Clinical Research in Cardiology (2019) 108:1140–1146
https://doi.org/10.1007/s00392-019-01449-3

ORIGINAL PAPER

# Long-term follow-up of implantable cardioverter-defibrillators in Short QT syndrome

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Received: 4 November 2018 / Accepted: 5 March 2019 / Published online: 16 March 2019


## Abstract

**Background** Short QT syndrome (SQTS) is associated with sudden cardiac death and implantable cardioverter-defibrillator (ICD) implantation is recommended in this rare disease. However, only a few SQTS families have been reported in literature with limited follow-up data.

**Objectives** In the recent study, we describe the outcome data of 57 SQTS patients receiving ICD implantation. This includes seven SQTS families consecutively admitted to our hospital between 2002 and 2017 as well as patients reported in published literature.

**Methods** Seven SQTS patients admitted to our hospital were followed up. Additionally, 7 studies out of a total of 626 researched articles were identified through systematic database search (PubMed, Web of Science, Cochrane Library, and Cinahl) and their data analyzed according to our model.

**Results** Complications during a median follow-up time of 67.4 months (IQR 6–162 months) were documented in 31 (54%) patients. Inappropriate shocks were seen in 33% due to T wave oversensing (8.7%), supraventricular tachycardia (19%), lead failure and fracture (21%). Further complications were infection (10%), battery depletion (7%) and psychological distress (3.5%). Appropriate shocks were documented in 19%. Three patients (5%) were treated with s-ICD due to recurrent complications of transvenous ICD.

**Conclusion** ICD therapy is an effective therapy in SQTS patients. However, it is also associated with significant risk of device-related complications.

**Keywords** Short QT syndrome · Sudden cardiac death · ICD-related complications

## Introduction

Short QT syndrome (SQTS) is a rare channelopathy associated with a bevy of symptoms like syncope and palpitations, whilst predisposing the patient to a higher risk for developing atrial fibrillation, atrial flutter, and life-threatening arrhythmias leading to sudden cardiac death [1–5]. The first SQTS cases were reported in 2000, and although significant progress has been achieved in the last decade, the diagnostic and treatment approach may still challenge physicians. Survivors of SCD as well as their relatives continue to be at high risk for developing recurrent ventricular tachyarrhythmia events. Implantable cardioverter-defibrillator (ICD) therapy, remains to date, the suggested treatment strategy for survivors of SCD [6–8]. Recently however, the analysis of data from other channelopathies such as Brugada

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00392-019-01449-3) contains supplementary material, which is available to authorized users.

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syndrome (BrS) has shown that ICDs are frequently associated with complications and inappropriate shocks, both of which remain high regardless of careful device implantation and programming [9].

We now report the experience of ICD implantation and their outcome in 57 SQTS patients, which include 7 consecutive SQTS families, who presented themselves in our hospital as well as other SQTS patients drawn from a systematic literature review of SQTS studies and case reports.

## Methods

SQTS was defined according the ESC criteria of 2015 [10]. These criteria essentially highlight the probability of diagnosing SQTS in a patient. Additionally, as a part of family screening, all first- and second-degree relatives were evaluated.

Syncope was defined as the transient loss of consciousness in the absence of other causes. An arrhythmic event was a documented ventricular fibrillation/ventricular tachycardia (VF/VT) requiring resuscitation and/or defibrillation.

Of the ten families admitted to our hospital with suspected SQTS, only seven families fulfilled the SQTS criteria. The cascade of family screening helped clinch the diagnosis of SQTS in nine affected relatives. The QT interval was measured using the tangent method in the precordial lead presenting the highest T wave amplitude in V2 or V3.

For purposes of genetic screening, DNA sequencing using next-generation sequencing (NGS) of affected genes (KCNH2, KCNQ1, KCNJ2, CACNA1C, CACNB2 and CACNA2D1) of SQTS 1–6 was analyzed. The study was consistent with the local Ethics Committee of the University hospital Mannheim. A diagnosis of SQTS was established only after a thorough review by two experienced and independent cardiologists.

### Systematic literature review

A literature search (PubMed, Web of Science, Cochrane Library, and Cinahl) was performed with limits including publication dates (up to 2018), English language and human subjects. The studies selected for our analysis included the mixed criterion of SQTS and ICD implantation (Fig. 1).

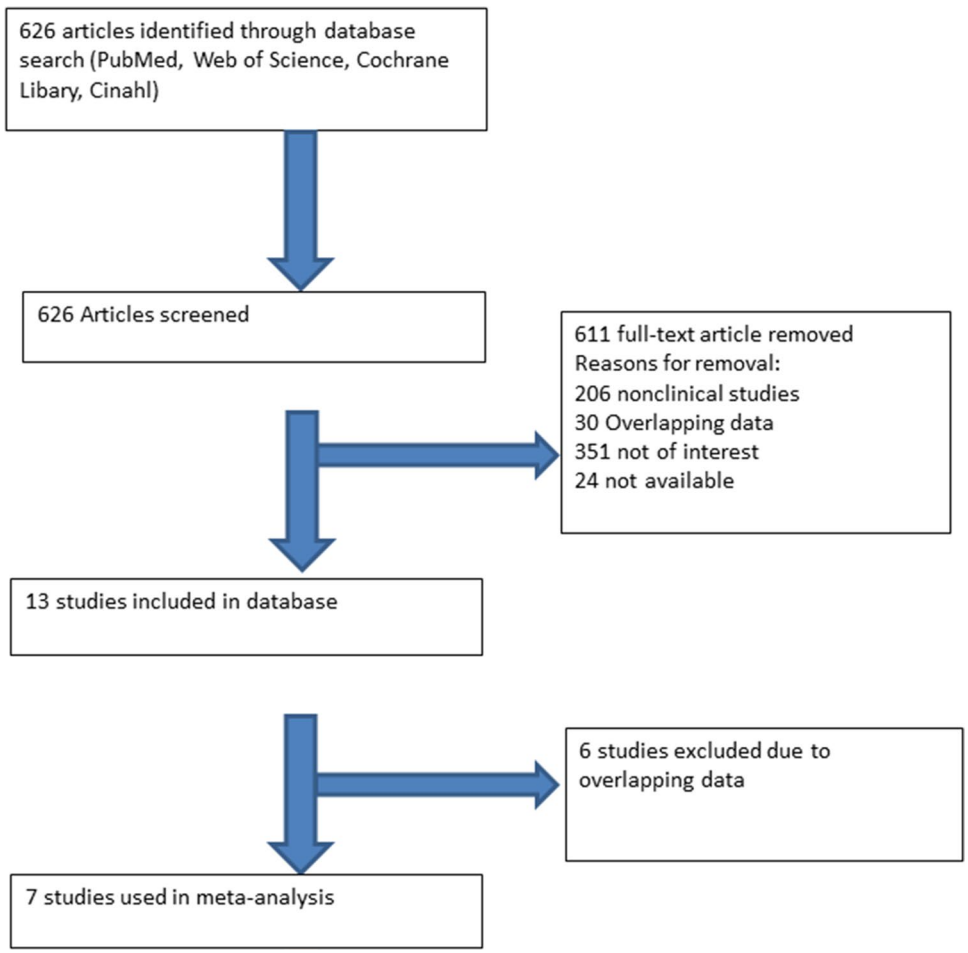


**Fig. 1** Flowchart presenting a systematic literature review using PubMed, Web of Science, Cochrane Library and Cinahl. Seven studies reporting the outcome of ICD in SQTS patients were included

Case reports or studies not reporting on outcome of ICD after implantation were excluded.

### Statistics

Data are presented as mean ± SD for continuous variables with a normal distribution, median (interquartile range) for continuous variables with a non-normal distribution, and as frequency (%) for categorical variables. The Kolmogorov–Smirnov test was used to assess normal distribution. Student's *t* test and the Mann–Whitney *U* test were used to compare continuous variables with normal and non-normal distributions, respectively. The Chi-squared test or Fisher's exact test was used to compare categorical variables.

## Results

### Demographics of seven SQTS families

Baseline characteristics of SQTS patients are illustrated in Table 1. Seven independent families were prospectively followed. 17 SQTS patients were identified. The QTc interval was 324.9 ± 40.8 ms. The majority of patients and their relatives presented with symptoms such as syncope (29%), palpitation (47%), atrial fibrillation (41%) and atrial flutter (11%). Aborted SCD occurred in two (11.7%) patients and a total of five patients (29.41%) underwent an ICD implantation for primary and/or secondary prevention. Three of these patients were based on the high risk of SCD due to an abbreviated QTc interval < 300 ms as well as the presence of recurrent SCD in the family. A SQTS-related gene was detected in 13 patients as follows: KCNH2 $n=4$, CACNA1C $n=3$ and CACNB2 $n=6$.

### Systematic literature review

The use of a systematic literature review helped isolate 7 studies/cases with a pool of 52 SQTS patients, and these were identified to be eligible for follow-up of outcome after ICD implantation. Thus, adding up the five patients registered in our hospital database, our study included a total of 57 SQTS patients [1, 2, 11–15] (Table 2, Table S1). The shortest follow-up time was 6 months. With the exception of Bun et al., all other studies reported ICD complication in 30–80% of implanted patients after a follow-up at 60.4 months. Out of 57 ICD patients, 11 (19%) patients suffered life-threatening arrhythmias which were treated by the ICD. A total of three patients (5%) from the total cohort were treated with a subcutaneous ICD (s-ICD) after suffering more than one complication, which also included lead failure. No s-ICD-related complications were documented during median follow-up of 1 year (IQR 1–5 years).

### ICD-related complications of 57 SQTS patients

A total of 57 SQTS patients were treated with an ICD over a median follow-up time of 67.4 months (IQR 6–162 months). Complications were documented in 31 (54%) patients, Fig. 2. Inappropriate shocks (33%) were particularly due to T wave oversensing (8.7%), supraventricular tachycardia (19%), lead failure and fracture (21%). Further complications were Infection (10%), battery depletion (7%) and psychological distress (3.5%).Of note, patient with s-ICD ($n=3$) did not suffer any complications over 1 year of follow-up. Whereas 19 patients implanted with a transvenous ICD suffered from inappropriate ICD shocks, none of the 3 patients with s-ICD suffered from any inappropriate shocks.

## Discussion

We have described the clinical profile as well as short- and long-term outcomes of ICD implantation in our study population and found the following: (1) the risk of SCD in SQTS patients is high and ICD implantation is suggested; (2) up to 17.5% of appropriate ICD therapies were documented; (3) ICD-related complications are common with an incidence rate of almost 54%; (4) s-ICD implantation is a safe treatment approach in SQTS patients with recurrent transvenous ICD complications.

A total of six SQTS subtypes have been described till now. A gain in potassium channels affecting the KCNH2, KCNQ1 and KCNJ2 genes was found in SQTS 1–3 [3], while a loss of calcium channels affecting subunits of calcium-encoding genes including CACNA1C, CACNB2 and CACNA2D1 occurred in SQTS 4, SQTS 5 and SQTS 6. Nevertheless, a genetic analysis did not identify a cause in almost 75% of the cases [16, 17]. An overlap syndrome, wherein SQTS is accompanied with BrS, has also been reported [2, 18]. The causes of acquired SQTS include electrolyte imbalances as in hyperkalemia or hypercalcemia, myocardial ischemia, acidosis or carnitine deficiency. Hyperthermia could also cause a shortened QT interval, as could drugs such as digitalis, acetylcholine, catecholamines or ATP-sensitive K+ channel activators.

ICD therapy is the suggested treatment strategy in survivors of SCD [6]. Extrapolating this risk profile, data drawn from relatives of patients affected with SCD has shown that they also pose a high risk for cardiac arrest. As the abbreviated QTc interval, electrophysiological characteristics including inducibility of ventricular arrhythmia are not predictors of SCD in SQTS, a risk stratification of these patients could challenge physicians [2].

In the current study, we describe our single-center experience in seven SQTS families. ICD implantation was documented in five patients. The rate of ICD complication was

**Table 1** Baseline characteristics of patients with SQTS

| Study | El-Battrawy et al. [4] (*n* = 17) | Sun et al. [11] (*n* = 1) | Bun et al. [12] (*n* = 1) | Mazzanti et al. [2] (*n* = 73) | Giustetto et al. [1] (*n* = 53) | Villafane et al. [13] (*n* = 25) | Mondoly et al. [14] (*n* = 1) | Sarquella-Brugada et al. [15] (*n* = 3) |
|---|---|---|---|---|---|---|---|---|
| Demographics | | | | | | | | |
| Age, mean (range) (n) | 42.45 (15–69) | 45 | 28 | 26 | 26 (17–39) | 15 (9–18) | 30 | After birth |
| Symptoms, *n* (%) | | | | | | | | |
| Syncope | 5 (29.41%) | 0 (0%) | 0 (0%) | 12 (16.43%) | 8 (15.08%) | 4 (16%) | – | 0 (%) |
| Palpitation | 8 (47.05%) | 0 (0%) | 0 (0%) | 7 (9.58%) | 13 (24.52%) | 4 (16%) | – | 0 (%) |
| Sudden cardiac death | 2 (11.76%) | 0 (0%) | 1 (100%) | 20 (27.39%) | 18 (33.96%) | 6 (24%) | – | 0 (%) |
| Atrial flutter | 2 (11.76%) | 0 (0%) | 0 (0%) | 0 (0%) | 8 (15%) | 0 | – | 0 (%) |
| Atrial fibrillation | 7 (41.17%) | 0 (0%) | 0 (0%) | 1 (1.4%) | 0 (0%) | 4 (16%) | – | 3 (100%) |
| ECG data, mean | | | | | | | | |
| QTc (ms) | 324 | 298 | 320 | 329 | 314 | 312 | 330 | 283 |
| Device implantation, *n* (%) | | | | | | | | |
| Yes | 5 (29.41%) | 1 (100%) | 1 (100%) | 16 (21.91%) | 24 (45.28%) | 11 (44%) | 1 (100%) | 2 (66.66%) |
| No | 11 (64.70%) | 0 | 0 (0%) | 57 (78.08%) | 29 (54.71%) | 14 (56%) | 0 (%) | 1 (33.33%) |
| Reveal recorder | 1 (5.88%) | 0 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (%) | 0 (%) |
| Complications, *n* (%) | | | | | | | | |
| Yes | 4 (80%) | 1 (100%) | 0 (0%) | 5 (31.25%) | 14 (58.33%) | 9 (81.8%) | 1 (100%) | 1 (50%) |
| No | 1 (20%) | 0 (0%) | 1 (100%) | 11 (68.75) | 10 (41.66%) | 2 (18) | 0 (0%) | 1 (50%) |
| Adequate shocks, *n* (%) | 1 (5.8%) | 0 (0%) | 0 (0%) | 7 (43.75%) | 1 (4.16%) | 2 (18%) | 0 (0%) | 0 (0%) |
| Genetic screening, *n* (%) | | | | | | | | |
| Unknown mutation | 5 (29.41%) | 1 (100%) | 0 (0%) | 0 (0%) | 0 | 0 (0%) | 1(100%) | 2 (66.66%) |
| CaCN2b | 6 (35.29%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (3.7%) | 0 (0%) | 0 (0%) | 0 (%) |
| CaCNA1c | 3 (17.64%) | 0 (0%) | 0 (0%) | 1 (1.36%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (%) |
| KCNH-2 | 4 (23.52%) | 0 (0%) | 0 (0%) | 5 (6.8%) | 0 (0%) | 2 (8%) | 0 (0%) | 0 (%) |
| KCNQ1 | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1.36%) | 0 (0%) | 1 (4%) | 0 (0%) | 1 (33.33%) |
| KCNJ2 | 0 (0%) | 0 (0%) | 0 (0%) | 3 (4.10%) | 0 (0%) | 2 (8%) | 0 (0%) | 0 (%) |
| SCN5a | 1 (5.88%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (%) | 0 (0%) | 0 (%) |
| HERG | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 11 (20.75%) | 0 (%) | 0 (0%) | 0 (%) |
| Negative mutation | 0 (0%) | 0 (0%) | 1 (100%) | 51 (69.86%) | 12 (22.64%) | – | 0 (0%) | 0 (%) |
| Follow-up time, mean (months) | 162 | 6 | 6 | 60 | 64 | 70.8 | 120 | 96 |

*ICD* implantable cardioverter-defibrillator, – no information

documented in 80% of the cases. Lead fracture was the reason for s-ICD implantation in two patients.

The addition of further SQTS patients treated with ICDs drawn from a systemic literature review of published data to our patient cohort revealed a complication rate of 54% triggered by inappropriate shocks due to T wave oversensing, lead fracture and documented supraventricular tachycardia with increased ventricular rate. Additionally, psychological distress was documented in up to 3% of the cases.

Since SQTS and BrS belong to the spectrum of early repolarization syndrome, we compared their findings on ICD outcome. Data on BrS after a mean follow-up of 9 years showed that appropriate shock is common in 20% of the cases [19]. Complications are reported to occur in up to 29%

**Table 2** Detailed description documented ICD complications

| Number of patients ($n=57$) | Patients with complication | Which complication | Follow-up (months) | Study |
|---|---|---|---|---|
| 5 | 4 (80%) | Inappropriate shocks (3×)<br>T wave oversensing (2×)<br>Supraventricular tachycardia (1×)<br>Infection (1×)<br>lead failure (4×)<br>Battery depletion (4×) | 162 | El-Battrawy et al. [4] |
| 1 | 1 (100%) | Inappropriate shock (1×)<br>T wave oversensing | 6 | Sun et al. [11]<br>Inappropriate ICD discharge due to T wave oversensing in a patient with Short QT syndrome |
| 1 | 0 (0%) | None | 6 | Bun et al. [12]<br>Electrical storm in Short QT syndrome successfully treated with isoproterenol |
| 16 | 5 (31.25%) | Inappropriate shocks (2×)<br>Atrial fibrillation with rapid ventricular response (1×)<br>Sinus tachycardia (1×)<br>Infection requiring device extraction (2×)<br>Psychological distress (1×) | 60 | Mazzantii et al. [2]<br>Novel insight into the natural history of Short QT syndrome |
| 24 | 14 – *4* (58.3–*16.6%*) | Inappropriate shocks (8×) – *2*<br>T wave oversensing (4×) – *2*<br>Supraventricual tachycardia (4×) – *1*<br>ICD lead replacement<br>Lead fracture (3×) – *1*<br>Infection (4×) – *1*<br>Psychological distress (1×) | 64 | Giustetto et al. [1]<br>Long-term follow-up of patients with Short QT syndrome |
| 11 | 9 (81.8%) | Inappropriate shock (7×)<br>Atrial fibrillation with rapid ventricular response (1×)<br>Sinus tachcardia (3×)<br>Supraventricular tachycardia (1×)<br>Ventricular lead failure (3×)<br>Ventricular lead failure (no shock) 1× | 70.8 | Villafane et al. [13]<br>Long-term follow-up of a pediatric cohort with Short QT syndrome |
| 1 | 1 (100%) | Lead failure (1×) of a transvenous ICD after 9 years of implantation<br>Follow-up of s-ICD for 1 year without any complications | 120 | Mondoly et al. [14]<br>Use of a subcutaneous ICD in a patient with Short QT syndrome |
| 2 | 1 (50%) | RV lead failure (1×) | 96 | Sarquella-Brugada et al. [15]<br>Short QT and atrial fibrillation: a KCNQ1 mutation-specific disease. Late follow-up in three unrelated children |

Included Patients in Giustetto et al. [1] from our cohort were excluded in the overall analysis. Values in italics is substraction of the complications of our patients

of BrS patients with ICDs, which is lower than our data on SQTS patients.

Since the prevalence of SQTS is low, there is relatively little experience with drug treatment regimens. A few drugs such as disopyramide, nifekalant, quinidine, flecainide, sotalol and ibutilide have been tested in small patient series with SQTS1, but only quinidine has been shown to be effective [1, 20–22]. Recently published data have shown that quinidine reduces the risk of SCD in SQTS. However, quinidine may cause some side effects including gastrointestinal intolerance leading to discontinuation of treatment in up to 12% of cases [23].

Although these data highlight a relatively high risk for complications, we should emphasize that ICD implantation is the only effective treatment option for SQTS patients having a life-expectancy of > 30 years and at risk of SCD. The high rate of complications which might be associated with worse clinical outcome essentially necessitates proper case selection and close follow-up.

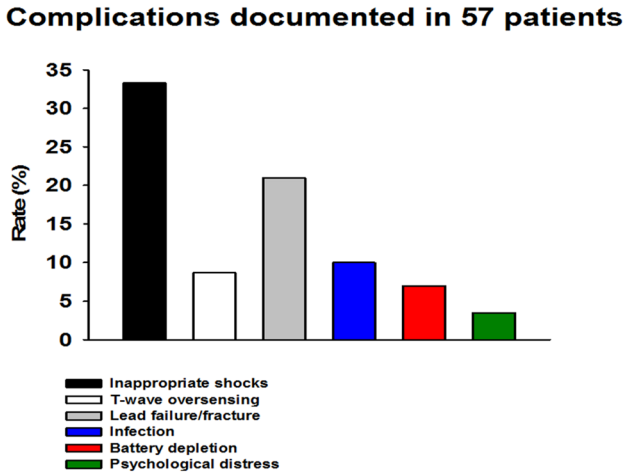


**Fig. 2** An overview showing ICD-related complications of 57 SQTS patients including consecutive patients of our institution

Due to the high number of complications in SQTS patients with ICD implantation, the indication should be evaluated by a referral center with good experience in SQTS to avoid overtreating patients with this disease. Whereas the rate of appropriate shocks was high (19%), the complication rate is also high (54%) over follow-up. Therefore, patients should be well informed about possible complications including inappropriate shocks, lead fracture, infection, and battery depletion, which may lead to psychological problems especially in young patients. Of note, risk stratification strategies in SQTS are not feasible at this moment. Despite advantages in SQTS, the greatest challenge for the management of patients with SQTS remains identifying risk factors for arrhythmic events. Scoring systems, which have included clinical and ECG criteria and or electrophysiology workup did not help to identify high-risk patients. But nevertheless, it seems that a survived cardiac arrest is a strong predictor of recurrent arrhythmia events [2]. Our data show that five SQTS patients should be treated to prevent one SCD. In addition, we present that our 3 patients treated with s-ICD did not suffer from any complications including inappropriate shocks as compared to 19 inappropriate shocks of patients treated with a transvenous ICD. Previously published data showed that s-ICD might be a feasible treatment in young patients with inherited channelopathies [24]. A case–control study presented equal or even better physical well-being of patients with the s-ICD [25]. The lower complication rate including inappropriate shocks might be associated with lower psychological disorders [24]. Therefore, s-ICD implantation might be a good treatment approach in SQTS to minimize the complication rate of these patients. Therefore, a follow-up of SQTS patients is recommended in referral centers.

## Conclusion

ICD therapy is an effective therapy in high-risk patients with SQTS. However, it is also associated with a significant risk of device-related complications. Special care during ICD implantation, adequate device programming, and regular follow-up in a specialized cardiogenetic unit is recommended. s-ICD implantation might be an appropriate alternative to avoid the high complication rate of transvenous ICD. However prospective multicenter registries are warranted.

### Study limitations

First, ICD indications have not been homogeneous throughout the study; arrhythmic risk factors are less clear, and, therefore, some patients had an ICD implanted for reasons other than symptoms or family history of SCD. Second, due the low number of events and use of different study groups, our analysis may have lacked necessary predictors. Finally, even though this is the longest follow-up duration reported in published literature, it may still not be sufficient to fully understand the true outcome of SQTS patients with an ICD.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

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