

Table 1. EHRA/HRS/APHRS/LAHS 2022 Consensus Statement on genetic testing. Genes implicated in catecholamine polymorphic ventricular tachycardia (CPVT)

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

AD, autosomal dominant; AR, autosomal recessive.

^a*TECRL* and *TRDN* may result in a CPVT-LQTS overlap phenotype consisting of modest QTc-prolongation and adrenergically triggered ventricular arrhythmia.

Table 2. Diagnosis

ESC 2022 GI on VA and SCD. Recommendations for the management of patients with catecholaminergic polymorphic ventricular tachycardia

Diagnosis

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

Table 3. Genetic testing

AHA/ACC/HRS 2017 GL on VA/SCD. CPVT

Genetic counseling and genetic testing for patients with clinical VT or exertional syncope IIa-B-NR

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

EHRA/HRS/APHRS/LAQRS 2022 Consensus Statement on genetic testing.

Impact of genetic testing for the index case

Disease	Diagnostic	Prognostic	Therapeutic
CPVT	+++	+	+

Recommendations

Should do

In any patient satisfying the diagnostic criteria for CPVT (such as Class 1 clinical diagnosis or CPVT diagnostic score ≥ 3.5), molecular genetic testing for the currently established definite/strong evidence CPVT-susceptibility genes: RYR2, CASQ2, CALM1-3, TRDN, and TECRL.

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

Predictive genetic testing in related children at risk of inheriting a P/LP variant from birth onward (any age).

May do

In phenotype-positive CPVT patients who are negative for those established CPVT-susceptibility genes, genetic testing for CPVT phenocopies resulting from pathogenic variants in the KCNJ2, SCN5A, and PKP2 genes.

In patients with a modest phenotype for CPVT (i.e. CPVT diagnostic score ≥ 2 but $< 3.5^*$), genetic testing for the established definite/strong evidence CPVT-susceptibility genes: RYR2, CASQ2, CALM1-3, TRDN, and TECRL.

ESC 2022 GL on VA and SCD. Recommendations for genetic testing (Class I)

Proband

Initial clinical test

Cornerstone for diagnosis

Exercise test

Other tests/processes

Exclude phenocopy*/SHD

Follow-up

1-3 years dependent on level of risk

Relatives

Clinical screening

ECG

Exercise test

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

*: A phenocopy has characteristics of a genetic disease but is produced environmentally

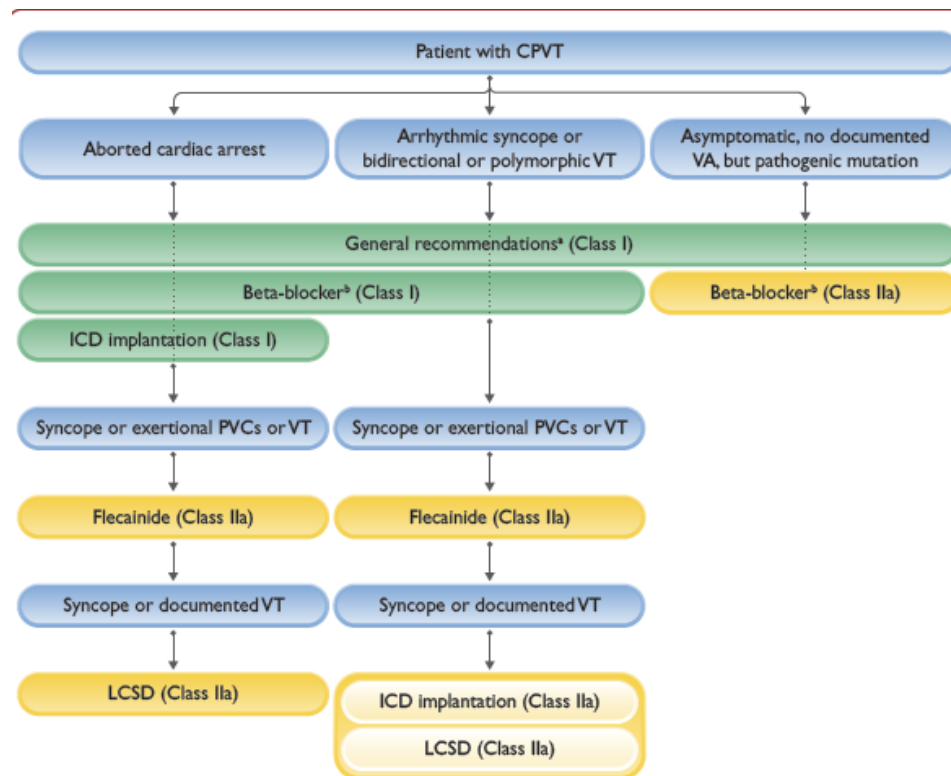


Figure 1. ESC 2022 GL on VA and SCD. Management of patients with catecholaminergic polymorphic ventricular tachycardia.

CPVT, catecholaminergic polymorphic ventricular tachycardia; ICD, implantable cardioverter defibrillator; LCSD, left cardiac sympathetic denervation; PVC, premature ventricular complex; VA, ventricular arrhythmia; VT, ventricular tachycardia.

a General recommendations: avoidance of competitive sports, avoidance of strenuous exercise, avoidance of stressful environments.

b Preferred beta-blockers: nadolol, propranolol.

Table 4. Therapy of CPVT**AHA/ACC/HRS 2017 GL on VA/SCD. CPVT**

Beta blockers	I-B-NR
Combination medication therapy (e.g., beta blocker, flecainide), left cardiac sympathetic denervation, and/or an ICD In patients with recurrent sustained VT or syncope, while receiving adequate or maximally tolerated beta blocker.	I-B-NR

ACC/AHA/HRS 2017 GL on syncope. CPVT

Exercise restriction in syncope of suspected arrhythmic etiology	I-C-LD
Beta blockers lacking intrinsic sympathomimetic activity in stress-induced syncope	I-C-LD
Flecainide in patients who continue to have syncope of suspected ventricular arrhythmia despite beta-blocker therapy	IIa-C-LD
ICD therapy in patients with a history of exercise or stress-induced syncope despite optimal medical therapy or left cardiac sympathetic denervation	IIa-B-NR
Verapamil with or without beta-blocker therapy in patients who continue to experience syncope or ventricular arrhythmia	IIb-C-LD
Left cardiac sympathetic denervation in syncope and symptomatic ventricular arrhythmia despite optimal medical therapy	IIb-C-LD

ESC 2022 GI on VA and SCD. Recommendations for the management of patients with catecholaminergic polymorphic ventricular tachycardia***General recommendations***

Avoidance of competitive sports, strenuous exercise, and exposure to stressful environments for all patients with CPVT. I C

Therapeutic interventions

Beta-blockers, ideally non-selective (nadolol or propranolol) in all patients with a clinical diagnosis of CPVT	I C
ICD implantation combined with beta-blockers and flecainide in CPVT patients after aborted CA	I C
Therapy with beta-blockers for genetically positive CPVT patients without Phenotype	IIa C

LCSD 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	IIa C
ICD implantation in patients with CPVT who experience arrhythmogenic syncope and/or documented bidirectional/PVT while on highest tolerated beta-blocker dose and on flecainide	IIa C
Flecainide in patients with CPVT who experience recurrent syncope, polymorphic/bidirectional VT, or persistent exertional PVCs, while on beta-blockers at the highest tolerated dose	IIa C
PES is not recommended for stratification of SCD risk.	III C
CA, cardiac arrest; CPVT, catecholaminergic ventricular tachycardia; ECG, electrocardiogram; ICD, implantable cardioverter defibrillator; LCSD, left cardiac sympathetic denervation; PVT, polymorphic ventricular tachycardia; VT, ventricular tachycardia.	

Table 5. ESC 2025 GL on pregnancy. CPVT

Beta-blockers ^c , with pre-pregnancy dose and with nadolol and propranolol as drugs of choice, are recommended during pregnancy and lactation in women with CPVT. ^{43,148,252}	I	C
Flecainide, in addition to beta-blockers, is recommended in women with CPVT who experience cardiac events such as syncope, VT, or cardiac arrest during pregnancy.	I	C
It is recommended that women with CPVT who are stable on beta-blockers (nadolol or propranolol as drugs of choice) and flecainide before pregnancy continue both drugs during pregnancy and post-partum.	I	C
The use of beta-blockers ^c during pregnancy and lactation should be considered in phenotype-negative women with a CPVT P/LP variant. ¹⁴⁸	IIa	C
Left cardiac sympathetic denervation should be considered before pregnancy in high-risk women with CPVT who are not adequately protected by pharmacological therapies or with appropriate ICD shocks despite optimal medical therapy. ²⁵²	IIa	C

CPVT, catecholaminergic polymorphic ventricular tachycardia; P/LP, pathogenic/likely pathogenic