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Association Between Syncope Trigger Type and Risk of Subsequent Life-Threatening Events in Patients With Long QT Syndrome

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IMPORTANCE Syncope is the most powerful predictor for subsequent life-threatening events (LTEs) in patients with congenital long QT syndrome (LQTS). Whether distinct syncope triggers are associated with differential subsequent risk of LTEs is unknown.

OBJECTIVE To evaluate the association between adrenergic (AD)– and nonadrenergic (non–AD)-triggered syncopal events and the risk of subsequent LTEs in patients with LQT types 1 to 3 (LQT1-3).

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included data from 5 international LQTS registries (Rochester, New York; the Mayo Clinic, Rochester, Minnesota; Israel, the Netherlands, and Japan). The study population comprised 2938 patients with genetically confirmed LQT1, LQT2, or LQT3 stemming from a single LQTS-causative variant. Patients were enrolled from July 1979 to July 2021.

EXPOSURES Syncope by AD and non-AD triggers.

MAIN OUTCOMES AND MEASURES The primary end point was the first occurrence of an LTE. Multivariate Cox regression was used to determine the association of AD- or non–AD-triggered syncope on the risk of subsequent LTE by genotype. Separate analysis was performed in patients with β-blockers.

RESULTS A total of 2938 patients were included (mean [SD] age at enrollment, 29 [7] years; 1645 [56%] female). In 1331 patients with LQT1, a first syncope occurred in 365 (27%) and was induced mostly with AD triggers (243 [67%]). Syncope preceded 43 subsequent LTEs (68%). Syncopal episodes associated with AD triggers were associated with the highest risk of subsequent LTE (hazard ratio [HR], 7.61; 95% CI, 4.18-14.20; $P < .001$), whereas the risk associated with syncopal events due to non-AD triggers was statistically nonsignificant (HR, 1.50; 95% CI, 0.21-4.77; $P = .97$). In 1106 patients with LQT2, a first syncope occurred in 283 (26%) and was associated with AD and non-AD triggers in 106 (37%) and 177 (63%), respectively. Syncope preceded 55 LTEs (56%). Both AD- and non–AD-triggered syncope were associated with a greater than 3-fold increased risk of subsequent LTE (HR, 3.07; 95% CI, 1.66-5.67; $P \leq .001$ and HR, 3.45, 95% CI, 1.96-6.06; $P \leq .001$, respectively). In contrast, in 501 patients with LQT3, LTE was preceded by a syncopal episode in 7 (12%). In patients with LQT1 and LQT2, treatment with β-blockers following a syncopal event was associated with a significant reduction in the risk of subsequent LTEs. The rate of breakthrough events during treatment with β-blockers was significantly higher among those treated with selective agents vs nonselective agents.

CONCLUSION AND RELEVANCE In this study, trigger-specific syncope in LQTS patients was associated with differential risk of subsequent LTE and response to β-blocker therapy.

Supplemental content

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Congenital long QT syndrome (LQTS) is an inherited channelopathy that is associated with increased risk of cardiac events, manifested most commonly as syncope or, less commonly but more severely, as life-threatening events (LTEs), including aborted cardiac arrest and sudden cardiac death.[1] Prior studies have demonstrated that in each of the most common LQTS genotypes (LQT types 1 to 3), LQTS-associated cardiac events were associated with several genotype-specific triggers.[2,3] In LQT1, most cardiac events were shown to be associated with exercise or adrenergic (AD) activity; in LQT2, cardiac events were shown to be associated more often with arousal triggers; and in LQT3, most events occurred during rest or sleep.[2-4] Cardiac or arrhythmogenic syncope is the most common first symptom among patients with LQTS and is the most powerful predictor of subsequent LTEs.[5-7] However, to our knowledge, there are no data on the association between specific syncope trigger types (AD-associated syncope vs non-AD-associated syncope) and the risk of subsequent, more severe LTEs.

We hypothesized that distinct syncope triggers (AD vs non-AD) would have a differential association with subsequent LTE by genotype and response to β-blocker therapy. To test this hypothesis, we investigated the association between trigger-specific syncope events with the risk of subsequent LTEs in 2938 patients with genetically confirmed LQT1, LQT2, or LQT3 enrolled in 5 worldwide LQTS registries.

Key Points

Question Is there an association between the trigger type of a syncope and risk of subsequent life-threatening events (LTEs) in patients with congenital long QT syndrome (LQTS)?

Findings In this cohort study involving 2983 patients, syncopal episodes associated with adrenergic triggers were associated with the highest risk of subsequent LTE in patients with LQT type 1, followed by patients with type 2, and no risk was found among those with type 3. For syncopal episodes associated with nonadrenergic triggers, only patients with LQT type 2 were at an increased risk of subsequent LTE.

Meaning The findings indicate that trigger-specific syncope in patients with LQTS was associated with differential risk of subsequent LTE.

Methods

Study Population

The study population comprised all 2938 patients with mutually exclusive LQT1-3 genotype positivity from 5 international LQTS registries who had complete data regarding probable LQTS-associated cardiac events and their temporal triggers.[1] Patients were enrolled from Rochester, New York (n = 2017); the Mayo Clinic in Rochester, Minnesota (n = 966); the Netherlands (n = 83); Israel (n = 52), and Japan (n = 29) between July 1979 and July 2021. Patients were excluded from the analysis if they had more than 1 LQTS-causative variant, experienced aborted cardiac arrest or death or were lost to follow-up before age 1 year, or did not have data on trigger or β-blocker treatment (eFigure 1 in Supplement 1). Data were recorded on prospectively designed forms yearly and by events. In all centers, institutional review board approval was obtained for this type of study. All patients provided written informed consent before enrollment in the corresponding registry. The study was approved by the University of Rochester Research Subject Review Board.

Genotype Characterization

Patients with LQT1-3 genotype were identified with the use of standard genetic tests performed in academic molecular genetic research laboratories. Genetic alterations of the amino acid sequence were characterized by location in the channel protein and by the type of pathogenic variant (missense, splice site, in-frame insertions or deletions, nonsense [stop codon], and frameshift) as elaborated in the eAppendix in Supplement 1. Accordingly, patients were classified as having LQT1-3 based on their particular disease-causative variant.[8,9]

Definitions and End Points

LQTS-associated syncope in the registries was defined as a transient loss of consciousness with abrupt onset and offset in a setting strongly suggestive of having stemmed from LQTS-associated torsades de pointes (ie, cardiac, arrhythmic, or torsadogenic syncope) by review of patient data and clinical manifestation of the event. In the main analysis, triggered cardiac syncope events were categorized into 2 main groups by the trigger reported to be associated with that syncope event:

1. AD, defined as syncope that occurred during arousal triggers (loud noise or acute emotional arousal) and exercise triggers (vigorous physical activity or swimming).
2. Non-AD, comprising mostly syncope that occurred at rest and a heterogeneous group of the remaining identified triggers (eTable 1 in Supplement 1).

The primary end point of the study was the first occurrence of LTE, defined as first occurrence of 1 of the following: ventricular arrhythmia treated with shock, aborted cardiac arrest (requiring external defibrillation as part of the resuscitation), or LQTS-related sudden cardiac death, whichever occurred first, from birth through age 40 years (to avoid non-LQTs-related cardiovascular events that are secondary to age-related comorbidities or atherosclerosis).

Statistical Analysis

The clinical characteristics of study patients were compared by the occurrence of trigger-specific syncope group by using the χ^2 test for categorical variables and the *t* test and the Mann-Whitney-Wilcoxon test for continuous variables. The association of the triggered syncope with the risk of subsequent LTE was tested in 2 different models (eFigure 2 in Supplement 1):

1. First triggered syncope event main model: association of the patient's first triggered syncope with subsequent LTE. Multivariate Cox proportional hazards regression analysis was carried out to evaluate the independent contribution of the different syncope triggers (first occurrence for triggered syncope in a patient) to the risk of first subsequent

occurrence of LTE (following the triggered syncope event) during follow-up.
2. Multiple-triggered syncopal events model: we created time-dependent variables for each triggered syncopal event in a patient (ie, first and recurrent syncope) and evaluated their independent contribution to the risk of subsequent LTE. The proportional hazards assumption was checked using a multivariate Cox regression model by use of the above-listed time-dependent covariates created by interacting survival time with the various covariates and testing for statistical significance using the likelihood ratio test. This analysis was carried out to test the independent contribution of each syncopal event from the time of that event to the next syncope, LTE event, or last follow-up (or no other event occurring during follow-up).

All regression models were adjusted for age and sex interaction, corrected QT interval at baseline (derived from first recorded electrocardiogram), the use of β-blockers, and center. In all models, syncope and β-blocker use were used as time-dependent covariables.

Data on β-blocker therapy, including information on type (selective vs nonselective), medication start and stop, and switching to a different β-blocker, are captured prospectively in the registry. Kaplan-Meier survival curves were used to illustrate and compare the residual event rate of LTE despite β-blocker therapy (recommended dosages for β-blocker therapy are listed in eTable 2 in Supplement 1). Follow-up time began at the time of β-blocker therapy initiation (and not at birth) or at the time of syncope if β-blocker therapy was initiated prior to the first syncopal event (as long as the patient was still taking the medication). In these cases, follow-up started at the time of syncope to evaluate the residual effect of LTE while taking β-blocker therapy following the syncope event. In addition, event rate per treatment interval by β-blocker therapy type (cardiac selective vs nonselective) was performed. In each LQT type, time intervals were created. The time interval takes into consideration the type of β-blocker therapy and the type of syncope. One patient can have several intervals. An interval starts at the commencement of β-blocker therapy and ends when the therapy was stopped (or switched), an LTE has occurred, or at the end of follow-up. The LTE rates are categorized based on the presence, absence, and type of syncope during each treatment interval and by the type of β-blocker. All statistical tests were 2-sided, and a *P* value less than .05 was considered statistically significant. Analyses were carried out with SAS version 13.4 (SAS Institute).

Results

A total of 2938 patients were included (mean [SD] age at enrollment, 29 [7] years; 1645 [56%] female). **Table 1** lists the baseline characteristics of the total study population based on the 2 main trigger groups of syncope. The mean (SD) time receiving β-blocker therapy for the total population was 15 (7) years.

Triggered Syncope in Patients With LQT1

A total of 1331 patients (45%) had LQT1. Among them, a first syncope occurred in 365 (27%) and was associated with AD triggers in 243 (67%) and non-AD triggers in 122 (33%) (**Figure 1**). The most common trigger was vigorous physical activity (exercise) and was reported in 154 individuals (42%) (eTable 1 in Supplement 1).

A subsequent postdiagnosis and post-initial therapy LTE occurred in 63 patients with LQT1 (5%). Figure 1A shows that 38 patients (60%) with LQT1 with an LTE had a prior sentinel event of AD-associated syncope; 5 (8%) were by a non-AD syncope, and in 20 individuals (32%), the LTE was the sentinel event. A total of 20 AD-associated LTEs (69%) were preceded by a syncope with a similar AD trigger (eTable 3 in Supplement 1).

In the first event analysis, a first AD-triggered syncope event was the most powerful predictor of subsequent LTE and was associated with a near 8-fold (hazard ratio [HR], 7.61; 95% CI, 4.18-14.20; *P* < .001) increased risk of subsequent LTE (**Table 2**). In contrast, the association of a first non-AD-triggered syncope with the risk of subsequent LTE was statistically nonsignificant (HR, 1.50; 95% CI, 0.21-4.77; *P* = .97; Table 2). In the first and recurrent analysis, AD-triggered syncopal events were associated with a nearly 6-fold (HR, 5.95; 95% CI, 3.10-11.40; *P* < .001) increased risk of subsequent LTEs, and the association of non-AD-triggered syncopal events with the risk of subsequent LTEs was statistically nonsignificant (HR, 1.20; 95% CI, 0.35-4.20; *P* = .77) (Table 2).

AD triggers were further subcategorized as exercise or arousal based (**Table 3**). Syncope triggered by exercise-related AD triggers was associated with the highest risk of subsequent LTE (exercise-related HR, 7.63; 95% CI, 3.53-16.50; *P* < .001; arousal-related HR, 5.08; 95% CI, 1.78-14.46; *P* < .001; rest HR, 1.87; 95% CI, 0.38-9.14; *P* = .44).

Triggered Syncope in Patients With LQT2

A total of 1106 study patients (38%) had LQT2. Among them, a first syncope occurred in 283 (26%) and was associated with AD triggers in 106 (37%) and non-AD triggers in 177 (63%) (Figure 1). The most common trigger was sudden noise, which was reported in 39 individuals (14%) (eTable 4 in Supplement 1). LTE occurred in 98 patients with LQT2. Figure 1 shows that 23 LTEs (23%) were preceded by AD-associated syncope and 32 (33%) by non-AD syncope, and 43 LTEs (44%) were not preceded by a syncopal event. Among patients with LTE with an AD trigger, 4 (24%) had a prior AD syncope (eTable 5 in Supplement 1).

First-event analysis showed that both first syncope trigger types (AD and non-AD) were associated with a similar risk of subsequent LTE (AD trigger HR, 3.07; 95% CI, 1.66-5.67; *P* = .001; non-AD trigger HR, 3.45; 95% CI, 1.96-6.06; *P* < .001) (Table 2). Similarly, in first and recurrent analysis, both presenting and recurrent syncope trigger types were associated with a similar risk of subsequent LTE (AD HR, 2.82; 95% CI, 1.53-5.18; *P* < .001 and non-AD HR, 3.09; 95% CI, 1.76-5.41; *P* < .001) (Table 2). The risk associated with arousal, exercise, rest, and other triggers was similar (Table 3).

Table 1. Baseline Characteristics

Clinical characteristic	No. (%)					
	No syncope	Adrenergic syncope	Nonadrenergic syncope	*P* value[a]	*P* value[b]	*P* value[c]
No. of patients	2227	368	343	NA	NA	NA
Female	1160 (52)	232 (63)	240 (70)	<.001	<.001	.05
Male	1067 (48)	136 (37)	103 (30)			
Family history						
LQTS	55 (60)	71 (66)	51 (61)	.38	.89	.48
Syncope/ACA	39 (43)	68 (64)	45 (55)	.005	.13	.22
SCD	466 (58)	96 (44)	80 (44)	<.001	<.001	.92
Date of enrollment						
1980-1989	245 (11)	82 (22)	44 (12)	.01	.79	.01
1990-1999	468 (21)	109 (30)	105 (31)	.009	.83	<.001
2000-2009	824 (37)	111 (30)	110 (32)	.01	.67	.07
2010-2019	690 (31)	66 (18)	84 (25)	<.001	.018	.01
ECG at enrollment, mean (SD)						
QRS, ms	80 (15)	80 (14)	81 (15)	.48	.57	.91
RR, ms	803 (236)	880 (216)	857 (222)	<.001	.002	.24
QTc, ms	467 (42)	497 (52)	487 (57)	<.001	.12	.07
QTp in lead V2	0.32 (0.06)	0.36 (0.05)	0.34 (0.07)	<.001	<.001	.001
Genotype						
LQT1	966 (44)	243 (65)	122 (33)	<.001	.002	<.001
LQT2	823 (40)	106 (29)	177 (53)	.001	<.001	<.001
LQT3	438 (16)	19 (5)	44 (13)	<.001	.32	.003
Treatment prior to syncope[d]						
β-Blocker	929 (42)	32 (9)	53 (15)	<.001	<.001	.003
Treated at targeted β-blocker dose[e]	548 (59)	16 (50)	21 (40)	<.001	<.001	<.001
ICD	174 (8)	6 (2)	5 (1)	<.001	<.001	.67
Events during follow-up						
Life-threatening events	100 (4)	69 (19)	48 (14)	<.001	<.001	.23
Aborted cardiac arrest	44 (2)	27 (7)	21 (6)	<.001	<.001	.51
LQTS death	37 (2)	15 (4)	6 (2)	.002	.90	.067
Noncardiac death	9 (1)	1 (0)	2 (1)	>.99	.66	.61
Torsades de pointes	11 (0)	20 (5)	22 (6)	<.001	<.001	.58

Abbreviations: ACA, aborted cardiac arrest; ECG, electrocardiogram; ICD, implantable cardioverter defibrillator; LQT1, long QT type 1; LQT2, type 2; LQT3, type 3; LQTS, LQT syndrome; QTc, corrected QT interval; QTp, QT interval from onset to peak; RR, R-R interval; SCD, sudden cardiac death.

[a] For the comparison between no syncope and adrenergic syncope.

[b] For the comparison between no syncope and nonadrenergic syncope.

[c] For the comparison between adrenergic syncope and nonadrenergic syncope.

[d] At the time of the syncope event or at the time of last follow-up for those without syncope.

[e] Recommended dosage for β-blockers is listed in eTable 2 in Supplement 1.

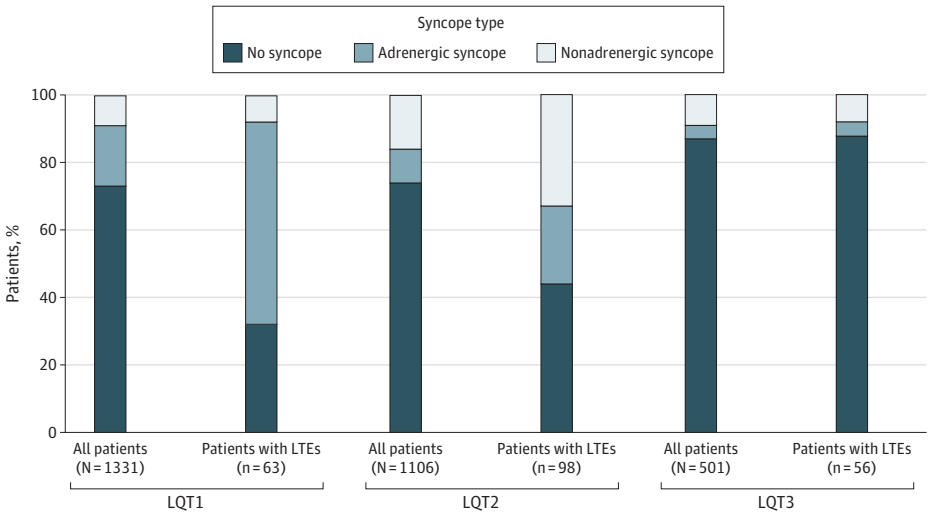
Triggered Syncope in Patients With LQT3

Among 501 patients with LQT3, a first syncope occurred in 63 (13%), with most of that subset (n = 44 [70%]) associated with non-AD triggers (Figure 1). The most common trigger was rest, reported in 27 individuals (42%) (eTable 6 in Supplement 1). LTE occurred in 56 patients (11%) with LQT3. Most LTE events represented the sentinel event as there was no prior syncopal episode in 49 individuals (88%) (Figure 1). Further analysis by LTE trigger type showed that in patients with LQT3, no AD-associated LTEs were preceded by syncope, and 6 of the non-AD LTEs (14%) were preceded by non-AD syncope (eTable 7 in Supplement 1). Separate multivariate regression models were not created in the LQT3 group owing to the relatively low number of preceding syncopal events (7 patients).

β-Blocker Therapy

β-Blocker therapy was associated with a 70% risk reduction of LTE in individuals with LQT1 (HR, 0.30; 95% CI, 0.15-0.64; *P* = .002) and 53% risk reduction in those with LQT2 (HR, 0.47; 95% CI, 0.24-0.94; *P* = .03) (eTable 8 in Supplement 1). **Figure 2** shows the rates of residual LTE among patients with LQT1 and LQT2 who were prescribed β-blocker therapy following the occurrence of syncope. In those with LQT1, the cumulative rate of LTE despite β-blocker therapy at 30 years was 20% following the occurrence of AD syncope and 4% non-AD, and 2% among those without syncope, respectively (*P* < .001 for the overall difference) (Figure 2A). In patients with LQT2, the cumulative rate of LTE despite β-blocker therapy at 30 years was 22% following the occur-

Figure 1. Distribution of the First Syncope Trigger Groups Among All Patients and Among Those With Subsequent Life-Threatening Events (LTEs)



LQT1 indicates long QT syndrome type 1; LQT2, type 2; LQT3, type 3.

rence of AD syncope, 19% following non-AD syncope, and 8% among those without syncope ($P < .001$ for the overall difference) (Figure 2B).

Separate analysis (Figure 2C) looking at the type of β-blocker therapy highlighted the importance of β-blocker therapy type (selective vs nonselective). In patients with LQT1, no LTE events were observed following non-AD syncope for both β-blocker therapy types. In contrast, among patients who experienced AD syncope, treatment with selective β-blocker therapy was associated with the highest rate of LTE (6.3 events per 1000 patient-years), whereas treatment with nonselective β-blocker therapy was associated with a low rate of LTE following AD syncope (less than 1 event per 1000 years), similar to the risk of those treated with β-blocker therapy who did not experience syncope (Figure 2C). In patients with LQT2, the rate of subsequent LTE was highest during treatment with selective β-blocker therapy (LTE event rate per 1000 patient-years: no syncope = 1.7; AD syncope = 1.6; non-AD syncope = 4.1) and was lowest when patients were taking nonselective β-blocker therapy zero (LTE event rate per 1000 patient years: no syncope = 0.6; AD syncope = 0.0; non-AD syncope = 1.1) (Figure 2C).

Discussion

This cohort study provides several important implications relating to the importance of trigger-specific risk-assessment of cardiac or arrhythmogenic syncope in patients with LQTS. First, the findings show that there is an association between trigger type and risk of subsequent LTE by genotype. In LQT1, the risk of LTE was highest and most pronounced following the occurrence of AD-associated syncope, whereas in LQT2, both AD and non-AD-associated syncope events were associated with a similar increase in the risk of subsequent LTE. In contrast, among patients with LQT3, most LTEs occurred as the patient's sentinel event. Second, our findings confirm prior data on genotype-specific triggers in congenital LQTS and extend these data to an association between syncope- and LTE-specific triggers by genotype. Third, we have shown that appropriate β-blocker therapy type selection is crucial and that β-blocker therapy remains a critical therapeutic option.

Triggered Syncope in Patients With LQT1

Consistent with prior reports,[2,3] our study shows that in individuals with LQT1, most syncope are associated with AD triggers, specifically vigorous exercise activity. Extending these data, we show that AD-associated syncope was associated with a pronounced more than 10-fold increased risk of subsequent LTE, whereas non-AD-associated syncope was not associated with a statistically significant increased risk of subsequent LTE compared to no syncope. Specifically, previous exercise-triggered syncope (most occurring while undiagnosed and therefore untreated) was associated with the highest risk of subsequent LTE while receiving therapy (a nearly 12-fold risk increase). Among patients receiving β-blocker therapy, AD syncopal events that occurred during β-blocker therapy were associated with the most prominent residual risk during β-blocker therapy and the highest matching rate with the LTE. In other words, patients with syncope triggered by exercise remained at higher risk of LTEs triggered by exercise despite β-blocker therapy.

These findings suggest that AD syncope may be a marker of increased susceptibility to LTE in patients with LQT1. This increased association with AD triggers seems to be driven by several genetic factors. Shimizu et al[10] demonstrated that sympathetic stimulation in patients with transmembrane mutation (55% of the mutations in the LQT1 cohort in the present study) was associated with corrected QT interval prolongation and an increase in risk of cardiac events. Furthermore, the S2-S3 and S4-S5 C-loop variants (the second most preva-

Table 2. Multivariate Time-Dependent Cox Models Evaluating the Association of First Syncope With Subsequent Life-Threatening Events (LTEs) by Trigger Type in Patients With Genetically Confirmed Long QT (LQT) Types 1 and 2[a]

Variable	Hazard ratio (95% CI)	*P* value
First event analysis		
LQT1 (n = 1331)		
First syncope (n = 365), adrenergic syncope[b]	7.61 (4.18-14.20)	<.001
First LTE (n = 63), nonadrenergic syncope[b]	1.50 (0.21-4.77)	.97
β-Blocker therapy[c]	0.30 (0.15-0.64)	.002
LQT2 (n = 1106)		
First syncope (n = 283), adrenergic syncope[d]	3.07 (1.66-5.67)	<.001
First LTE (n = 98), nonadrenergic syncope[b]	3.45 (1.96-6.06)	<.001
β-Blocker therapy[c]	0.47 (0.24-0.94)	.03
Recurrent event analysis		
LQT1 (n = 1331)		
Adrenergic syncope events (n = 561), adrenergic syncope[d]	5.95 (3.10-11.40)	<.001
Nonadrenergic syncope events (n = 256), nonadrenergic syncope[b]	1.20 (0.35-4.20)	.77
β-Blocker therapy[c]	0.30 (0.12-0.74)	.009
LQT2 (n = 1106)		
Adrenergic syncope events (n = 270), adrenergic syncope[d]	2.82 (1.53-5.18)	<.001
Nonadrenergic syncope events (n = 371), nonadrenergic syncope[b]	3.09 (1.76-5.41)	<.001
β-Blocker therapy[c]	0.53 (0.26-1.06)	.07

[a] All models were further adjusted for sex and age interaction, corrected QT interval at baseline (derived from first recorded electrocardiogram), β-blocker treatment, birth decade, and center. β-Blocker and syncope were assessed as time-dependent variables.

[b] Surgery or anesthesia, fever or illness, missed dose of β-blocker, drugs or alcohol, menses, pregnancy or postpartum, diet, extreme heat, or syncope that occurred during rest.

[c] Among patients with complete information regarding β-blocker therapy (type, start date, switch date, off dates) throughout their entire follow-up period.

[d] Including vigorous activity, swimming or pool activity, loud noise, or acute emotional arousal.

lent variants in patients with LQT1)[11] in region of the Kv7.1 channel can modify the function of voltage-gated potassium channels, including functional interaction with the auxiliary *KCNE1* subunits and the modulation of AD channel regulation through protein kinase A.[12,13]

Triggered Syncope in Patients With LQT2

Previous studies[2,4] have reported that the most common trigger is arousal in patients with LQT2. In our study, comprising a larger sample of patients (n = 1106) with LQT2 compared to prior reports (n = 234), most of the syncope events occurred during rest (34%), followed by arousal or noise triggers (24%). Syncope at rest was not only common, but also associated with risk of subsequent LTE. Thus, in patients with LQT2, syncope seems to be associated with risk regardless of the underlying trigger (AD or non-AD). Previous reports have shown that patients with LQT2 receiving β-blocker therapy are still at risk of cardiac events despite medical therapy.[14-16] These findings are similar to our findings and suggest that medical therapy with β-blockers is helpful yet may not fully protect against subsequent LTE in patients with LQT1-2 with syncope. Our study shows that in patients with LQT2, prescribed β-blocker therapy the residual rate of LTE following triggered syncope (regardless of the trigger) remained prominent and was similar to the high rate of events observed in patients with LQT1 with AD syncope.

Syncope in Patients With LQT3

Zareba et al[17] reported that the main presenting symptom in patients with LQT3 was LTE, which often occurs during the first year of life or early childhood. This observation may have translated into a higher use of implantable cardioverter defibrillators, even in patients with asymptomatic LQT3, since risk stratification in this population is more challenging.[16-20] We have recently shown that a history of syncope in patients with LQT3 was associated with a 12-fold increase in risk of subsequent LTE independent of other risk factors[18] and can

Table 3. Multivariate Time-Dependent Cox Models Evaluating the Association of Adrenergic Syncope With Subsequent Life-Threatening Events (LTEs) in Patients With Genetically Confirmed Long QT (LQT) Types 1 and 2[a]

LQT type	Variable	Hazard ratio (95% CI)	*P* value
LQT1 (n = 1331)			
First syncope (n = 365); first LTE (n = 63)	Exercise-adrenergic syncope[b]	7.63 (3.53-16.50)	<.001
	Arousal-adrenergic syncope[c]	5.08 (1.78-14.46)	.001
	Rest	1.87 (0.38-9.14)	.44
	Other[d]	NA[e]	
LQT2 (n = 1106)			
First syncope (n = 283); first LTE (n = 98)	Exercise-adrenergic syncope[b]	2.73 (1.13-6.57)	.03
	Arousal-adrenergic syncope[c]	3.27 (1.62-6.57)	<.001
	Rest	3.33 (1.70-6.53)	<.001
	Other[d]	3.64 (1.81-7.33)	<.001

[a] All models were further adjusted for age and sex interaction, corrected QT interval at baseline (derived from first recorded electrocardiogram), β-blocker treatment, birth decade, nonadrenergic syncope, and center. β-Blocker and syncope were assessed as time-dependent variables. Reference group is no syncope.

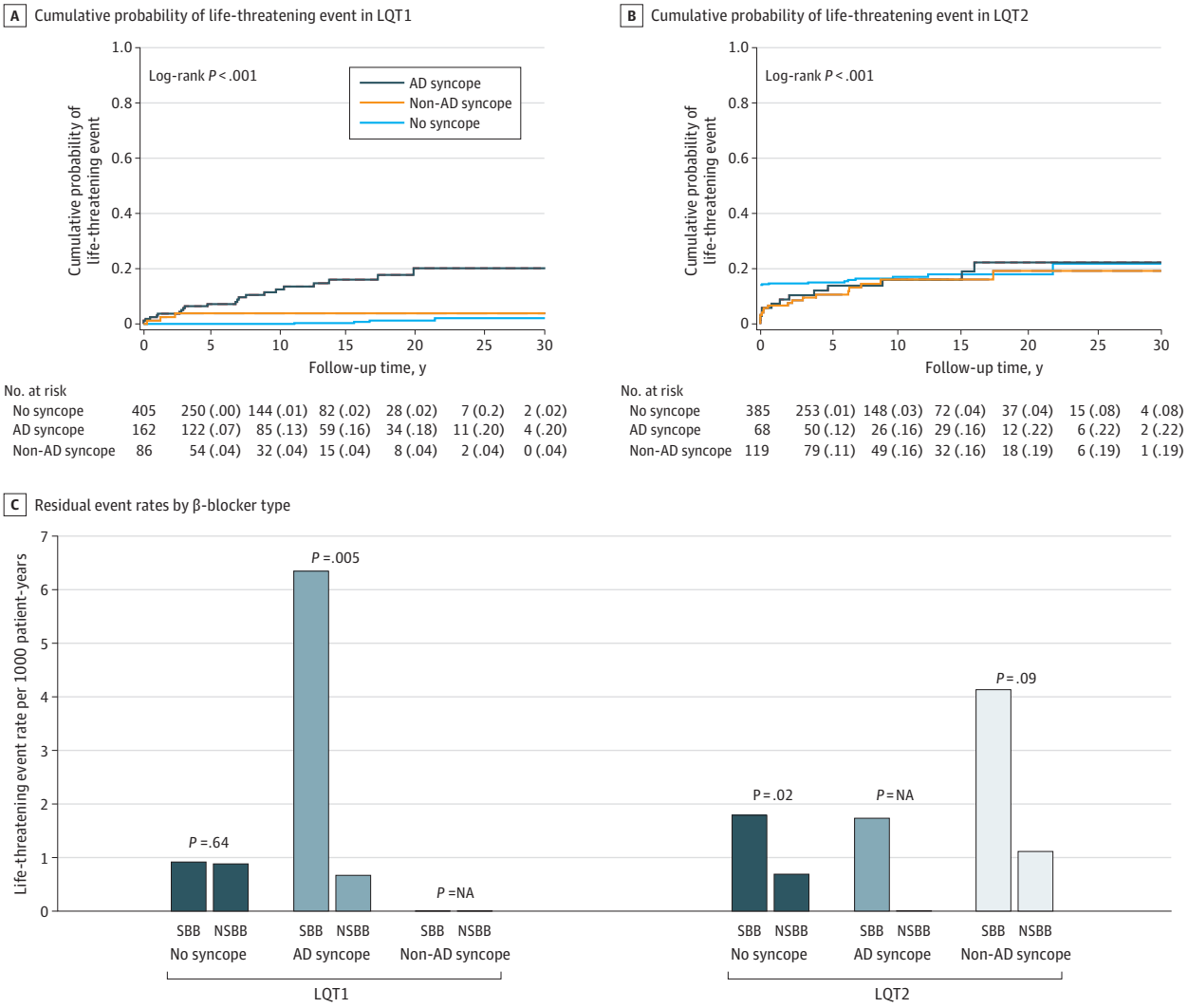
[b] Including swimming or pool activity.

[c] Including loud noise or acute emotional arousal.

[d] Comprising mostly syncope that occurred at rest and a heterogeneous group of the remaining identified triggers.

[e] Zero LTE events were seen in patients who had syncope due to other triggers.

Figure 2. Life-Threatening Events in Patients With Long QT (LQT) Syndrome With β-Blocker Therapy



Displayed are the event rates of life-threatening cardiac events per 1000 patient years in patients with LQT types 1 and 2 (LQT1 and 2) who were treated with β-blockers. In each LQT type, time intervals were created, taking into consideration the type of β-blocker and the type of syncope. One patient can have several intervals. An interval starts at the time of β-blocker therapy initiation and ends when the therapy was stopped, a life-threatening event has occurred, or at the end of follow-up. The event rates are categorized based on the presence, absence, and type of syncope during each treatment interval and by the type of β-blocker. The *P* value is for the comparison between selective β-blocker and nonselective β-blocker. In cases where the event rate was zero, the *P* value was not calculated. Life-threatening cardiac events included aborted cardiac arrest, appropriate ventricular fibrillation terminating implantable cardioverter-defibrillator shock, or LQT syndrome–attributable sudden cardiac death. Adrenergic (AD) triggers and non-AD triggers are listed in eTable 1 in Supplement 1.

be used along with corrected QT interval duration for risk stratification prior to a decision on the need for an implantable cardioverter defibrillator in patients with this genotype.[18] Furthermore, our prior study reported that β-blocker therapies are effective in the treatment of patients with LQT3, with a more pronounced effect among male patients.[18] Therefore, we recommend using nonselective β-blocker therapy as first-line therapy in patients with LQT3 with close monitoring and appropriate risk-stratification approaches. In the present study, we show that in patients with LQT3, most LTEs were not preceded by a syncope event (preceding syncope occurred only in 7 patients). Nevertheless, based on our prior report,[18] syncope should still be considered a risk factor for subsequent LTE, despite its rarer occurrence in patients with LQT3.

Management Implications

Syncope is common in patients with LQTS (24% in this study). Nevertheless, current US and European guidelines for the management of LQTS do not provide proposed management for patients presenting with syncope.[19,20] Our findings suggest that trigger-associated risk should be used to guide genotype-specific management in LQTS. eFigure 3 in Supplement 1 provides a proposed flow diagram on our recommendation for treatment of patients with LQT1-3 who present with syncope. Treatment of a patient with known LQT1 or LQT2 who presents for evaluation following a probable LQTS-attributable syncopal episode should start with acquiring information regarding the underlying trigger and whether the patient has been adequately treated with

β-blocker therapy. In patients with syncope who were not treated with β-blocker therapy, treatment with a nonselective β-blocker (such as nadolol or propranolol) should be initiated and up-titrated to the patient's highest tolerated dose, and patients should be carefully monitored for medication adherence. Lack of medication adherence has been established as a primary reason for LQTS-associated breakthrough syncope or LTE.[21]

Our observations highlight the efficacy of β-blocker therapy when correctly selected. Our study, including nearly 3000 patients with genetically confirmed LQT1-3, showed that optimization of β-blocker therapy was associated with a substantial reduction in LTEs even following a high-risk syncope event compared with no β-blocker therapy. First, the critical importance of medication adherence must be emphasized. Second, the choice and dose of β-blocker is highly important. A breakthrough event while a patient is taking a β-1-selective β-blocker, like atenolol or metoprolol, vs a breakthrough event while a patient is taking a nonselective β-blocker, such as nadolol or propranolol, will have different implications. The former represents a breakthrough while essentially being untreated while the latter would compel a careful review of dose, medication adherence, etc. Third, if the breakthrough LQTS-associated syncope or LTE occurred while compliant on a reasonable dose of a preferred β-blocker, then review and implementation of an intensified treatment program should follow, such as left cardiac sympathetic denervation surgery or the addition of medications like spironolactone and mexiletine.[22-24] In LQT2, intentional atrial pacing might be considered.[25] If recurrent syncope occurs while a patient is receiving optimized intensified medical therapy, an implantable cardioverter-defibrillator should be considered following class IIa indication with evidence for about 73% reduction in mortality in these patients.[26]

Limitations

This study has limitations. Data on triggers for syncope were obtained through prespecified questionnaires from patients, family members, or primary care physicians. Although this information was corroborated by the study coordinators through oral interviews, it is limited by its subjective nature. Importantly, the categorization of triggers into AD and non-AD might be challenging in certain conditions. Some of the triggers may have a dual mechanism that includes activation of the adrenergic as well as the non-AD pathways. Furthermore, it should be noted that syncope triggers that were categorized in the present study as other-specific composed a heterogeneous group. Thus, the results related to risk factors for this end point may reflect either a specific trigger or a combined effect of multiple triggers. Another limitation is the relatively high percentage of unreported triggers for LTEs, which may impact the cross-tabulation analyses. Data regarding β-blocker therapy adherence may be incompletely captured in a real-world registry setting, which may have affected our interpretation of associations with β-blocker therapy. Although this is the largest study, to our knowledge, to evaluate the effect of syncope in patients with LQT3, the relatively small number of patients and corresponding low number of LTEs in this group is a major limitation. The study might have been underpowered to evaluate the exact association of previous syncope triggers with risk of subsequent LTE in patients with LQT3.

Conclusions

The findings in this study indicate an association between syncope episode triggers and risk of subsequent LTEs and response to therapy by genotype. These data may be useful for improved genotype-specific risk stratification and management in LQTS.

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