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Risk of Cardiac Events in Long QT Syndrome Patients When Taking Anti-Seizure Medications

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Abstract

Many anti-seizure medications (ASMs) affect ion channel function. We investigated whether ASMs alter the risk of cardiac events in patients with corrected QT (QT_c) prolongation. The study included people from the Rochester-based Long QT Syndrome (LQTS) Registry with baseline QT_c prolongation and history of ASM therapy (n=296.) Using multivariate Anderson-Gill models

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DSA: Conceived and designed study, analyzed data, interpreted results, drafted the manuscript and figures, Principal Investigator

YB: Guided study design, interpreted results

BP: Constructed dataset, created analytical software

SM: Guided statistical analyses, interpreted results

RAG: Interpreted results, edited the manuscript

RTD: Interpreted results, edited the manuscript

AJM: Founded and maintains LQTS registry, interpreted results, edited manuscript

Conflict of Interest:

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we assessed the risk of recurrent cardiac events associated with ASM therapy. We stratified by LQTS genotype and predominant mechanism of ASM action (Na⁺ channel blocker & GABA modifier.) There was an increased risk of cardiac events when participants with QT_c prolongation were taking vs. off ASMs (HR 1.65, 95%-CI 1.36–2.00, $p<0.001$). There was an increased risk of cardiac events when LQTS2 (HR 1.49, 95%-CI 1.03–2.15, $p=0.036$), but not LQTS1 participants were taking ASMs (interaction, $p=0.016$.) Na⁺ channel blocker ASMs were associated with an increased risk of cardiac events in participants with QT_c prolongation, specifically LQTS2, but decreased risk in LQTS1. The increased risk when taking all ASMs and Na⁺ channel blocker ASMs was attenuated by concurrent beta-adrenergic blocker therapy (interaction, $p<0.001$.) GABA modifier ASMs were associated with an increased risk of events in patients not concurrently treated with beta-adrenergic blockers. Female participants were at an increased risk of cardiac events while taking all ASMs and each class of ASMs. Despite no change in overall QT_c duration, pharmacogenomic analyses set the stage for future prospective clinical and mechanistic studies to validate that ASMs with predominantly Na⁺ channel blocking actions are deleterious in LQTS2, but protective in LQTS1.

Keywords

Long QT Syndrome; Arrhythmia; Antiepileptic Drug; Sudden Cardiac Death; SUDEP; Sodium channel; Epilepsy

Introduction

ASMs are associated with an increased risk of sudden cardiac death (SCD) and sudden unexpected death in epilepsy (SUDEP).(1–3) Many anti-seizure medications (ASMs) alter ion channel activity.(3) For example, phenytoin, carbamazepine, and lamotrigine are Na⁺ channel blockers, while phenobarbital is a gamma-aminobutyric acid (GABA) enhancing drug(4–6). Many ASMs have multiple effects, some of which are incompletely understood. Since there is overlap in subtypes of ion channels expressed in the heart and brain,(7) it is important to assess the cardiac safety of ASMs.

There is not a clear consensus whether ASMs are associated with changes in ECG measures and risk of arrhythmias.(8–12) Cellular expression studies indicate that several ASMs block the rapid delayed rectifier K⁺ current (I_{Kr}), which contributes to action potential repolarization in the heart.(13, 14) Yet, in both healthy and epilepsy patient populations, these ASMs that block I_{Kr} are not associated with corrected QT (QT_c) prolongation on the cardiac ECG or increased risk of arrhythmias.(10, 15–17) While none of the ASMs examined in this study are on the Credible Meds list of drugs that increase the risk of torsades-de-pointes,[dataset](18) it remains unknown whether ASMs are safe in patients with underlying inherited or acquired alterations in cardiac electrical function.

Long QT Syndrome (LQTS) mutations disturb the balance between depolarizing and repolarizing currents throughout the cardiac activation-recovery process, leading to QT_c prolongation and an increased risk of arrhythmias and SCD.(19) There is also a strong association between LQTS and seizures.(20–22) We recently showed that LQTS patients with seizures exhibit an increased risk for ventricular tachyarrhythmias.(20) As many LQTS

patients take ASMs for seizures, and ASMs are used for pain control and as mood stabilizers, it is important to assess whether ASMs affect the risk of cardiac arrhythmias in these populations.

Using the Rochester-based LQTS Patient Registry, we compared the rate and risk of recurrent cardiac events when participants with QT_c prolongation and a history of ASM therapy were taking (on) vs. off ASMs. Since the registry includes a relatively large number of LQTS1 (n=46) and LQTS2 (n=76) participants on ASMs, we specifically assessed whether there were LQTS genotype differences in the risk of cardiac events when on ASMs. Due to differing mechanisms of ASM action, we also assessed the risk of cardiac events when LQTS participants were on each or a combination of classes of ASMs (i.e., Na⁺ channel blocker, GABA modifier, & concurrent Na⁺ channel blocker and GABA modifier ASMs). We hypothesized ASMs are associated with an increased risk of cardiac events in patients with reduced repolarization reserve (i.e., those with QT_c prolongation).

Methods

Study Cohort

The Rochester-based LQTS Registry provides a wealth of clinical, pharmacologic, and genetic information about LQTS probands and their affected and unaffected family members.⁽¹⁹⁾ LQTS diagnosis was made by QT_c prolongation and/or LQTS genetic testing. Information was collected from extensive baseline/enrollment and yearly followup participant questionnaires, genetic reports, and physician reports. Information important to this study included results from genetic testing, the dates of ECG measurements and cardiac events, as well as the name and start (on) and end (off) date of taking each medication. Patient reported information was confirmed by reviewing the initial and yearly physician reports. The period on ASMs and beta-adrenergic blockers was defined as the dates the participant reported in the enrollment and yearly follow-up questionnaires being prescribed the medication, plus the dates the medication was listed in the medical records.

The study included consented participants with QT_c prolongation and a history of ASM therapy, and stratified by LQTS genotype (LQTS1 vs. LQTS2). Importantly, in every participant there was a period where the participant was taking (on) an ASM, as well as off all ASMs. Therefore, we performed detailed assessments of the risk of recurrent cardiac events when on ASMs. The QT duration was defined from the start of the Q wave to the end of the T wave when it reached the isoelectric baseline, and corrected for heart rate using the Bazett formula (QT_c). Baseline QT_c duration was measured from the initial ECG at enrollment. The patient cohort included those with QT_c prolongation (male QT_c>450ms, female QT_c>470ms, n=296); participants with QT_c prolongation were sub-divided into (1) LQTS1 genotype positive (n=46), and (2) LQTS2 genotype positive (n=76.) 13 patients with LQTS3-12 mutations were included in the QT_c prolongation group, but due to low numbers were not stratified by LQTS genotype. In the remaining 158 participants with QT_c prolongation, the LQTS mutation was unknown. All LQTS genotype positive participants had only one mutant LQTS gene. Follow-up was from birth to 40 years of age, loss of follow-up, death, or December 2016, with no race/ethnicity or sex restrictions. The number

of participants and total time on all ASMs and each class/combination of ASMs were similar in LQTS1 vs. LQTS2 (eTable 1).

Outcome Measures

Similar to our recent study(20), cardiac events were defined as aborted cardiac arrest (ACA), SCD, and ventricular tachyarrhythmias (sustained ventricular tachycardia, torsades-de-pointes, and ventricular fibrillation). This information was documented in medical records, implantable cardiac defibrillator (ICD) interrogation, and telemetric/Holter monitoring, as well as ambulatory and in-hospital ECG recordings. In all groups, each type of cardiac event was documented. Outcome measures included: (1) rate of recurrent cardiac events when participants were taking (on) ASMs and off all ASMs (normalized to 100 person years); and, (2) multivariate adjusted time-dependent risk of recurrent cardiac events when taking ASMs. As the underlying cause for each syncopal event was not known, it was not classified as a cardiac event, especially since this is a cohort of participants with a history of seizures. In addition, since episodes of non-sustained ventricular tachycardia might be missed, they were not classified as cardiac events.

eTable 2 lists the ASMs taken by patients in the LQTS Registry, their predominant mechanism(s) of action(4–6, 23), and the number of participants in each group that took each ASM. ASMs were classified by their predominant mechanism of action: (1) Na⁺ channel blocker, (2) GABA modifier, and/or (3) Other (e.g., Ca²⁺, synaptic vesicle protein 2A, & glutamate blockers.) While ASMs may have additional known/unknown mechanisms of action, we limited our classification to their major mechanism(s) of action. ASMs with more than one major mechanism of action were classified in multiple groups (e.g., divalproex and topiramate.) We assessed the risk of cardiac events on each or a combination of classes of ASMs (Figure 1). We also confirmed our results assessing the risk of cardiac events on a commonly used Na⁺ channel blocker ASM (phenytoin) or GABA modifier ASM (phenobarbital), as well as high sensitivity analyses in participants with a history of cardiac events.

Study Approval

The LQTS Registry is approved by the University of Rochester Research Subject Review Board (RSRB00025305). All data were handled in accordance with applicable laws and the Code of Ethics of the World Medical Association. HIPAA requirements for accounting for disclosure, consent, and withdrawal of consent were followed. Written informed consent was obtained from all participants/guardians in the study.

Statistics

In a cohort of participants with QT_c prolongation and a history of ASM therapy, the risk of recurrent cardiac events associated with ASM usage was tested using multivariate Anderson-Gill Model recurrent event analysis (hazard ratio (HR), 95% confidence interval (CI), *p* value). 95% of all participants with QT_c prolongation developed 10 arrhythmic events. Participants were censored at 10 events to prevent participants who developed frequent cardiac events from having an undue influence on the risk assessments.

All risk assessments were performed adjusting for LQTS comorbidities, concomitant medications, and sex. Specifically, we adjusted for baseline QT_c duration, beta-adrenergic blockers were modeled using a time-dependent covariate, and we applied a non-parametric stratification for sex. Recurrent risk assessments on each or a combination of classes of ASMs, were performed in one model using a categorical variable with 5 levels (Figure 1): (1) on Na⁺ channel blocker ASMs, (2) on GABA modifier ASMs, (3) on Other ASMs, (4) concurrently on Na⁺ channel blocker and GABA modifier ASMs, and (5) Off all ASMs (reference). The risk of recurrent cardiac events on Other ASMs is not displayed as it is a heterogeneous group of ASM mechanisms of action, and the number of participants and events were too low to calculate the risk.

To further explore the ASM-class specific risk of cardiac events, we assessed the risk of cardiac events associated with time-dependent phenytoin (Na⁺ channel blocker ASM) and phenobarbital (GABA modifier ASM) use. For risk analyses on phenytoin and phenobarbital we stratified for sex, and adjusted for baseline QT_c duration, time-dependent beta-adrenergic blocker usage, and non-phenytoin or non-phenobarbital ASM therapy, respectively.

We tested for differences in the risk of cardiac events associated with time-dependent ASM use in LQTS1 vs. LQTS2 participants, in the absence vs. co-presence of beta-adrenergic blockers, and male vs. female participants. We estimated the effects using interaction terms in the models and the *p*-values were reported for each comparison. Paired t-tests were applied to assess differences in ECG measures on vs. off ASMs, in participants that had at least one ECG measurement each on and off ASMs. Significance was defined as *p*<0.05. All analyses were conducted using SAS software version 9.4 (SAS Institute, North Carolina).

Results

ASMs are associated with LQTS genotype-specific differences in the risk of cardiac events

The baseline characteristics were similar in LQTS1 and LQTS2 participants (Table 1 & eTable 1.) There were no differences in sex, total time of follow-up, percentage with a history of beta-adrenergic blocker therapy, percentage of participants and time on ASMs, age of baseline ECG (i.e., enrollment), baseline QT_c duration, and percentage of participants with a history of cardiac events in the LQTS1 vs. LQTS2 groups. None of the ASMs are classified on the CredibleMeds list of medications associated with an increased risk of torsades-de-pointes, even under certain conditions, such as LQTS, drug overdose, or co-administration of potentially harmful interacting drugs. [dataset](18) Yet, there was a 1.8-fold higher rate and increased adjusted risk of cardiac events when participants with QT_c prolongation were taking (on) ASMs vs. off all ASMs (HR 1.65, 95% CI 1.36–2.00, *p*<0.001, Figure 2.) Also, while there were not enough events to calculate the risk of cardiac events when on ASMs, LQTS genotype negative participants with normal QT_c durations (i.e., unaffected family members of the proband, n=64) did not exhibit an increased rate of cardiac events when on vs. off ASMs (0.59 vs. 1.82 events per 100 person years, respectively.)

LQTS1 and LQTS2 participants had similar baseline QT_c durations and prevalence of cardiac events (Table 1 & eTable 2). In a multivariate model of LQTS1 and LQTS2

participants, which included a stratification term for sex and adjustments for baseline QTc duration, and time dependent beta blocker and ASM usage, LQTS2 participants were at an increased risk of cardiac events (HR 1.43, 95% CI 1.04–1.97, $p=0.03$). There were LQTS genotype-specific differences in the rate and risk of cardiac events when on vs. off ASMs. LQTS2 participants had a 1.8-fold higher rate of cardiac events when on ASMs, while LQTS1 participants had a 65% reduction in the rate of cardiac events when on ASMs (Figure 2A.) Furthermore, there was an increased risk of cardiac events when LQTS2 (HR 1.49, 95% CI 1.03–2.15, $p=0.036$), but not LQTS1 participants (HR 0.47, 0.20–1.11, $p=0.085$), were on ASMs (interaction, $p=0.016$, Figure 2B.) Sub-analyses of the rate/risk of ventricular tachyarrhythmias and ACA/SCD yielded similar results to the composite endpoint of cardiac events (eTable 3).

Predominant mechanism of ASM action confers differing risks of cardiac events

We investigated the rate of cardiac events on vs. off each class of ASMs. As shown in eTable 1, the number of participants with a history of each type of ASM therapy, and the total time on each class of ASMs, were similar in LQTS1 and LQTS2 participants. Participants with QTc prolongation, including LQTS2, had a 2-fold higher rate of cardiac events when on vs. off Na⁺ channel blocker ASMs (Figure 3A & 3C.) In contrast, there was an 80% lower rate of cardiac events when LQTS1 participants were on vs. off Na⁺ channel blocker ASMs (Figure 3B.)

Due to multiple mechanisms of ASM action and polytherapy, in a single multivariate model we assessed the risk of cardiac events when on each class of ASM; off all ASMs was the reference. Time-dependent Na⁺ channel blocker ASM therapy were associated with LQTS genotype specific differences in the risk of cardiac events. There was an increased risk of cardiac events when participants with QTc prolongation ($p<0.001$), including LQTS2 participants ($p=0.011$), were on Na⁺ channel blocker ASMs (Figure 3D & 3F.) In contrast, there was a decreased risk of cardiac events when LQTS1 participants were on Na⁺ channel blocker ASMs ($p<0.05$, Figure 3E.) Regardless of the group, time-dependent GABA modifier ASM use was not associated with a change in the risk of cardiac events (Figure 3D–F.) In participants with QTc prolongation, concurrent Na⁺ channel blocker and GABA modifier ASM usage was associated with a significantly increased risk of cardiac events (Figure 3D.)

We confirmed these results by assessing the risk of cardiac events when on select ASMs, in which the predominant mechanism of action was either Na⁺ channel blockade (e.g. phenytoin) or GABA modification (e.g. phenobarbital.) Consistent with Figure 3, there were LQTS genotype differences in the risk of cardiac events when LQTS1 and LQTS2 participants were on phenytoin ($p=0.020$, eFigure 1). Furthermore, LQTS2 participants were at an increased risk of cardiac events when on phenytoin ($p<0.001$). There was no difference in the risk for cardiac events when LQTS1 or LQTS2 participants were on phenobarbital.

Concurrent beta-adrenergic blocker-ASM therapy and participant gender are associated with differences in the risk of cardiac events

As beta-adrenergic blockers are the major form of anti-arrhythmic therapy for LQTS,(19) all above analyses included a covariate for time-dependent beta-adrenergic blocker therapy. Additionally, in participants with QT_c prolongation we examined the time-dependent risk of recurrent cardiac events when participants were on ASMs in the absence and co-presence of beta-adrenergic blockers. In the absence of concurrent beta-adrenergic blocker therapy, all ASMs and each class of ASMs were associated with an increased risk of cardiac events (Figure 4A & 4C). In contrast, concurrent beta-adrenergic blocker and ASM treatment blunted the increased risk for cardiac events (with vs. without beta-adrenergic blocker interaction; all ASMs, $p<0.001$, Na⁺ channel blocker ASMs, $p<0.001$). There were no differences in the risk of cardiac events when on GABA modifier ASMs ($p=0.094$) or concurrent Na⁺ channel blocker and GABA modifier ASMs ($p=0.546$) in the absence vs co-presence of beta-adrenergic blockers (Figure 4C.) Similar ASM class-specific analyses in LQTS1 and LQTS2 participants with QT_c prolongation was not possible due to an insufficient number of participants and events on or off beta-adrenergic blockers.

As the risk of cardiac events differ in male vs. female participants,(20, 24, 25) all analyses included a non-parametric adjustment term for sex. Further analyses indicated that male and female participants with QT_c prolongation differ in their risk of cardiac events when on all ASMs (male vs. female interaction, $p<0.001$), GABA modifier ASMs ($p=0.027$), and concurrent Na⁺ channel blocker and GABA modifier ASMs ($p=0.011$, Figure 4B & D.) Female participants with QT_c prolongation were at an increased risk of cardiac events when on all ASMs, Na⁺ channel blocker ASMs, GABA modifier ASMs, and concurrent Na⁺ channel blocker and GABA modifier ASMs (Figure 4B & D.) Similarly, female LQTS2 participants with QT_c prolongation were at an increased risk of cardiac events when taking all ASMs (female: HR 1.86, 95% CI 1.23–2.82, $p=0.003$; male: HR 0.64, 95% CI 0.27–1.52, $p=0.308$; male vs. female interaction, $p=0.029$). Similar to the overall LQTS1 population (Figure 2B), LQTS1 male and female participants each exhibited a non-significant reduction in the risk of cardiac events when on all ASMs (male, HR 0.59, 95% CI 0.05–5.48, $p=0.645$; female, 0.45, 0.17–1.15, $p=0.095$; male vs. female interaction, $p=0.820$). There was not enough power to calculate the hazard ratios for male and female LQTS1 and LQTS2 participants on each class of ASMs.

High Sensitivity Analyses

We also confirmed the above results by performing high sensitivity analyses in symptomatic participants (1 cardiac event during follow-up). Consistent with Figure 2, participants with QT_c prolongation, including LQTS2 participants, exhibited a 1.9–2.6-fold higher rate and increased risk of cardiac events when on vs. off ASMs ($p<0.001$, eFigure 2). On the other hand, LQTS1 patients exhibited a 52% reduced rate and a lower risk for cardiac events when on ASMs ($p=0.008$). Furthermore, we confirmed that LQTS genotype, predominant mechanism of ASM action, concurrent beta adrenergic blocker therapy and female sex are all associated with differing risks of cardiac events when on vs. off ASMs (eFigure 3 & 4).

To enable more rigorous “high sensitivity” analyses, we limited our analyses to participants with a cardiac event before the initiation of the first ASM. This refinement reduced the number of participants in each group, which unfortunately limited our ability to perform multivariate risk analyses. Nevertheless, in this refined cohort, time-dependent ASM therapy was associated with an increased rate of cardiac events among all participants with QT_c prolongation, including LQTS2 participants, but a reduced rate in LQTS1 participants (eTable 4).

ECG measures when LQTS participants were on and off ASMs

In a subset of participants with ECG recordings during periods of on and off ASMs, we tested for differences in ECG measures when on vs. off ASMs (Table 2 & eTable 5). In male participants with QT_c prolongation, the QT_c duration was shorter when on vs. off GABA modifier ASMs. Also, participants with QT_c prolongation had slower heart rates when on vs. off all and Na⁺ channel blocker ASMs. All other QT_c, heart rate, and QRS measurements did not differ when each group of patients, including male and female participants with QT_c prolongation, were on vs. off all ASMs and each class of ASMs. Sub-analyses indicated that patients with a longer QT_c duration when on vs. off ASMs were at a higher risk of cardiac events when on vs. off ASMs (HR 4.03, 95% CI 2.69–6.06, $p < 0.001$), compared to those with QT_c shortening when on vs. off ASMs (HR 1.26, 95% CI 0.83–1.91, $p = 0.274$, interaction $p < 0.001$).

Discussion

In LQTS patients and their affected family members with a history of ASM therapy we assessed the time-dependent risk of recurrent cardiac events when participants were taking ASMs vs. off all ASMs. This study reveals that when selecting ASMs in patients with prolonged QT_c durations one should carefully consider LQTS genotype, predominant mechanism of ASM action, concurrent beta-adrenergic blocker therapy, and female sex. Our results establish a platform for LQTS patient-specific predictions for the risk of cardiac events when taking ASMs, and thus, help to guide future LQTS patient/genotype-specific ASM interventions.

Drugs are often repurposed to treat additional pathologies. For example, numerous anti-arrhythmic drugs produce pro- and anti-convulsant effects.(9) Ranolazine and GS967, which are late Na⁺ channel blocker anti-arrhythmic agents originally used to treat angina pectoris, (26) also reduce neuronal Na⁺ current, spontaneous and repetitive hippocampal and pyramidal neuron firing, the number of seizures, and improve survival in several models of epilepsy.(27, 28) Quinidine, a class IA antiarrhythmic drug, reduces the incidence of seizures and improves psychomotor development in migrating partial seizures of infancy, secondary to a gain-of-function mutation in KCNT1.(29)

In contrast to the dual efficacy of many drugs, numerous drugs (e.g., some antihistamines, antipsychotics, antidepressants, and antimicrobials agents) exert substantial off-target cardiac effects including QT_c prolongation and increased risk for developing lethal ventricular arrhythmias.(3, 18, 30) Despite numerous cellular studies(13, 14), patient case studies(9–11), and a recent review,(12) it remains unclear, with often competing results,

whether ASMs are associated with changes in ECG measures, and the risk of arrhythmias and SUDEP. For example, cellular expression studies indicate that lamotrigine, phenytoin, and phenobarbital inhibit I_{Kr} , which is mutated in LQTS2 and critical for cardiomyocyte repolarization.(13, 14) Lamotrigine slows the rate of depolarization and contraction in isolated myocytes/tissue(16). In contrast, clinical studies in healthy people and elderly patients with newly diagnosed epilepsy indicate that lamotrigine does not alter the QT_c or QRS duration.(15–17). Phenytoin is associated with arrhythmias due to QT_c prolongation and atrio-ventricular block.(9) Yet other studies report phenytoin has no effect on the QT_c duration or risk of arrhythmias,(10) or even that it suppresses arrhythmias.(11) Therapeutic serum levels of carbamazepine promote bradycardia and induce atrio-ventricular delay/block.(31, 32) Several ASMs, carbamazepine and lamotrigine in particular, suppress autonomic tone, and thus, predispose patients to arrhythmias.(33, 34) Yet, another study in patients with medical refractive epilepsy reported no change in any ECG measures or autonomic tone (i.e., heart rate variability) upon withdraw of ASMs.(8) Importantly, while ASMs may be safe in the general population with normal QT_c intervals, it remains unknown whether ASMs are associated with a change in the risk of arrhythmias in patients genotype/phenotype positive for LQTS. This is a major premise of the current study; as patients with LQTS are at risk of seizures(20, 21), and many are on ASMs, it is important to assess the cardiac safety of ASMs in these individuals (i.e., risk of cardiac events.)

The clinical and genetic biomarkers for the highest risk of SUDEP remain incompletely understood. Cardiac arrhythmias are one of several proposed mechanisms for SUDEP.(35) Poor seizure control, ASM polytherapy, drug-drug interactions, and long duration epilepsy are all risk factors associated with arrhythmias and SUDEP.(1, 9, 35) ASM usage is associated with a 2.6-fold increase in the risk of SCD in people with and without epilepsy. (2) Similar to our results, SCD risk is greatest in people on Na^+ channel blocker ASMs; non- Na^+ channel blocker ASMs do not increase the risk of SCD.(2) Female patients with epilepsy are at a higher risk of SUDEP when on vs. off lamotrigine.(36) Yet, as discussed above, it remains incompletely understood whether ASMs are associated with an increased risk of arrhythmias and SUDEP(9–12) in patients genotype/phenotype positive for LQTS.

Our results indicate that the risk of recurrent cardiac events was higher when people with an underlying alteration in cardiac electrical function (i.e., baseline QT_c prolongation) were taking ASMs, particularly Na^+ channel blocker ASMs. In line with our results, phenobarbital (GABA modifier ASM) is not associated with QT_c prolongation, but rather has been shown to lead to QT shortening and arrhythmia suppression(37). Future studies are needed to identify the molecular and electrophysiological mechanisms why LQTS2, but not LQTS1, patients are at an increased risk of cardiac events when on ASMs, as well as the effect that concurrent beta-adrenergic blocker therapy and patient gender have on the QT_c duration and risk of cardiac events. It is plausible that a mild ASM-mediated reduction in I_{Kr} may not reduce the repolarization reserve enough to effect the QT_c and risk of arrhythmias in patients with normal levels of I_{Kr} . In contrast, since LQTS2 patients already have a reduction in I_{Kr} , an additional ASM-mediated reduction in I_{Kr} (e.g., phenytoin & lamotrigine(13, 14)) may serve as a “double hit” to reduce the repolarization reserve sufficient to promote the initiation of an arrhythmia. In LQTS, late Na^+ channel blockers (e.g., ranolazine and phenytoin) restore the balance between depolarizing and repolarizing

current, reduce the rate of triggered activity, and thus exert anti-arrhythmic effects(11, 26). Future studies will be needed to determine the interplay between these proposed pro-/anti-arrhythmic mechanisms.

As ASMs perturb ion channel function,(3, 13, 14) we hypothesized ASM-mediated alterations in ECG measures provide a potential explanation for changes in the risk of cardiac events when patients are on vs. off ASMs. ECG measures in a sub-set of patients with resting ECG recordings each on and off ASMs for the most part do not suggest ASMs alter cardiac electrical function. Yet, the subset of patients that developed QT_c prolongation when on ASMs were at an increased risk of cardiac events when on ASMs. In contrast, patients with QT_c shortening when on ASMs did not exhibit a change in the risk of cardiac events when on ASMs. The lack of change in ECG measures challenge our above hypotheses of I_{Kr} and late Na⁺ current blockade. While QT prolongation is associated with ventricular arrhythmias, it is not a perfect surrogate of cardiac events (38, 39). Also, it is important to note that this is a retrospective study and it was not designed to assess the effect of ASMs on the ECG. ECG measures need to be thoroughly examined prospectively in a larger cohort of patients, with predesigned protocols including repeated measurements, dose dependent sampling, and controlled for various covariates. Importantly, LQTS patients develop arrhythmias in the presence of pro-arrhythmic triggers(40). For example, LQTS1 patients develop arrhythmias during exercise, especially swimming. Emotional stress and auditory stimuli are associated with arrhythmias in LQTS2. These triggers were likely not present during these resting ECG recordings. Thus, it is possible that in the presence of LQTS pro-arrhythmic triggers, ASMs may be associated with changes in the QT_c duration, and thus risk of cardiac events. Future LQTS patient, animal, and cellular studies in the presence of pro-arrhythmic triggers are needed to determine the mechanisms that underlie the LQTS genotype-specific pro- and anti-arrhythmic effects of ASMs. LQTS is a multi-system disease.(20–22, 41) We recently demonstrated a 3-fold higher prevalence of seizures in LQTS genotype positive vs. negative patients; seizures are the strongest independent risk factor for cardiac arrhythmias in LQTS patients.(20) However, the underlying mechanisms for these dual neuro-cardiac pathologies remain unknown. In addition to LQTS genes being expressed in the brain and heart,(42–44) this study demonstrates Na⁺ channel blocker ASMs alter cardiac electrical function in ways that either decrease (LQTS1) or increase (LQTS2) a patient's risk for potentially fatal arrhythmias. These results establish the basis for future prospective clinical studies and database analyses, as well as mechanistic cellular, organ, and whole animal experimental studies. Future studies in a dataset with comprehensive cardiac and neurological records and in an animal model with LQTS (42) will enable assessments of the interaction and temporal correlation between seizure and cardiac events in LQTS. In contrast to our previous study, this study did not compare patients with a history of ASM use (seizure group) vs. no history of ASMs (non-seizure group). Within a population of patients that all took ASMs, we compared the time-dependent risk of cardiac events when they were taking (on) vs. not taking (off) ASMs. In contrast to the increased risk of cardiac events in LQTS1 patients with vs. without a history of seizures,(20) the current study indicates that regardless of a history of seizures, LQTS1 patients are actually at a decreased risk of cardiac events when on vs. off Na⁺ channel blocker ASMs.

Many ASMs are also prescribed for mood stabilization, pain management, and other conditions. Thus, similar to ASMs increasing the risk of SCD in non-epileptic patients,(2) our results extend beyond epilepsy and suggest caution when prescribing ASMs to patients with QT_c prolongation.

Female LQTS patients are at a higher risk of arrhythmias, and the incidence of LQTS and drug related arrhythmias is higher in women (45). Sex-specific differences in cardiac ion channel expression are observed following puberty. For example, there are lower levels of *KCNH2*, *minK*, *Kir2.3*, *Kv1.4*, *KChIP2*, *SUR2*, and *Kir6.2* K⁺ channel transcript and protein expression, and corresponding ion currents, in cardiac myocytes from female vs. male animals/patients (46, 47). An ASM-mediated further reduction in these K⁺ currents would reduce the amount of repolarizing current, which may increase the QT_c duration, and increase the susceptibility for the initiation of arrhythmias (47, 48). In addition, L-type Ca²⁺ current density is higher in hearts from female vs. male animals (47). Hearts from female animals exhibit greater dispersion of Na⁺ channel density and repolarization.(45) Females patients after puberty have longer QT_c durations (48, 49). Differences in ion channel expression, action potential and QT_c duration, and incidence of triggered/arrhythmogenic beats are reversed upon the addition of testosterone to cardiomyocytes from female animals, orchiectomy, and ovaectomy (45–48). Many QT_c prolonging (i.e., I_{Kr} blocking) drugs are associated with a higher incidence of arrhythmias in female vs. male patients(48). Thus, sex-specific differences in the time-dependent risk of recurrent cardiac events and QT_c duration when participants are taking ASMs may be related to female patients having reduced and dispersion of repolarization reserve, due to lower levels of K⁺ channel expression and higher levels of Ca²⁺ channel expression. These sex-specific differences provide substrates for arrhythmogenesis.

Our study has limitations. This study was non-randomized and retrospective up until the date of enrollment, thus limiting the amount of information available. However, after enrollment detailed patient, genetic, and physician reports documenting all medical events and therapeutic interventions were collected prospectively. Due to the absence or limited information available regarding ASM dosage, adherence, and the reason to start or stop all ASMs or specific classes of ASM therapy, it was not possible to control for these factors in the study. The LQTS Registry has limited documentation of seizure events. Thus, we were not able to control for seizure severity/type or the anti-seizure/convulsant efficacy of ASMs. While we showed an association between beta-adrenergic blocker therapy and the risk of cardiac events on vs. off ASMs, we did not have enough participants and events to assess the impact of other cardiac therapies (eTable 1). Importantly, 31% of the participants had ICDs. While ICDs do not affect the susceptibility for cardiac events, they served to enhance our ability to capture cardiac events.LQTS3 patients are classically prescribed Na⁺ channel blocker anti-arrhythmic agents; however, there were only 11 LQTS3 participants with a history of ASM therapy. We did not have enough statistical power to assess the recurrent risk of cardiac events when LQTS3 participants were taking ASMs. While there was not a higher rate of cardiac events when LQTS negative participants with normal QT_c durations were on vs. off ASMs, we were unable to perform recurrent risk analyses. Nevertheless, consistent with previous studies,(8, 10, 15–17) our results indicate that ASMs do not increase the rate of cardiac events within the general LQTS genotype- and phenotype-negative population.

People with QT_c prolongation are at an increased risk of cardiac events when on vs. off ASMs. Pharmacogenomic analyses indicate there are LQTS genotype and ASM class specific differences in the risk of cardiac events when patients are taking ASMs. Na⁺ channel blocker ASMs are associated with an increased the risk of cardiac events in LQTS2 patients, and are protective in LQTS1 patients. Despite GABA modifier ASMs not being associated with a change in the overall risk of cardiac events, sub-analyses indicate caution needs to be applied when initiating GABA modifier ASM therapy in the absence of beta adrenergic blocker therapy, or GABA modifiers in female participants with QT_c prolongation. In patients with QT_c prolongation, the increased risk of cardiac events is blunted when ASMs are taken concurrently with beta-adrenergic blockers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

ASM	anti-seizure medication
GABA	gamma-aminobutyric acid
ECG	electrocardiogram
LQTS	Long QT Syndrome
Na⁺Ch	Na ⁺ channel
QT_c	corrected QT
SCD	sudden cardiac death
SUDEP	sudden unexpected death in epilepsy

References

1. Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case-control study. *Lancet*. 1999; 353(9156):888–93. [PubMed: 10093982]
2. Bardai A, Blom MT, van Noord C, Verhamme KM, Sturkenboom MC, Tan HL. Sudden cardiac death is associated both with epilepsy and with use of antiepileptic medications. *Heart*. 2015; 101(1):17–22. [PubMed: 25031263]

3. Feldman AE, Gidal BE. QTc prolongation by antiepileptic drugs and the risk of torsade de pointes in patients with epilepsy. *Epilepsy & behavior* : E&B. 2013; 26(3):421–6.
4. Sills, G. Chapter 25: Mechanisms of action of antiepileptic drugs. In: Sander, J.Walker, MC., Smalls, JE., editors. *Epilepsy 2011: From Science to Society A Practical Guide to Epilepsy ILAE (UK Chapter) and the National Society for Epilepsy*. London, UK: 2011.
5. Macdonald RL, Kelly KM. Antiepileptic drug mechanisms of action. *Epilepsia*. 1995; 36(Suppl 2):S2–12.
6. Rogawski MAC, JE. Chapter 43: Mechanisms of ACTION of Antiepileptic Drugs. In: Gidal BEG, H.Sirven, J., Loddenkemper, T., editors. *Wylkie's Treatment of Epilepsy*. 6th. Section A. Lippincott Williams & Wilkins; Philadelphia, PA: 2014. p. 1-8.PART IV: MEDICATIONS ANTIEPILEPTIC
7. Glasscock E. Genomic biomarkers of SUDEP in brain and heart. *Epilepsy & behavior* : E&B. 2014; 38:172–9.
8. Stefani M, Arima H, Mohamed A. Withdrawal of anti-epileptic medications during video EEG monitoring does not alter ECG parameters or HRV. *Epilepsy Res*. 2013; 106(1–2):222–9. [PubMed: 23664147]
9. Borowicz KK, Banach M. Antiarrhythmic drugs and epilepsy. *Pharmacol Rep*. 2014; 66(4):545–51. [PubMed: 24948053]
10. Evers ML, Izhar A, Aqil A. Cardiac monitoring after phenytoin overdose. *Heart Lung*. 1997; 26(4): 325–8. [PubMed: 9257143]
11. Wang LW, Subbiah RN, Kilborn MJ, Dunn RF. Phenytoin: an old but effective antiarrhythmic agent for the suppression of ventricular tachycardia. *The Medical journal of Australia*. 2013; 199(3):209–11. [PubMed: 23909546]
12. Aurlen D, Gjerstad L, Taubøll E. The role of antiepileptic drugs in sudden unexpected death in epilepsy. *Seizure: European Journal of Epilepsy*. 2016
13. Danielsson BR, Lansdell K, Patmore L, Tomson T. Effects of the antiepileptic drugs lamotrigine, topiramate and gabapentin on hERG potassium currents. *Epilepsy Res*. 2005; 63(1):17–25. [PubMed: 15716081]
14. Danielsson BR, Lansdell K, Patmore L, Tomson T. Phenytoin and phenobarbital inhibit human HERG potassium channels. *Epilepsy Res*. 2003; 55(1–2):147–57. [PubMed: 12948624]
15. Dixon R, Alexander S, Brickel N. Effect of lamotrigine on the PR interval in healthy subjects. *Br J Clin Pharmacol*. 2011; 71(6):961–2. [PubMed: 21564165]
16. Dixon R, Job S, Oliver R, Tompson D, Wright JG, Maltby K, et al. Lamotrigine does not prolong QTc in a thorough QT/QTc study in healthy subjects. *Br J Clin Pharmacol*. 2008; 66(3):396–404. [PubMed: 18662287]
17. Saetre E, Abdelnoor M, Amlie JP, Tossebro M, Perucca E, Tauboll E, et al. Cardiac function and antiepileptic drug treatment in the elderly: a comparison between lamotrigine and sustained-release carbamazepine. *Epilepsia*. 2009; 50(8):1841–9. [PubMed: 19400874]
18. Woosley, R., Heise, CW., Romero, KA. QT Drugs List. [Available from: <https://crediblemeds.org/>]
19. Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol*. 2008; 51(24):2291–300. [PubMed: 18549912]
20. Auerbach DS, McNitt S, Gross RA, Zareba W, Dirksen RT, Moss AJ. Genetic biomarkers for the risk of seizures in long QT syndrome. *Neurology*. 2016; 87(16):1660–8. [PubMed: 27466471]
21. Johnson JN, Hofman N, Haglund CM, Cascino GD, Wilde AA, Ackerman MJ. Identification of a possible pathogenic link between congenital long QT syndrome and epilepsy. *Neurology*. 2009; 72(3):224–31. [PubMed: 19038855]
22. Anderson JH, Bos JM, Cascino GD, Ackerman MJ. Prevalence and spectrum of electroencephalogram-identified epileptiform activity among patients with long QT syndrome. *Heart Rhythm*. 2014; 11(1):53–7. [PubMed: 24103226]
23. Ochoa W JR. Antiepileptic Drugs. 2016 [updated 03/08/2016].
24. Locati EH, Zareba W, Moss AJ, Schwartz PJ, Vincent GM, Lehmann MH, et al. Age- and sex-related differences in clinical manifestations in patients with congenital long-QT syndrome: findings from the International LQTS Registry. *Circulation*. 1998; 97(22):2237–44. [PubMed: 9631873]

25. Migdalovich D, Moss AJ, Lopes CM, Costa J, Ouellet G, Barsheshet A, et al. 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. *Heart Rhythm*. 2011; 8(10):1537–43. [PubMed: 21440677]
26. Antzelevitch C, Burashnikov A, Sicouri S, Belardinelli L. Electrophysiologic basis for the antiarrhythmic actions of ranolazine. *Heart Rhythm*. 2011; 8(8):1281–90. [PubMed: 21421082]
27. Anderson LL, Thompson CH, Hawkins NA, Nath RD, Petersohn AA, Rajamani S, et al. Antiepileptic activity of preferential inhibitors of persistent sodium current. *Epilepsia*. 2014; 55(8):1274–83. [PubMed: 24862204]
28. Kahlig KM, Hirakawa R, Liu L, George AL Jr, Belardinelli L, Rajamani S. Ranolazine reduces neuronal excitability by interacting with inactivated states of brain sodium channels. *Mol Pharmacol*. 2014; 85(1):162–74. [PubMed: 24202911]
29. Bearden D, Strong A, Ehnot J, DiGiovine M, Dlugos D, Goldberg EM. Targeted treatment of migrating partial seizures of infancy with quinidine. *Ann Neurol*. 2014; 76(3):457–61. [PubMed: 25042079]
30. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med*. 2004; 350(10):1013–22. [PubMed: 14999113]
31. Celik IE, Akyel A, Colgecen M, Ozeke O. A rare cause of 2:1 atrioventricular block: carbamazepine. *Am J Emerg Med*. 2015; 33(10):1541 e3–4.
32. Kasarskis EJ, Kuo CS, Berger R, Nelson KR. Carbamazepine-induced cardiac dysfunction. Characterization of two distinct clinical syndromes. *Arch Intern Med*. 1992; 152(1):186–91. [PubMed: 1728915]
33. Lossius MI, Erikssen JE, Mowinckel P, Gulbrandsen P, Gjerstad L. Changes in autonomic cardiac control in patients with epilepsy after discontinuation of antiepileptic drugs: a randomized controlled withdrawal study. *Eur J Neurol*. 2007; 14(9):1022–8. [PubMed: 17718695]
34. Hainsworth AH, McNaughton NC, Pereverzev A, Schneider T, Randall AD. Actions of sipatrigine, 202W92 and lamotrigine on R-type and T-type Ca²⁺ channel currents. *Eur J Pharmacol*. 2003; 467(1–3):77–80. [PubMed: 12706458]
35. Surges R, Thijs RD, Tan HL, Sander JW. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. *Nat Rev Neurol*. 2009; 5(9):492–504.
36. Aurlen D, Larsen JP, Gjerstad L, Tauboll E. Increased risk of sudden unexpected death in epilepsy in females using lamotrigine: a nested, case-control study. *Epilepsia*. 2012; 53(2):258–66. [PubMed: 22126371]
37. Christidis D, Kalogerakis D, Chan TY, Mauri D, Alexiou G, Terzoudi A. Is primidone the drug of choice for epileptic patients with QT-prolongation? A comprehensive analysis of literature. *Seizure*. 2006; 15(1):64–6. [PubMed: 16309926]
38. Waring WS. Clinical use of antidepressant therapy and associated cardiovascular risk. *Drug Healthc Patient Saf*. 2012; 4:93–101. [PubMed: 22936860]
39. Frommeyer G, Eckardt L. Drug-induced proarrhythmia: risk factors and electrophysiological mechanisms. *Nat Rev Cardiol*. 2016; 13(1):36–47. [PubMed: 26194552]
40. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation*. 2001; 103(1):89–95. [PubMed: 11136691]
41. Locke GR 3rd, Ackerman MJ, Zinsmeister AR, Thapa P, Farrugia G. Gastrointestinal symptoms in families of patients with an SCN5A-encoded cardiac channelopathy: evidence of an intestinal channelopathy. *Am J Gastroenterol*. 2006; 101(6):1299–304. [PubMed: 16771953]
42. Goldman AM, Glasscock E, Yoo J, Chen TT, Klassen TL, Noebels JL. Arrhythmia in heart and brain: KCNQ1 mutations link epilepsy and sudden unexplained death. *Sci Transl Med*. 2009; 1(2):2ra6.
43. D'Adamo MC, Catacuzzeno L, Di Giovanni G, Franciolini F, Pessia M. K(+) channelopathy: progress in the neurobiology of potassium channels and epilepsy. *Frontiers in cellular neuroscience*. 2013; 7:134. [PubMed: 24062639]

44. Hartmann HA, Colom LV, Sutherland ML, Noebels JL. Selective localization of cardiac SCN5A sodium channels in limbic regions of rat brain. *Nat Neurosci.* 1999; 2(7):593–5. [PubMed: 10404176]
45. Barajas-Martinez H, Haufe V, Chamberland C, Roy MJ, Fecteau MH, Cordeiro JM, et al. Larger dispersion of INa in female dog ventricle as a mechanism for gender-specific incidence of cardiac arrhythmias. *Cardiovasc Res.* 2009; 81(1):82–9. [PubMed: 18805783]
46. Gaborit N, Varro A, Le Bouter S, Szuts V, Escande D, Nattel S, et al. Gender-related differences in ion-channel and transporter subunit expression in non-diseased human hearts. *J Mol Cell Cardiol.* 2010; 49(4):639–46. [PubMed: 20600101]
47. Jonsson MK, Vos MA, Duker G, Demolombe S, van Veen TA. Gender disparity in cardiac electrophysiology: implications for cardiac safety pharmacology. *Pharmacology & therapeutics.* 2010; 127(1):9–18. [PubMed: 20462510]
48. James AF, Choisy SC, Hancox JC. Recent advances in understanding sex differences in cardiac repolarization. *Prog Biophys Mol Biol.* 2007; 94(3):265–319. [PubMed: 15979693]
49. Furukawa T, Kurokawa J. Regulation of cardiac ion channels via non-genomic action of sex steroid hormones: implication for the gender difference in cardiac arrhythmias. *Pharmacology & therapeutics.* 2007; 115(1):106–15. [PubMed: 17583354]

Background

Long QT Syndrome (LQTS) is due to mutations in ion channel genes expressed in the brain and heart. LQTS patients are at a high risk of arrhythmias and sudden death. As there is a high prevalence of seizures in LQTS, and anti-seizure medications (ASMs) act on ion channels expressed in the brain and heart, it is important to assess the cardiac safety of ASMs in patients with LQTS.

Translational Significance

Pharmacogenomic analyses indicate there are LQTS genotype and ASMs class specific risks of cardiac events. These results establish the basis for future prospective clinical studies, and mechanistic cellular and animal studies.

Figure 1. ASM-class specific analyses

Flow chart of ASMs grouped by the predominant mechanism of action, and the number of participants with QT_c prolongation on each class of ASMs. NA, Na⁺ channel (Na⁺Ch) blocker ASMs; GA, GABA modifier ASMs; Other, ASMs with the predominant mechanism of action other than Na⁺ channel blockade and GABA modification. Several participants had a history of taking more than one ASM during follow-up.

Figure 2. LQTS genotype-specific differences in the rate and risk of cardiac events when on vs. off ASMs

A. Rate of recurrent cardiac events (ACA, SCD, ventricular tachyarrhythmia) when participants are on and off ASMs. **B.** Multivariate time-dependent analyses of the risk for recurrent cardiac events when participants are on ASMs. Adjustments for time dependent beta-adrenergic blocker use, baseline QT_c duration, and stratified for sex. We estimated the LQTS genotype specific effects using an interaction term in the model.

Figure 3. LQTS genotype- and ASM-class specific differences in the rate/risk for cardiac events Rate (A–C) and multivariate adjusted time-dependent risk (D–F) of recurrent cardiac events (ACA, SCD, ventricular tachyarrhythmia) when participants are on and off Na⁺ channel (Na⁺+Ch) blocker ASMs, GABA modifier ASMs, and concurrent Na⁺Ch blocker and GABA modifier ASMs. **A & D.** All participants with QT_c prolongation. **B & E.** LQTS1 participants with QT_c prolongation. **C & F.** LQTS2 participants with QT_c prolongation. Adjustments for time dependent beta-adrenergic blocker use, baseline QT_c duration, time dependent Other ASM use, and stratified for sex. Interaction between each class of ASMs (*p*=ns.)

Figure 4. Concurrent beta-adrenergic blocker ASM therapy and participant gender are associated with differences in the risk of cardiac events

Multivariate adjusted time-dependent analyses of the risk for recurrent cardiac events (ACA, SCD, ventricular tachyarrhythmia) in participants with QT_c prolongation on all ASMs in the absence & co-presence of beta-adrenergic blocker therapy (**A**), and in male & female participants (**B**). Risk analyses of time-dependent Na⁺ channel (Na⁺Ch) blocker ASM, GABA modifier ASM, and concurrent Na⁺Ch blocker and GABA modifier ASM therapy in the absence & co-presence of beta-adrenergic blockers (**C**), and in male & female participants (**D**). Adjustments for time dependent beta-adrenergic blocker use, baseline QT_c duration, and stratified for sex. Panels C & D are also adjusted for time dependent Other ASM use. Differences in the risk of cardiac events on ASMs in the absence vs. co-presence of beta-adrenergic blocker therapy, and in male vs. female participants were modeled using interaction terms.

Table 1

Baseline characteristics: QT_c prolongation group includes LQTS1 and LQTS2 participants, plus participants with LQTS3-12 mutations and LQTS genotype unknown.

Clinical Characteristics	QT _c prolongation	QT _c Prolongation		LQTS1 vs. LQTS2 (<i>p</i> value)
		LQTS1	LQTS2	
# of participants	296	48	76	
Male, #(%)	85(29)	13(27)	20(26)	0.925
Follow-up, yrs, mean±SD	32±11	34±10	36±8	0.151
Beta-adrenergic blockers	238(80)	38(79)	63(83)	0.603
Number of participants and time on ASMs				
# of participants with a history of All ASMs (%)	296(100)	48(100)	76(100)	1.000
Total time on All ASMs, yrs, mean±SD	6.96±7.72	6.54±7.20	8.74±9.35	0.35
Total Time off All ASMs, yrs, mean±SD	25.36±12.10	26.98±10.48	26.89±10.05	0.973
ECG, mean±SD				
Age at baseline ECG, yr	23±14	22±15	25±13	0.215
QT _c , sec	524±57	533±60	530±55	0.768
Number of Participants with Cardiac Events (%)				
Ventricular Tachyarrhythmias (VT, VF, TdP)	140(47)	19(40)	38(50)	0.257
Aborted cardiac arrest (ACA) & Sudden cardiac death (SCD)	86(29)	9(19)	22(29)	0.201
Cardiac events (VT, VF, TdP, ACA, SCD)	156(53)	19(40)	42(55)	0.089

Table 2
ASMs are not associated with an overall change in QT_c duration

Average±SD among participants that had the ECG measurement both on and off all ASMs (top), and each class of ASMs (middle: participants with QT_c prolongation; bottom: LQTS1 and LQTS2 participants with QT_c prolongation).

Group	On vs. Off All ASMs	QT _c Prolongation	QT _c Prolongation	
			LQTS1	LQTS2
All Participants w/ QT _c Prolongation	ON	509±56	513±64	521±55
	OFF	506±47	505±50	510±43
	<i>p</i> -value	0.571 (n=95)	0.594 (n=15)	0.445 (n=25)
Male Participants w/ QT _c Prolongation	ON	499±58	479±90	518±44
	OFF	506±57	469±14	508±47
	<i>p</i> -value	0.523 (n=30)	0.839 (n=5)	0.613 (n=9)
Female Participants w/ QT _c Prolongation	ON	514±55	530±43	523±61
	OFF	506±42	523±53	511±42
	<i>p</i> -value	0.222 (n=65)	0.462 (n=10)	0.570 (n=16)

Group	On vs. Off Each Class of ASMs	Na ⁺ Channel Blocker ASMs	GABA Modifier ASMs	Na ⁺ Blocker & GABA Modifier ASMs
All Participants w/ QT Prolongation	ON	515±52	491±56	501±60
	OFF	511±45	500±50	494±37
	<i>p</i> -value	0.586 (n=56)	0.397 (n=25)	0.590 (n=26)
Male Participants w/ QT Prolongation	ON	515±52	468±55	448±34
	OFF	509±46	507±78	473±26
	<i>p</i> -value	0.687 (n=21)	0.012 (n=9)	0.224 (n=5)
Female Participants w/ QT _c Prolongation	ON	515±53	504±53	513±59
	OFF	513±45	496±29	498±38
	<i>p</i> -value	0.723 (n=35)	0.570 (n=16)	0.344 (n=21)

Group	On vs. Off Each Class of ASMs	Na ⁺ Channel Blocker ASMs	GABA Modifier ASMs	Na ⁺ Blocker & GABA Modifier ASMs
LQTS1 Participants w/ QT Prolongation	ON	558±56	463±42	492±43
	OFF	532±58	475±26	494±31
	<i>p</i> -value	0.388 (n=7)	0.496 (n=4)	0.904 (n=5)
LQTS2 Participants w/ QT Prolongation	ON	518±47	510±48	523±81
	OFF	515±42	508±36	490±45
	<i>p</i> -value	0.879 (n=17)	0.943 (n=5)	0.480 (n=6)