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ORIGINAL RESEARCH

Outcome by Sex in Patients With Long QT Syndrome With an Implantable Cardioverter Defibrillator

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BACKGROUND: Sex differences in outcome have been reported in patients with congenital long QT syndrome. We aimed to report on the incidence of time-dependent life-threatening events in male and female patients with long QT syndrome with an implantable cardioverter defibrillator (ICD).

METHODS AND RESULTS: A total of 60 patients with long QT syndrome received an ICD for primary or secondary prevention indications. Life-threatening events were evaluated from the date of ICD implant and included ICD shocks for ventricular tachycardia, ventricular fibrillation, or death. ICDs were implanted in 219 women (mean age 38±13 years), 46 girls (12±5 years), 55 men (43±17 years), and 40 boys (11±4 years). Mean follow-up post-ICD implantation was 14±6 years for females and 12±6 years for males. At 15 years of follow-up, the cumulative probability of life-threatening events was 27% in females and 34% in males (log-rank P=0.26 for the overall difference). In the multivariable Cox model, sex was not associated with significant differences in risk first appropriate ICD shock (hazard ratio, 0.83 female versus male; 95% CI, 0.52–1.34; P=0.47). Results were similar when stratified by age and by genotype: long QT syndrome type 1 (LQT1), long QT syndrome type 2 (LQT2), and long QT syndrome type 3 (LQT3). Incidence of inappropriate ICD shocks was higher in males versus females (4.2 versus 2.7 episodes per 100 patient-years; P=0.018), predominantly attributed to atrial fibrillation. The first shock did not terminate ventricular tachycardia/ventricular fibrillation in 48% of females and 62% of males (P=0.25).

CONCLUSIONS: In patients with long QT syndrome with an ICD, the risk and rate of life-threatening events did not significantly differ between males and females regardless of ICD indications or genotype. In a substantial proportion of patients with long QT syndrome, first shock did not terminate ventricular tachycardia/ventricular fibrillation.

Key Words: female ■ implantable cardioverter defibrillator ■ life threatening events ■ long QT syndrome ■ sex

In patients with congenital long QT syndrome (LQTS), the risk of cardiac events differs by sex and age. Female patients with LQTS have an increased risk for cardiac events in adulthood,[1] whereas males tend to have a higher event rate in childhood.[2,3] During puberty, the QT interval in males tends to shorten, whereas in females, there is no significant difference in QT duration over time, resulting in a longer QT interval in adult women compared with adult men.[4] Previous observations[3,5] showed that males with LQTS have a higher risk and earlier onset of cardiac events than females before the age of 16 years. In adulthood (age 18–40 years), there is a sex-related difference: female patients with LQTS experience more events than males.[3,5,6] The sex-specific risk of cardiac events is further influenced by LQTS genotype and QTc duration, and this complex relationship between age, sex, genotype, and QTc duration may influence the clinical

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CLINICAL PERSPECTIVE

What Is New?

- Implantable cardioverter defibrillator (ICD) was significantly more frequently implanted in females than males, although the distribution of females and males is similar in a large long QT syndrome (LQTS) registry.
- Among patients with LQTS at high enough risk to receive an ICD, the risk and rate of life-threatening cardiac events (aborted cardiac arrest, LQTS death, or an appropriate ICD shock) did not significantly differ between males and females regardless of ICD indications or genotype.
- Incidence of inappropriate ICD shocks was higher in males versus females, predominantly attributed to atrial fibrillation, and in a substantial proportion of patients with LQTS, first shock did not terminate ventricular tachycardia/ventricular fibrillation.

What Are the Clinical Implications?

- Our data can be used for improved risk stratification for life-threatening cardiac events in patients with high-risk LQTS implanted with an ICD.
- The high frequency of ineffective and inappropriate ICD therapies, together with lower men referral for ICD, raise important clinical concerns in the LQTS patient population and require further research to optimize patients' management.

Nonstandard Abbreviations and Acronyms

LQTS	long QT syndrome
LTE	life-threatening event

course of the disease in patients with LQTS and therapeutic decisions, including receipt of an implantable cardioverter defibrillator (ICD).[6,7]

The prospective Rochester LQTS-ICD registry provided a unique opportunity to assess whether a patient's sex influences outcome in patients with high-risk LQTS with ICD. The specific aims of the present study were to (1) compare the baseline clinical characteristics of men and women with LQTS and an ICD, (2) compare the incidence and risk of life-threatening events (LTE) in both groups, and (3) identify unique risk factors associated with appropriate and inappropriate ICD shocks by sex in patients with LQTS.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

The Rochester-based LQTS registry includes detailed clinical, pharmacologic, and genetic information about international LQTS probands and their affected and unaffected family members.[8] The LQTS-ICD registry is a prospective registry of 360 patients from the general LQTS registry that has further information regarding ICD programming, interrogations, and arrhythmias. The study population consisted of all 360 patients from the prospective Rochester LQTS-ICD registry with an implanted ICD. The LQTS registry is approved by the University of Rochester Research Subject Review Board (RSRB00025305). All participants gave informed consent. Clinical information was obtained using prespecified data forms, with follow-up information acquired annually. The baseline ECG was used for QTc and heart rate measurements. Indications for ICD shock therapy were categorized according to the history preceding ICD implantation. The follow-up interval (follow-up is annual) began on the day of the ICD implantation and continued until device removal or deactivation (if not reimplanted) or to age 50 (to avoid ischemic heart disease becoming a competing risk factor for ventricular arrhythmia). Results of genetic testing were available in about 60% of the studied patients. Subgroups of children (age <18 years) and adults (age ≥18 years) were analyzed separately by sex.

Device Interrogation

ICD interrogation data were collected periodically and adjudicated by 2 physicians (S.R., W.Z.) for rhythm diagnosis and to determine the appropriateness of ICD shock therapy. In the majority of cases, electrophysiologist's written notes and interpretation of arrhythmia and ICD therapy without accompanying electrograms were analyzed. Initial ICD programming parameters and changes in ICD programming over time were not available in a majority of patients.

Outcome Measures and Genetic Testing

The primary outcome of the current study was the occurrence of a first LTE defined as aborted cardiac arrest, LQTS-related death, or appropriate ICD shock). This information is based on both the reported information from the registry regular follow-up and the analysis of electrograms. The effect of sex on the primary end point was further tested in genotype-positive long QT syndrome type 1 (LQT1), long

QT syndrome type 2 (LQT2), and long QT syndrome type 3 (LQT3) patients separately. Risks of first appropriate ICD shock therapy, recurrent ICD therapies, and the response to ICD therapies by sex were also evaluated. The triggered appropriate events were categorized into 4 subgroups by the trigger reported to be associated with that event, including (1) rest, defined as shock that occurred during rest or sleep without known trigger; (2) arousal triggers, defined as loud noise or acute emotional arousal; (3) exercise triggers, defined as vigorous physical activity or swimming; and (4) other specific triggers, comprising a heterogeneous group of the remaining identified triggers, including fever or illness, bathing or showering, pregnancy/childbirth or menstrual related, medication initiation or change, extreme heat, special diet or eating disorder, and surgery. The risk and reasons for inappropriate ICD shock therapy were also compared between females and males.

Shock failure was defined if the first shock did not terminate the underlying arrhythmia. This could be attributed to failure of the defibrillator to terminate the arrhythmia but also to recurrent arrhythmia within minutes or seconds following the shock.

ICD indication was categorized as primary prevention or secondary prevention.

Statistical Analysis

Baseline clinical characteristics were compared between males and females using the χ^2 test or Fisher exact test for categorical variables and the *t* test for continuous variables. The cumulative probability of LTE and ICD shock therapies was analyzed using Kaplan–Meier method with comparisons of cumulative events rates by the log-rank test. Multivariable Cox regression models adjusted for β-blocker therapy (time-dependent variable) and QTc (Bazett formula) at baseline were performed to evaluate the effect of sex on different outcomes. A similar model stratified by childhood versus adolescence was used to avoid violation of the results. Event rates per 100 patient-years were calculated by dividing the total number of all events by the patient-years of follow-up and multiplying the results by 100, with comparisons of the event rates by the negative binominal regression. All statistical tests were 2-sided, and a *P* value of <0.05 was considered statistically significant. Analyses were carried out with SAS software (version 9.4, SAS Institute, Cary, NC).

RESULTS

Patients' baseline clinical characteristics, medical treatment, and indications for an ICD stratified by sex are shown in Table 1. In the general LQTS registry, the distribution of female versus male is similar because of the genetic nature of the disease (13 141 females and 12 879 males). ICD was significantly more frequently implanted in females than males (2% versus 0.7%; *P*<0.0001, respectively). In our cohort of patients with LQTS with an ICD, there were 219 women (mean age 38±13 years at implantation), 46 girls (age at implantation 12±5 years), 55 men (age at implantation 43±17 years), and 40 boys (age at implantation 11±4 years). In all, females comprised 74% of the entire cohort. Females were significantly older than males at the time of ICD implantation (mean age 34±16 years versus 30±16 years, respectively; *P*=0.009). Median date of implantation among females was August 2002 (December 1986–January 2017) and was September 2003 (December 1990–September 2013) among males. The mean QTc interval was similar in both males and females, 502±61 milliseconds in females and 504±64 milliseconds in males. The frequency of genotype-positive LQT1, LQT2, and LQT3 patients was also similar according to sex.

Aborted cardiac arrest for secondary prevention was the indication for ICD placement in 26% of females and 20% of males. In both groups, the most common indication for ICD implantation was for suspected arrhythmogenic syncope and did not differ by sex nor by prior use of a β-blocker drug (Table 1).

Life-Threatening Cardiac Events

During the mean follow-up of 13±6 years, risk of first LTE did not differ significantly by sex: 64 (24%) in females and 27 (28%) in males (log-rank *P*=0.41). At 15 years (Figure 1A), the cumulative probability of LTE was 27% in females and 34% in males (log-rank *P*=0.37 for the overall difference). Similar associations between sex and LTE were observed when these outcomes were analyzed according to patient age at implantation. Accordingly, in children (implanted before the age of 18 years), at 15 years from implantation the cumulative incidence of LTE was 35% in females and 34% in males (*P*=0.87 for the overall comparison). Similar findings were observed in adults: at 15 years, the cumulative incidence of LTE was 36% in males compared with 24% in females (*P*=0.55 for the overall comparison; Figure 1B and 1C).

The cumulative probability of a first appropriate ICD shock did not differ by sex (Figure 2). By 15 years, 25% of females and 32% of males had received an appropriate ICD shock (log-rank *P*=0.34).

The cumulative probabilities of an LTE did not significantly differ between females versus males in each tested genotype group: LQT1, LQT2, and LQT3 (Figure S1A through S1C). Moreover, it is worth mentioning that the vast majority of the LTE were appropriate shocks. LQTS-related death was seen in only 2 patients: 1 male and 1 female.

Table 1. Clinical Characteristics of Females Versus Males With LQTS With ICDs

	Female, N=265		Male, N=95		*P* Value
No. of patients in the LQTS registry	13 141		12 879		0.93
Clinical characteristics	Children (n=46)	Adults (n=219)	Children (n=40)	Adults (n=55)	
Age of first CE, mean±SD, y	9±6	24±15	7±5	29±23	0.012
Median date of enrollment*	April 2005	June 2005	February 2005	April 2007	
Age at ICD, mean±SD, y	12±5	38±14	11±4	43±17	0.009
Median date of ICD implantation†	July 2002	October 2002	August 2002	April 2005	
Median length of follow-up (IQR), y	14 (9–18)	14 (9–18)	12 (8–15)	15 (12–18)	
QTc, mean±SD, milliseconds	516±76	499±57	519±72	492±55	0.98
LQT1, n (%)	10 (29)	39 (25)	11 (37)	2 (6)	0.38
LQT2, n (%)	9 (26)	72 (47)	9 (30)	22 (67)	0.42
LQT3, n (%)	4 (12)	12 (8)	3 (10)	5 (15)	0.33
Treatment before ICD, n (%)					
BB	38 (83)	165 (75)	37 (93)	34 (62)	0.71
Pacemaker	6 (13)	37 (17)	4 (10)	5 (9)	0.11
LCTD	1 (2)	8 (4)	0	1 (2)	0.47
Sodium channel blockers	2 (4)	8 (4)	3 (8)	2 (4)	0.55
Indications for ICD, n (%)					
Ventricular tachycardia‡	7 (15)	51 (23)	5 (13)	5 (9)	0.23
Syncope on BB	14 (30)	67 (31)	12 (30)	13 (24)	0.54
Syncope off BB	20 (44)	110 (50)	16 (40)	23 (42)	0.81
Aborted cardiac arrest	8 (17)	71 (32)	6 (15)	15 (27)	0.56
Torsades de pointes	3 (7)	38 (17)	6 (15)	7 (13)	0.54
Treatment after ICD, n (%)					
BB	45 (98)	200 (91)	39 (98)	47 (85)	0.55
Sodium channel blockers	5 (11)	28 (13)	7 (18)	6 (11)	0.76

P value is for the comparison between males vs females. BB indicates β-blocker; CE, cardiac event; ICD, implantable cardioverter defibrillator; LCTD, left cardiac sympathetic denervation;LQT1, long QT syndrome type 1; LQT2, long QT syndrome type 2; LQT3, long QT syndrome type 3; and LQTS, long QT syndrome.

*Enrollment date range in females, February 2000 to October 2018; males, March 2000 to December 2017.

†ICD implantation date range in females, December 1986 to January 2017; males, December 1990 to September 2013.

‡Sustained ventricular tachycardia other than torsades de pointes.

Appropriate ICD Shock Therapy in Patients With LQTS by Sex

In a multivariable Cox model (Table 2), QTc ≥550 milliseconds was associated with increased risk for first appropriate ICD shock therapy (hazard ratio, 2.3; 95% CI, 1.4–3.6; *P*=0.0004). According to this multivariable model when also adjusted for age, patient sex was not associated with the risk of first appropriate ICD shock therapy. Similar results were obtained for the children/adolescence stratified model (Table S1).

The cumulative probability of a first appropriate ICD shock in patients implanted for secondary prevention (aborted cardiac arrest) did not significantly differ between females and males (35% and 36%, respectively, at 15 years, log-rank *P*=0.77; Figure S2A). Among ICD recipients with an indication of primary prevention, the cumulative probability of LTE did not significantly differ between females and males (24% versus 26%, respectively, log-rank *P*=0.83; Figure S2B).

The proportion of patients with a first appropriate ICD shock did not significantly differ between males and females (Table 3). Among females, 61 patients had 675 appropriate shocks attributed to ventricular tachycardia or ventricular fibrillation, and 25 males had 196 appropriate shocks attributed to ventricular tachycardia or ventricular fibrillation. The rate of appropriate ICD shocks per 100 person-years was 20 in females versus 17 in males (*P*=0.72).

In the ICD registry, 80% of the patients have reported on the preceding trigger for appropriate ICD shock. In both sexes, the leading trigger was rest/sleep (41% of the appropriate shocks in females and 47% in males).

Failure of Appropriate ICD Shock and/or Recurrent Arrhythmia

The first ICD shock was unsuccessful in terminating a detected ventricular arrhythmia in a significant portion

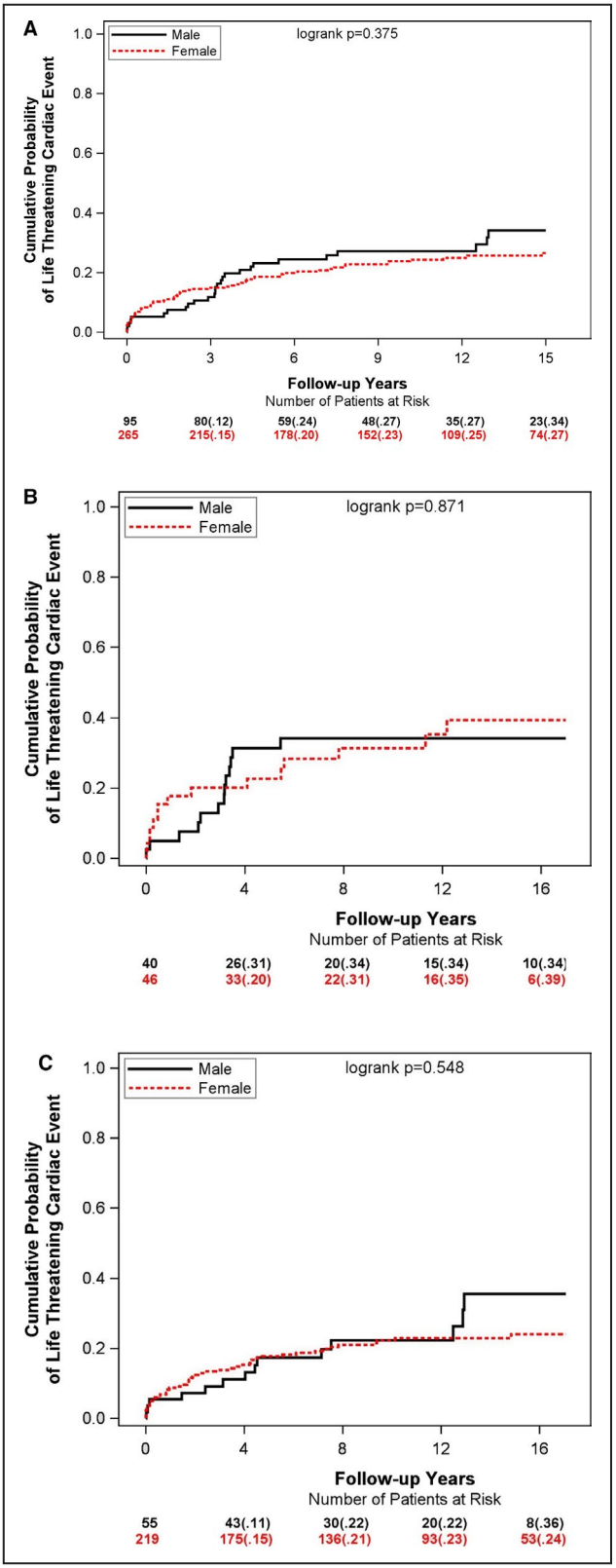

Figure 1. Cumulative probability of life-threatening cardiac events (aborted cardiac arrest, long QT syndrome–related death, or appropriate defibrillator shock) by sex.
A, All patients; **B**, children only; **C**, adults only.

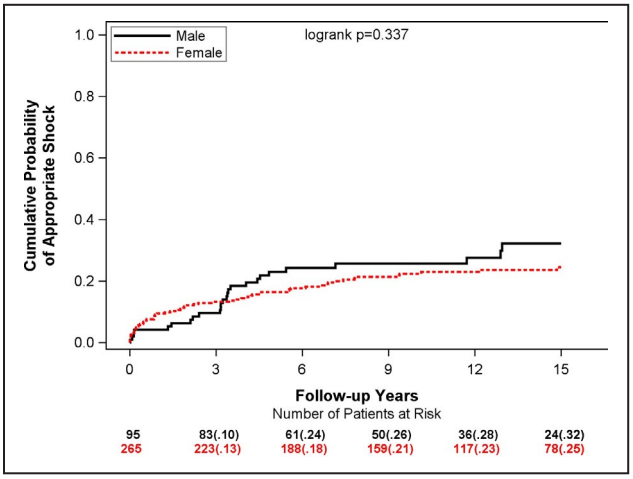

Figure 2. Cumulative probability appropriate implantable cardioverter defibrillator shock by sex in patients with long QT syndrome.

of both male (n=16/25, 62%) and female (n=29/61, 48%) patients (*P*=0.25). When data were analyzed for all recurrent ICD shocks combined (among those who's first shocks did not terminate the arrhythmia), the ICD shock failed to terminate the ventricular arrhythmia in 65% of episodes in females and similarly in 61% of episodes in males (*P*=0.39). In both groups, 4% of the episodes (defined as within 1 hour) needed more than 5 shocks to terminate the arrhythmia. In a multivariable Cox model adjusted for relevant covariates, QTc ≥550 milliseconds was associated with 2.8 increased risk (*P*=0.04) for nonresponse to ICD shocks in terminating the underlying ventricular arrhythmia.

Inappropriate ICD Shock Therapy

During the mean follow-up of 13±6 years, the risk of a first inappropriate ICD shock therapy did not significantly differ by sex: 61 (23%) females and 27 (28%) males (log-rank *P*=0.41). At 15 years (Figure 3), the cumulative probability of inappropriate ICD shock therapy was 24% in females and 34% in males (log-rank *P*=0.18 for the overall comparison).

T wave oversensing was observed in 12% of females and 19% of males and was the leading cause of inappropriate ICD shock therapy per episode (Table 4). Atrial fibrillation/flutter occurred in 15 male patients (16%) compared with only 6 patients (2%) in the female group (*P*=0.001).

Overall, the number of patients with inappropriate ICD shock episodes did not significantly differ between females and males (1.8 versus 2.1 per 100 patient-years, respectively, *P*=0.39). However, males had significantly more recurrent inappropriate ICD shock episodes than females (Table 5; 4.2 versus 2.7 per 100 patient-years, respectively; *P*=0.018).

Table 2. Multivariable Cox Model Predicting First Appropriate ICD Shock

Variable	Hazard Ratio	95% CI	*P* Value
Female sex	0.83	0.52–1.34	0.47
Age at implantation, per y	0.99	0.98–1.12	0.46
QTc ≥550 milliseconds	2.34	1.43–3.62	<0.001
Prior syncope while on BB	1.29	0.77–1.97	0.33
Time-dependent BB	0.67	0.40–1.13	0.13

BB indicates β-blocker; and ICD, implantable cardioverter defibrillator.

DISCUSSION

This study evaluated the incidence of appropriate and inappropriate ICD shocks in patients with high-risk LQTS stratified by sex. Interestingly, ICD was significantly more frequently implanted in females than males, although the distribution of females and males is similar in the large LQTS registry. Despite the general impression that adult females with LQTS have a higher risk of LTE than males, our study indicates that when selected high-risk patients are considered, the risk of LTE does not significantly differ by sex. This observation challenges the bias that men with LQTS qualifying for an ICD might be at lower risk of ICD therapies than women with LQTS. Men and women with LQTS qualifying for an ICD for primary or secondary prevention indications do not differ in their subsequent risk of recurrent arrhythmias resulting in ICD treatment.

Table 3. Appropriate ICD Shocks in LQTS Females Versus Males

All Patients with ICDs	Females, N=265	Males, N=95	*P* Value
Patients with first appropriate ICD shock, n (%)	61 (23)	26 (27)	0.41
No. of patients with first shock terminating VT/VF, n (%)	32 (52)	9 (38)	0.25
No. of patients in whom first shock did not terminate VT/VF, n (%)	29 (48)	16 (62)	0.25
VT/VF episodes* that needed more than 2 shocks, n (%)	48 (7)	20 (10)	0.17
VT/VF episodes that needed more than 5 shocks, n (%)	26 (4)	7 (4)	1.00
No. of appropriate shocks attributed to VT/VF	675	196	
No. of appropriate shocks that did not terminate the VT/VF arrhythmic event† (% all shocks)	436 (65)	120 (61)	0.39
Preceding triggers for first appropriate ICD shock, n (%)†			
Rest or sleep	20 (42)	9 (47)	0.78
Emotional or vocal arousal	3 (6)	1 (5)	0.92
Vigorous exercise activity	13 (26)	4 (21)	0.76
Other specific triggers	13 (26)	5 (26)	0.91

ICD indicates implantable cardioverter defibrillator; LQTS, long QT syndrome; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*One episode is defined as within a 1-hour period.

†For example, a patient can have a VT storm and can receive 8 shocks within 20 minutes, however, the arrhythmia continues after the shock. After 22 minutes from the start of arrhythmia, the ninth shock that was delivered terminated the arrhythmia. In this case, we calculated for 8 events in which the shock did not terminate the arrhythmia.

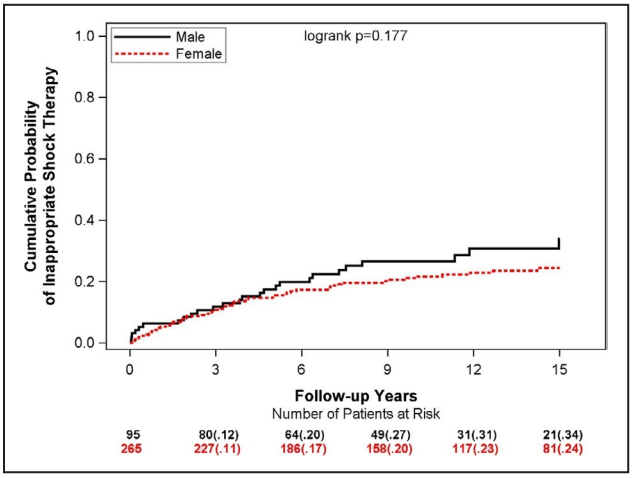

Figure 3. Cumulative probability of inappropriate implantable cardioverter defibrillator shocks by sex in patients with long QT syndrome.

Second, the rate of failure of the first ICD shock and/or recurrent arrhythmia is high, as more than half of the episodes do not convert ventricular tachyarrhythmias, a failure rate that did not differ by sex. Third, inappropriate shocks are frequent and attributed most often to T wave oversensing in both men and women. Conversely, the rate of inappropriate ICD shocks attributed to atrial fibrillation or atrial flutter was significantly higher in males than females.

Beginning at puberty, sex-related differences in the QT interval become apparent on the surface ECG, and differences in cardiac repolarization between men and women become noticeable in healthy subjects and in patients with LQTS.[4,9] Females have longer QTc intervals, and sex is considered to be an important independent risk factor in the evaluation of cardiac events among patients with LQTS.[3] Results from prior studies demonstrate that during childhood, male patients with LQTS have a higher event rate than females, whereas after puberty, risk reversal occurs, and females maintain a higher risk than males during adulthood.[3,8,10] Moreover, the role of female sex varies strongly based on the genotype of the disease and the definition of cardiac events. Previous studies have demonstrated that among LQT2 patients, female sex was associated with an increased risk for cardiac events,[11] whereas it was associated with a decreased risk in LQT1 patients.[12] In our study, however, we were unable to demonstrate significant differences in the rate of LTE between males and females. Our results showed consist

Table 4. Reasons for Inappropriate Shock Episodes* per Patient by Sex

Variable	Females, N=265	Males, N=95	*P* Value
Patients with inappropriate ICD therapy, n (%)	61 (23)	27 (28)	0.39
Patients with T wave oversensing, n (%)	33 (12)	18 (19)	0.72
Patients with lead malfunction, n (%)	26 (10)	11 (12)	0.33
Patients with atrial fibrillation/flutter, n (%)	6 (2)	15 (16)	0.001
Patients with supraventricular tachycardia, n (%)	23 (9)	7 (7)	0.09
Patients with "other reasons," n (%)	5 (2)	5 (5)	0.51

ICD indicates implantable cardioverter defibrillator.
*Episode is defined as within a 1-hour period.

findings when also stratified by LQTS genotype. In this study, follow-up began upon ICD implantation, at which time females were older than males (34 versus 30 years, *P*=0.009). Yet event rates (for all end points together or each separately) did not significantly differ between groups during follow-up. The results were similar when we tested for the effect of sex in children (implanted before the age of 18 years) and adults separately.

What Explains the Apparent Different Results in the Current Study?

The fact that ICD was significantly more frequently implanted in females than males although the distribution of females and males is similar in the large LQTS registry supports previous observations that generally speaking, female subjects are at higher risk than males for cardiac events. Preselection of high-risk patients, many of them with prior aborted cardiac arrest, may contribute to the apparent absence of significant differences in the risk of cardiac events between males and females with LQTS during follow-up. Patients with LQTS with ICD usually have a more severe presentation of the disease that merits such therapy, which is associated with a significant risk for cardiac events[13]; accordingly, both males and females are considered high-risk patients and have increased risk for LTE, in which the effect of sex becomes less important.

Ineffective ICD Shock Therapy in Terminating Ventricular Tachycardia/ Ventricular Fibrillation

Failure of ICD shock therapy to terminate detected episodes of ventricular tachycardia/ventricular fibrillation is generally infrequent among ICD recipients including those with ischemic and nonischemic cardiomyopathies.[14,15] However, in patients with Brugada syndrome, or hypertrophic cardiomyopathy, a high defibrillation threshold (minimum amount of energy needed to terminate the arrhythmia) has been reported.[16–19]

Our study found that in more than half of the patients with LQTS, the first ICD shock did not terminate the detected ventricular arrhythmia. This might be secondary to true failure of the ICD to terminate the arrhythmia and/or to a storm of arrhythmias. Patients with LQTS and patients with inherited catecholaminergic polymorphic ventricular tachycardia have attenuation of localized neural/sympathetic chain release of norepinephrine and an increased ventricular fibrillation threshold (the minimum electrical value able to trigger fibrillation), which might contribute to difficulties

Table 5. Number of Inappropriate ICD Shocks in Females Versus Males and the Underlying Etiology (per 100 Patient-Years)

	Female, N=265	Male, N=95	*P* Value
No. of patients with inappropriate shocks (%)	61 (23)	27 (28)	
No. of inappropriate shock episodes	93	56	
No. of patients with inappropriate shock episode per 100 patient-years	1.8	2.1	0.39
No. of inappropriate shock episodes per 100 patient-years	2.7	4.2	0.018
No. of inappropriate shock episodes per 100 patient-years attributed to			
Lead malfunction	0.8	0.8	0.82
Atrial fibrillation/flutter	0.1	1.1	0.002
Supraventricular tachycardia	0.7	0.5	0.79
T wave oversensing	1	1.4	0.43
Other	0.1	0.3	0.68

ICD indicates implantable cardioverter defibrillator.

in converting their fast ventricular rhythms. This important observation warrants further investigation into the device programming and the nature of underlying arrhythmias.

Role of the T Wave Oversensing and Atrial Fibrillation/Flutter in Patients With LQTS With ICD

LQTS is associated with abnormal T wave morphology, and qualitatively described T waves have been identified for each major LQTS subtype, which might lead to differences in the incidence of T wave oversensing by an ICD within this population.[20,21] Our study confirms that T wave oversensing is a leading cause for inappropriate ICD shocks. However, such oversensing resulting in an inappropriate shock was seen in all genotypes and did not significantly differ between males and females.

In our study, both males and females had a significant number of inappropriate ICD shocks attributed to atrial fibrillation. Such an association between atrial fibrillation and LQTS was reported in previous studies. In the current study, at the end of follow-up (similar duration for both sexes) the rate of new atrial fibrillation was significantly higher in male patients than females (16% versus 2%; P=0.001) despite being younger than females. This observation is consistent with previous studies, which found that the estimated prevalence of atrial fibrillation is significantly lower in females than in males and that male subjects are usually diagnosed with atrial fibrillation at a younger age than females.

Limitations

The modest size of the current study cohort may have limited the analytical power to detect differences according to sex. We also had limited systematic data on ICD programming and thus are unable to provide specific recommendations regarding ICD programming that might enhance shock efficacy and/or minimize inappropriate shocks in this population. Furthermore, the electrograms of the arrhythmia episodes were available in only 16% of the reports, making it difficult to distinguish between true failure of ICD shock and/or recurrent of the ventricular arrhythmia in the entire cohort. Nevertheless, in these cases without electrograms we had access to electrophysiologist's interpretation of arrhythmia and therapy. Yet our results remained similar when analyzing only patients with available electrograms or those with reports only.

Importantly, the rate results (Tables 3 through 5) apply to the date of the last follow-up or at the age of 50 (prespecified as detailed in the Methods section), therefore our rates may not be applicable for children. Yet the Cox model was stratified by childhood versus adolescence and obtained consistent results.

CONCLUSIONS

Among patients with LQTS at high enough risk to receive an ICD, the probability of life-threatening cardiac events following defibrillator implantation did not differ between males and females. Moreover, the risk for LTE did not significantly differ according to genotype or the underlying indication for the ICD implantation. The high frequency of ineffective and inappropriate ICD therapies raise important clinical concerns in the LQTS patient population and requires further research to optimize patients' management.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Table S1
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Multivariable Cox Model Predicting First Appropriate ICD Shock Stratified by Childhood vs. Adolescence.

Variables	Hazard Ratio	95% Confidence Interval	*P* Value
Female sex	0.81	0.50-1.31	0.38
Age at implantation (per year)	0.99	0.97-1.02	0.38
QTc ≥ 550 ms	2.33	1.48-3.68	<0.001
Prior syncope while on BB	1.32	0.81-2.14	0.26
Time dependent BB	0.66	0.39-1.12	0.13

BB – beta-blockers

Figure S1A. Cumulative probability of life threatening cardiac events (aborted cardiac arrest, LQTS related death or appropriate defibrillator shock) by sex in LQT1 patients.

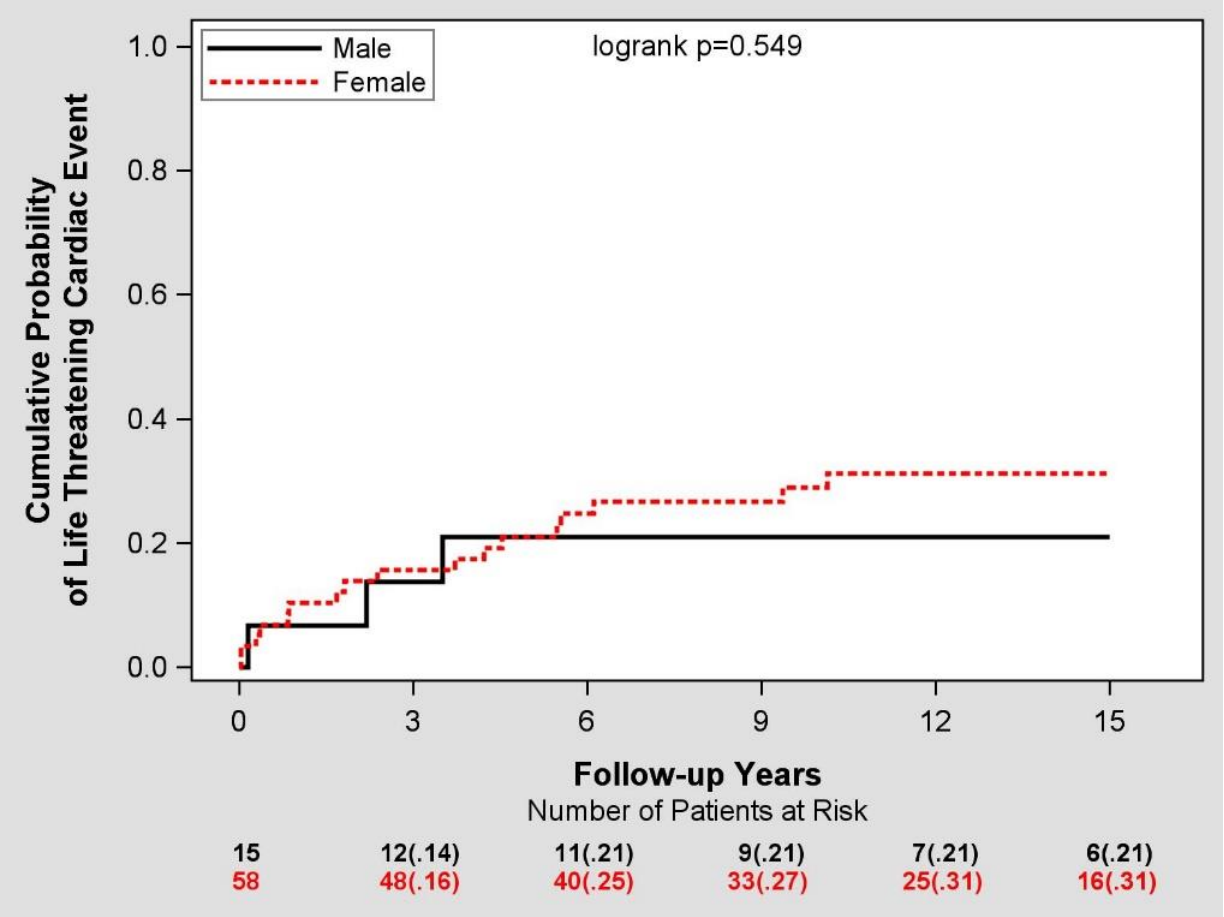

Figure S1B. Cumulative probability of life threatening cardiac events (aborted cardiac arrest, LQTS related death or appropriate defibrillator shock) by sex in LQT2 patients.

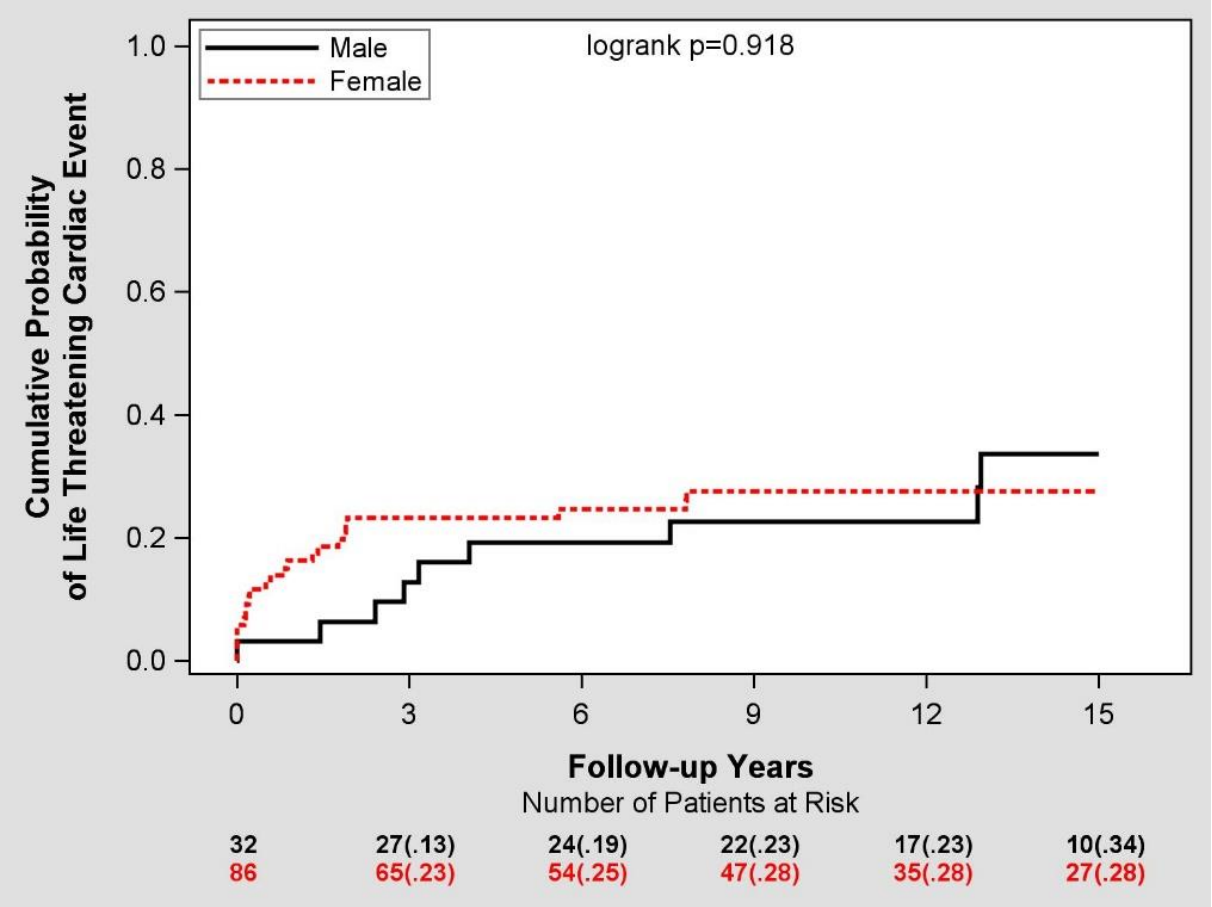

Figure S1C. Cumulative probability of life threatening cardiac events (aborted cardiac arrest, LQTS related death or appropriate defibrillator shock) by sex in LQT3 patients.

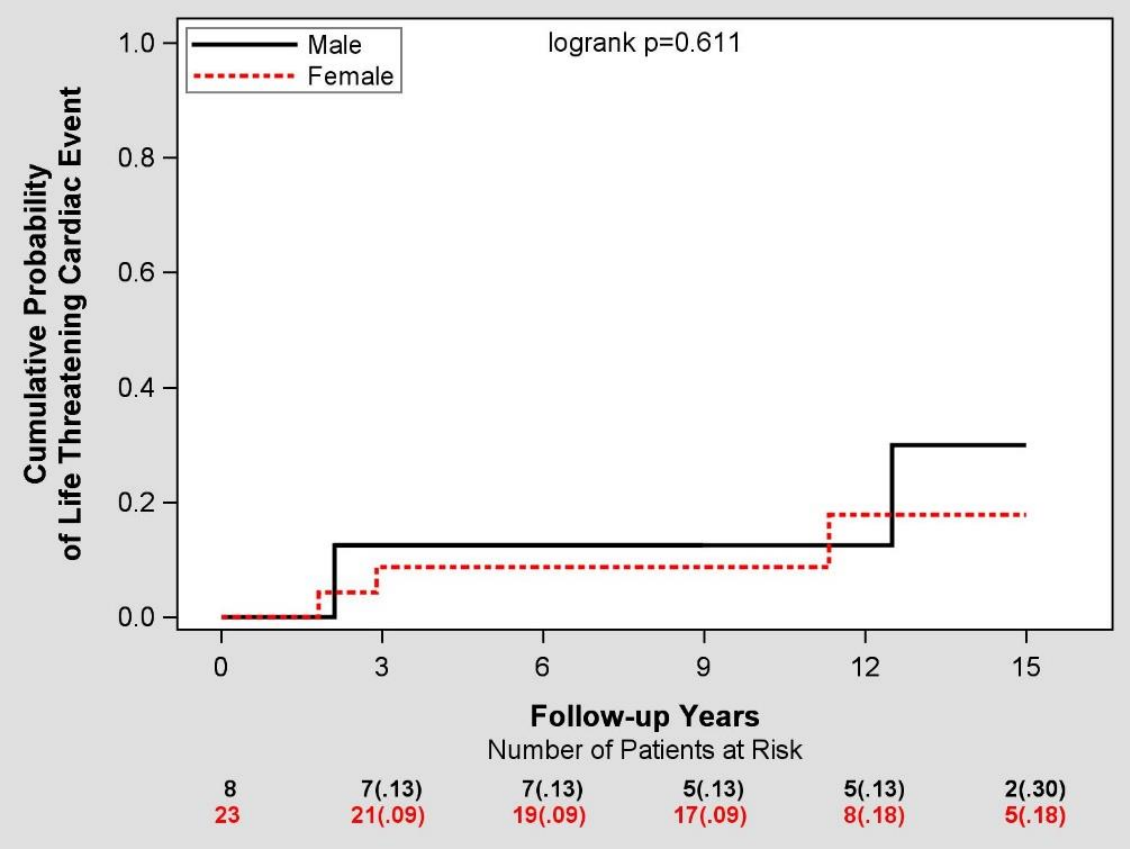

Figure S2A. Cumulative probability of life threatening cardiac events (aborted cardiac arrest, LQTS related death or appropriate defibrillator shock) by sex in patients with LQTS and ICD implanted for secondary prevention.

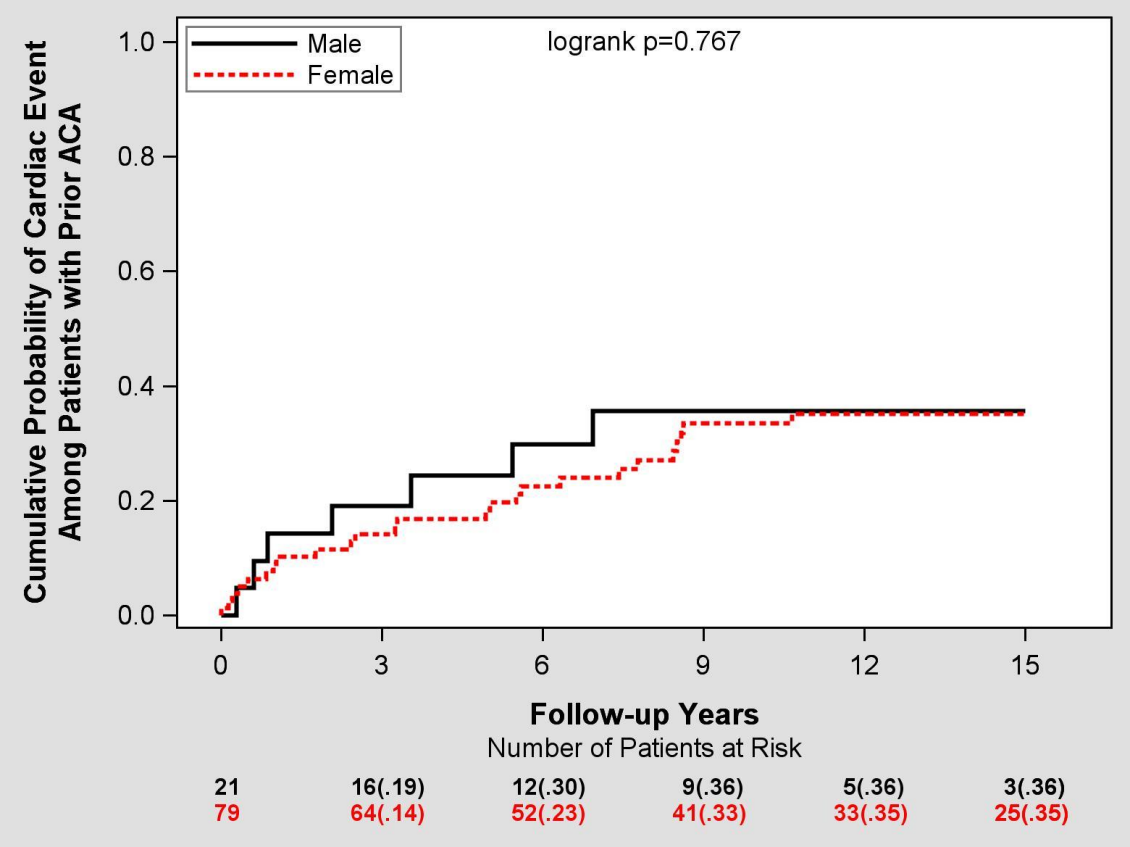

Figure S2B. Cumulative probability of life threatening cardiac events whichever occurs first (aborted cardiac arrest, LQTS related death or appropriate defibrillator shock) by sex in patients with LQTS and ICD implanted for primary prevention.