed (2 owing to supraventricular tachycardia [1 event in each group] and 2 owing to atrial fibrillation with rapid ventricular rates [1 event in each group]).



Patients at Risk

Control	25	21	15	15	13	10	9	9	8	8	8	7	7	7	5	5	4	4	3	1	0
Ablation	25	24	21	20	20	17	15	13	12	10	9	8	7	7	7	5	4	4	4	3	0

Figure 3
Kaplan-Meier curves comparing VF-free survival after the first ablation procedure between the ablation and control groups. CI = confidence interval; HR = hazard ratio; VF = ventricular fibrillation.

Clinical outcomes of catheter ablations (randomized, registry, and crossover patients)

To investigate factors influencing ablation outcomes, we analyzed combined data from 42 patients who ultimately underwent ablation therapy, including the 25 patients originally randomized to the ablation arm, 8 of 13 control-arm patients who experienced ICD discharges and subsequently crossed over to ablation, and 9 of 10 eligible patients who declined randomization but opted for catheter ablation (1 patient from this subset was lost to follow-up and excluded from analysis).

Of these 42 patients, 40 (85%) had a spontaneous type 1 Brugada ECG pattern, and 13 (31%) showed combined Brugada and ER ECG patterns (Table 2). Before ablation, 33 patients (79%) had experienced ICD shocks owing to recurrent VF episodes, ranging from 1 to more than 20 episodes per patient within the 6 months preceding the procedure. All patients had inducible sustained polymorphic VT/VF.

After ablation, 35 patients (83%) demonstrated normalization of their type 1 Brugada ECG pattern, whereas the remaining 7 (17%) continued to demonstrate a type 1 Brugada ECG (5 spontaneous and 2 after ajmaline challenge). Repeating EPS after completion of the ablation procedure was performed in 34 patients; of those, only 8 patients (20%) had inducible VF. During the follow-up after this first ablation, 35 patients (83%) became VF free and received no ICD discharges.

Table 2 Clinical characteristics of all patients who underwent catheter ablation

Characteristics	Results
Number of patients	42
Age, y, mean ± SD (median)	43.2 ± 11.5 (41)
Gender (M/F)	All M
Symptoms (N = 42)	
Aborted cardiac arrests/VF, n (%)	37 (88)
Arrhythmogenic syncope/VF, n (%)	5 (12)
Family history (N = 42)	
Positive, n (%)	16 (38)
Type 1 Brugada ECG (N = 42)	
Spontaneous, n (%)	40 (95)
With sodium channel blockade, n (%)	2 (5)
Concomitant early repolarization ECG (N = 13)	
Inferior wall only, n (%)	10 (77)
Inferolateral, n (%)	1 (8)
Lateral wall only, n (%)	2 (15)
Distribution of patients according to the number of VF episodes on ICD (N = 42)	
No episode, n (%)	9 (21)
1–5 episodes, n (%)	8 (19)
5–9 episodes, n (%)	12 (29)
10–20 episodes	9 (21)
>20 episodes	4 (10)
SCN5A mutation (N = 34)	
SCN5A tested positive, n (%)	6 (18), only 1 pathogenic, the rest VUS

ECG = electrocardiogram; F = female; ICD = implantable cardioverter-defibrillator; M = male; SD = standard deviation of a sample; VF = ventricular fibrillation; VUS = variant of unknown significance.

Among the 7 patients who did not respond to the initial ablation, 6 had a combined ER and Brugada ECG pattern and 5 of these 6 patients had normalization of the Brugada ECG pattern after ablation. The single patient without a concomitant ER pattern maintained the Brugada ECG pattern after ablation. VF-free survival rates were better among patients with pure Brugada ECG than those with concomitant ER pattern (HR, 0.08; 95% confidence interval, 0.01–0.64; $P = 0.002$; Figure 4). Essentially, all patients with BrS without concomitant ER remained free of VF events after a single ablation, except for 1 patient whose Brugada ECG pattern persisted, suggesting an ongoing arrhythmogenic substrate.

Four of the 7 patients who failed the initial ablation underwent a second procedure. The remaining 3 chose not to pursue further ablation owing to infrequent, asymptomatic, nocturnal VF episodes triggering ICD shocks during sleep. Three of the 4 patients undergoing a second ablation became VF free. The remaining patient experienced VF recurrence associated with thyrotoxicosis; subsequent attempts at a third ablation were complicated by pericardial adhesions. He received quinidine therapy temporarily, which was discontinued owing to drug unavailability; however, he has remained VF free for the past 20 months. Overall results (Figure 5), including repeat ablations in 4 patients and a mean follow-up of 38.54 months (standard error, 5.40), yielded an overall success rate of 38 of 42 patients (90%), with an average of 1.1 ± 0.3 ablation sessions.

Discussion

Over the past decade, numerous observational and meta-analysis studies have demonstrated the benefits of catheter ablation in preventing recurrent VF episodes among patients with symptomatic BrS.[12,13,18,19] However, until now, randomized controlled trials validating the long-term efficacy and safety of this approach for BrS were lacking. The BRAVE study is the first prospective randomized trial designed specifically to fill this knowledge gap.

The DSMB's recommendation to terminate the trial early was based on definitive evidence of ablation's efficacy. As shown in Figure 2, the ablation group experienced significantly fewer VF events than the control group over a median follow-up of approximately 3 years.

Furthermore, an analysis of combined data from all patients undergoing ablation, including randomized, crossover, and those who declined randomization but chose ablation, revealed that VF-free survival was achieved in 83% after the first ablation and 90% after repeat ablation (in 4 patients). The few patients experiencing recurrent VF episodes generally found them infrequent and tolerated them without pursuing additional ablation. Hemopericardium in 1 patient was the sole major complication, resolving with no long-term consequences.

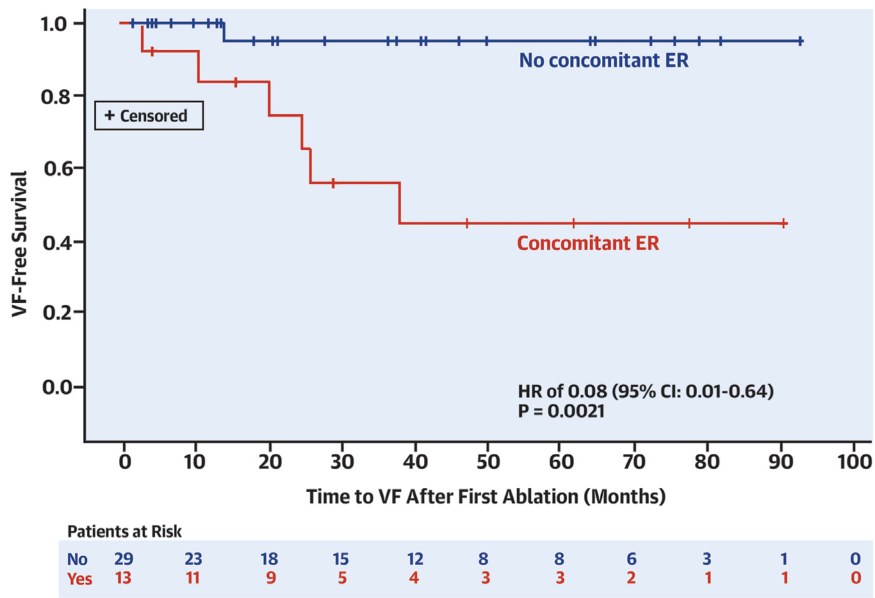


Figure 4
Kaplan-Meier curves comparing VF-free survival after the first ablation between patients with Brugada syndrome alone and those with combined Brugada and ER electrocardiogram patterns. CI = confidence interval; ER = early repolarization; HR = hazard ratio; VF = ventricular fibrillation.

As in the Brugada Ablation of VF Substrate Ongoing Multicenter Registry (BRAVO) and other observational studies, patients who exhibited a combined BrS + ER pattern and/or retained a Brugada ECG after ablation had a higher risk of VF recurrence.[12] Importantly, those with a purely Brugada pattern that was eliminated (especially if type I pattern elimination was confirmed by ajmaline administration) had no VF recurrence. Further improvements in mapping techniques, ablation tools, and substrate identification—particularly for patients with combined ER and BrS—are essential to achieve higher success rates during the first ablation session.

Our results also underscore the importance of BrS substrate ablation as an important therapeutic option for BrS treatment.

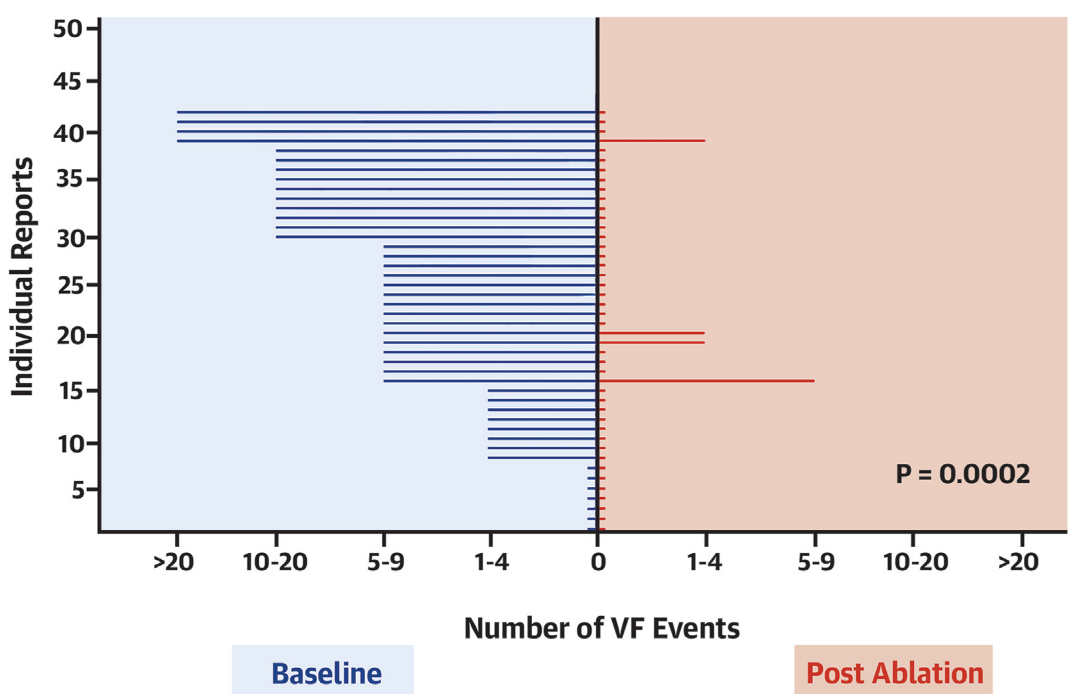


Figure 5
Individual patient data illustrating the number of VF episodes and implantable cardioverter-defibrillator shocks before and after catheter ablation of VF substrates in 42 patients. Each line on either side of the vertical ablation line represents 1 patient and their corresponding VF/shock episodes. VF = ventricular fibrillation.

Thus far, ablation may be the only treatment modality shown to truly prevent VF recurrence in symptomatic BrS. Although quinidine may also reduce recurrence, it is unavailable in many parts of the world and may cause significant side effects during long-term treatment.[10] The availability of a catheter-based therapy capable of preventing VF and offering good long-term outcomes represents a significant advance for this patient population.

Nevertheless, one must recognize that percutaneous epicardial mapping and ablation is an invasive procedure that carries inherent risks. It necessitates experienced operators and an adept electrophysiology team and should be performed at centers equipped for complex ablation procedures with expertise in epicardial mapping.[20] It must also be emphasized that our data apply to patients with symptomatic BrS and should not be misconstrued as support for indiscriminate ablation in patients with low-risk, asymptomatic BrS, as defined in the 2022 ESC guidelines.[3] Similarly, given that the control arm received no quinidine, our results should not be extrapolated to patients with symptomatic BrS who are well controlled with quinidine therapy.

A key question then arises: could ablation—without ICD backup—be appropriate for certain high-risk BrS subsets, particularly high-risk asymptomatic patients with variable expressions of BrS or those with unexplained syncope? Future randomized trials may be necessary to investigate these specific populations[21]

Study limitations

The coronavirus disease 2019 pandemic halted patient enrollment for nearly 3 years, slowing accrual. Although one could argue that the sample size was small, the interim analysis with 50 randomized patients showed unequivocal superiority of ablation over control, achieving a type I error of 0.05 with 80% statistical power and offering robust long-term follow-up data.

Conclusion

The BRAVE trial provides the first prospective, randomized evidence that catheter ablation of arrhythmogenic substrates significantly reduces VF recurrences in patients with symptomatic BrS implanted with an ICD. Ablation not only prevents new VF events but also seems to be safe, with minimal procedural complications.

The BRAVE study's findings strongly support epicardial ablation as a first-line therapy for recurrent VF, especially in resource-limited settings where quinidine is unavailable or poorly tolerated. Future research should clarify whether ablation alone might suffice for selected high-risk BrS subgroups without ICD backup, potentially offering a curative strategy for this life-threatening condition.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2025.04.033.

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