Contemporary Outcomes in Patients With Long QT Syndrome

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ABSTRACT

BACKGROUND Long QT syndrome (LQTS) is a potentially lethal cardiac channelopathy with a 1% to 5% annual risk of LQTS-triggered syncope, aborted cardiac arrest, or sudden cardiac death.

OBJECTIVES This study sought to evaluate LQTS outcomes from a single center in the contemporary era.

METHODS The authors conducted a retrospective study comprising the 606 patients with LQTS (LQT1 in 47%, LQT2 in 34%, and LQT3 in 9%) who were evaluated in Mayo Clinic’s Genetic Heart Rhythm Clinic from January 1999 to December 2015. Breakthrough cardiac events (BCEs) were defined as LQTS-attributable syncope or seizures, aborted cardiac arrest, appropriate ventricular fibrillation-terminating implantable cardioverter-defibrillator shocks, and sudden cardiac death.

RESULTS There were 166 (27%) patients who were symptomatic prior to their first Mayo Clinic evaluation. Median age at first symptom was 12 years. Treatment strategies included no active therapy in 47 (8%) patients, beta-blockers alone in 350 (58%) patients, implantable cardioverter-defibrillators alone in 25 (4%) patients, left cardiac sympathetic denervation alone in 18 (3%) patients, and combination therapy in 166 (27%) patients. Over a median follow-up of 6.7 (IQR: 3.9 to 9.8) years, 556 (92%) patients have not experienced an LQTS-triggered BCE. Only 8 of 440 (2%) previously asymptomatic patients have experienced $\leq 1$ BCE. Among the 30 patients with $\geq 2$ BCEs, 2 patients have died and 3 LQT3 patients underwent cardiac transplantation.

CONCLUSIONS Although outcomes have improved markedly, further optimization of treatment strategies is still needed given that 1 in 4 previously symptomatic patients experienced at least 1 subsequent, albeit nonlethal, LQTS-triggered cardiac event. (J Am Coll Cardiol 2017;70:453–62) © 2017 by the American College of Cardiology Foundation.
Long QT syndrome (LQTS) is one of the most common cardiac channelopathies that predisposes patients to arrhythmogenic syncope, seizures, and sudden cardiac death (SCD) (1-3). Clinical expressivity of LQTS ranges from a lifelong asymptomatic state with no electrocardiographic findings (i.e., concealed LQTS) to frequent, recurrent LQTS-triggered torsades culminating in SCD (4,5). Despite numerous genotype-phenotype correlation studies, the extreme variance in expressivity makes it difficult for the patient and the physician to accurately predict the chance of experiencing an LQTS-related breakthrough cardiac event (BCE).

Current knowledge regarding treated and untreated cardiac event rates in patients with LQTS stems from initial retrospective and prospective studies from international LQTS registry data, or small, single-center studies generally evaluating a specific treatment (e.g., beta-blockers and left cardiac sympathetic denervation [LCSD]). It has been reported that untreated asymptomatic patients with genotyped LQTS have a high risk of any cardiac event and SCD (36% and 13%, respectively, in a 28-year follow-up) (6). As first shown in 1985, beta-blockers drastically reduced mortality (from event rates ranging from as high as 71% in previously untreated asymptomatic patients to 6% in patients on therapy), and for these past 30 years beta-blocker therapy has been the initial treatment of choice (7). Recent studies have focused mostly on evaluating outcomes of single-treatment modalities. Beta-blockers (chiefly nadolol and propranolol) reduce mortality to approximately 0.5% to 2% during a follow-up of 5 to 10 years (8,9). However, despite this significant decrease in mortality, beta-blocker-treated LQTS patients continue to have an annualized BCE rate of around 3% (8,9). For those patients with recurrent BCEs despite pharmacotherapy, LCSD significantly reduces the number of BCEs (10-12).

Given that our current outcome estimates are derived mostly from multicenter or registry-based studies, we sought to evaluate the outcomes of patients with congenital LQTS who were evaluated and treated in single specialty center dedicated to patients with genetic heart rhythm diseases such as LQTS.

**METHODS**

We performed a retrospective review of the electronic medical records of 606 patients who were evaluated and treated for LQTS at Mayo Clinic’s Genetic Heart Rhythm Clinic between the years of 1999 and 2015. For all patients, the electronic medical records were reviewed for demographics, clinical symptomatology, family history, genetic studies, LQTS-directed therapy, and occurrence of LQTS-related BCEs. A patient was considered symptomatic if he or she had an LQTS-related cardiac symptom prior to diagnosis (fetal arrhythmia, arrhythmogenic syncope or seizure, or cardiac arrest). Patients were included if they met any of the following diagnostic criteria for LQTS using the 2013 Heart Rhythm Society guidelines at the time of last medical record review: presence of LQTS risk score ≥3.5, unequivocal pathogenic mutation, or QTc interval of 480 to 499 ms on repeated electrocardiograms without secondary cause (13). The patient’s QTc interval was measured on their first Mayo Clinic electrocardiogram using the Bazett formula by computer and manually verified (M.J.A.).

The primary outcome evaluated was the occurrence of an LQTS-related BCE, which was defined as arrhythmogenic syncope, seizure, aborted cardiac arrest (ACA), an appropriate VF-termination implantable cardioverter-defibrillator (ICD) shock, or SCD after their first evaluation at our specialty center. Because the vast majority of the patients did not have an internal loop recorder to confirm that the BCE of syncope or seizure was indeed an LQTS-triggered torsadogenic episode, arrhythmogenic syncope and arrhythmogenic syncope with subsequent seizures was a clinical judgment call adjudicated by a single genetic cardiologist (M.J.A.) after thorough review of the event during the patient’s face-to-face clinical evaluation or telecommunication. Arrhythmogenic syncope was defined as a sudden loss of consciousness with spontaneous recovery and excluded all events assessed to be likely vasovagal in nature (e.g., emotional reactions, in the setting of heat or dehydration, and abrupt postural changes). Arrhythmogenic seizure was defined as sudden loss of consciousness with subsequently observed generalized tonic or clonic seizure activity with spontaneous recovery. Seizures assessed to be focal, febrile, or acquired were excluded. Treated follow-up was defined as time from initial Mayo Clinic evaluation until last evaluation, provider-patient communication regarding LQTS-related events, or censored at December 1, 2015. Annual event rate was defined as the proportion of patients with at least 1 BCE divided by the number of median follow-up years.

Statistical analysis was performed by using Wilcoxon test for nonparametric measures, and multiple comparisons of nonparametric measures were performed using the Steel-Dwass test. For the purposes...
of this study, all continuous data were described as median (interquartile range [IQR]). The Fisher exact test was used to compare cohort characteristics, where type I error was minimized using Bonferroni correction for multiple comparisons. Kaplan-Meier survival curves were created with censoring at first BCI or last follow-up, and used to compare outcomes based on symptomatic status and LQTS genotype. Both LQT4-17 and genotype-negative or phenotype-positive groups were removed from Kaplan-Meier analysis due to small numbers. All tests were performed using JMP software version 12.0 (SAS Institute, Cary, North Carolina).

RESULTS

The demographics of the entire LQTS cohort of 606 patients (356 female patients [59%]) are detailed in Table 1, where the median age of diagnosis was 14.7 (IQR: 6.8 to 31.8) years of age and the median QTc interval was 465 (IQR: 441 to 490) ms. Genetic testing was positive in 592 (98%) patients, of whom 287 (47%) were LQT1 (KCNQ1), 204 (34%) were LQT2 (KCNH2), 56 (9%) were LQT3 (SCN5A), 29 (5%) had multiple LQTS-associated mutations (LQTM), and 16 (3%) were LQT4-17. Overall, the median treated follow-up was 6.7 (IQR: 3.9 to 9.8) years.

A detailed comparison of baseline cohort characteristics by those patients who were symptomatic versus those who were asymptomatic prior to diagnosis is also given in Table 1. Importantly, the symptomatic group had a longer median QTc interval (484 ms vs. 459 ms; \( p = 0.0004 \)) when compared with LQT1 (460 [IQR: 439 to 486] ms; \( p = 0.002 \)) compared with the rest of the group (LQT2: 459 [IQR: 438-480] ms vs. 484 [459-513] ms; \( p = 0.0001 \)).

When comparing the clinical characteristics by genotype (Table 2), patients with LQTM had a significantly longer median QTc interval (485 [IQR: 460 to 502] ms) when compared with LQT1 (460 [IQR: 439 to 486] ms; \( p = 0.02 \)). Compared with the rest of the LQTS genotypes, significantly fewer LQT1 patients (62 [22%]; \( p = 0.002 \)) and significantly more patients with LQT3 (17 [58%]; \( p = 0.0004 \)) presented with LQTS symptoms prior to diagnosis. Patients with LQTM had a significantly earlier age of first event compared with patients with LQT2 (\( p = 0.04 \)); patients with LQT3 mutations had a significantly earlier age of first event compared with patients with LQT1 (\( p = 0.03 \)) and LQT2 (\( p = 0.03 \)). None of the patients with LQT4-17 had a family history of SCD, which was significantly lower when compared with the rest of the group (\( p = 0.0002 \)). Also, genotype-negative or phenotype-positive patients were significantly less likely to have a family history of LQTS when compared with all other groups (\( p = 0.0004 \)).

The individualized treatment programs ranged from intentional nontreatment (preventative measures only including LQTS-related lifestyle recommendations such as avoidance of QT prolonging medications, dehydration, and electrolyte imbalances, as well as education on and a strong recommendation to purchase an automated external defibrillator) to triple therapy that involved a combination of pharmacotherapy, LCSD, and ICD (Table 3 and Figure 1). LQTS-directed therapy listed, from most common to least, were: beta-blockers alone in 350 (58%) patients; beta-blockers with ICD in 78 (13%) patients; intentional nontreatment in 47 (8%) patients; beta-blockers with LCSD in 33 (5%) patients; ICD alone in 25 (4%) patients; beta-blockers, LCSD, and ICD in 21 (3%) patients; and LCSD alone in 18 (3%) patients. The rest of the therapeutic combinations together accounted for the remaining 34 (6%) patients.

Though ICD monotherapy, LCSD monotherapy, or intentional nontherapy are not typically considered,
there were instances where these LQTS-directed treatment options were seen as the best approach in the patient's individualized treatment plan, balancing the future risk of event, medication or procedure side effects, and compliance. Specifically, the 47 patients on no active therapy were considered extremely low risk based on a median older age of diagnosis (39 [IQR: 17 to 53]) years), lower median QTc interval (445 [IQR: 427 to 474] ms), and the fact that almost all patients (45 [96%]) had been lifelong asymptomatic at the time of their first evaluation. Most of the 58 patients with either LCSD or ICD monotherapy were considered moderate-high-risk patients, but were unable to take beta-blockers due to significant daily medication-related side effects resulting in persistent noncompliance.

Treatment outcomes of the entire cohort, comparisons between symptomatic and asymptomatic patients, and comparisons by LQTS genotype are detailed in Tables 4 and 5. Overall, of the 606 patients, only 50 (8%) patients experienced ≥1 LQTS-triggered BCE during a median treated follow-up of 6.7 (IQR: 3.9 to 9.8) years (4,316 total patient-years). This included 20 (3%) patients with only a single BCE, 21 (3%) patients with 2 to 5 Bces, 6 (1%) patients with 6 to 10 Bces, and 3 (<1%) patients with >10 Bces. This amounted to an annual event rate of 1.2% (1.2% of patients had at least 1 BCE per year). The types of BCE observed, from most to least common, were appropriate ventricular fibrillation-terminating ICD shock, syncope or seizure secondary to a suspected LQTS-triggered arrhythmia, ICD storm, ACA, and death. This data as well as the frequency of each type of BCE observed is summarized in Online Table 1. The breakdown of event burden before and after the patients' Mayo Clinic evaluation and treatment are described and shown in Figure 2. As a tertiary care center, 158 (26%) patients had been referred from an outside institution for further treatment guidance after the LQTS diagnosis had been determined and initial treatment for LQTS had already commenced. Among this physician-referred subset, 70 (44%) patients were asymptomatic prior to diagnosis. Among all 166 previously symptomatic patients, 125 (75%) realized a significant decrease in event burden. Conversely, 42 (25%) of these patients experienced subsequent LQTS-triggered Bces.

Overall, the BCE-free survival was 96% at 1 year, 93% at 5 years, and 90% at 10 years for the entire cohort (Figure 3A). In fact, there were only 2 LQTS-related deaths (~0.3% overall, 1% among previously...
symptomatic patients) (Online Table 2) and 3 (<0.5%) heart transplants in over 4,000 collective years of treated follow-up (14). Demographics and clinical details for these 5 cases are summarized in Online Table 2. As previously shown, LQTS patients with symptomatic expression of their disease were more likely to have BCEs. Therefore, our initial comparison of treatment outcomes was by LQTS symptoms prior to diagnosis and is detailed in Table 4. Previously symptomatic LQTS patients had a significantly higher percentage of patients who had a BCE compared with asymptomatic LQTS patients (25% vs. 2%; $p = 0.0001$), a significant difference between BCE-free survival (Figure 3B) ($p = 0.0001$), and a significantly higher annual event rate in symptomatic patients when compared with asymptomatic patients (3.7%/year vs. 0.3%/year; $p = 0.0001$). The BCE-free survival for the asymptomatic cohort was 99.3% at 1 year, 98.7% at 5 years, and 96.9% at 10 years. In comparison, the BCE-free survival for the symptomatic group was 87.1% at 1 year, 76.9% at 5 years, and 71.6% at 10 years (Figure 3B). There were no significant differences between treated follow-up years between asymptomatic and symptomatic patients.

Furthermore, within the symptomatic group, there were 27 (16%) patients who experienced their sentinel event during the first year of life compared with 139 (84%) patients whose sentinel event occurred after 1 year of age. When comparing treatment outcomes between these groups, the patients who presented before 1 year of age showed significantly worse outcomes as demonstrated by higher percentage of patients who experienced a BCE, compared with those who presented after 1 year of age (67% vs. 17%; $p < 0.0001$). Additionally, all 3 of the patients who have undergone transplant and 1 of the 2 patients who succumbed subsequently to SCD were among these 27 patients who presented before 1 year of age.

As beta-blockers have been the gold standard of LQTS-directed pharmacotherapy, we further analyzed if there was a sex-specific risk associated with treatment outcomes. In our cohort of patients treated by a single LQTS specialist, we did not see evidence of a sex-specific effect of beta-blockers, even when subdividing by genotype (Online Table 3). Specifically, among 497 patients on beta-blockers (some treated with concomitant Na blockers or LCSD), there was no statistical difference between female (23 of 290 [7.9%]) and male (17 of 207 [8.2%]) patients who went on to have at least 1 BCE during treated follow-up. Even when removing the potential protective effect of the either LCSD and sodium-channel blockers ($n = 428$ patients on beta-blockers alone), there were no statistical differences between female (11 of 255 [4%]) and male (3 of 173 [2%]) patients in BCEs during follow-up. Similarly, no significant sex-associated differences were seen when subdividing this group by the 3 canonical LQTS genotypes (LQT1, LQT2, LQT3) (Online Table 3).

A comparison of treatment outcomes by LQTS genotype is detailed in Table 5. Both patients with LQT54-17 or genotype negative or phenotype positive were not included in statistical analysis due to low number of patients in these subgroups. There were a significantly higher proportion of patients with LQTM (8 [28%]; $p = 0.001$) or LQT3 (11 [20%]; $p = 0.004$) who had ≥1 BCE when compared with the rest of the LQT genotypes. There was a significant difference in BCE-free survival by genotype ($p < 0.0001$), as shown

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<th>Table 4</th>
<th>Treatment Outcomes and Comparison by Symptomatic Status</th>
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<tr>
<td></td>
<td>Entire Cohort (N = 606)</td>
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<tr>
<td>Follow-up, yrs</td>
<td>6.7 (3.9–9.8)</td>
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<tr>
<td>Event/total</td>
<td>50/606 (8%)</td>
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<tr>
<td>Annual event rate, %/yr*</td>
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<td>Event burden</td>
<td>NA</td>
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*The incidence of a patient with any breakthrough cardiac event (BCE) per yr.
in Figure 3C. One-year and 10-year BCE-free survival was highest in patients with LQT1 (98% and 95%, respectively), whereas 1-year BCE-free survival was lowest in patients with LQT3 (66% and 74%, respectively). Treated follow-up duration was similar between all LQTS genotypes.

**DISCUSSION**

Although the understanding of the pathophysiology, diagnosis, and treatment has advanced considerably since the sentinel description of this disease nearly 60 years ago, the study of its overall outcomes is sparse due to the low prevalence of disease, and has depended on retrospective analysis from multicenter- or registry-based data. Often, patients included in these studies are risk stratified and treated differently from institution to institution with clinical data collected in different ways, complicating generalizability. Given the high clinical stakes for the patient, the marked heterogeneity in expressivity of the genetic substrates, and the multitude of treatment options (beta-blockers, sodium channel blockers, LCSD, and ICD, to name just 4), we undertook the largest single-center outcome study of LQTS patients to date to help better understand the expected genotype- and phenotype-derived incidences of BCEs in the contemporary era.

Until now, our understanding regarding untreated mortality due to SCD or cardiac arrest in LQTS patients comes primarily from 2 studies. In 1985, Schwartz (7) first showed the mortality in untreated symptomatic LQTS patients was extremely high at 71%. Later in 2003, Priori et al. (6) found that even among 647 previously asymptomatic LQTS patients, 13% experienced a sentinel event of ACA or SCD in the untreated state, over a mean follow-up of 28 years before 40 years of age. Following elucidation of the genetic underpinnings of LQTS along with increased availability of clinical genetic testing, we have learned that approximately 25% of LQTS patients have concealed (electrocardiographically normal) LQTS, thereby increasing the prevalence of the disease and decreasing its global severity (4). Beta-blockers, LCSD, and ICD are the principal treatment modalities in LQTS with clear benefit in primary and secondary prevention of SCD in patients with LQTS. In 1985, Schwartz and Locati (15) first showed that beta-blockers can decrease the mortality from 71% to 6% after prospectively following 200 patients. In more recent studies, the reported mortality in patients treated with beta-blockers (with a small percentage of patients with concomitant LCSD) has ranged between 1% and 7% within 5 to 10 years of follow-up (8,9,16). Here, in our patient-tailored treatment program, we report an extremely low mortality of 2 of 606 (0.3%).

<table>
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<th>TABLE 5 Treatment Outcomes and Comparison by LQTS Genotype</th>
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<td>Follow-up, yrs</td>
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<td>Patients with cardiac event</td>
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<td>Annual event rate, %/yr</td>
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<tr>
<td>Event burden</td>
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<tr>
<td>0 BCE</td>
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<tr>
<td>1 BCE</td>
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<td>2–5 BCEs</td>
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<tr>
<td>6–10 BCEs</td>
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<td>&gt;10 BCEs</td>
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Values are median (interquartile range) or n (%), unless otherwise indicated. *Bonferroni correction was used to reduce type I error. †The incidence of a patient with any breakthrough cardiac event (BCE) per year. These patients were excluded from statistical analysis. Bold indicates significant findings.

Abbreviations as in Table 1.
cases overall or 2 of 167 (1%) previously symptomatic cases with similar follow-up.

Though the incidence of LQTS-associated mortality in a treated cohort has decreased sharply, a significant number of previously symptomatic patients continue to have BCEs (syncope, seizure, and ICD shocks) despite maximal therapy. And although, like mortality, a decrease in BCEs has been observed over the last few decades, risk stratification and outcomes can still be improved. In fact, our study suggests that when managed and treated at a dedicated specialty center, anticipated outcomes may exceed expectations that were gleaned from previous studies. In our cohort, there was a significantly lower incidence of patients with 1 or more BCE while under treatment when compared with previous studies: 8% with at least 1 BCE over nearly 7 years follow-up compared with a previously reported 16% to 33% over 5 treated

(A) Breakthrough cardiac event (BCE)-free survival curve for entire long QT syndrome (LQTS) cohort. (B) Comparison of BCE-free survival by symptom status. The blue line represents patients who were asymptomatic at the time of diagnosis and the orange line represents the patients who were symptomatic at the time of diagnosis. (C) Comparison of BCE-free survival by LQTS genotype. LQT1 patients are represented by the blue line. LQT2 patients are represented by the orange line. LQT3 patients are represented by the gray line. Patients with multiple long QT syndrome-associated mutations (LQTM) are represented by the red line.
Among both asymptomatic and previously symptomatic subsets, there have been less BCEs than previously reported: 99% BCE-free survival at 5 years among asymptomatic patients in this study compared with 94% from a prior study, and 77% BCE-free survival at 5 years among previously symptomatic patients in this study compared with 68% from a prior study (8).

Akin to previous observations, our cohort also suggests strong genotype-specific risk for recurrent BCEs. Our data show that patients with LQT3 and patients with LQTM are at highest risk of BCEs when compared with LQT1 and LQT2 patients (17). However, even among these genotypic higher-risk subsets, overall improvements in BCE-free survival when compared with historical cohorts are seen.

This study sheds light on number of important facets of outcomes in patients with LQTS in the contemporary era. First, LQTS-associated mortality should be rare. Mortality has significantly decreased in appropriately risk stratified and treated LQTS patients, even with the majority of patients being treated without an ICD. Second, the incidence of LQTS-related BCEs in patients treated at a single LQTS specialty center is less than previously reported, whether looking at the cohort as a whole, divided by symptomatic status, or by genotype (Central Illustration). Third, compared with previous studies, the majority of patients in our cohort were diagnosed while asymptomatic (73% vs. 36% to 53%), which may be evidence of the changing landscape of LQTS in the contemporary era (8,16). This finding is likely due to treated patients living longer, increased awareness of the importance of family screening, wider availability of comprehensive genetic testing, and subsequent cascade testing of the proband’s relatives (18). Last, 2 potential distinct subgroups within LQTS emerge. The first is a growing group of patients with concealed and asymptomatic disease who have a very mild or no LQTS expressivity and may not need active therapy. The second is a group of...
of patients with malignant LQTS (i.e., patients with severe LQTS expressivity who, despite current therapy, continue to have higher rates of BCEs). In both of these groups, further improvements in risk stratification and treatment are necessary.

**STUDY LIMITATIONS.** As with clinical retrospective research, this study has limitations including referral bias and retrospective data abstraction. Mayo Clinic’s Genetic Heart Rhythm Clinic receives many patients from outside medical centers, and information regarding past medical history is limited to documentation obtained elsewhere and patient recollection. As a single center, all patients were evaluated, risk stratified, counseled, and treated by a single genetic cardiologist (M.J.A.). LQTS is an uncommon disease, and cohort characteristics vary. Outcomes have not been reported on a generalized scale; therefore, comparisons with previous studies are imperfect and must take into consideration the study institution’s cohort characteristics. In fact, the overall decreased mortality and decreased incidence of BCEs compared with previous studies is likely due to patient-tailored risk stratification, LQTS-directed therapy, and a slightly milder LQTS phenotype overall in comparison with previous registry studies. Although our cohort had similar proportion of LQTS subtypes, in comparison with previous studies there were fewer patients who presented with symptoms (27% vs. 47% to 64%), and a shorter QTc interval (465 ms vs. 492 to 520 ms) (8,16). When comparing the patients in our symptomatic cohort with previous studies, we also observed differences regarding onset of first symptom. LQT1 became symptomatic later (45% symptomatic by 10 years of age vs. 54%, respectively), LQT2 became symptomatic earlier (57% symptomatic by 16 years of age vs. <50%, respectively), and LQT3 became symptomatic markedly earlier (75% symptomatic by 16 years of age vs. <50%, respectively) (19). However, among our LQT3 patients, a large proportion of patients presented with neonatal malignant LQT3 (9 of 14 [64%]), skewing our LQT3 population to an earlier age of presentation. Nevertheless, when we compared the BCE rates between our symptomatic cohorts and previously published symptomatic cohorts, there has been a favorable reduction in BCEs.

**CONCLUSIONS**

With careful evaluation, risk stratification, and treatment almost all asymptomatic LQTS patients should remain asymptomatic. After establishing a robust, patient-tailored, LQTS-directed treatment program, the annual mortality rate should be extremely low. However, although mortality is rare (<1% of patients in over 4,000 patient-years) and outcomes have improved in comparison with previous studies, nearly 1 in 4 symptomatic patients still experienced at least 1 nonlethal, BCE. This indicates that there is still need for improved risk stratification and optimization of their treatment program.

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KEY WORDS breakthrough cardiac events, genetics, long QT syndrome, LQTS, outcomes

APPENDIX For supplemental tables, please see the online version of this article.