Risk of Cardiac Events Associated With Antidepressant Therapy in Patients With Long QT Syndrome

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Patients with long QT syndrome (LQTS) are at a high risk of cardiac events. Many patients with LQTS are treated with antidepressant drugs (ADs). We investigated the LQTS genotype-specific risk of recurrent cardiac arrhythmic events (CAEs) associated with AD therapy. The study included 59 LQT1 and 72 LQT2 patients from the Rochester-based LQTS Registry with corrected QT (QT_c) prolongation and a history of AD therapy. Using multivariate Anderson-Gill models, we estimated the LQTS genotype-specific risk of recurrent CAEs (ventricular tachyarrhythmias, aborted cardiac arrest, or sudden cardiac death) associated with time-dependent ADs. Specifically, we examined the risk associated with all ADs, selective serotonin reuptake inhibitor (SSRI), and ADs classified on the CredibleMeds list (*www.CredibleMeds.org*) as "Conditional" or "Known risk of Torsades de pointes (TdP)." After adjusting for baseline QT_c duration, sex, and time-dependent beta-blocker usage, there was an increased risk of recurrent CAEs associated with ADs in LQT1 patients (hazard ratio = 3.67, 95% confidence interval 1.98-6.82, $p < 0.001$) but not in LQT2 patients (hazard ratio = 0.89, 95% confidence interval 0.49-1.64, $p = 0.716$; LQT1 vs LQT2 interaction, $p < 0.001$). Similarly, LQT1 patients who were on SSRIs or ADs with "Known risk of TdP" had a higher risk of recurrent CAEs than those patients off all ADs, whereas there was no association in LQT2 patients. ADs with "Conditional risk of TdP" were not associated with the risk of recurrent CAEs in any of the groups. In conclusion, the risk of recurrent CAEs associated with time-dependent ADs is higher in LQT1 patients but not in LQT2 patients. Results suggest a LQTS genotype-specific effect of ADs on the risk of arrhythmic events. **(Am J Cardiol 2018;121:182–187)**

Long QT syndrome (LQTS) is a genetic disease due to mutations in genes encoding cardiac ion channels (or interacting) proteins.[1,2] LQT1 and LQT2 are due to loss-of-function mutations in *KCNQ1* (LQT1) and *KCNH2* (LQT2) genes that encode cardiac slow and rapid delayed rectifier potassium channels, respectively.[3] These mutations lead to corrected QT (QT_c) prolongation on the cardiac electrocardiogram (ECG) and a higher risk of ventricular arrhythmias and sudden cardiac death (SCD).[3] The disease manifestations may raise psychological burdens, such as depression,[4,5] and many patients with LQTS are treated with antidepressant drugs (ADs).[6] Many studies investigating the proarrhythmic effect of ADs used QT duration as the end point.[7,8] However, QT prolongation is not a perfect surrogate for ventricular arrhythmias.[9,10] Case reports[11,12] and epidemiological studies[13–18] with a clinical end point yielded mixed results whether ADs are associated with a higher risk of ventricular arrhythmias and SCD. Because patients with LQTS are at an increased risk of ventricular arrhythmias, AD use in this clinical population requires careful evaluation. The present study evaluated the LQTS genotype-specific risk of recurrent cardiac arrhythmias associated with AD use.

Methods

The Rochester-based LQTS Registry includes detailed clinical, pharmacologic, and genetic information about LQTS probands and their affected and unaffected family members.[19] A 12-lead ECG was obtained at enrollment. QT_c duration was calculated using the Bazett formula. The present study consisted of 59 LQT1 and 72 LQT2 patients with QT_c prolongation (male $QT_c > 450$ ms, female $QT_c > 470$ ms) and a history of AD use (Supplementary Table S1). All patients had only 1 mutant LQTS gene. The LQTS Registry is approved by the University of Rochester Research Subject Review Board (RSRB00025305). HIPAA requirements for accounting for disclosure, consent, and withdrawal of consent

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See page 186 for disclosure information.

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were followed. There was no race or ethnicity or gender restriction for inclusion.

The primary end point was cardiac arrhythmic events (CAEs). This was a composite endpoint of recurrent ventricular tachyarrhythmia (sustained ventricular tachycardia, Torsades de pointes [TdP], and ventricular fibrillation), aborted cardiac arrest (ACA), and SCD. Multiple sources were used to ascertain the end point. For probands, ventricular tachyarrhythmia and ACA were collected from both patients' self-reports and physicians' reports. For family members, ventricular tachyarrhythmias and ACA were first assessed by direct contact with patients or relatives and then by medical record review of self-reported cardiac events. Implantable cardiac defibrillator (ICD) interrogations were obtained from patients in the LQTS ICD Registry. All SCDs were adjudicated by LQTS investigators based on medical records and descriptions surrounding death.

AD and beta-blocker use, drug name, and dates of start or discontinuation of drugs were collected from enrollment and annual follow-up questionnaires from patients and physicians. We examined the risk of recurrent CAEs associated with overall AD use, as well as the most commonly used AD group, selective serotonin reuptake inhibitors (SSRIs). Furthermore, ADs were classified according to the CredibleMeds QTDrug list classification of the risk of TdP.[20] The risk of TdP was assigned based on multiple sources of evidence (e.g., FDA's Adverse Event Reporting System, case reports of TdP, studies of QT prolongation, and laboratory studies of relevant pharmacologic action).[21] Drugs were classified as (1) not on the CredibleMeds QTDrug list; (2) Conditional risk of TdP (these drugs prolong QT and have a risk of developing TdP but only under certain known conditions such as overdose or drug-drug interaction); (3) Possible risk of TdP (these drugs can cause QT prolongation but there is insufficient evidence that the drugs, when used as directed in labeling, have a risk of causing TdP); and (4) Known risk of TdP (these drugs prolong QT intervals and have a risk of TdP when used as directed in labeling).[21]

Comparisons of clinical characteristics between LQT1 and LQT2 patients were performed by chi-square test for categorical variables and two-sample *t*-test or Mann-Whitney U test (for skewed distributions) for continuous variables. Incidence rates of recurrent CAEs were calculated as the number of events per 100 patient-year.

We performed Andersen-Gill models[22] with time-dependent AD use (a patient's status of AD use could switch between on and off ADs over time) to assess the association of on versus off ADs with the risk of recurrent CAEs. Follow-up was from birth to (1) last contact, (2) death due to reasons other than SCD, (3) March 2016, or (4) SCD or 10th CAEs (97% of all patients developed ≤10 ventricular arrhythmic events), whichever occurred first. To estimate the hazard ratios (HRs) of recurrent CAEs associated with ADs by LQTS genotype, we fitted a model including time-dependent ADs, LQTS genotype (LQT1 vs LQT2), and an interaction term of these 2 variables. As many patients with LQTS were prescribed SSRIs, we also assessed the risk of recurrent CAEs associated with SSRIs in LQT1 and LQT2 patients separately. Briefly, SSRIs were analyzed as a time-dependent categorical variable with 4 mutually exclusive groups: on SSRIs only, on other ADs only, on SSRIs and other ADs simultaneously, and off all ADs. We presented the HR of CAEs associated with on SSRIs only versus off all ADs.

Next, we estimated the HR of recurrent CAEs associated with ADs in each class on the CredibleMeds list. We analyzed ADs as a time-dependent categorical variable with 5 levels. At any given time point, patients were classified into 5 mutually exclusive groups: (1) patients on ADs that are not on the CredibleMeds list, (2) patients on ADs with "Conditional risk of TdP," (3) patients on ADs with "Possible risk of TdP," (4) patients on ADs with "Known risk of TdP," and (5) patients off all ADs (reference group). If a patient was on more than 1 class of ADs simultaneously, the patient was classified in the AD group with the highest risk level (known > possible > conditional > not on the list). To further estimate the effect of the most commonly used drug in the "Known risk of TdP" and SSRI groups (citalopram), we compared the risk of recurrent CAEs between patients on citalopram with those patients off all ADs, in a similar way as described previously (with 6 mutually exclusive groups: on citalopram, on other ADs with "Known risk of TdP," on ADs with "Possible risk of TdP," on ADs with "Conditional risk of TdP," on ADs not on the list, and off all ADs).

Using SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina), all analyses were stratified by sex and were adjusted for baseline QT_c duration and time-dependent beta-blocker therapy. Significance (2-tailed tests) was defined as $p < 0.05$.

Results

Table 1 lists the clinical and demographic characteristics of the study population. There was no difference in follow-up duration and total time on any ADs, SSRIs, and ADs in each CredibleMeds risk of TdP classes between LQT1 and LQT2 patients. Baseline QT_c was similar between the 2 groups. There were 53 CAEs in 59 LQT1 patients during a mean follow-up of 53 ± 20 years, and 91 CAEs in 72 LQT2 patients during a mean follow-up of 48 ± 17 years. The percentage of patients who developed CAEs during follow-up was higher in LQT2 patients than in LQT1 patients (54% vs 25%).

In both groups, patients had a higher incidence rate of CAEs when on versus off ADs (Figure 1). LQT1 patients had a greater difference in the rate of CAEs on versus off ADs (5.73 vs 1.20 CAEs per 100 patient-year) compared with LQT2 patients (3.58 vs 2.53 CAEs per 100 patient-year). As shown in Figure 2, after stratifying for sex and adjusting for baseline QT_c and time-dependent beta-blocker therapy, there was an increased risk of recurrent CAEs when LQT1, but not LQT2, patients were on ADs (LQT1 vs LQT2 interaction, $p < 0.001$.).

Similar to the results of overall AD use, both groups had higher rates of CAEs when on SSRIs compared with off all ADs (Figure 1). LQT1 patients had a greater difference in the rate of CAEs while on SSRIs versus off all ADs compared with LQT2 patients. After adjusting for the same covariates as above, we observed similar LQTS genotype-specific effects of SSRIs on the risk of recurrent CAEs. LQT1, but not LQT2, patients were at an increased risk of recurrent CAEs on SSRIs versus off all ADs (Figure 2).

As ADs with "Possible risk of TdP" and ADs not on the CredibleMeds list had 0 CAEs in many groups, rates of

Table 1
Patient characteristics

Characteristics	QT_c prolongation		
	LQT1 (n = 59)	LQT2 (n = 72)	p value (LQT1 vs. LQT2)
Male participants	9 (15%)	26 (36%)	***0.007***
Follow-up (years)	53 ± 20	48 ± 17	0.163
ADs use and time on ADs			
Overall ADs	59 (100%)	72 (100%)	1.000
Total time per patient on any ADs (years)	5.92 ± 5.60	5.44 ± 5.01	0.965
SSRIs	48 (81%)	53 (74%)	0.294
Total time per patient on SSRI (years)	5.00 ± 4.98	3.28 ± 3.61	0.065
ADs with Conditional TdP risk	41 (69%)	38 (53%)	0.052
Total time per patient on ADs with Conditional TdP risk (years)	3.02 ± 4.05	2.47 ± 4.46	0.146
ADs with Possible TdP risk	5 (8%)	8 (11%)	0.616
Total time per patient on ADs with Possible TdP risk (years)	0.43 ± 2.36	0.33 ± 1.24	0.628
ADs with Known TdP risk	21 (36%)	31 (43%)	0.385
Total time per patient on ADs with Known TdP risk (years)	2.34 ± 4.09	1.74 ± 2.94	0.832
ADs not on the CredibleMeds list	10 (17%)	18 (25%)	0.263
Total time per patient on ADs not on the CredibleMeds list (years)	0.76 ± 2.31	1.14 ± 2.82	0.279
Anti-arrhythmic Treatment			
Beta-blockers	50 (85%)	66 (92%)	0.216
Left cardiac sympathetic denervation	0	4 (6%)	0.127
Pacemaker	4 (7%)	19 (26%)	***0.003***
Implantable Cardiac Defibrillator	26 (44%)	43 (60%)	0.074
Electrocardiogram			
Age at baseline ECG (years)	36 ± 20	29 ± 16	***0.048***
RR (sec)	893 ± 198	879 ± 195	0.691
PR (sec)	161 ± 27	149 ± 25	***0.015***
QRS (sec)	82 ± 14	85 ± 21	0.355
QT_c (sec)	515 ± 52	519 ± 53	0.572
Number of patients with cardiac arrhythmic events (CAEs)			
Ventricular tachyarrhythmias	15 (25%)	36 (50%)	***0.004***
Aborted cardiac arrest (ACA)	6 (10%)	13 (18%)	0.202
Sudden cardiac death (SCD)	0	1 (1%)	1.000
CAEs (Ventricular tachyarrhythmias, ACA, or SCD)	15 (25%)	39 (54%)	***<0.001***

Data are mean ± SD for continuous variables and number of patients (%) for categorical variables. p values < 0.05 denoted in bold/italics

ADs = antidepressant drugs; CAEs = cardiac arrhythmic events; LQTS = long QT syndrome; SSRIs = selective serotonin reuptake inhibitors; TdP = Torsades de pointes; ACA = aborted cardiac arrest; SCD = sudden cardiac death.

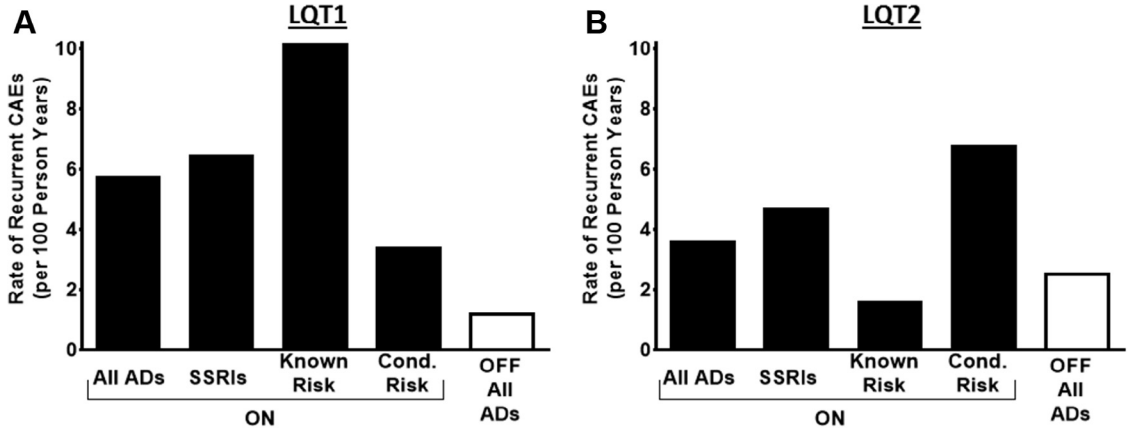

Figure 1. Rate of recurrent CAEs (ACA, SCD, ventricular tachyarrhythmia, censored at 10 events) while on all ADs, SSRI ADs, ADs classified on the CredibleMeds List as Known risk of TdP and Conditional (Cond) risk of TdP, and off all ADs. *(A)* LQT1. *(B)* LQT2. ADs = antidepressant drugs; CAEs = cardiac arrhythmic events; Cond = conditional; LQTS = long QT syndrome; SSRIs = selective serotonin reuptake inhibitors; TdP = Torsades de pointes; ACA = aborted cardiac arrest; SCD = sudden cardiac death.

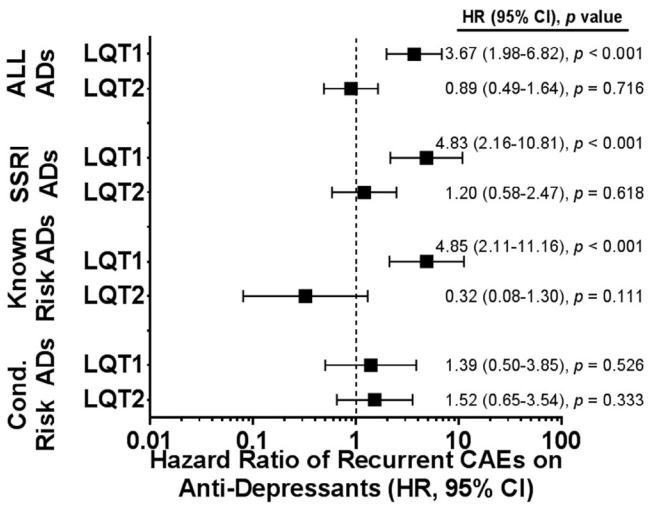

Figure 2. LQT1 patients are at an increased risk of CAEs when on ADs. Hazard ratios of recurrent CAEs associated with all ADs, SSRI ADs, ADs with Known risk of TdP, and ADs with Conditional risk of TdP. Patients off all ADs were used as the reference group. Models were stratified by sex, and adjusted for baseline QT_c duration and time-dependent beta-blocker usage. ADs = antidepressant drugs; CAEs = cardiac arrhythmic events; Cond = conditional; HR = hazard ratio; LQTS = long QT syndrome; SSRIs = selective serotonin reuptake inhibitors; TdP = Torsades de pointes; ACA = aborted cardiac arrest; SCD = sudden cardiac death.

recurrent CAEs and HR estimates are not presented for these 2 groups. As shown in Figure 1, LQT1 patients had a higher rate of CAEs while on ADs with "Known risk of TdP" versus when off all ADs, whereas LQT2 patients had a lower rate of CAEs while on ADs with "Known risk of TdP" versus off all ADs.

Consistent with findings of overall ADs and SSRIs, the LQTS genotype-specific effect on the risk of CAEs was also observed for ADs with "Known risk of TdP." LQT1 patients on ADs with "Known risk of TdP" had a higher risk of recurrent CAEs compared with those off all ADs (Figure 2). In contrast, in LQT2 patients, the risk did not differ significantly when on ADs with "Known risk of TdP" versus off all ADs. ADs with "Conditional risk of TdP" were not associated with a change in the risk of recurrent CAEs in any group. Furthermore, in LQT1 patients, we examined the most commonly used AD in the "Known risk of TdP" group, citalopram (17 patients reported a history of citalopram usage), which is a SSRI. LQT1 patients on citalopram were at an increased risk of recurrent CAEs compared with those off all ADs ([HR = 6.79, 95% confidence interval 3.18–14.51, $p < 0.001$). Due to limited number of LQT2 patients on citalopram, we were unable to compute the HR for citalopram in LQT2 patients.

Discussion

This study provides insights into the LQTS genotype-specific effect of ADs on the risk of recurrent CAEs. We observed an increased risk of recurrent CAEs associated with overall AD use, SSRIs, and ADs with "Known risk of TdP" in LQT1, but not in LQT2 patients.

Findings from previous epidemiologic studies investigating the association between ADs and the risk of cardiac events are inconsistent.[13,14,16,17] These studies used administrative databases and included diverse clinical populations. A study using a case-time-control design demonstrated an increased risk of out-of-hospital cardiac arrest associated with ADs, specifically SSRIs and tricyclic antidepressants.[13] The increased risk associated with SSRIs was primarily driven by citalopram.[13] In line with these results, we found an increased risk of recurrent CAEs associated with overall AD use, SSRIs, and citalopram versus off all ADs in the LQT1 group. Several other studies compared citalopram with a specific AD. In a large Canadian cohort, citalopram was associated with a higher risk of cardiac events within 90 days of citalopram prescription compared with paroxetine or sertraline.[18] In contrast, 2 large studies of Medicaid enrollees reported no change in the risk of SCD or ventricular arrhythmias associated with citalopram compared with reference antidepressants (fluoxetine, paroxetine, or sertraline).[14,17]

Our finding of ADs classified on the CredibleMeds list as "Known risk of TdP" is consistent with a Swedish case-control study of people 65 years and older, although for a different end point. This Swedish study reported a higher all-cause mortality associated with both ADs with "Known risk of TdP" and ADs with "Conditional risk of TdP."[23]

It should be noted that different from previous studies that used large administrative databases and included diverse clinical populations, our study focused on patients with LQTS from the Rochester-based LQTS Registry. Although administrative databases provide very large sample size, they are prone to nondifferential outcome misclassification.[24] Ventricular arrhythmias may be fatal and thus not identified if they occur outside hospital settings.[17,24] In our study, SCD was assessed by direct contact with relatives or friends of the deceased and all cases were adjudicated by LQTS investigators based on a description of the circumstances around death and medical records. Moreover, 53% of our study population had an ICD implanted. ICD interrogation provided ECG recordings of arrhythmic events that occurred outside the hospital. Thus, our study likely captured arrhythmic events more accurately than studies using administrative datasets.

QT prolongation through blockade of cardiac rapid delayed rectifier potassium current (I_{Kr}) is the primary proposed proarrhythmic mechanism for ADs.[7,8,25–28] Some ADs have other adverse cardiovascular effects such as increased heart rate, increased sympathetic activity, decreased heart rate variability, and cardiac conduction delays.[28,29] To explore potential mechanisms, we compared ECG measures (heart rate, QT_c, and QRS durations) in patients with ECG recordings both on and off ADs. In both LQT1 and LQT2 patients, we did not observe significant difference in these ECG measures while on versus off ADs (Supplementary Table S2). These ECG results are only preliminary due to limited sample size and uncontrolled confounding (e.g., age, ECG readers, and medications at multiple ECG recordings per patient) and need to be examined in a larger prospective cohort with more rigorous control for confounders.

The mechanisms for the LQTS genotype-specific effect are unclear. We propose 2 potential mechanisms. First, LQT2 mutations in *KCNH2*, particularly those in the pore-S6 region, which has been suggested as the binding region for hERG blockers,[30,31] may lead to the lack of target or binding sites for ADs to bind and exert I_{Kr} blocking effects. Therefore, LQT2

patients may be unaffected by the proarrhythmic effect of ADs. Although we were not powered to perform multivariable analysis by mutation location, exploratory descriptive analyses suggested patients with LQT2 S5-pore-S6 domain mutations (n = 18) had a lower rate of recurrent CAEs when on versus off ADs (Supplementary Figure S1). These results indicate LQT2-pore mutations may alter the ability of ADs to exert I_{Kr} blocking effects. Our second proposed mechanism is increased sympathetic activity associated with some ADs. Previous studies suggested that tricyclic antidepressants and SNRIs were associated with increased sympathetic activity,[29] which is an established trigger for arrhythmias in LQT1 patients.[32] Although emotion and stress are triggers for arrhythmias in LQT2 patients, lethal events arise under many conditions that are not associated with increased sympathetic tone.[33] It is also possible that both mechanisms operate simultaneously.

Our study has limitations that need to be considered. Except for citalopram, our limited sample size did not allow us to thoroughly examine the risk of CAEs associated with specific ADs. Although the use of ADs and SSRIs was associated with an increased risk of CAEs in LQT1 patients, it does not imply that all ADs and all SSRIs are associated with an increased risk of CAEs in LQT1 patients. Future prospective studies in a large cohort of patients with LQTS are needed to confirm these results, and rigorously examine the risk of CAEs associated with specific ADs.

There is an increase in the risk of recurrent CAEs associated with overall AD use, SSRIs, and ADs with "Known risk of TdP," such as citalopram, in LQT1 patients, but not in LQT2 patients. Results from the study establish the basis for future studies to investigate the mechanisms for this LQTS genotype-specific effect of ADs. It is important to consider genotype when prescribing ADs to patients with LQTS.

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Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, https://doi.org/10.1016/j.amjcard.2017.10.010.

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