

Table 1. EHRA/HRS/APHRS/LAHS 2022 Consensus Statement on genetic testing. Genes implicated in long QT syndrome (LQTS)

Gene	Locus	Phenotype—syndrome	Protein (functional effect)	Frequency	ClinGen classification
<i>KCNQ1</i>	11p15.5	LQTS, JLNS	Loss-of- I_{Ks} channel function	40–55%	Definitive
<i>KCNH2</i>	7q35-36	LQTS	Loss-of- I_{Kr} channel function	30–45%	Definitive
<i>SCN5A</i>	3p21-p24	LQTS	Increase in $I_{Na1.5}$ channel function	5–10%	Definitive
<i>CALM1</i>	14q32.11	LQTS	L-type calcium channel ($\uparrow$)	<1%	Definitive
<i>CALM2</i>	2p21	LQTS	L-type calcium channel ($\uparrow$)	<1%	Definitive
<i>CALM3</i>	19q13.32	LQTS	L-type calcium channel ($\uparrow$)	<1%	Definitive
<i>TRDN</i>	6q22.31	Recessive LQTS	L-type calcium channel ($\uparrow$)	<1%	Strong
<i>KCNE1</i>	21q22.1	LQTS, JLNS, a-LQTS	Loss-of- I_{K} channel function	<1%	Strong in aLQTS, definitive in JLNS
<i>KCNE2</i>	21q22.1	a-LQTS	Loss-of- I_{K} channel function	<1%	Strong in aLQTS
<i>KCNJ2</i>	17q23	ATS	Loss-of- I_{K1} channel function	<1%	Definitive in ATS
<i>CACNA1C</i>	12p13.3	TS, LQTS	L-type calcium channel ($\uparrow$)	<1%	Definitive in TS, moderate in LQTS

Functional effect: ($\downarrow$) loss-of-function or ($\uparrow$) gain-of-function at the cellular *in vitro* level.
a-LQTS, acquired-long QT syndrome; ATS, Andersen-Tawil syndrome; JLNS, Jervell and Lange-Nielsen syndrome; RWS, Romano-Ward syndrome; TS, Timothy syndrome.

Table 2. Schwartz scoring system for the diagnosis of Long QT syndrome

Criteria	Points
Electrocardiographic findings^a	
QTc^a	
≥ 480 ms	3
460–479 ms	2
450–459 (male) ms	1
QTc ^b 4th minute of recovery from exercise stress test ≥ 480 ms	1
Torsade de pointes ^c	2
T-wave alternans	1
Notched T-wave in three leads	1
Low heart rate for age ^d	0.5
Clinical history	
Syncope^c	
With stress	2
Without stress	1
Congenital deafness	0.5
Family history	
Family members with definite LQTS ^e	1
Unexplained sudden cardiac death below age 30 among immediate family members ^e	0.5

LQTS SCORE: ≤ 1 point: low probability of LQTS. 1.5 to 3 points: intermediate probability of LQTS. ≥ 3.5 points high probability.

^a In the absence of medications or disorders known to affect these electrocardiographic features.

^b QTc calculated by Bazett's formula where QTc. QT/SQR(RR).

^c Mutually exclusive.

^d Resting heart rate below the 2nd percentile for age.

^e The same family member cannot be counted in A and B

Schwartz PJ, Crotti L. QTc behavior during exercise and genetic testing for the long-QT syndrome. *Circulation*. 2011;124:2181-4.

Table 3. Diagnosis of LQTS**ESC 2022 GL on VA and SCD. Recommendations for the management of patients with long QT syndrome*****Diagnosis***

LQTS is diagnosed with either QTc ≥ 480 ms in repeated 12-lead ECGs with or without symptoms or LQTS diagnostic score >3 .	I C
In patients with clinically diagnosed LQTS, genetic testing and genetic counselling.	I C
LQTS is diagnosed in the presence of a pathogenic mutation, irrespective of the QT duration.	I C
LQTS diagnosis in the presence of a QTc ≥ 460 ms and >480 ms in repeated 12-lead ECGs in patients with an arrhythmic syncope in the absence of secondary causes for QT prolongation.	IIa C
Routine diagnostic testing with epinephrine challenge is not recommended in LQTS.	III C

ESC 2022 GL on VA and SCD. Recommendations for management of patients with Andersen–Tawil syndrome***Diagnosis***

Genetic testing in patients with suspected Andersen–Tawil syndrome.	I C
Andersen–Tawil syndrome in patients without SHD who present with at least two of the following: • Prominent U waves with or without prolongation of the QT interval • Bidirectional and/or polymorphic PVCs/VT • Dysmorphic features • Periodic paralysis • KCNJ2 pathogenic loss of function mutation.	IIa C

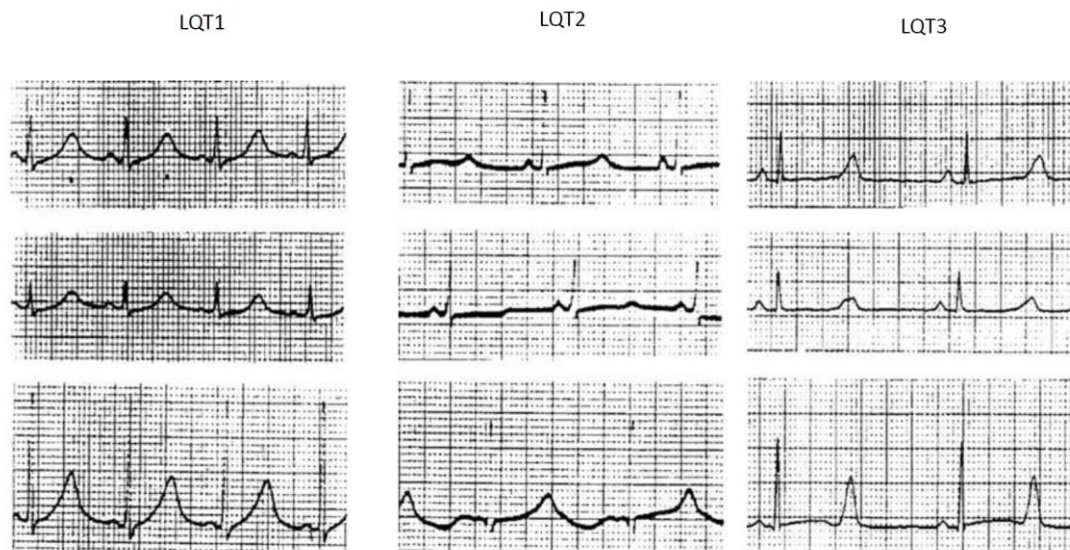


Figure 1. QT prolongation in the major three LQT syndromes.

T-wave morphology by LQTS genotype: LQT1: typical broad-based T-wave pattern (corrected QT [QTc] 570 ms); LQT2: typical bifid T-wave (QTc 583 ms); and LQT3: typical late-onset peaked/biphasic T-wave (QTc 573 ms).

Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol.* 2008;51:2291-300.

Tangent method



Threshold method

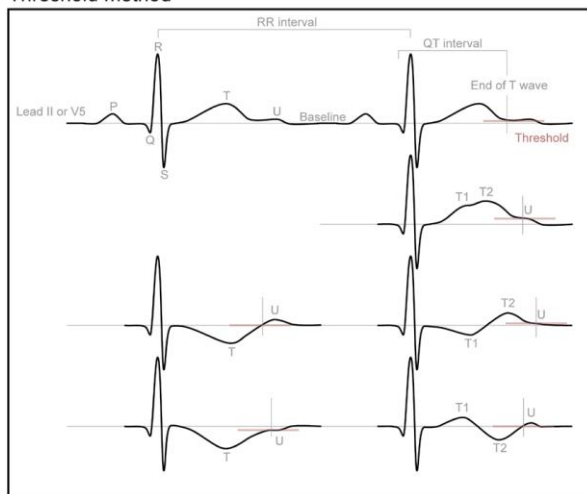


Figure 2. The tangent and threshold methods.

The second component of the T wave (T2) was included, and the U wave was excluded from QT interval analyses.

Vink AS, et al. Determination and Interpretation of the QT Interval. Comprehensive Analysis of a Large Cohort of Long QT Syndrome Patients and Controls. *Circulation*. 2018.

Table 4. Genetic testing**AHA/ACC/HRS 2017 GL on VA/SCD. Cardiac channelopathies**

Genetic counseling and genetic testing in patients with clinically diagnosed long QT syndrome I-B-NR

Genetic counseling and mutation-specific genetic testing in first-degree relatives of patients who have a causative mutation for long QT syndrome. I-B-NR

ESC 2022 GL on VA and SCD. Genetic tests and suggested work-up of probands and relatives with primary electrical diseases**Proband****Initial clinical test****Cornerstone for diagnosis**

ECG

Exercise test

Other tests/processes

Exclude acquired LQTS

Follow-up

1-3 years dependent on level of risk

Relatives**Clinical screening**

ECG

Exercise test (when feasible)

From birth

Follow-up

Positive phenotype and/or Class IV/V variant: 1-3 years dependent on level of risk

Negative phenotype and no Class IV/V variant: Discharge

*: Including neonatal genetic testing.

EHRA/HRS/APHRS/LAHRs 2022 Consensus Statement on genetic testing.**Impact of genetic testing for the index case**

Disease	Diagnostic	Prognostic	Therapeutic
LQTS	+++	+++	+++

Recommendations**Should do**

Molecular genetic testing for definitive disease associated genes (currently KCNQ1, KCNH2, SCN5A, CALM1, CALM2, and CALM3), for all index patients with a high probability diagnosis of LQTS, based on examination of the patient's clinical history, family history, and ECG characteristics obtained at baseline, during ECG Holter recording and exercise stress test (Schwartz Score ≥ 3.5 ,

Analysis of specific genes for patients with a specific diagnosis as follows: KCNQ1 and KCNE1 in patients with Jervell and Lange-Nielsen syndrome, CACNA1C in Timothy syndrome, KCNJ2 in Andersen–Tawil syndrome, and TRDN in patients suspected to have triadin knockout syndrome.

Variant-specific genetic testing for family members and appropriate relatives following the identification of the disease-causing variant.

Predictive genetic testing in related children is recommended from birth onward (any age).

May do

Analysis of CACNA1C and KCNE1 in all index patients in whom a cardiologist has established a diagnosis of LQTS with a high probability, based on examination of the patient’s clinical history, family history, and ECG characteristics obtained at baseline, during ECG Holter recording and exercise stress test (Schwartz Score ≥ 3.5).

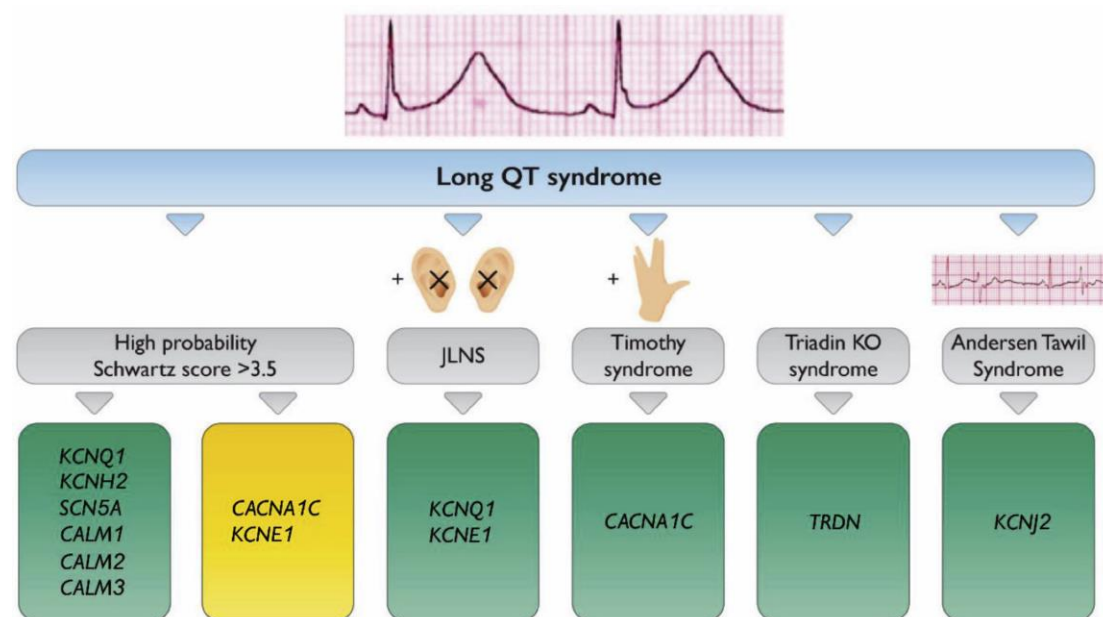


Figure 3. EHRA/HRS/APHRS/LAHS 2022 Consensus Statement on genetic testing. Clinical algorithm for genetic testing and family screening in long-QT syndrome.

Table 5. Therapy of long QT syndrome.**AHA/ACC/HRS 2017 GL on VA/SCD**

ICD* in patients with a sudden cardiac arrest.	I-B-NR
A beta blocker in resting QTc > 470 ms	I-B-NR
Additional medications (guided by consideration of the particular LQTS type), left cardiac sympathetic denervation, and/or an ICD, in high-risk patients with symptomatic long QT syndrome in whom a beta blocker is ineffective or not tolerated.	I-B-NR
Additional medications (guided by consideration of according to the particular LQTS type) or left cardiac sympathetic denervation, in patients with recurrent appropriate ICD shocks.	I-B-NR
Ambulatory ECG monitoring, recording the ECG lying and immediately on standing, and/or exercise treadmill testing for establishing a diagnosis and monitoring the response to therapy in suspected LQTS.	IIa-B-NR
Chronic therapy with a beta blocker in patients with LQTS and a resting QTc <470 ms	IIa-B-NR
Left cardiac sympathetic denervation or an ICD in asymptomatic patients and a resting QTc >500 ms while receiving a beta blocker.	IIb-B-NR
QT-prolonging medications	III-B-NR Harm

*If meaningful survival of greater than 1 year is expected

ACC/AHA/HRS 2017 GL on syncope. LQTS

Beta-blocker therapy, in the absence of contraindications, as a first-line therapy in patients with LQTS and suspected arrhythmic syncope	I-B-NR
ICD implantation in patients with LQTS and suspected arrhythmic syncope who are on beta-blocker therapy or are intolerant to beta-blocker therapy	IIa-B-NR
Left cardiac sympathetic denervation (LCSD) in patients with LQTS and recurrent syncope of suspected arrhythmic mechanism who are on beta-blocker therapy or are intolerant to beta-blocker therapy	IIa-C-LD

ESC 2022 GL on VA and SCD. Recommendations for the management of patients with long QT syndrome

General recommendations to prevent SCD

The following is recommended in LQTS: I C

- Avoid QT-prolonging drugs.^a
- Avoid and correct electrolyte abnormalities.
- Avoid genotype-specific triggers for arrhythmias.

Beta-blockers, ideally non-selective beta-blockers (nadolol or propranolol), in LQTS patients with documented QT interval prolongation, to reduce risk of arrhythmic events. I B

Mexiletine in LQT3 patients with a prolonged QT interval. I C

Beta-blockers in patients with a pathogenic mutation and a normal QTc interval. IIa B

Risk stratification, prevention of SCD and treatment of VA ICD implantation in addition to beta-blockers in LQTS patients with CA. I B

ICD implantation in patients with LQTS who are symptomatic^b while receiving beta-blockers and genotype-specific therapies. I C

LCSD in patients with symptomatic^b LQTS when: I C
(a) ICD therapy is contraindicated or declined;
(b) patient is on beta-blockers and genotype-specific drugs with an ICD and experiences multiple shocks or syncope due to VA.

Either ICD or LCSD in patients with symptomatic^b LQTS, when beta-blockers and genotype-specific therapies are not tolerated or contraindicated at the therapeutic dose. IIa C

In LQTS, calculate the arrhythmic risk before initiation of therapy based on the genotype and the duration of QTc interval. IIa C

ICD in asymptomatic LQTS patients with high-risk profile (according to the 1-2-3 LQTS Risk calculator) in addition to genotype-specific medical therapies (mexiletine in LQT3 patients). IIb B

Invasive electrophysiologic study is not recommended in LQTS. III C

CA, cardiac arrest; ECG, electrocardiogram; ICD, implantable cardioverter defibrillator; LCSD, left cardiac sympathetic denervation; LQTS, long QT syndrome; SCD, sudden cardiac death; VA, ventricular arrhythmia.

^a <http://www.crediblemeds.org>

^b Arrhythmic syncope or haemodynamically non-tolerated VA.

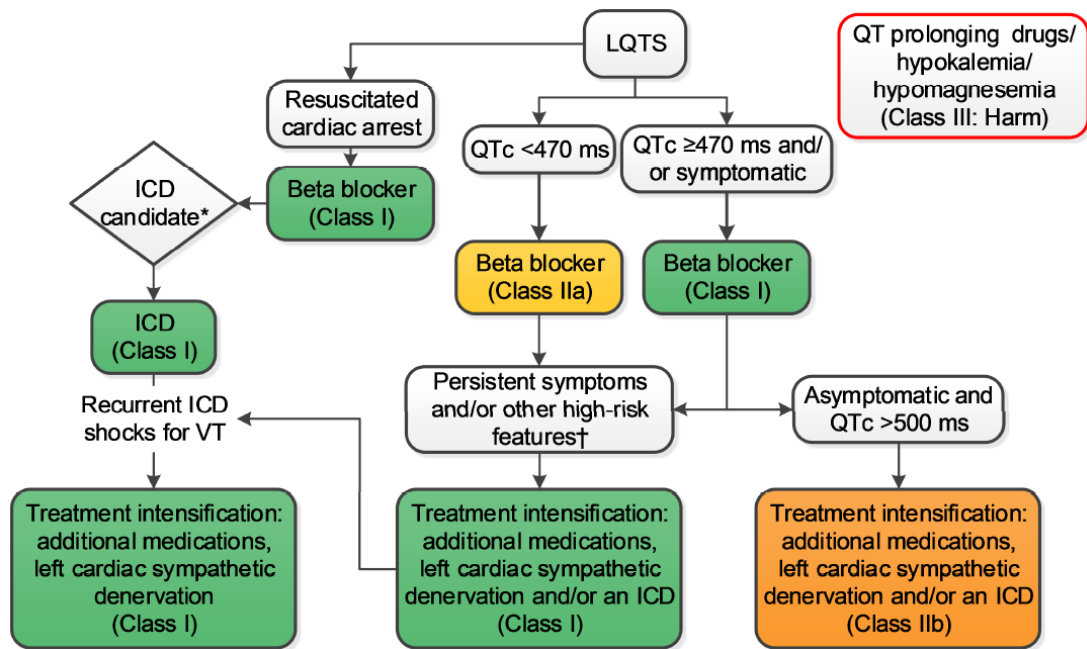


Figure 4. AHA/ACC/HRS 2017 GL on VA/SCD. Prevention of SCD in Patients With Long QT Syndrome

*ICD candidacy as determined by functional status, life expectancy, or patient preference.

†High-risk patients with LQTS include those with QTc >500 ms, genotypes LQT2 and LQT3, females with genotype LQT2, <40 years of age, onset of symptoms at <10 years of age, and patients with recurrent syncope.

ICD indicates implantable cardioverter-defibrillator; LQTS, long-QT syndrome; VT, ventricular tachycardia.

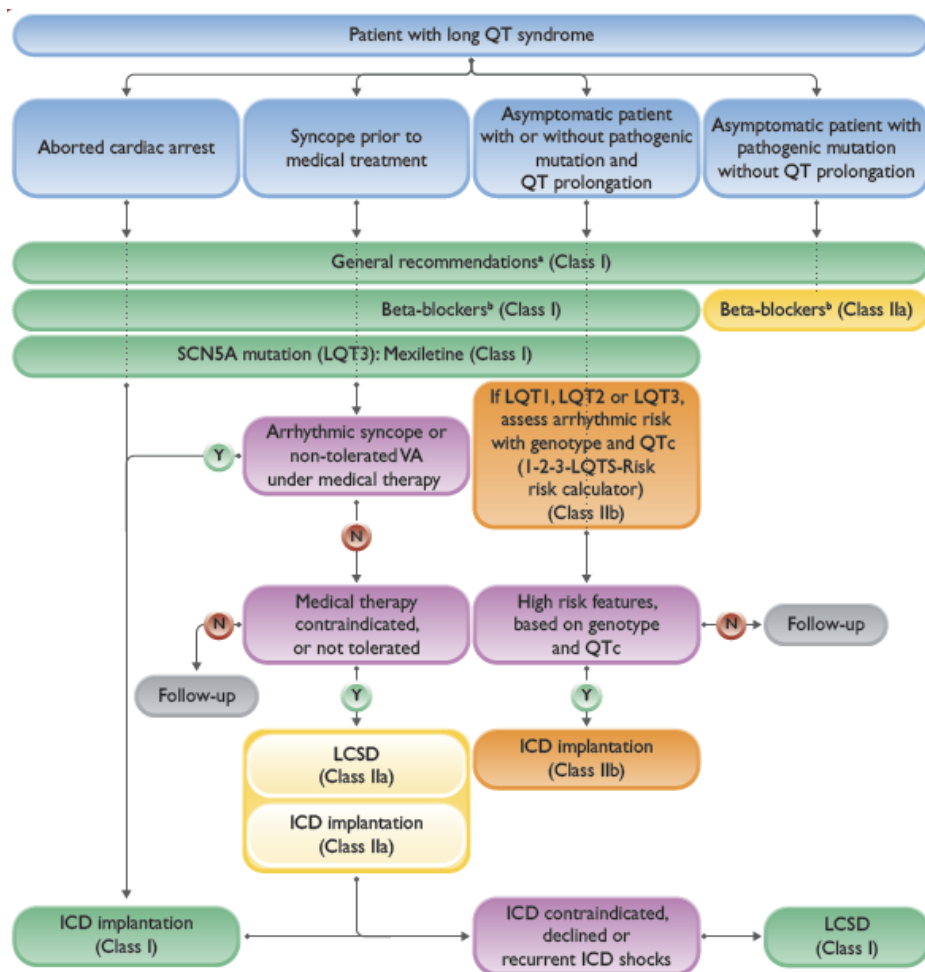


Figure 5. ESC 2022 GL on VA and SCD. Algorithm for the management of patients with long QT syndrome.

ICD, implantable cardioverter defibrillator; LCSD, left cardiac sympathetic denervation; LQT, long QT; N, No; VA, ventricular arrhythmia; Y, Yes.

a General recommendations: avoidance of QT-prolonging drugs (<http://www.crediblemeds.org>), correction of electrolyte abnormalities (hypokalaemia, hypomagnesaemia, and hypocalcaemia), avoidance of genotype-specific triggers for arrhythmias (strenuous swimming in LQT1, exposure to loud noises in LQT2).

b Preferred beta-blockers: nadolol and propranolol.

Table 6. ESC 2022 GL on VA and SCD. Recommendations for management of patients with Andersen–Tawil syndrome

Risk stratification, prevention of SCD and treatment of VA

ICD implantation in patients with Andersen–Tawil syndrome after aborted CA or not-tolerated sustained VT.	I C
Beta-blockers and/or flecainide with or without acetazolamide in patients with Andersen–Tawil syndrome to treat VA.	IIa C
An ILR in patients with Andersen–Tawil syndrome and unexplained syncope.	IIa C
ICD in patients with Andersen–Tawil syndrome who have a history of unexplained syncope or suffer from tolerated sustained VT.	IIb C

CA, cardiac arrest; ICD, implantable cardioverter defibrillator; ILR, implantable loop recorder; PVCs, premature ventricular complexes; SCD, sudden cardiac death; SHD, structural heart disease; VA, ventricular arrhythmia; VT, ventricular tachycardia.

Table 7. ESC 2020 GL on Sports. Recommendations for exercise in long QT syndrome

All exercising individuals with LQTS with prior symptoms or prolonged QTc should be on therapy with beta-blockers at target dose.	I B
Exercising individuals with LQTS should avoid QT prolonging drugs (www.crediblemeds.org) and electrolyte imbalances such as hypokalaemia and hypomagnesaemia.	I B
Shared decision making regarding sports participation in patients with genotype-positive/phenotype-negative LQTS (i.e. <470/480 ms in men/women). Type and setting of sports (individual vs. team), type of mutation, and extent of precautionary measures should be considered in this context.	IIa C
Participation in high-intensity recreational and competitive sports, even when on beta-blockers, is not recommended in individuals with a QTc>500 ms or a genetically confirmed LQTS with a QTc>_470 ms in men or >_480 ms in women.	III B
Participation in competitive sports (with or without ICD) is not recommended in individuals with LQTS and prior cardiac arrest or arrhythmic syncope.	III C

ICD = implantable cardioverter defibrillator; LQTS = long QT syndrome.

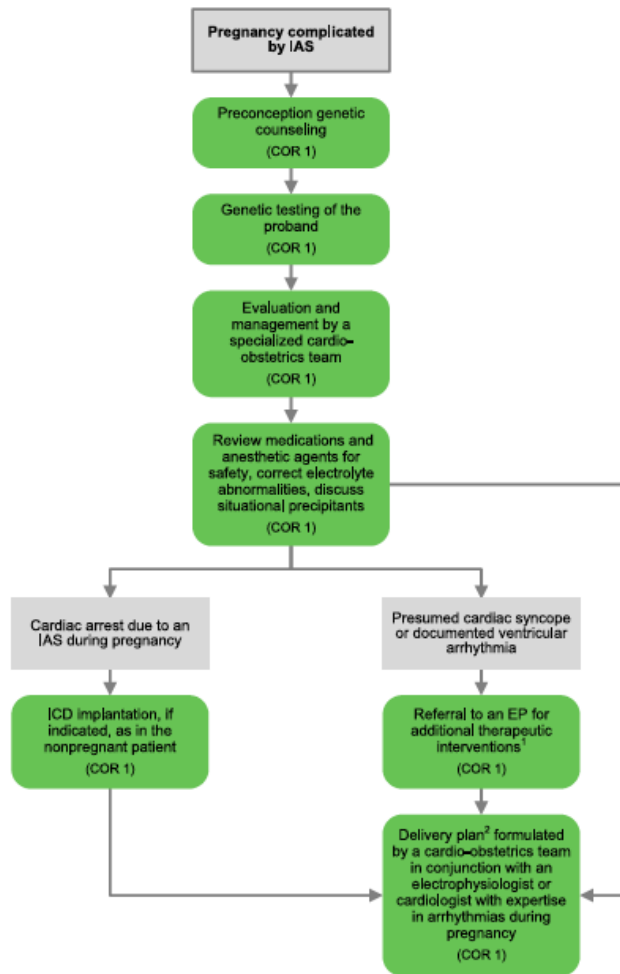


Figure 6. 2023 HRS expert consensus statement on the management of arrhythmias during pregnancy. Algorithm for the evaluation and management of pregnancies complicated by inherited arrhythmia syndromes (IAS).

1 Therapeutic interventions include escalation of pharmacological therapy and possible implantable cardioverter defibrillator (ICD) implantation.

2 Delivery plan may include continuous electrocardiogram monitoring in accordance with the level of risk and delivery at a facility capable of advanced cardiac life support for pregnancy.

EP: electrophysiologist.

Table 8. ESC 2025 GL on pregnancy. Long QT syndrome

Beta-blockers ^c , with pre-pregnancy dose and with nadolol and propranolol as drugs of choice, are recommended during pregnancy in women with LQTS. ^{312-316,335}	I	B
It is recommended to continue beta-blocker therapy during lactation in women with LQTS to reduce arrhythmic risk. ^{148,336}	I	B
Pre-pregnancy beta-blocker dose of nadolol or propranolol, is recommended in women with LQT2, particularly in the post-partum period, which represents a high-risk period for life-threatening arrhythmias. ^{148,313,315}	I	B
In women carrying a LQTS P/LP variant and who are phenotype-negative, use of beta-blockers ^c during pregnancy, post-partum, and lactation should be considered. ¹⁴⁸	IIa	C
Left cardiac sympathetic denervation should be considered before pregnancy in high-risk woman with LQTS who are not adequately protected by pharmacological therapies or who have appropriate ICD shocks despite optimal medical therapy. ²⁵²	IIa	C

LQT2, long QT syndrome type 2; P/LP, pathogenic/likely pathogenic;