EP IMAGE

Remission of Abnormal Conduction and Repolarization in the Right Ventricle After Chemotherapy in Patients With Anterior Mediastinal Tumor

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A 22-year-old man with no significant past medical history presented with dry cough that lasted for a couple of months. The patient denied accompanying shortness of breath, palpitation, edema, high fever, or syncope. He had no family history of sudden death. On examination, he was afebrile with a blood pressure of 106/63 mm Hg, pulse rate of 88 beats/min, and normal oxygen saturation. His heart sound was normal without a pericardial rub. ECG (Fig. 1A) displayed a terminal r wave (arrow a) and ST-segment elevation (arrow b) followed by negative deflection of T wave (arrow c) in lead V_1. Chest computed tomography (Fig. 1A) revealed the existence of demarcated tumor in the anterior mediastinal space that attached to the pericardium in front of the right atrium and ventricle. The tumor encompassed the right ventricular outflow tract (arrow) but did not show invasion into the intrapericardial space. The tumor was histologically diagnosed with the large B cell lymphoma from a specimen obtained by needle biopsy. He started to undergo chemotherapy including cyclophosphamide, vincristine, doxorubicin, rituximab, and prednisolone. Two months after the chemotheraphy, chest computed tomography confirmed that the lymphoma size was reduced, which was almost invisible (Fig. 1B). At that time, ECG showed the disappearance of a late r′ wave and ST-segment elevation in lead V_1 (Fig. 1B). These findings indicate that coinciding with the shrinkage of anterior mediastinal tumor, conduction disturbance, and abnormal repolarization in the right ventricle were resolved. No life-threatening arrhythmic event occurred during the follow-up.

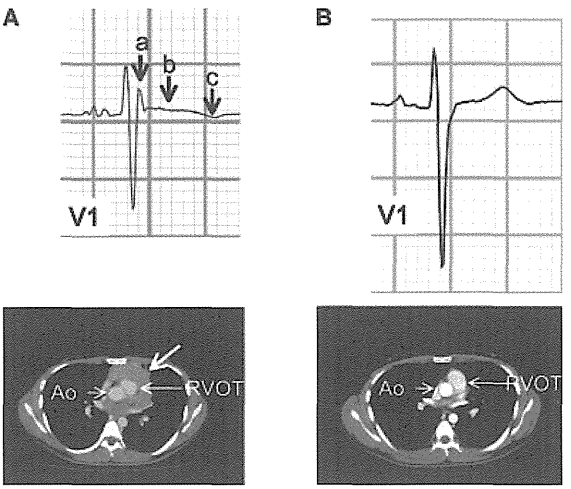

Figure 1. *A and B: ECG recording in lead V_1 and contrast-enhanced computed tomography scan before and after chemotherapy, respectively. Ao = Aorta; RVOT = right ventricular outflow tract.*

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Risk for Life-Threatening Cardiac Events in Patients With Genotype-Confirmed Long-QT Syndrome and Normal-Range Corrected QT Intervals

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Objectives This study was designed to assess the clinical course and to identify risk factors for life-threatening events in patients with long-QT syndrome (LQTS) with normal corrected QT (QTc) intervals.

Background Current data regarding the outcome of patients with concealed LQTS are limited.

Methods Clinical and genetic risk factors for aborted cardiac arrest (ACA) or sudden cardiac death (SCD) from birth through age 40 years were examined in 3,386 genotyped subjects from 7 multinational LQTS registries, categorized as LQTS with normal-range QTc (≤440 ms [n = 469]), LQTS with prolonged QTc interval (>440 ms [n = 1,392]), and unaffected family members (genotyped negative with ≤440 ms [n = 1,525]).

Results The cumulative probability of ACA or SCD in patients with LQTS with normal-range QTc intervals (4%) was significantly lower than in those with prolonged QTc intervals (15%) ($p < 0.001$) but higher than in unaffected family members (0.4%) ($p < 0.001$). Risk factors ACA or SCD in patients with normal-range QTc intervals included mutation characteristics (transmembrane-missense vs. nontransmembrane or nonmissense mutations: hazard ratio: 6.32; $p = 0.006$) and the LQTS genotypes (LQTS type 1:LQTS type 2, hazard ratio: 9.88; $p = 0.03$; LQTS type 3:LQTS type 2, hazard ratio: 8.04; $p = 0.07$), whereas clinical factors, including sex and QTc duration, were associated with a significant increase in the risk for ACA or SCD only in patients with prolonged QTc intervals (female age >13 years, hazard ratio: 1.90; $p = 0.002$; QTc duration, 8% risk increase per 10-ms increment; $p = 0.002$).

Conclusions Genotype-confirmed patients with concealed LQTS make up about 25% of the at-risk LQTS population. Genetic data, including information regarding mutation characteristics and the LQTS genotype, identify increased risk for ACA or SCD in this overall lower risk LQTS subgroup. (J Am Coll Cardiol 2011;57:51–9) © 2011 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ACA = aborted cardiac arrest
ECG = electrocardiographic
LQTS = long-QT syndrome
LQT1 = long-QT syndrome type 1
LQT2 = long-QT syndrome type 2
LQT3 = long-QT syndrome type 3
QTc = corrected QT interval
SCD = sudden cardiac death

Congenital long-QT syndrome (LQTS) is an inherited channelopathy characterized by a prolonged corrected QT interval (QTc) at rest that is associated with an increased predisposition for polymorphic ventricular arrhythmias and sudden cardiac death (SCD) in young subjects without structural heart disease (1). To date, more than 500 mutations have been identified in 12 LQTS-susceptibility genes, with the long-QT syndrome type 1 (LQT1), long-QT syndrome type 2 (LQT2), and long-QT syndrome type 3 (LQT3) genotypes constituting more than 95% of genotype-positive LQTS and approximately 75% of all LQTS (2). Risk assessment in affected patients with LQTS relies primarily on a constellation of electrocardiographic (ECG) and clinical factors, including QTc interval and age-sex interactions (3–6). In addition, there is increasing evidence that genetic information and the molecular and cellular properties of the LQTS-causative mutation may identify subjects with increased risk for cardiac events (7–10). Despite these recent advances, however, currently there are limited data regarding the clinical course and risk factors for life-threatening events in patients with LQTS with normal resting QTc values, so-called silent mutation carriers, concealed LQTS, or normal–QT interval LQTS.

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In the present study we used combined data from 7 national LQTS registries to: 1) compare the clinical courses of patients with LQTS and normal-range QTc intervals to those of patients with prolonged QTc intervals and of genotype-negative unaffected family members; and 2) identify specific clinical and genetic risk factors for life-threatening cardiac events in patients with LQTS with normal-range QTc intervals.

Methods

Study population. The study population comprised 3,386 genotyped subjects drawn from the Rochester, New York, enrolling center (center 1) of the International LQTS Registry (n = 2,630), the Netherlands LQTS Registry (n = 391), and the Japanese LQTS Registry (n = 205), as well as from data submitted by other investigators specifically for this collaborative mutation analysis project from Denmark (n = 90), Italy (n = 28), Israel (n = 25), and Sweden (n = 17). Patients were derived from 552 proband-identified *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3) families. The proband in each family had otherwise unexplained, diagnostic QTc prolongation or experienced LQTS-related symptoms. Patients were excluded from the study if they had: 1) >1 LQTS identified mutation (n = 70); 2) Jervell and Lange-Nielsen syndrome with deafness and 2 *KCNQ1* mutations or 1 known *KCNQ1* mutation and congenital deafness (n = 2); and 3) no identified mutation on genetic testing with prolonged QTc interval (>440 ms [n = 428]).

Data collection and end point. Routine clinical and rest ECG parameters were acquired at the time of enrollment in each of the registries. Measured parameters on the first recorded electrocardiogram included QT and R-R intervals in milliseconds, with QT interval corrected for heart rate using Bazett's (11) formula. Clinical data were collected on prospectively designed forms with information on demographic characteristics, personal and family medical histories, ECG findings, therapies, and events during long-term follow-up. Data common to all LQTS registries involving genetically tested subjects were electronically merged into a common database for the present study. In addition, information regarding QT interval–prolonging medications and triggers for cardiac events was collected through a specific questionnaire for patients enrolled the U.S. portion of the registry.

The primary end point of the study was the occurrence of a first life-threatening cardiac event, comprising aborted cardiac arrest (ACA; requiring external defibrillation as part of the resuscitation or internal defibrillation in patients with implantable cardioverter-defibrillators) or LQTS-related SCD (abrupt in onset without evident cause, if witnessed, or death that was not explained by any other cause if it occurred in a nonwitnessed setting such as sleep). In the multivariate models, follow-up was censored at age 41 years to avoid the influence of coronary disease on the occurrence of cardiac events. We also evaluated a secondary end point that included the occurrence of a first cardiac event of any type during follow-up (comprising syncope [defined as transient loss of consciousness that was abrupt in onset and offset], ACA, or SCD).

Phenotype characterization. For the purpose of this study, the QTc interval was categorized as normal range (≤440 ms) or prolonged (>440 ms) according to accepted criteria for the phenotypic definition of LQTS (12). Using this definition, the study population were categorized into 3 genotype and QTc subgroups: 1) LQTS with normal-range QTc interval (n = 469), comprising patients identified to have LQT1 to LQT3 mutations with QTc intervals ≤440 ms; 2) LQTS with prolonged QTc interval (n = 1,392), comprising patients with LQT1 to LQT3 mutations with QTc intervals >440 ms; and 3) unaffected family members (n = 1,525), comprising registry subjects from genotype-positive proband-identified families who were genetically tested and found to be negative for the LQTS-associated mutation, with QTc intervals ≤440 ms (i.e., genetically and phenotypically unaffected family members).

Genotype characterization. The *KCNQ1*, *KCNH2*, and *SCN5A* mutations were identified with the use of standard genetic tests performed in academic molecular genetics laboratories, including the Functional Genomics Center, University of Rochester Medical Center, Rochester, New York; Baylor College of Medicine, Houston, Texas; Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, Minnesota; Boston Children's Hospital, Boston, Massachusetts; the Laboratory of Molecular Genetics, National Cardiovascular Center, Suita, Japan; the Department of Clinical Genetics, Academic Medical Center, Amsterdam, the Netherlands; and the Molecular Cardiology Laboratory, Policlinico S. Matteo and University of Pavia, Pavia, Italy.

Genetic alterations of the amino acid sequence were characterized by location and by the type of the specific mutation. The transmembrane region of each of the 3 LQTS channels was defined as: 1) amino acid residues from 120 through 355 in the *KCNQ1*-encoded Kv7.1 channel (S1 to S6 region); 2) amino acid residues from 398 through 657 (S1 to S6 region) in the *KCNH2*-encoded Kv11.1 channel; and 3) amino acid residues 129 through 417, 713 through 940, 1201 through 1470, and 1523 through 1740 in the *SCN5A*-encoded Nav1.5 channel (13). On the basis of prior studies that demonstrated the functional and clinical importance of missense mutations that are located in the transmembrane region of these LQTS-associated channels (9,10), mutation categories were pre-specified in the primary analysis as transmembrane-missense (mutations of the missense type in any of the 3 transmembrane regions described previously) versus nontransmembrane or nonmissense (i.e., any other identified LQT1 to LQT3 mutation that was not transmembrane-missense).

Statistical analysis. The clinical characteristics of study patients were compared by genotype and QTc categories using chi-square tests for categorical variables and *t* tests and Mann-Whitney-Wilcoxon tests for continuous variables. The Kaplan-Meier estimator was used to assess the time to a first life-threatening event and the cumulative event rates by risk groups and risk factors, and groups were compared using the log-rank test.

Cox proportional hazards regression analysis was carried out in the total study population and separately in the subset of patients with genotype-positive LQTS. Pre-specified covariates in the total population model included the 3 genotype and QTc categories, sex, and time-dependent beta-blocker therapy. The models comprising genotype-positive patients included the following pre-specified covariates: QTc category (normal range [≤440 ms] vs. prolonged [>440 ms]), the LQT1 to LQT3 genotypes, mutation location and type, sex, QTc duration (assessed both as a continuous measure [per 10-ms increase] and as a categorical covariate [dichotomized at the median value of each QTc category and assessed in separate models]), time-dependent beta-blocker therapy, and a family history of SCD in a first-degree relative. The effect of each covariate on outcome in each QTc category (i.e., in patients with LQTS with normal-range and prolonged QTc intervals) was assessed using interaction-term analysis, with interactions tested 1 at a time. Estimates of predictor hazard ratios in the separate normal and prolonged QTc categories were obtained using these interactions. To avoid violation of the proportional hazards assumption due to sex-risk crossover during adolescence, we used an age-sex interaction term in the multivariate models.

Because almost all the subjects were first-degree and second-degree relatives of probands, the effect of lack of independence between subjects was evaluated in the Cox model with grouped jackknife estimates for family membership (14). All grouped jackknife standard errors for the covariate risk factors fell within 3% of those obtained from the unadjusted Cox model, and therefore only the Cox model findings are reported. The statistical software used for the analyses was SAS version 9.20 (SAS Institute Inc., Cary, North Carolina). A 2-sided significance level of 0.05 was used for hypothesis testing.

Results

The spectrum and number of LQT1-associated, LQT2-associated, and LQT3-associated mutations by the pre-specified location and type categories are presented in Online Table 1. Totals of 100, 177, and 41 different mutations were identified in the *KCNQ1*-encoded Kv7.1, *KCNH2*-encoded Kv11.1, and *SCN5A*-encoded Nav1.5 ion channels, respectively. Study patients with identified LQTS mutations exhibited a very wide QTc interval distribution (Fig. 1), ranging from a minimum of 350 ms to a maximum of 800 ms (mean 450 ± 56 ms; median 440 ms; interquartile range: 410 to 480 ms). QTc distribution was similar among the 3 LQTS genotypes. Four hundred sixty-nine LQTS mutation–positive patients exhibited normal-range QTc intervals, constituting 25% of identified cases.

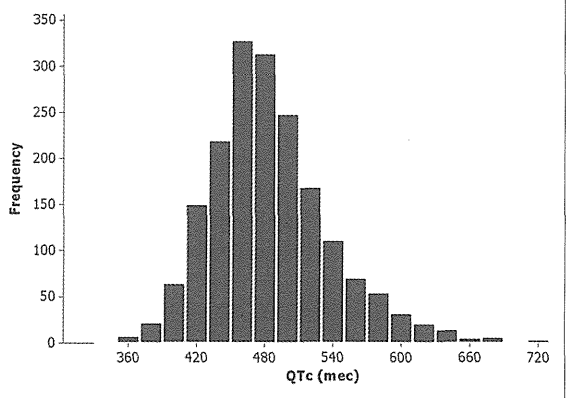

Figure 1 Distribution of QTc Interval Duration in Genotype-Positive Patients With LQTS

Distribution of corrected QT (QTc) interval durations in genotype-positive study patients. LQTS = long-QT syndrome.

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Table 1 Baseline and Follow-Up Characteristics of the Study Population by Genotype-Phenotype

Characteristic	Unaffected Family Members (n = 1,525)	Patients With LQTS With Normal-Range QTc Intervals (n = 469)	Patients With LQTS With Prolonged QTc Intervals (n = 1,392)
Female	52%	48%	61%*†
Family history of SCD	8%	12%	19%*†
QTc interval (ms)			
Mean ± SD	412 ± 22	419 ± 20	501 ± 48
Median (IQR)	420 (400–430)	420 (410–440)	490 (470–520)
Proband	8%	8%	29%*†
RR interval (ms)			
Mean ±SD	793 ± 221	888 ± 236	848 ± 214*†
Median (IQR)	800 (640–930)	900 (740–1,040)	840 (700–1,000)*†
Genotype			
LQT1	NA	40%	39%
LQT2	NA	45%	47%
LQT3	NA	16%	14%
Mutation: TM-MS			
Overall	NA	35%	43%
LQT1	NA	45%	61%
LQT2	NA	16%	29%†
LQT3	NA	64%	31%†
Therapies			
Beta-blockers	6.2%	38%	54%*†
Pacemaker	0.3%	0.6%	5%*†
LCSD	0.1%	0.2%	1.4%*†
ICD	0.6%	6%	14%*†
Events			
Syncope	10%	21%	40%*†
ACA	0.2%	1.3%	8.4%*†
SCD	0.1%	1.5%	4.4%*†
ACA/SCD‡§	0.3%	2.8%	11.3%*

*$p < 0.05$ for the comparison among the 3 genotyped categories. †$p < 0.05$ for the comparison between genotype-positive patients with QTc intervals ≤440 ms and genotype-positive patients with QTc intervals >440 ms. ‡Appropriate ICD shocks constituted 0.04% of ACAs in genotype-positive patients with QTc intervals ≤440 ms and 1.4% of ACAs in genotype-positive patients with QTc intervals >440 ms. §Only the first event for each patient was considered.

ACA = aborted cardiac arrest; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; LCSD = left cardiac sympathetic denervation; LQT1 = long-QT syndrome type 1; LQT1 = long-QT syndrome type 2; LQT3 = long-QT syndrome type 3; LQTS = long-QT syndrome; MS = missense; NA = not applicable; QTc = corrected QT; SCD = sudden cardiac death; TM = transmembrane.

The clinical characteristics of the total study population by genotype and QTc subgroup are shown in Table 1. The frequency of probands (defined in the registry as the first person in a family, living or deceased, identified to have LQTS by the enrollment center) was highest in patients with prolonged QTc intervals, whereas most patients with normal-range QTc intervals (92%) were asymptomatic at the time of genetic testing. The frequency of female subjects was similar between the unaffected subjects and patients with LQTS with normal-range QTc intervals and higher in patients with prolonged QTc intervals. In mutation carriers, the frequency of the 3 main LQTS genotypes was similar between patients with and without prolonged QTc intervals. However, patients with LQT1 and LQT2 with prolonged QTc intervals had a higher frequency of transmembrane-missense mutations compared with the corresponding genotype carriers who had normal-range QTc intervals. LQTS-related therapies were administered to a significantly higher frequency of patients with prolonged QTc intervals than to subjects in the other 2 subgroups (Table 1).

Clinical course by genotype and QTc subgroup. Kaplan-Meier survival analysis (Fig. 2) demonstrated a relatively low rate of ACA or SCD in patients with LQTS with normal-range QTc intervals (4% at age 40 years and 10% at age 70 years). Event rates were significantly higher in patients with prolonged QTc intervals (15% and 24% at age 70 years; log-rank $p < 0.001$ for the comparison with the normal-range QTc subgroup) and significantly lower in unaffected family members (0.4% and 1% at age 70 years; log-rank $p < 0.001$ for the comparison with the normal-range QTc subgroup and for the overall difference among the 3 subgroups). Notably, life-threatening events in patients with normal-range QTc intervals occurred mostly after age 10 years, whereas patients with prolonged QTc intervals exhibited an earlier onset of life-threatening events (Fig. 2).

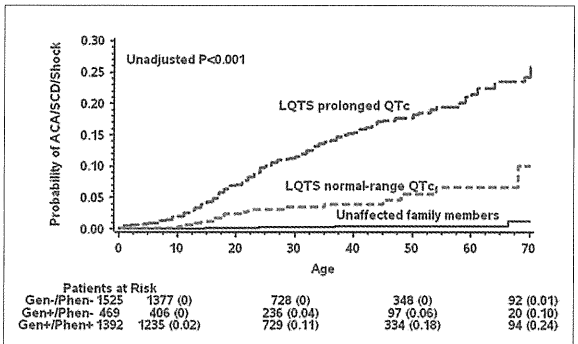

Figure 2 Rate of ACA or SCD by Genotype and QTc Category

Kaplan-Meier cumulative probabilities of aborted cardiac arrest (ACA) and sudden cardiac death (SCD) by genotype and corrected QT (QTc) subgroup. LQTS = long-QT syndrome.

After multivariate adjustment for sex, time-dependent beta-blocker therapy, and a family history of SCD in a first-degree relative, patients with LQTS with normal-range QTc intervals were shown to have a significant 72% ($p < 0.001$) lower risk for ACA or SCD compared with patients with prolonged QTc intervals but also exhibited a >10-fold increase in the risk for life-threatening events compared with unaffected family members (Table 2). Histories of syncope were present in 62% of patients with LQTS with normal-range QTc intervals who had life-threatening events during follow-up. Accordingly, when the composite secondary end point of a first cardiac event of any type was assessed (comprising mainly non-life-threatening syncopal episodes), patients with normal-range QTc intervals were consistently shown to be at a lower risk compared with those with prolonged QTc intervals (hazard ratio [HR]: 0.47; 95% confidence interval [CI]: 0.33 to 0.59; $p < 0.001$) and at a higher risk compared with unaffected family members (HR: 5.20; 95% CI: 4.19 to 6.44; $p < 0.001$).

Risk factors for ACA or SCD in patients with LQTS with and without prolonged QTc intervals. Interaction-term analysis demonstrated significant differences in risk factors for life-threatening events between the 2 LQTS subgroups (Table 3). In patients with normal-range QTc intervals, the LQT1 and LQT3 genotypes were associated with respective 10- and 8-fold increases in the risk for life-threatening events compared with the LQT2 genotype. In contrast, in patients with prolonged QTc intervals, the LQT1 genotype was associated with one-half the risk of the LQT2 genotype ($p = 0.002$), with a statistically significant genotype–by–QTc subgroup interaction ($p = 0.006$) (Table 3, first row), and the LQT3 genotype showed a similar risk to the LQT2 genotype, without a statistically significant genotype–by–QTc subgroup interaction (Table 3, second row).

The location and type of the LQTS mutation were shown to be significant risk factors for ACA or SCD in patients with normal-range QTc intervals. In this LQTS subset, transmembrane-missense mutations were associated with a pronounced >6-fold ($p = 0.006$) increase in the risk for ACA or SCD compared with nontransmembrane or nonmissense mutations. In contrast, in patients with prolonged QTc intervals, transmembrane-missense mutations were not independently associated with outcomes (Table 3, third row). Notably, when the secondary end point of cardiac events of any type was assessed, transmembrane-missense mutations were shown to be an independent risk factor in both LQTS subgroups (normal-range QTc interval, HR: 1.71; 95% CI: 1.16 to 2.34; prolonged QTc interval, HR: 1.39; 95% CI: 1.17 to 1.65).

Consistent results demonstrating an association between transmembrane-missense mutations and the risk for ACA or SCD in patients with normal-range QTc intervals were shown when the reference group (comprising nontransmembrane or nonmissense mutations) was further divided into 3 subcategories, including nonmissense mutations in the transmembrane region, missense mutations in the nontransmembrane region, and nonmissense mutations in the nontransmembrane region (HR >4.0 for all 3 comparisons). Accordingly, patients with normal-range QTc intervals with transmembrane-missense mutations experienced a relatively high rate of ACA or SCD during follow-up (9% at age 40 years and 21% at age 70 years), whereas patients with normal-range QTc intervals with other mutations had a very low event rate (1% at age 40 years and 5% at age 70 years; log-rank p for overall difference = 0.005) (Fig. 3A). In contrast, in patients with prolonged QTc intervals, there was no statistically significant difference in the rate of ACA or SCD between the 2 mutation categories (16% and 14% at 40 years, respectively, $p = 0.18$) (Fig. 3B).

Clinical and ECG factors, including sex and QTc duration, were shown to be associated with a significant increase in the risk for ACA or SCD only in patients with prolonged QTc intervals (Table 3, rows 4 to 6). In contrast, in patients

Table 2 Multivariate Analysis: Risk for ACA or SCD Among the 3 Genotype and QTc Categories*

Genotype and QTc Subgroup	HR	95% CI	p Value
LQTS with prolonged QTc interval vs. unaffected family members	36.53	13.35–99.95	<0.001
LQTS with normal-range QTc interval vs. unaffected family members	10.25	3.34–31.46	<0.001
LQTS with normal-range QTc interval vs. LQTS with prolonged QTc interval	0.28	0.16–0.49	<0.001

*Model also adjusted for sex (female age >13 years) and time-dependent beta-blocker therapy.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

Table 3 Risk Factors for ACA or SCD in Patients With LQTS by QTc Interval Category*

Variable	LQTS and Normal-Range QTc Interval		LQTS and Prolonged QTc Interval		
	HR (95% CI)	p Value	HR (95% CI)	p Value	p Value for Interaction
Genotype					
LQT1 vs. LQT2	9.88 (1.26–37.63)	0.03	0.53 (0.35–0.79)	0.002	0.006
LQT3 vs. LQT2	8.04 (0.85–36.03)	0.07	1.07 (0.70–1.63)	0.77	0.08
Mutation location and type					
TM-MS vs. non-TM-MS	6.32 (1.71–23.33)	0.006	1.24 (0.88–1.76)	0.22	0.02
Sex					
Female age >13 yrs vs. male age >13 yrs	1.32 (0.42–4.17)	0.64	1.90 (1.26–2.86)	0.002	0.53
QTc interval (ms)					
Per 10-ms increase	1.20 (0.81–1.78)	0.35	1.08 (1.05–1.10)	<0.001	0.58
≥Median vs. <median†	1.03 (0.36–2.98)	0.95	2.96 (2.06–4.26)	<0.001	NA

*Cox proportional hazards regression modeling was carried out in models that included all patients with genotype-positive LQTS (n = 1,861). Covariates in the models included QTc category (≤440 ms vs. >440 ms), genotype, mutation location and type, sex, QTc interval (assessed as a continuous measure [per 10-ms increase]), time-dependent beta-blocker therapy, and a family history of SCD; the effect of each covariate in patients with normal-range (≤440 ms) and those with prolonged (>440 ms) QTc intervals was assessed by interaction-term analysis, with interactions tested 1 at a time. Estimates of predictor hazard ratios in the separate normal-range and prolonged QTc interval groups were obtained using these interactions. Virtually identical results for all pre-specified risk factors were also obtained from the models that did not include appropriate ICD shocks as part of the composite end point. †Results were obtained from separate models that assessed the risk associated with QTc values greater than or equal to the median in patients with LQTS with normal-range QTc intervals (median 420 ms) and prolonged QTc intervals (median 500 ms).

Abbreviations as in Tables 1 and 2.

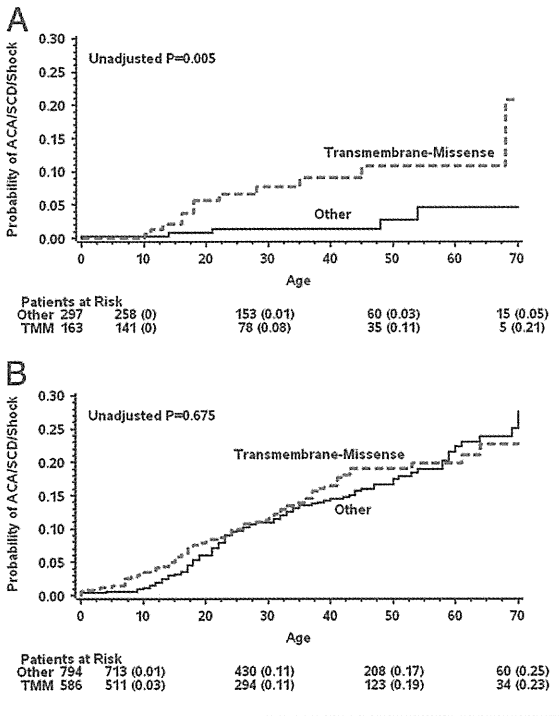

Figure 3 Rate of ACA or SCD in Patients With Normal-Range and Prolonged QTc Intervals by Mutation Location and Type

Kaplan-Meier cumulative probabilities of aborted cardiac arrest (ACA) and sudden cardiac death (SCD) by mutation location and type in patients with long-QT syndrome (LQTS) with **(A)** corrected QT (QTc) intervals ≤440 ms and **(B)** QTc intervals >440 ms.

with normal-range QTc intervals, sex was not a significant risk factor, and QTc duration was not independently associated with a significant increase in the risk for ACA or SCD when assessed as a continuous measure or when dichotomized at the median value (≥420 ms).

As suggested previously (15), the presence of a family history of SCD in any first-degree relative was not shown to be an independent predictor of ACA or SCD in patients with either normal-range QTc intervals (HR: 0.89; 95% CI: 0.63 to 1.25; $p = 0.50$) or prolonged QTc intervals (HR: 1.40; 95% CI: 0.32 to 6.17; $p = 0.65$) after adjustment for genetic and clinical factors.

Beta-blocker therapy was administered to 38% of patients who had normal-range QTc intervals compared with 54% of the patients who had prolonged QTc intervals ($p < 0.001$) (Table 1). Treatment with beta-blockers was associated with an overall significant 25% reduction in the risk for ACA or SCD in the total study population (95% CI: 0.70 to 0.80; $p < 0.001$), with similar effects in patients with normal-range QTc intervals and those with prolonged QTc intervals (p for beta-blocker–by–LQTS subset interaction = 0.45).

Characteristics of fatal or near-fatal cases with a normal-range QTc intervals. The characteristics of patients with normal-range QTc intervals who experienced ACA or SCD during follow-up are shown in Table 4. The mean age at occurrence of the lethal or near-lethal event in this population was 25.9 ± 4.5 years. Nine of the patients (53%) who experienced events were women, and 4 (24%) were treated with beta-blockers are the time of the events. In patients with normal-range QTc intervals with available data regarding therapies and triggers at the time of the events, none were reported as being treated with a QT interval–prolonging drugs at the time of ACA or SCD, and the majority of the lethal or near-lethal events were not associated with exercise or arousal triggers (Table 4).

Table 4 Characteristics of ACA and SCD Cases With Normal-Range QTc Intervals

Case	Event	Event Age (yrs)	Female	QTc Interval (ms)	BB†	LCSD‡	PM†	ICD†	QT PD	Trigger*	Genotype	Mutation Location and Type
1	SCD	0.5	–	390	–	–	–	–	–	NA	LQT3	Non-TM-MS
2	ACA	10		430	–	–	–	–	–	Exercise	LQT1	TM-MS
3	ACA/shock	11	+	400	–	–	–	+	–	Non-E/A	LQT1	TM-MS
4	SCD	13	–	440	+	–	–	–	NA	NA	LQT1	TM-MS
5	ACA	14	–	410	–	–	–	–	–	Exercise	LQT1	Non-TM-MS
6	SCD	16	+	420	–	–	–	–	–	Non-E/A	LQT3	TM-MS
7	ACA	16	+	440	–	–	–	–	–	Arousal	LQT1	TM-MS
8	SCD	18	–	430	+	–	–	–	–	Non-E/A	LQT1	TM-MS
9	ACA	18	+	410	–	–	–	–	–	Exercise	LQT1	TM-MS
10	SCD	21	+	380	–	–	–	–	–	Arousal	LQT2	Non-TM-MS
11	SCD	22	–	440	–	–	–	–	NA	NA	LQT1	TM-MS
12	SCD	28	–	410	–	–	–	–	–	Exercise	LQT1	TM-MS
13	ACA	35	+	420	–	–	–	–	–	Non-E/A	LQT3	TM-MS
14	ACA	46	+	440	+	–	–	–	NA	NA	LQT2	TM-MS
15	SCD	48	–	430	+	–	–	–	–	Non-E/A	LQT2	Non-TM-MS
16	ACA	54	+	420	–	–	–	–	–	Non-E/A	LQT3	Non-TM-MS
17	SCD	69	–	380	–	–	–	–	NA	NA	LQT1	TM-MS

*Data regarding triggers for cardiac events and treatment with QT interval–prolonging medications were available for study patients who were enrolled in the U.S. portion of the International LQTS Registry. †At time of event. ‡Implanted or performed before event.

BB = beta-blocker therapy; E/A = exercise/arousal trigger for event; NA = not available; PM = pacemaker; QT PD = QT interval–prolonging drug; other abbreviations as in Tables 1 and 2.

Discussion

In this study, we assessed the clinical courses and risk factors for life-threatening events in LQTS patients with genetically-confirmed LQTS who do not exhibit the disease's phenotypic hallmark of QT interval prolongation, otherwise referred to as concealed LQTS, normal–QT interval LQTS, or genotype-positive/ECG phenotype–negative LQTS. Similar to prior studies (16), we have shown that patients with LQT1 to LQT3 exhibit a wide QTc distribution, with approximately 25% having QTc intervals well within the normal range. The rate of ACA or SCD in patients with LQTS with normal-range QTc intervals was shown to be very low (4% from birth through age 40 years, corresponding to an approximate event rate of 0.13% per year). Comparatively, however, this very low risk subset of the LQTS population still exhibited a >10-fold increase in the risk for life-threatening events compared with genetically and phenotypically unaffected family members. Importantly, predictors of life-threatening events were shown to be significantly different between LQTS patients with and without prolonged QTc intervals. In the latter LQTS subgroup, genetic data, including knowledge of genotype and mutation characteristics, were shown to identify the risk for ACA or SCD, whereas in the former LQTS subgroup, female sex in the post-adolescence period and QTc duration were identified as the predominant risk factors for life-threatening events.

The clinical courses of patients with LQTS are variable because of incomplete penetrance (17). They are influenced by age, genotype, sex, environmental factors, therapy, and possibly other modifier genes (1–10). Recent studies from the International LQTS Registry that assessed the risk for life-threatening events in patients with LQTS have consistently demonstrated that ECG and clinical risk factors, including the QTc interval and age-sex interactions, identify increased risk in the LQTS population (3–5). These studies, however, included mainly phenotype-positive patients with LQTS with QTc intervals ≥ 450 ms. Thus, the effect of genetic data on outcomes in these studies was not statistically significant after adjustment for the ECG and clinical factors. The present study population, comprising 1,861 genetically confirmed patients with the LQT1 to LQT3 genotypes, extends the data derived from prior studies and demonstrates that risk factors for life-threatening events are significantly different between patients with LQTS with and without QTc prolongation. Consistent with prior studies, we have shown that in patients with LQTS who exhibit prolonged QTc durations, ECG information and clinical factors can be used to identify the risk for life-threatening events. In contrast, in mutation-positive subjects with normal-range QTc intervals, genetic factors, including knowledge of the LQTS genotypes and the mutation location and type, identified patients who were at an increased risk for ACA or SCD after adjustment for ECG and clinical data.

Sex was not a significant risk factor for cardiac events in patients with normal-range QTc intervals. Furthermore, patients with normal-range QTc intervals displayed a similar frequency of women as unaffected family members, whereas the frequency of women was significantly higher among patients with prolonged QTc intervals. These findings are in accordance with earlier evidence of longer QTc intervals in LQTS women than in men (18), resulting in a marked female predominance in phenotypically affected patients (3–5). The biologic basis for this sex difference might be the down-regulation of expression of cardiac potassium-channel genes by female

sex hormones, which have been shown to prolong the QT interval in both congenital and drug-induced LQTS (19,20). These hormonal effects may explain the present findings of a lower frequency of LQTS women with normal-range QTc intervals.

Recent genotype-phenotype studies have shown that missense mutations located in the transmembrane region, which is responsible for forming the ion conduction pathway of the channel, are associated with a significantly higher risk for cardiac events compared with mutations that are located in other regions of the LQTS channel (9,10). The present study also shows that transmembrane-missense mutations are associated with a significantly higher risk for cardiac events of any type (predominated by syncopal episodes) in patients with LQTS with both normal-range and prolonged QTc intervals. However, our findings suggest that data regarding mutation characteristics are important for the assessment of life-threatening events (comprising ACA and SCD) mainly in patients with normal-range QTc intervals, in whom information derived from ECG and clinical data is more limited. In this LQTS subset, missense mutations located in the transmembrane region were shown to be associated with a >6-fold increase in the risk for life-threatening events and with a clinically meaningful rate of ACA or SCD (9%) from birth through age 40 years.

The mechanisms relating to the occurrence of life-threatening ventricular tachyarrhythmias in phenotype-negative patients with LQTS are not clear. In the present study, none of the patients with normal-range QTc intervals who experienced ACA or SCD took QT interval–prolonging medications at the time of the events. Furthermore, most events in patients with normal-range QTc intervals were not related to exercise or arousal triggers (Table 4). An ECG tracing from a patient with the LQT1 genotype who developed arrhythmic events despite a normal-range QTc interval showed spontaneous generation of polymorphic ventricular tachycardia without preceding extrasystolic pauses or sudden sinus rate acceleration (Fig. 4), possibly explaining the occurrence of ACA or SCD in study patients with normal-range QTc intervals who were treated with beta-blockers at the time of the events.

Study limitations. Most study patients did not undergo comprehensive genetic testing for all currently known mutations that may predispose to arrhythmic risk. Thus, it is possible that the coexistence of modifier genes affected the outcomes of patients with LQTS with normal-range QTc intervals who experienced life-threatening cardiac events. In addition, to provide an estimation of event rates among unaffected family members, we included in the control group subjects who were both genotype negative and also had normal-range QTc intervals (and excluded genotype-negative subjects with prolonged QTc intervals due to possible unidentified mutations in this subset). Therefore, the overall frequency of genotype-positive subjects in the total population may not represent the true penetrance of LQTS in affected families.

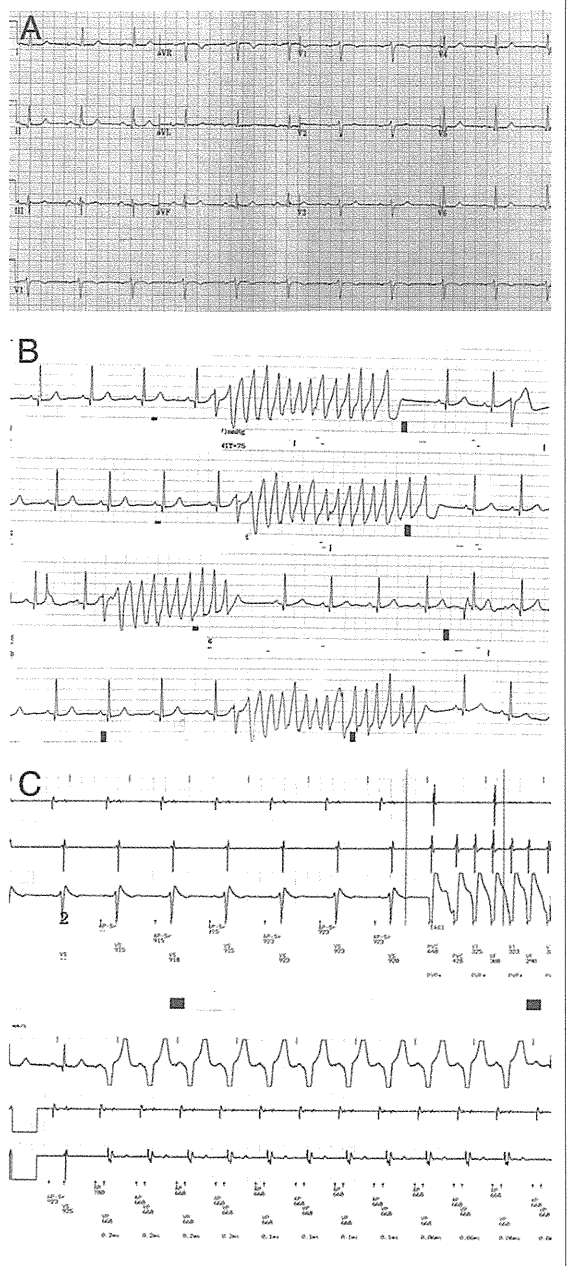

Figure 4 **Polymorphic Ventricular Tachycardia in a Patient With a Normal-Range QTc Interval**

Spontaneous generation of polymorphic ventricular tachycardia in a patient with long-QT syndrome type 1 with a normal-range corrected QT (QTc) interval. **(A)** The patient had a QTc duration of 410 ms on baseline electrocardiography. **(B)** Electrocardiographic tracing at the time of arrhythmic event demonstrates sinus rate with an RR interval of 1,000 ms without significant QT prolongation before the arrhythmia. **(C)** The patient was treated with nadolol and received an implantable cardioverter-defibrillator but continued to exhibit arrhythmic episodes that were recorded on implantable cardioverter-defibrillator interrogation.

The threshold value of 440 ms for the definition of a normal-range QTc in the present study was based on the diagnostic criteria for LQTS proposed by Schwartz et al. (12), which define a prolonged QTc interval as ≥450 ms in male patients and ≥460 ms in female patients. We chose to use a uniform approach by selecting 440 ms as the upper limit of normal rather than having separate phenotypic definitions for male and female patients. It should also be noted that 2.5% of infants and 10% to 20% of adults exceed this cutoff (21). Thus, the 440-ms value is not meant to suggest an LQTS diagnosis on its own.

Conclusions

The present study shows that patients with LQTS who exhibit normal-range QTc intervals constitute approximately 25% of the LQTS population and have a significantly lower risk for life-threatening events compared with phenotypically affected patients but also exhibit a significant increase in the risk of ACA or SCD compared with unaffected family members. Missense mutations in the transmembrane regions of the ion channels, mainly in patients with LQT1 and LQT3, were shown to identify patients with normal-range QTc intervals who have an increased risk for ACA or SCD. In contrast, increments in QTc duration were not shown to be significantly associated with increased risk for life-threatening events in this population. These findings suggest that: 1) risk assessment in phenotype-negative family members of LQTS probands should include genetic testing, because a positive genetic test result in a family member with a normal-range QTc interval implies an overall >10-fold increase in the risk for ACA or SCD compared with a negative test result in an unaffected family member; 2) genetic data may be used to identify phenotype-negative patients with LQTS who are at increased risk for fatal ventricular tachyarrhythmias independently of QTc duration; and 3) LQTS mutation–positive patients with normal-range QTc intervals who are identified as having increased risk for life-threatening events on the basis of genotype and mutation characteristics (i.e., LQT1 and LQT3 with transmembrane-missense mutations) should be carefully followed and receive a similar management strategy as phenotype-positive patients with LQTS, including avoidance of QT-prolonging medications (22), routine therapy with beta-blockers, and possibly implantable cardioverter-defibrillator therapy in those who remain symptomatic despite medical therapy. Conversely, patients with the lowest risk profile of already low risk, concealed LQTS (i.e., concealed LQT2 and non-transmembrane-missense LQT1 and LQT3) may represent the nominally near zero risk subpopulation(s) of LQTS in need of only preventative health recommendations such as QT drug avoidance.

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Key Words: corrected QT interval ▪ long-QT syndrome ▪ sudden cardiac death.

APPENDIX

For a table about *KCNQ1*, *KCNH2*, and *SCN5A* mutations by amino acid coding, frequency, location, and type, please see the online version of this article.

Mutation and gender-specific risk in type 2 long QT syndrome: Implications for risk stratification for life-threatening cardiac events in patients with long QT syndrome

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BACKGROUND Men and women with type 2 long QT syndrome (LQT2) exhibit time-dependent differences in the risk for cardiac events. We hypothesized that data regarding the location of the disease-causing mutation in the *KCNH2* channel may affect gender-specific risk in LQT2.

OBJECTIVE This study sought to risk-stratify LQT2 patients for life-threatening cardiac events based on clinical and genetic information.

METHODS The risk for life-threatening cardiac events from birth through age 40 years (comprising aborted cardiac arrest [ACA] or sudden cardiac death [SCD]) was assessed among 1,166 LQT2 male (n = 490) and female (n = 676) patients by the location of the LQTS-causing mutation in the *KCNH2* channel (prespecified in the primary analysis as pore-loop vs. non–pore-loop).

RESULTS During follow-up, the cumulative probability of life-threatening cardiac events years was significantly higher among LQT2 women (26%) as compared with men (14%; $P < .001$). Multivariate analysis showed that the risk for life-threatening cardiac events was not significantly different between women with and without pore-loop mutations (hazard ratio 1.20; $P = .33$). In contrast, men with pore-loop mutations displayed a significant >2-fold higher risk of a first ACA or SCD as compared with those with non–pore-loop mutations (hazard ratio 2.18; $P = .01$). Consistently, women experienced a high rate of life-threatening events regardless of mutation location (pore-loop: 35%, non–pore-loop: 23%), whereas in men the rate of ACA or SCD was high among those with pore-loop mutations (28%) and relatively low among those with non–pore-loop mutations (8%).

CONCLUSION Combined assessment of clinical and mutation-specific data can be used for improved risk stratification for life-threatening cardiac events in LQT2.

KEYWORDS Long QT syndrome; Pore-loop mutations; Sudden cardiac death; Gender

ABBREVIATIONS ACA = aborted cardiac arrest; **ECG** = electrocardiogram; **ICD** = implantable cardioverter-defibrillator; **LQTS** = long QT syndrome; **LQT2** = long QT syndrome type 2; **QTc** = corrected QT; **SCD** = sudden cardiac death

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Conflict of interests/disclosure: Dr. Ackerman is a consultant for Biotronik, Boston Scientific, Medtronic, PGx Health, and St. Jude Medical; and has intellectual property in PGx Health. Dr. Kaufman receives grant support from CardioDx, Cambridge Heart Inc., and St. Jude Medical. All other authors have reported that they have no relationships to disclose.

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Introduction

Long QT syndrome (LQTS) is an inherited arrhythmogenic disorder caused by mutations in several cardiac ion channel genes.[1] Clinically, LQTS is identified by abnormal QT interval prolongation on the electrocardiogram (ECG) and is associated with arrhythmogenic syncope and sudden arrhythmic death (SCD).[1,2] Type 2 long QT (LQT2), the second most common variant of LQTS, is characterized by mutations in the α subunit of the *KCNH2* channel, which conducts the rapid delayed rectifier potassium current (I_{Kr}) in cardiac myocytes.[1,2–4] Recent data show that mutations in the *KCNH2* pore-loop region, which is responsible for forming the ion conduction pathway of the channel, are associated with a significantly higher risk of cardiac events as compared with mutations that are located in other regions of the channel.[5,6] Furthermore, the clinical course of LQT2 patients was shown to be associated with major time-dependent gender differences, wherein women display a significantly higher risk for cardiac events than men after the onset of adolescence.[7] Prior studies in LQT2 patients, however, evaluated mainly the combined end point of any cardiac event during follow-up (comprising mostly nonfatal syncopal episodes) and did not relate gender-specific risk to mutation location in this population. Accordingly, the present study was carried out in a population of 1,166 genetically confirmed LQT2 patients from Multinational LQTS Registries and was designed to: (1) evaluate time-dependent gender differences in the risk of life-threatening cardiac events (comprising aborted cardiac arrest [ACA] or SCD) in LQT2 patients; (2) relate gender-specific risk for life-threatening events in this population to the location of the LQT2-causing mutation in the *KCNH2* channel; and (3) develop a risk stratification scheme among LQT2 patients that combines clinical and mutation-specific data.

Methods

Study population

The study population was composed of 1,166 subjects derived from (n = 263) proband-identified families with genetically confirmed *KCNH2* mutations. Patients were drawn from the Rochester, New York, enrolling center (center 1) of the International LQTS Registry (n = 761), the Netherlands LQTS Registry (n = 214), and the Japanese LQTS Registry (n = 95), as well as from data submitted by other investigators specifically for this collaborative mutation analysis project: Denmark (n = 62), Israel (n = 24), and Sweden (n = 10). The proband in each family had otherwise unexplained diagnostic QTc prolongation or experienced LQTS-related symptoms. Patients were excluded from the study if they had >1 LQTS-causing mutation (n = 11).

Data collection and management

For each patient, personal history including cardiac events, ECGs, and therapies, as well as family history, were obtained at enrollment. Clinical data were then collected yearly on prospectively designed forms with information on demographic characteristics, personal and family medical history, ECG findings, medical therapies, left cardiac sympathetic denervation, implantation of a pacemaker or an implantable cardioverter-defibrillator (ICD), and the occurrence of LQTS-related cardic events. The QT interval was corrected for heart rate using the Bazett formula.[8] Data common to all LQTS registries involving genetically tested individuals were electronically merged into a common database for the present study.

Genotype characterization

KCNH2 mutations were identified with the use of standard genetic tests performed in academic molecular genetic research laboratories and/or in commercial laboratories. Genetic alterations of the amino acid sequence were characterized by location in the channel protein and by the type of mutation (missense, splice site, in-frame insertions/deletions, nonsense [stop codon], and frameshift).[9] The transmembrane region of the *KCNH2* encoded protein was defined as the coding sequence involving amino acid residues from 404 through 659 (pore-loop region: 548-659), with the N-terminus region defined before residue 404, and the C-terminus region after residue 659.

Pore-loop mutations disrupt normal channel gating[10] and were shown to be associated with a significantly higher risk of cardiac events as compared with mutations in each of the other regions of the *KCNH2* channel.[5,6] Accordingly, mutation location was categorized in the primary analysis of the present study as pore-loop vs. non–pore-loop. In a secondary analysis, non–pore-loop mutations were further subcategorized into those located in the transmembrane (non–pore-loop) region and in the C/N-terminus regions. Mutation type was categorized as missense vs. nonmissense. The specific mutations included in the present study, by location, type, and number of patients, are detailed in Supplementary Table 1. The distribution of study mutations in the *KCNH2* channel, by the relative number of patients, is shown in Figure 1.

End point

The primary end point of the study was the occurrence of a first life-threatening cardiac event, comprising ACA (requiring defibrillation as part of resuscitation), or LQTS-related SCD (abrupt in onset without evident cause, if witnessed, or death that was not explained by any other cause if it occurred in a nonwitnessed setting such as sleep). To further validate the consistency of the results among patients who received an ICD during follow-up, we also assessed a secondary end point comprising the first occurrence of ACA, SCD, or appropriate ICD shock during follow-up.

Statistical analysis

The baseline and follow-up clinical characteristics of the study population were evaluated using the χ^2 test for categorical variables, and the t test and the Mann-Whitney-Wilcoxon test for continuous variables. The cumulative probability of a first ACA or SCD by gender and by muta-

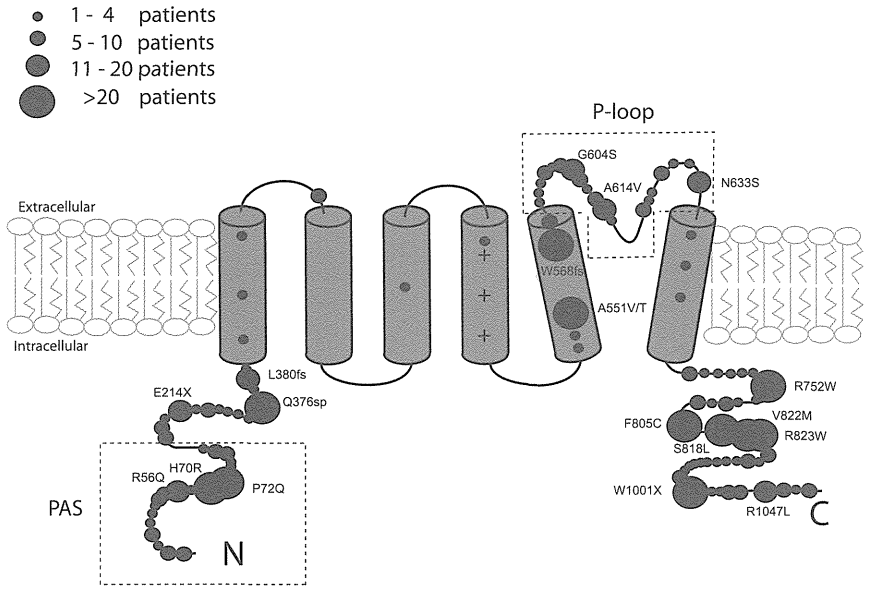

Figure 1 Distribution of mutations in the *KCNH2* potassium channel among study patients.

tion location was assessed by the Kaplan-Meier method, and significance was tested by the log-rank test. Follow-up data were censored at age 40 to avoid confounding by acquired cardiovascular disease. Multivariate Cox proportional hazards regression models were used to evaluate the independent contribution of clinical and genetic factors to the first occurrence of ACA or SCD. Prespecified covariates in the total population model included gender, QTc duration (categorized as ≥500 ms vs. <500 ms), mutation location and type (as defined above), the occurrence of syncope during follow-up, and medical therapy with blockers. Syncope and β-blocker therapy were assessed as time-dependent covariates in the multivariate models. The effect of each covariate in male and female subjects was assessed by interaction-term analysis (i.e., by including a gender-by-risk factor interaction term in the multivariate models), with interactions tested one at a time. To avoid violation of the proportional hazards assumption due to gender-risk crossover during adolescence, we used an age-gender interaction term in the multivariate models. Patients without available baseline QTc data (n = 150) were included as a separate (QTc-missing) covariate in the multivariate models.

Using the Cox model that included interactions among gender, mutation location, QTc duration, and time-dependent syncope, covariate patterns with similar estimated hazard ratios were united to form time-dependent risk groups.

Because almost all the subjects were first- and second-degree relatives of probands, the effect of lack of independence between subjects was evaluated in the Cox model with grouped jackknife estimates for family membership.[11] All grouped jackknife standard errors for the covariate risk factors fell within 3% of those obtained from the unadjusted Cox model, and therefore only the Cox model findings are reported. The statistical software used for the analyses was SAS version 9.20 (SAS Institute Inc, Cary, North Carolina). A 2-sided 0.05 significance level was used for hypothesis testing.

Results

The clinical characteristics of the study patients by gender are shown in Table 1. Baseline QTc was somewhat higher among women; however, the frequency of patients with prolonged QTc (≥500 ms) was similar in men and women. In addition, the frequency of patients with pore-loop mutations was the same in the 2 groups. During follow-up, there was no statistically significant difference between men and women in the frequency of medical therapy with β-blockers, whereas the frequency of device therapy (including pacemakers and ICDs) was significantly higher among women. The frequency of both nonfatal syncopal episodes and life-threatening cardiac events during follow-up was significantly higher among women as compared with men (Table 1).

Risk factors for ACA or SCD in the total LQT2 population

During follow-up, 179 (15%) study patients experienced the primary end point of a first ACA or SCD. Event rates were similar between men and women during childhood, whereas after onset of adolescence and during adulthood, LQT2 women experienced a significantly higher rate of ACA or SCD as compared with LQT2 men (Fig. 2). Accordingly, the cumulative probability of a first ACA or SCD from birth through age 40 years was significantly higher in women (26%) as compared with men (14%; $P < .001$ [Fig. 2]).

Table 1 Baseline and follow-up characteristics of the study population by gender

Characteristics	Male N = 490	Female N = 676	*P* value
QTc (ms)			
Continuous, means ± SD	478 ± 57	484 ± 52	.02
≥500, %	32	34	.44
RR (s), means ± SD	860 ± 250	856 ± 216	.91
Location of mutation			
Pore-loop, %	28	28	.93
Non–pore-loop:			
TM, %	4	4	.98
N-term/C-term, %	35	34	.98
Type of mutation			
Missense, %	65	68	.33
Nonmissense, %	35	32	
LQTS therapies			
β-blockers, %	52	55	.22
Pacemaker, %	3	6	.02
LSCD, %	0.6	2	.12
ICD, %	8	16	<.001
Cardiac events during follow-up			
Syncope, %	24	46	<.001
ACA, %	3	9	<.001
SCD, %	8	12	.02
Appropriate ICD shocks, %	1.5	1.9	.58
First SCD or ACA, %*	10	19	<.001

ACA = aborted cardiac arrest; ICD = implantable cardioverter-defibrillator; LCSD = left cervical sympathetic denervation; LQTS = long QT syndrome; SCD = sudden cardiac death; TM = transmembrane; QTc = corrected QT; RR = relative risk.
*Only the first event for each patient was considered.

Multivariate analysis in the total study population (Table 2) showed that during childhood (ages 0 to 13 years), the risk of ACA or SCD was similar between women and men (hazard ratio [HR] 1.53; $P = .33$), whereas after the onset of adolescence (age >13 years), women showed a significantly higher risk for ACA or SCD as compared with men (HR 2.23; $P < .001$). Mutations located in the pore-loop region of the *KCNH2* channel were shown to be associated with a significant 39% ($P = .04$) increase in the risk for ACA or SCD as compared with other ion channel mutations (Table 2). Results were similar when the secondary end point of a first ACA, SCD, or appropriate ICD shock was assessed.

Table 2 Multivariate analysis: risk factors for ACA/SCD among all LQT2 patients*

Risk factor	Relative risk		
	Hazard ratio	95% confidence interval	*P* value
Gender: female vs. male			
Age group: 0 to 13 years	1.53	0.72–3.26	.33
Age group: 14 to 40 years	2.23	1.55–3.21	<.001
Mutation location			
Pore-loop vs. non–pore-loop	1.39	1.02–1.91	.04
Pore-loop vs. C/N-term	1.44	1.06–1.97	.02
TM (nonpore) vs. C/N-term	0.91	0.45–1.87	.80
Mutation type			
Missense vs. nonmissense	0.87	0.62–1.23	.43
QTc duration (ms)			
≥500 vs. <500	3.24	2.05–5.12	<.001
Time-dependent syncope			
Syncope vs. no syncope	3.15	2.26–4.38	<.001

Abbreviations as in Table 1.
*Models were further adjusted for missing QTc values, time-dependent β-blocker therapy, and the occurrence of syncope prior to the end point (assessed as a time-dependent covariate).

Gender-specific risk factors for life-threatening cardiac events in LQT2 patients

Kaplan-Meier survival analysis showed that the cumulative probablity of ACA or SCD by age 40 years was high in women with or without pore-loop mutations (35% and 23%, respectively; $P = .02$ [Fig. 3]). In contrast, in men the rate of ACA or SCD was high among those with pore-loop mutations (28%) and relatively low among non–pore-loop mutations carriers (8%; $P < .001$ [Fig. 4]). Consistent with these findings, gender-specific multivariate analysis (Table 3) showed that the risk for ACA or SCD was not significantly different among women with or without pore-loop mutations (HR 1.20; $P = .33$), whereas men with pore-loop mutations showed a significantly higher risk for ACA or SCD as compared with

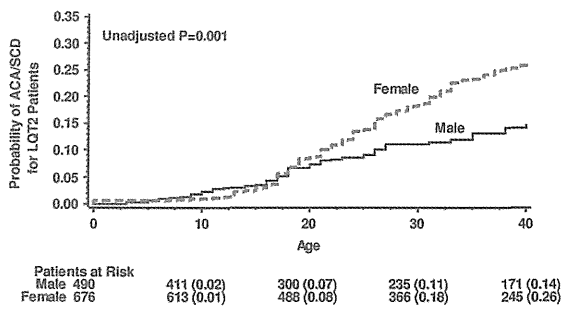

Figure 2 Kaplan-Meier estimates of the cumulative probability of aborted cardiac arrest or sudden cardiac death in LQT2 patients by gender. ACA = aborted cardiac arrest; LQT2 = long QT syndrome type 2; SCD = sudden cardiac death.

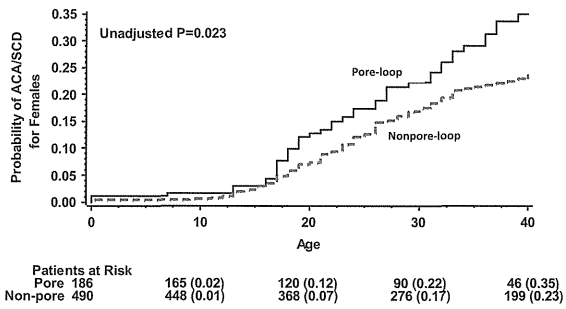

Figure 3 Kaplan-Meier estimates of the cumulative probability of aborted cardiac arrest or sudden cardiac death in LQT2 women by mutation location. ACA = aborted cardiac arrest; LQT2 = long QT syndrome type 2; SCD = sudden cardiac death.

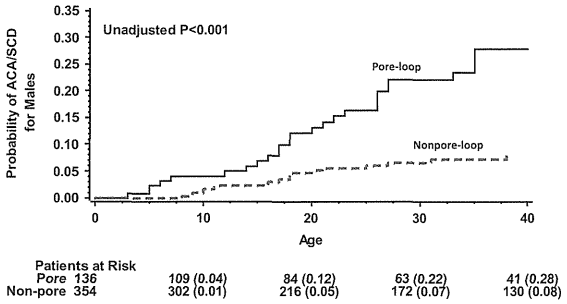

Figure 4 Kaplan-Meier estimates of the cumulative probability of a first aborted cardiac arrest or sudden cardiac death in LQT2 men by mutation location. ACA = aborted cardiac arrest; LQT2 = long QT syndrome type 2; SCD = sudden cardiac death.

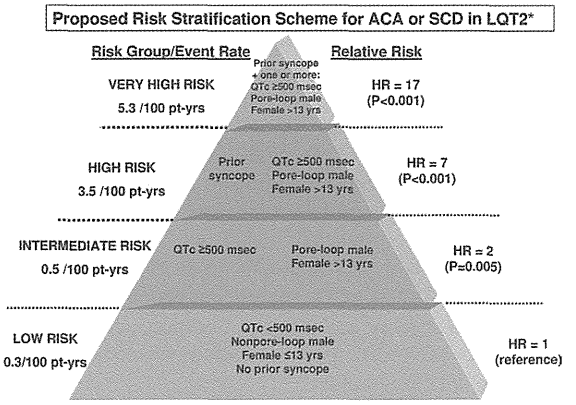

Figure 5 Proposed scheme for risk stratification for the end point of ACA or SCD in LQT2 patients by gender, mutation location, QTc, and a history of prior syncope. *Hazard ratios and score estimates were obtained from a multivariate Cox model that included interactions among the identified risk factors (categorized by QTc duration, time-dependent syncope, gender, and mutation location); decimal points in HRs are rounded to the nearest whole number; event rates per 100 person-years were calculated by dividing the number of life-threatening cardiac events (comprising ACA or SCD) in each risk category by the total follow-up time in the category (with follow-up censored after the occurrence of a ACA) and multiplying the result by 100. ACA = aborted cardiac arrest; HR = hazard ratio; LQT2 = long QT syndrome type 2; SCD = sudden cardiac death; QTc = corrected QT.

men without pore-loop mutations (HR 2.18; P = .01). Results for both men and women were consistent when the reference group of non–pore-loop mutations was further subcategorized into the transmembrane (non–pore-loop) and C/N-terminus regions (Table 3).

QTc ≥500 ms was associated with >2-fold and >4-fold risk increase in men and women, respectively, whereas the mutation-type was not associated with a statistically significant risk increase (Table 3). Similarly, the occurrence of syncope during follow-up was associated with nearly a 3-fold increase in the risk of subsequent ACA or SCD in men, with a >3-fold risk increase in women (Table 3).

Time-dependent medical therapy with β-blockers was associated with a significant 61% reduction in the risk of ACA or SCD in the total study population (HR 0.39 [95% confidence interval 0.20 to 0.74]). The benefit of treatment with β-blockers was not significantly different between men and women (P value for β-blocker–by–gender interaction = 0.23).

Risk stratification for ACA or SCD in LQT2 patients

Using interaction terms among risk factors related to gender, mutation location, QTc duration, and time-dependent syncope in the time-dependent Cox models, we identified 4 risk groups with significantly different risk for the end point of ACA or SCD (Fig. 5): (1) a low-risk group, comprising LQT2 patients with no risk factors (i.e., QTc <500 ms, no prior syncope, male subjects without pore-loop mutations or female subjects ≤13 years of age); (2) an intermediate-risk

Table 3 Multivariate analysis: risk factors for ACA/SCD among LQT2 patients by gender*†

	LQT2 male subjects		LQT2 female subjects	
	Hazard ratio (95% confidence interval)	P value	Hazard ratio (95% confidence interval)	P value
Mutation location				
Pore-loop vs. non–pore-loop	2.18 (1.28–3.72)	.01	1.20 (0.83–1.74)	.33
Pore-loop vs. C/N-term	2.04 (1.15–3.61)	.01	1.18 (0.81–1.70)	.39
TM (nonpore) vs. C/N-term	NA‡		1.25 (0.60–2.58)	.56
Mutation type				
Missense vs. nonmissense	0.56 (0.29–1.06)	.08	1.29 (0.82–1.74)	.25
QTc duration (ms)				
≥500 vs. <500	2.16 (1.08–5.06)	.03	4.05 (2.33–7.04)	<.001
Time-dependent syncope				
Syncope vs. no syncope	2.83 (1.36–5.58)	.01	3.32 (2.19–4.87)	<.001

Abbreviations as in Table 1.

*Findings were further adjusted for missing QTc values, time-dependent β-blocker therapy, and the occurrence of syncope prior to the end point (assessed as a time-dependent covariate).

†Models were carried out in the total population using interaction-term analysis, with interactions tested one at a time; all interaction P values were >.05.

‡Hazard ratio was not computed due to a low event rate in male patients with TM mutations.

group (HR vs. low-risk group = 2.14; P =.005), including (a) male subjects with pore-loop mutations or women >13 years of age (regardless of mutation location) and no additional risk factors; and (b) patients with QTc ≥500 ms and no additional risk factors; (3) a high-risk group (HR vs. low-risk group = 7.22; P <.001), including (a) patients with prior syncope and no additional risk factors, and (b) male subjects with pore-loop mutations or female subjects >13 years of age with QTc ≥500 ms, but without prior syncope; and (4) a very-high-risk group (HR vs. low-risk group = 17.01; P <.001), comprising patients who experienced prior syncope and also had 1 or more additional risk factor (i.e., QTc ≥500 ms, male with a pore-loop mutation or female >13 years old).

The nature of time-dependent covariates precludes assessment of cumulative event rates based only on the covariate pattern at the time origin. Therefore, to obtain an estimate of event rates, we adjusted the number of events for the follow-up time in each risk group. Thus, among very-high-risk patients the rate of ACA or SCD was 5.3 per 100 patient-years; high-risk patients experienced 3.5 life-threatening cardiac events per 100 patient-years; intermediate-risk patients had an event rate of 0.5 per 100 patient-years, whereas among low-risk patients the rate of ACA or SCD was only 0.3 per 100 patient years (Fig. 5).

Discussion

The present study is the first to assess gender differences in the risk of life-threatening cardiac events in LQT2, and to relate gender-specific risk in this population to the location of the disease-causing mutation. We have shown that among patients with LQT2: (1) both men and women have a relatively low rate of ACA or SCD during childhood, whereas after the onset of adolescence and throughout adulthood women show a significantly higher rate of life-threatening events as compared with men; (2) the risk of ACA or SCD in women is high regardless of the location of the disease-causing mutation in the *KCNH2* channel, whereas pore-loop mutations identify increased risk for ACA or SCD in men; and (3) combined assessment of clinical and mutation-specific risk factors can be used for improved risk stratification for life-threatening cardiac events in patients with LQT2.

In a prior study, Zareba et al.[7] assessed age-dependent gender differences in the risk of cardiac events (comprising mostly nonfatal syncopal episodes) among 533 genotyped patients from the International LQTS Registry. The study included 209 LQT2 patients, and showed that in this population no significant gender-related differences in the risk of cardiac events were present duirng childhood, whereas in the age range of 16 through 40 years, LQT2 women had >3-fold higher risk of cardiac events as compared with men.[7] Possibly due to sample size limitations, the study did not identify a significant gender-related risk difference when the more severe end point of a first life-threatening cardiac event was assessed. The present study comprises the largest LQT2 population reported to date of 1,166 patients. We have shown that after the onset of adolescence there is a pronounced increase in the risk of ACA or SCD among LQT2 women (resulting in a cumulative event rate of 26% by age 40 years), whereas the risk of ACA or SCD among LQT2 men remains significantly lower throughout follow-up (resulting in a cumulative event rate of 14% by age 40 years). These age-gender risk differences in the clinical course of LQT2 patients may be mediated by the opposing effects of male and female sex hormones on the potassium channel. Testosterone was found to shorten the action potential duration and the QT interval through enhancement of the I_{Kr} current,[12,13] and thus may be associated with QT shortening in male subjects after childhood. In contrast, estrogen was shown to exhibit both acute and genomic effects on I_{Kr}, including reduction in channel function and prolongation of ventricular repolarization.[14,15] Thus, LQT2 women who harbor mutations impairing potassium channel activity may be specifically sensitive to estrogen activity that may result in an increase in the risk for arrhythmic events after the onset of adolesence.

Recent data from the International LQTS Registry show that the location of the mutation in the ion channel is an important determinant of arrhythmic risk in LQTS patients. In a study of 201 LQT2 subjects with a total of 44 different *KCNH2* mutations, Moss et al.[5] showed that subjects harboring pore mutations exhibited a more severe clinical course and experienced a higher frequency of cardiac events, occurring at an earlier age, than did subjects with nonpore mutations. Consistent with these findings, in a more recent study, Shimizu et al.[6] showed that mutations in the pore region were associated with a greater risk of cardiac events as compared with mutations located in other regions in the *KCNH2* channel. The pore region forms the potassium conductance pathway, and most mutations present in this region have a dominant-negative effects on I_{Kr},[10] suggesting that the pore region is critical for channel function. The findings of the present study are consistent with the previous link of high cardiac risk to pore-domain mutations, and show that the presence of pore-loop mutations was independently associated with a significant 39% increase in the risk of ACA or SCD in the total LQT2 population. Our findings, however, extend prior data and show a differential effect of mutation-related risk between LQT2 men and women. Thus, among men the presence of pore-loop mutations was associated with >2-fold (P = .01) increase in the risk of ACA or SCD, whereas women with pore-loop mutations did not display a significant increase in risk as compared with those with non–pore-loop mutations. Accordingly, by age 40 years the rate of life-threatening cardiac events among men with pore-loop mutations was >3-fold higher as compared with those with other mutations (28% vs. 8%, respectively), whereas the corresponding event rates among women were high regardless of mutation location (35% and 23%, respectively). Possible mechanisms that may explain the observed gender-related differences include the fact that estrogen increases I_{Kr} independently of mutation location, thereby increasing ar-

rhythymic risk even among women who carry lower-risk (nonpore) mutations in the *KCNH2* channel. In contrast, the protective effects of testosterone on I_{Kr} and ventricular repolarization in postadolescent male subjects result in a reduction in the risk of arrhytmic events among carriers of low-risk mutations, with a possible remaining residual risk in men who harbor higher-risk mutations in the functionally more important pore-loop region.

In a prior study, Priori et al.[16] proposed a risk stratification scheme for LQTS patients that is based on the LQTS genotype, QTc, and gender. This study, however, assessed a composite end point of cardiac events of any type, comprising mostly nonfatal symcopal episodes,[16] whereas the large sample size of genotyped LQT2 patients in the present study facilitated for the first time the development of a risk stratification scheme for the end point of life-threatening cardiac events within the LQT2 population. We show that combined assessment of clinical and genetic data, related to mutation location, can be used to identify risk groups of LQT2 patients with a significantly different risk of ACA or SCD and with a pronounced difference in the rate of ACA or SCD during follow-up. These findings suggest that risk stratification in LQTS should combine clinical and mutation-related risk factors that are specific for each of the 3 main LQTS genotypes.

Prior data suggest that LQT2 patients expereince a relatively high rate of cardiac events during β-blocker therapy.[17] In the present study, medical therapy with β-blockers was associated with a pronounced 61% reduction in the risk of ACA or SCD in the total LQT2 population. However, the present findings also suggest that careful follow-up, with consideration of ICD therapy for primary prevention, is warranted in high- and very-high-risk LQT2 patients. These patient subsets were shown to experience 3.5 to 5.3 events per 100 patient years (which corresponds to a high rate of 1.5 to 2.1 life-threatening cardiac events per patient from birth through age 40 years) despite frequent usage of β-blocker therapy (>80%).

Study limitations

We did not carry out expression studies to assess the effects of estrogen and testosterone on ion channel mutations by their location. Therefore, further studies are necessary to evaluate the mechanism related to the observed gender-specific risk related to mutation location.

Because of sample size limitations, we did not carry out comprehensive analysis of the relation between all function regions of the *KCNH2* channel (including the PAS, CNBD, and other C-terminus and and N-terminus domains) and gender-specific risk. However, the results from the secondary analysis in which non–pore-loop mutations were further subcategorized into mutations in the transmembrane and C/N-terminus regions support the consistency of our findings.

Conclusions and clinical implications

The present study shows a distinct association between mutation characteristics and time-dependent differences in the clinical course of LQT2 patients. We have shown that after the onset of adolescence, women with and without high-risk mutations show increased risk for life-threatening cardiac events, whereas the risk of ACA or SCD in men is increased only among carriers of the higher-risk pore-loop mutations. Thus, a comprehensive approach that combines clinical and genetic data should be used for risk assessment and management of LQTS patients.

Appendix

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.hrthm.2011.03.049.

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Flecainide Therapy Reduces Exercise-Induced Ventricular Arrhythmias in Patients With Catecholaminergic Polymorphic Ventricular Tachycardia

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Objectives This study evaluated the efficacy and safety of flecainide in addition to conventional drug therapy in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT).

Background CPVT is an inherited arrhythmia syndrome caused by gene mutations that destabilize cardiac ryanodine receptor Ca^{2+} release channels. Sudden cardiac death is incompletely prevented by conventional drug therapy with β-blockers with or without Ca^{2+} channel blockers. The antiarrhythmic agent flecainide directly targets the molecular defect in CPVT by inhibiting premature Ca^{2+} release and triggered beats in vitro.

Methods We collected data from every consecutive genotype-positive CPVT patient started on flecainide at 8 international centers before December 2009. The primary outcome measure was the reduction of ventricular arrhythmias during exercise testing.

Results Thirty-three patients received flecainide because of exercise-induced ventricular arrhythmias despite conventional (for different reasons, not always optimal) therapy (median age 25 years; range 7 to 68 years; 73% female). Exercise tests comparing flecainide in addition to conventional therapy with conventional therapy alone were available for 29 patients. Twenty-two patients (76%) had either partial ($n = 8$) or complete ($n = 14$) suppression of exercise-induced ventricular arrhythmias with flecainide ($p < 0.001$). No patient experienced worsening of exercise-induced ventricular arrhythmias. The median daily flecainide dose in responders was 150 mg (range 100 to 300 mg). During a median follow-up of 20 months (range 12 to 40 months), 1 patient experienced implantable cardioverter-defibrillator shocks for polymorphic ventricular arrhythmias, which were associated with a low serum flecainide level. In 1 patient, flecainide successfully suppressed exercise-induced ventricular arrhythmias for 29 years.

Conclusions Flecainide reduced exercise-induced ventricular arrhythmias in patients with CPVT not controlled by conventional drug therapy. (J Am Coll Cardiol 2011;57:2244–54) © 2011 by the American College of Cardiology Foundation

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a malignant inherited arrhythmia syndrome characterized by physical or emotional stress-induced bidirectional or polymorphic ventricular tachycardia (VT) in structurally

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normal hearts, with a high fatal event rate in untreated patients (1–3). Approximately 60% of CPVT patients have mutations in genes encoding the cardiac ryanodine receptor Ca^{2+} release channel (RyR2) or cardiac calsequestrin (4–6), and these cause spontaneous RyR2 channel openings (7,8). The resulting increase in cytosolic Ca^{2+} triggers delayed afterdepolarizations, ventricular premature beats (VPBs), and ventricular tachycardia, especially under conditions of β-adrenergic stimulation (9,10).

Hence, β-blockers are considered first-line therapy, but unfortunately they are not completely effective in preventing life-threatening arrhythmias (1–3,11–16). An implantable cardioverter-defibrillator (ICD) is often used in patients who continue to have ventricular arrhythmias despite β-blocker therapy. However, ICDs are not fully protective and can be proarrhythmic in CPVT patients because both appropriate and inappropriate ICD shocks can trigger catecholamine release, subsequently resulting in multiple shocks (arrhythmic storm), and death (17,18). Thus, additional therapy is desired for CPVT. Small case series show that left cardiac sympathetic denervation is effective in patients who are insufficiently protected by β-blocker therapy and/or experiencing too many ICD shocks (19–22).

Recently, we discovered that the antiarrhythmic agent flecainide directly blocks RyR2 channels, prevents RyR2-mediated premature Ca^{2+} release, and suppresses triggered beats in myocytes isolated from mouse hearts lacking calsequestrin, an animal model of CPVT (23). This effect is not mediated by Na^{+}-channel block, the conventional mode of action thought to underlie flecainide activity, but rather can be attributed to open state block of RyR2 channels (that is, flecainide directly targets the molecular defect responsible for the arrhythmogenic Ca^{2+} waves that trigger CPVT in vivo) (24). In preliminary work, flecainide also appeared to be effective in 2 highly symptomatic CPVT patients (23).

Here we collate the data from every CPVT patient started on flecainide at 8 international centers and report on the efficacy and safety of flecainide treatment in CPVT.

Methods

Participants and study design. To better understand the efficacy and safety of flecainide in CPVT, we reviewed the chart of each consecutive CPVT patient in whom flecainide was started at 8 tertiary referral centers in the Netherlands, Canada, France, Israel, Japan, and the United States before December 2009. All patients had a clinical diagnosis of CPVT (based on exercise-induced bidirectional or polymorphic VT in the absence of structural cardiac disease) and a putative pathogenic mutation in the gene encoding RyR2 or cardiac calsequestrin. Determination of flecainide starting dose and dosing increases were made by the treating physician as part of specialized clinical care. Data collection and analysis were done retrospectively by chart review and were approved by the institutional review board at each participating institution.

Abbreviations and Acronyms

CPVT = catecholaminergic polymorphic ventricular tachycardia

ICD = implantable cardioverter-defibrillator

NSVT = nonsustained ventricular tachycardia

RyR2 = cardiac ryanodine receptor Ca^{2+} release channel

VPB = ventricular premature beat

VT = ventricular tachycardia

Primary and secondary outcome measures. Couplets or VT during exercise are significantly associated with future arrhythmic events in CPVT (2). Because all patients were monitored by repeat exercise testing as part of routine clinical care, we used the reduction of ventricular arrhythmias during exercise testing as the primary outcome measure. The effect of flecainide was quantified by comparing the ventricular arrhythmia score (see later text) of the last exercise test on conventional therapy with the ventricular arrhythmia score of the first exercise test after a minimum of 5 days on the stable flecainide dose. Only patients on an unchanged or lower β-blocker dose during flecainide treatment were included in the primary analysis. Depending on the site, exercise testing was performed using a treadmill (standard or modified Bruce protocols) or bicycle ergometer.

Secondary outcome measures were the incidence of arrhythmic events (defined as syncope, aborted cardiac arrest, appropriate ICD shocks, and sudden cardiac death), assessment of well-being and side effects of flecainide, and monitoring of proarrhythmic effects of flecainide, in particular QRS duration during exercise and increase in the ventricular arrhythmia burden (25,26).

Definitions of ventricular arrhythmia. Exercise testing was analyzed and scored using the following pre-defined parameters (modified from Rosso et al. [27]): 1) ventricular arrhythmia score, defined by the worst ventricular arrhythmia (1, no or isolated VPBs; 2, bigeminal VPBs and/or frequent VPBs [>10 per min]; 3, couplet; and 4, nonsustained ventricular tachycardia [NSVT], ≥3 successive VPBs); 2) the presence of either of the parameters of the ventricular arrhythmia score or the presence of bidirectional VT (>3 successive VPBs with a beat-to-beat alternating right and left QRS axis); 3) sinus rate at the onset of ventricular arrhythmias, most often an isolated VPB; 4) maximum number of VPBs during a 10-s period; and 5)

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Table 1 Baseline Characteristics and Flecainide Therapy Parameters

Patient #	Sex	Mutation*	Age at First Symptom, yrs	Proband or Relative	Presenting Symptom	Age at Diagnosis, yrs	Aborted Cardiac Arrest	ICD	Age at Baseline, yrs	Drug Therapy at Baseline, mg (mg/kg body weight)	Indication for Starting Flecainide Treatment	Daily Starting/Stable Flecainide Dose, mg (mg/kg body weight)†	Follow-Up, months	Response to Flecainide Treatment	Side Effects of Flecainide
1‡	F	A4091T	5	Proband	Seizure	6	Yes	Yes	13	Nadolol 160 (2.4), verapamil 180 (2.7)§	NSVT (on Holter recordings)	300 (4.5)	25	Complete	None
2	F	R2401H	6	Proband	Syncope	6	No	No	7	Nadolol 15 (0.9)	NSVT (on Holter recordings)	96 (5.6)/120 (7.1)	22	None	None
3‡	M	CASQ2: 532+ 1G>A	NA	Relative	None	3	No	Yes	12	Metoprolol 125 (2.3), verapamil 120 (2.2)§	NSVT (on ICD recordings) + frequent ICD shocks	100 (1.9)/150 (2.8)	28	Complete	None
4‡	F	E4076K	28	Relative	Syncope	31	No	No	37	Metoprolol 100 (1.6)	Couplets + side effects	100 (1.6)/150 (2.4)	23	Partial	None
5	F	S4124G	NA	Relative	None	31	No	No	36	Bisoprolol 5 (0.08), verapamil 240 (3.7)§	NSVT + side effects	100 (1.5)/150 (2.3)	28	Partial	None
6	F	S4124G	45	Proband	Syncope	50	No	No	68	Bisoprolol 2.5 (0.04)	NSVT + side effects	75 (1.2)/150 (2.4)	13	Partial	Sinus arrest and dizziness
7	F	S4124G	26	Relative	Aborted cardiac arrest	26	Yes	No	41	None‖	NSVT	150 (2.2)	22	Partial	Dizziness
8‡	M	S4124G	8	Relative	Syncope	8	No	No	10	Metoprolol 50 (1.9)	Couplets	50 (1.9)/100 (3.7)	22	Partial	None
9‡	M	E4187Q	NA	Proband	None (detected by cardiological examination after SCD of his son)	47	No	No	53	Metoprolol 200 (2.4)	NSVT + side effects	150 (1.7)	20	Partial	None
10‡	M	E4187Q	NA	Relative	None	19	No	Yes	25	Metoprolol 200 (2.7)	NSVT	150 (2.0)	20	None	None
11‡	F	E4187Q	NA	Relative	None	14	No	Yes	20	Metoprolol 150 (2.6)	NSVT	100 (1.8)	20	Complete	None
12‡	M	E4187Q	NA	Relative	None	11	No	Yes	17	Metoprolol 100 (1.6)	NSVT	100 (1.6)/300 (4.8)	20	Partial	None
13	F	E1724K	13	Relative	Syncope	13	No	No	25	Metoprolol 25 (0.4)	Couplets	100 (1.3)¶#	NA#	NA#	Fatigue, dizziness, chest pain
14	F	E1724K	9	Proband	Syncope	15	No	No	50	Sotalol 160 (2.1)	Bigeminy/frequent VPBs + side effects	100 (1.3)	20	None	None
15‡	M	R420W	NA	Relative	None	38	No	No	49	Metoprolol 100 (1.3)	Couplets	150 (1.9)/300 (3.9)	19	Complete	None
16‡	M	R420W	NA	Relative	None	12	No	No	16	Metoprolol 100 (1.7)	NSVT	100 (1.7)	19	Complete	None
17	F	Y4962C	NA	Relative	None	41	No	No	45	Atenolol 25 (0.4)	NSVT	150 (2.5)	12	Complete	None
18‡	F	M2605V, A4510T, 14757-6_7CT>TA	NA	Proband	None (detected by exercise testing at pre-participation screening)	40	No	No	40	Metoprolol 100 (1.4)	Couplets	200 (2.9)	18	Partial	None

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