Asthma and the risk of cardiac events among patients with long QT syndrome after age 40

Alon Barsheshet, MD,[1] Ilan Goldenberg, MD,[2] Kirill Buturlin, MD,[1] Aharon Erez, MD,[1] Gustavo Goldenberg, MD,[2] Itamar Zahavi, BS,[2] Bronislava Polonsky, MS,[2] Scott McNitt, MS,[2] Mehmet Aktas, MD,[2] Wojciech Zareba, MD, PhD,[2] Gregory Golovchiner, MD[1]

From the [1]Department of Cardiology, Rabin Medical Center, Faculty of Medicine, Tel Aviv University, Petah Tikva, Israel, and [2]Clinical Cardiovascular Research Center, University of Rochester Medical Center, Rochester, New York.

BACKGROUND Limited data exist on the impact of asthma on long QT syndrome (LQTS) in middle-aged and older adults.

OBJECTIVE This study aimed to examine the association between asthma, β2-agonist treatment, and cardiac events (CEs) in LQTS patients over 40 years of age.

METHODS The risk of CEs (comprising syncope, aborted cardiac arrest, implantable cardioverter-defibrillator shock, or sudden cardiac death) from age 40 through 75 years, by the presence of asthma with and without treatment with a β2-agonist inhaler, was assessed among 1020 LQTS patients from the Rochester LQTS Registry.

RESULTS Among 1020 LQTS patients, 162 (16%) had asthma by age 40 years or subsequent follow-up, with 63% treated with a β2-agonist inhaler. Patients with asthma vs no asthma had a higher cumulative rate of CEs from age 40 through 75 years (44% vs 26%, $P < .001$). Consistently, multivariate analysis showed that asthma was associated with a 2-fold (hazard ratio 1.97, $P = .001$) increased risk of CEs. Subgroup analysis showed that the association of asthma with CEs was consistent within risk subsets of LQTS patients, including QTc duration, syncope prior to age 40 years, β-blocker use, sex, and LQTS genotype (all P values for risk subset-by-asthma interaction $>.10$). Asthma patients with LQTS who were treated with a β2-agonist inhaler did not show an increased risk compared with those who were not treated (hazard ratio 1.02, $P = .963$).

CONCLUSION The presence of asthma is associated with increased risk of CEs among middle-aged and older patients with LQTS regardless of baseline risk factors or treatment with a β2-agonist inhaler.

KEYWORDS Asthma; Long QT syndrome; Syncope; Implantable cardioverter-defibrillator; Sudden cardiac death

(Heart Rhythm O2 2025;6:188–194)

Introduction

Congenital long QT syndrome (LQTS) is a genetic cardiac disorder characterized by a prolonged QT interval on the electrocardiogram due to mutations affecting potassium, sodium, or calcium ion channels in the heart. Prolonged QT interval increases susceptibility to arrhythmias, notably torsades de pointes, which can lead to syncope, aborted cardiac arrest (ACA), or sudden cardiac death (SCD).

Most studies evaluating risk factors for cardiac events (CEs) in individuals with LQTS have focused on assessing their clinical course from birth through age 40 years. Importantly, asthma and the use of β2-agonist inhalers, alongside other risk factors, have been associated with an increased risk of LQTS-related CEs during the first 4 decades of life.[1,2]

Asthma is a prevalent condition in both pediatric and adult populations, but it differs in its underlying causes, clinical presentation, disease progression, and treatment strategies between these groups.[3] Despite evidence showing that LQTS remains a significant risk for CEs beyond age 40 years,[4] there are limited data on how asthma and its treatment affect the risk of clinical arrhythmic events in LQTS patients after this age.

In this study, we aimed to assess (1) whether asthma treatment affects the risk of CEs (including syncope, ACA, appropriate implantable cardioverter-defibrillator [ICD] shocks, or LQTS-related SCD) in individuals with LQTS who were followed beyond the age of 40 years; and (2) whether the effect of asthma on the clinical course of older LQTS patients is mediated through treatment with β2-agonist inhalers.

Address reprint requests and correspondence: Dr Alon Barsheshet, Cardiology Department, Rabin Medical Center, 39 Jabotinsky Street, Petah Tikva, Israel 4941492. E-mail address: barshesheta@gmail.com.

2666-5018/

https://doi.org/10.1016/j.hroo.2024.11.007

KEY FINDINGS

- Asthma was associated with a 2-fold increase in the risk of cardiac events among long QT syndrome (LQTS) patients over 40 years of age, independent of other factors such as QTc duration, prior syncope, β-blocker use, sex, and LQTS genotype.
- Unlike in younger patients, the use of β2-agonist inhalers did not further increase the risk of cardiac events in asthma patients with LQTS, suggesting that the elevated risk is primarily associated with asthma itself, rather than its treatment.
- Asthma patients were more frequently prescribed selective β-blockers, which are commonly used for asthma patients requiring β-blockers but are known to be less effective in treating LQTS.
- These findings underscore the importance of careful management and monitoring for patients with both asthma and LQTS to ensure effective asthma control while minimizing the risk of cardiac complications related to QT interval prolongation.

Methods

Study cohort

The research cohort was derived from the Rochester LQTS Registry, comprising LQTS subjects who were followed beyond the age of 40 years. Patients were included if they had a pathogenic or likely pathogenic LQTS variants or a QTc $\geq$450 ms in males or $\geq$470 ms in females. Patients with multiple LQTS-causing mutations (n = 32) and those harboring an LQTS genotype other than LQTS 1 to 3 (n = 24) were excluded from the study. The final analyzed study population included 1020 patients. All participants provided informed consent, wherein they consented to their inclusion in the registry and participation in subsequent clinical studies. The protocols for the Rochester LQTS Registry and its substudies were approved by the Institutional Review Board at the University of Rochester Medical Center. The research reported in this paper adhered to the Helsinki Declaration guidelines.

Data acquisition, follow-up, and endpoints

Clinical data were acquired as previously described.[4] Briefly, a comprehensive medical history was obtained upon enrollment, and ongoing clinical information was systematically recorded at yearly intervals during each visit or medical encounter using prospectively designed forms. The QTc interval, as per Bazett's formula, was evaluated based on a 12-lead electrocardiography (ECG) obtained at enrollment and subsequently assessed from follow-up ECGs. The QTc parameter selected for this study was determined based on the maximum QTc duration recorded before the age of 40 years or the initial ECG after the age of 40 years for individuals lacking prior ECG data.

LQTS gene mutations were detected through standard genetic testing conducted in academic molecular-genetic laboratories linked to the Rochester LQTS Registry.

Information regarding non-LQTS comorbidities was obtained through baseline and follow-up questionnaires that are sent to enrolled subjects age 40 years or older during the annual follow-up evaluation. The diagnosis of asthma was based on data from prespecified medical questionnaires. The administration of inhaled β2-agonists, inhaled corticosteroids, theophylline, leukotriene modifiers like montelukast, and mast cell stabilizers such as cromolyn was seen as additional confirmation of asthma diagnosis. Asthma presence was evaluated as a time-dependent variable, incorporating the date of asthma diagnosis based on completed forms.

Follow-up data on β-blocker therapy included initiation and cessation dates, if applicable. Information on other LQTS-related therapeutic interventions, including pacemaker or ICD implantation, as well as left cervical sympathetic denervation, was also recorded prospectively.

The primary endpoint in the current study was defined as the first occurrence of syncope, ACA, ICD shock, or SCD between the ages of 40 and 75 years. Thus, clinical follow-up for all patients began at age 40 years.

Statistical analysis

The baseline and follow-up clinical characteristics of the study population were analyzed using chi-square or Fisher's exact tests for categorical variables and the Mann-Whitney-Wilcoxon test for continuous variables. To explore the unadjusted relationship between CE and time-dependent asthma, a Simon and Makuch plot was displayed, which is an expansion of the Kaplan-Meier plot with respect to time-dependent covariates. The Mantel-Byar test was used for comparison of survival data with a time-dependent covariate. To evaluate independent association of clinical and genetic factors with first occurrence of a CE, multivariable Cox proportional hazards modeling was performed with decade was born (before January 1970 and after January 1970) strata, and robust standard errors were used to account for clustering of patients within family. Best stepwise variable selection method was applied selecting from the following list of potential covariates based on literature review and clinical judgment: sex, QTc $\geq$500 ms, coronary artery disease (CAD), hypertension, diabetes mellitus, hyperlipidemia, mitral valve prolapse documented by echocardiography, heart disease other than LQTS or CAD, asthma, autoimmune disorder, smoking, obstructive sleep apnea, menopause, cancer, high alcohol intake, syncope prior to age 40 years, time-dependent β-blocker use, and genotype mutations. The reduced model included all covariates at the $<$.05 significant level but forcing sex, time-dependent β-blocker use, and genotype mutations. Furthermore, specified subgroup analyses and test of interactions were investigated for CE outcome.

All statistical tests were 2-sided, and a P value of $<.05$ was considered statistically significant. Analyses were carried out with SAS software (version 9.4; SAS institute).

Results

Clinical features and genotype

The clinical features of 1020 participants in the study and the prevalence of concurrent medical conditions before reaching 40 years of age, as well as during follow-up in patients with and without asthma, are delineated in Table 1. Significant differences in baseline characteristics were noted among the 162 patients diagnosed with asthma as compared with the 858 patients without asthma. Those with asthma had a higher proportion of female participants, faster heart rates, and exhibited a higher incidence of coexisting medical conditions, including diabetes mellitus, hypertension, smoking, history of stroke, CAD, and obstructive sleep apnea in comparison with patients without asthma.

A total of 800 subjects, constituting 78% of the study cohort, underwent genetic testing. Among them, 710 (89%) subjects were found to carry an LQTS 1 to 3 mutation and were classified as LQT1, LQT2, or LQT3. The remaining 90 (11%) subjects who underwent genetic testing were not identified to carry a known LQTS mutation despite a clinical diagnosis of LQTS and were classified as having no known mutation detected (tested). Additionally, 220 (22%) LQTS patients were not genetically tested and thus were classified as having an unknown mutation status (not tested). Individuals diagnosed with asthma demonstrated a greater prevalence of LQT3-related mutations, while displaying a lower prevalence of LQT2-related mutations compared with those without asthma (Table 1). Patients with asthma were more likely to be treated with β-blockers and receive ICDs compared with those without asthma. Additionally, asthma patients were more frequently prescribed selective β-blockers, while no significant difference was found between the groups in the use of nonselective β-blockers.

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

Clinical characteristics	Asthma (n = 162)	No asthma (n = 858)	P value
Female	83	61	<.001
ECG parameters			
RR, ms	849 ± 160	909 ± 192	<.001
QT, ms	448 ± 62	458 ± 68	.041
QTc, ms	488 ± 46	484 ± 48	.244
QTc ≥500 ms	31	31	.811
Prior cardiac events before age 40 y			
Syncope	41	35	.113
ACA	7	5	.428
Appropriate ICD shock	2	1	.302
Cardiac events	43	36	.140
ACA or appropriate ICD shock	8	6	.317
Genotype related			
LQT1	31	29	.021
LQT2	25	33	
LQT3	15	7	
No mutation found (tested)	9	9	
Unknown mutation status (not tested)	19	22	
Comorbidities before age 40 y and during follow-up			
Diabetes mellitus	18	10	.005
Hypertension	45	35	.020
Hyperlipidemia	20	17	.322
Smoking	45	36	.036
Coronary artery disease	19	12	.020
Stroke	10	5	.015
Sleep apnea	12	6	.008
Cancer	9	8	.916
Therapies during follow-up after age 40 y			
β-blockers	72	64	.055
Selective β-blockers	53	42	.012
Nonselective β-blockers	37	34	.406
Pacemaker	4	4	.775
ICD	31	19	.001
β agonist inhaler	63	0	
Cardiac events during follow-up after age 40 y			
Syncope	25	14	<.001
ACA	5	2	0.115
LQTS-related SCD	1	0	0.500
Appropriate ICD shocks	6	3	.021
Cardiac event	31	17	<.001
Life-threatening event	10	5	.018
All-cause mortality	9	5	.046

Values are % or mean ± SD.

ACA = aborted cardiac arrest; ECG = electrocardiography; ICD = implantable cardioverter-defibrillator; LQTS = long QT syndrome; SCD = sudden cardiac death.

Clinical outcomes of LQTS patients by asthma status from age 40 through 75 years

Over a mean follow-up period of 21.4 ± 11.7 years, 197 (19%) patients encountered at least 1 CE. Among these, 162 patients had a syncope episode, 29 experienced ACA, 33 received appropriate ICD shocks, and 4 had LQTS-related SCD after reaching the age of 40 years. As shown in Table 1, the asthma group had a significantly higher incidence of syncope, ACA, appropriate ICD shocks, LQTS-related SCD, any CE, or death from any cause compared with the nonasthma group.

Figure 1 displays the Simon and Makuch estimates for CEs based on time-dependent development of asthma after age 40 years. At age 75 years, patients with asthma had a significantly higher cumulative probability of experiencing CEs (44%) compared with those without asthma (26%, Mantle-Byar $P = .002$).

In multivariate analysis (Table 2), asthma consistently emerged as a strong predictor of CEs among LQTS patients age 40 years and older, independently associated with a twofold higher risk of CEs ($P = .001$). Additionally, syncope before age 40 years and a prolonged QTc interval (≥500 ms) were identified as independent predictors of

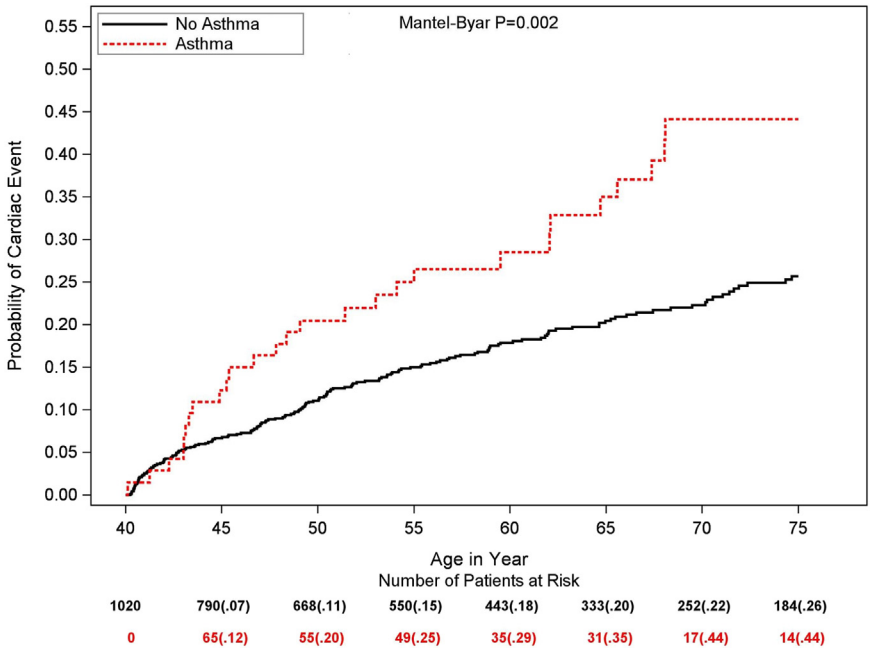

Figure 1 Simon and Makuch estimates for cardiac events by time-dependent asthma (values in parentheses are probability estimates).

CEs (hazard ratio [HR] 2.70, $P < .001$; and HR 1.57, $P = .007$, respectively). Conversely, other established LQTS-related risk factors such as sex, β-blocker use, and genotype did not show a statistically significant association with increased risk after adjusting for the presence of asthma (Table 2).

Subgroup analysis

Subgroup analysis (Figure 2) revealed no statistically significant difference in the relationship between asthma and CEs across risk subsets of LQTS patients, including β-blocker use, QTc duration, sex, history of syncope before age 40 years, and LQTS genotype (all P values for risk subset-by-CAD interaction $>.10$).

Effect of β2-agonist inhaler use on clinical outcomes among asthma patients

Among the study participants, 102 individuals received treatment with β2-agonist inhalers, representing 10% of the cohort (63% of those with asthma). The use of β2-agonist inhalers, compared with no treatment or other asthma treatments (including inhaled corticosteroids), was not associated with a further increased risk of CEs (HR 1.02, 95% confidence interval 0.51–2.04, $P = .963$). This suggests that the presence of asthma is associated with increased risk of CEs in older patients with LQTS, regardless of the treatment received.

Discussion

This study is the first to explore how asthma and the use of β2-agonist inhalers impact the clinical outcomes of patients with LQTS beyond the age of 40 years. Our findings indicate that (1) asthma is associated with a 2-fold higher risk of CEs during follow-up ($P = .001$); (2) this association remains consistent across various risk subgroups of LQTS patients, including those with very long QTc duration (≥500 ms) and moderately long QTc, individuals with or without a history of syncope before age 40 years, users of β-blockers, and patients of different sexes and LQTS genotypes; and (3) unlike younger patients, the risk associated with asthma in patients with LQTS remains consistent regardless of treatment, and therefore does not appear to be influenced by the use of β2-agonist inhalers.

Table 2 Multivariate analysis: risk factors for cardiac events among all LQTS patients

	HR	95% CI	*P* value
Syncope prior to age 40 y	2.70	1.93–3.77	<.001
Asthma	1.97	1.32–2.96	.001
QTc ≥500 ms	1.52	1.12–2.08	.007
Women vs men	1.17	0.86–1.61	.321
Time dependent β-blocker use	0.96	0.69–1.33	.792
LQTS genotype*			
LQT2 vs LQT1	1.42	0.98–2.05	.066
LQT3 vs LQT1	1.07	0.59–1.93	.825
No mutation found (tested) vs LQT1	0.98	0.54–1.77	.953
Unknown mutations (not tested) vs LQT1	1.40	0.94–2.09	.102

Cardiac events indicate syncope, aborted cardiac arrest, sudden cardiac death, or implantable cardioverter-defibrillator shock.

CI = confidence interval; HR = hazard ratio; LQTS = long QT syndrome.
*The global *P* value was .274 for testing the association between LQTS genotype and cardiac events.

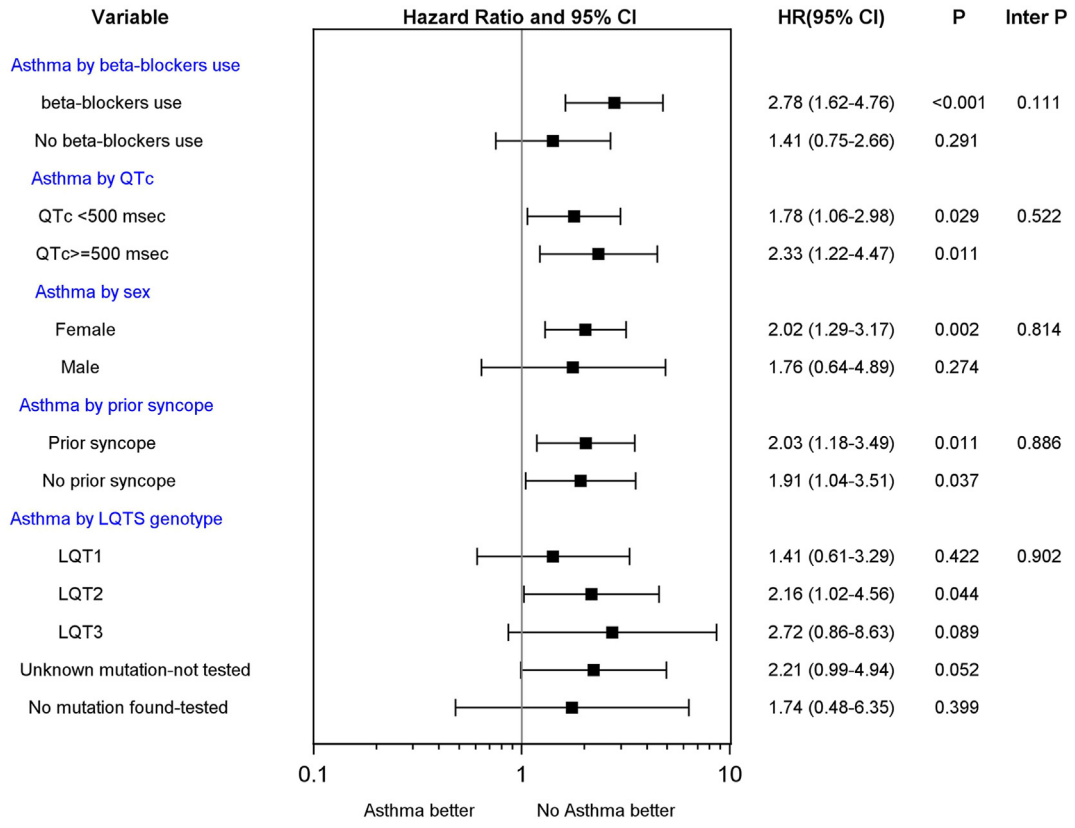

Figure 2 Asthma vs no asthma and risk of cardiac events in subgroups of patients. Tests of interactions were performed using a single interaction term, except for the model investigating asthma by long QT syndrome (LQTS) genotype using 4 interaction terms. CI = confidence interval; HR = hazard ratio.

Clinical factors affecting outcome in LQTS after age 40 years

Most studies exploring the clinical factors influencing the prognosis of LQTS have focused on younger populations (under 40 years of age) identifying factors like age, sex, QTc duration, resting heart rate, history of syncope, mutation location and type, and β-blocker response as key influences.[5,6] However, data on middle-aged and older patients with LQTS are limited. The international LQTS registry indicates that in those over 40 years, predictors of ACA or SCD include prolonged QTc, recent syncope, genotype positivity, and the LQT3 genotype.[4] Additionally, another study identified CAD as a factor increasing the risk of CEs in LQTS patients over 40 years.[7] However, the effect of other comorbidities, such as asthma, on CEs in this age group has not yet been studied.

Potential mechanisms related to the effect of asthma on the risk of arrhythmic events in LQTS patients after age 40 years

Asthma is a heterogeneous disease characterized by chronic inflammation of the airways. It is defined by a history of respiratory symptoms that vary in intensity and frequency, along with intermittent expiratory airflow limitation.[3] While asthma is often considered a condition affecting children and young adults, a substantial proportion of older adults are also affected. Among individuals age 35 years and older, the prevalence of asthma in the United States is estimated to be between 8% and 12%.[8,9] Asthma in pediatric and adult populations exhibits distinct etiologies, symptomatology, disease progression, and management strategies. Pediatric asthma is frequently precipitated by allergens, viral infections, and environmental pollutants. In contrast, adult-onset asthma may be induced by nonallergic triggers such as occupational exposures, with more persistent and severe symptoms, often resembling chronic obstructive pulmonary disease. Pediatric management emphasizes precise dosing of inhaled corticosteroids with consideration for growth impacts, whereas adults may require escalated inhaled corticosteroid dosages and comprehensive management of comorbid conditions.[3] The cornerstone of asthma treatment involves the use of inhaled corticosteroids, often combined with β2-agonist inhalers. Stimulation of β2-adrenergic receptors leads to an activation of adenylyl cyclase, increase in cyclic adenosine monophosphate, smooth muscle relaxation, and bronchial dilatation. Cardiac muscle primarily has β1-adrenoceptors but also has a significant number of β2-adrenoceptors at a 2.5:1 ratio. Hence, even selective β2-agonists can cause cardiac adverse effects.[10–12]

Our findings suggest for the first time that the association between asthma and the risk of CEs in older LQTS patients

does not appear to be mediated by the use of β2-agonist inhalers. We demonstrated that LQTS patients with asthma who were treated with β2-agonist inhalers did not have a higher risk of CEs compared with those not treated with these medications. Therefore, it seems that asthma itself is a strong risk factor for arrhythmic events, independent of its treatment.

Asthma can potentially impact individuals with LQTS in several ways: acute asthma exacerbations can lead to hypoxia and respiratory distress. Hypoxia may prolong the QT interval and trigger arrhythmias in individuals with LQTS who are predisposed to CEs during stress or low oxygen conditions.[13,14] Emotional stress is a well-established trigger for CEs in LQTS, particularly in LQT2.[15] Therefore, stress and anxiety caused by asthma exacerbations may similarly increase the risk of arrhythmias in LQTS patients. In addition, systemic corticosteroids use can potentially affect electrolyte balance and increase the risk of arrhythmias in LQTS patients.[9] In the current study, patients with asthma were more frequently prescribed selective β-blockers, which are commonly used for asthma patients requiring β-blockers but are known to be less effective in treating LQTS. It is possible that the risk increase associated with asthma may be related to inadequate LQTS β-blocker therapy.

Comparison with previous studies

A previous study from the International Long QT Syndrome Registry investigated the link between asthma and the risk of CEs (first occurrence of syncope, ACA, or SCD) from birth to age 40 years in 4310 LQTS patients and their unaffected family members. It was found that asthma significantly increased the risk of CEs in both affected LQTS patients (QTc $>$ 0.46; HR 1.32, $P = .048$) and borderline-affected family members (QTc 0.44–0.46; HR 2.08, $P = .004$).[1] In another study, the risk of CEs in LQTS patients treated with β2-agonist inhalers for asthma was examined in 3287 patients with QTc $>$ 450 ms. β2-agonist therapy was associated with a 2-fold increase in CE risk (HR 2.00, $P = .003$). This study found β2-agonist therapy to be a stronger predictor of CEs than asthma.[2] However, both studies were limited by a lack of detailed LQTS genotype data, as less than a third of participants were genotyped, restricting assessment of genotype-specific risks. The current study extends the previous findings by exploring the relationship between asthma, β2-agonist therapy, and the risk of CEs in patients older than 40 years of age. We found that LQTS patients with asthma have a 2-fold increased risk of CEs after age 40 years, over a mean follow-up of 21.4 ± 11.7 years. Extensive genetic data were included, with 78% of the cohort undergoing genetic testing and 89% having LQT1 to LQT3–related mutations. The risk association remained consistent across various risk subgroups of LQTS patients, including different LQTS genotypes. Unlike the previous study, which identified β2-agonist therapy as a stronger predictor of CEs than asthma in LQTS patients from birth to age 40 years, the current study found that LQTS patients with asthma treated with a β2-agonist inhaler did not have a higher risk compared with those who were not treated.

Limitations

The observational design of this study limits the ability to establish causation. Asthma diagnosis was determined through questionnaires and interviews that inquired if the patient had ever been diagnosed with asthma and gathered data on asthma medications as additional confirmation of the diagnosis, without relying on objective measures like spirometry or methacholine sensitivity tests. Nonetheless, we consider our asthma diagnosis reliable, as this method is widely accepted in the pulmonology literature, and multiple studies show strong agreement between asthma status defined from administrative health data and self-report.[16,17] Rousseau and colleagues[16] evaluated the agreement between 30 years of administrative health data and self-reported asthma in 81,496 individuals, with agreement rates of 88% to 91%. The study also lacks objective measures of asthma severity, which could impact the findings. A multivariate analysis was conducted to evaluate the independent effects of clinical and genetic factors on the first occurrence of a CE, selecting from many potential covariates. However, some confounders may remain unaccounted for, and the observed differences in event rates could also be influenced by additional comorbidities related to asthma.

The composite endpoint is primarily driven by syncope, resulting in insufficient power to draw significant conclusions regarding ACA or SCD.

Summary and clinical implications

Previous studies have demonstrated that asthma comorbidity increases the risk of CEs in LQTS patients younger than 40 years. Despite potential differences in asthma's etiology, phenotype, and response to therapy in adults, our current study shows a similar rise in CE risk associated with asthma in adult LQTS patients. However, in contrast to the finding in LQTS asthma patients younger than 40 years, the use of beta mimetics for asthma treatment did not further increase this risk after age 40 years. Therefore, all older LQTS patients with asthma should be considered at higher risk, regardless of their treatment regimen. Careful management and monitoring are essential for patients with both asthma and LQTS to achieve effective asthma control while minimizing cardiac complications due to QT interval prolongation. We suggest considering nonselective β-blockers as a potential treatment to prevent life-threatening arrhythmic events. If patients are intolerant or nonselective β-blockers are contraindicated, close monitoring is required, and alternative therapies should be considered if syncope occurs during β-blocker treatment, such as ICD implantation, sympathectomy, or mexiletine (in cases of LQT2–3). Further research is essential to clarify the

mechanisms driving the increased CE risk associated with asthma in the middle-aged and older LQTS patients.

Funding Sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures: The authors have no conflicts to disclose.

Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: All participants provided informed consent, wherein they consented to their inclusion in the registry and participation in subsequent clinical studies.

Ethics Statement: The protocols for the Rochester LQTS Registry and its substudies were approved by the Institutional Review Board at the University of Rochester Medical Center. The research reported in this paper adhered to the Helsinki Declaration guidelines.

References

1. Rosero SZ, Zareba W, Moss AJ, et al. Asthma and the risk of cardiac events in the Long QT syndrome. Long QT Syndrome Investigative Group. Am J Cardiol 1999;84:1406–1411.
2. Thottathil P, Acharya J, Moss AJ, et al. International Long QT Syndrome Investigative Group. Risk of cardiac events in patients with asthma and long-QT syndrome treated with beta(2) agonists. Am J Cardiol 2008;102:871–874.
3. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention (2024 update). Available at: https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf. Accessed September 1, 2024.
4. Goldenberg I, Moss AJ, Bradley J, et al. Long-QT syndrome after age 40. Circulation 2008;117:2192–2201.
5. Goldenberg I, Moss AJ, Peterson DR, et al. Risk factors for aborted cardiac arrest and sudden cardiac death in children with the congenital long-QT syndrome. Circulation 2008;117:2184–2191.
6. Krahn AD, Laksman Z, Sy RW, et al. Congenital Long QT Syndrome. JACC Clin Electrophysiol 2022;8:687–706.
7. Sze E, Moss AJ, Goldenberg I, McNitt S, et al; International Long QT Syndrome Investigative Group. Long QT syndrome in patients over 40 years of age: increased risk for LQTS-related cardiac events in patients with coronary disease. Ann Noninvasive Electrocardiol 2008;13:327–331.
8. National Center for Health Statistics, Centers for Disease Control and Prevention. 2019 National Health Interview Survey (NHIS) Data. Table 4-1. Available at: https://www.cdc.gov/asthma/nhis/2019/table4-1.htm. Accessed July 1, 2024.
9. Nanda A, Baptist AP, Divekar R, et al. Asthma in the older adult. J Asthma 2020;57:241–252.
10. del Monte F, Kaumann AJ, Poole-Wilson PA, Wynne DG, Pepper J, Harding SE. Coexistence of functioning beta 1- and beta 2-adrenoceptors in single myocytes from human ventricle. Circulation 1993;88:854–863.
11. Brodde OE. Beta-adrenoceptors in cardiac disease. Pharmacol Ther 1993;60:405–430.
12. Gupta P, O'Mahony MS. Potential adverse effects of bronchodilators in the treatment of airways obstruction in older people: recommendations for prescribing. Drugs Aging 2008;25:415–443.
13. Roche F, Reynaud C, Pichot V, et al. Effect of acute hypoxia on QT rate dependence and corrected QT interval in healthy subjects. Am J Cardiol 2003;91:916–919.
14. Ebrahimian S, Sillanmaki S, Hietakoste S, et al. Beat-to-beat cardiac repolarization lability increases during hypoxemia and arousals in obstructive sleep apnea patients. Am J Physiol Heart Circ Physiol 2024;326:H1094–H1104.
15. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation 2001;103:89–95.
16. Rousseau MC, Conus F, El-Zein M, Benedetti A, Parent ME. Ascertaining asthma status in epidemiologic studies: a comparison between administrative health data and self-report. BMC Med Res Methodol 2023;23:201.
17. Yousif A, Dault R, Courteau M, et al. TORSADE Cohort Working Group. The validity of diagnostic algorithms to identify asthma patients in healthcare administrative databases: a systematic literature review. J Asthma 2022;59:152–168.