

# Epicardial ablation in high-risk Brugada syndrome to prevent ventricular fibrillation: results from a randomized clinical trial

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## Aims

Epicardial ablation for Brugada syndrome (BrS) has shown promise in reducing ventricular fibrillation (VF), but its role remains controversial due to the lack of randomized trials. This study evaluates the efficacy of catheter ablation in high-risk BrS patients.

## Methods and results

This prospective, single-centre, randomized (2:1) study enrolled BrS patients with cardiac arrest (CA) or appropriate ICD therapies. All patients had an ICD and were randomized to undergo epicardial ablation (ablation group) or no ablation (control group). Enrolment began in September 2017 and prematurely terminated in February 2024. The primary endpoint was freedom from VF recurrences. Secondary endpoints included procedure safety, ICD-related complications, and quality-of-life assessment. Forty patients (83% male, mean age  $43.7 \pm 12.1$ ) were randomized: 26 in the ablation group and 14 in the control group. Thirty-six patients received appropriate ICD therapies before enrolment: 24 (92%) in the ablation group and 12 (86%) in the control group. One patient in the ablation group experienced a post-procedural pericardial effusion requiring pericardiocentesis. Thirteen patients (33%) had major ICD-related complications. After a mean follow-up of  $4.0 \pm 1.7$  years, freedom from VF recurrence was 96% (25/26) in the ablation group and 50% (7/14) in the control group ( $P < 0.001$ ). No unexplained or arrhythmic deaths occurred during follow-up.

## Conclusion

Epicardial catheter ablation was associated with a reduction in VF recurrence compared with ICD therapy alone. These findings support the use of epicardial ablation in high-risk BrS patients.

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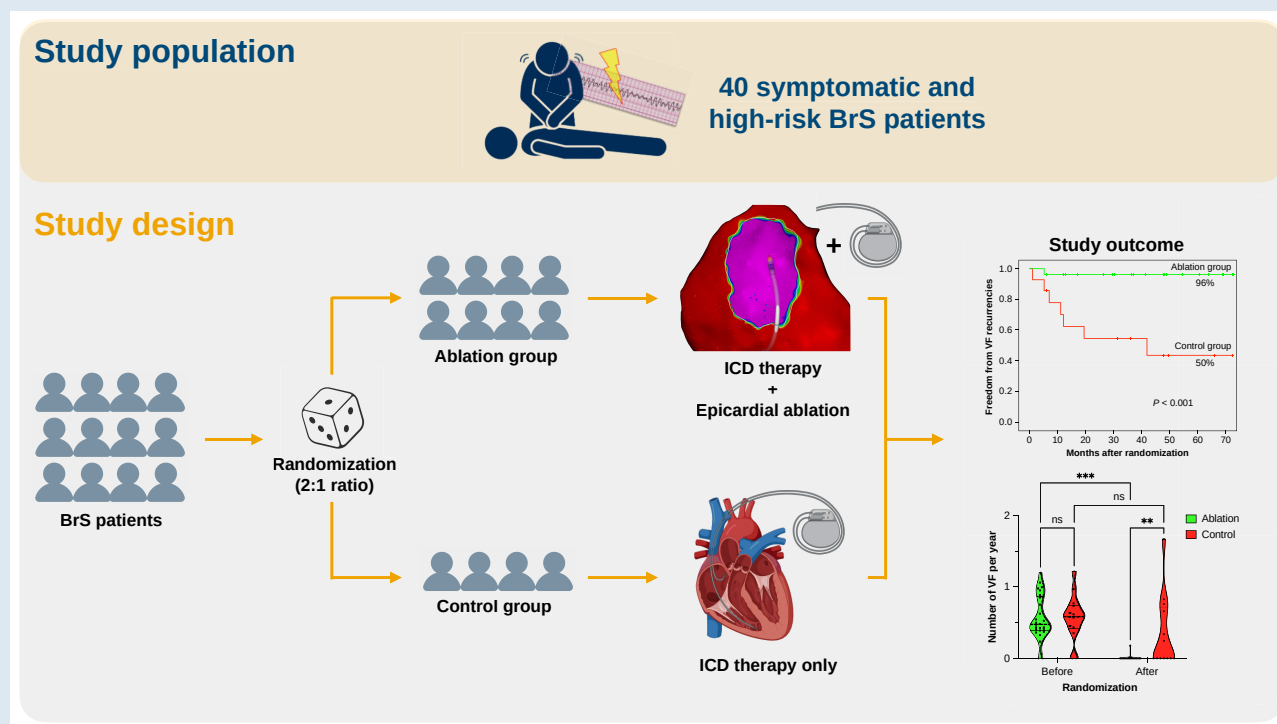
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## Graphical Abstract



## Keywords

Arrhythmogenic substrate • Brugada syndrome • Cardiac arrest • Epicardium • ICD • Ventricular fibrillation

## What's New

- This is a randomized clinical trial demonstrating that epicardial substrate ablation significantly reduces ventricular fibrillation (VF) recurrences in high-risk Brugada syndrome patients compared with ICD therapy alone (96 vs. 50%,  $P < 0.001$ ).
- Ablation led to complete elimination of epicardial abnormalities, stable ECG normalization, and non-inducibility of VF.
- Patients with VF storm have significantly larger and more abnormal epicardial substrates, reinforcing the link between substrate burden and arrhythmic risk in Brugada syndrome.
- These results highlight the potential of epicardial substrate ablation as a viable therapeutic option in high-risk Brugada syndrome patients, offering a disease-modifying strategy to prevent VF recurrences.

## Introduction

Since its first description, Brugada syndrome (BrS) has been recognized as one of the leading causes of sudden cardiac death (SCD) due to ventricular fibrillation (VF) in young individuals.<sup>1,2</sup> Despite advances in the understanding of the genetic basis, particularly variants in the *SCN5A* gene, the clinical management of BrS, especially in high-risk individuals, remains a therapeutic challenge. For several years, the standard approach mainly relied on the use of an implantable cardioverter defibrillator (ICD), which is effective in preventing SCD but does not attenuate the VF recurrences.<sup>1</sup> Furthermore, ICD therapy can be associated with adverse complications (i.e. malfunction, infection, and inappropriate shocks), resulting in severe psychological impacts.<sup>3,4</sup> Indeed, there is a growing reluctance to receive

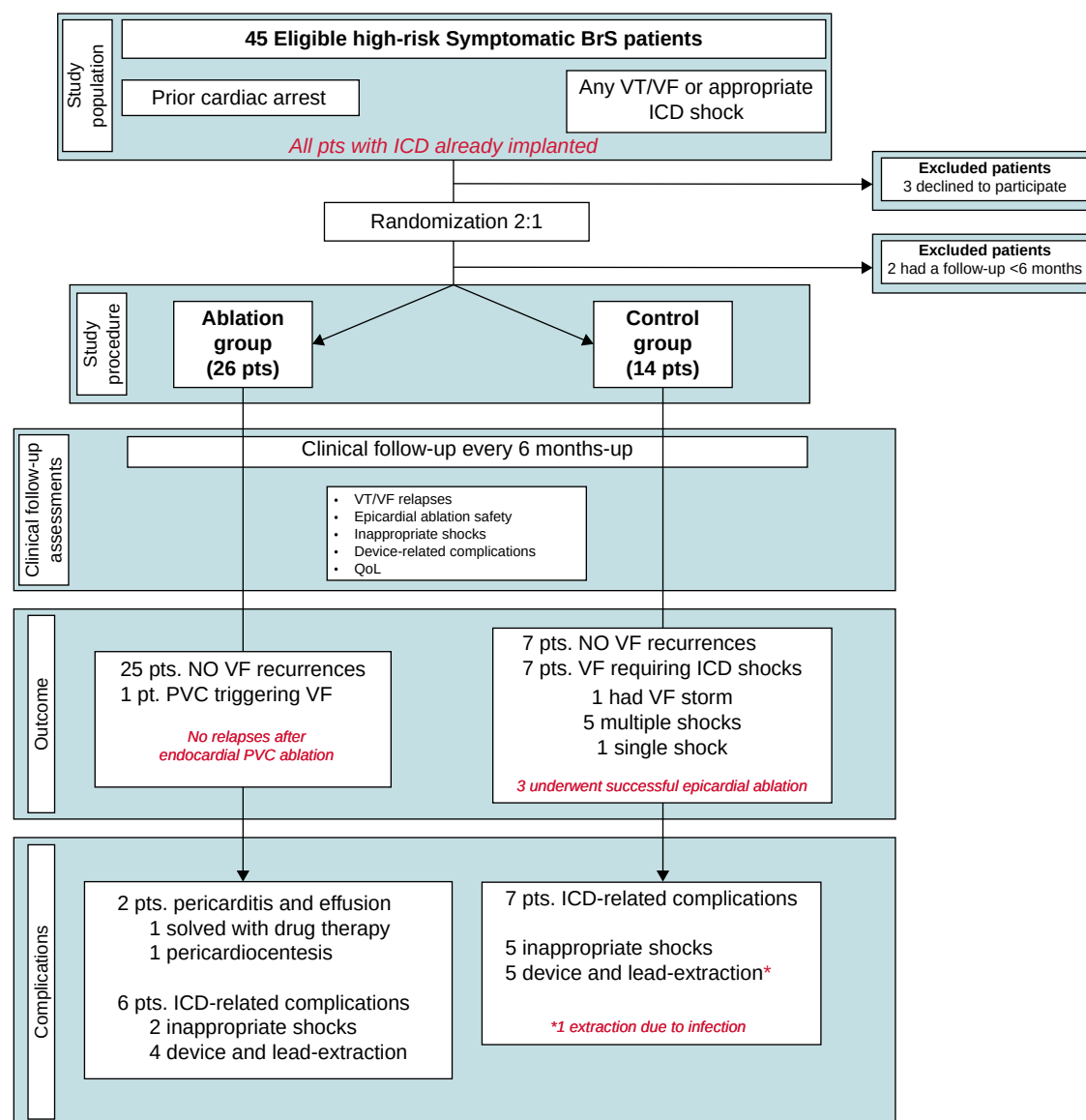
an ICD implant, particularly in younger patients, due to both its associated complications and the perception of it as a lifestyle-improving disability. Conversely, although chronic pharmacological therapy with quinidine is effective in attenuating VF episodes in many symptomatic patients, its widespread use may be limited by side effects that affect patient adherence and lack of global availability. Despite these challenges, quinidine remains a valuable treatment option.<sup>5</sup>

Initial pioneering studies have identified a discrete arrhythmogenic substrate located in the epicardium of the right ventricle (RV), harbouring electrophysiological abnormalities that served as a target for catheter ablation.<sup>6–9</sup> Accordingly, the presence and electrophysiological properties of the arrhythmogenic substrate have shown a crucial role in the clinical manifestation, alongside the natural history of BrS,<sup>8,10–13</sup> thus representing a key phenotypic expression of the disease. After early endeavours in targeting these abnormalities, the use of radiofrequency ablation has shown increasingly promising results in mitigating recurrent VF, thereby gaining broader acceptance and application within the electrophysiological community.<sup>9</sup> However, the long-term efficacy and safety of this approach in high-risk BrS patients have not been adequately assessed through rigorous clinical trials. Therefore, we conducted a prospective randomized study to define the role of catheter ablation among the therapeutic strategies in high-risk BrS.

## Methods

## Study design

This trial was a prospective, single-centre, randomized (before ablation) study evaluating the efficacy of adjunctive arrhythmogenic substrate ablation on top of ICD therapy for the treatment of symptomatic high-risk BrS. Consenting eligible subjects were randomly assigned (2:1) to undergo



**Figure 1** This flowchart outlines the study design, participant randomization, and clinical outcomes of all enrolled patients.

ablation (ablation group) or not (control group) (Figure 1). Primary endpoint consisted of evaluating freedom from any VF recurrence in both study groups. In the event of arrhythmia recurrences, the primary endpoint was reached and recorded as an event. Patients were then treated according to the centre's standard clinical practice and clinical indication. The subsequent treatment and outcome were not included in the statistical analysis as the primary endpoint had already been reached. Crossover between the two study arms was not allowed during the entire study period. Further details are available in the [Supplementary Materials](#).

The study protocol was approved by the institutional ethics committee, and all patients provided written informed consent. The trial was conducted in accordance with the Declaration of Helsinki, and it was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03294278).

## Study population

All consecutive patients referred to the Arrhythmology Department of IRCCS Policlinico San Donato for BrS management were evaluated for study eligibility. Medical history, physical examination, baseline

electrocardiogram (ECG), and history of ventricular arrhythmias were obtained in all patients. All patients were screened for *SCN5A* variants using genomic DNA with Next Generation Sequencing (TruSight One kit, NextSeq platform). We used ACMG classification, considering only pathogenic (P) and likely pathogenic (LP) variants, and excluding benign (B), likely benign (LB), and variants of unknown significance (VUS).<sup>10</sup>

Study inclusion criteria consisted of (i) spontaneous or drug-induced type 1 Brugada ECG pattern; (ii) BrS symptoms. Symptomatic BrS was defined as a history of cardiac arrest (CA) and/or a history of appropriate ICD therapy due to VF episodes; (iii) previous ICD implantation. High-risk BrS was identified by the presence of these features, specifically CA survival or appropriate ICD discharges. VF storm was defined as having three or more VF episodes within 24 h. None of the patients had overt structural heart disease demonstrated by advanced imaging techniques.

At the start of this study in 2017, all eligible patients were informed about the randomized trial and offered participation to gather robust data on the efficacy and benefits of ablation. Those who declined the trial but wished to undergo ablation, or refused the procedure altogether, were included in the

registry (NCT03106701), which comprises the cohort described in our recent publication.<sup>13</sup>

After randomization, any antiarrhythmic therapy, including quinidine, was discontinued in the ablation group. In the control group, patients already receiving chronic quinidine therapy prior to randomization continued the medication, as discontinuation was deemed unethical. Initiating new quinidine therapy was not allowed for individuals who were not already receiving this treatment. All authors had full access to all data in the study and take responsibility for its integrity and data analysis. Further methodological details are provided in the [Supplementary Materials](#).

## Electrophysiological study and mapping procedure

Electrophysiological study (EPS) was performed as previously described.<sup>8</sup> None of the patients had prior mapping or ablation procedures. We performed high-resolution endocardial and epicardial electroanatomical maps in all patients, at baseline conditions and after sodium channel blocker (SCB) challenge (ajmaline, 10 mg/min, up to 1 mg/kg or BrS type 1 appearance),<sup>14</sup> to adequately define the arrhythmogenic substrate, by means of a 3D mapping system (CARTO 3, Biosense Webster, Diamond Bar, CA, USA) using high-density decapolar mapping catheter (DecaNAV, Biosense Webster; 1 mm electrodes with 2–8–2 inter-electrode spacing). The electrograms (EGMs) were classified as abnormal if they met at least one of the following characteristics: (i) a wide duration (>110 ms) with fragmented component (>3 distinct peaks); (ii) late component of low voltage amplitude ranging from 0.05 to 1.5 mV; and (iii) distinct delayed or discrete double components exceeding the end of the QRS complex. All potential duration maps (PDMs) were created by measuring the duration of each bipolar EGM using custom-made dedicated software (PDM software, Biosense Webster), as previously reported.<sup>8,10,12</sup> Total signal duration was measured for each potential before and after drug challenge, as previously described.<sup>12</sup> The arrhythmogenic substrate was identified as the epicardial regions exhibiting abnormal electrophysiological EGMs. The potential duration map was created by collecting the duration of each EGM.

As a result, a colour-coded map was obtained showing the regions displaying the shortest (red colour) and the longest (purple colour) durations. Arrhythmogenic substrate areas were measured and validated by two expert electrophysiologists using the CARTO3 system. Further details are available in the [Supplementary Materials](#).

## Radiofrequency catheter ablation

The area of arrhythmogenic substrate was mapped with a higher point density to delineate the extent of such regions of interest. All abnormal signals identified by electroanatomic mapping were considered targets for ablation. Radiofrequency catheter ablation aimed to eliminate all abnormal epicardial electrical activity using an irrigated-tip ablation catheter (Thermocool SmartTouch SF, Biosense Webster). Radiofrequency energy was delivered point-by-point over the epicardial area that exhibited the abnormal signals. Each application lasted 5–20 s. A 40–55 W power control mode was used with an irrigation rate of 15 mL/min for RF applications. The aim of the ablation was to eliminate the abnormal signals mentioned above (EGM homogenization of the described epicardial area).<sup>8,13</sup> In all procedures, remapping with an intravenous SCB was performed to confirm the elimination of the abnormal epicardial EGMs. The endpoint of the procedure was the complete elimination of all abnormal EGMs and the disappearance of the BrS ECG pattern, which was confirmed by the SCB test, as previously described.<sup>8</sup> Further details regarding remapping after repeat SCB administration are available in the [Supplementary Materials](#).

At the end of the procedure, venous and arterial sheaths were withdrawn immediately, whereas complete pericardial fluid removal and subsequent intrapericardial steroid (triamcinolone acetate 2 mg/kg) was injected, as standard practice. Patients were followed up at 1, 3, 6, and 12 months for the first year and every 6 months thereafter. ICDs were interrogated at each visit, and arrhythmia logs were retrieved. The primary endpoint was recurrent VF requiring ICD intervention. In both study groups, patients with VF relapse(s) were offered ablation on a case-by-case basis.

## Statistical analysis

The study was powered to detect a 20% absolute difference in the primary endpoint rate between groups, assuming a 0.05 type I error, a 0.10 type II

error (90% power), exponential time-to-event distributions, and 2-year event-free rates of 90% in the ablation group and 70% in the control group. For a two-sided log-rank test, 150 subjects (45 in the control group and 105 in the ablation group) would have been required to reject the null hypothesis of no difference.

During the study, our centre's growing experience with ablation treatment and the positive perception about the procedure's outcomes led to a progressive decline in the enrolment rate. High-risk patients who met the trial's inclusion criteria increasingly refused randomization, as many were referred to our centre specifically for the ablation procedure. By February 2024, considering that the last patient was enrolled in February 2023, an independent panel of experts (see [Supplementary Materials](#)) recommended terminating enrolment due to the low recruitment rate and the unrealistic prolongation of the enrolment phase to reach the initial target population. The investigators were asked to conclude study procedures to ensure at least a 1-year follow-up after randomization for all patients included in the trial. The primary endpoint statistical analysis was conducted after the completion of this follow-up using all available data. The ethics committee was informed accordingly.

Continuous variables are presented as mean  $\pm$  standard deviation or as median and interquartile range (IQR). Binary variables are expressed as absolute values and percentages and compared with the  $\chi^2$  test or Fisher's exact test. The Wilcoxon test was used to compare the number of arrhythmic episodes before and after ablation. Log-rank test by Kaplan–Maier curve analysis were used to assess the clinical outcome overtime. As a sensitivity analysis, a non-parametric bootstrap procedure with 500 replications was applied to the log-rank test to assess the robustness of the difference in VF-free survival between the study groups after randomization. The analysis of the improvement of functional status as measured by SF-36, EQ-5D questionnaires have been performed first with an ANOVA overall test and then with pairwise comparisons. *P*-value <0.05 was considered statistically significant (SPSS, v.23, IBM SPSS Statistics and GraphPad Prism, v.10).

## Results

### Study population characteristics

Among 45 eligible patients who initially accepted to participate in the study, 3 later opted out after reconsidering the procedure. From the remaining 42 patients, 2 who were randomized to receive ablation had less than 6 months of follow-up and were therefore excluded from the current analysis. Neither experienced any VF events following the ablation procedure. Thus, 40 patients (33 males, 83%; mean age  $43.7 \pm 12.1$  years) are part of the current study having consented to participate. All patients were symptomatic, having survived a previous CA and/or experienced appropriate ICD therapies due to spontaneous VF, as detailed in [Table 1](#) and [Supplementary material online, Table S1](#), the inclusion criteria in the Methods Section, and the [Supplementary Materials](#). They were randomized to receive arrhythmogenic substrate ablation (26 patients, ablation group) or not (14 patients, control group). At the time of randomization, 22 showed a spontaneous type 1 pattern (15/26 ablation vs. 7/14 control group, *P* = 0.74), 30 had family history of SD before the age of 40 years old (18/26 ablation vs. 12/14 control group, *P* = 0.45), 15 had SCN5A variants (9/26 ablation vs. 6/14 control group, *P* = 0.74). Before randomization, 36 patients (90%) experienced appropriate ICD therapies due to recurrent VF: 24/26 (92%) in the ablation group and 12/14 (86%) in the control group (*P* = 0.60). Eight patients (20%) had experienced VF storms (5 in ablation vs. 3 in control group, respectively; *P* = 1.00).

In the ablation group, quinidine therapy was discontinued at the time of randomization, 1 week prior to the procedure, and was not resumed. Whereas, in the control group, quinidine therapy was not interrupted when already prescribed before randomization (10/26 ablation vs. 5/14 control group, *P* = 1.00). [Figure 1](#) indicates the flow of the study population. Clinical characteristics are summarized in [Table 1](#).

**Table 1** Clinical characteristics of the study population

|                                                            | Overall (n = 40)  | Ablation group (n = 26) | Control group (n = 14) |
|------------------------------------------------------------|-------------------|-------------------------|------------------------|
| Male, n (%)                                                | 33 (82.5)         | 21 (80.8)               | 12 (85.5)              |
| Age, mean $\pm$ SD                                         | 43.7 $\pm$ 12.1   | 44.3 $\pm$ 12.5         | 42.5 $\pm$ 11.5        |
| Spontaneous type 1, n (%)                                  | 22 (55)           | 15 (58)                 | 7 (50)                 |
| Family history of sudden death, n (%)                      | 30 (75)           | 18 (70)                 | 12 (86)                |
| Cardiac arrest survivors, n (%)                            | 24 (60)           | 16 (62)                 | 8 (57)                 |
| SCN5A LP/P variant, n (%)                                  | 15 (38)           | 9 (35)                  | 6 (42.8)               |
| Prior VF storm, n (%)                                      | 8 (20)            | 5 (19.2)                | 3 (21.4)               |
| Spontaneous VF requiring ICD therapy, n (%)                | 36 (90)           | 24 (92)                 | 12 (86)                |
| VF number before randomization, median (IQR)               | 3 (2–7)           | 3 (2–6.75)              | 3.5 (2–7.75)           |
| Months from index event to the randomization, median (IQR) | 55.3 (47.1–100.2) | 53.8 (43.7–125.3)       | 55.8 (51.7–89.9)       |
| Months from last event to the randomization, median (IQR)  | 3 (2–4)           | 3 (2–4)                 | 3 (2–4)                |
| Prior quinidine therapy, n (%)                             | 16 (40)           | 10 (38.5)               | 5 (35.7)               |

Abbreviations: ICD, implantable cardioverter defibrillator; IQR, interquartile range; LP/P, likely pathogenic/pathogenic; SD, standard deviation; VF, ventricular fibrillation.

**Table 2** Arrhythmogenic substrate characteristics in the ablation group

|                                                                  | Overall (n = 26) | VF storm (n = 5) | No VF storm (n = 21) | P-value |
|------------------------------------------------------------------|------------------|------------------|----------------------|---------|
| Baseline substrate size (cm <sup>2</sup> ) (mean $\pm$ SD)       | 13.2 $\pm$ 5.7   | 18.2 $\pm$ 1.9   | 12.1 $\pm$ 5.7       | 0.026   |
| Substrate size after ajmaline (cm <sup>2</sup> ) (mean $\pm$ SD) | 23.3 $\pm$ 9.5   | 31.0 $\pm$ 14.1  | 21.3 $\pm$ 7.0       | 0.032   |
| Baseline potential duration (ms) (mean $\pm$ SD)                 | 116.6 $\pm$ 35.9 | 146.8 $\pm$ 18.9 | 111.3 $\pm$ 35.9     | 0.044   |
| Potential duration after ajmaline (ms) (mean $\pm$ SD)           | 210.1 $\pm$ 29.0 | 235.1 $\pm$ 24.2 | 203.5 $\pm$ 27.4     | 0.027   |

Abbreviations: ms, millisecond; SD, standard deviation.

Further details regarding potential duration maps are available in the [Supplementary Materials](#).

## Arrhythmogenic substrate characterization and catheter ablation

All patients in the ablation group successfully underwent endo-epicardial mapping, as previously described.<sup>8</sup> No electrophysiological abnormalities could be identified in the endocardial surface of the RV. The average arrhythmogenic substrate extent was  $13.2 \pm 5.7$  cm<sup>2</sup> at baseline and  $23.3 \pm 9.5$  cm<sup>2</sup> after ajmaline administration (Table 2). Patients with higher VF burden and prior VF storm showed more pronounced epicardial abnormalities (Table 2). The radiofrequency ablation time was  $26.8 \pm 13.2$  min. Electrophysiological abnormalities all clustered in the anterior and outflow tract of the right ventricle (RV and RVOT) in the epicardial surface (Figure 2). Moreover, three patients showed further electrical abnormalities that could be identified in the inferior region of epicardial RV (in one patient), and in the infero-lateral left ventricle (in two patients with concomitant early repolarization pattern; Figure 3).

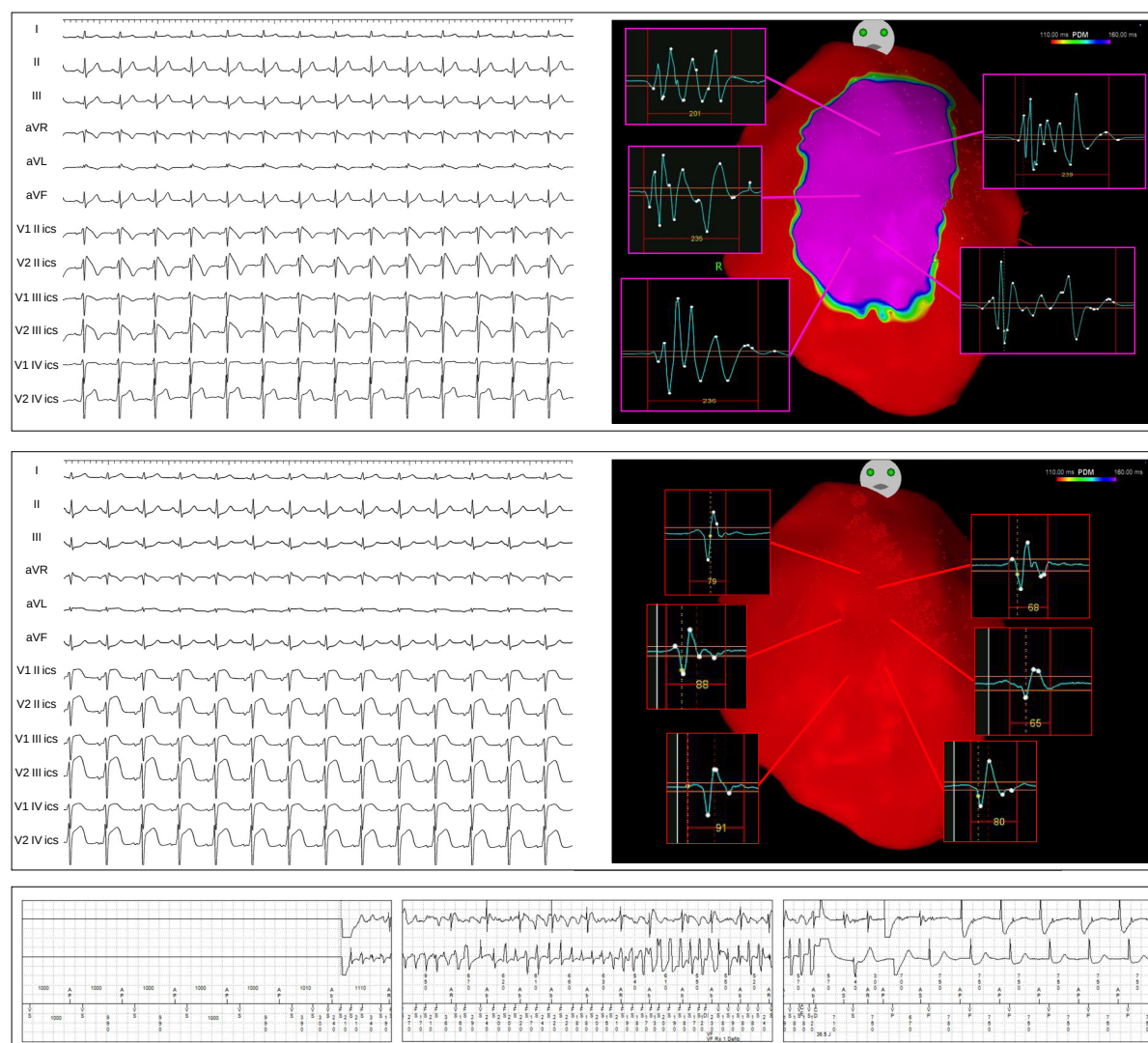
Complete substrate elimination was successfully achieved in all patients. Immediately after the procedure, stable ECG pattern normalization with no VF inducibility despite ajmaline challenge was achieved in all subjects. After ablation, only one patient, who had a non-inducible type 1 pattern during the SCB test, experienced a non-sustained, self-limiting inducible VF. We attributed this to the proarrhythmic effect of ajmaline administered a few minutes before the EPS. This event could also be

due to epicardial inflammation secondary to extensive ablation. Nevertheless, the patient did not experience any VF relapses.

Immediately after the procedure and at discharge, all patients showed stable ECG normalization with disappearance of type 1 BrS pattern. No patient in the ablation group received antiarrhythmic drugs after the procedure, as per the study protocol. No deaths or severe life-threatening adverse events occurred at the end of the procedure. Following ablation, pericarditis with pericardial effusion occurred in two patients (2/26, 7.5%), which was managed with colchicine and non-steroidal anti-inflammatory drugs. In one case, this condition resolved after pericardiocentesis without further recurrences.

## Long-term clinical outcome of the study population

After a median of 48.4 months (IQR: 31.0–70.6) after randomization, the survival curve demonstrates that freedom from VF recurrences was significantly higher in the ablation group compared to the control group (96 vs. 50%, log-rank  $P < 0.001$ ; Figure 4). The statistically significant difference between groups was confirmed using a non-parametric bootstrap applied to the log-rank test as a sensitivity analysis ( $P = 0.033$ ; Figure 4; [Supplementary material online, Table S2](#)). Within the study cohorts, there were no arrhythmic or cardiac deaths during follow-up. All



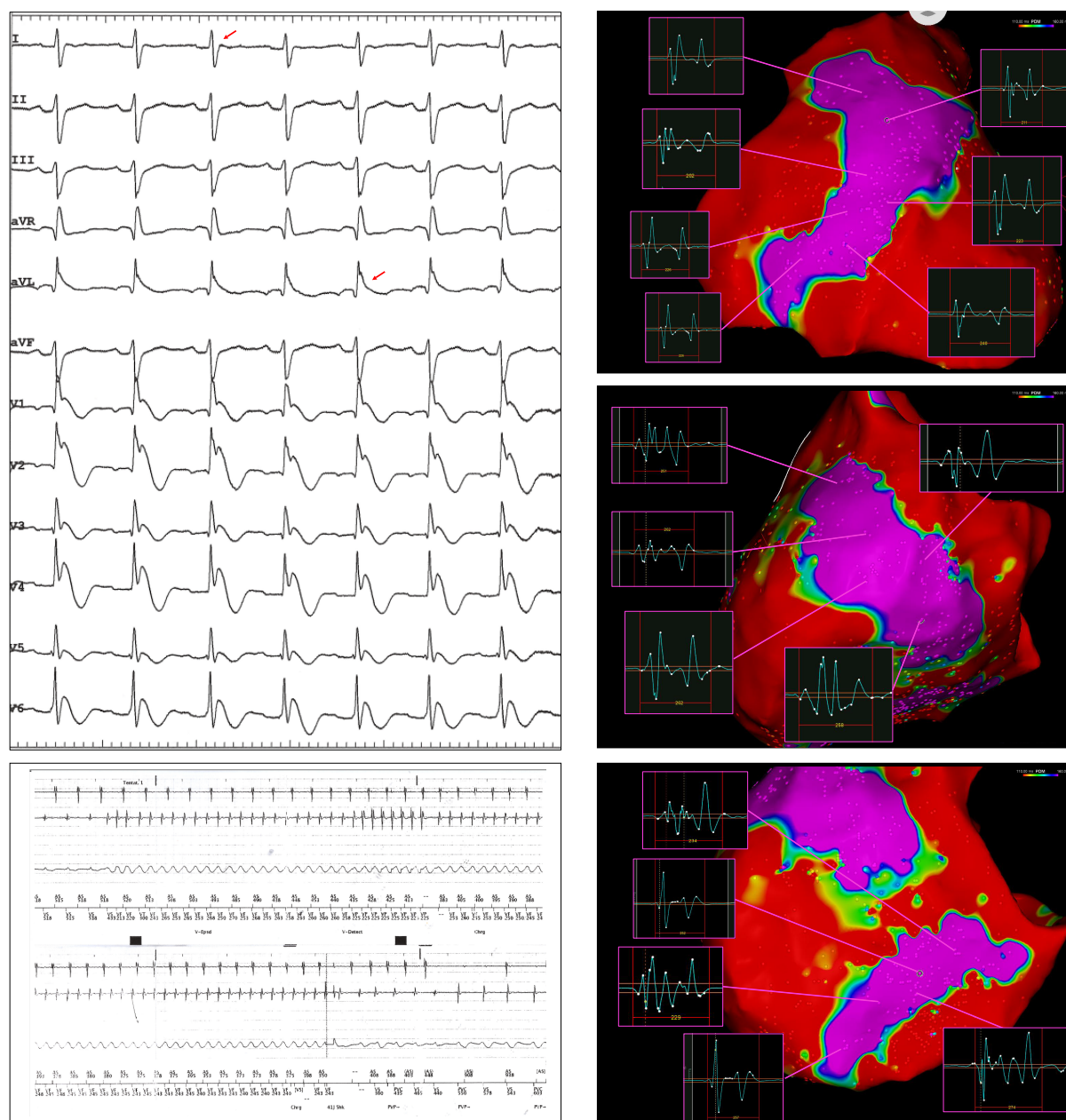
**Figure 2** Exemplary case of a Brugada syndrome (BrS) patient displaying a spontaneous type 1 pattern and having a history of ICD discharges, as shown in the bottom panel, who underwent epicardial ablation. *Top Panel:* On the top left, the ECG exhibits the spontaneous type 1 BrS pattern. To the right, the electroanatomic map illustrates the cardiac substrate, with colour-coded regions indicating areas of electrical activity. The purple regions denote areas with abnormal electrograms, characterized by fragmented signals and prolonged durations ( $>160$  ms). The red regions indicate areas with normal electrogram (EGM) signals of short duration ( $<110$  ms). *Middle Panel:* The middle-left panel shows the ECG tracings post-ablation, revealing a normalized ECG pattern, which suggests a successful alteration of the arrhythmic substrate. The corresponding electroanatomic map on the right no longer shows the purple regions, indicating the removal of the previously identified abnormal substrate. The post-ablation signals are of normal duration and devoid of late activity, further confirming the effective ablation of the arrhythmic substrate. *Bottom Panel:* The bottom panel displays the ECG recording of an ICD discharge, demonstrating the last clinical arrhythmic event before randomization assignment to catheter ablation.

patients had at least one arrhythmic event (spontaneous VF or CA) within the 6 months prior to randomization [median time from the last episode to randomization: 3 months (IQR: 2–4), Figure 4].

In the ablation group, the median number of VF episodes was 3 (IQR: 2–7) before the randomization (from the first symptom to the randomization) within median 71.6 (IQR: 56.5–112.7) months ( $0.56 \pm 0.31$  VF episodes per year). The number of events significantly reduced after ablation (Figure 5). After a single procedure, 25 of 26 (96%) patients remained free of VF recurrences during a median follow-up period of 48.4 months (IQR: 31.6–69.0) (Figure 4). The patient experiencing VF recurrence showed an endocardial RVOT-PVC triggering VF in the

setting of hypokalaemia, in the absence of an inducible type 1 BrS pattern at SCB test. Before ablation, he experienced a previous VF storm with a total number of eight appropriate ICD therapies. He successfully underwent catheter ablation at the endocardial site, and he did not experience further arrhythmia recurrences. No endocardial abnormalities could be documented during this procedure.

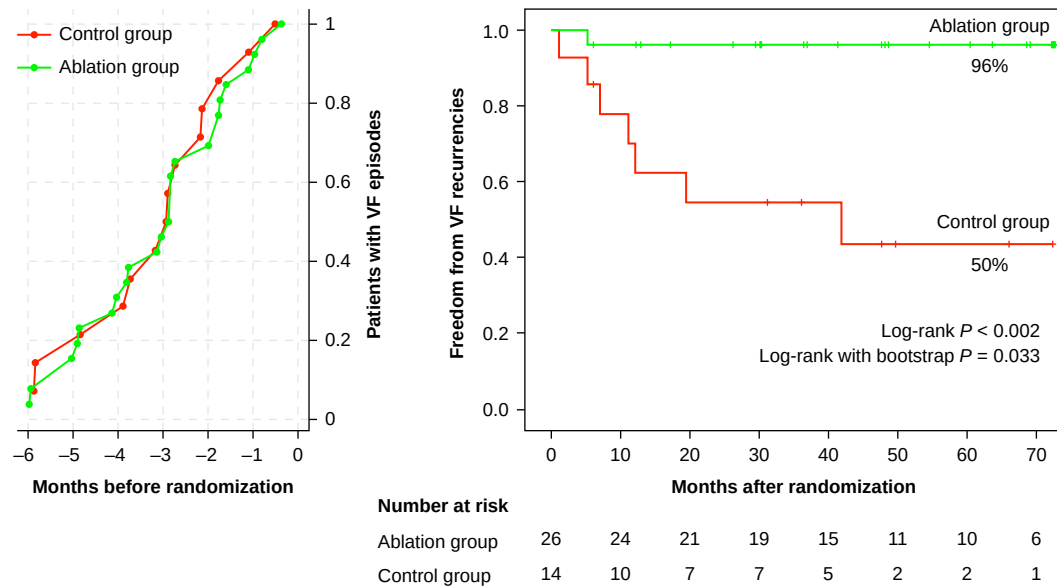
In the control group, the mean number of VF events was 3.5 (IQR: 2–7) before the randomization (from the first symptom to the randomization) within 72.5 months (IQR: 52.5–113.7) ( $0.57 \pm 0.32$  VF episodes per year). Over a median follow-up period of 48.3 months (IQR: 32.5–70.6) after randomization, seven patients (7/14, 50%)



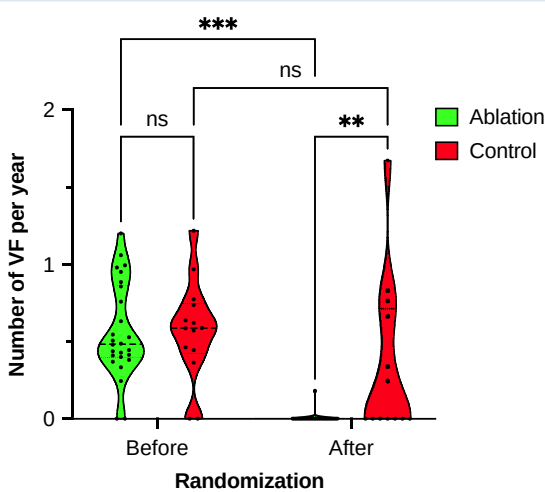
**Figure 3** Exemplary case of a Brugada syndrome (BrS) patient presenting a spontaneous type 1 ECG pattern in the right precordial leads positioned from the second to the fourth intercostal space, and a late depolarization pattern in the lateral leads (indicated by red arrows; top left panel). This patient had a history of multiple ICD discharges, with the most recent event depicted in the bottom left panel. Epicardial mapping reveals diffuse electrical activity concentrated in the anterior wall of the RV, extending from the right ventricular outflow tract (RVOT) to the inferior aspect (top right panel), as well as in the lateral (middle right panel) and inferior walls (bottom right panel) of the left ventricle. Following extensive substrate homogenization, there was normalization of the ECG pattern which persisted in the follow-up (see [Supplementary material online, Figure S1](#)), and the patient experienced no VF recurrences during the follow-up period.

continued to experience VF episodes. Of them, only two patients were under chronic therapy with quinidine at a sufficient but potentially suboptimal dosage (range 600–750 mg daily). The other three patients either spontaneously discontinued the medication or took it inconsistently due to side effects, resulting in poor adherence. In these five patients, the median quinidine dose was 450 mg (IQR 300–750 mg). The post-randomization VF burden remained similar to the pre-randomization phase, but was significantly higher

compared with the ablation group following the ablation ( $P < 0.001$ , [Figure 5](#)). One patient had a single shock for VF recurrence, whereas the remaining six experienced two or more ICD discharges. Of note, one of them experienced a VF storm. At the time of VF recurrence, catheter ablation was proposed to all seven patients. Of them, five underwent successful epicardial ablation, including those with prior storm, whereas the remaining two declined the procedure and preferred quinidine therapy.



**Figure 4** The left panel displays the cumulative failure function of arrhythmic episodes during the 6 months preceding randomization. The right panel illustrates freedom from VF recurrence after randomization in the ablation group (green line) and the control group (red line). In both plots, Time 0 represents the date of randomization.



**Figure 5** This violin plot compares the burden of VF episode rate per year before and after randomization in the study population: the ablation group (green) and the control group (red). After treatment, the ablation group experienced a significant decrease in VF episodes. Following randomization, the rate of VF events per year was significantly lower in the ablation arm compared with the control group. Abbreviations: \*\*\* and \*\* marks indicate P-value < 0.001 and < 0.002, respectively; 'ns', not statistically significant.

## ICD-related complications and quality of life assessment

Thirteen patients (13/40, 33%) experienced ICD-related complications (6/26 in ablation vs. 7/14 in control group, respectively,  $P = 0.155$ ). Two patients (15%) experienced a single ICD shock, whereas five (38%) had

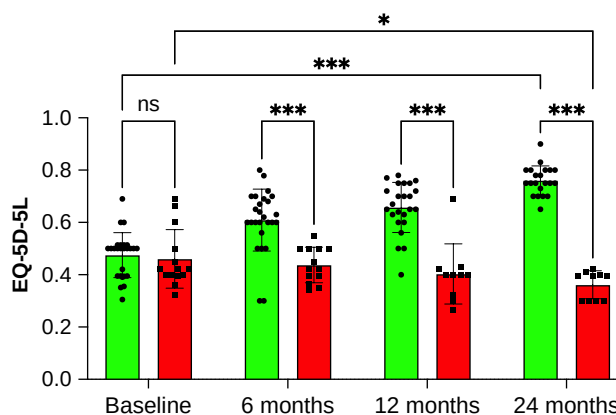
received two or more episodes of inappropriate discharges. Among them, four (4/7, 57%) had inappropriate ICD shocks due to supraventricular tachyarrhythmias (SVTs) and three (3/7, 43%) due to noise on the ventricular channel after lead fracture. The SVTs were due to rapid atrial fibrillation in one and AV nodal reentrant tachycardias in three patients, respectively. All of them received successful catheter ablation and did not experience further arrhythmia recurrences nor inappropriate ICD interventions. No inappropriate therapies in our cohort led to VF requiring subsequent ICD intervention.

Among patients who experienced ICD-related complications, nine with a transvenous device (9/40, 22.5%; 4 in the ablation group and 5 in the control group) required lead extraction. Complications included ventricular lead malfunction due to fracture, necessitating extraction and replacement in eight cases, and one case of device infection leading to ICD removal and reimplantation. These complications were not directly associated with the ablation procedure. Notably, no complications occurred among S-ICD recipients.

Figure 6 and Supplementary material online, Table S3 show that QoL measures through the SF-36 and EQ-5D were clinically comparable at baseline, respectively. Both physical and mental functionality scores showed different changes over time in each group. In the ablation group, patients reported a more significant improvement in all physical and mental health status compared with those in the control group.

## Discussion

The management of BrS has long been a topic of intense research and clinical debate.<sup>6,7</sup> The advent of catheter ablation as a therapeutic strategy has opened new avenues for treatment, particularly in patients at high risk of arrhythmic events. This randomized clinical trial provides further convincing evidence of the efficacy of epicardial ablation in reducing VF episodes in symptomatic patients. Our results underscore the potential of catheter ablation not only to reduce the burden of arrhythmias but also to improve outcomes in patients whose therapeutic options were limited to ICD treatment and pharmacological



**Figure 6** Quality of life measures by the means of the EQ-5D-5L score questionnaire, indicating better performance in the ablation group compared with the control group. Abbreviations: \*\*\* and \* marks indicate  $P$ -value  $<0.001$  and  $<0.033$ , respectively; 'ns', not statistically significant.

interventions. The basis of this study is based on the hypothesis that targeting the arrhythmogenic substrate by epicardial ablation may be a more definitive approach for the treatment of recurrent VF in BrS. By comparing the outcomes of patients randomized to either ablation or standard ICD therapy, our results clearly demonstrate the success rate in preventing VF recurrence in the ablation group and greater efficacy than ICD therapy alone (96 vs. 50%).

## Epicardial substrate ablation in managing ventricular fibrillation in Brugada syndrome

The randomized design of this study provides a higher level of evidence than previous observational reports and helps to mitigate potential bias. The arrhythmogenic substrate of BrS is characterized by epicardial electrophysiological abnormalities, which represent the hallmark signature and phenotype of the disease.<sup>10</sup> These results are in line with current pathophysiological findings on BrS, where the substrate has been identified as a crucial player in arrhythmogenesis and prognosis of the disease.<sup>10,11,13</sup> The epicardial abnormalities are identifiable and serve as a target for treating symptomatic BrS patients and potentially those deemed at high-risk of SCD.<sup>8,9,11,13</sup> This confirms previous ablation experiences in managing symptomatic BrS, including the large-scale experiences reported by our group and the BRAVO consortium.<sup>9,13</sup> The similar approaches shown in these studies, the high success rate (86–98%) and the very low complication rates (2–4%) demonstrate the safety and efficacy of epicardial ablation in BrS. Most importantly, the consistency of success rates across different geographic and demographic settings underscores the universal applicability of the procedure and thus the value of this strategy in the treatment of BrS. In our experience, once the arrhythmogenic substrate has been appropriately identified, its elimination can alter the phenotypic expression of the disease, as easily demonstrated by the disappearance of the type 1 BrS pattern or its non-inducibility after SCB testing.<sup>8</sup> Throughout the entire follow-up period after ablation, almost all patients were free of VF recurrence, and none of them had recurrence of the BrS ECG pattern, confirming the initial promising experience in terms of reduction of ICD shock rate and change in phenotype.<sup>8,9,13</sup> Indeed, the normalization of the ECG pattern may in turn indicate the elimination of the epicardial abnormalities targeted by ablation.

However, to achieve the results reported in this study, two key methodological steps must be performed: (i) *Accurate identification of*

*the arrhythmogenic substrate*. This step involves the use of SCBs to fully reveal subtle epicardial EGM abnormalities that define the precise area to be treated; (ii) *Re-evaluation of the substrate after ablation with SCB*. Re-testing with SCBs at the end of the procedure is crucial to verify the complete elimination of the arrhythmogenic substrate. Both steps are necessary for a successful clinical outcome. For this reason, elimination of the persistent type 1 pattern is a predictor of success after epicardial ablation.<sup>8,9</sup>

On the other hand, only one patient in the ablation group had recurrences due to endocardial RVOT PVCs that triggered VF in association with hypokalaemia. No PVCs were documented at the time of the index procedure. This may illustrate the need to eliminate any potential trigger and then target the arrhythmogenic substrate. Considering that this was the only patient in whom an endocardial focus was observed in the entire ablation cohort, it is unlikely that this endocardial site, where ablation was successful, represents a proarrhythmic effect of the initial epicardial ablation. This is also explained by the short duration of radiofrequency applications in the epicardium leading to non-transmural lesions, which makes an iatrogenic scar extremely difficult, as has also been shown previously.<sup>8,9</sup> Moreover, removal of the epicardial abnormalities resulted in suppression of malignant ventricular arrhythmias during follow-up, providing further evidence that these regions exert an arrhythmogenic effect in BrS patients.

## Catheter ablation efficacy vs. ICD therapy alone

In the control group, 50% of patients continued to experience VF episodes requiring ICD discharges. This seemingly unusually high event rate in our study is what could be expected due to the different inclusion criteria of our study compared with previous studies.<sup>15–19</sup> Namely, our population includes high-risk BrS patients with prior CA who had already experienced VF episodes at baseline, in contrast to previous work such as the Finger study,<sup>15</sup> which examined the natural history of BrS patients after the first clinical symptom. In fact, our study includes only patients with recurrent ventricular arrhythmias, which are comparable to a subset of the more severe patients in the other studies.<sup>15,20</sup> Moreover, previous studies, such as the Finger study, calculated the recurrence rate from the index event (i.e. CA),<sup>15</sup> whereas our recurrence rate was calculated from the time of randomization, which was after the index event. Our population had a higher arrhythmic risk: 21% had a history of arrhythmic storm (data from the Finger study not reported)

and 86% had a positive family history of SCD, compared with 10% in the Finger study.<sup>15</sup>

To our knowledge, there are no current data on the recurrence risk of appropriate shocks in ICD patients who have already received appropriate therapies, as was the case in this cohort. Longer follow-up data from the Sabrus Registry could provide valuable insights into this gap.<sup>21</sup> In addition, Figure 5 shows that the event rate per year before and after randomization in the control group did not change over time. This consistency underscores the inherently high risk in our patient population. Moreover, in this study, only two of five patients on drug therapy continued to take hydroquinidine at an adequate, but still suboptimal, dose (range 600–750 mg daily). However, poor adherence and side effects led to suboptimal dosing and discontinuation of the drug in many cases, which may have compromised its overall efficacy. These different results suggest that while pharmacologic treatment may attenuate VF episodes and ICD may acutely terminate a ventricular arrhythmia, targeting the arrhythmogenic substrate by epicardial ablation may provide sustained protection, especially in BrS patients with high VF burden. The latter could be due to several factors, including erratic plasmatic concentrations of the drug and poor patient compliance, which may compromise the overall efficacy of pharmacologic therapy. Conversely, once radical epicardial substrate elimination is demonstrated, mechanistic ablation treatment may ensure an excellent outcome.

It is important to clarify that this study does not make a direct comparison between the efficacy of quinidine and epicardial ablation and that any information on drug therapy is outside the scope of this study due to poor adherence. Nevertheless, chronic pharmacological therapy with quinidine has been shown to be effective in attenuating VF episodes in many symptomatic patients and remains a valuable treatment option.<sup>5,16</sup> Future studies are needed to establish the most effective first-line therapeutic strategy in this population (ablation vs. pharmacological therapy).

## Complications and quality of life assessment among high-risk Brugada patients

Many individuals with ICDs face challenges related to device complications and impacts on their quality of life.<sup>3,4</sup> Despite current ESC guidelines recommendations, ICD implantation may not be considered straightforward by patients with BrS who may refuse for different reasons, a globally accepted therapeutic strategy to prevent SCD.<sup>1,22,23</sup> In fact, ICD patients are more likely to develop depression and anxiety<sup>23</sup> and score lower on quality-of-life measures than patients in the ablation cohort, as was the case in this study. Managing BrS involves addressing the physical and psychological effects of having an implanted device, particularly in young adults.

We have observed an unexpectedly high rate of ICD-related complications in both study arms, which might be relevant for young patients with a long-life expectancy. While the rate of inappropriate shocks in our study (18%) is consistent with the literature,<sup>17,18</sup> the rate of lead extractions due to ICD malfunction (22%) is higher than previous reports (10–15%).<sup>17,18,24</sup> This higher rate may be attributed to the predominance of transvenous ICDs in our cohort, whereas broader adoption of subcutaneous ICDs could potentially reduce this risk. Importantly, no procedural factors were identified that could be clearly associated with the subsequent need for device extraction, supporting the interpretation that these events were more likely related to the well-recognized long-term risks of transvenous ICD systems in young individuals. Nevertheless, we still believe that ICD therapy remains the first choice to protect high-risk BrS patients and is also part of our study protocol, as all patients who underwent ablation were implanted

with an ICD. Nevertheless, the results of this study offer valuable insights for both patients and clinicians, providing robust evidence that catheter ablation effectively improves quality of life by reducing the incidence of appropriate ICD shocks in BrS individuals with recurrent-VF episodes.<sup>25</sup>

## Catheter ablation in BrS management: future perspectives

Given the high efficacy of catheter ablation and the potential risks of complications associated with ICDs, the use of ablation strategies for patients refusing an ICD is promising and deserves further attention.<sup>26,27</sup> This speculation is fuelled by the recent experience of Li et al.<sup>26</sup> who demonstrated that catheter ablation can be an effective alternative for high-risk symptomatic BrS patients who refuse ICD therapy. Although these results align with previous studies and our current experience with high-risk patients, they should be confirmed by multicenter studies before recommending the procedure widely without the ICD safety net.<sup>9,13</sup>

The present study could promote further research into the value of catheter ablation for treating high-risk symptomatic BrS patients, leading to more effective and patient-centred treatment strategies. Similar to advances in treating substrate-based malignant ventricular arrhythmias in cardiomyopathies,<sup>28</sup> where early ablation shows promise in improving clinical outcomes, our findings might encourage earlier ablation of the arrhythmogenic substrate in BrS. This approach could minimize long-term risks and improve the quality of life associated with ICDs in this patient population. Identifying patients who may benefit most from early intervention is becoming a key research focus. Despite the enthusiasm for reducing the VF burden in these patients, these claims should be taken cautiously, also due to the relatively limited sample size. Currently, the excellent results may not be reproducible in all centres, especially those with less experience. Poorly performed ablation carries significant risks.

At this stage, catheter ablation can be considered an adjunctive treatment to ICD therapy, potentially improving patient outcomes and quality of life. The study's findings may prompt active research into integrating ablation into the standard care regimen for BrS and defining its role in other clinical settings to optimize patient care without compromising safety.

## Limitations

This randomized study investigates the efficacy of catheter ablation in addition to ICD therapy in the absence of antiarrhythmic drugs. The main limitation of the trial is that it did not reach formal completion according to the initial study design. Early termination was deemed necessary due to the high rate of patients who met the inclusion criteria but refused randomization, resulting in an unrealistic prolongation of the enrolment phase. Moreover, the findings indicated an initial underestimation of the treatment effect size of the ablation, which significantly mitigates concerns about potential loss of study power due to the early termination (see [Supplementary Materials](#)).

Initially, a formal Data Safety Monitoring Board was not established, as safety and protocol adherence were overseen by the Ethics Committee, which included a bioinformatics expert in clinical trials, and the study principal investigator. Given resource constraints and the exploratory nature of the study, these measures were deemed sufficient to maintain safety and data integrity. Additionally, during the trial, an independent panel of cardiology experts was convened to review study progress and provide guidance, effectively mitigating potential concerns. This study is also limited by its relatively small sample size, the inherently erratic and clustered nature of VF events in Brugada syndrome without a uniform distribution overtime (less than one per year

in this cohort), and the 4-year follow-up duration which, although sufficient to demonstrate a significant reduction in VF recurrence, remains short relative to the long lifespan of this young population.

The study was designed in 2017, when the role of catheter ablation was still being debated. Therefore, none of the patients in the ablation arm received quinidine to avoid confounding factors when assessing the clinical value of catheter ablation.

Quinidine plasma levels were not available, and suboptimal dosing combined with poor drug tolerance may have significantly influenced outcomes in the control group. These factors likely contributed to the observed arrhythmic recurrences, rather than indicating a lack of efficacy of quinidine itself. As such, no conclusions regarding the effectiveness of quinidine can be drawn from this study, and no formal comparison between pharmacological therapy and ablation was intended or should be inferred.

At this stage, no conclusions can be drawn for other patient populations with a different clinical profile. This study and the recent experience of different groups may open new avenues for this therapeutic option, especially in young individuals who refuse an ICD or who experience device-related complications. However, a higher-than-expected incidence of device-related malfunction that required lead extraction was observed in both study arms, which may not be applicable to other patient groups.

The safety and efficacy of substrate ablation depends largely on the expertise of the electrophysiology team managing the SCBs and the ability of the operator to thoroughly eliminate the arrhythmogenic substrates. As a result, the broad applicability of these results may be limited, especially in centres that are not fully equipped for epicardial procedures or that have less experience in the use of SCBs.

## Conclusions

This randomized trial demonstrates the safety and efficacy of epicardial substrate ablation in preventing VF recurrence in high-risk Brugada syndrome patients over a long follow-up period. These results highlight the potential of substrate ablation to become a treatment option for high-risk BrS patients in addition to ICD therapy. These results encourage further research to evaluate the role of catheter ablation as a stand-alone option in the management of BrS.

## Supplementary material

Supplementary material is available at *Europace* online.

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**Conflict of interest:** The authors have nothing to disclose.

## Data availability

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

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