Update in inherited arrhythmia

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COI Disclosure

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ESC GUIDELINES

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC)

Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC)

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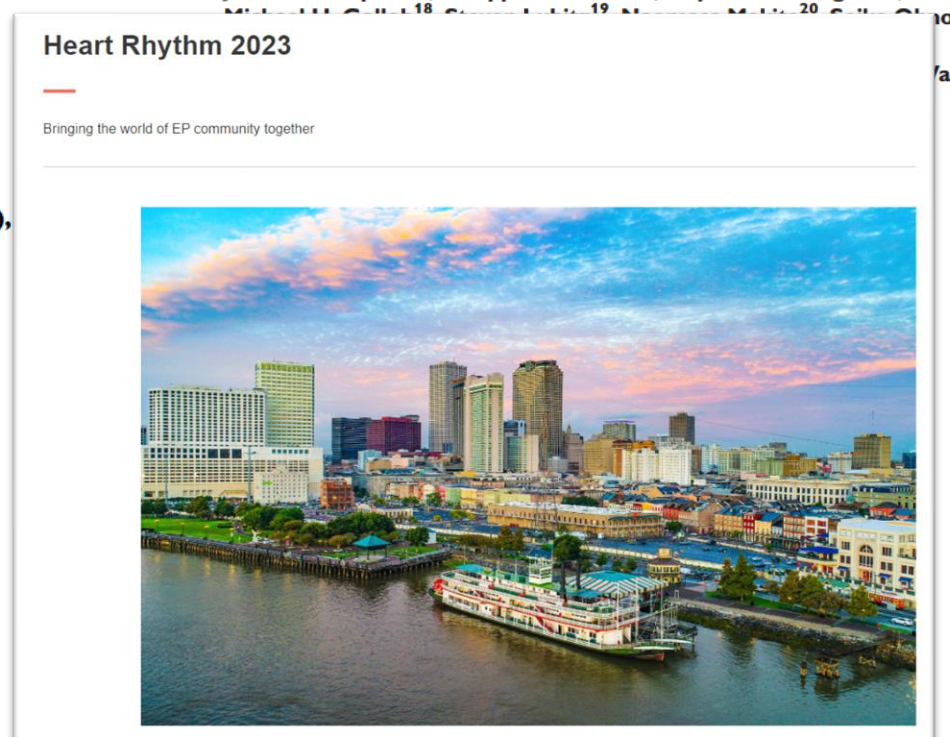
POSITION PAPER

European Heart Rhythm Association (EHRA)/ Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases

Arthur A. M. Wilde (EHRA Chair)[1,*,†,‡,¶], Christopher Semsarian (APHRS Co-Chair)[2,*,†], Manlio F. Márquez (LAHRS Co-Chair)[3,*,†], Alireza Sepehri Shamloo[4], Michael J. Ackerman[5], Euan A. Ashley[6], Eduardo Back Sternick[7], Héctor Barajas-Martinez[8], Elijah R. Behr[9,¶], Connie R. Bezzina[11,‡], Jeroen Breckpot[12,‡], Philippe Charron[13,‡], Priya Chockalingam[14], Lia Crotti[15,16,17,‡,¶],



KHRS 2023

Changes in recommendations since 2015 ESC guideline

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Changes in recommendations since 2015

Primary electrical disease and selected populations	2015	2022
ICD implantation is recommended in patients with LQTS who are symptomatic[b] while receiving beta-blockers and genotype-specific therapies.	IIa	I
ICD implantation should be considered in patients with CPVT who experience arrhythmic syncope and/or documented bidirectional/PVT while on the highest tolerated beta-blocker dose and on flecainide.	I	IIa
Pre-participation cardiovascular evaluation of competitive athletes should be considered.	I	IIa
Catheter ablation of triggering PVCs and/or RVOT epicardial substrate should be considered in BrS patients with recurrent appropriate ICD shocks refractory to drug therapy.	IIb	IIa
LCSD should be considered in patients with diagnosis of CPVT when the combination of beta-blockers and flecainide at therapeutic dosage are either not effective, not tolerated, or contraindicated.	IIb	IIa

New recommendations in 2022

Newly added diseases

Idiopathic VF	
It is recommended that idiopathic VF is diagnosed in a SCA survivor, preferably with documentation of VF, after exclusion of an underlying structural, channelopathic, metabolic, or toxicological aetiology.	I
Isoproterenol infusion, verapamil, or quinidine for acute treatment of an electrical storm or recurrent ICD discharges should be considered in idiopathic VF.	IIa
Quinidine should be considered for chronic therapy to suppress an electrical storm or recurrent ICD discharges in idiopathic VF.	IIa
Clinical testing (history, ECG, and high precordial lead ECG, exercise test, echocardiogram) of first-degree family members of idiopathic VF patients may be considered.	IIb
In idiopathic VF patients, genetic testing of genes related to channelopathy and cardiomyopathy may be considered.	IIb
Long QT syndrome	
In patients with clinically diagnosed LQTS, genetic testing, and genetic counselling are recommended.	I
Beta-blockers, ideally non-selective beta-blockers (nadolol or propranolol), are recommended in LQTS patients with documented QT interval prolongation, to reduce risk of arrhythmic events.	I
Mexiletine is indicated in LQT3 patients with a prolonged QT interval.	I
In LQTS, it should be considered to calculate the arrhythmic risk before initiation of therapy based on the genotype and the duration of QTc interval.	IIa
ICD implantation may be considered 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
Routine diagnostic testing with epinephrine challenge is not recommended in LQTS.	III

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

Brugada syndrome	
Genetic testing for *SCN5A* gene is recommended for probands with BrS.	I
BrS should be considered in patients with no other heart disease and induced type 1 Brugada pattern who have at least one of the following: • Arrhythmic syncope or nocturnal agonal respiration • A family history of BrS • A family history of SD (<45 years old) with a negative autopsy and circumstance suspicious for BrS	IIa

Early repolarization syndrome	
It is recommended that the ERP is diagnosed as J-point elevation of ≥1 mm in two adjacent inferior and/or lateral ECG leads.	I
It is recommended that the ERS is diagnosed in a patient resuscitated from unexplained VF/PVT in the presence of ERP.	I

CPVT	
Genetic testing and genetic counselling are indicated in patients with clinical suspicion or clinical diagnosis of CPVT.	I
Beta-blockers, ideally non-selective (nadolol or propranolol) are recommended in all patients with a clinical diagnosis of CPVT.	I
Epinephrine or isoproterenol challenge may be considered for the diagnosis of CPVT when an exercise test is not possible.	IIb
Short QT syndrome	
Genetic testing is indicated in patients diagnosed with SQTS.	I
SQTS should be considered in the presence of a QTc ≤320 ms.	IIa
SQTS should be considered in the presence of a QTc ≥320 ms and ≤360 ms and arrhythmic syncope.	IIa
ILR should be considered in young SQTS patients.	IIa

2022 ESC guideline for prevention of VA and SCD

Diagnosis

Recommendations	Class[a]	Level[b]
Diagnosis		
It is recommended that 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 are recommended.	I	C
It is recommended that LQTS is diagnosed in the presence of a pathogenic mutation, irrespective of the QT duration.	I	C
The LQTS diagnosis should be considered 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.[952,962,963]	IIa	C
Routine diagnostic testing with epinephrine challenge is not recommended in LQTS.	III	

Genetic testing and counselling (Class I) : new

Arrhythmic syncope & 460≤QTc<480 in repeated ECGs : LQTS

2022 ESC guideline for prevention of VA and SCD

General recommendation to prevent SCD

The following is recommended in LQTS: • Avoid QT-prolonging drugs.[c] • Avoid and correct electrolyte abnormalities. • Avoid genotype-specific triggers for arrhythmias.[943]	I	C
Beta-blockers, ideally non-selective beta-blockers (nadolol or propranolol), are recommended in LQTS patients with documented QT interval prolongation, to reduce risk of arrhythmic events.[940,945,946]	I	B
Mexiletine is indicated in LQT3 patients with a prolonged QT interval.[948]	I	C
Beta-blockers should be considered in patients with a pathogenic mutation and a normal QTc interval.[82]	IIa	B
Risk stratification, prevention of SCD and treatment of VA		
ICD implantation in addition to beta-blockers is recommended in LQTS patients with CA.[952,953,962,963]	I	B
ICD implantation is recommended in patients with LQTS who are symptomatic[d] while receiving beta-blockers and genotype-specific therapies.	I	C

IIa (2015) → I (2022)

Nonselective BB (nadolol or propranolol)

Mexiletine in LQTS 3 with a prolonged QT
(IIb in 2015 ESC guideline)

LCSD is indicated in patients with symptomatic[d] LQTS when: (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.[541,957–959]	I	C

IIa (2015) → I (2022)

In LQTS, it should be considered to calculate the arrhythmic risk before initiation of therapy based on the genotype and the duration of QTc interval.[940]	IIa	C

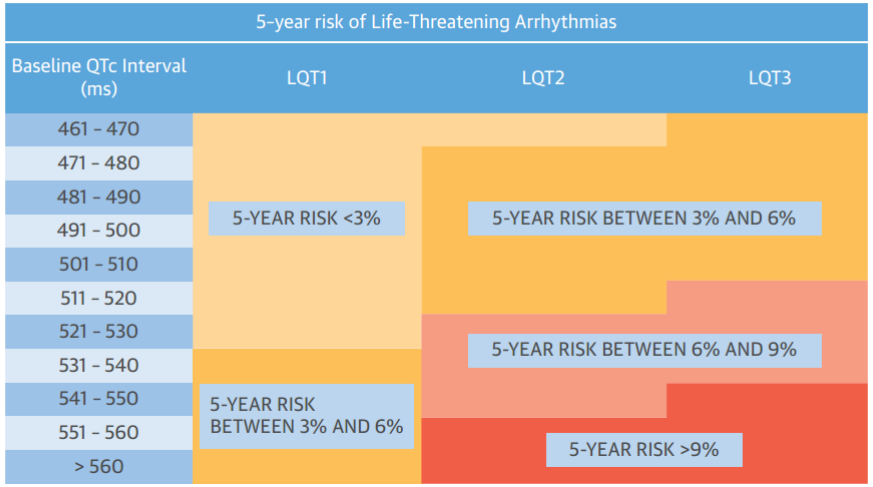
Arrhythmic risk score

Arrhythmic risk score in LQTS

Interplay Between Genetic Substrate, QTc Duration, and Arrhythmia Risk in Patients With Long QT Syndrome

Andrea Mazzanti, MD,[a,b] Riccardo Maragna, MD,[a] Gaetano Vacanti, MD,[a] Nicola Monteforte, MD,[a] Raffaella Bloise, MD,[a] Maira Marino, RN,[a] Lorenzo Braghieri, MD,[a] Patrick Gambelli, BSc,[a] Mirella Memmi, BSc,[a] Eleonora Pagan, MSc,[c] Massimo Morini, DEng,[a,d] Alberto Malovini, BSc,[a] Martin Ortiz, MD,[e] Luciana Sacilotto, MD,[a] Riccardo Bellazzi, PhD,[d] Lorenzo Monserrat, MD, PhD,[e] Carlo Napolitano, MD, PhD,[a] Vincenzo Bagnardi, PhD,[c] Silvia G. Priori, MD, PhD[a,b,f]

FIGURE 2 5-Year Risk of Life-Threatening Arrhythmic Events by Genotype for Each 10-ms Increment of QTc Duration for Patients Are Not Receiving Beta-Blockers



5-year risk of life-threatening arrhythmia based on genotype (1,2,3) and QTc interval

J Am Coll Cardiol 2018;71:1663–71

ESC European Society of Cardiology
Europace (2022) 24, 614–619
doi:10.1093/europace/euab238

CLINICAL RESEARCH
Long QT syndrome

Independent validation and clinical implications of the risk prediction model for long QT syndrome (1-2-3-LQTS-Risk)

Andrea Mazzanti [1,2,3], Alessandro Trancuccio [1,2,3], Deni Kukavica [1,2,3], Eleonora Pagan [4], Meng Wang[5], Muhammad Mohsin[1], Derick Peterson[5], Vincenzo Bagnardi[4], Wojciech Zareba [6]*, and Silvia G. Priori [1,2,3]*

- N=1689
- C-index of 0.69 [95% CI: 0.61–0.77]

Risk score derivation

Based on the multivariable analysis already published in our previous work,[4] we derived the equation to calculate the individual 5-year risk of experiencing an LAE based on (i) genotype and (ii) QTc interval duration:

$$\hat{P}_{LAE\ at\ 5\ years} = 100 \times (1 - 0.9849143482^{\exp(Prognostic\ Index)}),$$

where Prognostic Index = 0.01365×(QTc−469.9075194) + 0.83454×LQT2 + 0.94523×LQT3.

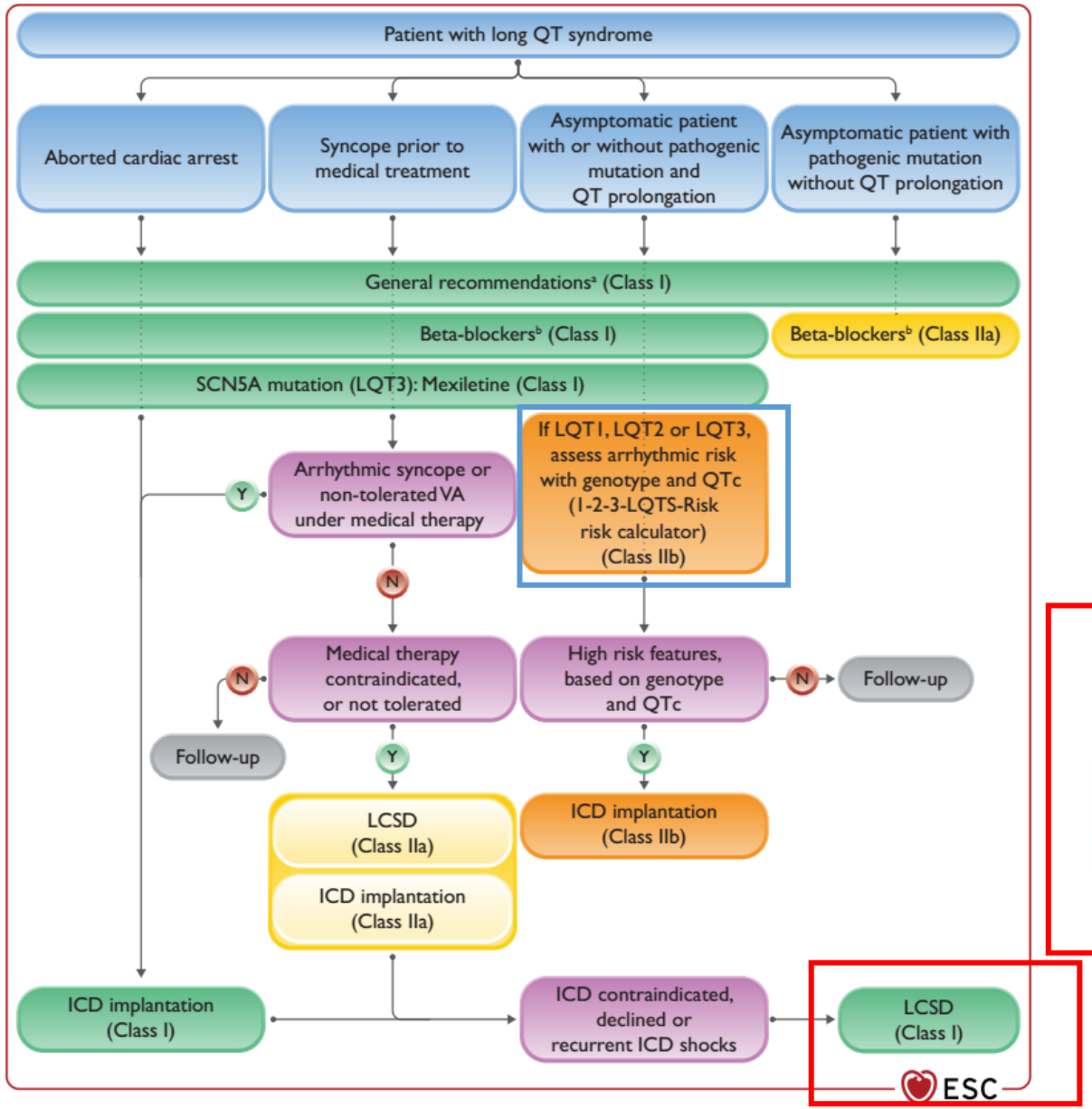
- 5 year risk more than 5% as the most balanced cut-off for ICD implantation.

Table 2 Simulating choice of the most balanced cut-off for 5-year-risk threshold calculated using 1-2-3-LQTS-Risk model for ICD implantation in 1710 LQTS patients of the Pavia cohort

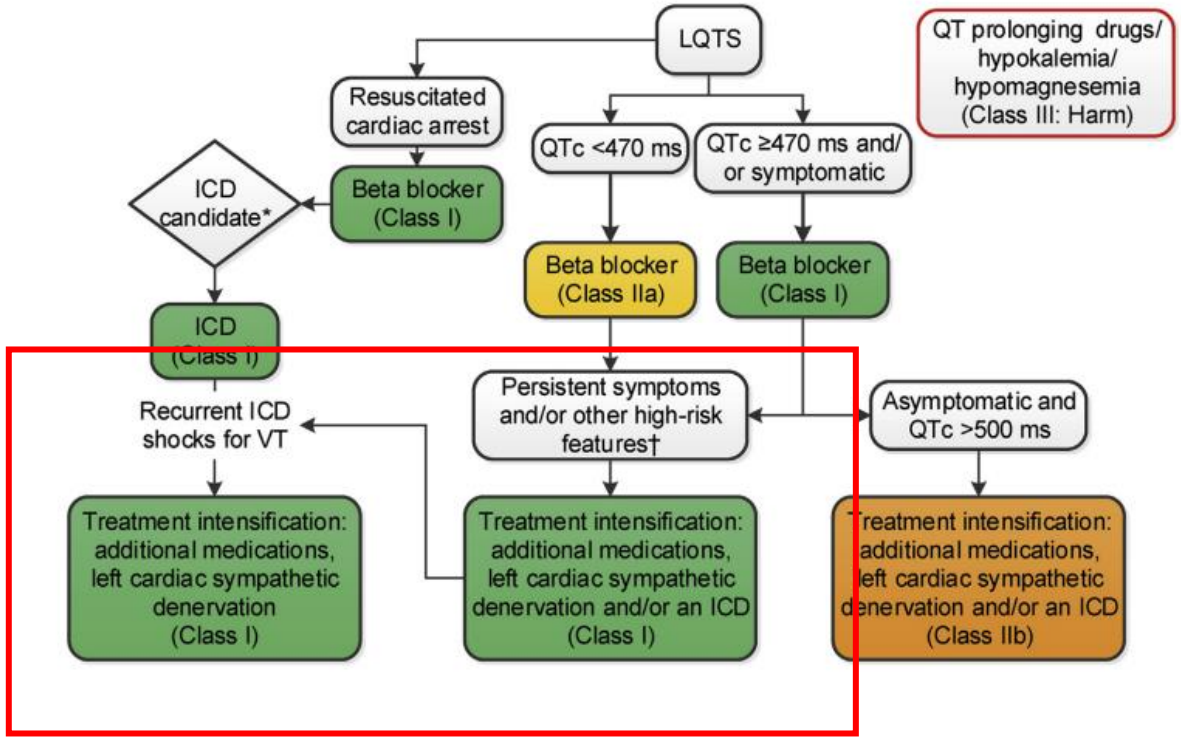
Cut-off for ICD implantation	LAE at 5 years (n = 43)		No LAE at 5 years (n = 1667)		NNT (95% CI)
	ICD	No ICD	ICD	No ICD	
5-Year risk ≥3%	35 (81%)	8 (19%)	531 (32%)	1136 (68%)	19 (13.3–29.1)
5-Year risk ≥4%	32 (74%)	11 (26%)	327 (20%)	1340 (80%)	13 (9.0–19.6)
5-Year risk ≥5%	**30 (70%)**	**13 (30%)**	**211 (13%)**	**1456 (87%)**	**9 (6.3–13.6)**
5-Year risk ≥6%	24 (56%)	19 (44%)	146 (9%)	1521 (91%)	8 (5.5–13.1)
5-Year risk ≥7%	21 (49%)	22 (51%)	106 (6%)	1561 (94%)	7 (4.6–11.5)

Europace 2022;24:614-619

1. Long QT syndrome



2022 ESC guideline



2017 AHA guideline

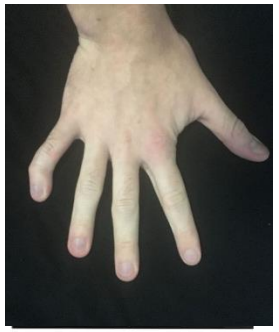
Andersen-Tawil syndrome

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

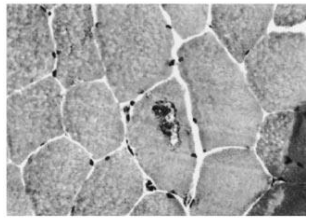
- **LQTS 7**
- KCNJ2 mutation: KCNJ2, encodes inward rectifying potassium channel Kir2.1
- prominent U wave
- Ventricular arrhythmia (bidirectional VT)
- Dysmorphologies and periodic paralysis

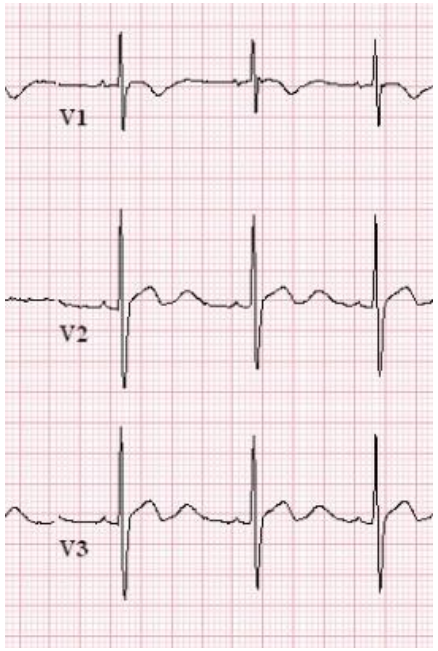

(A)


(B)


(C) Clinodactyly

(D)


(E)



2022 ESC guideline for prevention of VA and SCD

Diagnosis

Diagnosis		
It is recommended that CPVT is diagnosed in the presence of a structurally normal heart, normal ECG, and exercise- or emotion-induced bidirectional, or PVT.	I	C
It is recommended that CPVT is diagnosed in patients who are carriers of a mutation in disease-causing genes.	I	C
Genetic testing and genetic counselling are indicated in patients with clinical suspicion or clinical diagnosis of CPVT.	I	C
Epinephrine or isoproterenol challenge may be considered for the diagnosis of CPVT when an exercise test is not possible.	IIb	C

New recommendations in ESC guideline
IIa in 2017 HRS guideline

Table 7 Genes implicated in catecholamine polymorphic ventricular tachycardia (CPVT)

Gene	Locus	Phenotype—syndrome	Protein (functional effect)	Frequency	ClinGen classification
RyR2	1q43	CPVT/AD	RyR2 (↑); inappropriate Ca^{2+} release from the SR	60–70%	Definite
CASQ2	1p13.1	CPVT/AR	Inappropriate Ca^{2+} release from the SR	±5%	Definite
CASQ2	1p13.1	CPVT/AD	Inappropriate Ca^{2+} release from the SR	±5%	Moderate
CALM 1–3	14q32.11 2p21 19q13.32	CPVT/AD	↑ RyR2 binding affinity resulting in inappropriate Ca^{2+} release from the SR	<1%	Strong
TECRL[a]	4q13.1	CPVT/AR	Altered Ca^{2+} homeostasis, possibly linked to fatty acid/lipid metabolism	<1%	Definite
TRDN[a]	6q22.31	CPVT/AR	↓ expression leading to remodelling of the cardiac dyad/calcium release unit	<1%	Definite
KCNJ2	17q24.3	ATS/AD	Loss-of-I_{K1} channel function	<1%	Definite

2022 ESC guideline for prevention of VA and SCD
2022 EHRA/HRS expert consensus on the state of genetic testing for cardiac diseases

2. CPVT

Therapeutic interventions		
Beta-blockers, ideally non-selective (nadolol or propranolol) are recommended in all patients with a clinical diagnosis of CPVT.[1045,1048,1059]	I	C
ICD implantation combined with beta-blockers and flecainide is recommended in CPVT patients after aborted CA.[1045,1047,1060]	I	C
Therapy with beta-blockers should be considered for genetically positive CPVT patients without phenotype.[1047,1050]	IIa	C
LCSD should be considered in patients with diagnosis of CPVT when the combination of beta-blockers and flecainide at therapeutic dosage are either not effective, not tolerated, or contraindicated.[1056]	IIa IIb → IIa	C
ICD implantation should be considered in patients with CPVT who experience arrhythmogenic syncope and/or documented bidirectional/PVT while on highest tolerated beta-blocker dose and on flecainide.[1047,1050]	IIa I → IIa	C
Flecainide should be considered in patients with CPVT who experience recurrent syncope, polymorphic/bidirectional VT, or persistent exertional PVCs, while on beta-blockers at the highest tolerated dose.[1052,1053,1060]	IIa	C

022

Nonselective BB (nadolol or propranolol)

Patients with aborted cardiac arrest
→ ICD implantation with BB+ flecainide

New recommendation :
Left Cardiac sympathetic denervation
(previously IIb in ESC, I as tx intensification in 2017 HRS)

Recommendations for Catecholaminergic Polymorphic Ventricular Tachycardia
References that support the recommendations are summarized in Online Data Supplement 41.

COR	LOE	Recommendations
I	B-NR	1. In patients with catecholaminergic polymorphic ventricular tachycardia, a beta blocker is recommended (S6.9.1.2-1,S6.9.1.2-2).
I	B-NR	2. In patients with catecholaminergic polymorphic ventricular tachycardia and recurrent sustained VT or syncope, while receiving adequate or maximally tolerated beta blocker, treatment intensification with either combination medication therapy (e.g., beta blocker, flecainide), left cardiac sympathetic denervation, and/or an ICD is recommended (S6.9.1.2-2—S6.9.1.2-6).
IIa	B-NR	3. In patients with catecholaminergic polymorphic ventricular tachycardia and with clinical VT or exertional syncope, genetic counseling and genetic testing are reasonable (S6.9.1.2-7).

2022 ESC guideline for VA and SCD
2017 HRS guideline for VA and SCD

KHRS 2023

Diagnosis

Diagnosis		
It is recommended that BrS is diagnosed in patients with no other heart disease and a spontaneous type 1 Brugada ECG pattern.[974–976]	I	C
It is recommended that BrS is diagnosed in patients with no other heart disease who have survived a CA due to VF or PVT and exhibit a type 1 Brugada ECG induced by sodium channel blocker challenge or during fever.[135,136,975,981,982]	I	C
Genetic testing for *SCN5A* gene is recommended for probands with BrS.[164,1016]	I	C
BrS should be considered in patients with no other heart disease and induced type 1 Brugada pattern who have at least one of: • Arrhythmic syncope or nocturnal agonal respiration • A family history of BrS • A family history of SD (<45 years old) with a negative autopsy and circumstance suspicious for BrS.	IIa	C

- Spontaneous type 1 Brugada ECG pattern (I, C)
- Induced type 1 Brugada ECG + cardiac arrest d/t VF (I, C)
- Induced type I Brugada
  + arrhythmic syncope or nocturnal agonal respiration
  + FHx of Brs
  + FHx of SCD (<45 years old) (IIa, C)
- Genetic testing of SCN5A is recommended (I,C)
  - genetic yield 20%

Table 8 Gene implicated in Brugada syndrome

Gene	Locus	Phenotype—syndrome	Protein (functional effect)	Frequency	ClinGen c
SCN5A	3p22.2	BrS/AD	Loss of $I_{Na1.5}$ channel function	15–30%	Definite

BrS may be considered as a diagnosis in patients with no other heart disease who exhibit an induced type 1 Brugada ECG.[136,973,975,978,984,985]	IIb	C

2022 ESC guideline for prevention of VA and SCD

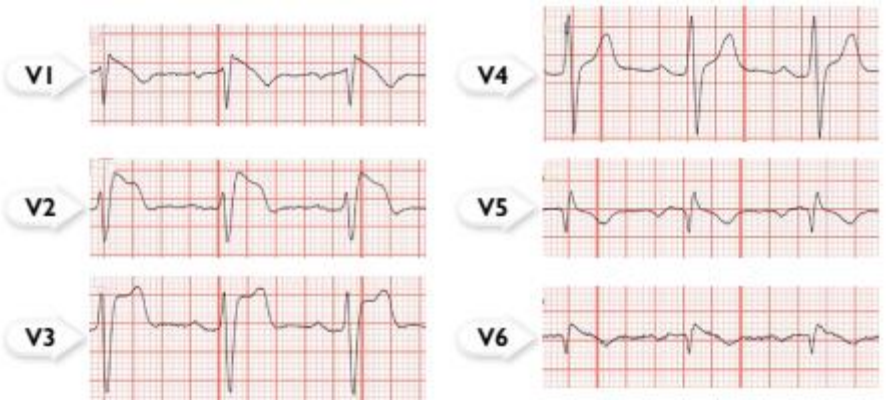
Risk stratification, prevention of SCD

Risk stratification, prevention of SCD and treatment of VA		
ICD implantation is recommended in patients with BrS who: (a) Are survivors of an aborted CA and/or (b) Have documented spontaneous sustained VT.[980,990–992]	I	C
ICD implantation should be considered in patients with type 1 Brugada pattern and an arrhythmic syncope.[990,992,996]	IIa	C
Implantation of a loop recorder should be considered in BrS patients with an unexplained syncope.[997,999]	IIa	C
Quinidine should be considered in patients with BrS who qualify for an ICD but have a contraindication, decline, or have recurrent ICD shocks.[922,1006,1007]	IIa	C
Isoproterenol infusion should be considered in BrS patients suffering electrical storm.[1008]	IIa	C
Catheter ablation of triggering PVCs and/or RVOT epicardial substrate should be considered in BrS patients with recurrent appropriate ICD shocks refractory to drug therapy.[1010–1015]	IIa	C

New

IIb → IIa

PES may be considered in asymptomatic patients with a spontaneous type I BrS ECG.[155]	IIb	B
ICD implantation may be considered in selected asymptomatic BrS patients with inducible VF during PES using up to 2 extra stimuli.[155]	IIb	C
Catheter ablation in asymptomatic BrS patients is not recommended.	III	C



2022 ESC guideline for prevention of VA and SCD

Diagnosis

Diagnosis		
It is recommended that the ERP is diagnosed as J-point elevation of ≥1 mm in two adjacent inferior and/or lateral ECG leads.[1017,1018]	I	C
It is recommended that the ERS is diagnosed in a patient resuscitated from unexplained VF/PVT in the presence of ERP.[1017,1018]	I	C
In an SCD victim with a negative autopsy and medical chart review, and an ante-mortem ECG demonstrating the ERP, the diagnosis of ERS should be considered.[1017,1018]	IIa	C
First-degree relatives of ERS patients should be considered for clinical evaluation for ERP with additional high-risk features.[c,1022,1037]	IIa	B

ER pattern

Genetic testing in ERS patients may be considered.[1023,1025]	IIb	C
Clinical evaluation is not recommended routinely in asymptomatic subjects with ERP.[1038,1039]	III	C
Risk stratification, prevention of SCD and treatment of VA		
ICD implantation is recommended in patients with a diagnosis of ERS who have survived a CA.[1017]	I	B
Isoproterenol infusion should be considered for ERS patients with electrical storm.[1017,1030–1032]	IIa	B
Quinidine in addition to an ICD should be considered for recurrent VF in ERS patients.[922,1030,1033]	IIa	B
ILR should be considered in individuals with ERP and at least one risk feature[d] or arrhythmic syncope.[1020]	IIa	C
PVC ablation should be considered in ERS patients with recurrent VF episodes triggered by a similar PVC non-responsive to medical treatment.[1010]	IIa	C
ICD implantation or quinidine may be considered in individuals with ERP and arrhythmic syncope and additional risk features.[d,1030,1033]	IIb	C

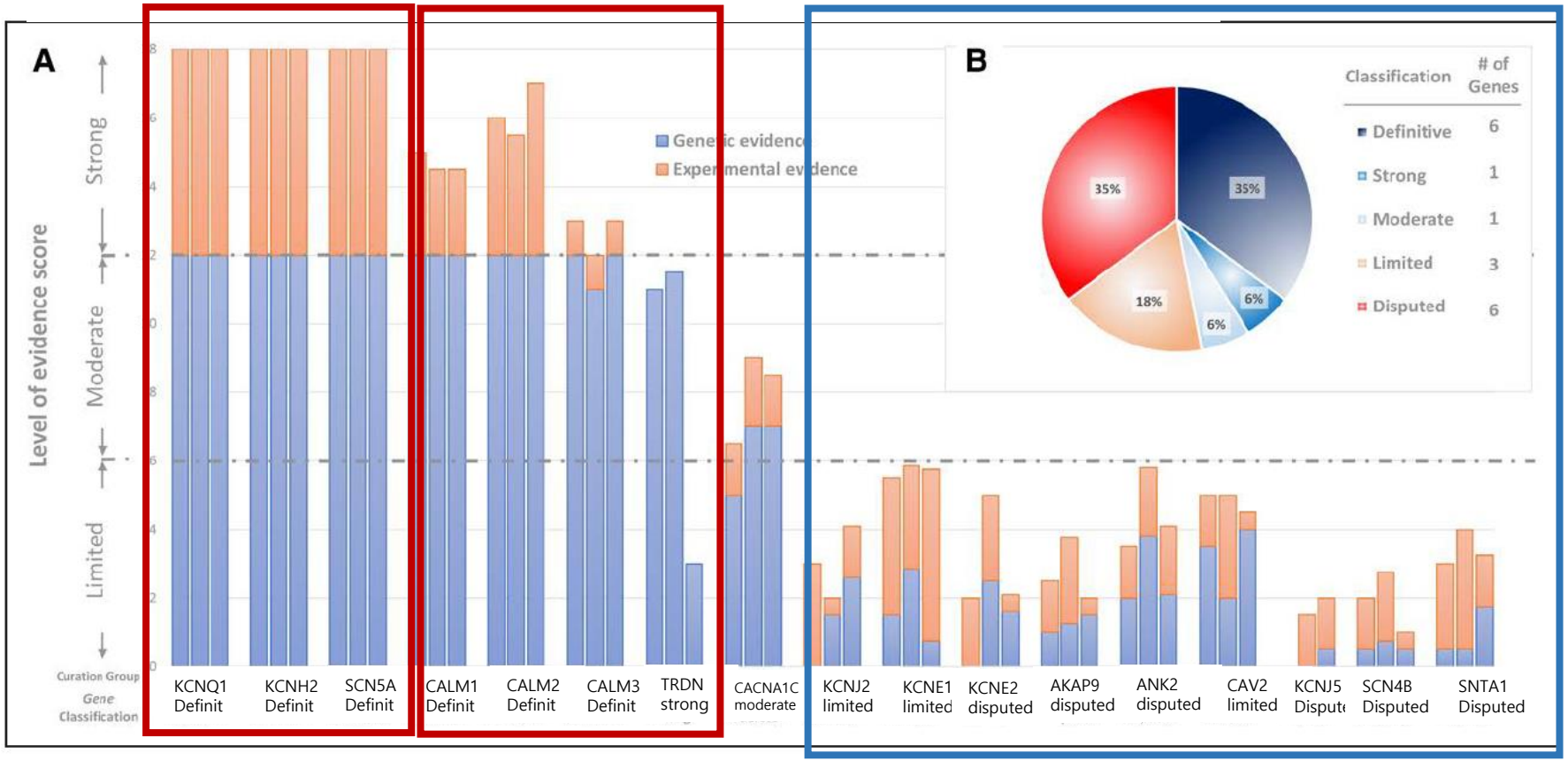
c ERP high-risk features: J waves>2 mm, dynamic changes in J point and ST
d High-risk ERP: FHx of unexplained SD<40 years, family history of ERS

2022 ESC guideline for prevention of VA and SCD

Consensus for the genetic testing

ORIGINAL RESEARCH ARTICLE

An International, Multicentered, Evidence-Based Reappraisal of Genes Reported to Cause Congenital Long QT Syndrome



Definitive genes for typical LQTS or atypical LQTS

Limited or disputed evidence for congenital long QTS

Circulation. 2020;141:418–428. DOI:0.1161/CIRCULATIONAHA.119.043132

Consensus for the genetic testing

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Europace (2022), 00, 1–61
https://doi.org/10.1093/europace/euac030

POSITION PAPER

European Heart Rhythm Association (EHRA)/ Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus St testing for car

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Table 6 Genes implicated in long QT syndrome (LQTS)

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

Functional effect: (↓) loss-of-function or (↑) 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.

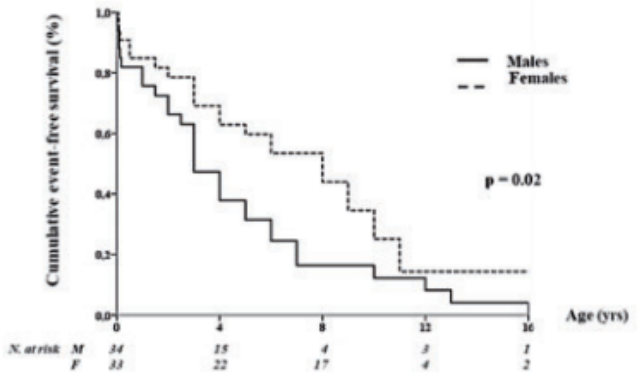
LQTS 1,2,3

2022 EHRA/HRS expert consensus on the state of genetic testing for cardiac diseases

Calmodulopathy

Calmodulin : Ca++ dependent inactivation of L-type Ca++ channels
Required for IKs activation during sympathetic activation

- Extremely rare and severe
- Median age at first cardiac event 4 years
- Trigger for arrhythmic events: adrenergic stimuli in 81% of patients
- Major arrhythmic events in 68% of patients
- Sudden cardiac death in 27%



PREVALENT PHENOTYPES

***CALM*-LQTS** (49%)
- Mean QTc 594±73 ms
- Late onset peaked T-waves
- Perinatal presentation in 58%
- Median age of onset 1.5 years
- Life-threatening arrhythmias in 78%

***CALM*- CPVT** (28%)
- All symptomatic for cardiac events 48% with major arrhythmic events
- Median age of onset 6.0 years

Calmodulopathy
→ severe form of LQTS or CPVT

European Heart Journal 2019;35:2964–2975

• Calmodulopathy

Long QT syndrome

Recommendations	Consensus statement instruction
Molecular genetic testing for definitive disease associated genes (currently *KCNQ1*, *KCNH2*, *SCN5A*, *CALM1*, *CALM2*, and *CALM3*) should be offered to 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, Supplementary *Table S2*).[a]	
Analysis of specific genes should be offered to 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.	
An analysis of *CACNA1C* and *KCNE1* may be performed 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).[a]	

In patients without LQTS mutation
In 2013 trio exome sequencing
→ *CALM1 and CALM2*
→ CALM1 in NGS panel (2015)
→ CALM1-3 in NGS panel (2021)
→ Molecular screening with NGS panel

Phenotype(+) genotype(-) patients with LQTS and CPVT, who underwent NGS panel before 2021
→ consider CALM genetic testing

CPVT

Recommendation	Consensus statement instruction	Ref.
In any patient satisfying the diagnostic criteria for CPVT (such as Class 1 clinical diagnosis[a] or CPVT diagnostic score >3.5[b]), molecular genetic testing is recommended for the currently established definite/strong evidence CPVT-susceptibility genes: *RYR2*, *CASQ2*, *CALM1-3*, *TRDN*, and *TECRL*.		91,141–145

2022 LQTS EHRA/HRS/APHRS/LAHRS Expert Consensus Statement on Genetic Testing
Crotti L et al. circulation 2013:;127:1009-1017

• Sports participation in patients with LQTS

Cardiac Events During Competitive, Recreational, and Daily Activities in Children and Adolescents With Long QT Syndrome

J Am Heart Assoc. 2017;6:e005445. D

Kristina D. Chambers, BA; Virginie Beausejour Ladouceur, MD; Mark E. Alexander, MD, FHRS; Robyn J. Hylind, MS; Laura Bevilacqua, MD; Douglas Y. Mah, MD; Vassilios Bezzerides, MD, PhD; John K. Triedman, MD, FHRS; Edward P. Walsh, MD, FHRS; Dominic J. Abrams, MD, MRCP

Boston

- Beta-blockers (99%), ICD (16%), left cardiac sympathetic denervation (4%)
- No Cardiac event in competitive athletes.

➔ In appropriately managed children with LQTS, cardiac event rates were low and occurred during recreational but not competitive activities.

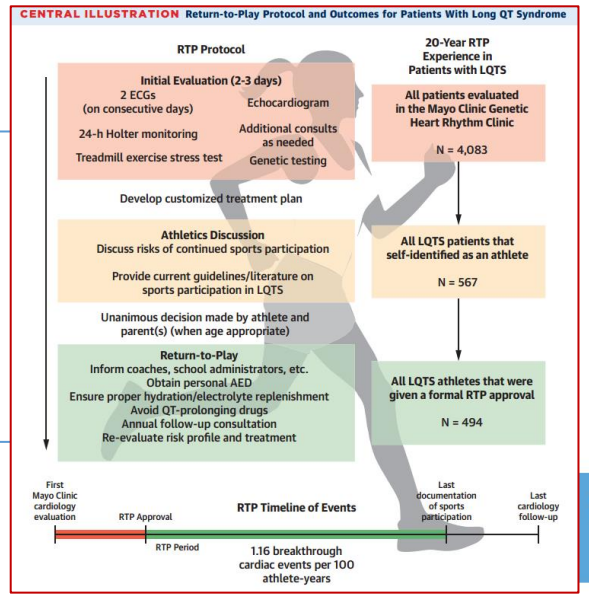
Return-to-Play for Athletes With Long QT Syndrome or Genetic Heart Diseases Predisposing to Sudden Death

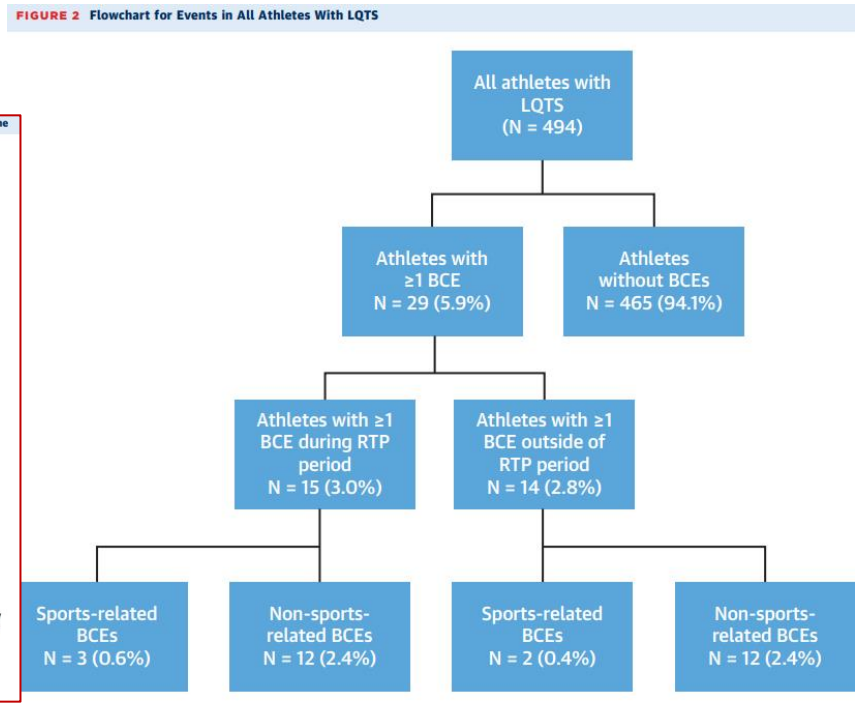
J Am Coll Cardiol 2021;78:594–604

Kathryn E. Tobert, BA,[a] J. Martijn Bos, MD, PhD,[a,b,c] Ramin Garmany, BS,[a,d] Michael J. Ackerman, MD, PhD[a,b,c]

Mayo

No mortality
5.9% nonlethal cardiac event
- 0.6% sports-sports related
Event rate 1.16 nonlethal event per 100 athlete-years of FU





ESC European Society of Cardiology
Europace (2022) **24**, 1675–1683
https://doi.org/10.1093/europace/euac047

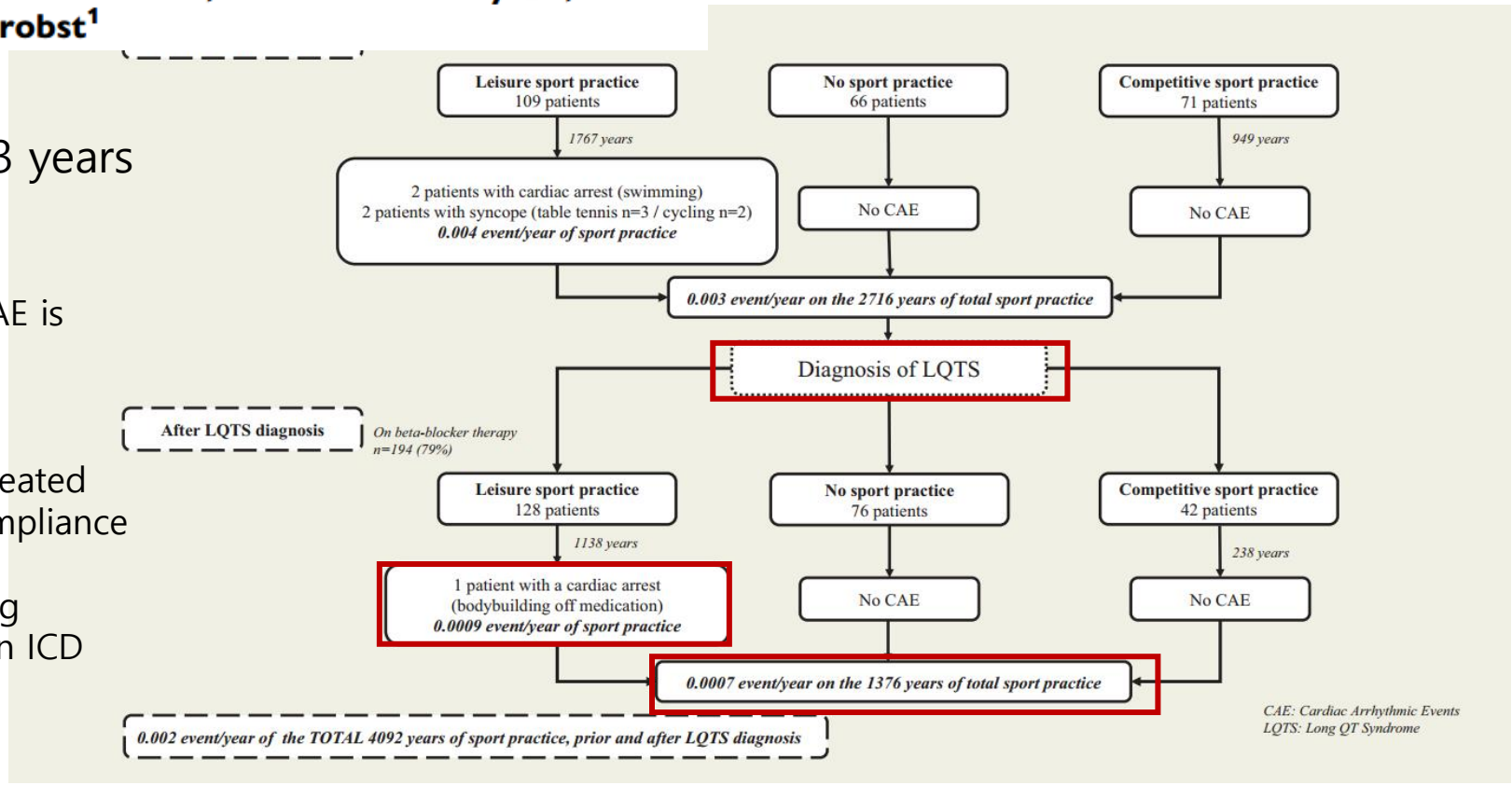
Does sports participation increase risk in patients with long QT syndrome? Results from a large French cohort

Caroline Davydoff [1], Antoine Andorin [1]*, Damien Minois [1], Marine Arnaud [1], Mathilde Minier[1], Frédéric Sacher[2], Raphael Martins[3], Nicolas Clementy [4], Jean-Baptiste Gourraud[1], and Vincent Probst[1]

Europace 2022;24:1675-1683

246 patients with median age 43 years

- After the diagnosis, the occurrence of CAE is very low during sports practice, even in competitive practice
- There was no CAE in patients properly treated with beta-blocker therapy with good compliance
- Only 1 patient had a cardiac arrest during bodybuilding, appropriately treated by an ICD discharge, with BB noncompliance



Sports restrictions in long QT syndrome

- Historically, LQTS was a contraindication for any type of sports (2005 European Guideline)
- Recreational and competitive sports in patients with LQTS is evolving

  → encourage recreational physical activity in medically treated, stable patients with its many health benefits
- One specific contraindication is swimming alone for LQT1 patients
- Extent to which exercise increases this risk and worsens disease progression remains incompletely known

- Shared decision making based on informed discussion with patients/family is important on an individual level.

J Am Coll Cardiol EP 2022;8:687–706

Summary

- Genetic testing is recommended in clinically diagnosed LQTS, suspected ATS, and CPVT (Class I)
- Genetic testing for SCN5A in BrS

- Nadolol or propranolol are preferred beta-blockers in LQTS and CPVT patients (Class I)
- Nonselective beta-blocker for LQTS, mexiletine for LQTS3 with QT prolongation (Class I)
- Left cardiac denervation plays an important role in the management of CPVT and LQTS patients
- A type I Brugada ECG pattern provoked by sodium channel blocker in the absence of other findings dose not diagnose the BrS

- Calomodulopathy gene test should be considered in LQTS or CPVT patients with genotype (-)
- Sports restriction in LQTS is changing : based on medication compliance, presence of ICD, AED, education / discussion on an individual level.

Thank you for your attention!