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Who Are the Long-QT Syndrome Patients Who Receive an Implantable Cardioverter-Defibrillator and What Happens to Them?

Data From the European Long-QT Syndrome Implantable Cardioverter-Defibrillator (LQTS ICD) Registry

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Background—A rapidly growing number of long-QT syndrome (LQTS) patients are being treated with an implantable cardioverter-defibrillator (ICD). ICDs may pose problems, especially in the young. We sought to determine the characteristics of the LQTS patients receiving an ICD, the indications, and the aftermath.

Methods and Results—The study population included 233 patients. Beginning in 2002, data were collected prospectively. Female patients (77%) and LQT3 patients (22% of genotype positive) were overrepresented; mean QTc was 516 ± 65 milliseconds; mean age at implantation was 30 ± 17 years; and genotype was known in 59% of patients. Unexpectedly, 9% of patients were asymptomatic before implantation. Asymptomatic patients, almost absent among LQT1 and LQT2 patients, represented 45% of LQT3 patients. Patients with cardiac symptoms made up 91% of all study participants, but only 44% had cardiac arrest before ICD implantation. In addition, 41% of patients received an ICD without having first been on LQTS therapy. During follow-up, 4.6 ± 3.2 years, at least 1 appropriate shock was received by 28% of patients, and adverse events occurred in 25%. Appropriate ICD therapies were predicted by age < 20 years at implantation, a QTc > 500 milliseconds, prior cardiac arrest, and cardiac events despite therapy; within 7 years, appropriate shocks occurred in no patients with none of these factors and in 70% of those with all factors.

Conclusions—Reflecting previous concepts, ICDs were implanted in some LQTS patients whose high risk now appears questionable. Refined criteria for implantation, reassessment of pros and cons, ICD reprogramming, and consideration for other existing therapeutic options are necessary. (*Circulation*. 2010;122:1272-1282.)

Key Words: arrhythmia ■ defibrillation ■ genetics ■ heart arrest ■ long QT syndrome

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There is a continuous growth in the number of implantable cardioverter-defibrillators (ICDs) used to prevent fatal outcomes associated with life-threatening arrhythmic episodes in a variety of cardiac diseases. Most of these patients are in their 6th to 7th decade of life. However, the increasing awareness and diagnoses of genetically mediated arrhythmogenic disorders have dramatically augmented the number of young individuals who receive an ICD. This creates a host of new questions and problems, largely related to the long-term consequences of an early implantation with the attendant numerous generator replacements and possible lead-related problems; furthermore, given the impact on quality of life, it mandates verification of appropriateness of the indications for ICD implantations used in clinical practice.

Clinical Perspective on p 1282

We addressed these issues in the long-QT syndrome (LQTS), which, with a prevalence close to 1 in 2000 live births,¹ is probably the most important life-threatening arrhythmogenic ion channel disease that manifests in the young.^{2,3} Under the auspices of the Working Group on Arrhythmias of the European Society of Cardiology (now the European Heart Rhythm Association), we initiated in 2002 the European ICD-LQTS Registry with the main objectives of assessing the current indications to implant according to clinical history, response to previous therapy, and specific genotype and evaluating the clinical course after ICD implantation. Here, we report our findings, which carry significant implications for the management of patients with LQTS.

Methods

Study Population

The study population was drawn from the European LQTS ICD Registry. This international collaborative research project began in 2002 to enroll LQTS patients with an ICD. By the end of the study, data were available for 233 patients implanted in Belgium, Finland, France, Germany, Hungary, Italy, the Netherlands, Sweden, and Switzerland. Patients from extra-European countries (Argentina, Australia, New Zealand, Saudi Arabia, South Africa) but included in the Pavia databases were also enrolled. Patients were included if diagnosed with LQTS and implanted with an ICD; those with concurrent cardiac comorbidities potentially confounding the clinical presentation and the subsequent indication to ICD implantation were excluded. Although the pre-enrollment clinical information was retrospective in nature, prospective follow-up data on patients and ICDs were collected at regular intervals. At the time of enrollment and follow-up, prespecified questionnaires were used to collect data on demographics, genotype, personal and family clinical history, ECG measurements, treatment, response to therapy both before and after the ICD implantation, technical and functional characteristics of the devices, delivered therapies, revisions, and device-related complications. As for the clinical preimplantation history, patients were categorized as asymptomatic or symptomatic on the basis of a previous history of cardiac events, defined as syncope or aborted cardiac arrest (ACA) requiring resuscitation maneuvers with or without external defibrillation. To differentiate truly asymptomatic patients, those with documented self-terminating arrhythmias (ventricular tachycardia [VT]/torsades de pointes) were considered symptomatic even in the absence of a frank loss of consciousness and classified in the syncope group. Patients were considered to be on treatment only if they were on antiadrenergic (β -blockers and left cardiac sympathetic denervation [LCSD]) or antiarrhythmic (sodium channel-blockers) ther-

apy. Patients on treatment with other antiarrhythmic drugs (eg, sotalol, amiodarone) were not considered on LQTS therapy. In the postimplantation period, the outcome was any therapy from the ICD, both appropriate and inappropriate shocks, according to device interrogation data. Any ICD therapy not delivered for VT or ventricular fibrillation (VF) was deemed inappropriate, and the rhythm triggering therapy was categorized as supraventricular tachyarrhythmias, including sinus tachycardia or inappropriate sensing. A few ICD therapies were unclassified because of missing or incomplete data. Electric storm was defined as the occurrence of 3 or more separate episodes of VT/VF within a 24-hour period requiring ICD therapy. Post-ICD implantation complications were classified as major or minor adverse events, depending on their inherent risk of death/disability.

Scoring System

We developed a scoring system to evaluate the likelihood of appropriate ICD therapy based on an incremental number of coexisting risk factors. Baseline variables significantly associated with the outcome at univariate analysis were then included in a multivariate Cox model and tested for their significance and independence in predicting the incidence of appropriate shocks during follow-up. Four variables were identified. First, the QT interval was categorized into 3 levels— ≤ 500 , >500 to 550 , and >550 milliseconds—and received 0, 1, and 2 points, respectively. Second, for age at the decision to implant, the cutoff was ≤ 20 years, and we used the actual implantation date as a proxy for when this medical decision was made. Third, for cardiac events on therapy, we meant any cardiac event that occurred while on therapy. The fourth variable, cardiac arrest, is self-explanatory. The last 3 factors were treated as binary variables (yes/no), and their positive presence received 1 point each. Previously symptomatic patients who on therapy had no cardiac events in the >10 years preceding the decision to implant received -1 point.

Statistical Analysis

Continuous variables are expressed as mean and SD; whenever the distribution was skewed, median and interquartile range (IQR) are also reported. Comparisons of these variables among groups were performed by *t* test and ANOVA or by their nonparametric equivalents. Discrete variables were presented as absolute and relative frequencies and were compared by the χ^2 test. Kaplan-Meier survival curves were evaluated by the log-rank test. To assess the contribution of baseline characteristics of patients in predicting the likelihood of appropriate shocks from the ICD during follow-up, multivariate Cox proportional-hazard regression analysis was used. Incidence rates of therapies delivered by ICDs and 95% confidence intervals (CIs) were computed by dividing the number of patients with a first shock by the total number of person-years. Similarly, shock counts per person-year were calculated and presented as mean yearly events with exact 95% CIs based on a Poisson distribution.

All patients signed an informed consent form approved by the local Institutional Review boards. All authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Before ICD Implantation

Table 1 shows the clinical characteristics of the study population. Female gender was overrepresented (180, 77%). The mean QTc was clearly prolonged (516 ± 65 milliseconds) and was significantly longer in symptomatic compared with asymptomatic patients at baseline (519 ± 64 versus 476 ± 67 milliseconds; $P=0.005$) but was not influenced by symptom severity (517 ± 59 versus 522 ± 69 milliseconds for syncope and ACA, respectively; $P=0.56$). Surprisingly, however, 13% of the implanted patients had a normal QT interval; many of them were LQT3 patients. The vast majority (212,

Table 1. Baseline Characteristics of All Patients According to Genotype

| | All Patients (n=233) | LQT1 (n=37) | LQT2 (n=61) | LQT3 (n=31) | Double Mutations (n=15) | <i>P</i> |
|---|-------------------------|----------------|----------------|----------------|----------------------------|----------|
| Female gender, n (%) | 180 (77) | 31 (84) | 50 (82) | 20 (64) | 8 (53) | 0.032 |
| QTc, ms* | 516±65 | 524±65 | 512±59 | 484±66 | 593±82 | <0.001 |
| >500, n (%) | 124 (54) | 20 (54) | 34 (57) | 12 (40) | 15 (100) | 0.002 |
| ≤440, n (%) | 31 (13) | 2 (5) | 7 (12) | 10 (33) | 0 | 0.002 |
| FH-SCD, n (%)† | 93 (41) | 16 (44) | 28 (47) | 18 (60) | 6 (46) | 0.60 |
| Pre-ICD symptoms (any cardiac event), n (%) | 212 (91) | 36 (97) | 59 (97) | 17 (55) | 15 (100) | <0.001 |
| ACA | 102 (44) | 16 (43) | 27 (44) | 8 (26) | 7 (47) | |
| Syncope‡ | 110 (47) | 20 (54) | 32 (52) | 9 (29) | 8 (53) | |
| Asymptomatic | 21 (9) | 1 (3) | 2 (3) | 14 (45) | 0 | |
| On therapy, n (%) | 138 (59) | 29 (78) | 41 (67) | 12 (39) | 13 (87) | 0.001 |
| β-blockers | 133 (96) | 29 (100) | 40 (98) | 9 (75) | 13 (100) | |
| Sodium channel blockers | 14 (10) | 1 (3) | 1 (2) | 5 (42) | 0 | |
| Pacemaker | 19 (14) | 3 (10) | 1 (2) | 1 (8) | 2 (15) | |
| LCSD | 26 (19) | 3 (10) | 8 (19) | 2 (17) | 6 (46) | |
| Events on therapy, n (%) | 107 (78) | 24 (83) | 30 (73) | 5 (42) | 12 (92) | 0.018 |
| Median age at first event (IQR), y | 18 (7–33) | 14 (5–27) | 17 (13–25) | 17 (11–40) | 2 (0–3) | <0.001 |
| Median age at implantation (IQR), y | 29 (16–40) | 31 (17–53) | 28 (18–35) | 27 (16–43) | 13 (8–23) | 0.004 |

FH indicates family history.

*For 4 patients, these data are missing.

†For 9 patients, these data are missing.

‡For 2 patients, episodes of self-terminating VT/torsades de pointes were documented in absence of a frank loss of consciousness.

91%) of the patients were symptomatic at baseline, with almost equal proportions of those who had experienced syncope only (47%) and those with cardiac arrest (44%). More than half of the patients (60%) with syncope only had at least one of these events despite therapy. In 38 of the 102 patients (37%) who experienced a cardiac arrest, this was the presenting sign.

Unexpectedly, 21 patients (9%) were asymptomatic before ICD implantation. Compared with those with prior cardiac events, asymptomatic patients showed a stronger family history for sudden cardiac death (SCD; 71% versus 38%; $P=0.003$) and less frequent use of antiadrenergic or antiarrhythmic therapies in the pre-ICD period (38% versus 61%; $P=0.039$), and 14 of them (67%) were LQT3 mutation carriers.

Therapy

By our definition, only 138 (59%) of the patients were on treatment before the ICD implantation; except for 2 individuals treated with only LCSD because of intolerance to or refusal of β-blockers, all patients were on β-blockers and/or sodium channel blockers, and among them, 36 received 1 or more additional therapies (24 LCSD and 19 pacemaker). Occurrence of cardiac events and/or documented major ventricular tachyarrhythmias involved 78% of the patients on therapy.

Genotype

Disease-causing mutations were identified in 138 patients (59%). There were 37 LQT1, 61 LQT2, and 31 LQT3 patients. Nine were carriers of double mutations; among

them, 4 had the Jervell and Lange-Nielsen syndrome. Whereas absolute figures point to a moderately higher proportion of LQT2 patients among those with a known genotype (44% versus 27% LQT1 and 22% LQT3), *SCN5A* mutation carriers are clearly over-represented in this group as they constitute no more than 10% of the entire LQTS population. We assumed that 6 additional patients were carriers of double mutations despite being genotype negative or not being tested because they had been diagnosed as affected by the Jervell and Lange-Nielsen syndrome on the basis of a congenital neurosensory deafness in addition to marked QT prolongation and a very severe phenotype.⁴

A comparison of baseline clinical characteristics among the genetic subtypes (Table 1) showed that LQT3 patients more frequently had a normal QT interval (QTc ≤440 milliseconds) and were less likely to be treated by antiadrenergic and/or antiarrhythmic therapy and to experience cardiac events while on these therapies before ICD implantation. As expected,^{4,5} known or assumed double-mutation carriers showed a more severe phenotype, with longer QT intervals, a younger age at symptom onset, and a higher incidence of cardiac events despite therapy. They were also more frequently male compared with LQT1, LQT2, and LQT3 patients.

Genotype played a role in influencing the indication to implant (Figure 1). Although there was no difference across the genetic groups in the clinical severity of cardiac events (syncope or ACA) in the pre-ICD period, asymptomatic patients among LQT1 patients, LQT2 patients, and double-mutation carriers were almost completely absent in contrast

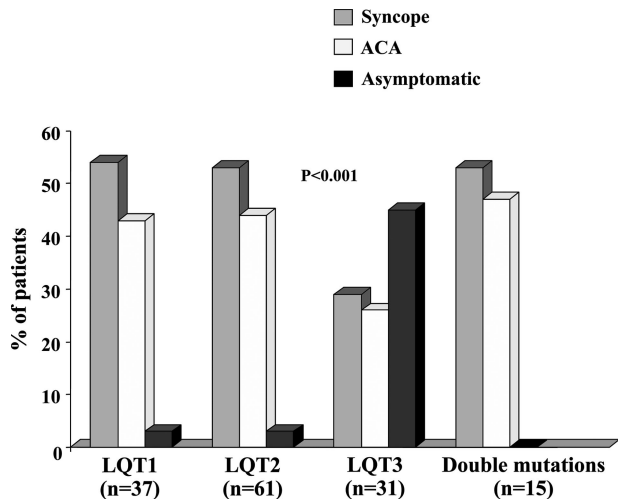


Figure 1. Pre-ICD history of cardiac events according to genotype.

to 45% of LQT3 patients who received an ICD without having suffered any prior cardiac event.

ICD Implantation

A first ICD was implanted in the study population between December 1989 and April 2009. As a reflection of the increasing use of these devices in LQTS patients, 86% of all first implantations were performed between 1999 and 2009 and 39% in the last 5 years.

The mean age at implantation was 30 ± 17 years (median, 29 years; IQR, 16 to 40 years; range, 6 months to 76 years), with no significant difference between symptomatic and asymptomatic patients (30 ± 17 versus 26 ± 13 years, respectively; $P=0.33$). As shown in Figure 2, 12% of patients were initially implanted in their first decade; of note, 24% of the population was >40 years of age at the time of the implantation. This latter subgroup ($n=56$; 95% symptomatic, 86% female, 59% of known genotype) showed no significant difference in all analyzed demographic and clinical features at baseline compared with those implanted before 40 years of age, with the only exceptions of having experienced cardiac events while on therapy more frequently (94% versus 74%; $P<0.02$) and of having a QTc >500 less frequently (39%

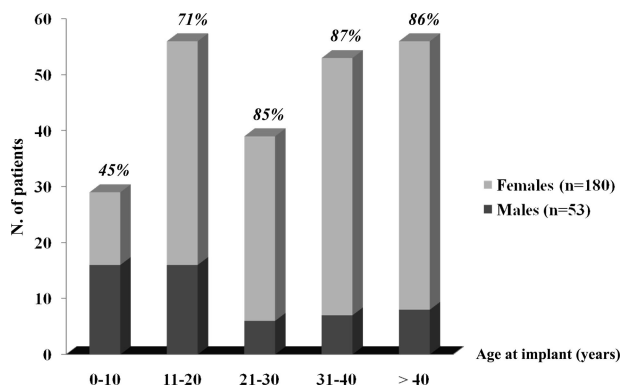


Figure 2. Distribution of patients at implantation by age and gender. Numbers above the histograms represent the percentages of female patients.

versus 59% $P=0.01$) than patients implanted earlier. Almost 50% of these older patients (29 of 56) had their first event after 40 years of age, and for 6 of 29, the event was associated with QT-prolonging drugs use,⁶ hypokalemia, or fever. Female patients were prevalent in all age classes but not among the youngest implanted patients.

The mean time elapsed from any first event to ICD implantation was 8 ± 12 years (median, 4 years; IQR, 0 to 12 years). For patients who suffered syncope only, the mean time elapsed from the first event to ICD implantation was 8.5 ± 11 years (median, 4 years; IQR, 0 to 12 years). About one third of them (35%) received the ICD ≤ 1 year after the first syncope, which was the only event in 56% of them. For patients with a pre-ICD history of ACA, the mean time elapsed from the first ACA to ICD implantation was 2 ± 5 years (median, 0 years; IQR, 0 to 3 years). Among the patients who suffered a first ACA, 73% received the ICD within the same year, and 80% received the ICD within the following 3 years. For the 20 patients implanted >3 years after the first ACA, most ($n=16$, 80%) had recurrent events (syncope or a second ACA) despite therapy. However, for 2 patients, it was a clinical decision without new events, and 2 others requested the ICD. Interestingly, all 4 individuals were long-standing asymptomatic patients at time of implantation, having experienced no more events during a mean of 18 years (range, 10 to 33 years) preceding ICD implantation. Therefore, the pre-ICD clinical history does not always accurately reflect the actual indication to implant in all patients. This needs to be taken into account when modeling the likelihood of shocks during follow-up according to the history of symptoms. Accordingly, in building our risk score, we have subtracted 1 point for patients on therapy and without cardiac events during the 10 years preceding ICD implantation.

ICD Characteristics

For 229 patients (98%), the characteristics of the first implanted ICDs were known. Epicardial implantations were performed in 8 patients. All other patients received transvenous lead systems. Single-chamber ICDs were initially implanted in 129 patients (56%); in this group, the more common programmed pacing mode was VVI at a mean rate of 45 bpm (median, 40 bpm; IQR, 40 to 45 bpm). These devices were implanted more frequently in pediatric patients (<20 years of age) than in adults (77% versus 45%). Among the 100 patients (44%) who received as first implantation a dual-chamber ICD, the prevalent (76%) programmed pacing mode was DDD/DDDR/DDI with a mean lower rate of 59 bpm (median 60 bpm; IQR, 50 to 70); another 24% of patients were programmed in AAI/AAIR/AAI-DDD with a mean lower rate of 70 bpm (median, 70 bpm; IQR, 60 to 80 bpm). During the last 5 years, the number of dual-chamber ICDs has increased. After the initial implantation, replacing the devices to upgrade to dual-chamber systems was performed in 6 patients, after multiple episodes of torsades de pointes/VF to exploit pacing therapy with the goal of preventing bradycardia-dependent torsades de pointes and of allowing higher doses of β -blockers.

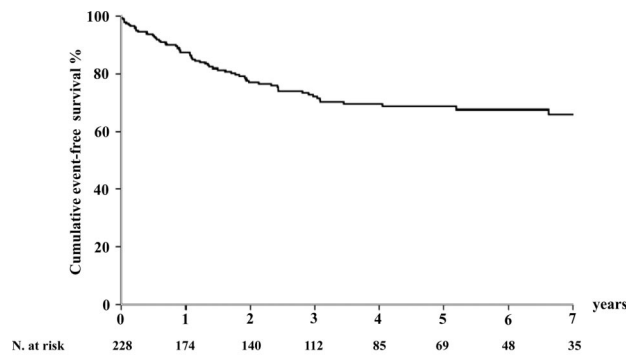


Figure 3. Cumulative event-free survival for a first appropriate ICD shock in the study population.

After ICD Implantation

Adequate follow-up information was available for 228 of 233 patients (98%). During a mean observation time of 4.6 ± 3.2 years (median, 4 years; IQR, 2 to 7 years), 7 patients died at a mean age of 47 years, 6 of a noncardiac cause and 1 of a nonarrhythmic cardiovascular event.

According to ICD interrogation data, 65 patients (28%; 8 with double mutations) received at least 1 appropriate shock. Time to the first appropriate shock is shown in Figure 3. The vast majority of these events occurred within the first 2 years of follow-up. Multiple shocks (≥ 2 anytime during follow-up) occurred in 42 patients; repetitive discharges, fulfilling our definition of arrhythmic storm, were observed in 17 patients (7%). Most of the patients with appropriate shocks (89%) were on prescribed medication at the time of the antitachycardia therapy. Inappropriate shocks occurred in 25 patients (11%); 13 of them also experienced appropriate shocks. Most common causes for inappropriate therapy from the ICD were inappropriate sensing or supraventricular tachycardia. In 15 of these 25 patients, lead revision ($n=8$) or reprogramming (change in pacing mode, increase in basal pacing rate, increase in VF cutoff limit, delay in detection interval to shock) of the device ($n=7$) was performed after an inappropriate therapy from the ICD. None of the baseline characteristics considered, including age at implantation, was significantly associated with the occurrence of inappropriate shocks. Table 2 summarizes numbers, incidence rates, and rhythms associated with all the recorded ICD shock episodes.

The likelihood of appropriate therapy from the device was assessed according to predefined baseline characteristics of patients (Table 3). A significant association was observed between the severity of the pre-ICD clinical presentation and the probability of appropriate ICD therapy during follow-up ($P=0.019$). Indeed, of the 65 patients who received appropriate shocks, only 2 (3%) were previously truly asymptomatic patients, but both had a QTc of 600 milliseconds; 26 (40%) had a prior syncope (independently of β -blockers); and 37 (57%) had survived a prior ACA.

When the incidence of appropriate shocks according to the severity of prior cardiac events was examined, taking into account whether these events occurred on or off therapy, interesting findings emerged. Indeed, survivors of a prior ACA despite therapy, mostly also with preceding syncope on therapy, had a significantly greater probability of appropriate

Table 2. Rhythm Responsible for ICD Shock Episodes

| | Patients, n | Shocks, n |
|---|-----------------|-----------|
| Appropriate* | 63 | 1159 |
| Ventricular tachyarrhythmia in VF zone† | 24 | 194 |
| Ventricular tachyarrhythmia in VT zone‡ | 18 | 329 |
| Both tachyarrhythmias in VT/VF zone | 21 | 636 |
| Unclassified* | 2 | |
| Median event count per patient (IQR) | 0 (0–1) | |
| Incidence rate per 100 person-years (95% CI)§ | 7.8 (5.9–9.9) | |
| Mean yearly event rate | 1.1 (1.06–1.19) | |
| Inappropriate*¶ | 19 | 86 |
| Atrial fibrillation | 1 | 2 |
| Supraventricular tachycardia | 7 | 21 |
| Abnormal sensing | 9 | 51 |
| Lead fracture/dislodgment | 3 | 12 |
| Unclassified* | 6 | |
| Median event count per patient (IQR) | 0 (0–0) | |
| Incidence rate per 100 person-years (95% CI)§ | 2.0 (1.2–3.2) | |
| Mean yearly event rate | 0.08 (0.07–0.1) | |

*There were 65 patients with appropriate and 25 patients with inappropriate shocks. For this analysis, 2 of 65 and 6 of 25 patients with missing data on the exact rhythm, timing, or number of shocks (“unclassified”) were not counted.

†Detection cutoff for VF, 283 ± 22 milliseconds.

‡Detection cutoff for VT, 342 ± 40 milliseconds.

§Number of patients with a first appropriate or inappropriate shock over a total risk exposure time of 807 and 929 person-years, respectively.

||Computed over a median follow-up time of 3.9 years (IQR, 2.1 to 6.8 years).

¶One of the 19 patients had shocks for 2 different causes.

shocks compared with patients in whom ACA occurred off therapy (Figure 4). Of note, in 45% of this latter group of patients, ACA was the presenting sign, and in 19% of them, the event occurred during incidental triggering conditions such as use of QT-prolonging drugs, fever, hypokalemia, or inability to take medications.

In contrast, we were surprised not to find differences in the probability of future appropriate shocks according to history of syncope on or off therapy (Figure 5A). Despite the seeming strength of the data, this finding did not fit our clinical experience. A more in-depth analysis revealed that among the patients with syncope off therapy, the probability of appropriate shocks was strongly influenced by the degree of QT interval prolongation (Figure 5B) or by the presence of a global risk indicator, which included 1 or more of the following: QTc >550 milliseconds, other ECG risk markers (atrioventricular block, T-wave alternans, marked bradycardia), presence of double mutations, or inability to receive β -blockers (Figure 5C).

Patients with appropriate shocks had a significantly longer mean QTc value, more frequently had a QTc >500 milliseconds and >550 milliseconds, were more likely to have

Table 3. Comparison of Patients With and Without Appropriate ICD Shocks

| | Patients With Appropriate Shocks (n=65) | Patients Without Appropriate Shocks (n=163) | P |
|--|---|---|--------|
| Female gender, n (%) | 50 (77) | 127 (78) | 0.87 |
| QTc, ms | 542±65 | 506±63 | <0.001 |
| >500, n (%) | 46 (72) | 77 (48) | 0.001 |
| >550, n (%) | 26 (41) | 34 (21) | 0.003 |
| FH-SCD, n (%) | 23 (36) | 69 (44) | 0.29 |
| Pre-ICD history of cardiac events, n (%) | | | 0.019 |
| Asymptomatic | 2 (3) | 18 (11) | |
| Syncopal | 26 (40) | 82 (50) | |
| ACA | 37 (57) | 63 (39) | |
| Pre-ICD therapy, n (%) | 43 (66) | 93 (57) | 0.21 |
| Events on therapy | 40 (93) | 66 (71) | 0.001 |
| Genotype, n (%) | | | <0.05 |
| LQT1 | 13 (20) | 24 (15) | |
| LQT2 | 12 (18) | 47 (29) | |
| LQT3 | 5 (8) | 25 (15) | |
| Double mutations, n (%) | 8 (12) | 7 (4) | |
| Median age at first event, y | 12 (3–22) | 20 (12–36) | <0.001 |
| Median age at implantation, y | 17 (8–31) | 33 (18–43) | <0.001 |
| Median time of follow-up, y | 4.5 (2–8) | 4 (2–6) | 0.078 |

FH indicates family history.

experienced cardiac events despite therapy, and were significantly younger at implantation than those who received no ICD therapies. Neither gender nor a positive family history for SCD showed an association with the probability of ICD therapy during follow-up. Similarly, no significant difference was observed among the 3 main genetic subtypes, whereas the double-mutation carriers had a significantly higher rate of appropriate ICD therapy compared with LQT2 and LQT3 (Figure 6).

Scoring System

At univariate analysis, a prior ACA, cardiac events despite therapy, a markedly prolonged QTc, and younger age at

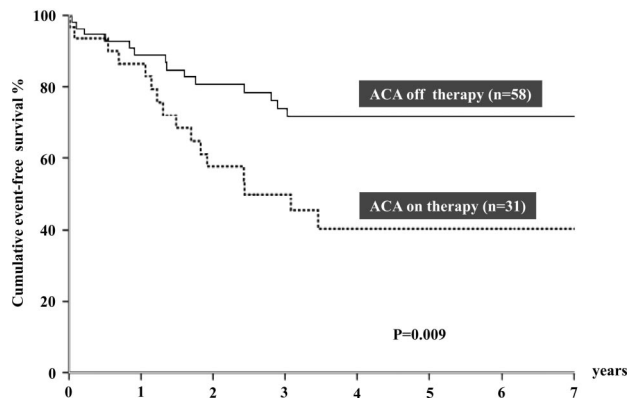


Figure 4. Cumulative event-free survival for a first appropriate ICD shock according to a prior ACA on or off therapy.

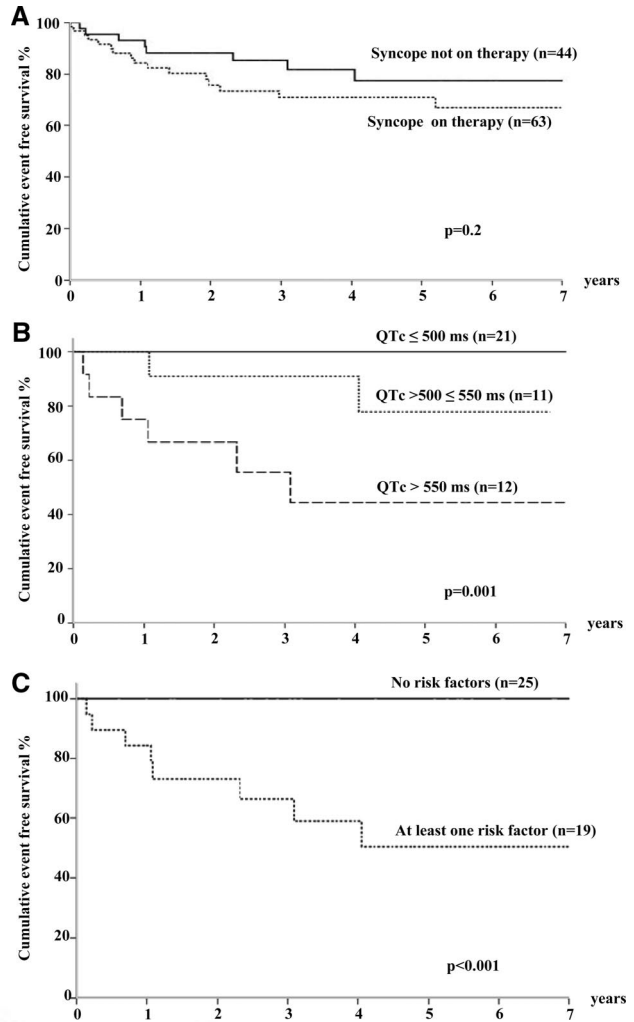


Figure 5. A, Cumulative event-free survival for a first appropriate ICD shock according to a prior history of syncope on or off therapy. B and C, Only the 44 patients with syncope off therapy. Cumulative event-free survival for a first appropriate ICD shock is shown according to (B) the degree of QT interval prolongation and (C) the presence of a global risk indicator including at least one of the following factors: QTc >550 milliseconds, ECG markers of risk, intolerance to β -blockers, or double mutations.

implantation appeared to be potentially useful risk stratifiers to predict the probability of appropriate therapies from the ICD, thus allowing the identification of those patients expected to benefit most from the implantation.

After the univariate analysis, a multivariate Cox model (Table 4) identified all 4 selected variables as independent predictors of future appropriate shocks, allowing their combination and the development of a score (M-FACT) based on the number of these risk factors when coexisting in the same patient (Table 5).

Figure 7A shows that in the entire population, the 7-year cumulative survival to a first appropriate shock decreased from 100% for patients with no risk factors to 30% for patients with ≥ 4 point score, with a progressively lower probability of escaping shocks according to the increasing number of risk factors ($P < 0.001$). Figure 7B shows that when the same analysis was performed after exclusion of the patients with a prior ACA, the pattern remained

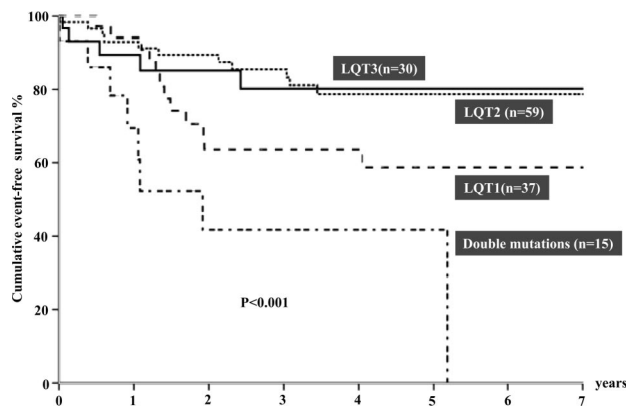


Figure 6. Cumulative event-free survival for a first appropriate ICD shock according to genotype.

essentially the same. In low-risk patients (score 0 to 1), the 7-year cumulative survival to first appropriate shock for the 2 subsets was 88% (95% CI, 78 to 94) and 97% (95% CI, 87 to 99).

Bradycardia Pacing

As a secondary analysis, we explored the potential effect of antibradycardia pacing on the predefined end point of appropriate ICD therapies. Dichotomization at 70 bpm of the lower pacing rate at first implantation revealed no differences in the rate of appropriate shocks. However, when this effect was evaluated within the M-FACT score, an interesting trend was observed (see the online-only Data Supplement): High-risk patients (score 4 to 5) appeared to benefit most from bradycardia pacing ≥ 70 bpm. Although no differences could be found among intermediate-risk patients (score, 2 to 3), none of the low-risk patients (score, 0 to 1) with a pacing rate ≥ 70 bpm had appropriate shocks.

Reinterventions and Complications

Among the 228 patients with adequate follow-up information, 103 patients (45%) underwent at least 1 revision of the ICD. The most frequent cause of reintervention was battery depletion performed at least once in 81 patients (36%) after a mean time of 4.7 ± 1.6 years after initial implantation. Among these patients, 2 had a premature ICD substitution resulting from elective replacement indicator 6.5 and 10 months after the implantation because of multiple appropriate shocks. Fifty-eight patients (25%) suffered from at least 1 acute and/or chronic adverse event associated with the surgical procedure of ICD implantation and/or with both lead and generator functioning. Thus, there was a total of 67 complications

Table 4. Multivariate Risk Predictors of Appropriate Shock During Follow-Up in Patients With an ICD

| Clinical Variables | Hazard Ratio (95% CI) | P |
|---------------------------|-----------------------|-------|
| Prior ACA | 1.81 (1.09–3.0) | 0.023 |
| Events on therapy | 1.81 (1.08–3.0) | 0.025 |
| Age at implantation <20 y | 2.3 (1.38–3.8) | 0.001 |
| QTc* | 1.41 (1.03–1.92) | 0.03 |

*This 3-level (≤ 500 , >500 to ≤ 550 , and >550 milliseconds) factor was treated as a continuous variable, its linear effect having been evaluated.

Table 5. M-FACT* Risk Score

| | -1 Point | 0 Points | 1 Point | 2 Points |
|---------------------------------|----------|------------|-----------------|----------|
| Event-free on therapy for >10 y | Yes | | | |
| QTc, ms | | ≤ 500 | $>500-\leq 550$ | >550 |
| Prior ACA | | No | Yes | |
| Events on therapy | | No | Yes | |
| Age at implantation, y | | >20 | ≤ 20 | |

*Acronym derived from M (minus 1 point for being free of cardiac events while on therapy for >10 years), F (500- and 550-millisecond QTc), A (age ≤ 20 or >20 years at implantation), C (cardiac arrest), and T (events on therapy).

occurring at different times during follow-up, all requiring medical or surgical interventions for correction or frequent ICD surveillance (Table 6).

Among major adverse events, device-related infection and endocarditis in 7 patients were the more common complications, accounting for 47%. Lead-related complications also were frequent in this group; 2 patients required open chest surgery.

In addition, among minor adverse events, lead-related complications were prevalent, affecting 24 patients (11%). Independently of battery change, 6 patients received an elective ICD replacement because of system malfunction (n=2) or as an upgrade to a dual-chamber system (n=4). Manufacturers' advisories, on either generator or lead, in-

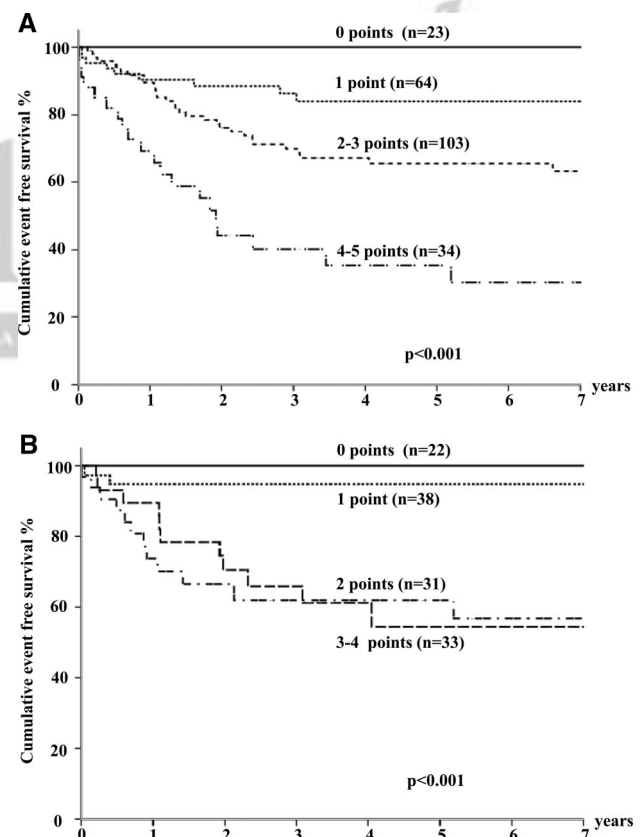


Figure 7. Cumulative event-free survival for a first appropriate ICD shock according to an increasing risk score in (A) all patients and (B) patients with no prior ACA.

Table 6. Complications After ICD Implantation*

| | |
|---|----|
| Total patients with at least 1 adverse event, n | 58 |
| Major adverse events | |
| Pericardial tamponade | 1 |
| Cardiac perforation with or without pericardial effusion | 3 |
| Lead revision requiring open chest surgery | 2 |
| Device-related infection/endocarditis | 7 |
| Right atrial thrombosis | 1 |
| Stroke | 1 |
| Total major adverse events, n | 15 |
| Minor adverse events | |
| Lead-related overall | 24 |
| Lead dislodgment | 7 |
| Lead fracture/insulation defect | 9 |
| Change in capture, sensing or defibrillation threshold | 7 |
| Exit block | 1 |
| Device-related overall | 10 |
| Device dislodgment requiring repositioning | 4 |
| Device malfunction requiring replacement/elective upgrading | 6 |
| Others | 6 |
| Phlebitis | 1 |
| Peripheral nerve injury | 1 |
| Keloid | 3 |
| Decubitus | 1 |
| Total minor adverse events, n | 40 |
| Manufacturers' advisories with or without replacements* | |
| Pulse generator | 7 |
| Lead | 5 |
| Total recalls, n | 12 |

*Requiring surgical extraction/replacement/repositioning and/or medical intervention.

involved 12 patients (5%) and led to replacement in 8. Age at implantation was not associated with any of these complications.

In 5 patients, the ICD was definitively removed or deactivated after a mean of 4 years after implantation without having delivered any therapy. Three were asymptomatic patients on β -blocker therapy; 1 had a terminal cancer; and 1 had an endocarditis-related emergency.

Discussion

The present study, based on the largest available series of LQTS patients who received an ICD, provides clinically relevant data, including some findings that were unexpected. The main findings include the following: a cardiac arrest before implantation had occurred in <50% of the patients; 10% of the patients never had a cardiac symptom before being implanted; women and LQT3 patients had a disproportionately high probability of being implanted with an ICD; and during an average follow-up of <5 years, adverse events, major and minor, occurred in 25% of the patients (n=58) excluding inappropriate shocks and in 31% including inappropriate shocks. It is likely that many of the appropriate shocks received by 28% of the patients might have been

avoided by different programming designed to allow short runs of torsades de pointes VT to self-terminate. These data should call attention to the appropriateness of the decision to implant an ICD in a significant number of LQTS patients and definitely mandate a reassessment of the ICD programming for LQTS patients.

Subgroups More Likely to Receive an ICD

Some of the baseline characteristics of the patients in whom this group of physicians decided to implant an ICD are not easy to explain. Others suggest that at the time of the implantation, the perception of the actual risk for these patients was probably incorrect.

The fact that almost 80% of the LQTS patients receiving an ICD are female might relate to their greater exposure to the risk of cardiac events compared with male patients from adult age on,^{7,8} especially among LQT2 patients, and possibly to female patients more frequently being users of QT-prolonging drugs.⁵ Indeed, this phenomenon becomes even more striking among patients implanted after 20 years of age, when this percentage becomes close to 90%; within this group, 51% of those genotyped were LQT2. Similarly, the greater arrhythmic risk among boys than girls during childhood^{9,10} fits with the overrepresentation of male patients with an ICD implanted before 10 years of age (Figure 2). Interestingly, during the last 5 years, the number of female patients has decreased, as has the number of LQT2 patients.

Another group overrepresented is LQT3 patients. Whereas they represent only 7% to 10% of the overall genotyped LQTS patients, they make up 22% of the genotyped LQTS patients receiving an ICD. Here, the explanation is likely to reflect the idea, accepted rather uncritically until a few years ago,¹¹ that nondevice therapies are ineffective in preventing deaths and the fact that ACA/SCD may often be their first clinical manifestation. As a consequence, there is the risk that once physicians are informed by the genetic laboratory that their patient carries a *SCN5A* mutation (most of the time even without any evidence that this is a disease-causing mutation^{11,12}), they are concerned with the presumed lack of effective therapies and may decide to proceed with an ICD implantation. This interpretation has the dramatic support of the percentage of asymptomatic patients who received an ICD based on genotype (Figure 1). Whereas this number ranged between 0% and 3% for patients with double mutations or LQT1 and LQT2, it skyrocketed to 45% for LQT3 patients. This tendency has had some justification until a few years ago, but recent data¹ and the present findings argue strongly for assessing the pros and cons of an ICD on the basis of the actual clinical risk of the individual patient.

Another factor probably contributed to the pattern observed in our study. The American College of Cardiology/American Heart Association/European Society of Cardiology practice guidelines for SCD¹³ recommend, albeit in Class IIb, prophylactic implantation of an ICD "for patients in categories possibly associated with higher risk of cardiac arrest such as LQT2 and LQT3." If left unchallenged, this recommendation might continue to influence physicians to implant ICDs for primary prevention in LQTS patients whose main risk

comes not from their actual clinical condition but from their genetic label.

Admittedly, LQT3 patients respond less well to β -blockers, but the available, albeit limited, data suggest that the worst response to medical therapy concerns mainly the patients with cardiac events in the first year of life and that the remaining patients fare rather well with β -blockers and/or LCSD.¹¹ Two previous studies have indicated the absence of ICD shocks during similar follow-up in 9 and 5 LQT3 patients who received an ICD because of their genotype.^{14,15} The same absence of shocks, but in a larger group of LQT3 patients, has been observed by Ackerman (personal communication).

Our interpretation of the present data and of the previous data on the therapy of genotype-positive LQTS patients³ suggests a more cautious approach before jumping from an *SCN5A* mutation to an ICD implantation in an asymptomatic individual and might also lead, after a full disclosure of the data available to the patients, to first implementing a preventive strategy based on β -blockade and possibly LCSD. This approach would still leave open the option of implanting an ICD if deemed appropriate.

Severity of Symptoms and ICD Implantation

We expected to find that the vast majority of ICD patients had suffered an ACA before the implantation. The reality is quite different. Indeed, 56% of the patients had no history of a cardiac arrest, and even more disquieting, 9% were completely asymptomatic.

If it is not the occurrence of an ACA to dictate the decision to implant an ICD, what is it then? Among those with syncope only, the reason was the occurrence of a cardiac event despite therapy for 60%. This is a reasonable approach supported by the guidelines,¹² even though some of us would recommend first proceeding with LCSD.

However, for the relatively large number of patients who had syncope off therapy and for completely asymptomatic patients, a total of 65 (50% of all patients with no prior ACA), it is more difficult to offer an explanation. In approximately two thirds of these cases, specific clinical conditions suggested imminent high risk (eg, very long sudden pauses in LQT3 patients, occurrence of T-wave alternans¹⁶ on therapy, a QTc exceeding 550 milliseconds) and justified these decisions. Other reasons included intolerance to β -blocker therapy mainly because of severe bradycardia, atrioventricular block, documented VT by the implantable loop recorder, or noncompliance with or refusal of therapy. For the remainder, most with a positive family history of SCD and/or a LQT3 genotype and some with inducibility of VF at electrophysiological study, the justification is less straightforward.

It is difficult to quantify the impact of concerns in terms of potential medico-legal implications arising from not having implanted an ICD in the case of a tragic outcome or the pressure posed by parents or patients. Indeed, if a patient with a life-threatening disorder, often with a SCD in a family member, insistently asks for an ICD regardless of his or her recent clinical history, fearing that medical or surgical therapy may be insufficient, then it becomes very difficult for any physician to refuse it. These considerations might have

contributed to our findings. Finally, within the patients with syncope off therapy, it is possible to identify subgroups at either significant or minimal risk of events on therapy.

ICD Effectiveness

The available data do not allow us to assess how many of the treated arrhythmias were destined to terminate spontaneously, and this might lead to overestimation of the number of adequate ICD shocks. Notably, most of the appropriate shocks (55%) occurred in just 21 patients (33% of the total), and 9 of them (43%) had several recurrent episodes fulfilling the definition of arrhythmic storm. Actually, among these 21 patients, 5 had ≥ 40 appropriate shocks. All of them survived a prior ACA (3 of 5 while on therapy), had a QTc > 500 milliseconds (close to or exceeding 600 milliseconds for 4 of 5 [mean, 610 ± 65 milliseconds]), and had events on therapy. In the majority of these patients, both a VT zone (mean cycle length, 319 ± 69 milliseconds; mean detection time, 3.7 ± 3.7 seconds) and a VF zone (mean cycle length, 286 ± 16 milliseconds; mean detection time, 3.6 ± 2.4 seconds) were programmed.

In primary prevention patients, by prolonging the detection duration and increasing the heart rate threshold of tachycardia detection, it is possible to safely and substantially reduce the number of appropriate and inappropriate shocks by allowing spontaneous termination of tachyarrhythmias.¹⁷ Programming the device with a VT zone and a relatively short detection time leads to an overestimation of appropriate ICD shocks and may be contraindicated in LQTS patients who frequently have multiple brief arrhythmic episodes. Furthermore, it is important to avoid unnecessary shocks in LQTS patients because sympathetic hyperactivity after ICD discharge can trigger additional tachyarrhythmias and initiate electric storms. We recommend initially programming only the VF zone at a high rate with a long time for tachycardia detection.

The clinical nature of the scoring system, designed to predict before the ICD implantation the probability of appropriate shocks, precluded the inclusion of ICD programming details. Without reaching significant differences, the exploratory analysis of the potential effect of antibradycardia pacing on outcome suggests the consideration of a lower pacing rate of ≥ 70 bpm and, whenever feasible, a dual-chamber device in patients with a high-risk profile.

ICD Complications

The relatively high rate of inappropriate shocks and complications after ICD implantation increases the morbidity of this treatment modality in LQTS patients and worsens its risk-benefit ratio. Inappropriate shocks were caused mainly by abnormal sensing resulting from either T-wave oversensing or lead failure. The young age at implantation (76% of patients ≤ 40 years of age, 12% ≤ 10 years of age) supports the hypothesis that the high rate of lead failure is attributable to the activity-dependent increased strain on ICD leads. Another cause of inappropriate shocks was supraventricular tachycardia. Besides avoiding unnecessary shocks, prolonging the detection time and increasing the threshold of tachycardia detection may reduce inappropriate shocks

caused by supraventricular or sinus tachycardia, especially in young patients.

We observed 67 adverse events in 58 patients. Of these, the more severe adverse events resulted directly from the implantation surgery such as lead placement issues, infections, and vascular problems. Most of the minor complications were related to lead issues, including conductor fractures, insulation defects, and changes in electric characteristics. Generator-related problems that necessitated reoperation were less common. These findings substantiate the concerns about the long-term impact of implanting an ICD in young LQTS patients, likely to live another 7 to 8 decades after initial device implantation and who would be subject to multiple procedures for generator replacements and lead revisions/extractions with probable complications. This makes the implementation of loose and non-data-based indications for ICD implantation in LQTS patients no longer acceptable.

Study Limitations

The present data have all the limitations inherent in an observational design of a registry-based study. Because these data span 20 years, there was the potential for time-dependent differences relative to the patients' baseline characteristics or the technical features of devices. However, when the major findings were verified separately in those patients who received the ICD during the last 5 years and in all other patients, the only significant differences were a decrease in the number of female patients and LQT2 patients (probably representing the same phenomenon), an increase in double mutations, and an increase in the number of infectious complications possibly related to a trend toward an increase in dual-chamber ICDs.

The 4 variables used in the scoring system to predict the probability of appropriate ICD interventions are inherent characteristics of the same population to which the model was applied. In the absence of a control population, there is no validation of its performance; however, a prior history of ACA, events despite therapy, and a markedly prolonged QTc are all known risk factors in LQTS populations. Age at implantation reflects the age-dependent risk exposure to cardiac events, which is part of the natural history of LQTS.

The multicenter nature of the study might have been a limitation if a single center had quantitatively dominated and thereby possibly skewed the results. Because this was not the case, it is actually a significant strength of the study, which represents the current approach to the problem in Europe and in a few additional countries, not just a single-center experience.

As is typical of this type of study, it is not possible to always be sure that patients with events before ICD or shocks after ICD were receiving adequate doses of β -blockers and/or that they were fully compliant.

Implications for Management

On the basis of these data and in combination with our clinical experience in the management of LQTS patients, the following groups of LQTS patients seem logical candidates for an ICD implantation: (1) all those who have survived an ACA on

therapy; (2) many of those who have survived an ACA off therapy, except those with a reversible/preventable cause, but noting that for most LQT1 grown-up patients, full-dose β -blockers might be sufficient.⁵ On the basis of additional considerations, eg, duration of the QT interval, this may lead to an open discussion with patients and family; (3) patients who continue to have syncope despite full-dose β -blockade whenever the option of LCSD either is not available or is discarded after discussion with the patients; (4) all patients with 2 mutations who continue to have syncope despite β -blockade; and (5) exceptionally, the rare asymptomatic patients with a QTc >550 milliseconds who also manifests signs of high electric instability (eg, T-wave alternans) or other evidence of being at very high risk (eg, very long sinus pauses that might favor early afterdepolarizations).

With the caution necessary when dealing with relatively small subgroups and with a 0 point estimate, patients with an M-FACT score of 0 should receive an ICD only on the basis of very cogent, patient-specific arguments. For them, the odds are not in favor of benefit from the ICD. Finally, we believe that with careful programming (eg, using only the VF zone at high rate, with a long time for tachycardia detection and perhaps antibradycardia pacing), it might be possible to reduce the number of both inappropriate shocks and appropriate but not necessary shocks, with significant benefits for the quality of life of these patients.

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CLINICAL PERSPECTIVE

The key therapies for long-QT syndrome (LQTS) are β -blockers, left cardiac sympathetic denervation (LCSD), and the implantable cardioverter-defibrillator (ICD). The ICD, despite concerns about complications in the young, is being used in a growing number of patients. There are no adequate data on the patient characteristics associated with ICD implantation in clinical practice and on their outcome. We initiated a largely European LQTS ICD Registry. Among the 233 patients enrolled and with a mean follow-up close to 5 years, there was an excess of female patients and of LQT3 patients. Unexpectedly, 9% of the patients were asymptomatic when they received an ICD. Appropriate shocks were received by 28% of patients; adverse events occurred in 25%. We developed a scoring system based on simple, easily available clinical variables to verify possible prediction of appropriate shocks. These were predicted by age <20 years at implantation, a QTc >500 milliseconds, prior cardiac arrest, and cardiac events despite therapy; within 7 years, appropriate shocks occurred in no patients without any of these variables and in 70% of those with all of them. Our data suggest how to identify logical candidates for ICD implantation and indicate that some specific programming features may decrease the rate of unnecessary shocks. The relatively high incidence of complications within 5 years in a relatively young population calls for a reassessment of the criteria for implanting ICDs in LQTS patients. The proposed risk scoring system may increase the probability of a rational decision, balancing safety with quality of life.