Arrhythmia detection using an implantable loop recorder after a negative electrophysiology study in Brugada syndrome: observations from a multicenter international registry

Short title: ILR after a negative EPS in Brugada

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ABSTRACT:

Background: Risk stratification in Brugada syndrome (BrS) remains controversial. In this respect, the role of electrophysiology study (EPS) has been subject of debate. In some centers, it is common practice to use an implantable loop recorder (ILR) after a negative EPS to help risk stratification. However, the diagnostic value of this approach has never been specifically addressed.

Objective: To describe the baseline characteristics and the main findings of a diagnostic work-up strategy using an ILR after a negative EPS in BrS.

Methods: We conducted a retrospective international registry including patients with BrS and negative EPS (ie, non-inducible VT/VF) prior to ILR monitoring.

Results: 65 patients from 8 referral hospitals in the Netherlands, Spain and UK were included (mean age 39 ± 16 years, 72% males). The main indication for ILR monitoring was unexplained syncope/presyncope (66.1%). During a median follow-up of 39.0 months (Q1 25.0 – Q3 47.6), 18 patients (27.7%) experienced 21 arrhythmic events (AEs). None of the patients died during follow-up. Bradyarrhythmias were the most common finding (47.6%), followed by atrial tachyarrhythmias (38.1%). Only 3 patients presented ventricular arrhythmias. AEs were considered incidental in 12 patients (66.7%). In 11 patients (61.1%), AEs led to specific changes in treatment.

Conclusion: The use of ILR after a negative EPS in BrS was a safe strategy that reflected the high negative predictive value of EPS for ventricular arrhythmia in this syndrome. Additionally, it allowed the detection of AEs in a significant proportion of patients, with therapeutic implications in most of them.

Keywords: Brugada syndrome; Electrocardiography; Implantable loop recorder; sudden death; Ventricular arrhythmia.

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LIST OF ABBREVIATIONS:

AEs: arrhythmic events

BrS: Brugada syndrome

ECG: electrocardiogram

EPS: electrophysiology study

ICD: implantable cardioverter defibrillator

ILR: implantable loop recorder

SCD: sudden cardiac death

VAs: ventricular arrhythmias

INTRODUCTION:

Brugada syndrome (BrS) patients a are at increased risk of ventricular arrhythmias (VAs) and sudden cardiac death (SCD)[1,2]. The use of an implantable cardioverter-defibrillator (ICD) is the only effective treatment shown to reduce mortality in high-risk patients. Its indication is clear in patients who have experienced SCD or VAs (secondary prevention), and in patients with spontaneous type 1 Brugada ECG pattern and a history of cardiogenic syncope[3,4]. Risk stratification for arrhythmic events (AEs) in other clinical scenarios of this syndrome remains a challenge.

The arrhythmic risk of these patients might be additionally assessed through an electrophysiology study (EPS) with programmed ventricular stimulation (class IIb - level of evidence B)[4], although its use remains controversial and varies greatly amongst centers. The use of implantable loop recorders (ILRs) has become a common practice in many centers, especially in patients with atypical symptoms of unexplained origin, to offer prolonged monitoring and exclude the presence of significant arrhythmias[5]. In fact, recent guidelines give a "class IIa – level of evidence C" recommendation to the implantation of an ILR in BrS patients with unexplained syncope[4]. To date, there are no data on the utility and specific outcomes of the combination of these two strategies.

The aim of this study was to describe the clinical outcomes of using ILR in patients with BrS after a negative EPS (ie, non-inducibility of VAs), focusing on the indications, diagnostic yield, and therapeutic implications of this strategy in clinical practice.

METHODS:

Study population:

This was a retrospective multicenter observational study, with data collection from 8 referral hospitals in the Netherlands, Spain, and UK. Patients diagnosed with BrS who had received an ILR after a negative EPS were included. The diagnosis of BrS was performed by the responsible physicians at each of the participating centers, following the recommendations of current guidelines[4] and the Shanghai Score System for Diagnosis of BrS[6].

The characteristics of the EPS protocol slightly varied across the participating centers. Overall, the EPS protocol consisted of 2-3 ventricular extrastimuli, from 2 ventricular sites (apex and right ventricular outflow tract, except for one center n=10, where pacing was performed only from one site), at 2-4 pacing cycle lengths. Extrastimuli were delivered with 10-ms decrements up to the shortest coupling interval which resulted in ventricular capture, but without going below 200 ms. The EPS was considered negative when sustained VAs (ie, ventricular fibrillation, polymorphic or monomorphic ventricular tachycardia lasting >30 s or requiring urgent cardioversion) could not be induced at the end of the protocol.

It should be noted that preliminary results from the monitoring of some of the patients (n=39) included in this registry have been reported in previous publications[7–9].

Data collection:

Baseline characteristics of all patients were analyzed: age at diagnosis of BrS and at ILR implantation, gender, left ventricular ejection fraction (LVEF), history of atrial fibrillation (AF), type of ECG pattern (spontaneous, induced by fever or induced by drugs), genetic testing and family history of SCD. For risk stratification, Sieira[10] and Shanghai[6] scores were calculated in each patient. Despite being initially designed as a diagnostic tool for BrS, the Shanghai score can also help risk stratification in this syndrome, exhibiting a modest predictive value for significant AEs[6,11].

Additionally, variables related to the ILR implantation were also analyzed: reason for implantation, type of implanted device, monitoring time (until the last available follow-up, battery depletion or explantation), and diagnostic findings. Detection of any of the following types of arrhythmias during follow-up was considered a diagnostic finding: supraventricular tachycardia (SVT) other than sinus tachycardia, AF, VAs, and significant bradyarrhythmias, including sinus bradycardia (SB) with heart rate less than 40 bpm, sinus pause (SP) greater than 3 seconds, and high-grade atrioventricular block (HAVB). The possible correlation of detected arrhythmias with symptoms reported by each patient before implantation was studied. Therapeutic actions taken as a result of ILR findings were explored. Finally, baseline characteristics and variables related to the ILR were compared between the patients with AEs that led to therapeutic changes and the rest of the patients (those without actionable findings and those without arrhythmias during follow-up).

It should be mentioned that, due to the observational and retrospective nature of the study, the decision to consider an AE as clinically relevant (and take subsequent therapeutic decisions) was made according to the criterion of the treating physician in each participating center.

The study obtained initial approval from the ethics committee of Puerta de Hierro University Hospital. Subsequently, it also received approval from the ethics committees of the remaining participating centers in the registry. The research reported in this paper adhered to Helsinki Declaration as revised in 2013.

Statistical analysis:

Categorical variables were expressed as absolute value and percentage. Continuous variables were expressed as mean and standard deviation as a measure of dispersion, except for monitoring time with ILR, which was expressed as median and interquartile range (IQR). Chi-square test was used for the comparison of categorical variables. For the comparison of quantitative variables, Student's t-test for independent variables and Mann-Whitney U test were used. SPSS 26 (SPSS, Inc.; Chicago, Illinois, United States) data package was used for statistical analysis. A value of $p < 0.05$ was considered significant.

RESULTS:

Baseline characteristics of the study population:

A total of 65 patients (31 in UK, 27 in Spain and 7 in the Netherlands) were included, and their main characteristics are summarized in the graphical abstract and table 1. Of these, 48 (73.8%) were males. The mean ages at the diagnosis of BrS and at the implantation of the ILR were 37.7 ± 14.2 and 39.0 ± 14.0 years, respectively. Except for 4 patients aged between 11 and 15 years, the rest of the patients were >18 years old at the time of ILR implantation. The type I ECG pattern was spontaneous in 26 patients (40.0%), drug-induced in 34 patients (52.3%), and fever-induced in the remaining 5 patients (7.7%). Genetic testing was conducted in 48 patients (73.8%), yielding negative results in 29 (60.4%), positive results with a pathogenic or probably pathogenic SCN5A variant in 14 (29.2%), and positive results with a variant of unknown significance in 5 (10.4%). A total of 23 patients (35.4%) had a family history of SCD. All the patients but one had a normal left ventricular ejection fraction (>55%). A history of paroxysmal/persistent atrial

fibrillation was reported in 2 patients. The Sieira score for this group of patients was 1.8 ± 1.1, while the calculated Shanghai score was 4.0 ± 1.0, both indicative of an intermediate risk for the occurrence of life-threatening arrhythmias.

The majority of the patients (54/65, 83.1%) had previous symptoms that prompted the ILR implantation. The most frequent symptom was unexplained syncope or presyncope (n=43; 66.2%), followed by palpitations (n=10; 15.4%). In one patient, ILR was implanted after atypical chest pain. A total of 11 patients were asymptomatic; in these cases, the ILRs were implanted to complete the arrhythmic risk stratification, according to the local practice of each center.

ILR results:

The implantation of ILRs took place between 2003 and 2021. Most of the implanted devices (n=60; 92.3%) were Medtronic® Reveal, while 5 patients (7.7%) received a Confirm device (St. Jude Medical / Abbott®).

During a median follow-up of 39.0 months (IQR 25.0 – 47.6), a total of 21 arrhythmic events (AEs) were recorded in 18 patients (27.7%). As shown in figure 1, bradyarrhythmias were the most common finding (10/21; 47.6%) (figure 2), followed by SVT/AF (8/21; 38.1%). VAs represented the smallest proportion of all the AEs (3/21; 14.3%), including 2 cases of non-sustained ventricular tachycardia and one episode of symptomatic fast ventricular tachycardia (figure 3). In total, 3 patients experienced two types of AEs during the follow-up, combining the presence of bradyarrhythmias with the documentation of SVT/AF. It is important to note that no patients died during monitoring.

Detected AEs correlated with previously reported symptoms in 10 patients (15.4% of the total population, 23.3% of symptomatic patients, 55.6% of patients with arrhythmias during ILR monitoring), while in the rest of the patients, the recorded events were considered incidental findings. Patients with previous palpitations were more likely to present incidental AEs than patients with previous syncope/presyncope (50% vs 33.3%). However, this difference did not reach statistical significance (p=0.551).

Eight out of 43 patients presented recurrent syncope or presyncope in the presence of AEs. Additionally, a patient who had palpitations before ILR implantation reported intense dizziness related to significant sinus pauses. This implies that at least 13.8% of the patients included in the

study (50% of the patients with AEs) experienced syncope or presyncope during follow-up. However, this percentage may be underestimated, as we cannot rule out that more patients had syncope in the absence of AEs.

Therapeutic actions after ILR findings:

In 11 patients (16.9% of the total population, 61.1% of the patients with AEs during ILR monitoring), the detection of arrhythmias led to specific changes in treatment. These therapeutic changes, along with the baseline characteristics of the patients and the main diagnostic findings that led to these changes are detailed in table 2. It should be mentioned that, due to the retrospective nature of the study, the decision to consider an AE as clinically relevant (and take subsequent therapeutic decisions) was made according to the criterion of the treating physician in each participating center.

We compared the characteristics of the patients with AEs that led to therapeutic changes and the rest of the individuals included in the study (table 1). We did not find any statistically significant differences between both groups. All the patients with AEs and previous palpitations required therapeutic actions. Meanwhile, AEs in patients with previous syncope/presyncope were managed conservatively in half of the cases. Noticeably, none of the recorded incidental bradyarrhythmias (ie, not correlated with symptoms) led to therapeutic changes.

The flowchart in figure 4 summarizes the main findings of the study, including all the AEs that did not require therapeutic actions and were managed conservatively.

DISCUSSION:

The results of our study demonstrate that, in a BrS population of intermediate-risk and predominantly symptomatic (mostly with prior syncope/presyncope of unexplained origin), the implantation of an ILR after a negative EPS was a safe strategy that confirmed the existence of a low incidence of serious VAs. Simultaneously, it allowed the diagnosis of other types of arrhythmias. These arrhythmias were incidental findings (not correlated with previous symptoms) in a significant proportion of patients. However, it should be noted that in more than half of the cases, they were clinically relevant and led to specific therapeutic changes.

The implantation of an ICD is not a risk-free intervention. In patients with BrS, published series report a complication rate ranging from 16-28%, as well as a high incidence of inappropriate shocks, close to 18% in long-term follow-up[12]. This is particularly concerning in primary prevention, where the annual rate of appropriate therapies seems not to exceed that of inappropriate shocks or complications[13]. Inappropriate ICD interventions and ICD-related complications may lead to considerable morbidity[14]. Thus, there is a critical need to accurately identify BrS individuals at increased risk for cardiac arrest, both to minimize morbidity and to maximize efficient resource utilization. Both the performance of EPS and the use of ILR monitoring are elements that could add value to this process.

Regarding EPS, there is some controversy about its true utility[15–17]. The positive predictive value of EPS in BrS is poor, giving it a very limited role as a standalone tool in identifying patients who will experience serious arrhythmias in follow-up. This has also been observed in patients with drug-induced ECG patterns, a seemingly low-risk patient group[18,19]. In asymptomatic patients, the induction of VAs during EPS identifies individuals at higher risk of serious arrhythmias but with a high rate of false positives[19,20]. Although the use of less aggressive stimulation protocols seems to improve the specificity of the test[21,22], it is essential to contextualize the EPS result and consider other predictors of AEs to accurately estimate our patient's risk[23]. Most studies agree on the high negative predictive value of EPS, estimated between 95-98%[15–17]. The prognostic impact of a negative EPS may also extend in the long term[24]. Our results further emphasize this fact: among the 65 total patients, only 3 presented VAs during follow-up, resulting in a negative predictive value of 95%. This value increases to 98% when considering only the one patient with sustained VA. It is important to note that this low rate of ventricular arrhythmias is also attributed to the appropriate risk stratification carried out in each participating center in this study.

It is important to highlight that BrS is the hereditary cardiac rhythm disorder with the most evidence regarding the use of ILR for arrhythmia monitoring[25]. Similar to our study, bradyarrhythmias have been the most frequently reported findings when monitoring these patients with such devices[9,24]. Pathogenic variants in SCN5A have been suggested to be associated with sinus node dysfunction and even complete atrioventricular block[27,28]. However, it is also known that there is a high susceptibility to reflex cardioinhibitory responses in BrS[29–31]. In our study, many of the recorded bradyarrhythmias are likely to be reflex or neurally mediated. Unlike arrhythmia-induced syncope[32], neurally mediated syncope is not associated with a higher risk of serious adverse events in these patients[31,33]. Nevertheless, despite the theoretical

benignity of this type of reflex syncope, it is worth noting that nearly half of the patients with bradyarrhythmias received specific treatment (5/11: 3 pacemakers, 2 ICDs).

Clinical implications:

According to our results, the implantation of an ILR appears to be a useful strategy in a subset of BrS patients (ie, intermediate risk, unexplained symptoms). An ILR will allow us to: 1) confirm the low risk of serious ventricular arrhythmias conferred by the absence of inducibility in the EPS (electrophysiological study); 2) clarify in many cases the true mechanism of the symptoms presented by the patient; and 3) have the opportunity to diagnose other types of arrhythmias that, in a considerable percentage of cases, will have therapeutic implications and the potential to improve the quality of life and prognosis of some patients.

Limitations:

Our study has some limitations. First, the retrospective design and the restricted duration of the follow-up make difficult to confirm the long-term safety and utility of this strategy. Second, the limited size of our study likely hinders the ability to define the characteristics of the patients who would benefit most from an ILR after a negative EPS (ie, those in whom we may observe AEs with therapeutic implications). Third, the lack of uniformity in stimulation protocols across all participating centers may impact the definition of negative EPS. Nevertheless, we believe that the utilization of more conservative protocols (with up to 2 extra-stimuli) in some centers, which probably implies a higher rate of false negative results, underscores the high negative predictive value for the diagnosis of VA observed in our study. Finally, the highly selected nature of our study population imposes limitations on the external validation of our results.

We would like to mention that syncope in our study was defined as 'unexplained syncope,' indicating that its origin could not be determined despite thorough evaluation in each of the participating centers. This definition excludes cardiogenic syncope, but we cannot assure that some of these patients did not experience vasovagal syncope with atypical features.

CONCLUSIONS:

The present study represents the first specific analysis of the utility of the ILR in patients diagnosed with BrS and a lack of VA inducibility after EPS. Our study shows that ILR implantation fulfills its primary purpose of reconfirming the low risk (though not zero) of serious VAs after a negative EPS. This represents a reassuring strategy both for patients and clinicians. Moreover, it allows the documentation of other types of clinically relevant arrhythmias (mainly bradyarrhythmias) in a notable proportion of patients that may lead to specific therapeutic changes.

Further studies involving a larger number of patients and extended follow-up are necessary to confirm our findings and validate prolonged heart rhythm monitoring as a tool to enhance arrhythmic risk stratification in BrS. This is particularly crucial in certain clinical scenarios of this syndrome, where solid evidence regarding primary prevention of SCD is still lacking.

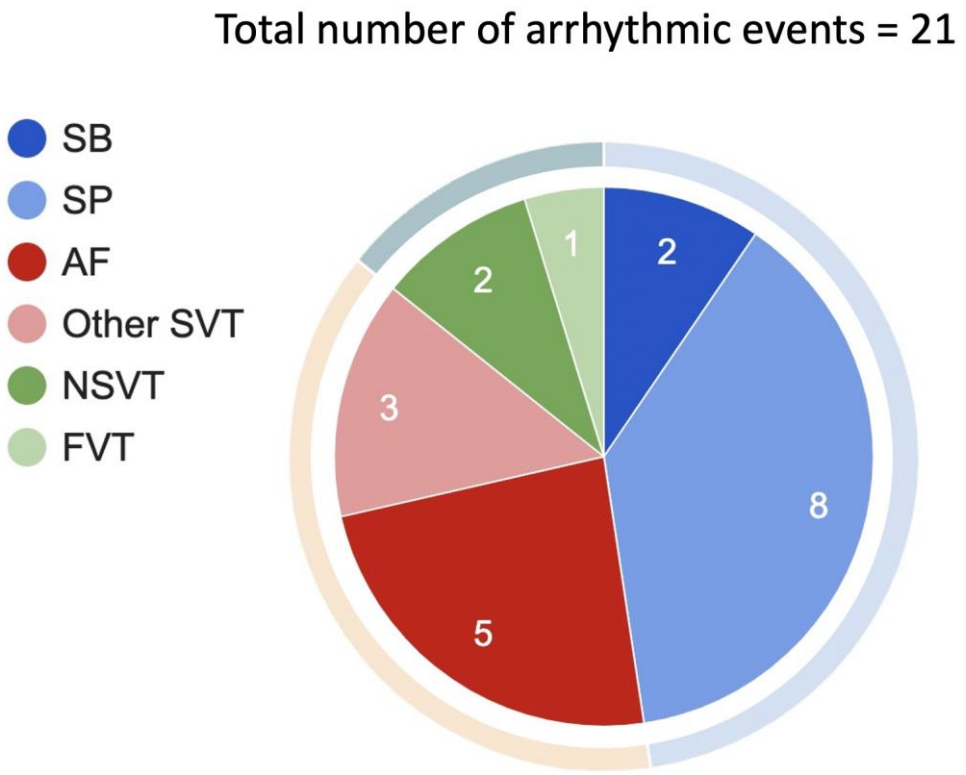

Figure 1. Distribution of the different types of arrhythmic events diagnosed with ILRs. AF: atrial fibrillation; FVT: fast ventricular tachycardia; NSVT: non-sustained ventricular tachycardia; SB: sinus bradycardia; SP: sinus pause; SVT: supraventricular tachycardia.

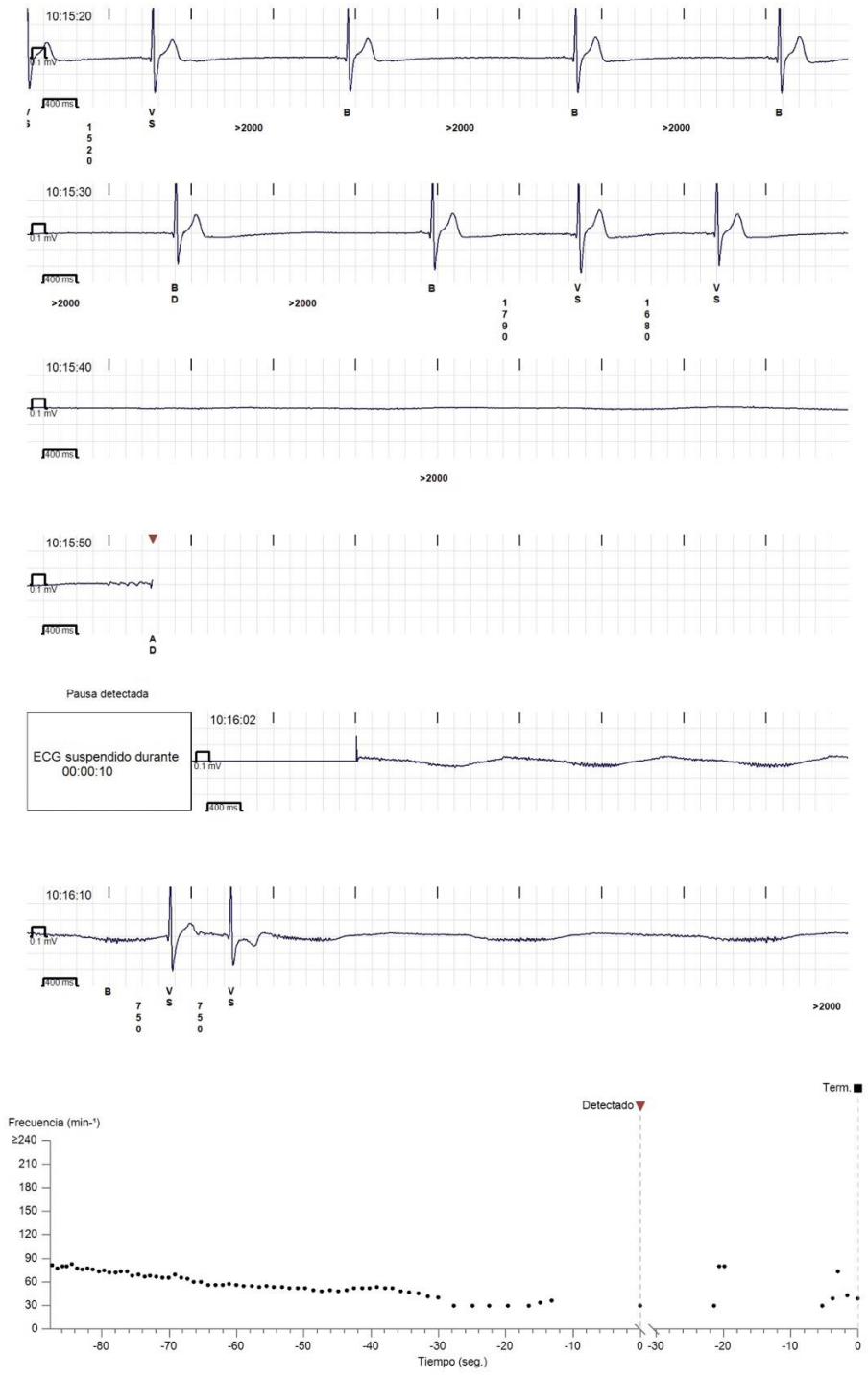

Figure 2. Example of bradyarrhythmia detected by ILR. A young female with a drug-induced type 1 Brugada ECG pattern and a history of unexplained syncope. An ILR was implanted after a negative EPS. This tracing shows progressive severe sinus bradycardia followed by a prolonged sinus pause. The presentation of this bradyarrhythmia suggests a neurally-mediated origin. The patient eventually received a pacemaker.

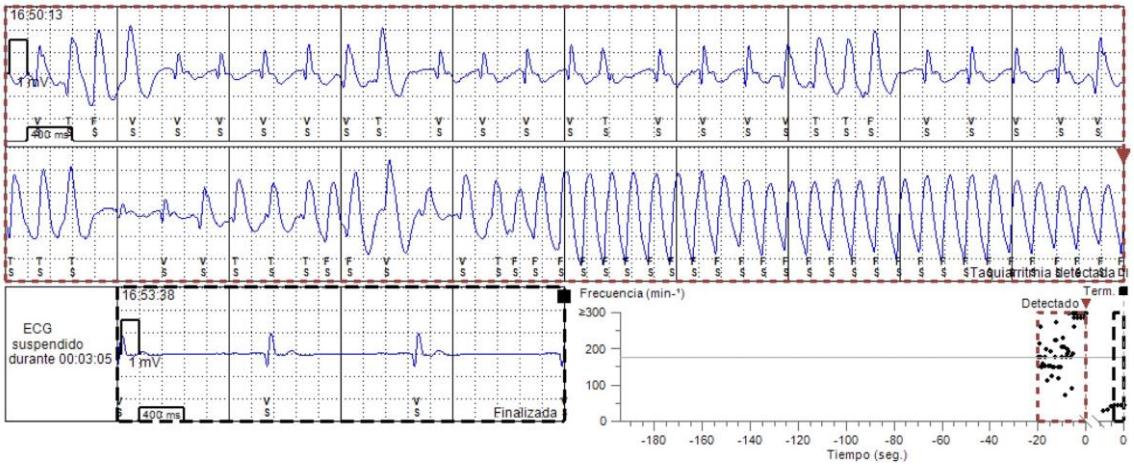

Figure 3. Example of VA detected by ILR. A 52-year-old male with a spontaneous Brugada ECG pattern and a prior unexplained syncope. An ILR was implanted after a negative EPS. This tracing shows the onset of a fast ventricular tachycardia (>300 bpm), preceded by supraventricular tachycardia, ventricular ectopy and bursts of nonsustained ventricular tachycardia. Following this event, which was symptomatic and led to syncope, the patient received an ICD.

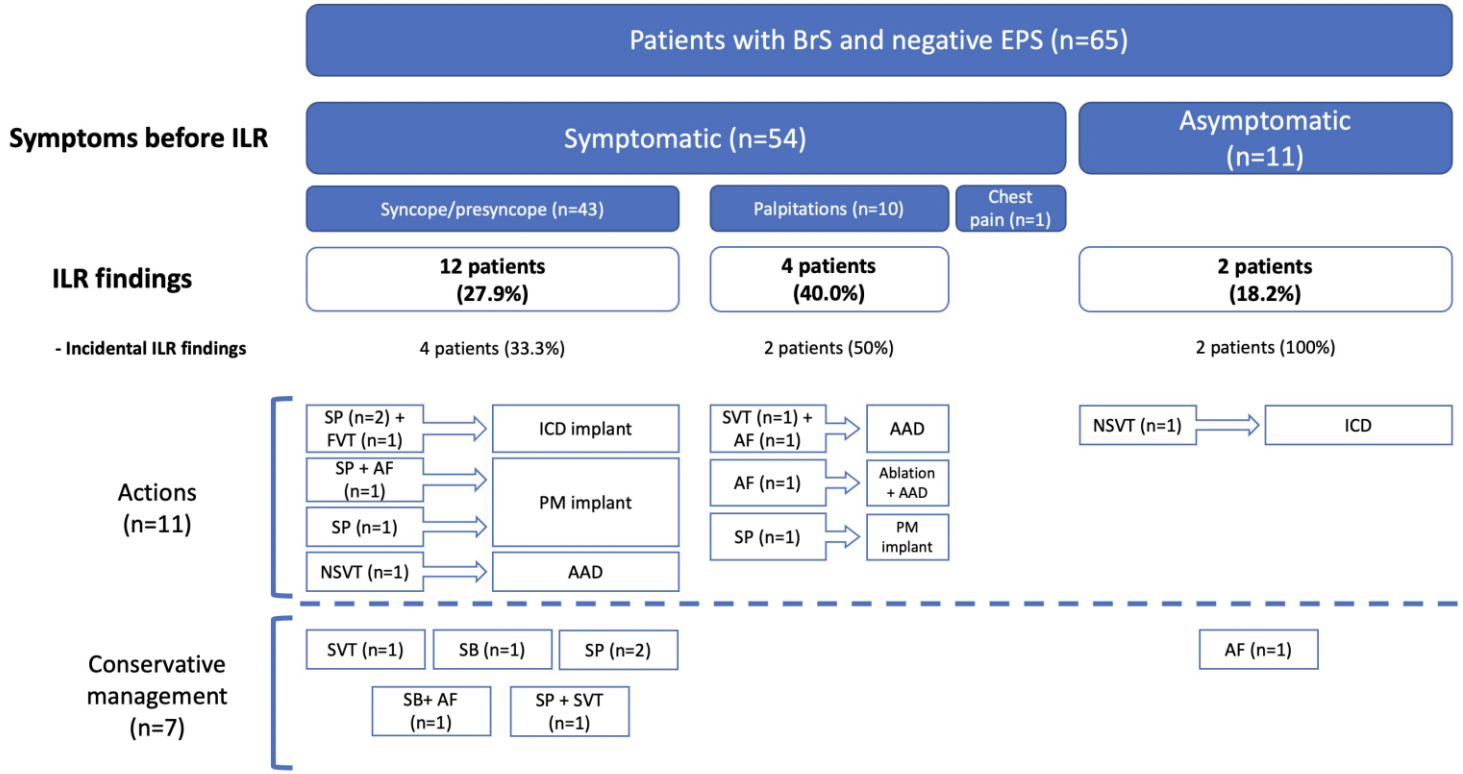

Figure 4. Summary flowchart of the study. AAD: antiarrhythmic drug; AF: atrial fibrillation; BrS: Brugada syndrome; EPS: electrophysiology study; FVT: fast ventricular tachycardia; ICD: implantable cardioverter defibrillator; ILR: implantable loop recorder; NSVT: non-sustained ventricular tachycardia; PM: pacemaker; SB: sinus bradycardia; SP: sinus pause; SVT: supraventricular tachycardia.

Table 1. Main characteristics of the study population and comparison between patients with and without arrhythmic events leading to therapeutic changes

	Total (n=65)	**Patients with AEs leading to therapeutic changes (n=11)**	**Patients with non-actionable AEs or without AEs (n=54)**	**p value**
Age at diagnosis (years)	37.7 ± 14.2	41.2 ± 16.9	37.0 ± 13.7	0.376
Age at ILR implant (years)	39.0 ± 14.0	42.6 ± 16.6	38.3 ± 13.4	0.360
Male (%)	48 (73.8%)	6 (54.5%)	42 (77.8%)	0.110
Type 1 ECG pattern:				0.271
- **Spontaneous (%)**	26 (40.0%)	3 (27.3%)	23 (42.6%)	
- **Drug-induced (%)**	34 (52.3%)	8 (72.7%)	26 (48.1%)	
- **Fever-induced (%)**	5 (7.7%)	0 (0.0%)	5 (9.3%)	
Genetic study:				0.688
- **Not performed (%)**	17 (26.2%)	4 (36.4%)	13 (24.1%)	
- **Negative (%)**	29 (44.6%)	4 (36.4%)	25 (46.3%)	
- **Positive P/LPV/VUS (%)**	19 (29.2%)	3 (27.2%)	16 (29.6%)	
Family history of SCD (%)	23 (35.4%)	4 (36.4%)	19 (35.2%)	0.941
History of persistent/paroxysmal AF	2 (3.1%)	0 (0.0%)	2 (2.8%)	0.517
Previous symptoms:				0.192
- **Asymptomatic**	11 (16.9%)	1 (9.1%)	10 (18.5%)	
- **Unexplained syncope/presyncope**	43 (66.2%)	6 (54.5%)	37 (68.5%)	
- **Palpitations**	10 (15.4%)	4 (36.4%)	6 (11.1%)	
- **Chest pain**	1 (1.5%)	0 (0.0%)	1 (1.9%)	
Sieira score	1.8 ± 1.1	1.4 ± 1.0	1.8 ± 1.1	0.189
Shanghai score	4.0 ± 1.0	3.6 ± 1.0	4.1 ± 1.0	0.158
Median ILR monitoring time (months)	39.0 (25.0 - 47.6)	33.8 (18.1 - 54.4)	39.5 (26.4 - 46.4)	0.726

AE: arrhythmic event; AF: atrial fibrillation; BrS: Brugada syndrome; ILR: implantable loop recorder; NSVT: non-sustained ventricular tachycardia; P/LPV: pathogenic/likely pathogenic variant; SCD: sudden cardiac death; VUS: variant of unknown significance

Table 2. Descriptions of the patients with arrhythmic events that led to specific changes in their treatments

Patient	Age at ILR implant (years)	Gender	Type 1 ECG pattern	Genetic study	Family history of SCD	Previous symptoms	Findings	Correlation with previous symptoms	Therapeutic actions
1	42	Female	Drug-induced	Not performed	Yes	Palpitations	Sinus pause	No*	PM implant
2	22	Female	Drug-induced	Negative	No	Syncope/presyncope	Sinus pause	Yes	PM implant
3	21	Female	Spontaneous	Positive PV	Yes	Palpitations	SVT	No	AAD
4	52	Male	Spontaneous	Not performed	No	Syncope/presyncope	Fast VT	Yes	ICD implant
5	42	Male	Spontaneous	Not performed	No	Palpitations	AF	Yes	Quinidine
6	57	Male	Drug-induced	Positive LPV	No	Syncope/presyncope	Sinus pause	Yes	ICD implant
7	58	Female	Drug-induced	Not performed	No	Syncope/presyncope	Sinus pause	Yes	ICD implant
8	73	Female	Drug-induced	Positive PV	Yes	Syncope/presyncope	Sinus pause + AF	Yes	PM implant + quinidine
9	42	Male	Drug-induced	Negative	Yes	Asymptomatic	Non-sustained VT	No	ICD implant
10	24	Male	Drug-induced	Negative	No	Syncope/presyncope	Non-sustained VT	Yes	AAD
11	35	Male	Drug-induced	Negative	No	Palpitations	Atrial fibrillation	Yes	AF ablation + AAD

(*): This patient experienced recurrent sinus pauses (up to 5 seconds duration) that were symptomatic (presyncope) and eventually received a PM

AAD: antiarrhythmic drug; AF: atrial fibrillation; ICD: implantable cardioverter defibrillator; ILR: implantable loop recorder; LPV: likely pathogenic variant; PM: pacemaker; PV: pathogenic variant; SCD: sudden cardiac death; SVT: supraventricular tachycardia; VT: ventricular tachycardia

REFERENCES:

1. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R: Present Status of Brugada Syndrome: JACC State-of-the-Art Review. Journal of the American College of Cardiology 2018; 72:1046–1059.

2. Krahn AD, Behr ER, Hamilton R, Probst V, Laksman Z, Han H-C: Brugada Syndrome. JACC: Clinical Electrophysiology American College of Cardiology Foundation, 2022; 8:386–405.

3. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al.: 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. Circulation American Heart Association, 2018; 138:e272–e391.

4. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al.: 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC). European Heart Journal 2022; 43:3997–4126.

5. Assaf A, Theuns DA, Michels M, Roos-Hesselink J, Szili-Torok T, Yap S-C: Usefulness of insertable cardiac monitors for risk stratification: current indications and clinical evidence. Expert Rev Med Devices 2023; 20:85–97.

6. Kawada S, Morita H, Antzelevitch C, et al.: Shanghai Score System for Diagnosis of Brugada Syndrome: Validation of the Score System and System and Reclassification of the Patients. JACC: Clinical Electrophysiology 2018; 4:724–730.

7. Sakhi R, Assaf A, Theuns DAMJ, et al.: Outcome of Insertable Cardiac Monitors in Symptomatic Patients with Brugada Syndrome at Low Risk of Sudden Cardiac Death. Cardiology 2020; 145:413–420.

8. Palacios-Rubio J, Massó-van Roessel A, Galizia-Brito V, Expósito-Pineda C, Grande-Morales C: Outcome of Insertable Cardiac Monitors in Symptomatic Patients with Brugada Syndrome at Low Risk of Sudden Cardiac Death. Cardiology 2021; 146:63–64.

9. Scrocco C, Ben-Haim Y, Devine B, et al.: Role of subcutaneous implantable loop recorder for the diagnosis of arrhythmias in Brugada syndrome: A United Kingdom single-center experience. Heart Rhythm 2022; 19:70–78.

10. Sieira J, Conte G, Ciconte G, et al.: A score model to predict risk of events in patients with Brugada Syndrome. Eur Heart J 2017; 38:1756–1763.

11. Rodríguez-Mañero M, Baluja A, Hernández J, et al.: Validation of multiparametric approaches for the prediction of sudden cardiac death in patients with Brugada syndrome and electrophysiological study. Rev Esp Cardiol (Engl Ed). 2022 Jul;75(7):559-567. English, Spanish.

12. El-Battrawy I, Roterberg G, Liebe V, et al.: Implantable cardioverter-defibrillator in Brugada syndrome: Long-term follow-up. Clin Cardiol 2019; 42:958–965.

13. Olde Nordkamp LRA, Postema PG, Knops RE, et al.: Implantable cardioverter-defibrillator harm in young patients with inherited arrhythmia syndromes: A systematic review and meta-analysis of inappropriate shocks and complications. Heart Rhythm 2016; 13:443–454.

14. Dereci A, Yap S-C, Schinkel AFL: Meta-Analysis of Clinical Outcome After Implantable Cardioverter-Defibrillator Implantation in Patients With Brugada Syndrome. JACC Clin Electrophysiol 2019; 5:141–148.

15. Probst V, Veltmann C, Eckardt L, et al.: Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada Syndrome Registry. Circulation 2010; 121:635–643.

16. Priori SG, Gasparini M, Napolitano C, et al.: Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. J Am Coll Cardiol 2012; 59:37–45.

17. Sieira J, Conte G, Ciconte G, et al.: Prognostic Value of Programmed Electrical Stimulation in Brugada Syndrome. Circulation: Arrhythmia and Electrophysiology American Heart Association, 2015; 8:777–784.

18. Russo V, Pafundi PC, Caturano A, et al.: Electrophysiological Study Prognostic Value and Long-Term Outcome in Drug-Induced Type 1 Brugada Syndrome: The IBRYD Study. JACC: Clinical Electrophysiology 2021; 7:1264–1273.

19. Russo V, Caturano A, Migliore F, et al.: Long-term clinical outcomes of patients with drug-induced type 1 Brugada electrocardiographic pattern: A nationwide cohort registry study. Heart Rhythm. 2024 Jan 18:S1547-5271(24)00026-2.

20. Gaita F, Cerrato N, Giustetto C, et al.: Asymptomatic Patients With Brugada ECG Pattern: Long-Term Prognosis From a Large Prospective Study. Circulation American Heart Association, 2023; 148:1543–1555.

21. Sroubek J, Probst V, Mazzanti A, et al.: Programmed Ventricular Stimulation for Risk Stratification in the Brugada Syndrome. Circulation American Heart Association, 2016; 133:622–630.

22. Takagi M, Sekiguchi Y, Yokoyama Y, et al.: The prognostic impact of single extra-stimulus on programmed ventricular stimulation in Brugada patients without previous cardiac arrest:

multi-centre study in Japan. Europace 2018; 20:1194–1200.

23. Rattanawong P, Mattanapojanat N, Mead-Harvey C, et al.: Predicting arrhythmic event score in Brugada syndrome: Worldwide pooled analysis with internal and external validation. Heart Rhythm 2023; 20:1358–1367.

24. Shinohara T, Takagi M, Kamakura T, et al.: Late life-threatening arrhythmia in patients with Brugada syndrome: Results from long-term follow-up in a large Japanese cohort. J Cardiovasc Electrophysiol. 2024 Feb 8.

25. Balfe C, Durand R, Crinion D, Ward D, Sheahan R: The evidence for the implantable loop recorder in patients with inherited arrhythmia syndromes: a review of the literature. Europace 2022; 24:706–712.

26. Kubala M, Aïssou L, Traullé S, Gugenheim A-L, Hermida J-S: Use of implantable loop recorders in patients with Brugada syndrome and suspected risk of ventricular arrhythmia. Europace 2012; 14:898–902.

27. Smits JPP, Koopmann TT, Wilders R, et al.: A mutation in the human cardiac sodium channel (E161K) contributes to sick sinus syndrome, conduction disease and Brugada syndrome in two families. J Mol Cell Cardiol 2005; 38:969–981.

28. Makiyama T, Akao M, Tsuji K, et al.: High risk for bradyarrhythmic complications in patients with Brugada syndrome caused by SCN5A gene mutations. J Am Coll Cardiol 2005; 46:2100–2106.

29. Letsas KP, Efremidis M, Gavrielatos G, Filippatos GS, Sideris A, Kardaras F: Neurally mediated susceptibility in individuals with Brugada-type ECG pattern. Pacing Clin Electrophysiol 2008; 31:418–421.

30. Yokokawa M, Okamura H, Noda T, et al.: Neurally mediated syncope as a cause of syncope in patients with Brugada electrocardiogram. J Cardiovasc Electrophysiol 2010; 21:186–192.

31. Olde Nordkamp LRA, Vink AS, Wilde AAM, et al.: Syncope in Brugada syndrome: prevalence, clinical significance, and clues from history taking to distinguish arrhythmic from nonarrhythmic causes. Heart Rhythm 2015; 12:367–375.

32. Mascia G, Bona RD, Ameri P, et al.: Brugada syndrome and syncope: a practical approach for diagnosis and treatment. Europace 2021; 23:996–1002.

33. Giustetto C, Cerrato N, Ruffino E, et al.: Etiological diagnosis, prognostic significance and role of electrophysiological study in patients with Brugada ECG and syncope. Int J Cardiol 2017; 241:188–193.

Figure 1

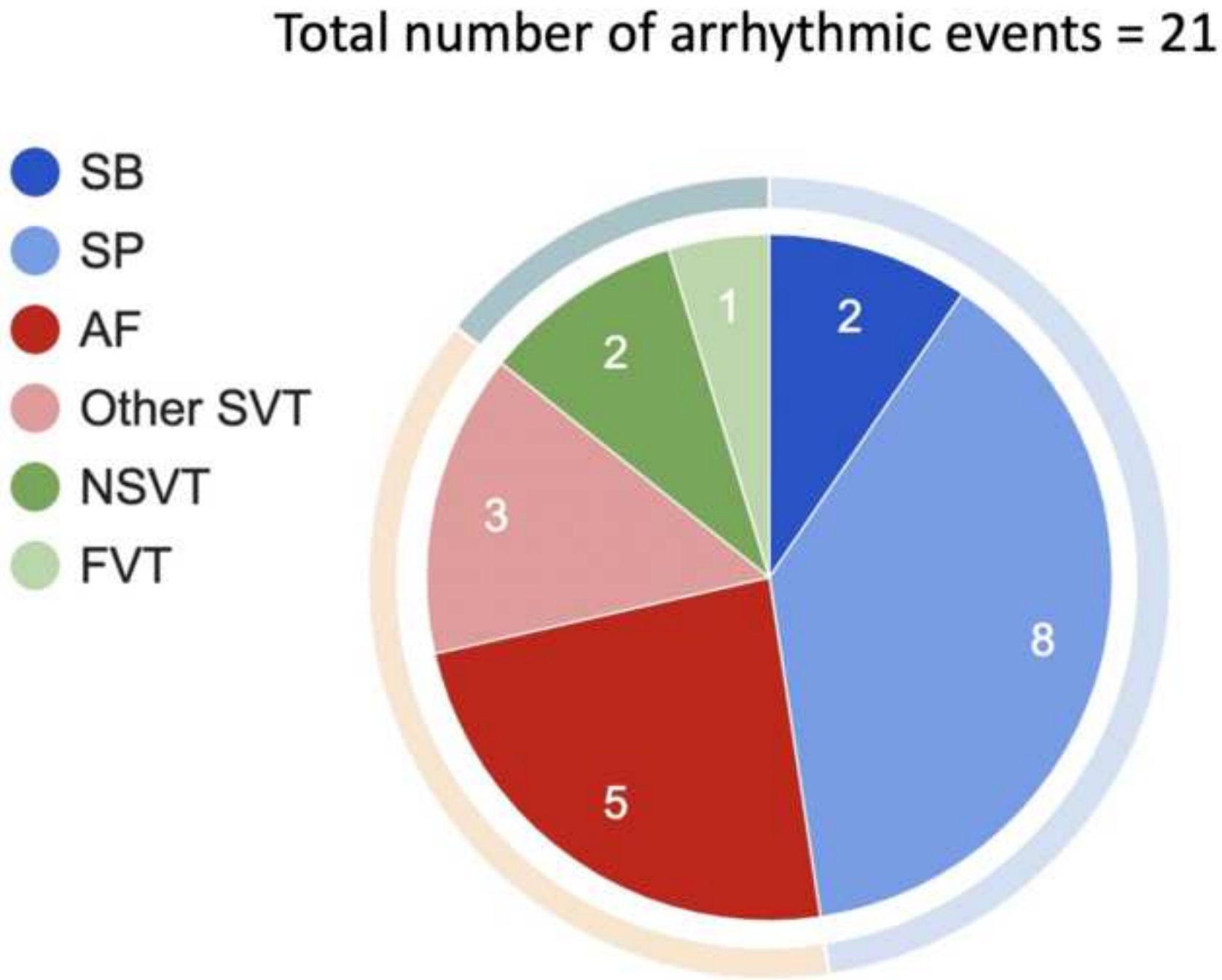

Figure 4

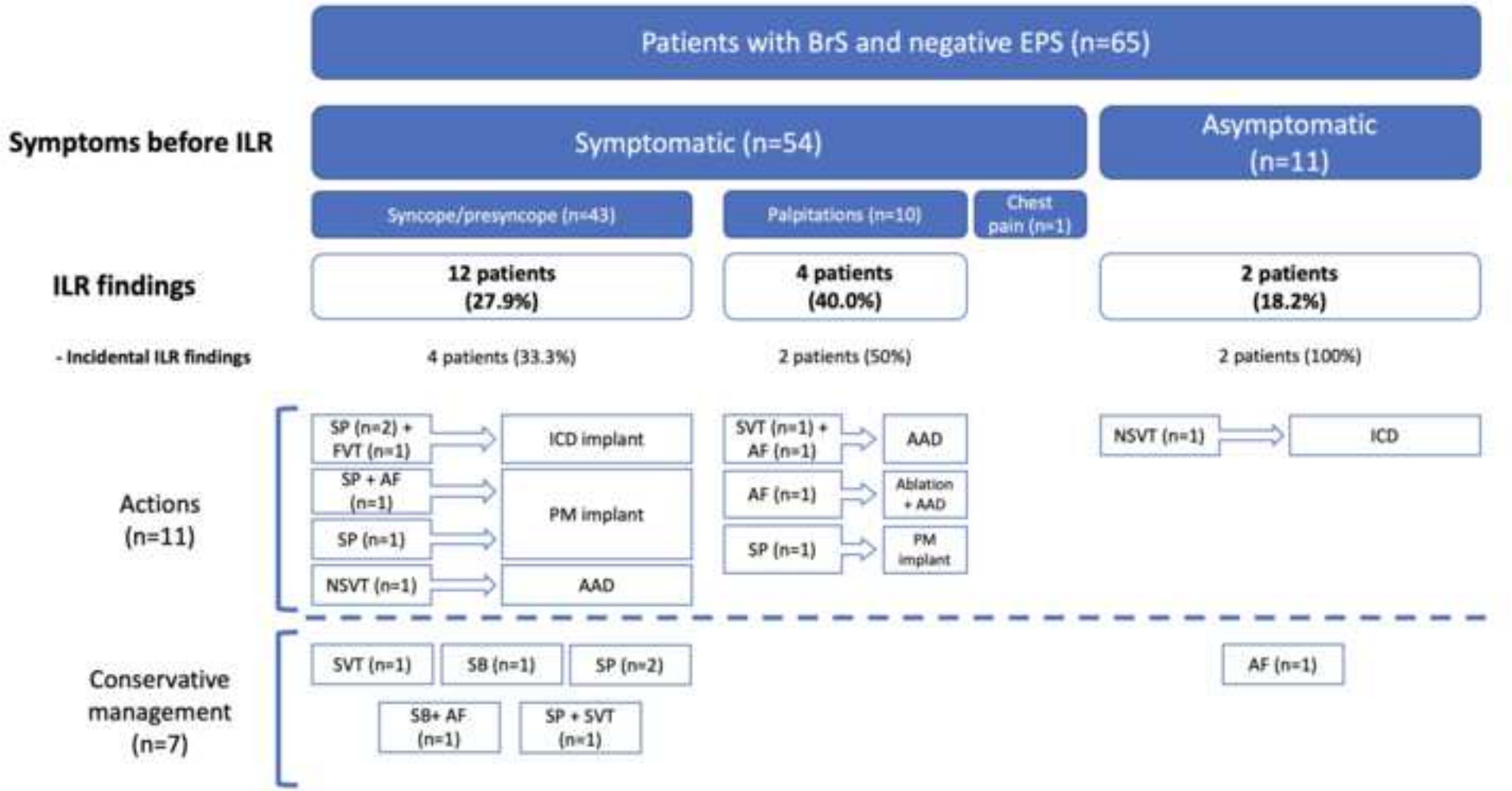

Figure 2

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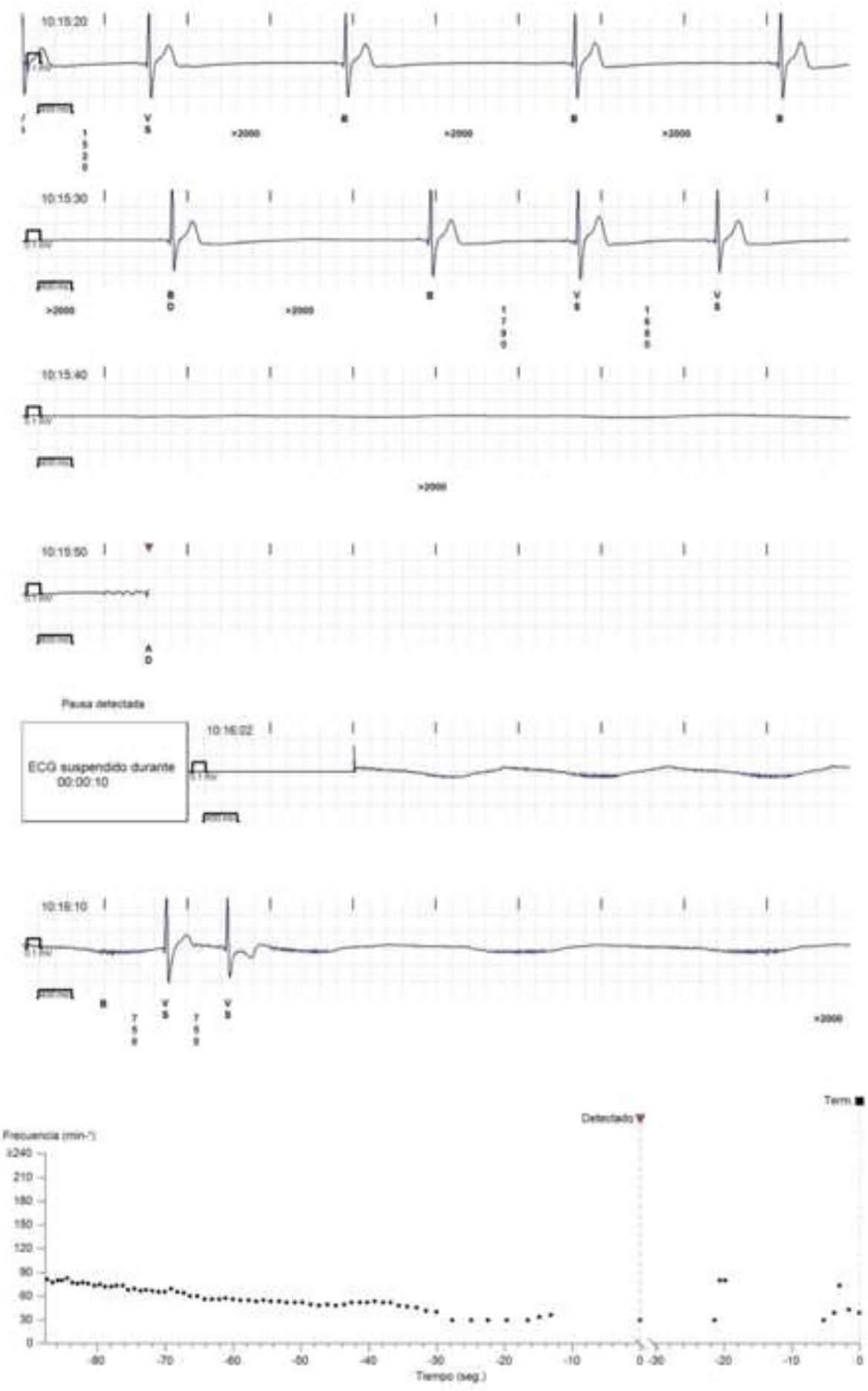

Figure 3

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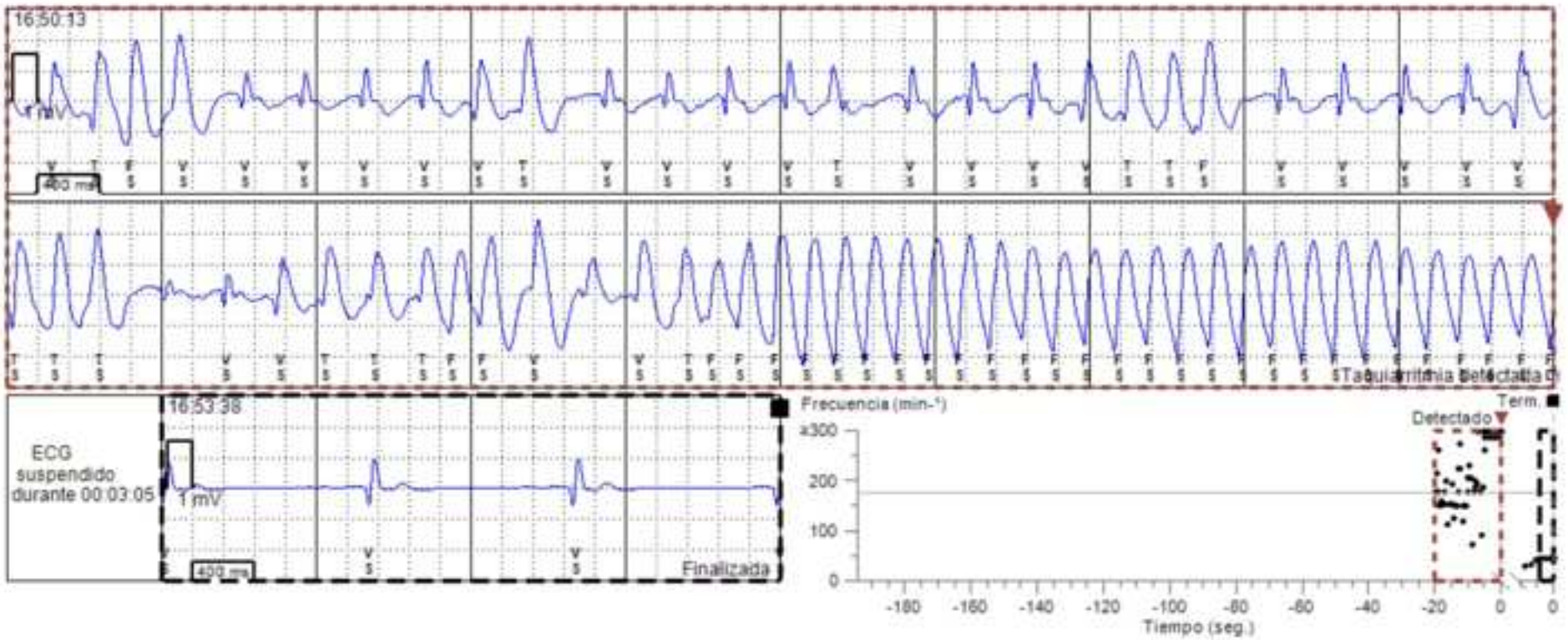

Graphical Abstract