**“Primum non nocere…” Explanting implantable cardioverter-defibrillators in patients with inherited arrhythmia syndromes - Case series**

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**Abstract**

**Introduction:** Patients with Inherited arrhythmia syndromes (IAS) are at risk for life-threatening arrhythmias that may present as a sudden cardiac arrest (SCA) or a cardiac syncope. The benefit of Implantable cardioverter-defibrillators (ICD) in patients with IAS should be weighted against the risk for adverse events.

This case-series describes patients diagnosed with an IAS, who were eventually reclassified in a low risk category and subsequently got their ICD explanted.

**Methods:** We selected patients who, 1) were diagnosed with an IAS, 2) presented with either a documented arrhythmic event or syncope presumed to be arrhythmic syncope, 3) followed by an ICD implant, and 4) in whom we decided to explant the pulse generator.

**Results:** Overall, eight patients fulfilled the inclusion criteria. Mean age at ICD implantation was 35±11.6 years. Mean length of ICD in situ was 4.9±3.6 years. None of the patients experienced a cardiac event. 2 patients presented with a presumed cardiac syncope, this diagnosis was rejected after guideline guided syncope evaluation including Tilt table testing. Alternative (pharmacological) therapy was started in six patients.

**Conclusion:** These cases illustrate the importance of re-evaluating ICD therapy in patients with IAS. This should be integrated in standard clinical care, even in patients with IAS who survived a SCA and long term critical follow up is available. In patients with IAS presenting with an presumed cardiac syncope, extensive guideline guided syncope evaluation, can be of additional value when syncope event remains unknown

**Key Words**Inherited Arrhythmia Syndromes, Arrhythmia, Syncope, Sudden cardiac arrest, Implantable cardioverter-defibrillators, Long QT syndrome, Brugada, catecholaminergic polymorphic ventricular tachycardia, Tilt Table Test.

**Introduction**

Patients diagnosed with inherited arrhythmia syndromes (IAS) are at risk of a sentinel event of life threatening ventricular arrhythmias.

These frequently manifests as a sudden cardiac arrest (SCA) or cardiac syncope. Although the mainstay and first line of therapy is beta blockade in the case of long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT), a natural reflex, often supported by guidelines, is insertion of an implantable cardioverter-defibrillator (ICD) to prevent sudden cardiac death (SCD). This reflexive tendency of clinicians may lead to overtreatment of these specific patient (1) and is in part the result of a knowledge gap, overestimation of SCD risk, and underestimation of ICD complications (2).

Indeed, for patients with an IAS who survive a SCA, ICD implantation is a class 1 recommendation (3). However, when the event concerns a syncope event distinguishing a cardiogenic seizure from others is of utmost importance, as it has great impact on the optimal clinical management (4,5).

Ongoing insights and improved diagnostics, in the field of IAS and the etiology of syncope has led to more conservative treatment strategies already. ICD therapy has not been associated with an improved impact on life expectancy in CPVT patients who presented with a sentinel SCA (6) and resuscitated LQTS type 1 patients are at low risk of recurrent events on the long term on betablocker therapy only (7). In these IAS optimal pharmacological therapy, sometimes combined with left cardiac sympathectomy, is sufficiently protective (7-9). The lack of data supporting the benefit of ICDs in these IAS (8), combined with the effectiveness of alternative treatment strategies, should encourage the treating physician to re-evaluate the ICD indication in these specific patients.

In this study, we describe eight patients, diagnosed with an IAS, who were eventually reclassified in a low risk category and subsequently got their ICD explanted after re-evaluating the etiology of the event or better treatment options emerged.

**Materials and methods**

We systematically evaluated all ICD extraction procedures in our tertiary centre, from January 2016 to June 2022, and selected patients (n=8) who, 1) were diagnosed with an IAS, 2) presented with either a documented arrhythmic event or syncope presumed to be arrhythmic syncope, 3) followed by an ICD implant, and 4) in whom we decided to explant the pulse generator with or without lead extraction. All patients provided written informed consent and agreed to participate in the research into inherited cardiac disease of the Amsterdam UMC. The study was approved by the local ethics committee (register number 2014\_003#C2021516)

Detailed clinical information was collected from electronic patient records. Each of these patient records was further reviewed to obtain the reasons behind their ICD explant, the details surrounding the implantation, and the time interval from implant to explant. Furthermore, details on post-ICD implantation outcomes, procedure of ICD removal, and details of treatment and outcome after explantation were collected. All patients

**Results**

Eight patients fulfilled the inclusion criteria. Table 1 shows an overview of the eight patients and Figure 1 illustrates the clinical course per case, since time of event. Four patients were diagnosed with LQTS (3 with LQT1 and 1 with LQT2), 3 with CPVT, and one with Brugada syndrome (BrS). Mean age at ICD implantation was 35±11.6 years. Mean follow-up was 9.6±5.8 years. Mean length of ICD in situ was 4.9±3.6 years. None of the patients experienced appropriate ICD therapy. 4/8 patients suffered from ICD-related complications. In 3 patients the syncope was re-evaluated and diagnosed as a vasovagal syncope after proper guideline guided syncope evaluation, in 2/3 of the syncope cases a tilt table test (TTT) confirmed this diagnosis with 100% certainty. Alternative (medical) therapy was started in 6/8 patients. During follow-up, this therapy was optimized. There were no extraction related complications. Cases 1-5 were correctly diagnosed before the ICD implant, whereas cases 6, 7 and 8 were diagnosed correctly after ICD implantation.

**Discussion**

First, do no harm. This series describes eight patients who have in common that with a diagnosis of an IAS an ICD was, probably prematurely, implanted. Overimplanting ICDs is not uncommon (1,8). This report emphasizes the role of critical follow up and appropriate re-evaluation of the syncope event (cases 2 and 5) and new insights in therapeutic choices in specific syndromes (cases 1, 3, 4, 6, 7 and 8).

The investigation of patients with IAS is best undertaken at a tertiary center with multidisciplinary care. The first line of therapy in beta blocker-naïve LQT1 and CPVT patients who survived a SCA, is pharmacological, beta blockade in LQTS and beta blocker and flecainide in CPVT. LSCD may be added in LQTS and CPVT. Contrary to the most recent guidelines (3), device therapy may be considered but should not always be the first choice. Preferably medical treatment strategy should be evaluated with extensive diagnostic tests like exercise stress testing and holter monitoring. Obviously patients must be educated in adherence to therapy, lifestyle changes and avoidance of certain drugs, as this is part of optimal medical care (6).

A potentially unnecessary ICD implantation can occur if the diagnosis cannot be determined immediately, to avoid over-implantation a wearable cardioverter defibrillator might be considered. This allows the treating physician a window for diagnosis, proper risk stratification and time to evaluate the effect of therapeutic interventions in cases with syncope/cardiac arrest of unknown origin (10).

This study also underlines that - as with any other patient with syncope - in patients with IAS, the work-up of an unexplained syncope should be guideline guided syncope evaluation in preferably a tertiary setting, emphasizing on thorough history taking. This is of paramount importance to establish a certain or highly likely diagnosis for the syncope event (11). Moreover, in these patients the interrogation of the ICD provides the best long term critical follow up to the physician, which is the gold standard in syncope. TTT in these patients can be of additional value but is not always essential. Although TTT remains a valuable clinical asset in patients with syncope of unknown origin, or for bio-feedback (12). Clinical physiological reasoning during history taking with knowledge of the pathophysiology of syncope helps the clinicians to reconstruct and risk stratify the syncope event. This in combination with the extensive and detailed available follow up, prevents blaming the genetic disorder to cause the syncope event and subsequently implanting an ICD.

Half of the patients included in this report, suffered from serious ICD-related complications. The harm of ICD therapy, has been well described before (2,13). The lifetime risk for complications, including systemic infection and device malfunction is even higher for young patients with IAS, as they have a very long life expectancy. The subcutaneous ICD (S-ICD) can avoid important complications associated with transvenous leads in IAS patients who do not need anti-bradycardia pacing (14), but not all these patients are qualified due to a higher risk of S-ICD screening failure (15). Hence, careful selection of device implantation and type of device, may have significant clinical benefits and improves the quality of life.

**Conclusion**

Always think twice before implanting an ICD in patients diagnosed with syncope and IAS. When an ICD is implanted, re-evaluation of ICD therapy in this patient group, should be part of standard clinical care, even in patients with IAS who survived a SCA and long term critical follow up is available.

TTT on top of an extensive guideline guided syncope evaluation, can be of additional value when syncope event remains unknown.

Optimal medical treatment in patients with LQTS and CPVT is preferred over device therapy. Device therapy should not be considered as first therapy, but only in those cases where there is really no other choice.

**References**

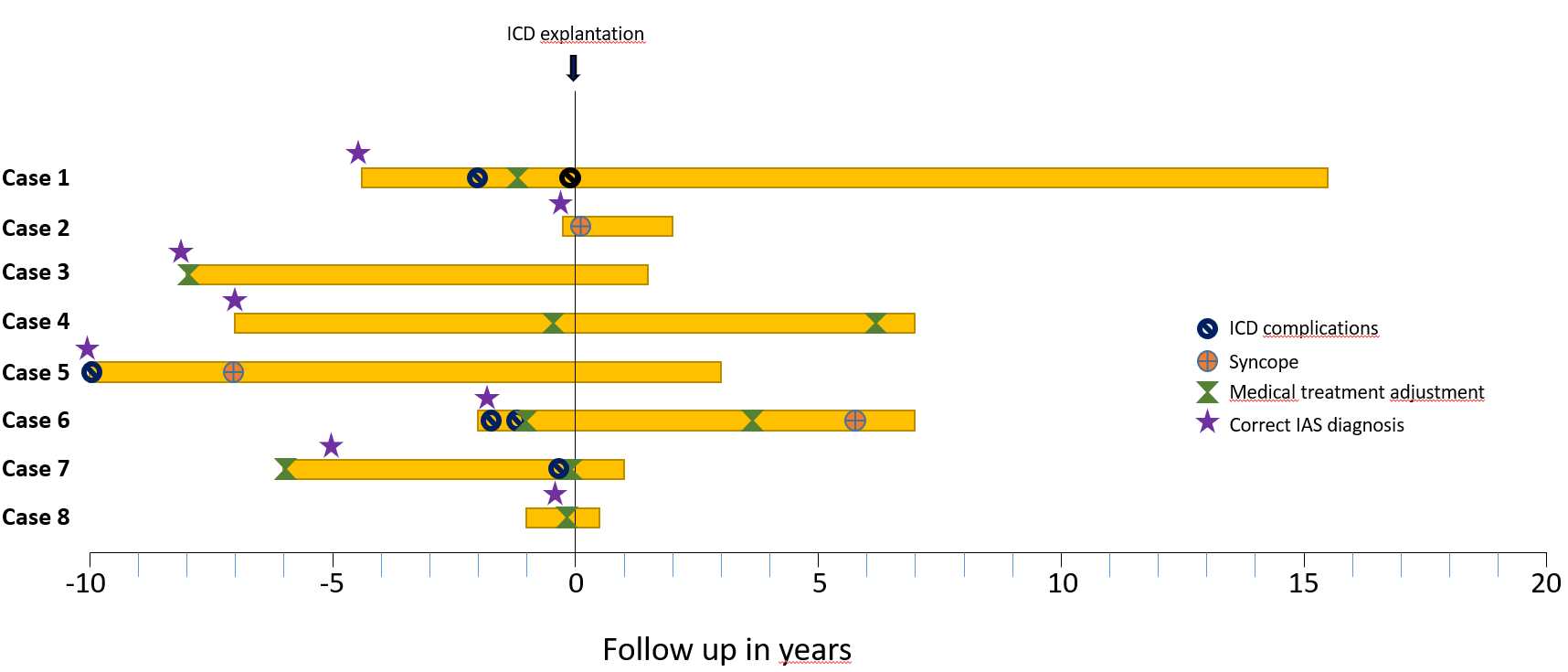
1. Gaba P, Bos JM, Cannon BC, Cha YM, Friedman PA, Asirvatham SJ, Ackerman MJ. Implantable cardioverter-defibrillator explantation for overdiagnosed or overtreated congenital long QT syndrome. Heart Rhythm. 2016 Apr;13(4):879-85.
2. Olde Nordkamp LR, Postema PG, Knops RE, van Dijk N, Limpens J, Wilde AA, de Groot JR. 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 Feb;13(2):443-54.
3. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, Charron P, Corrado D, Dagres N, de Chillou C, Eckardt L, Friede T, Haugaa KH, Hocini M, Lambiase PD, Marijon E, Merino JL, Peichl P, Priori SG, Reichlin T, Schulz-Menger J, Sticherling C, Tzeis S, Verstrael A, Volterrani M; ESC Scientific Document Group. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022 Aug 26:ehac262.
4. Olde Nordkamp LR, Ruwald MH, Goldenberg I, Wieling W, McNitt S, Polonsky B, Wilde AA, van Dijk N, Moss AJ. Syncope in genotype-negative long QT syndrome family members. Am J Cardiol. 2014 Oct 15;114(8):1223-8.
5. Olde Nordkamp LR, Vink AS, Wilde AA, de Lange FJ, de Jong JS, Wieling W, van Dijk N, Tan HL. Syncope in Brugada syndrome: prevalence, clinical significance, and clues from history taking to distinguish arrhythmic from nonarrhythmic causes. Heart Rhythm. 2015 Feb;12(2):367-75.
6. Vincent GM, Schwartz PJ, Denjoy I, Swan H, Bithell C, Spazzolini C, Crotti L, Piippo K, Lupoglazoff JM, Villain E, Priori SG, Napolitano C, Zhang L. High efficacy of beta-blockers in long-QT syndrome type 1: contribution of noncompliance and QT-prolonging drugs to the occurrence of beta-blocker treatment "failures". Circulation. 2009 Jan 20;119(2):215-21.
7. van der Werf C, Lieve KV, Bos JM, Lane CM, Denjoy I, Roses-Noguer F, Aiba T, Wada Y, Ingles J, Leren IS, Rudic B, Schwartz PJ, Maltret A, Sacher F, Skinner JR, Krahn AD, Roston TM, Tfelt-Hansen J, Swan H, Robyns T, Ohno S, Roberts JD, van den Berg MP, Kammeraad JA, Probst V, Kannankeril PJ, Blom NA, Behr ER, Borggrefe M, Haugaa KH, Semsarian C, Horie M, Shimizu W, Till JA, Leenhardt A, Ackerman MJ, Wilde AA. Implantable cardioverter-defibrillators in previously undiagnosed patients with catecholaminergic polymorphic ventricular tachycardia resuscitated from sudden cardiac arrest. Eur Heart J. 2019 Sep 14;40(35):2953-2961.
8. Roston TM, Krahn AD, Ong K, Sanatani S. The merits of the ICD for inherited heart rhythm disorders: A critical re-appraisal. Trends Cardiovasc Med. 2020 Oct;30(7):415-421.
9. Wilde AAM, Amin AS, Postema PG. Diagnosis, management and therapeutic strategies for congenital long QT syndrome. Heart. 2022 Mar;108(5):332-338.
10. Reek S, Burri H, Roberts PR, Perings C, Epstein AE, Klein HU; EHRA Scientific Documents Committee (as external reviewers):, Lip G, Gorenek B, Sticherling C, Fauchier L, Goette A, Jung W, Vos MA, Brignole M, Elsner C, Dan GA, Marin F, Boriani G, Lane D, Blomström-Lundqvist C, Savelieva I. The wearable cardioverter-defibrillator: current technology and evolving indications. Europace. 2017 Mar 1;19(3):335-345.
11. de Jong JSY, Blok MRS, Thijs RD, Harms MPM, Hemels MEW, de Groot JR, van Dijk N, de Lange FJ. Diagnostic yield and accuracy in a tertiary referral syncope unit validating the ESC guideline on syncope: a prospective cohort study. Europace. 2021 May 21;23(5):797-805.
12. Sutton R, Fedorowski A, Olshansky B, Gert van Dijk J, Abe H, Brignole M, de Lange F, Kenny RA, Lim PB, Moya A, Rosen SD, Russo V, Stewart JM, Thijs RD, Benditt DG. Tilt testing remains a valuable asset. Eur Heart J. 2021 May 1;42(17):1654-1660.
13. El-Battrawy I, Roterberg G, Liebe V, Ansari U, Lang S, Zhou X, Borggrefe M, Akin I. Implantable cardioverter-defibrillator in Brugada syndrome: Long-term follow-up. Clin Cardiol. 2019 Oct;42(10):958-965.
14. Kuschyk J, Müller-Leisse J, Duncker D, Tülümen E, Fastenrath F, Fastner C, Kruska M, Akin I, Liebe V, Borggrefe M, Veltmann C, Rudic B. Comparison of transvenous vs subcutaneous defibrillator therapy in patients with cardiac arrhythmia syndromes and genetic cardiomyopathies. Int J Cardiol. 2021 Jan 15;323:100-105.
15. Conte G, Kawabata M, de Asmundis C, Taravelli E, Petracca F, Ruggiero D, Caputo ML, Regoli F, Chierchia GB, Chiodini A, Del Bufalo A, Moccetti T, Goya M, Hirao K, Vicentini A, De Ferrari GM, Brugada P, Auricchio A. High rate of subcutaneous implantable cardioverter-defibrillator sensing screening failure in patients with Brugada syndrome: a comparison with other inherited primary arrhythmia syndromes. Europace. 2018 Jul 1;20(7):1188-1193.

Table 1: Demographic and clinical characteristics of the 8 cases\*

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Case** | **Sex** | **Diagnosis**  **IAS** | **Genetic variant** | **ICD indication** | **Details event** | **Age at implantation** | **Proband status** | **Family history SCA** | **Appropriate shock** | **ICD complications** | **Reason for explantation** | **Medical treatment** |
| 1 | F | LQTS I | KCNQ1  c.820A>G  p.Ile274Val | OHCA | Ventricular fibrillation due to low potassium and a prolonged QT interval | 39 | Index | No | No | Technical problems leading to generator replacement  Lead fracture | Recognized event from index event that did not require ICD therapy | Metoprolol |
| 2 | F | LQTS I | KCNQ1  c.1795-2A>G | Presumed arrhythmic Syncope | syncope in shopping mall during conversation. She felt suddenly very warm before syncope. | 52 | FM | No | No | no | Positive TT with recognition for syncope event | Declined beta blockade |
| 3 | F | LQTS I | KCNQ1  c.1031C>T  p.Ala344Val | SCA (IHCA) | TdP in the setting of Drug induced QT prolongation on top of unrecognized Congenital LQTS. Arrhythmic storm upon isoprenaline administration. | 34 | Index | SCA mother 56Y | No | no | Circumstances during SCA.  Diagnosis does not require ICD therapy | Propranolol |
| 4 | F | LQTS 2 | KCNH2  c.2906delG  p.Gly969fs | TdP | TLOC two months after labor, during admission TdP | 30 | index | Father VF and ICD, no medication | No | no | Event when untreated, subsequent optimal medical treatment. | Propranolol  Mexiletine |
| 5 | M | BrS |  | Presumed arrhythmic syncope | syncope at work. Felt lightheaded during conversation before syncope.  Ajmaline provocation showed a type 1 Brugada pattern | 47 | Index | No | No | Pocket hemorrhage | Positive TT with recognition for the syncope event | - |
| 6 | M | CPVT | RYR2  c.848+1G>A | OHCA | Ventricular fibrillation after light exercise initially diagnosed as LQTS | 22 | Index | SCD 19y (uncle) | No | Innapropriate shocks  Lead fracture | Event when untreated, optimal medical treatment  (ICD complications) | Metoprolol  Flecainide  Renal sympathetic denervation |
| 7 | F | CPVT | RYR2  c.1081T>C p.Cys361Arg | OHCA | Ventricular fibrillation during dance exhibition. Initially diagnosed as LQTS | 15 | Index (de novo) | No | No | Early end of life due to battery depletion e.c.i. | Not recommended in CPVT due to risk of VT storm | Propranolol |
| 8 | F | CPVT | CASQ2  c.164A>G p.Tyr55Cys c.115G>A p.Glu39Lys | OHCA | Ventricular fibrillation during a birthday party | 41 | Index | SCD 10y  (Brother) | No | No | Event when untreated, optimal medical treatment | Propranolol  Flecainide |

\* IAS denotes inherited arrhythmia syndrome, ICD implantable cardioverter-defibrillator, SCA sudden cardiac arrest, LQTS Long QT syndrome, CPVT catecholaminergic polymorphic ventricular, KCNQ1 potassium voltage-gated channel subfamily Q member 1, KCNH2 potassium voltage-gated channel subfamily H member 2, RYR2 ryanodine receptor 2, CASQ2 Calsequestrin 2, TdP Torsade de Pointes, OHCA out-of-hospital cardiac arrest, IHCA in-hospital cardiac arrest, VF Ventricular fibrillation, c. DNA sequence change, p. amino acid change, FM Family member, TT Tilt table.

Figure 1: Follow up in years, per case.\*



\* The yellow bar, represents the follow up per patient, starting with the initial event of SCA or syncope and therefore the ICD implantation.