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Paediatric long QT syndrome: clinical outcomes and therapy in the Spanish National Registry

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Abstract

Background and Aims Congenital long QT syndrome (LQTS) is a heterogeneous disorder in which genotype and QTc duration modulate the risk of major arrhythmic events (MAEs), but contemporary paediatric outcome data remain limited. This study aimed to characterize clinical features, management strategies, and predictors of MAEs in a nationwide paediatric LQTS cohort.

Methods This retrospective multicentre study analysed children (<18 years) diagnosed with LQTS across 30 tertiary centres (2004–24) using 2022 European Society of Cardiology criteria. MAEs were defined as sudden cardiac death, aborted cardiac arrest, or appropriate implantable cardioverter-defibrillator (ICD) therapy.

Results The cohort included 371 children (58% male; median diagnosis age 6.0 years; interquartile range .25–11 years). Pathogenic/likely pathogenic variants were identified in 86.5%, mainly in *KCNQ1*, *KCNH2*, or *SCN5A*, while 5.7% harboured high-risk genotypes (Jervell–Lange-Nielsen, calmodulinopathies, *CACNA1C*/Timothy). Beta-blockers were prescribed in 92.4%. Over a median 6-year follow-up, 14 children (3.8%) experienced MAEs, which occurred predominantly in those with high-risk genotypes, QTc ≥550 ms or very early presentation. MAEs were rare in LQT1–3 with QTc <500 ms. Foetal/neonatal bradycardia (5.1%) correlated with high-risk genotypes and adverse outcomes. ICDs were implanted in 33 children (8.9%); 10 (30%) received appropriate therapies, and 8 (24%) experienced complications. Left cardiac sympathetic denervation was performed in 33 (8.9%), mainly high-risk patients, and was associated with >80% arrhythmia-free survival without major complications.

Conclusions In this nationwide paediatric LQTS cohort, MAEs were uncommon and clustered in children with malignant genotypes, markedly prolonged QTc and very early presentation, particularly foetal or neonatal bradycardia. These data support the current genotype and QTc-guided management strategy, with beta-blockers as the cornerstone therapy and selective use of left cardiac sympathetic denervation and ICDs in high-risk profiles.

Structured Graphical Abstract

Key Question

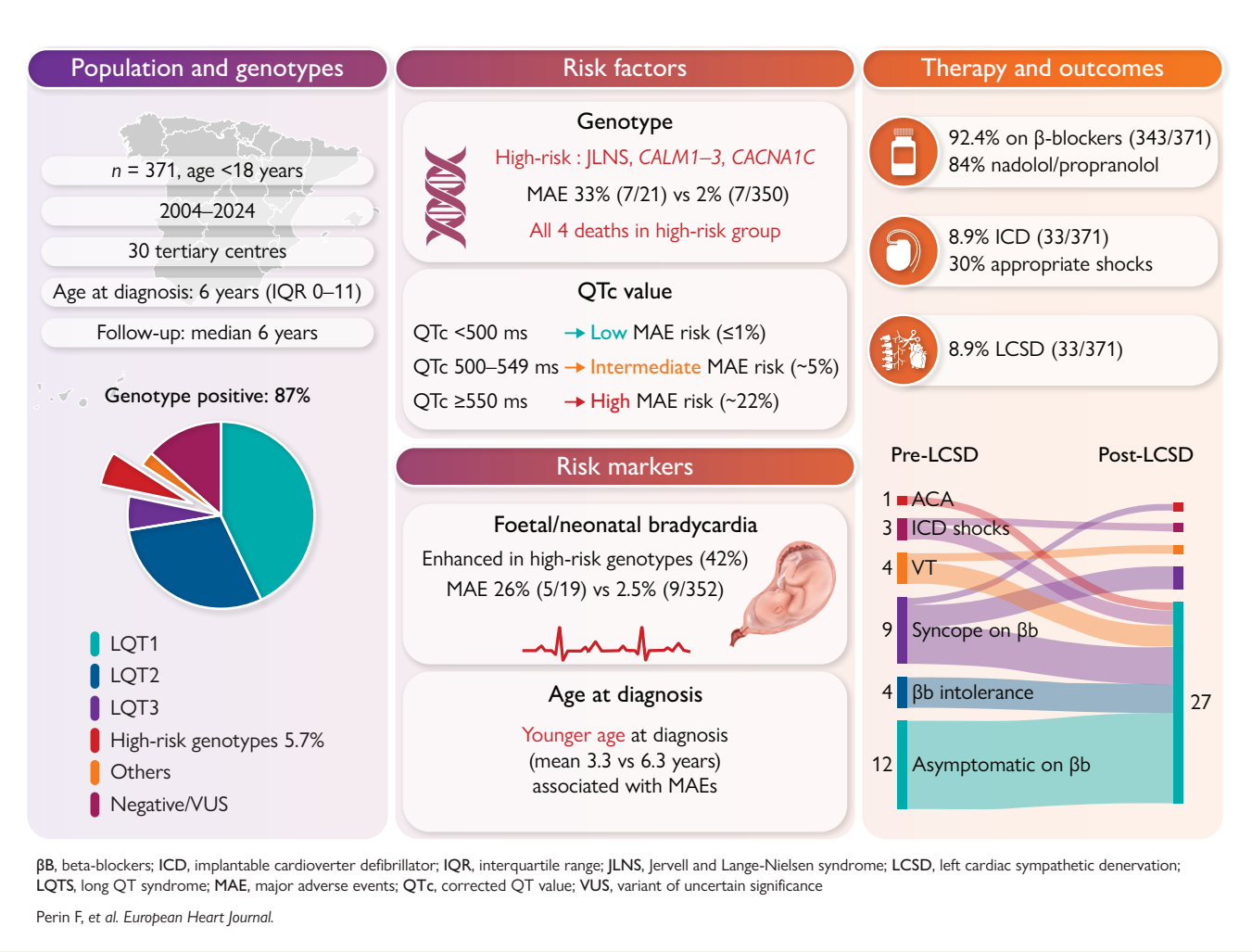
How is paediatric long QT syndrome (LQTS) managed in the Spanish public health system?

Key Finding

The assessment of a Spanish paediatric LQTS cohort showed widespread β-blocker use, relatively frequent left cardiac sympathetic denervation (LCSD) and cautious implantable cardioverter-defibrillator (ICD) implantation. Major events clustered in malignant genotypes, QTc ≥500 ms and early presentation (particularly foetal/neonatal bradycardia). In contrast, LQT1–3 with QTc <500 ms rarely experienced events while on medical therapy.

Take Home Message

These data support current genotype and QTc-guided management strategy, with β-blockers as the cornerstone therapy and selective use of LCSD and ICDs in high-risk profiles.



βB, beta-blockers; **ICD**, implantable cardioverter defibrillator; **IQR**, interquartile range; **JLNS**, Jervell and Lange-Nielsen syndrome; **LCSD**, left cardiac sympathetic denervation; **LQTS**, long QT syndrome; **MAE**, major adverse events; **QTc**, corrected QT value; **VUS**, variant of uncertain significance

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Overview of the multicentre paediatric congenital long QT syndrome cohort (*n*=371), including population characteristics, genotype distribution, predictors of major arrhythmic events (MAEs), and contemporary management. High-risk genotypes (JLN syndrome, CALM1–3, and CACNA1C variants), prolonged QTc value (particularly ≥550 ms), foetal/neonatal bradycardia, and younger age at diagnosis were associated with increased arrhythmic risk. β-blockers were the cornerstone therapy, whereas implantable cardioverter-defibrillators (ICDs) and left cardiac sympathetic denervation (LCSD) were selectively used in high-risk patients, supporting a genotype- and QTc value-guided risk stratification approach.

Keywords Long QT syndrome • Paediatrics • Genotype–phenotype correlation • Sudden cardiac death • Beta-blockers • Left cardiac sympathetic denervation

Introduction

Congenital long QT syndrome (LQTS) is the most common inherited arrhythmogenic ion channel disorder, affecting ~1 in 2000 individuals.[1] It is a leading cause of sudden cardiac death (SCD) in young individuals and children.[2] Advances in genetics have substantially expanded the recognized clinical spectrum of LQTS. While early descriptions focused largely on symptomatic individuals,[3,4] contemporary evidence suggests that up to 50% of affected individuals may be genotype-positive but phenotype-negative.[5]

In paediatric populations, a substantial proportion of diagnoses now occur through cascade genetic screening within families. Many of these children show minimal or no clinical expression. At the opposite end of the spectrum are high-risk paediatric patients, often presenting in early infancy with life-threatening arrhythmias. This group includes those with rare, severe forms such as Jervell and Lange-Nielsen syndrome (JLNS),[6,7] Timothy syndrome (TS) caused by pathogenic *CACNA1C* variants,[8,9] and calmodulinopathies due to *CALM* gene variants.[10] These high-risk genotypes represent the most severe spectrum of LQTS.[11] As a consequence of such a diverse clinical presentation of LQTS, effective risk stratification tools are essential to guide treatment decisions, aiming to balance the risk of life-threatening arrhythmias with the potential adverse effects of aggressive therapies, moving towards personalized medicine with individually tailored therapies.

Large international registries have substantially improved our understanding of LQTS, providing valuable insights into disease prevalence, genetic variants, clinical presentations, risk factors, and treatment outcomes.[12,13] However, large series focused on well-genotyped paediatric cohorts remain scarce.[14]

To expand the evidence derived from well-characterized paediatric populations, we established a nationwide, multicentre registry of children with LQTS followed in 30 Spanish hospitals over a 20-year period (2004–24). The aims of this study were: (i) to describe the clinical, electrocardiographic and genetic characteristics of paediatric LQTS; (ii) to characterize contemporary management patterns with beta-blockers, left cardiac sympathetic denervation (LCSD) and implantable cardioverter-defibrillators (ICDs) in a European public health system; and (iii) to explore how major arrhythmic events (MAEs) and other cardiac events (CEs) are distributed across simple, clinically recognisable risk markers, such as genotype, corrected QT (QTc) duration, and age or mode of presentation.

Methods

Study population and study design

We conducted a retrospective, multicentre, observational cohort study including children with LQTS followed in 30 Spanish hospitals with paediatric cardiology services (see Supplementary data online, *Figure S1*). Forty-seven centres were invited to participate in this initiative of the Spanish Society of Paediatric Cardiology, and 30 ultimately contributed data. Eligible patients were identified from institutional databases and clinical records, and anonymized data were entered into a national central registry. The study covered a 20-year period (2004–24) and reflects routine care in a public health system.

Eligibility for enrolment required a definitive diagnosis of LQTS before the age of 18 in accordance with the 2022 ESC guidelines,[15] defined as: (i) a QTc ≥480 ms on repeated 12-lead ECGs, with or without symptoms; (ii) a Schwartz diagnostic score >3.5; or (iii) the presence of a pathogenic/likely pathogenic (P/LP) variant in a LQTS-causing gene, regardless of QTc duration. For patients diagnosed before publication of the latest guidelines, eligibility was retrospectively re-evaluated using the current criteria. Patients with acquired or drug-induced LQTS were excluded.

Data collection and genetic analysis

A national collaborative core group was established, and cases were entered into a REDCap database hosted at Virgen de las Nieves University Hospital, Granada, Spain. REDCap (Research Electronic Data Capture)[16,17] is a secure, software platform designed to support data capture for research studies. Cases were screened from each group database, and inclusion criteria were systematically reviewed by a central review committee before the patient was enrolled into the registry.

Collected data included demographics, family and personal medical history, genotype, clinical tests including ECG parameters, echocardiography, 24-h Holter monitoring, exercise testing, and details of medical treatment and interventional therapies, as well as clinical outcomes and follow-up data. The reason and date of first diagnosis were recorded, as well as the timing of clinical and genetic confirmation. Electrocardiograms were obtained from all patients, with QT intervals measured in leads II and V5, and QTc calculated using Bazett's formula.[18] Probands were defined as the first family member diagnosed with LQTS based on clinical evaluation.

Genetic testing was performed according to local protocols, using Sanger sequencing or next-generation sequencing panels targeting LQTS-related genes. For this study, variants were centrally reviewed (updated November 2025) and classified as pathogenic (P) or likely pathogenic (LP), variants of uncertain significance (VUS), and benign or likely benign variants according to the American College of Medical Genetics and Genomics criteria[19] and public/curated databases and literature. Patients with a clear phenotype but without an identified P/LP variant were classified as genotype-negative.

Patients were classified into six groups according to their genetic status: (i–iii) the three major genotypes (LQT1-3) were evaluated as separate groups; (iv) a 'high-risk genotype' category comprised individuals harbouring *CALM1-3* deleterious variants, *CACNA1C* variants known to cause TS (*p.Gly402Ser* or *p.Gly406Arg*) or homozygous/compound-heterozygous *KCNQ1* variants associated with deafness (JLNS), in view of the rarity of these syndromes, their distinct molecular characteristics at the protein and action-potential levels, and their previously reported high incidence of MAEs[11]; (v) another group included patients with P/LP variants in other LQTS-associated genes; and (vi) a final group consisting of individuals with negative genetic findings or VUS.

Treatments

We recorded use of beta-blockers (agent, age at initiation, dose), additional antiarrhythmic drugs, LCSD, and ICD implantations. LCSD was performed by experienced surgeons using either thoracoscopic or open thoracotomy, in accordance with local institutional protocols at three referral centres. The procedure consisted of resection of the lower half of the stellate ganglion together with the ipsilateral sympathetic chain from T2 to T4. Regarding ICD data, age at implantation, indication (primary vs secondary prevention), system type (epicardial, transvenous, subcutaneous, extravascular), and subsequent device therapies and complications were documented. Treatment decisions were made by the managing teams at each centre following guidelines and local experience.

Outcomes

The primary endpoint was the occurrence of MAEs, defined as SCD, aborted cardiac arrest (ACA) requiring resuscitation or appropriate ICD therapy for ventricular tachycardia/fibrillation. Secondary endpoints included: (i) a composite of MAEs or syncope considered likely arrhythmic, defined as CE; (ii) any CE occurring while the patient was receiving beta-blocker therapy; (iii) time to first CE after treatment; (iv) change in event burden before and after LCSD in patients who underwent the procedure. For time-to-event analyses, time zero was defined as the date of LQTS diagnosis at the participating centre. Follow-up was censored at the last clinical contact or transition to adult care. Syncope was considered a CE when consistent with an arrhythmic mechanism and not explained by non-cardiac causes (e.g. clear vasovagal syncope, trauma, intoxication). Death from non-cardiovascular causes was also collected. All events were adjudicated by the investigators at each centre and reviewed centrally in case of uncertainty.

Handling of missing data

Due to the retrospective nature of the study, not all variables were available for every patient. We adopted a complete-case approach for each analysis: patients with missing data for a given variable were excluded only from that specific analysis. Denominators are provided in all tables and figures. No imputation of missing values was performed.

Statistical analysis

Continuous variables are summarized as medians and interquartile range (IQR) or means ± standard deviation, as appropriate; categorical variables as counts and percentages. Baseline characteristics were compared using χ^2 or Fisher's exact tests for categorical variables and Mann–Whitney *U* or Kruskal–Wallis tests for continuous variables, as appropriate.

Event-free survival for MAEs and for composite endpoints was estimated using Kaplan–Meier curves, with differences between groups assessed by the log-rank test. MAEs and ICD implantation were analysed as time-to-event outcomes. Associations between prespecified candidate risk markers (genotype group, QTc category, foetal/neonatal bradycardia, mode of presentation) and outcomes were evaluated using univariable Cox proportional hazards regression models. Given the limited number of MAEs, we did not construct multivariable models and did not attempt to identify independent predictors. To allow stable estimation of hazard ratios (HRs) and their 95% confidence intervals (CI), multilevel variables (genotype and QTc ranges) were recorded into clinically meaningful binary groups. The strength of association and predictive performance of baseline characteristics were quantified using HRs and Harrell's *C*-statistics.

All statistical tests were two-sided, and *P*-values are reported as descriptive measures of association. No adjustment was made for multiple comparisons; all inferential analyses should therefore be regarded as exploratory and hypothesis-generating. Analyses were performed using R (version 4.5.2).

Ethics

The study was approved by the Research Ethics Committee of the coordinating centre (approval number [0422-M1-23]) and by the local ethics committees of all participating institutions, in accordance with national regulations. Given the retrospective design and the use of pseudonymized data, the requirement for individual informed consent was waived or obtained as required by each committee. The study complies with the principles of the Declaration of Helsinki.

Results

Baseline clinical features

A total of 397 children with LQTS were initially identified and assessed for eligibility. Twenty-six patients were excluded because they did not meet the inclusion criteria, leaving 371 patients in the final cohort. Baseline characteristics of the study population are summarized in *Table 1*. Fifty-eight per cent were male, with a median age at diagnosis of 6.0 years (IQR .25–11). A P/LP variant was identified in 86.5% of cases. The distribution of affected genes is shown in *Figure 1A* with *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3) accounting for most genotypes. The predefined high-risk group included 21 patients: 16 with JLNS, 3 with *CALM* genes P/LP variants, and 2 with *CACNA1C* pathogenic variants (*Table 2*).

Mean QTc was 488 ± 46 ms (392–700 ms) (*Figure 1B*). Age at diagnosis and mean QTc differed across different genotypes (see supplementary data online, *Figure S2A* and *S2B*) and by proband status (see supplementary data online, *Figure S2C*).

Diagnosis occurred through family screening in approximately half of the cases, while symptomatic presentations accounted for a smaller proportion (*Figs 1C and 2A*). Reasons for diagnosis differed according to genotype and QTc (see supplementary data online, *Figure S3*). Notably, 42.1% of those diagnosed because of foetal/neonatal bradycardia harboured a high-risk genotype (5 out of 14 with sinus bradycardia and 3 out of 5 with atrioventricular block 2:1). Congenital heart disease (CHD) was identified in 6.2% of patients with LQT1, including tetralogy of Fallot ($n = 1$), complete transposition of the great arteries ($n = 1$), ventricular septal defects ($n = 6$), patent ductus arteriosus requiring percutaneous closure ($n = 1$), and aortic regurgitation ($n = 1$). CHD was also present in two patients with LQT2, one patient with LQT3, one patient with TS, and three patients with negative genetic testing. In addition, six patients in the cohort exhibited myocardial abnormalities. Genetic and clinical data related to CHD and myocardial abnormalities are summarized in Supplementary data online, *Table S1*.

Therapies

Medical therapy

Beta-blockers were prescribed in 343 of 371 (92.4%), most commonly nadolol (57%, mean dose 1.2 mg/kg/day) or propranolol (21%, mean dose 2 mg/kg/day), with good tolerance (1.7% discontinued). Sodium channel blockers were given to 12 out of 22 LQT3 patients, 9 of whom showed QTc shortening; among the 10 LQT3 patients that were not treated with sodium channel blockers, 9 had a normal QTc. Sodium channel blockers were also used in patients with *CALM 1-3* (1/3), TS (1/2), JLNS (1/16), and LQT1 (1/160).

ICD therapy

Thirty-three patients (8.9%) underwent ICD implantation at a mean age of 10.1 ± 4.9 years (range: 2 months to 19 years). Indications were secondary prevention after cardiac arrest (27.3%), syncope despite beta-blockers (27.3%), sustained ventricular arrhythmia (3%), and primary prevention (42.4%) in asymptomatic patients on beta-blockers but considered at particularly high risk based on QTc, genotype, symptoms, or a combination of these factors. High-risk genotypes accounted for

Table 1 Baseline clinical characteristics

Category	Total (*n* = 371)	LQT1 (*n* = 160)	LQT2 (*n* = 109)	LQT3 (*n* = 22)	High-risk genotypes (*n* = 21)	Other genotypes (*n* = 9)	Negative or VUS (*n* = 50)
Male sex	216 (58)	91 (57)	59 (54)	16 (73)	9 (43)	5 (56)	34 (68)
Proband status	186 (50.1)	74 (46)	40 (37)	14 (64)	19 (90)	4 (44.5)	35 (70)
Age at diagnosis, years	6 (.25–11)	6 (0–10)	6 (.75–10.3)	7.5 (1.5–11)	1 (0–3)	9 (7–12)	9 (6–13)
Diagnosis reason, %							
Family screening	49.9	54.3	63.3	36.5	9.5	55.6	28
Incidental finding	28	27.5	26.6	31.8	14.3	33.3	36
Syncope	15.1	11.3	9.2	22.7	28.7	11.1	32
ACA	1.9	1.9	.9	4.5	9.5	0	0
Foetal/neonatal bradycardia	5.1	5	0	4.5	38	0	4
Family history of SCD	22 (5.9)	8 (5)	7 (6.4)	1 (4.5)	2 (9.5)	0	4 (8)
Coexistent CHD	17 (4.6)	10 (6.2)	2 (1.8)	1 (4.5)	1 (4.8)	0	3 (6)
Baseline QTc	488 ± 46	481 ± 44	483 ± 37	496 ± 64	566 ± 56	452 ± 35	490 ± 23
Baseline QTc ≥500 ms	124 (33)	41 (26)	35 (32)	10 (45)	20 (95)	1 (11)	17 (34)
On βB after diagnosis	343 (92.4)	150 (93.8)	102 (93.6)	19 (86.4)	21 (100)	6 (66.6)	45 (90)
Nadolol	212 (57.1)	100 (62.5)	59 (54.1)	16 (72.7)	13 (61.9)	2 (22.2)	22 (44)
Propranolol	78 (21)	35 (21.9)	27 (24.8)	2 (9.1)	7 (33.3)	2 (22.2)	5 (10)
Selective βB	53(14.3)	15(9.4)	16 (14.7)	1 (4.5)	1 (4.8)	2 (22.2)	18 (36)
Sodium channel blockers	16 (4.3)	1 (.6)	0	12 (55)	3 (14.3)	0	0

Values are given as *n* (%), median (interquartile range), or mean ± standard deviation.
ACA, aborted cardiac arrest; βB, beta-blockers; CHD, congenital heart disease; LQT1, long QT syndrome type 1; LQT2, long QT syndrome type 2; LQT3, long QT syndrome type 3; LQTS, long QT syndrome; QTc, corrected QT value; SCD, sudden cardiac death; VUS, variant of uncertain significance.

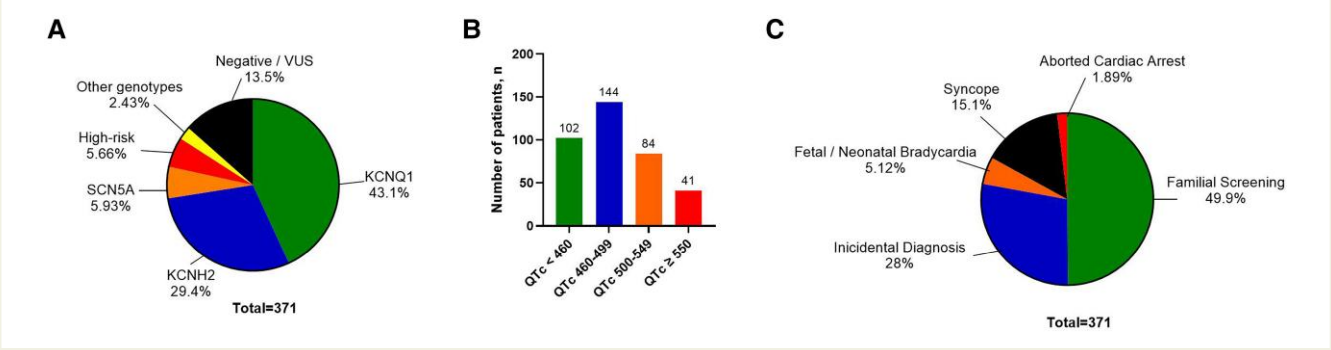

Figure 1 Baseline characteristics of the cohort. (*A*) Genotype distribution among 371 children with LQTS (2004–24), highlighting the high-risk subgroup (JLNS, *CALM1-3*, *CACNA1C*). (*B*) QTc distribution at diagnosis (mean 488 ± 46 ms). (*C*) Route to diagnosis: family screening, symptomatic presentation, incidental finding, and foetal/neonatal bradycardia. Abbreviations: LQTS, long QT syndrome; JLNS, Jervell and Lange-Nielsen syndrome; QTc, corrected QT value

36% of ICD cases (see supplementary data online, *Figure S4*). Characteristics of the ICD recipients compared to non-ICD patients are described in supplementary data online, *Table S2*. Devices included epicardial ($n = 6$, 3 later converted to transvenous), subcutaneous ($n = 7$), extravascular ($n = 1$), and transvenous systems (remaining 19 cases).

Left cardiac sympathetic denervation

LCSD was performed in 33 patients (8.9% of the total cohort) at a mean age of 9.3 years (range 0–17.9) across three referral centres. Notably, one patient underwent LCSD at just 8 days of life (see Supplementary data online, *Figure S5* for details on this case). The QTc value was significantly prolonged in the LCSD group compared to non-LCSD patients (522 ± 42 ms vs 484 ± 45 ms, $P < .001$). Most were genotype-positive (91%), including 11 with LQT1, 7 with LQT2, 1 with LQT3, and 11 JLNS. Indications included syncope despite beta-blockers ($n = 9$), sustained ventricular tachycardia ($n = 4$), ACA with ICD implantation ($n = 1$), appropriate ICD shocks ($n = 3$), beta-blocker intolerance/non-compliance ($n = 4$), and primary prevention ($n = 12$) (*Figure 3A*, adapted from the design of Dusi *et al.*,[11] and modified to include patient data from the current cohort). Primary prevention was considered for patients who were either asymptomatic or had experienced syncope prior to beta-blockers but were deemed high-risk based on factors such as resting QTc >500 ms, persistent T-wave alternans,[20] or the presence of high-risk genotypes such as JLNS (6 out of 12 primary prevention). Fifteen LCSD patients (45.5%) also had an ICD: 3 received the ICD before LCSD, 10 underwent LCSD prior to ICD implantation, and in 2 patients, both procedures were performed during the same period (*Figure 3B*). No major surgical complications were reported, although three patients experienced transient, mild complications (self-limiting ptosis and Harlequin-type sweating asymmetry).

Clinical outcomes

Over a median follow-up of 6 years (IQR 2–9), 14 of 371 children (3.8%) experienced at least one MAE, despite treatment. In one patient, MAE occurred in the setting of treatment non-adherence; however, additional events were observed despite subsequent reported adherence. Additional cases of likely arrhythmic syncope increased the total burden of CEs. As summarized in *Table 3*, MAEs occurred predominantly in children presenting with foetal/neonatal bradycardia or symptoms at baseline, whereas they were rare among those identified through screening or incidental ECG. Age at diagnosis was lower in children with MAEs (see Supplementary data online, *Figure S6*). Notably, two out of three children who experienced CEs during the first year of life (one with *CALM3*-related disease and two with LQT3) subsequently developed MAEs, including one death.

In univariable analysis, genotype and QTc duration were strongly associated with event distribution. MAEs were rare in LQT1–3 patients without additional risk factors. In contrast, high-risk genotypes were associated with the highest MAE and CE rates despite intensive therapy (*Tables 2* and *3*, *Figs 2B* and *4A* and *B*). Events in this group often occurred early in life (median age of MAEs 3 years). The hazard of MAEs was significantly higher in high-risk genotypes (HR 16.57, 95% CI 4.26–64.47, $P < .001$).

Within high-risk genotypes, patients experienced a severe clinical course despite beta-blocker therapy. Among JLNS patients, 25% developed MAEs, including one ACA and one SCD. *CALM*-related LQTS was particularly malignant: two of three patients died, and the other one had an ACA. Of the two TS patients, one experienced an ACA at 3 years, and the other died at 7 months.

Overall, four deaths occurred, all in patients with high-risk genotypes (see supplementary data online, *Table S3*). Two were SCDs: one JLNS patient at 12 years during swimming and one *CALM-2* patient at 20 months, both were on high-dose propranolol. Two deaths were extracardiac (not primarily attributable to arrhythmia). One occurred in a *CALM-3* patient at 5 years, despite ICD implantation at 2 months of life, from pulseless electrical activity following prolonged hypoglycaemia (previously reported[21]), and one TS patient at 7 months from complications during anaesthesia after pneumothorax and metabolic derangements, without hypoglycaemia. None of the deceased had undergone LCSD, and only one had an ICD.

Baseline QTc duration further stratified events. MAEs and CEs under treatment were concentrated among patients with markedly prolonged QTc (≥550 ms), with intermediate event

Table 2 Clinical and genetic data of high-risk genotype cases

Case	Sex	Gene (Hom/ Het)	Variant/s	Age at diagnosis	Age first symptom	Reason for diagnosis	QTc (ms)	ICD	LCSD	ACA	Death
1	M	*KCNQ1 (Hom)*	c.478- 2_487del	5	2	Syncope	520	Yes	Yes	No	No
2	F	*KCNQ1 (Hom)*	c.478- 2_487del	0	No sympt.	Screening	540	No	Yes	No	No
3	M	*KCNQ1 (Hom)*	c.728G > A	3	1.5	Syncope	500	Yes	Yes	No	No
4	F	*KCNQ1(Hom)*	c.1615C > T	10	8	Syncope	580	Yes	No	Yes	No
5	M	*KCNQ1 (Hom)* *KCNH2 (Het)* *AKAP2(Het)*	c. 604 + 1G > C c.38C > A c.7010A > G	0	No sympt.	Screening	580	Yes	No	No	No
6	F	*KCNQ1 (Hom)* *KCNH2 (Het)* *AKAP2(Het)*	c. 604 + 1G > C c.38C > A c.7010A > G	0	12	Bradycardia	580	No	No	No	Yes
7	M	*KCNQ1 (Het)* *KCNQ1 (Het)*	c.604 + 1G > C c.1513_1514del	0	No sympt.	Bradycardia	610	No	No	No	No
8	F	*KCNQ1 (Hom)*	c.1513_1514del	0	9	Bradycardia	550	Yes	No	No	No
9	M	*KCNQ1 (Hom)*	c.1784_1786del	0	4	Bradycardia	550	Yes	Yes	No	No
10	F	*KCNQ1 (Het)* *KCNQ1 (Het)*	c.200_210del c.898G > A	5	5	Syncope	550	Yes	Yes	No	No
11	M	*KCNQ1 (Het)* *KCNQ1 (Het)*	c.1630_1635delinsGTTGAGA c.965C > G	2	3	Deafness	596	No	Yes	No	No
12	F	*KCNQ1 (Hom)*	c.1784_1786del	0	No sympt.	Bradycardia	540	Yes	Yes	No	No
13	M	*KCNQ1 (Hom)*	c.403del	1	No sympt.	Deafness	575	Yes	Yes	No	No
14	F	*KCNQ1 (Hom)*	c.1772G > A	10	10	Syncope	500	No	Yes	No	No
15	M	*KCNQ1 (Het)* *KCNQ1 (Het)*	c.477 + 1G > A c.683 + 5G > A	1	2	Deafness	570	No	Yes	No	No
16	M	*KCNQ1 (Het)* *KCNQ1 (Het)*	c.965C > G c.1630_1635del	3	3	Syncope	490	No	Yes	No	No
17	M	*CALM2 (Het)*	c.293A > T	1	1	ACA	510	Yes	No	Yes	No
18	F	*CALM3 (Het)*	c.421G > A	0	.1	Bradycardia	600	Yes	No	Yes	Yes
19	M	*CALM2 (Het)*	c.422A > G	0	1.9	Bradycardia	700	No	No	No	Yes
20	F	*CACNA1C(Het)*	c.1216G > C	0	.6	Bradycardia	700	No	No	No	Yes
21	M	*CACNA1C(Het)*	c.1204G > A	3	3	ACA	550	Yes	No	Yes	No

ACA, aborted cardiac arrest; Het, heterozygous; Hom, homozygous; ICD, implantable cardioverter-defibrillator; LCSD, left cardiac sympathetic denervation; No sympt, no symptoms; QTc, corrected QT value.

rates in those with QTc 500–549 ms and very low rates in children with QTc <500 ms (*Table 3* and *Figure 4C* and *D*). Patients with QTc ≥500 ms showed a markedly increased risk of MAEs compared with those with QTc <500 ms. In the Cox proportional hazards model, QTc ≥500 ms was associated with a 26-fold higher hazard of experiencing the primary outcome (HR 26.3, 95% CI 3.4–201.3.1, $P = .001$). This association showed good apparent discrimination (*C*-statistic .81).

ICD outcomes

Among 33 ICD recipients (8.9% of all patients), 10 (30%) experienced at least one appropriate shock during a mean follow-up of 4.8 ± 3.7 years (range: 0–15 years). Two patients had arrhythmic storms. All patients with shocks were on therapy, although one episode followed beta-blocker non-compliance. Patients with appropriate shocks had longer QTc (573 ± 75 ms vs 526 ± 37 ms, $P = .106$) and were more likely to have experienced CEs despite treatment. Appropriate shocks were more common in those implanted after cardiac arrest (4/9) or syncope/ventricular tachycardia despite beta-blockers (4/10) compared to those who were asymptomatic on beta-blockers before implantation (2/14). Inappropriate shocks occurred in 2 patients (6%). Adverse events related to ICDs were reported in 8 patients (24%), most often due to lead malfunction ($n = 4$), including one case triggering an arrhythmic storm. Device replacement for skin erosion was required in 2 cases, one without

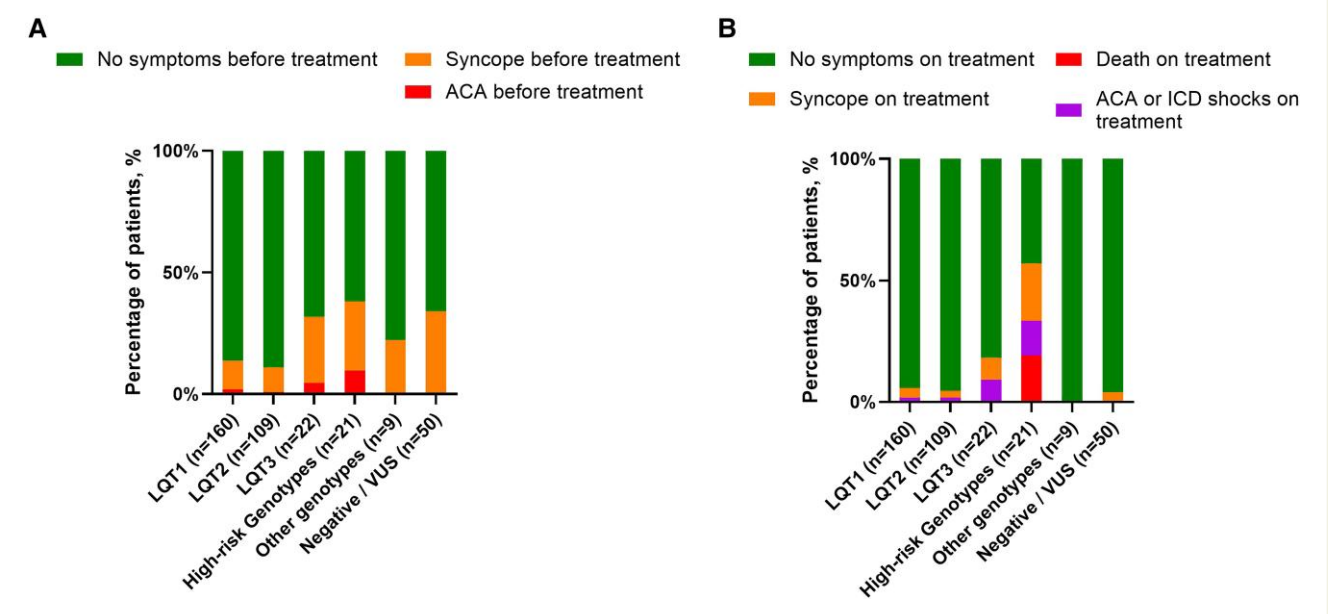

Figure 2 Event burden by genotype. (*A*) Rates of major arrhythmic events (MAEs) and of syncope before treatment across genetic groups: LQT1, LQT2, LQT3, high-risk genotypes (Jervell–Lange-Nielsen, *CALM1-3*, *CACN1C*), other genotypes, and negative genetics. (*B*) Rates of MAEs and of syncope after treatment across genetic groups: LQT1, LQT2, LQT3, high-risk genotypes, other genotypes, and negative genetics/VUS. Abbreviations: ACA, aborted cardiac arrest; ICD, implantable cardioverter–defibrillator; VUS, variant of unknown significance

reimplantation. Endocarditis occurred in 2 patients (6%). Five patients underwent additional procedures, including generator replacements (n = 3) and system upgrades (dual-chamber pacing in neonatal LQT3 and LQT1) to address recurrent arrhythmia and enable intensified medical therapy. Age at implantation was not associated with complications.

LCSD outcomes

A detailed analysis of outcomes after LCSD and their association with potential ICD implantation is shown in *Figure 3*. During a median follow-up of 6 years (range 1–12), 81.8% remained asymptomatic after LCSD. Six patients experienced CEs: in 3, LCSD was ineffective [LQT1 with complete transposition of the great arteries (n = 1), LQT2 (n = 1), and neonatal LQT3 (n = 1)], while in the remaining 3, event frequency decreased by >90%. Importantly, no SCD occurred post-procedure. When outcomes were analysed based on the indication for LCSD (*Figure 3A*), all patients treated for primary prevention, beta-blocker intolerance/non-compliance, or ACA off beta-blockers (along with ICD implantation) remained event-free. Among the three with prior ICD shocks, two had no further shocks, and one showed a marked reduction. In 12 patients who underwent LCSD as the sole initial adjunctive therapy for syncope or ventricular tachycardia despite beta-blockers, ICD implantation was avoided in six (*Figure 3B*). In the high-risk subgroup, LCSD was performed in 11 of 16 patients with JLNS (68.7%), but not in patients with calmodulinopathies or TS. The clinical course of JLNS patients after LCSD is illustrated in *Figure 5*. In this small subset, numerically fewer CEs were observed among those who underwent LCSD compared with JLNS children managed with beta-blockers alone.

Discussion

In this nationwide, multicentre cohort of 371 children with congenital LQTS managed in a European public health system, the overall incidence of MAEs was relatively low, with events clustering in a small subgroup of patients with malignant genotypes, markedly prolonged QTc, and very early presentation. Our findings highlight recognisable clinical and genetic profiles associated with higher or lower arrhythmic risk and reflect management patterns characterized by widespread beta-blocker use, frequent LCSD, and prudent ICD implantation in paediatric practice (see *Structured Graphical Abstract*).

Genotype and QTc as markers of arrhythmic risk

As expected, most children in our cohort carried P/LP variants in *KCNQ1*, *KCNH2*, or *SCN5A*, and their overall risk of MAEs under beta-blockers was low, consistent with previous reports.[22,23] In contrast, a distinct subset of high-risk genotypes such as JLNS, *CALM* gene-mediated LQTS, or *CACNA1C*-related TS accounted for all deaths and experienced a disproportionate share of MAEs despite aggressive management. These findings support the view that LQTS, although defined as a single diagnostic entity, encompasses a broad clinical spectrum with markedly different prognoses largely depending on underlying genotype.[11]

QTc duration at diagnosis further refined the risk. In our cohort, MAEs were concentrated among patients with QTc ≥550 ms, whereas children with QTc <500 ms without a high-risk genotype rarely experienced MAEs during follow-up. This reinforces QTc as a simple but powerful marker of arrhythmic risk, consistent with previous registries showing increasing

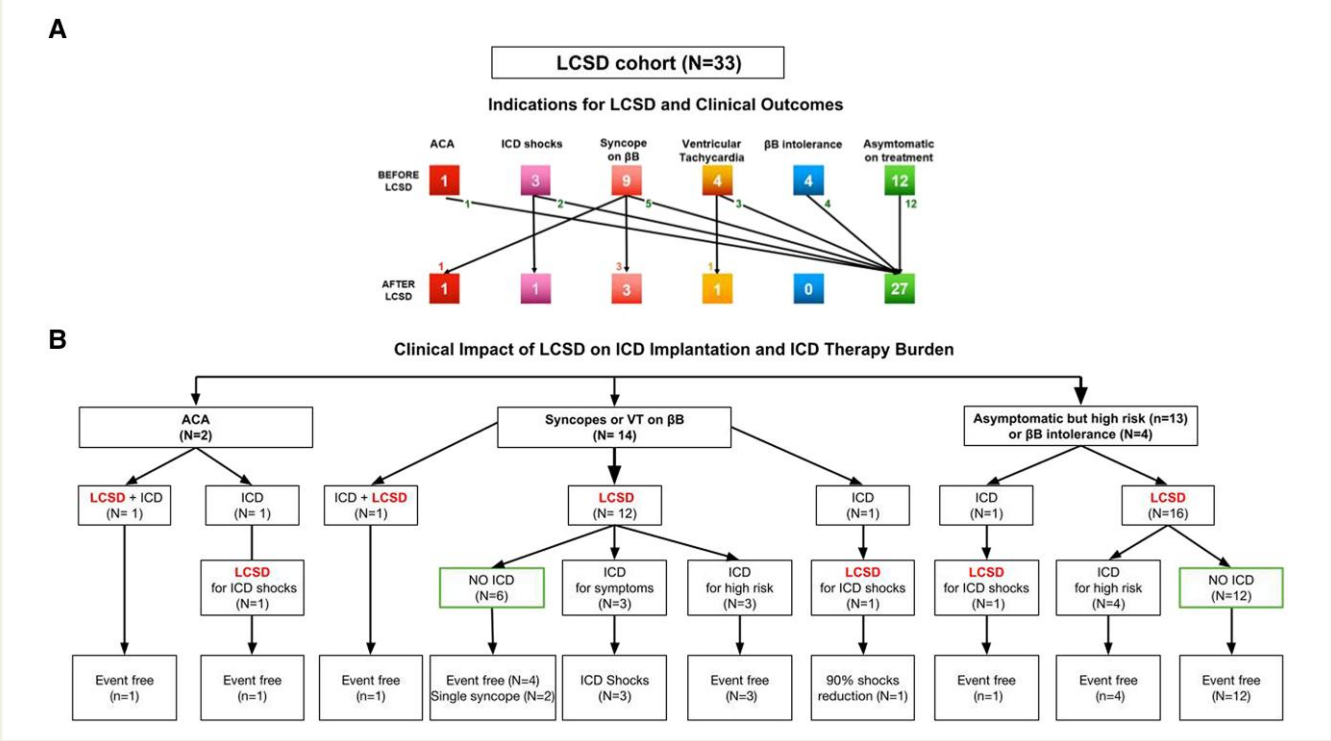

Figure 3 (*A* and *B*) Clinical indications and outcomes of LCSD and its impact on ICD use. Panel *A* shows the distribution of indications for LCSD and corresponding clinical status after the procedure, with connecting lines illustrating transitions from pre-LCSD indication to follow-up outcome. Panel *B* summarizes the clinical impact of LCSD on ICD implantation and ICD therapy burden in 33 patients followed for a median of 6 years. Among 14 patients presenting with syncope or ventricular tachycardia despite beta-blocker therapy, 12 received LCSD as the sole initial adjunctive strategy. Of these, 6 (50%) remained free from ICD implantation, while 6 required ICDs: 3 at a median age of 6 years for recurrent symptoms, and 3 for persistent high-risk features, with ICD implantation deferred a median of 6 years after LCSD. In 16 asymptomatic but high-risk individuals or patients intolerant to beta-blockers, LCSD allowed ICD avoidance in 12 patients (75%) and postponement in 4 patients, with a median deferral of 3 years; all remained event-free during follow-up. Among 3 patients undergoing LCSD for ICD shock reduction, arrhythmic burden was markedly reduced, with ≥90% shock reduction in all cases. Overall, LCSD enabled ICD avoidance or meaningful reduction across clinical presentations. Abbreviations: ACA, aborted cardiac arrest; βB, beta-blocker; ICD, implantable cardioverter-defibrillator; LCSD, left cardiac sympathetic denervation; VT, ventricular tachycardia

event rates above 500 ms.[5] Given the small number of events and the observational design, we do not propose new cut-offs or a 'zero-risk' group. Rather, our data should be interpreted as reinforcing the notion that markedly prolonged QTc,[3] particularly in combination with malignant genotypes, delineates a subset in whom close monitoring and early intensification of therapy are needed.

Foetal and neonatal bradycardia as a clinical red flag

A second important observation is the association between foetal/neonatal bradycardia and high-risk LQTS. Foetal/neonatal bradycardia is a recognized early manifestation of LQTS.[24,25] In our cohort, children diagnosed in the perinatal period due to sinus bradycardia or atrioventricular block were markedly enriched for high-risk genotypes and severe QTc prolongation, and contributed disproportionately to early MAEs. This aligns with prior descriptions of severe perinatal LQTS,[25,26] particularly in LQT3,[27] but extends these observations to a broader genotype spectrum in a national paediatric cohort.

Clinically, unexplained foetal or neonatal bradycardia should be considered a red flag for potentially malignant congenital LQTS. In such cases, early ECG evaluation, prompt genetic testing, and careful planning of delivery and postnatal management (preferably at specialized centres with experience in LQTS) appear warranted. Early initiation of beta-blockers and timely consideration of LCSD and/or ICD may be needed in selected cases. At the same time, foetal/neonatal bradycardia should be seen as part of an overall high-risk constellation (malignant genotype plus marked QTc), rather than an independent predictor.

Events in the first year of life

Two of three patients who experienced CEs within the first year of life experienced recurrent malignant arrhythmias or death, despite treatment. These findings underscore that CEs during infancy identify an extremely high-risk phenotype, consistent with previous reports.[28]

CHD and other structural cardiac anomalies

A higher-than-expected prevalence of CHD was observed in this cohort. While CHD occurs in ~8–9 per 1000 live births in

Table 3 Univariate Cox regression analysis for major arrhythmic events

Variable	Hazard ratio (95% CI)	*P*-value
Demographics		
Male sex (vs female)	.85 (.30–2.45)	.770
Age at diagnosis (years)	.92 (.80–1.05)	.201
Genotype (ref: LQT1)		
LQT2	.91 (.15–5.48)	.922
LQT3	4.48 (.75–26.89)	.101
High-risk (JLNS, *CALM1-3*, TS)	16.57 (4.26–64.47)	<.001
Baseline phenotype		
Proband status (vs family member)	7.12 (1.59–31.84)	.010
T-wave alternans	19.44 (6.71–56.29)	<.001
Family history of sudden cardiac death	.92 (.12–7.08)	.938
Structural abnormalities	4.29 (1.19–15.45)	.026
Reason for diagnosis (ref: screening)		
Syncope	8.03 (1.47–43.91)	.016
Aborted cardiac arrest	12.89 (1.17–142.30)	.037
Foetal/neonatal bradycardia	21.89 (4.23–113.20)	<.001
ECG findings (QTc)		
QTc group (overall)	-	<.001

High-risk genotypes included JLNS, calmodulinopathies (*CALM1-3*), and TS. The *P*-value for QTc group represents the overall comparison across 4 QTc categories: QTc <460 ms; QTc 460–499 ms; QTc 500–549 ms; QTc>550 ms. *P*-values are descriptive and were not adjusted for multiple comparisons.
CI, confidence interval; JLNS, Jervell and Lange-Nielsen syndrome; QTc, corrected QT value; TS, Timothy syndrome.

the general population,[29] a greater proportion was identified in our series, particularly among children with LQT1 (6.2%). Although some mild defects may reflect incidental findings or referral bias, major anomalies—including transposition of the great arteries and tetralogy of Fallot—were also present. Conotruncal defects have previously been reported in association with LQTS.[30] Although LQTS is generally considered uncommon among patients with CHD, its true prevalence may be underestimated as diagnosis may be challenging in this setting.[30] Therefore, the presence of CHD should not preclude consideration of congenital LQTS when QT prolongation is consistently observed.

Therapeutic strategies and outcomes

Our study reflects a therapeutic approach centred on beta-blockers, with selective ICD use and a prominent role for LCSD. Over 90% of children were treated with beta-blockers, and most remained event-free on this therapy alone, especially those with common genotypes and moderate QTc prolongation. This high treatment rate contrasts with the lower beta-blocker usage reported in the Rochester LQTS Registry,[31] where only 67% of patients received beta-blocking therapy, but is consistent with practices observed in other specialized LQTS centres.[14,32,33] Notably, a recent German paediatric LQTS registry[14] documented a nearly identical overall treatment rate (92.1%), although non-selective beta-blockers were prescribed less frequently (57% vs 84% of treated patients in our cohort). The authors reported no significant difference in efficacy between non-selective and selective beta-blockers—results that diverge from most recent evidence.[15,34]

Of particular interest, most of the children with concealed LQTS in our cohort were treated with beta-blockers, consistent with current Class IIa guideline recommendations.[15] However, whether all genotype-positive, phenotype-negative individuals require chronic therapy remains debated. Some authors suggest that carefully selected low-risk patients might be managed without beta-blockers.[35,36] As the number of genotype-positive, phenotype-negative diagnoses increases, robust evidence is urgently needed to clarify which patients truly benefit from therapy and in which cases treatment may be safely withheld. In the meantime, Spanish paediatric cardiologists appear to adopt a cautious approach, generally favouring treatment to minimize potential risk. Our data also confirm that high-risk genotypes require tailored therapy. Although numbers were small, all children with *CALM1-3* or *CACNA1C* variants experienced MAEs—within the first years of life, in line with earlier reports.[8–11] This extremely high-risk profile argues for early and proactive management, including discussion of ICD implantation at an early age. Within the high-risk subgroup, our cohort included a comparatively large number of JLNS patients, allowing meaningful observations despite the rarity of this genotype. In agreement with previous studies,[6,37] beta-blockers alone were often insufficient in JLNS. In our cohort, the relatively frequent use of LCSD and its association with reduced event burden in these children suggest that adjunctive strategies should be considered from early childhood.

Adjunctive therapies

ICDs remain a cornerstone for preventing SCD in patients with ACA or refractory cases. In our cohort, a smaller proportion of children received ICDs than in some previous series,[14,31,38] with a substantial proportion of implants performed in carriers of high-risk genotypes. Importantly, this more conservative strategy (with broad beta-blockers and selective sodium-channel blocker prescription, frequent LCSD, and fewer ICD implantations) did not lead to an increase in SCD/ACA events in our cohort. The rate of appropriate shocks was similar to that reported in a recent German paediatric cohort[14] and higher than in predominantly adult Rochester LQTS registry.[31] However, device-related complications occurred in about a quarter of ICD recipients, consistent with the substantial complication burden reported in paediatric ICD series[39] and other cohorts including both adult and paediatric patients.[13] Given that children may live for decades with an ICD, requiring multiple generator replacements and potential lead revisions or extractions, these findings emphasize the need for careful risk–benefit assessment and, where possible, for adjunctive strategies that may reduce the need for ICD implantation.[40]

In this context, LCSD offers a valuable complementary option. By reducing left-sided sympathetic input and ventricular

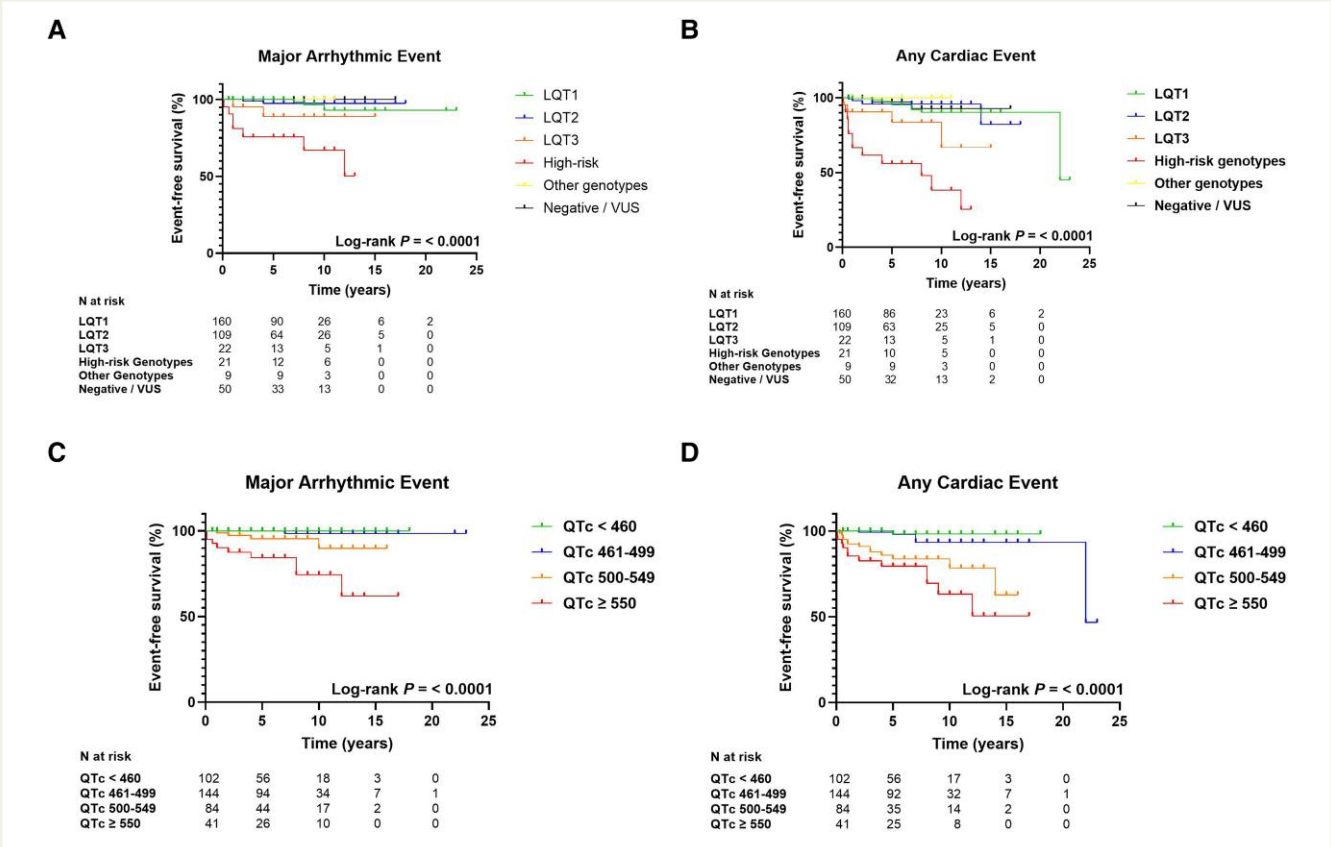

Figure 4 Event-free survival by genetics and QTc. (*A*) Kaplan–Meier curves for MAEs-free survival by genetic status: LQT1, LQT2, LQT3, high-risk genotypes (Jervell–Lange-Nielsen, *CALM1-3*, *CACN1C*), other genotypes, and negative genetics or VUS; $P < .0001$ (log-rank). (*B*) Kaplan–Meier curves for CE-free survival by genetic status: LQT1, LQT2, LQT3, high-risk genotypes (Jervell–Lange-Nielsen, *CALM1-3*, *CACN1C*), other genotypes, and negative genetics or VUS; $P < .0001$. (*C*) MAEs-free survival by QTc category, $P < .0001$. (*D*) Any CE-free survival by QTc category; $P < .0001$. Abbreviations: ACA, aborted cardiac arrest; ICD, implantable cardioverter–defibrillator; QTc, corrected QT value; VUS, variant of unknown significance

norepinephrine release, LCSD targets a key arrhythmogenic mechanism in LQTS, increases the ventricular fibrillation threshold, reduces repolarization dispersion and early afterdepolarizations, and lowers the risk of torsades de pointes and malignant ventricular arrhythmias.[41] Consistent with previous evidence,[11,32,33,37,42,43] LCSD in our cohort was associated with a marked reduction in arrhythmic burden in many high-risk children and allowed avoidance or postponement of ICD implantation in some. Importantly, no SCD occurred after LCSD, and the procedure showed an excellent safety profile even in small children and infants, when performed by experienced surgeons, aligning with previously reported outcomes.[2,37,42,43] Despite these advantages, and except for a few specialized centres,[43] LCSD continues to be underused globally, being performed in fewer than 2% of patients.[14,31,44,45] Our findings support broadening the role of LCSD beyond its traditional use as a rescue intervention after beta-blocker failure[37] towards consideration as an early or adjunctive strategy in selected high-risk children, as previously proposed by others.[2,11,43] In addition, both our data and prior reports[46] suggest that LCSD may represent a disease-modifying strategy in selected patients with LQTS, with the potential to avoid or postpone ICD implantation and decrease subsequent shock burden. Delaying ICD implantation through effective reduction of arrhythmic risk may be beneficial in the paediatric population, as implantation at an older age and larger body size could potentially reduce device-related complications.

However, LCSD does not provide complete protection, and its use should not preclude consideration of ICD therapy in high-risk patients. While our observations are encouraging and consistent with previous studies, they must be interpreted with caution. LCSD was not randomly allocated; recipients represented a highly selected high-risk subgroup, and the small sample size precludes definitive conclusions regarding comparative effectiveness vs ICD therapy or beta-blockers alone. Nevertheless, taken together with prior evidence, our findings support reconsideration of LCSD positioning within contemporary management algorithms. Given the significant device-related morbidity associated with ICDs, greater integration of LCSD into future European guideline updates may be warranted.

Limitations

This study has several limitations. Its retrospective observational design introduces potential information bias and limits causal inference, and patient identification at participating centres may

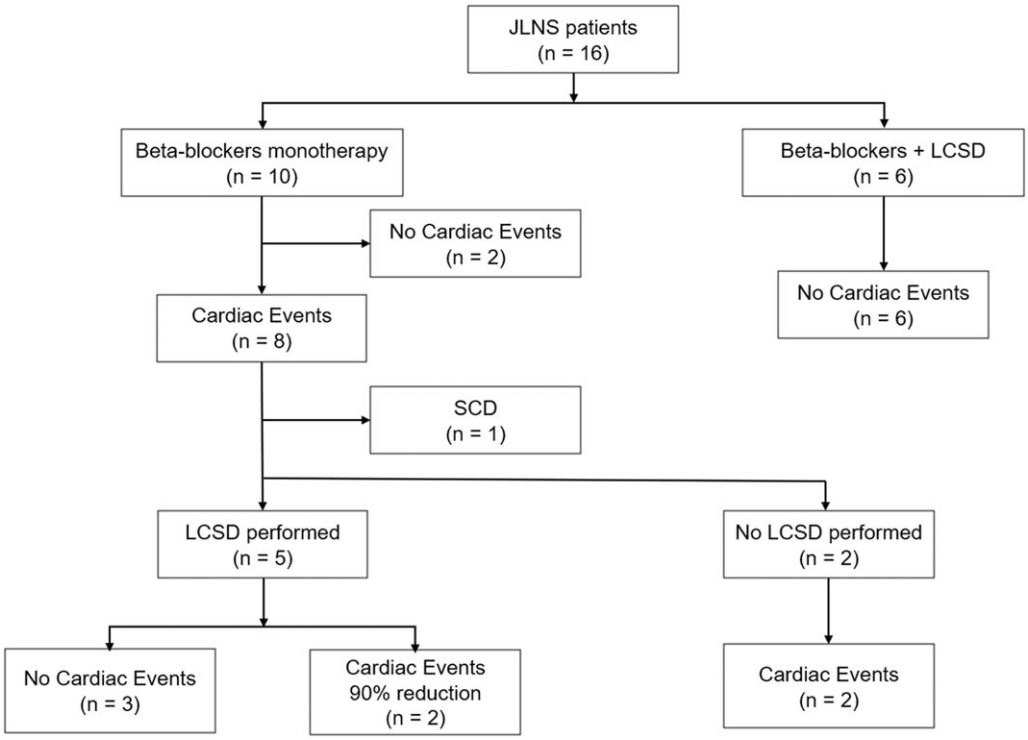

Figure 5 Flow diagram of 16 patients with Jervell and Lange-Nielsen syndrome (JLNS) according to the use of left cardiac sympathectomy (LCSD). This figure illustrates the clinical course under two treatment strategies: beta-blocker therapy alone (n = 10) and beta-blockers combined with LCSD (n = 6). Outcomes are categorized as: no cardiac events, ≥90% reduction in cardiac events, or occurrence of cardiac events. Cardiac events include likely arrhythmogenic syncope, aborted cardiac arrest, implantable cardioverter-defibrillator shocks, and sudden cardiac death. Abbreviations: LCSD, left cardiac sympathetic denervation; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death

have led to under-recognition of milder or undiagnosed cases. Although relatively large for a paediatric LQTS cohort, the small number of MAEs limited statistical power and precluded multivariable modelling. Genetic testing was performed over an extended period with evolving techniques, so some variant misclassification cannot be excluded despite central reclassification. In addition, treatment strategies were not standardized and reflected local clinical practice, introducing potential selection bias; therefore, findings regarding LCSD and ICD should be considered hypothesis-generating. Finally, no adjustment for multiple comparisons was performed, and *P*-values should be interpreted descriptively.

Conclusions and clinical implications

In a paediatric national cohort managed predominantly with beta-blockers, MAEs were uncommon and occurred mainly in children with high-risk genotypes, marked QTc prolongation, and very early presentation, particularly foetal or neonatal bradycardia. These profiles may help clinicians identify children who benefit from intensified monitoring, early consideration of LCSD, and timely discussion of ICD therapy.

Clinically, our data support a stepwise, risk-based strategy: children with LQT1–3, QTc <500 ms, and no malignant genotype show excellent outcomes on medical therapy alone, whereas those with QTc ≥500 ms and high-risk genotypes require early intensification. LCSD can be safely integrated into high-risk management and may reduce the need for ICD in selected cases. Despite the value of this first-ever comprehensive nationwide registry analysis in our country, prospective studies are needed to validate these thresholds and optimize sequencing of LCSD and ICD therapy in paediatric LQTS.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

The authors declare no conflicts of interest.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Ethical Approval

The study was approved by the Research Ethics Committee of the coordinating centre (approval number [0422-M1-23]) and by the local ethics committees of all participating institutions, in accordance with national regulations.

Pre-registered Clinical Trial Number

Not applicable.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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