Title: Role of subcutaneous Implantable Loop Recorder for the diagnosis of arrhythmias in Brugada Syndrome: a single United Kingdom centre experience.

Short title: Implantable Loop Recorder in Brugada Syndrome

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Abstract

Background: Experience with implantable loop recorders (ILR) in Brugada Syndrome (BrS) is limited.

Objective: We sought to evaluate the indications and yield of ILR monitoring in a single-centre BrS registry.

Methods: Demographic, clinical and follow-up data of BrS patients with ILR were collected.

Results: Of 415 BrS patients recruited consecutively, 50 (12%) received an ILR (58% males). Mean age at ILR implantation was 44±15 years. Thirty-one (62%) had experienced syncopal or pre-syncopal episodes, and 23 (46%) palpitations. During a median follow-up of 28 months (range 1-68), actionable events were detected in 11 subjects (22%); 7 had recurrences of syncope/presyncope, and in 4 defects in sinus node function or atrioventricular conduction were detected. New supraventricular tachyarrhythmias were recorded in 6 subjects; a run of fast non-sustained VT was detected in one patient. Patients implanted with an ILR were less likely to show a spontaneous type 1 pattern or depolarisation ECG abnormalities compared to those receiving a primary prevention ICD. Age at implantation, gender, Shanghai score and ECG parameters did not differ between subjects with actionable events and those without. Device-related complications occurred in 3 cases (6%).

Conclusion: In a large cohort of BrS patients, continuous ILR monitoring yielded a diagnosis of tachy- or brady-arrhythmic episodes in 22% of cases.

Recurrences of syncope were associated with brady-arrhythmic events. The use of ILR can be helpful in guiding the management of low/intermediate risk BrS patients and ascertaining the cause of unexplained syncope.

Keywords: Brugada Syndrome, Sudden Death, Ventricular Arrhythmias, ILR, ECG

Introduction

The Brugada Syndrome (BrS) is characterised by "coved" ST segment elevation ≥2 mm in the right precordial ECG leads (the type 1 pattern) and increased risk of ventricular arrhythmias (VAs) and sudden cardiac death (SCD) [1] [2]. The incidence of life-threatening VAs in previously asymptomatic subjects with BrS is estimated at 0.3 to 1 % per year [3] [4]. The only proven strategy for the prevention of SCD is the implantable-cardioverter defibrillator (ICD), which is recommended in patients with a previous aborted cardiac arrest/documented VAs and can be useful in patients with previous arrhythmic syncope and a spontaneous type 1 pattern [1] [2]. Several other clinical, ECG and invasive risk factors have been proposed in subjects without documented VAs [5], but risk stratification remains challenging. Subjects with BrS often suffer from neurocardiogenic or unexplained syncopal episodes as well as palpitations secondary to paroxysmal atrial arrhythmias (atrial fibrillation (AF), atrial tachycardia (AT) or atrioventricular nodal reentrant tachycardia (AVNRT). These have not been associated consistently with VAs during follow-up [6] [7] [8] [9] [10].

Implantable loop recorders (ILR) are indicated for investigation of syncope or palpitations in high-risk patients in whom comprehensive evaluation has not demonstrated a cause or led to treatment [11]. ILRs may therefore have a role in correlating symptoms and suspected VA in BrS patients [2] [12], avoid unnecessary ICD implantation and offer reassurance. However, the experience

with ILRs in BrS is limited [13] [14] [8]. This study sought to evaluate the indications for ILR implantation and the yield of ILR-guided diagnosis in a large single-centre cohort of BrS patients.

Methods

Study Population

Consecutive adult patients with a diagnosis of BrS were included from 2008 to June 2020. Subjects with significant coronary or cardiomyopathic disease or metabolic abnormality at time of type 1 ECG pattern were excluded. The study was approved by the regional ethics committee and Trust R&D. All the patients gave their informed consent for inclusion in the study.

Data collection

Retrospective demographic and clinical data, including symptoms, results of cardiac investigations and genetic tests, and details on device implantation were collected. Resting digital ECGs were analysed with software developed at the Institute of Health & Wellbeing, University of Glasgow [15] for ECG parameters: RR interval, P wave duration, PR interval, QRS duration, QT interval and QTc value, QRS fragmentation (defined as 2 or more spikes within the QRS complex in leads V1 to V3), Early Repolarisation Pattern [16], duration and amplitude of S wave in lead I, and Tpeak-Tend interval. Device data included date and

indication for implantation, duration of follow-up and classification of transmitted tracings. These were deemed actionable if the arrhythmia detected led directly to a change of medical or device therapy. Symptoms and arrhythmic events during follow-up were recorded. A 'Shanghai score' was calculated for each patient based on ECG, clinical, familial and genetic data [17].

Statistical Analysis

Descriptive statistics were used for demographic and clinical data. Categorical variables were expressed as number and percentages, while continuous variables were expressed as mean values with standard deviation (SD) if normally distributed, or as median with Interquartile Range (IQR) if not. Normally distributed data were compared with the Fisher's exact or χ^2 test (categorical data) and with one-way ANOVA or independent t-tests (continuous data). Non-parametric tests were used for non-normally distributed data. All P-values were two-sided, and statistical significance was accepted at $P < 0.05$, apart from tests involving multiple comparisons for which the Bonferroni correction was applied.

Results

Clinical population

Four-hundred-and-fifteen subjects were included. All underwent investigations to exclude BrS phenocopies [17]. A total of 50 (12%) received an ILR. Twenty-

nine (58%) were males, and 33 were Caucasian (66%). Twenty-nine subjects (58%) had a probable/definite diagnosis of BrS based on the Shanghai score. Mean age at ILR implantation was 44±15 years. Thirty-one subjects (62%) had experienced a prior syncopal or pre-syncopal episode; in 18 the syncope was considered reflex (preceded by characteristic vasovagal prodrome including nausea/vomiting, diaphoresis, pallor, blurred vision, palpitations and/or dyspnoea), or due to orthostatic hypotension (OH); 6 subjects had at least one syncopal episode deemed unexplained or suspicious of an arrhythmic origin; 7 only had pre-syncopal episodes without complete loss of consciousness. Palpitations were present in 23 subjects (46%), isolated (15 subjects) or in association with other symptoms. Three subjects were asymptomatic at presentation and another had a previous history of seizures. In these subjects the decision to implant an ILR relied mainly on the presence of a spontaneous type 1 BrS pattern; two of them also harboured a pathogenic *SCN5A* variant, and in one a run of monomorphic VT was triggered during programmed electrical stimulation. ***Supplementary Table 1*** details demographic, clinical, genetic, and follow-up data of the ILR cohort.

ILR results

The median follow-up time was 28 months (IQR 24, range 1-68). In two subjects the device was replaced after the end of life battery, while in three

cases (6%) it was explanted prematurely due to implant site infection (with subsequent re-implantation in one).

In total, continuous ILR monitoring detected actionable events in 11 subjects (22%) **(*Figure 1)***. There were no deaths. The median time from implantation to actionable event was 19 months (range 1 to 68 months). There were no differences between subjects who received an ILR-guided diagnosis and those without actionable events with regard to age at implantation, gender, Shanghai score at presentation, presence of spontaneous type 1, symptoms, results of electrophysiological study (EPS) and genetic background **(*Table 1)*.**

Previous syncope or pre-syncope

Of the 31 subjects with previous syncopal or pre-syncopal episodes, 7 (23%) had recurrences of symptoms: these were associated with brady-arrhythmias in all bar one.In two cases prolonged sinus pauses were recorded and a dual chamber ICD was implanted; in another subject paroxysmal complete atrioventricular block with pauses up to 15 s were recorded **(*Figure 2*)** and an ICD implanted; subsequently the same subject experienced episodes of AT. In all three cases the decision to implant an ICD was determined by patient choice after careful counselling about risk and benefits of defibrillator leads compared to pacing leads, and the presence of potential risk factors for SCD. One 71-year old female with a pathogenic *SCN5A* variant and paroxysmal AF suffered multiple pre-syncopal episodes with documented diurnal pauses (ranging from

2.2 to 6 seconds) whilst taking a low dose of a beta-blocker. She was counselled about device therapy and opted for a permanent pacemaker. In two subjects the analysis of the electrograms (EGMs) showed sinus bradycardia during the episodes, while in another no actionable events were documented and a diagnosis of partial epileptic seizures was subsequently made.

Recurrences of symptoms were more frequent in subjects with unexplained/suspected arrhythmic syncope (3/6, 50%) compared to those with suspected reflex/neurogenic syncope (3/18, 17%). Only one subject with pre-syncope had a recurrence, which was not deemed to be of cardiac origin (1/7, 14%). All subjects with previously unexplained syncope and recurrent episodes were diagnosed with sinus node dysfunction after detection of pathological sinus pauses, while in subjects with reflex syncope the available tracings showed sinus bradycardia in two cases, and paroxysmal complete AV block in another. In all subjects who underwent an EPS (18/31), programmed ventricular stimulation failed to induce sustained polymorphic VT/VF and the effective ventricular refractory periods were > 200 ms. In addition, the HV intervals were normal.

Eight patients with prior syncope activated the device because of sustained palpitations; in four, paroxysmal episodes of supraventricular arrhythmias were recorded, and catheter ablation was performed in three of them. In the other four cases, no actionable events were detected.

In one subject, no symptoms occurred and no arrhythmias were recorded during ILR monitoring. However, a 4-beat run of monomorphic NSVT was recorded on 24h Holter ECG after the explantation of the device.

Previous palpitations

Of the 15 patients presenting with palpitations only, 3 (20%) had a recurrence of symptoms. Episodes of AT/AF were recorded in one subject, who started hydroquinidine. Another subject with palpitations, family history of SCD, normal cardiac investigations, other than a 5-beat NSVT during 24h ambulatory monitoring, experienced an asymptomatic run of fast non-sustained polymorphic VT **(*Figure 3*)** and was offered an ICD. No arrhythmic episodes were recorded in the other subject with recurrent palpitation.

Other symptoms or no symptoms

One subject with previous seizures had an asymptomatic episode of AT recorded. The three subjects with no previous symptoms did not experience events during follow-up.

Comparison between subjects receiving ILR, ICD or no device therapy

We compared the demographic, clinical, ECG, and genetic characteristics of subjects without previous aborted cardiac arrest who received an ILR, an ICD or no device ***(Supplementary Table 2)***. Those who received an ICD in primary prevention were more likely to display a spontaneous type 1 pattern

compared to those receiving an ILR, whereas there were no differences in gender, age at implantation, Shanghai score, genetic background, inducibility of VF at EPS between the two groups. Subjects not receiving any device had a lower Shanghai score and lower prevalence of spontaneous type 1 pattern, *SCN5A* variants and VF inducibility during EPS. They also had lower prevalence of symptoms, i.e. syncope or presyncope, as compared to the other two groups. With regard to the baseline ECG characteristics and other markers of increased arrhythmic risk, subjects receiving an ICD showed broader QRS duration, had a higher prevalence of fragmented QRS compared to the other two groups, and longer PR interval with higher prevalence of first-degree AV block compared with the group not receiving any device. Increased Tpeak-Tend interval were observed in the ILR group compared to the group without devices.

Figure 4 illustrates the follow-up events in the three groups considered. There were no life-threatening arrhythmias detected in subjects receiving an ILR or not receiving any device, whereas in the ICD group three subjects experienced short runs of NSVT and three received appropriate ICD shocks on sustained VT/VF; interestingly, these latter occurred in 2 subjects without previous symptoms and one with palpitations. After the implantation of the ICD or PM in the ILR cohort, no events were recorded during a median follow-up of 1.5 years. In the group with no device implanted, there were four deaths due to non-cardiac causes.

Discussion

The present study details, to our knowledge, the largest experience of the use of ILRs in BrS reported so far. The main finding is that ILR monitoring detected an actionable arrhythmia in 22% of subjects considered to be at insufficient risk of life-threatening VAs to warrant immediate ICD implantation. Diagnoses were made in 4/7 of subjects who suffered a recurrence of syncope or pre-syncope and 5/10 subjects with symptomatic palpitations. Paroxysmal sinus node or atrioventricular conduction dysfunction caused unexplained and even presumed vasovagal/reflex syncope in BrS subjects, while supraventricular arrhythmias were detected in half of the subjects with recurrent palpitations.

There were no deaths or sustained VAs in subjects receiving an ILR; only one episode of fast polymorphic NSVT was detected at ILR interrogation in a subject without previous symptoms, prompting prophylactic ICD implantation. In another case a short run of NSVT was detected after the device explant. The median time from implantation to actionable events was 19 months, ranging from 1 to 68 months. This suggests that in some cases prolonged monitoring may be necessary.

The rate of complications from the ILR implant was 6% in our cohort. This is higher than previously reported in the literature [18] [19].

Syncope in Brugada syndrome

Syncope is a common symptom in BrS, affecting 24% to 34% of patients [6] [8] [7]; in the majority of cases, syncopal episodes appear to be vasovagal/reflex syncope or secondary to OH, and are associated with a good prognosis. Conversely, suspected arrhythmic syncope is associated with VAs during follow-up [20]. Moreover, increased vagal activity can trigger arrhythmic episodes in BrS and typical vasovagal prodromes are not exclusive to reflex syncope [21]. A significant proportion of syncopal episodes (30 to 39% in different case series) remains unexplained after comprehensive cardiac work-up. For this group the prognosis is less well defined, but the rate of recurrence is up to 53% [8] [7].

A previous study of ILRs for the diagnosis of unexplained syncope in subjects with cardiovascular disease indicated that the episodes were secondary to brady-arrhythmias in the vast majority of cases [22]. Experience with ILRs in BrS is more limited. In 2012 Kubala et al. reported ILR monitoring in 11 BrS subjects. Eight subjects had recurrence of syncope, with two experiencing sinus bradycardia and two second-degree AV block [13]. Giustetto et al. reported the use of ILR to help adjudicate the cause of syncope in 27 subjects [8]. A recent study of 20 Dutch BrS patients did not highlight recurrences or new episodes of syncope, although three patients required antiarrhythmic therapy or catheter ablation and one permanent pacing [14].

Our study confirmed the overall good prognosis for subjects with reflex/OH syncope although some did have actionable findings with one patient

requiring pacing for paroxysmal AV block, which had occurred without any change in sinus rate to indicate increased vagal tone. Furthermore, syncopal recurrences in our cohort were associated with conduction defects instead of VAs.

Supraventricular arrhythmias

New supraventricular arrhythmias, including AF, AT, and AVNRT occurred in 12% of subjects in our cohort, and were symptomatic in the majority of them. The mean age at detection was 49 ±16 years, in keeping with previous reports on AF in BrS [9] [10]. In our cohort, atrial arrhythmias were not associated with the occurrence of VAs.

ILR implantation in BrS

Figure 5 shows the trend of ILR implantations in BrS subjects symptomatic for pre-syncope and syncope in our centre; this steadily increased from 12% in 2006 to 51% in 2019, likely reflecting the evolution of guidelines endorsed by international cardiac societies for the evaluation of subjects with syncope and prevention of SCD [10] [11] [2]. In our experience, patients receiving an ILR were more likely to experience symptoms, i.e. syncope/ pre-syncope, while the presence of a spontaneous type 1 pattern and other ECG markers of risk (i.e. depolarisation abnormalities) were more often associated with ICD implantation ***(Supplementary Table 2).***

Type 1 pattern, EP studies and risk in BrS

Current expert consensus documents and guidelines recommend lifestyle measures to reduce the risk of arrhythmias in all BrS patients and suggest that the presence of a spontaneous type 1 pattern and previous arrhythmic syncope may support prophylactic ICD implantation [1] [2]. Yet none of the subjects with a spontaneous type 1 Brugada ECG in the ILR cohort had actionable events after recurrent syncope, and the only VA occurred in a subject with a sodium channel blocker induced pattern. However, due to the dynamic nature of the type 1 Brugada ECG [23] [24] we cannot exclude that subjects with recurrent syncope or presyncope never showed it.

The use of programmed electrical stimulation during EPS to identify the best candidates for a prophylactic ICD implantation is controversial [1] [4]. In our cohort, more than half of the subjects with previous syncope (18/31, 100% of those with recurrent episodes) underwent programmed electrical stimulation, which did not induce ventricular arrhythmias; in addition, effective ventricular refractory periods were always above 200 ms and HV intervals were normal. Syncopal recurrences were not associated with VAs lending support to the findings of Giustetto et al. who highlighted the negative predictive value of the EP study for VAs in BrS subjects with syncope [8]. Our findings would suggest that equivocal and even presumed reflex syncope in BrS may be attributable to sinus node or AV conduction defects rather than VAs or vagal triggers.

Conduction disease and SCN5A gene variants

Conduction disturbances are common in BrS [25] [26]. Subjects with pathogenic *SCN5A* variants display longer PR intervals, QRS durations and HV intervals and are more likely to suffer syncope [27] [28]. Furthermore, the clinical spectrum of loss-of-function *SCN5A* variants also includes sick sinus syndrome, isolated cardiac conduction defects, and AF [29]. In our ILR cohort, conduction disease was detected in only one patient with a pathogenic/likely pathogenic *SCN5A* variant, however the total number of genotyped subjects in our cohort (including those in whom the genetic test was not offered as the family's index case tested negative for mutations in SCN5A) is too small to make appropriate conclusions on the incidence of actionable events attributable to a specific genetic predisposition.

Clinical implications

Our findings support the use of ILR for monitoring and stratifying risk in symptomatic subjects with BrS and insufficient risk of life-threatening VAs to warrant immediate ICD implantation. In fact, an ILR-guided diagnosis was made in 57% of subjects with recurrent syncope (especially those with previous unexplained or suspected arrhythmic episodes), and 50% of subjects with symptomatic palpitations. This is especially important considering that palpitations are not usually associated with the presence of ventricular

arrhythmias [30], and therefore ICD implantation may not always be indicated. It is worth noting, however, that no clinical or ECG features allowed identification of subjects with actionable events at ILR interrogation, conceivably due to the small size of our cohort. With the increasing widespread use of non-invasive, commercially available wearable devices, it is foreseeable that a higher proportion of clinical and sub-clinical arrhythmias will be detected in subjects with BrS or other primary arrhythmia syndromes.

In the absence of precise risk stratification strategies, the decision to implant an ICD for primary prevention should rely on a multiparametric approach (including ECG and EP features, personal and family clinical history), recognising and communicating to the patient some of the inconsistencies in the literature: for example, the use of EP studies. In selected patient groups (e.g. those with atrioventricular and intraventricular conduction diseases, or multiple high risk features), the systematic use of ILR may reduce the burden of physical and psychological distress associated with ICD implantation and provide at the same time reassurance on symptoms. It should also consider patient preference and mindset, as device-related complications can be significant [31]. Due to limited data, recommendations on ILR re-implantation after previous unremarkable monitoring cannot be made; this may be reasonable in specific circumstances.

Limitations

This is a retrospective, observational, single-centre study. While this ensured consistent work up for the assessment of the individual risk, referral bias cannot be excluded. The number of patients included is relatively small. Head-up-tilt-test was not routinely used for the investigation of syncope and therefore the adjudication of unexplained/presumed arrhythmic syncope was made based on the clinical characteristics of the event. Further multicentre trials are needed in order to better understand the yield of ILR use for diagnosing dysrhythmias in low-to-moderate risk BrS.

Conclusion

Implantable cardiac monitor devices are useful to guide diagnosis in symptomatic BrS subjects deemed at insufficient risk of SCD to require immediate ICD implantation. Recurrent syncope, including unexplained episodes in subjects without spontaneous type 1 pattern and with negative EPS, is often secondary to conduction and sinus node dysfunction.

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References

1. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes: Document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Hear Rhythm. 2013 Dec;10(12):1932–63.
2. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Bloma N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the Europea. Vol. 36, European Heart Journal. Oxford University Press; 2015. p. 2793-2867l.
3. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, et al. Long-term prognosis of patients diagnosed with brugada syndrome: Results from the finger brugada syndrome registry. Circulation. 2010 Feb;121(5):635–43.
4. Sroubek J, Probst V, Mazzanti A, Delise P, Hevia JC, Ohkubo K, et al. Programmed ventricular stimulation for risk stratification in the Brugada syndrome: A pooled analysis. Circulation. 2016 Feb 16;133(7):622–30.
5. Vitali F, Brieda A, Balla C, Pavasini R, Tonet E, Serenelli M, et al. Standard ECG in Brugada Syndrome as a Marker of Prognosis: From Risk

Stratification to Pathophysiological Insights. J Am Heart Assoc. 2021;

6. Olde Nordkamp LRA, Vink AS, Wilde AAM, De Lange FJ, De Jong JSSG, Wieling W, et al. Syncope in Brugada syndrome: Prevalence, clinical significance, and clues from history taking to distinguish arrhythmic from nonarrhythmic causes. Hear Rhythm. 2015 Feb 1;12(2):367–75.

7. Sacher F, Arsac F, Wilton SB, Derval N, Denis A, De Guillebon M, et al. Syncope in Brugada syndrome patients: Prevalence, characteristics, and outcome. Hear Rhythm. 2012 Aug;9(8):1272–9.

8. Giustetto C, Cerrato N, Ruffino E, Gribaudo E, Scrocco C, Barbonaglia L, et al. Etiological diagnosis, prognostic significance and role of electrophysiological study in patients with Brugada ECG and syncope. Int J Cardiol. 2017 Aug 15;241:188–93.

9. Morita H, Kusano-Fukushima K, Nagase S, Fujimoto Y, Hisamatsu K, Fujio H, et al. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. J Am Coll Cardiol. 2002 Oct 16;40(8):1437–44.

10. Giustetto C, Cerrato N, Gribaudo E, Scrocco C, Castagno D, Richiardi E, et al. Atrial fibrillation in a large population with Brugada electrocardiographic pattern: Prevalence, management, and correlation with prognosis. Hear Rhythm. 2014 Feb;11(2):259–65.

11. Brignole M, Moya A, De Lange FJ, Deharo JC, Elliott PM, Fanciulli A, et al. 2018 ESC Guidelines for the diagnosis and management of syncope.

Vol. 39, European Heart Journal. Oxford University Press; 2018. p. 1883–948.

12. Brignole M, Vardas P, Hoffman E, Huikuri H, Moya A, Ricci R, et al. Indications for the use of diagnostic implantable and external ECG loop recorders. Europace. 2009;11(5):671–87.

13. Kubala M, Assou L, Traull S, Gugenheim AL, Hermida JS. Use of implantable loop recorders in patients with Brugada syndrome and suspected risk of ventricular arrhythmia. Europace. 2012 Jun;14(6):898–902.

14. Sakhi R, Assaf A, Theuns DAMJ, Verhagen JMA, Szili-Torok T, Roos-Hesselink JW, et al. Outcome of Insertable Cardiac Monitors in Symptomatic Patients with Brugada Syndrome at Low Risk of Sudden Cardiac Death. Cardiol. 2020 Jul 1;145(7):413–20.

15. Macfarlane PW, Devine B, Clark E. The University of Glasgow (Uni-G) ECG analysis program. Comput Cardiol. 2005;32:451–4.

16. MacFarlane PW, Antzelevitch C, Haissaguerre M, Huikuri H V., Potse M, Rosso R, et al. The early repolarization pattern: A consensus paper. J Am Coll Cardiol. 2015 Jul 28;66(4):470–7.

17. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, et al. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. In: Europace. Oxford University Press; 2017. p. 665–94.

18. Diederichsen SZ, Haugan KJ, Højberg S, Holst AG, Køber L, Pedersen KB, et al. Complications after implantation of a new-generation insertable cardiac monitor: Results from the LOOP study. Int J Cardiol. 2017 Aug 15;241:229–34.

19. Maines M, Zorzi A, Tomasi G, Angheben C, Catanzariti D, Piffer L, et al. Clinical impact, safety, and accuracy of the remotely monitored implantable loop recorder Medtronic Reveal LINQ TM. Europace. 2018 Jun 1;20(6):1050–7.

20. Mascia G, Della Bona R, Ameri P, Canepa M, Porto I, Brignole M. Brugada syndrome and syncope: A systematic review. J Cardiovasc Electrophysiol. 2020;31(12):3334–8.

21. Take Y, Morita H, Wu J, Nagase S, Morita S, Toh N, et al. Spontaneous electrocardiogram alterations predict ventricular fibrillation in Brugada syndrome. Hear Rhythm. 2011 Jul;8(7):1014–21.

22. Krahn AD, Klein GJ, Yee R, Takle-Newhouse T, Norris C. Use of an extended monitoring strategy in patients with problematic syncope. Circulation [Internet]. 1999;99(3):406–10. Available from: http://www.circulationaha.org

23. Cerrato N, Giustetto C, Gribaudo E, Richiardi E, Barbonaglia L, Scrocco C, et al. Prevalence of type 1 Brugada electrocardiographic pattern evaluated by twelve-lead twenty-four-hour holter monitoring. Am J Cardiol. 2015 Jan 1;115(1):52–6.

24. Gray B, Kirby A, Kabunga P, Freedman SB, Yeates L, Kanthan A, et al. Twelve-lead ambulatory electrocardiographic monitoring in Brugada syndrome: Potential diagnostic and prognostic implications. Hear Rhythm. 2017 Jun 1;14(6):866–74.

25. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol. 1992 Nov 15;20(6):1391–6.

26. Maury P, Rollin A, Sacher F, Gourraud JB, Raczka F, Pasquié JL, et al. Prevalence and prognostic role of various conduction disturbances in patients with the brugada syndrome. Am J Cardiol. 2013 Nov 1;112(9):1384–9.

27. Smits JPP, Eckardt L, Probst V, Bezzina CR, Schott JJ, Remme CA, et al. Genotype-phenotype relationship in Brugada syndrome: Electrocardiographic features differentiate SCN5A-related patients from non-SCN5A-related patients. J Am Coll Cardiol. 2002 Jul 17;40(2):350–6.

28. Meregalli PG, Tan HL, Probst V, Koopmann TT, Tanck MW, Bhuiyan ZA, et al. Type of SCN5A mutation determines clinical severity and degree of conduction slowing in loss-of-function sodium channelopathies. Hear Rhythm [Internet]. 2009;6(3):341–8. Available from: http://dx.doi.org/10.1016/j.hrthm.2008.11.009

29. Wilde AAM, Amin AS. Clinical Spectrum of SCN5A Mutations: Long

QT Syndrome, Brugada Syndrome, and Cardiomyopathy. Vol. 4, JACC: Clinical Electrophysiology. Elsevier Inc; 2018. p. 569–79.

30. Havakuk O, Viskin D, Viskin S, Adler A, Rozenbaum Z, Elbaz Zuzut M, et al. Clinical Presentation of Sustained Monomorphic Ventricular Tachycardia Without Cardiac Arrest. J Am Heart Assoc. 2020;9(22):e016673.

31. Olde Nordkamp LRA, Postema PG, Knops RE, Van Dijk N, Limpens J, Wilde AAM, et al. Implantable cardioverter-defibrillator harm in young patients with inherited arrhythmia syndromes: A systematic review and meta-analysis of inappropriate shocks and complications. Hear Rhythm. 2016 Feb 1;13(2):443–54.

Tables

Table 1.

Comparison of demographic, clinical, genetic and ECG data in the ILR, ICD, and no device cohorts

				P value		
	ICD = 58	**ILR = 50**	**NO DEVICE = 232**	**ILR vs ICD**	**ILR vs NO DEVICE**	**ICD vs NO DEVICE**
Age (y)	45 [IQR 18]	44 [IQR 23]	44 [IQR 25]	NS	NS	NS
Male	38 (66%)	29 (58%)	112 (48%)	NS	NS	NS
Shanghai score	4 [IQR 2] 42 (72%)	3.5 [IQR 1]	3 [IQR 2]	NS	NS	< 0.001 < 0.001

Probable/definite BrS		29 (58%)	104 (45%)	NS	NS	
P/LP SCN5A variant	18/43 (42%)	7/29 (24%)	21/115 (18%)	NS	NS	0.002
Positive EPS	9/24 (38%)	3/27 (11%)	1/45 (2%)	NS	NS	< 0.001
Symptoms • **Syncope/pre-syncope** • **Palpitations** • **Other**	40 (69%) 26 (65%) 8 (20%) 6 (15%)	47 (94%) 31 (66%) 15 (32%) 1 (2%)	84 (36%) 33 (39%) 36 (43%) 15 (18%)	0.001 NS NS NS	< 0.001 < 0.001 NS NS	< 0.001 < 0.001 NS NS
ECG parameters						
Spontaneous type 1	35 (60%)	18 (36%)	44 (19%)	0.01	0.008	< 0.001

RR	874±146	837±128	830±148	NS	NS	NS
PR	179±33	166±28	165±27	NS	NS	0.009
QRS	114±21	102±14	98±14	0.002	NS	< 0.001
QTc	424±25	424±21	424±24	NS	NS	NS
PR > 200 ms	14/57 (25%)	6/50 (12%)	25/226 (11%)	NS	NS	0.008
S wave in lead I ≥40 ms and/or ≥0.1 mV	35/58 (60%)	23/50 (46%)	118/232 (51%)	NS	NS	NS
Tpeak-Tend in V1-V4 ≥ 100 ms	32/58 (55%)	32/50 (64%)	89/232 (38%)	NS	0.001	NS
Fragmented QRS	9/58 (16%)	0/50 (0%)	8/232 (3%)	0.003	NS	0.002
Early repolarisation	6/58 (10%)	8/50	30/232	NS	NS	NS

		(16%)	(13%)			

1

2

Figures

Figure 1. Overview of ILR's cohort symptoms and actionable events.
BrS = Brugada Syndrome; ICD=Implantable Cardioverter Defibrillator; ILR = Implantable Loop Recorder; AF = Atrial Fibrillation; AT = Atrial Tachycardia; VT=Ventricular Tachycardia.

Figure 2. Paroxysmal complete third-degree AV block in one subject with previous syncope.

Figure 3. Late-onset run of polymorphic non-sustained VT in one subject with palpitations, family history of SCD and structurally normal heart.

Figure 4: Follow-up events according to device implantation and symptoms
NSVT = non-sustained ventricular tachycardia; SVT = supraventricular tachycardia; SCD = Sudden Cardiac Death.
† Appropriate shock = appropriate ICD intervention on VT/VF.

Figure 5: Device implantation trend in BrS patients with syncope or pre-syncope in our centre. Bars show the annual running total of subjects without devices (grey), with ICD (blue) and with ILR (orange).

Visual abstract

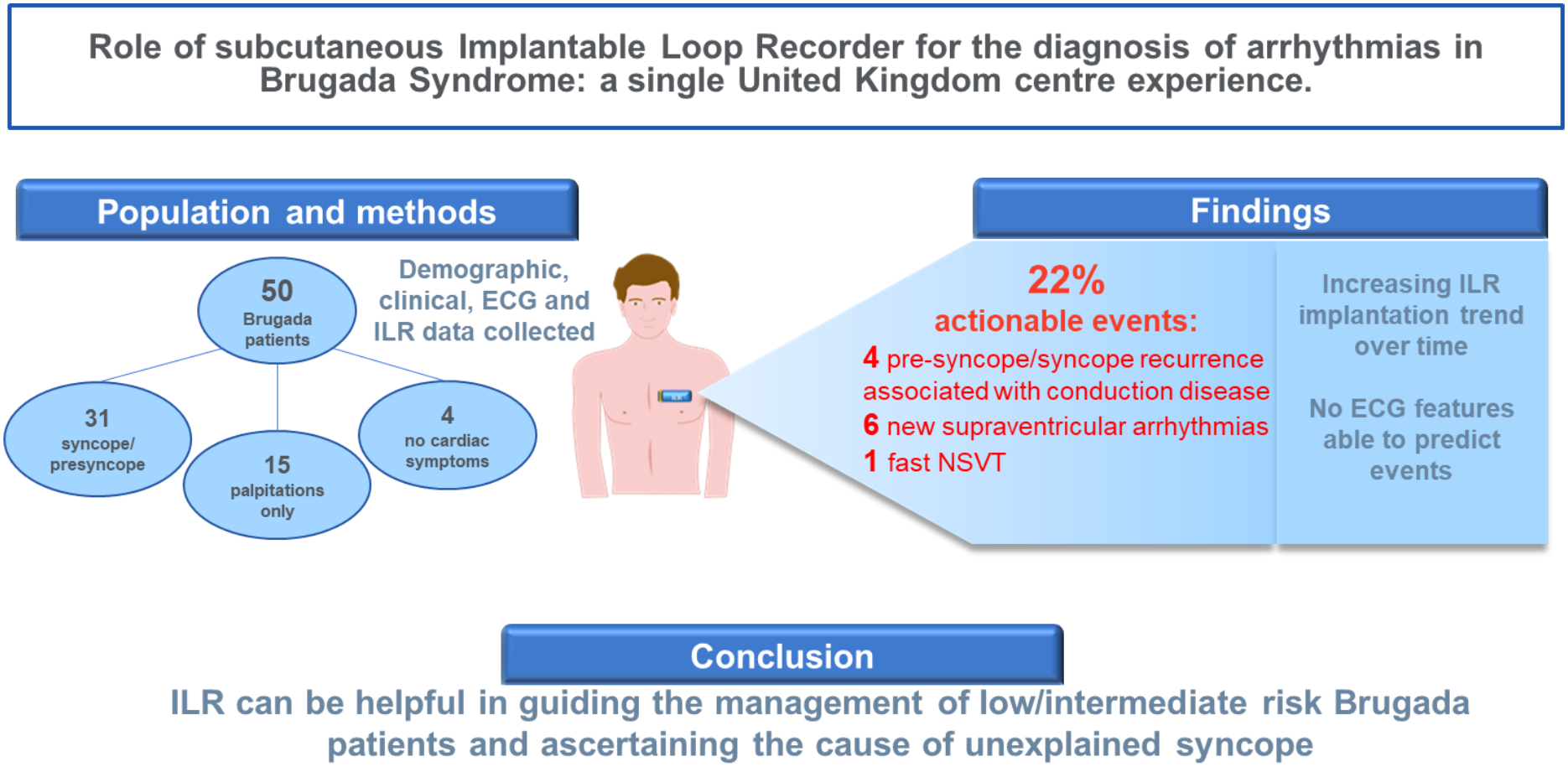


Figure 1


BrS patients implanted with ILR
n=50
Syncope
n=31
Palpitations
n=15
No cardiac symptoms
n=4
Recurrent syncope/presyncope
n=7
Activated device for palpitations
n=8
Actionable events on ILR
n=4
Actionable events on ILR
n=4
Actionable events on ILR
n=2
Actionable events on ILR
n=1
Pathologic sinus pause
n=2
AF, AT or AVNRT detected
n=4
AF, AT detected
n=1
AT detected
n=1
Paroxysmal complete AV block
n=1
Fast non-sustained polymorphic VT
n=1
Paroxysmal AF, diurnal pauses
n=1

Figure 2

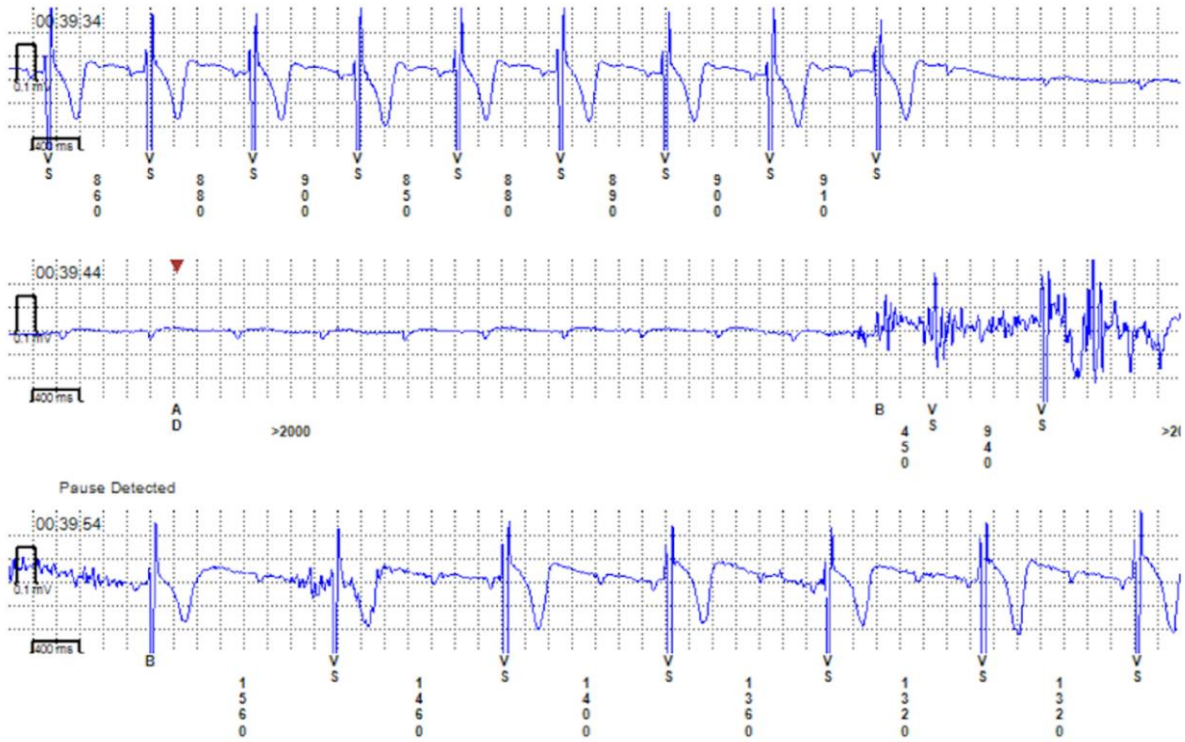

00:39:34
0.1 mV
400 ms
00:39:44
0.1 mV
400 ms
>2000
Pause Detected
00:39:54
0.1 mV
400 ms

Figure 3

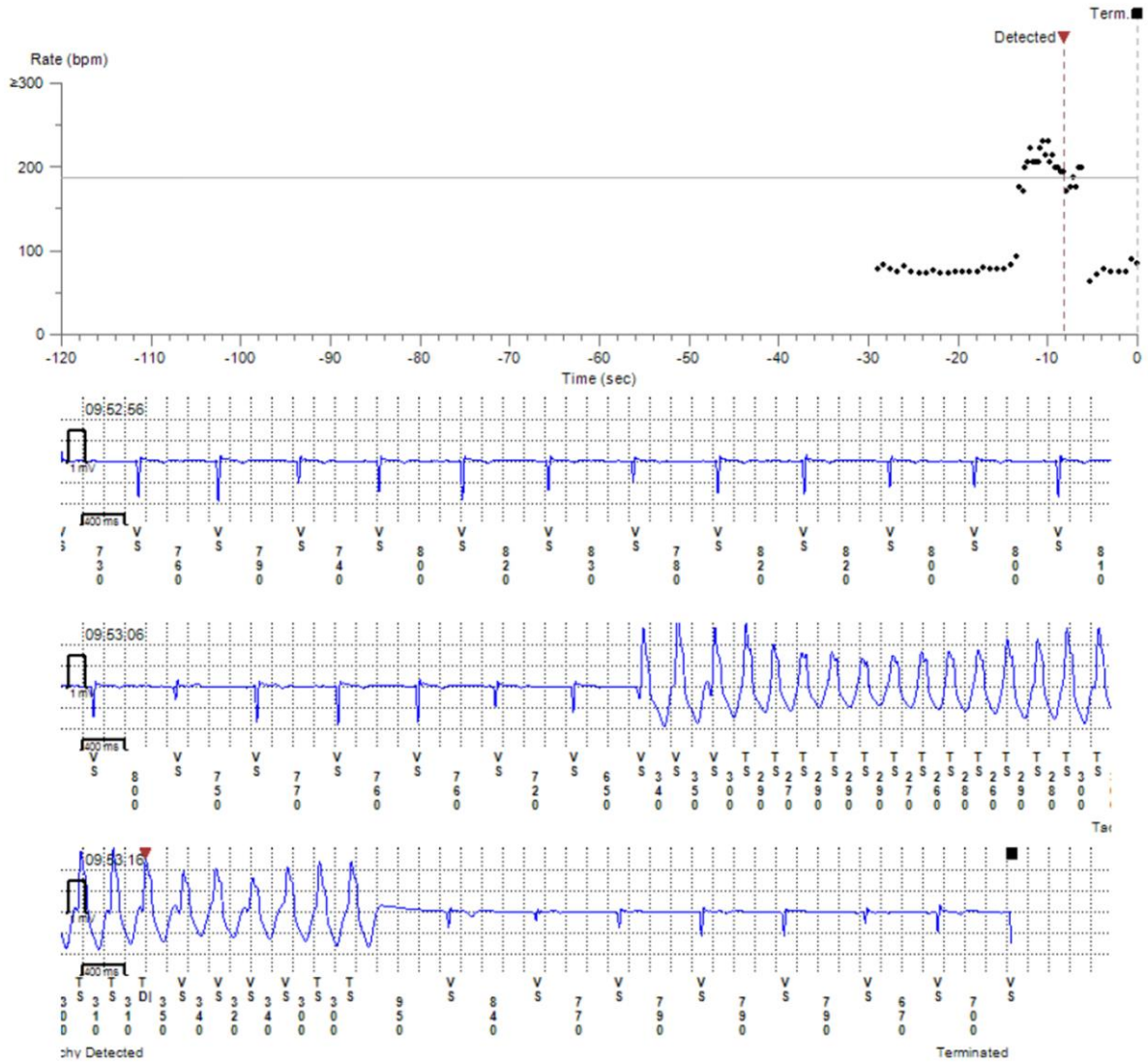

Term.
Detected
Rate (bpm)
≥300
200
100
0
-120
-110
-100
-90
-80
-70
-60
-50
-40
-30
-20
-10
0
Time (sec)
09:52:56
09:53:06
09:53:16
Terminated

Figure 4

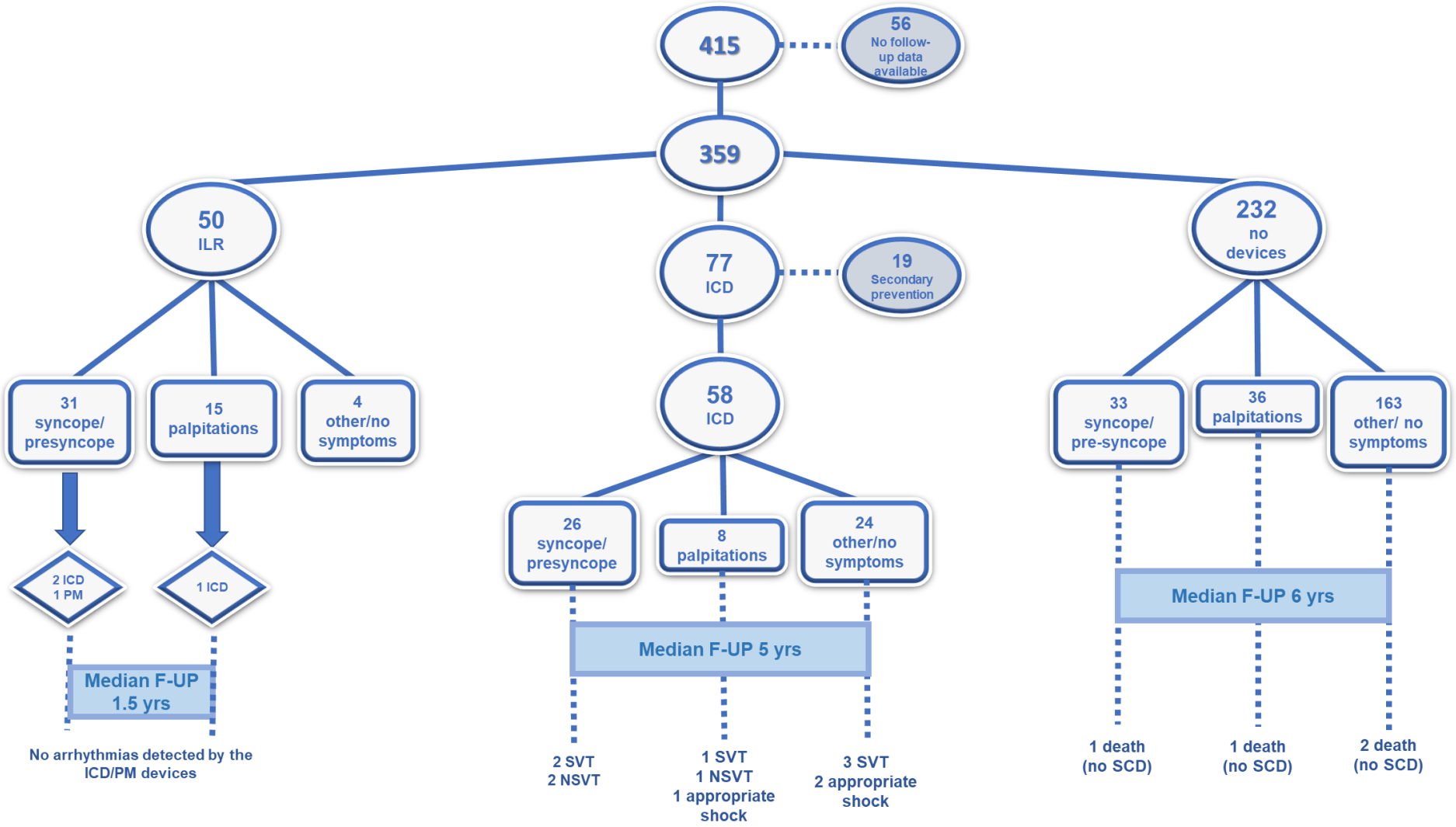
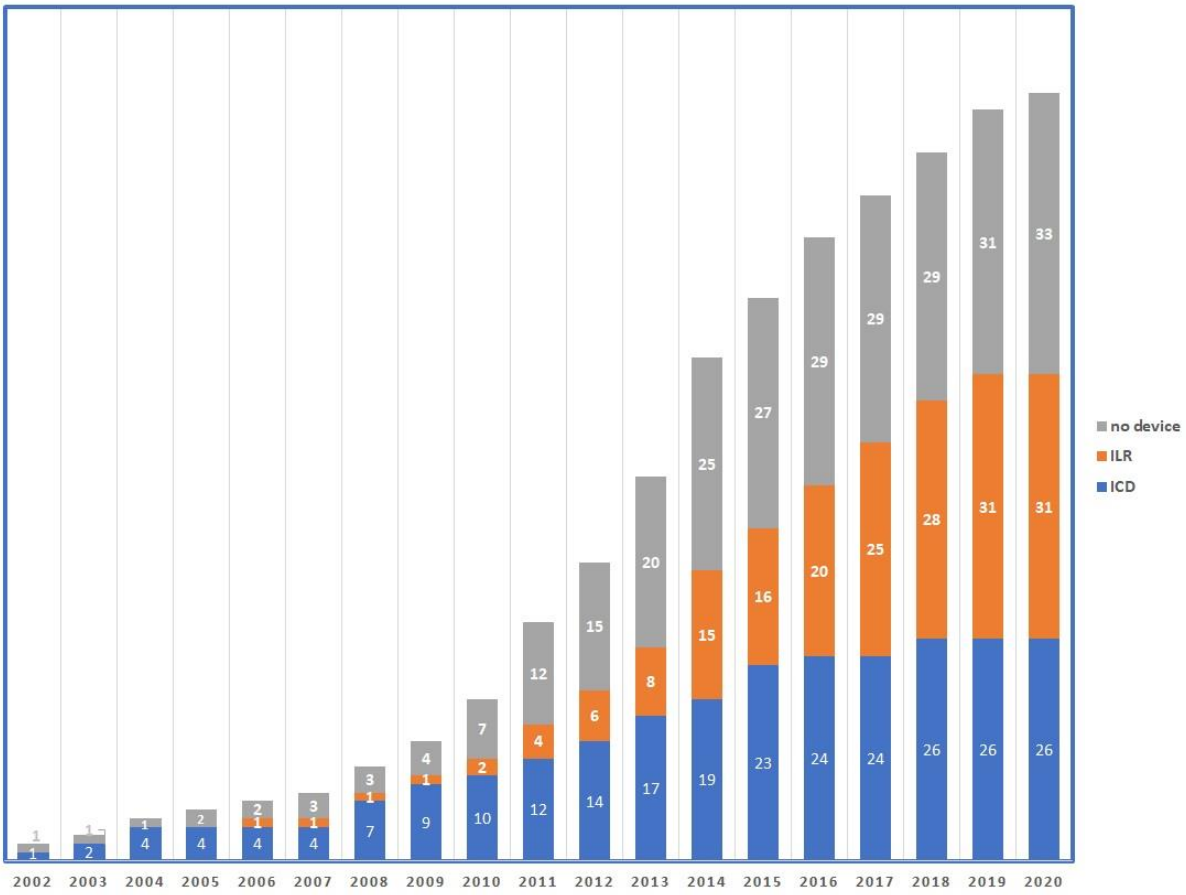

415
56
No follow-up data available
359
50
ILR
77
ICD
19
Secondary prevention
232
no devices
31
syncope/ presyncope
15
palpitations
4
other/no symptoms
58
ICD
33
syncope/ pre-syncope
36
palpitations
163
other/ no symptoms
2 ICD
1 PM
1 ICD
26
syncope/ presyncope
8
palpitations
24
other/no symptoms
Median F-UP 1.5 yrs
Median F-UP 5 yrs
Median F-UP 6 yrs
No arrhythmias detected by the ICD/PM devices
2 SVT
2 NSVT
1 SVT
1 NSVT
1 appropriate shock
3 SVT
2 appropriate shock
1 death (no SCD)
1 death (no SCD)
2 death (no SCD)

Figure 5


2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020
1 2 4 4 4 4 7 9 10 12 14 17 19 23 24 24 26 26 26
1 1 1 2 1 1 1 1 2 4 6 8 15 16 20 25 28 31 31
1 1 2 2 3 3 3 4 7 12 15 20 25 27 29 29 29 31 33
no device
ILR
ICD