Genetic secrets of the Heart: Improving Arrhythmia Treatment through Genetic Identification

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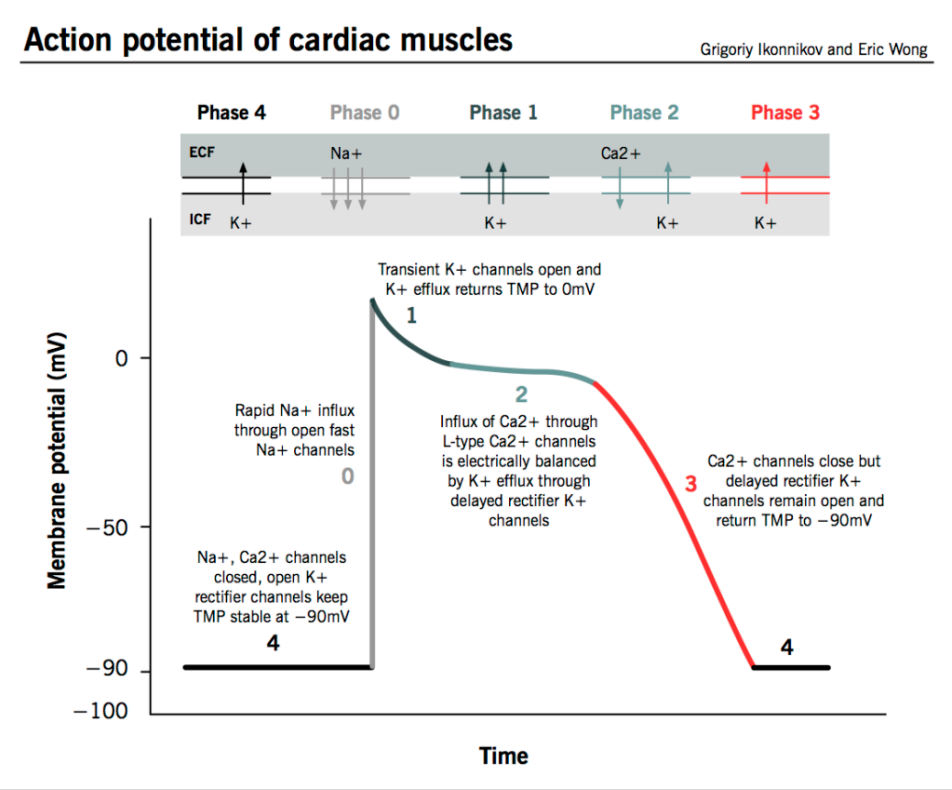
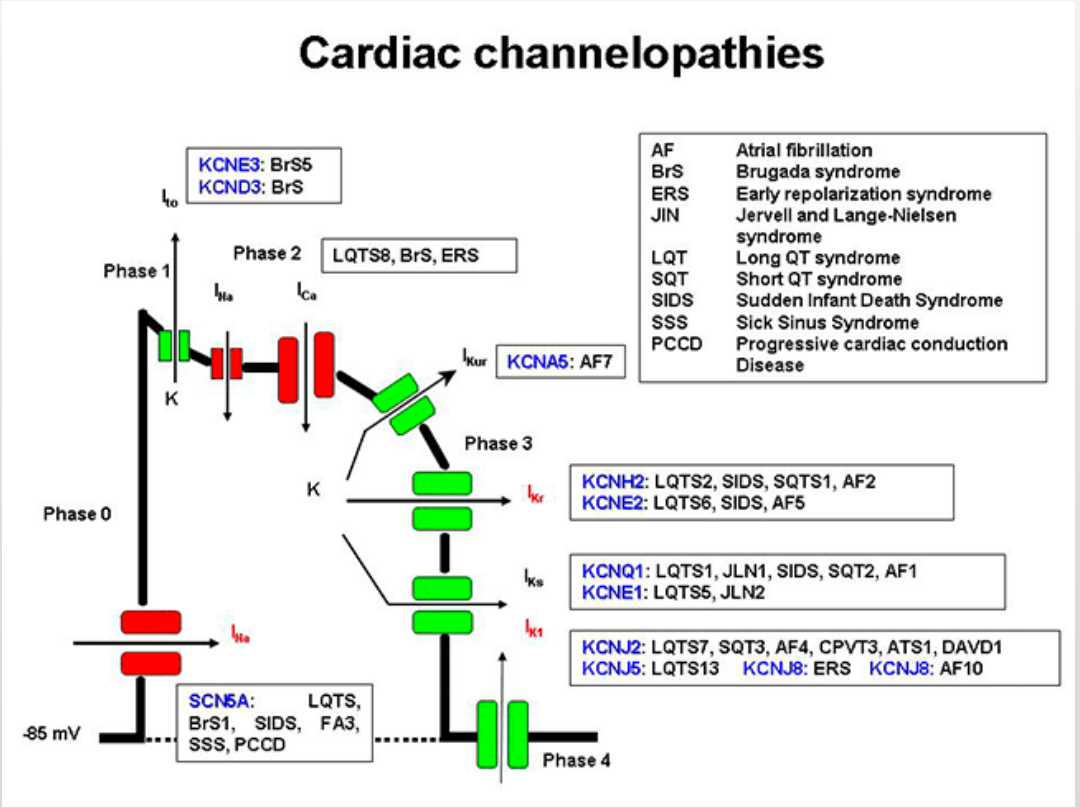
Cardiac channelopathies

- Refers to genetic disorders characterized by altered cardiac excitability, in the absence of structural cardiac involvement.





Arrhythmia Treatment through Genetic Identification

- Suspected genetic arrhythmia?

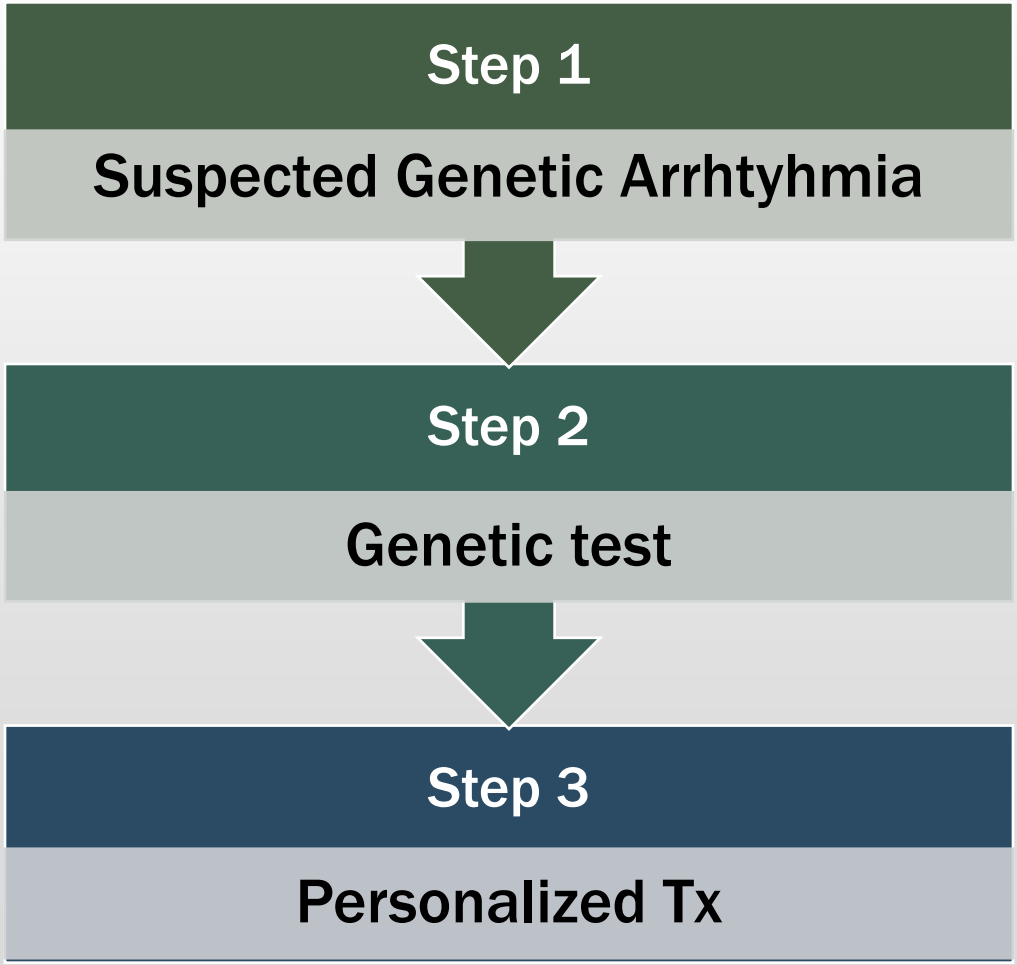
OHCA, ECG, FHx, young age

- Genetic test?

Pannel, Exome

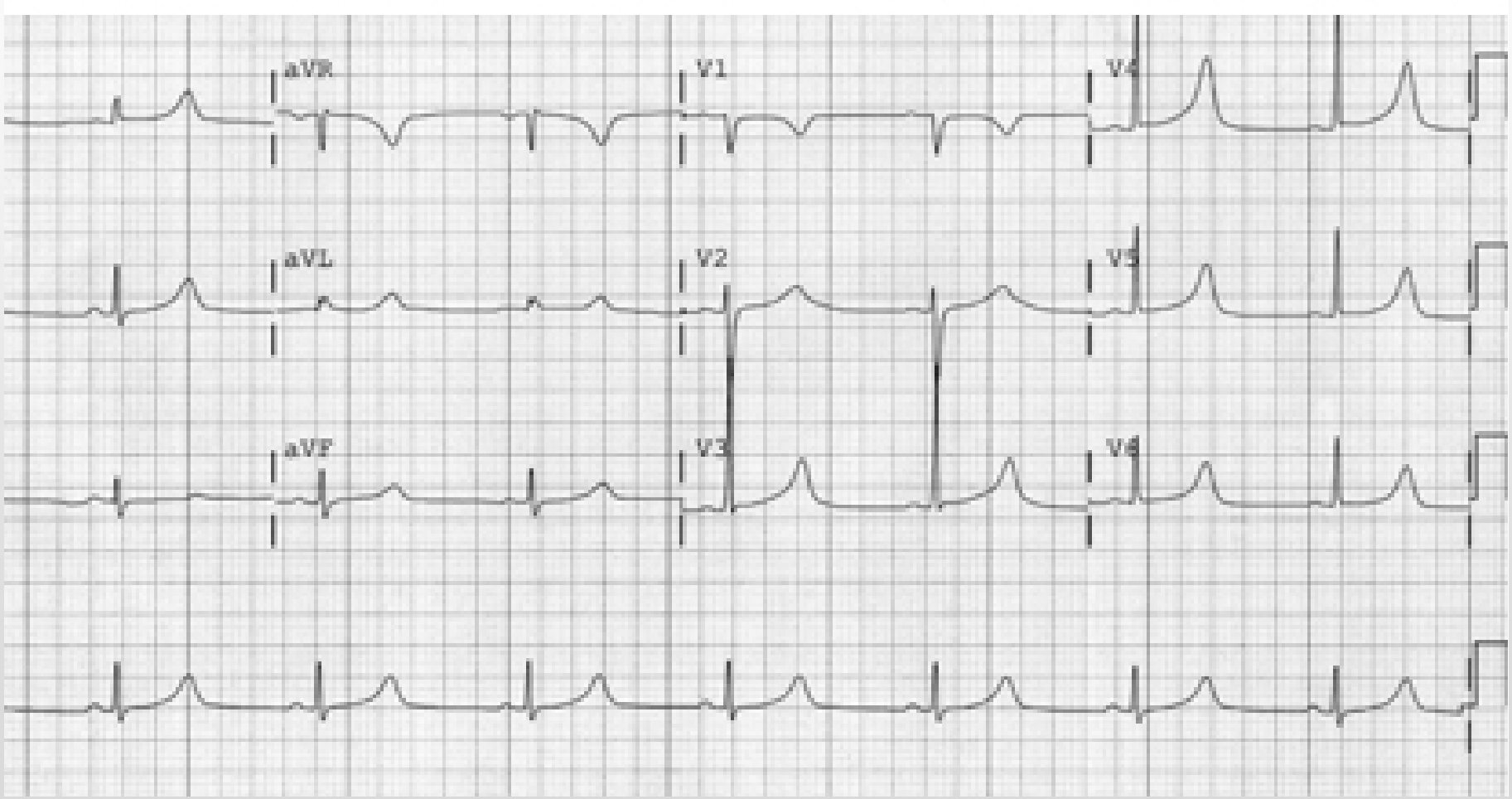
- Personalized treatment?

Triggers, Family screening, Drug therapy, ICD type



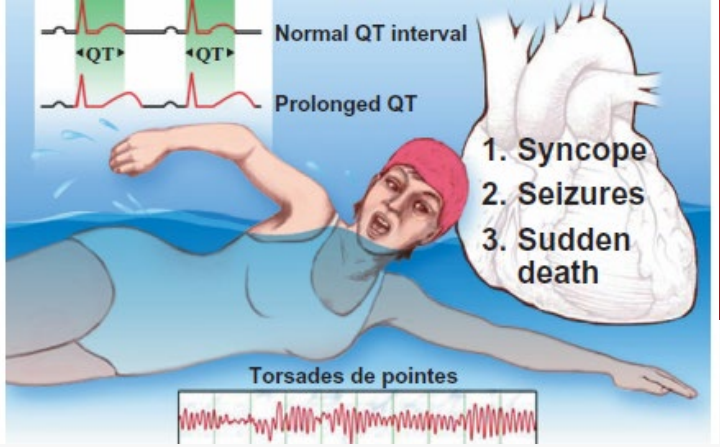
Examples

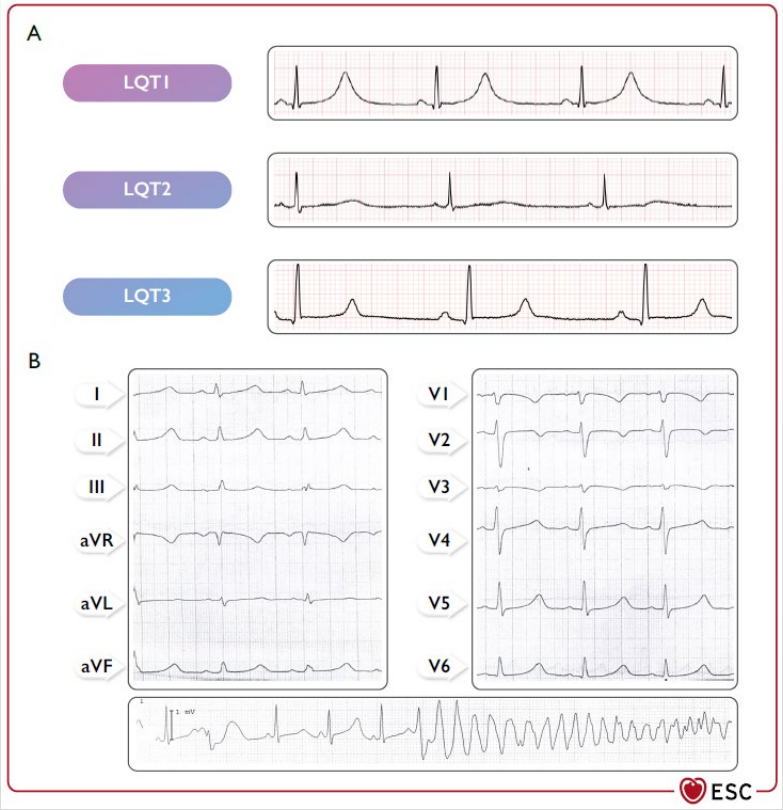
13 YO girl with syncope

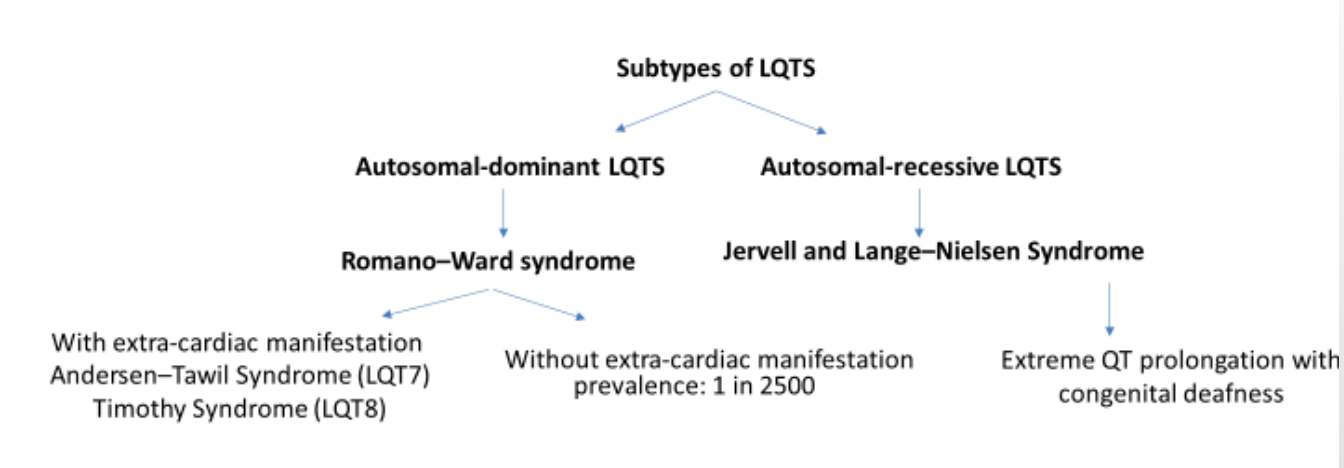


Long QT Syndrome

Abnormal QTc values > 470 ms (in males) and 480 ms (in females)







- Genetic screening identifies a mutation 75% of LQTS
- 3 main genes (KCNQ1 (LQT1), KCNH2 (LQT2) and SCN5A (LQT3)) account for 90% of positively genotyped cases.

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

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

LQTS genetic testing: Indications – Class I

Pretest probability of disease (i.e., the st
as

1)

2)

3)

an index case)

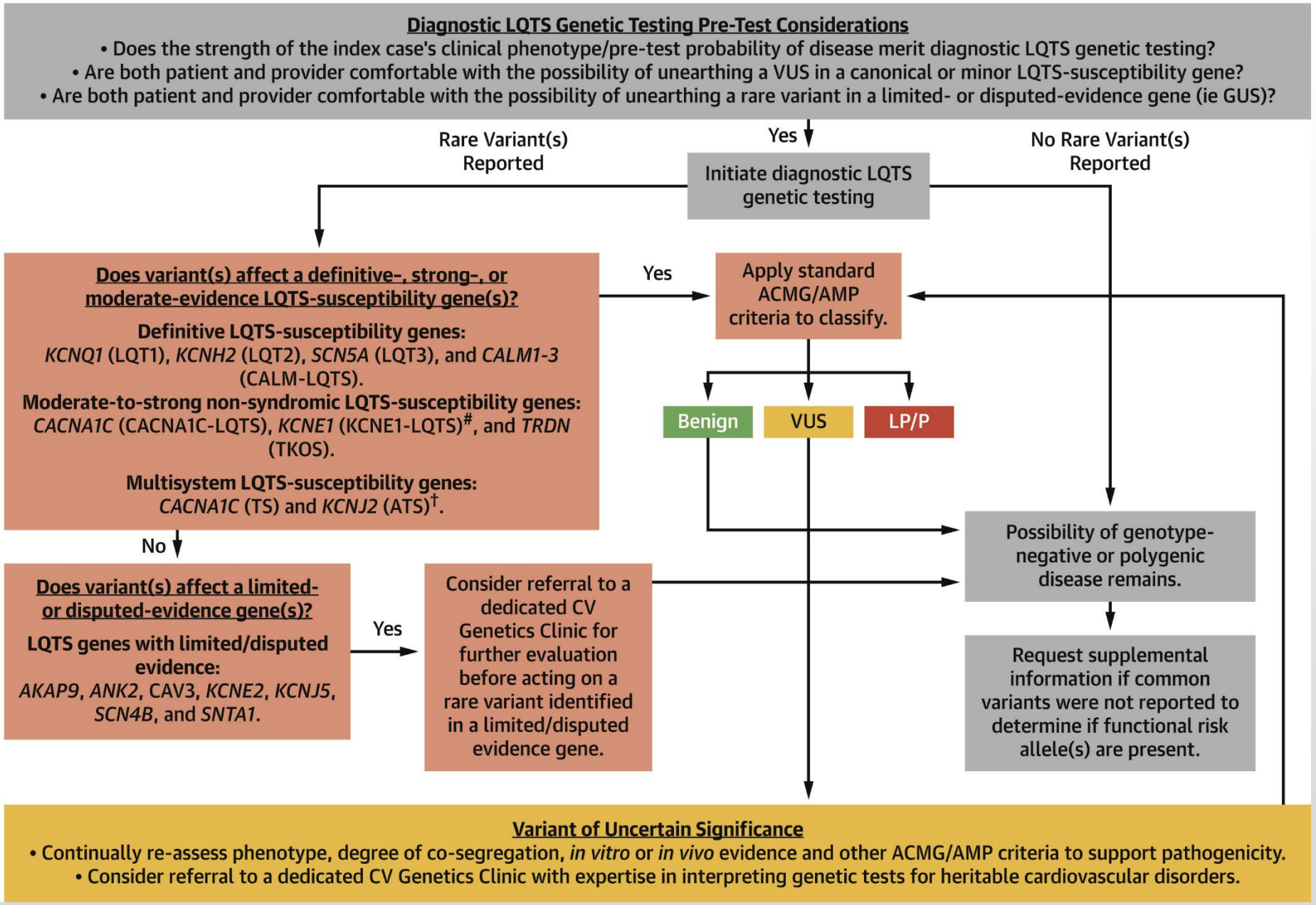
Findings			Points
ECG	QTc	≥480 ms	3.5
		=460–479 ms	2
	first-degree family		
Genetic finding	Pathogenic mutation		3.5

LQTS genetic testing: Indications – Class II

1) individuals with an intermediate clinical index of suspicion (i.e., Schwartz score 1.5 to 3);

2) asymptomatic patients without a family history of LQTS that display otherwise idiopathic QTc prolongation on serial ECGs (prepubertal ≥460 ms or postpubertal ≥480 ms)

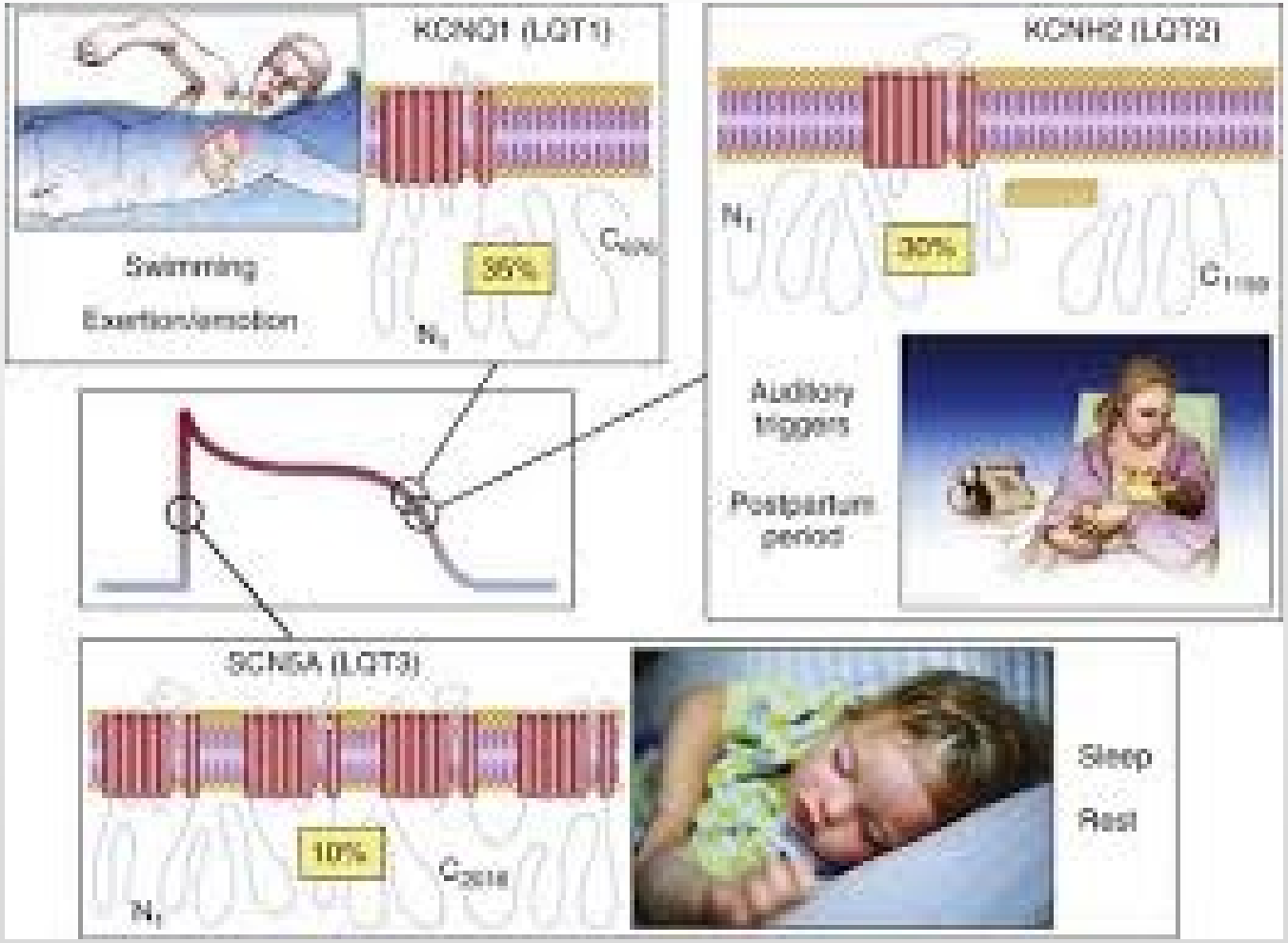
C



Giudicessi et al. Precision Medicine in CVD 4/5—Arrhythmias. JACC 2021

Triggers of arrhythmia

- Triggers include exercise, noise, emotion, sudden wakening from sleep by noise , swimming or diving.
- Swimming and exertion-induced cardiac events are strongly associated with **LQT1.**
- Auditory triggers and events during postpartum period occur in pts with **LQT2**.
- Events occurring during periods of sleep or rest are most common in **LQT3.**



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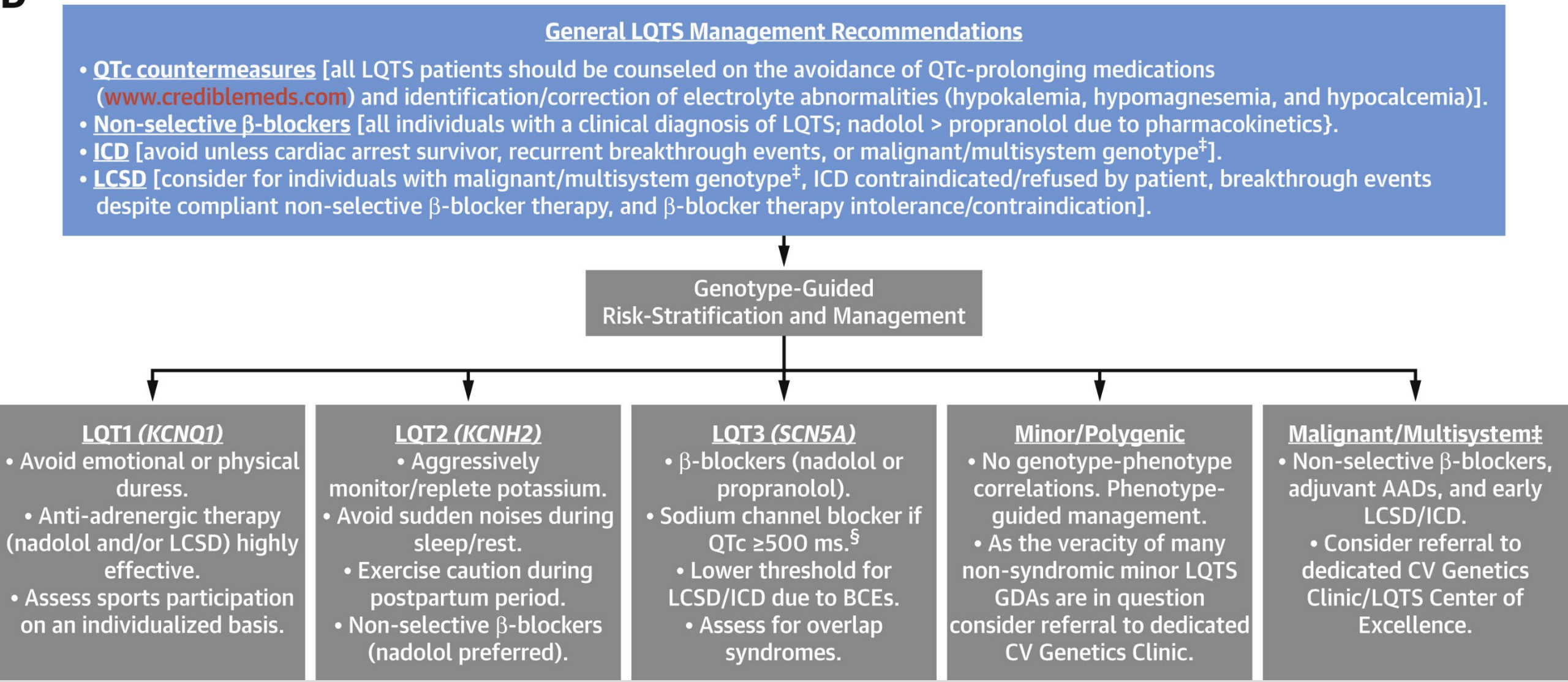
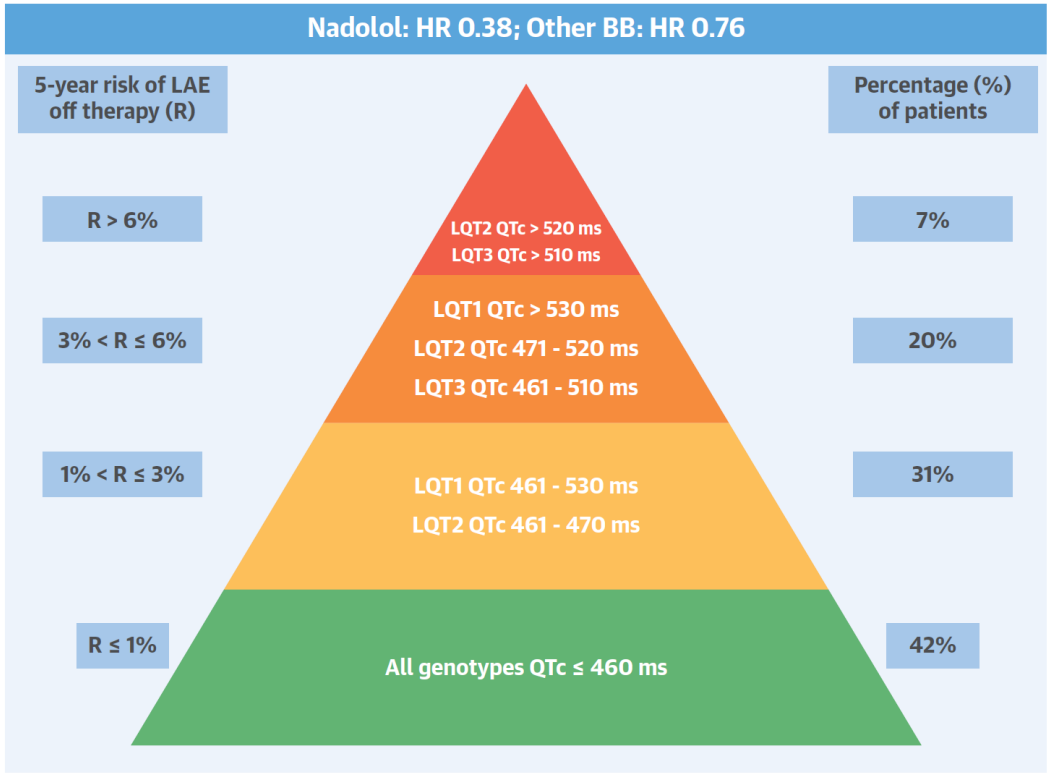


Giudicessi et al. Precision Medicine in CVD 4/5—Arrhythmias. JACC 2021

1-2-3-LQTS-Risk model

CENTRAL ILLUSTRATION 5-Year Risk of LAEs by Genotype and QTc Interval Before Therapy and Effect of BBs



Mazzanti, A. et al. J Am Coll Cardiol. 2018;71(15):1663–71.

Visualization of 5-year risk of LAEs by genotype and QTc interval before and after therapy according to models derived from the patient population of the present study. The **column to the left** indicates the cutoff of the 5-year risk of LAEs that corresponds to each color-coded group of patients characterized by QTc duration and genotype (from **green** [lower risk] to **red** [higher risk]). The **column to the right** indicates the percentage of patients in each color-coded category present in the cohort. The **bar on the top** shows the HR of patients treated with nadolol (HR: 0.38) and other BBs (selective BBs and propranolol; HR: 0.76) and can be used to estimate the residual risk for each group of patients when treated with BBs. BB = beta-blocker; HR = hazard ratio; LAEs = life-threatening arrhythmic events; QTc = corrected QT interval.

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)

ICD, implantable cardioverter-defibrillator; LQTS, long QT syndrome; LAE, life-threatening arrhythmic event; NNT, number need to treat; 95% CI, 95% confidence interval. In bold, the most balanced threshold for ICD implantation according to ROC analysis.

“Malignant” LQTS genotypes

High-risk genotypes frequently refractory to first-line LQTS-directed therapy:

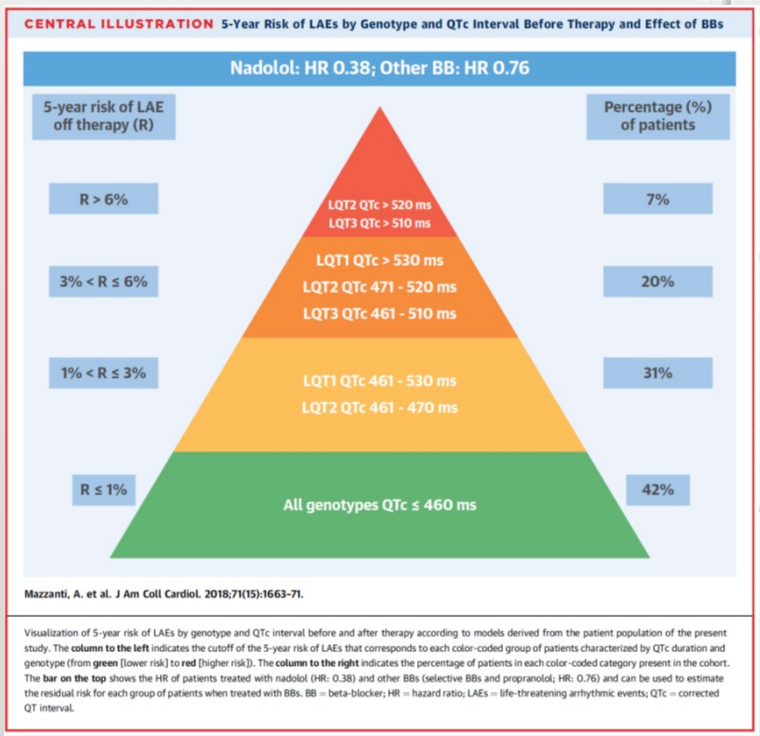
- Calmodulinopathic LQTS (ACMG pathogenic/likely pathogenic variants in CALM1–3)
- Jervell and Lange-Nielsen syndrome
- Timothy syndrome
- Triadin knock-out syndrome
- pathogenic/likely pathogenic LQTS-causative variants on > 1 canonical LQTS susceptibility allele (e.g., compound heterozygosity or digenic heterozygosity)

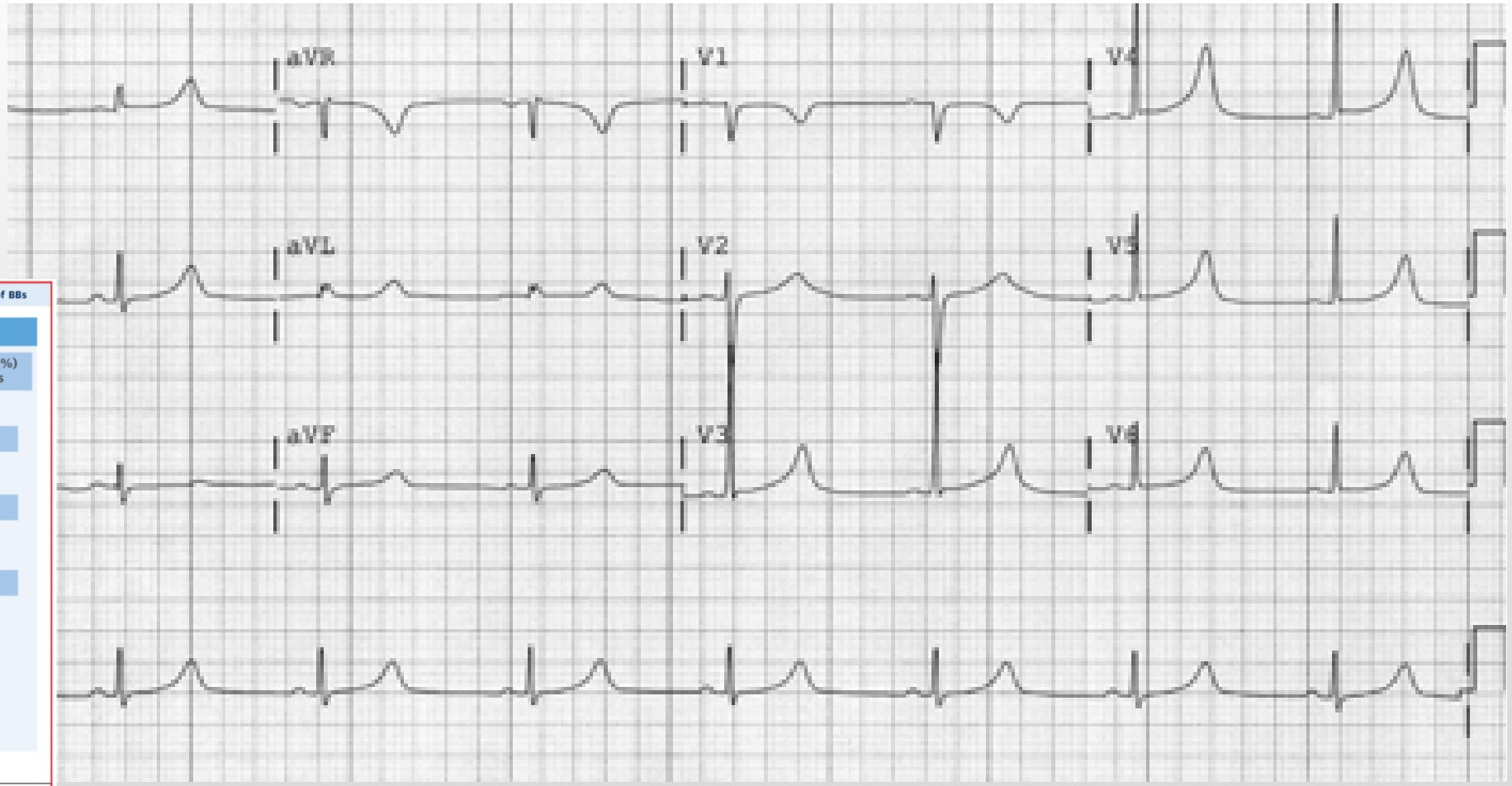
more aggressive management strategies, including early consideration of LCSD and ICD

13 YO girl with syncope

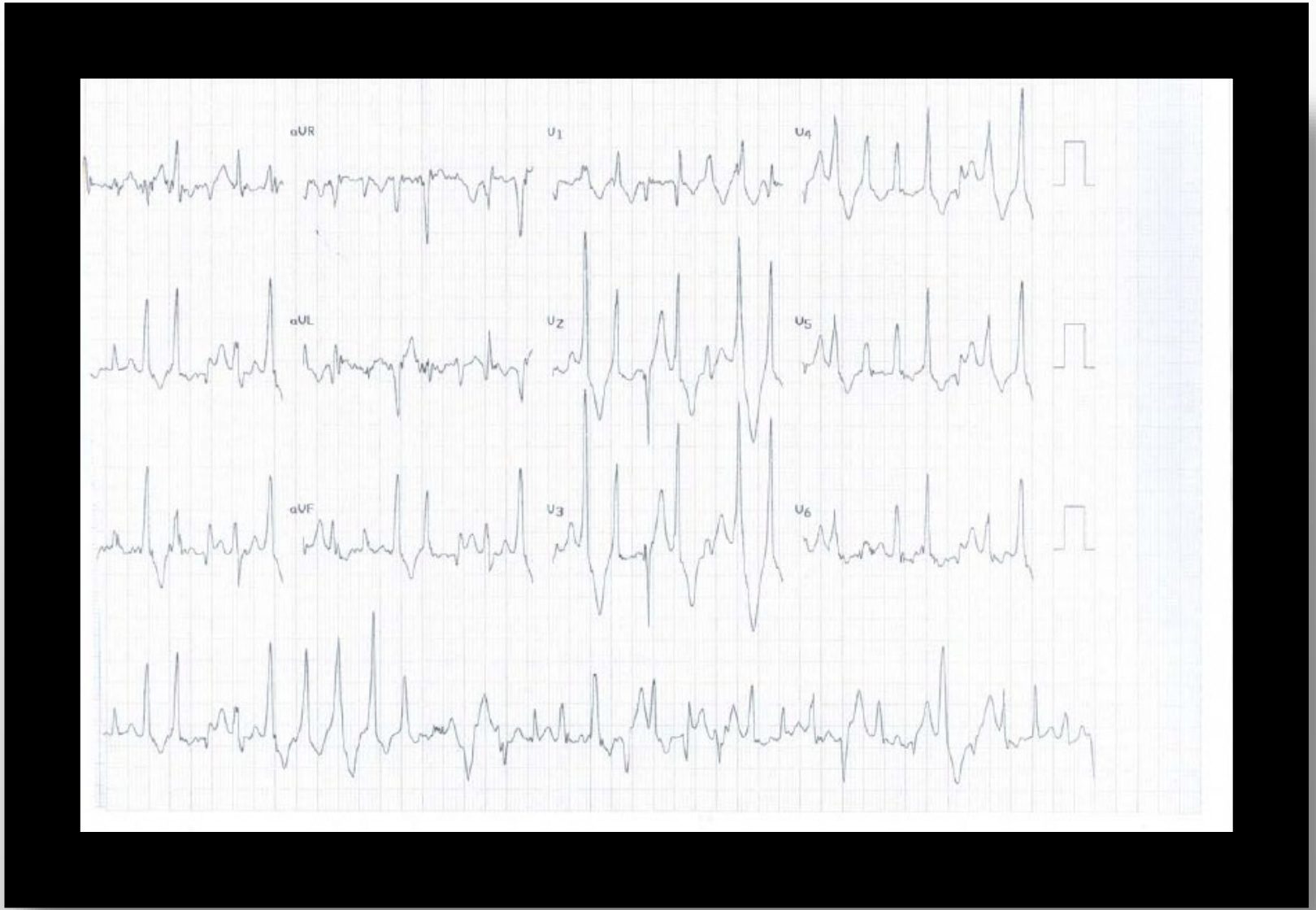
QTc ≥500 msec
KCNQ1 Pathogenic mutation

Specific Drug Tx –Nadolol
Family Screening



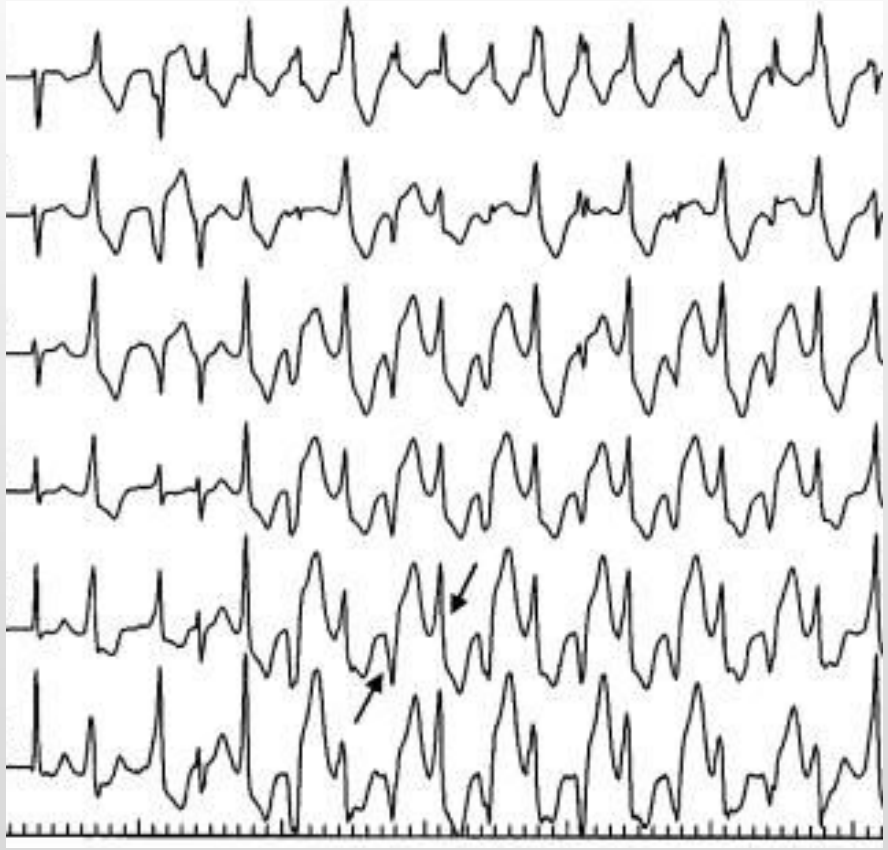


16 yo girl suddenly collapsed running into store



Catecholaminergic polymorphic ventricular tachycardia

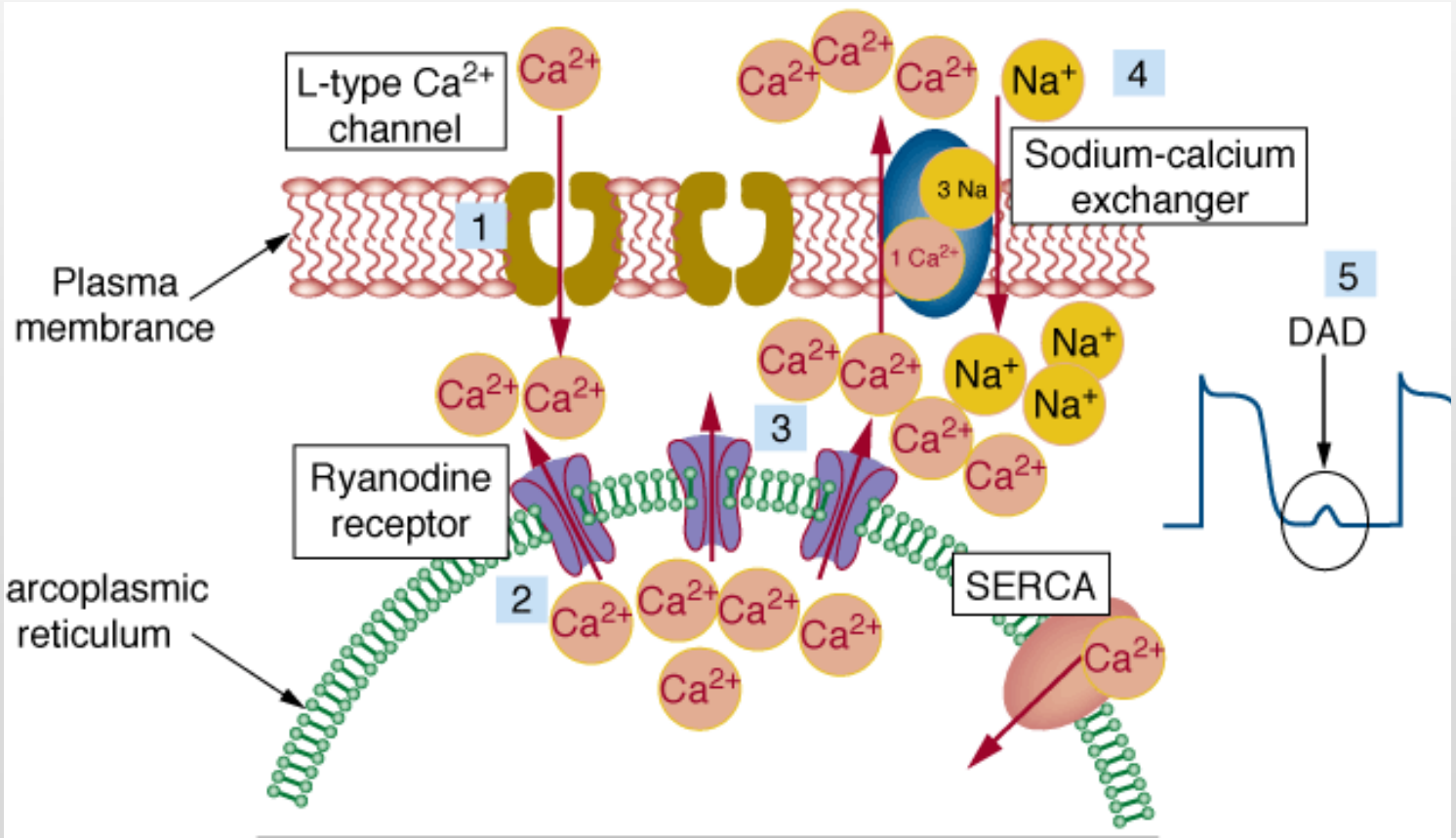
- A heritable disorder characterized by catecholamine induced bidirectional VT and PVT in the absence of SHD or ischemia.
- One of the most severe of the inherited arrhythmogenic disorders
- The disease has an estimated prevalence of 1 in 10 000



Two main genetic types (50-70%):

Autosomal dominant - mutations in the gene encoding the cardiac ryanodine receptor (RYR2). **RyR2** mediates release of Ca+ from SR which is required for myocardial contraction.

Autosomal recessive - mutations in the cardiac calsequestrin gene (CASQ2). **Calsequestrin 2 protein** is a protein in SR which binds large amounts of calcium.



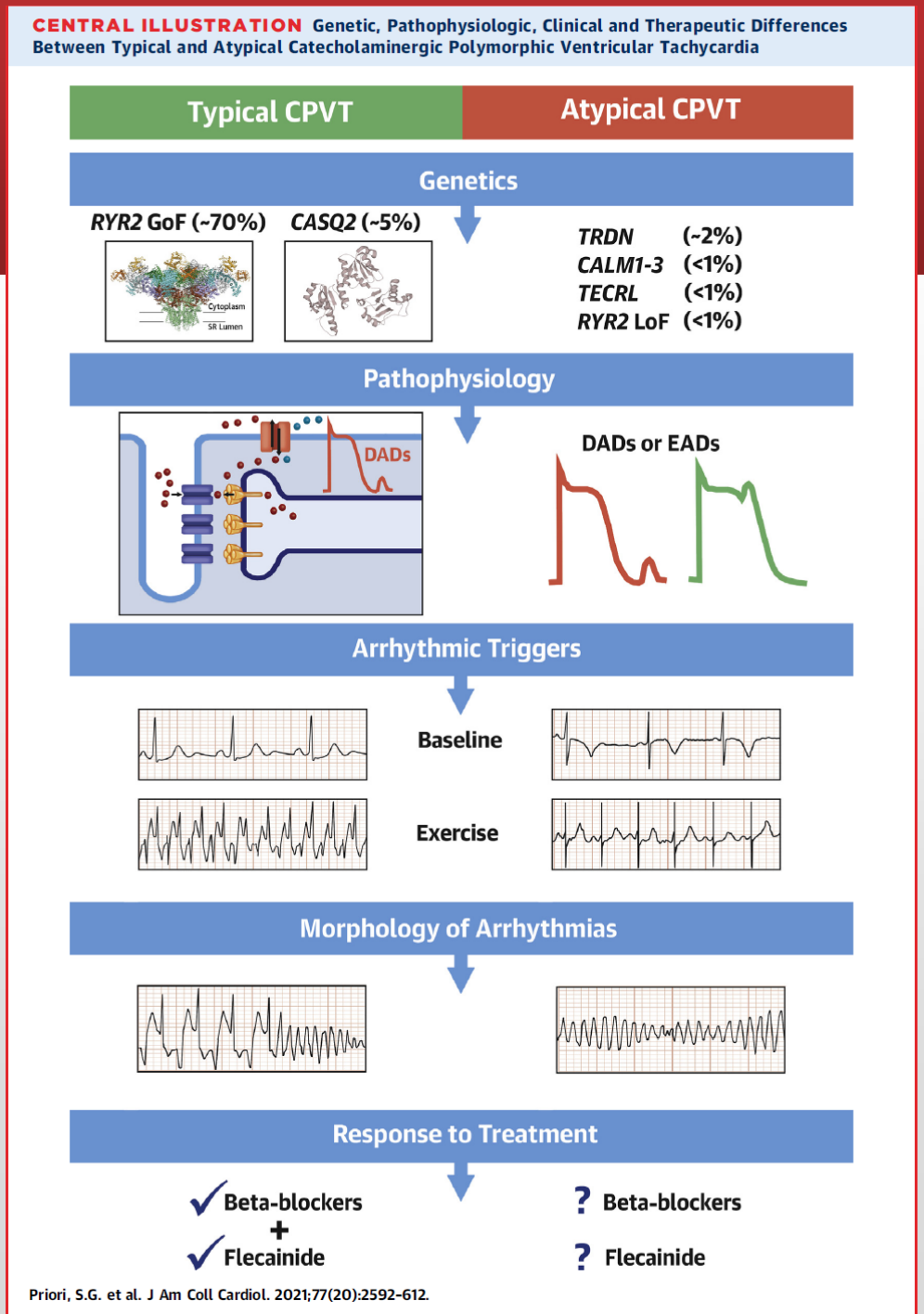
- Mutations in TRDN and CALM1-3 have been identified in **atypical** forms of catecholaminergic VAs. At the present time, however, it is unclear whether they are distinct arrhythmic entities.

Typical vs Atypical CPVT

phenotype

- *Typical CPVT* can be diagnosed with the demonstration of reproducible exercise-induced bidirectional or polymorphic VT in the presence of a structurally normal heart and normal baseline/resting EKG.

- *Atypical CPVT* is associated with arrhythmias and/or syncope / cardiac arrest triggered by adrenergic activation in the absence of a reproducible pattern of arrhythmias.



2022 ESC Guidelines for the management of patients with VAs and the prevention of SCD

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
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	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	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
PES is not recommended for stratification of SCD risk.	III	C

RYR2 LOSS-OF-FUNCTION VARIANTS
distinct entity of cardiac arrhythmia termed RyR2 Ca2+ release deficiency syndrome (CRDS)

- not all RYR2 pathogenic variants induce the gain-of-function effect associated with typical CPVT
- In 2002 , pathogenic RYR2 mutation (p.Ala4860Gly) where adrenergic activation did not induce typical bVT, but rather, caused VF
- it remains uncertain if they would respond to conventional therapy for CPVT
- in cardiac arrest survivor's carriers of a disruptive RYR2 mutation who do not develop bVT/pVT during exercise stress test, the diagnosis of LOF CVPT may be considered.

Postpacing abnormal repolarization in catecholaminergic polymorphic ventricular tachycardia associated with a mutation in the cardiac ryanodine receptor gene

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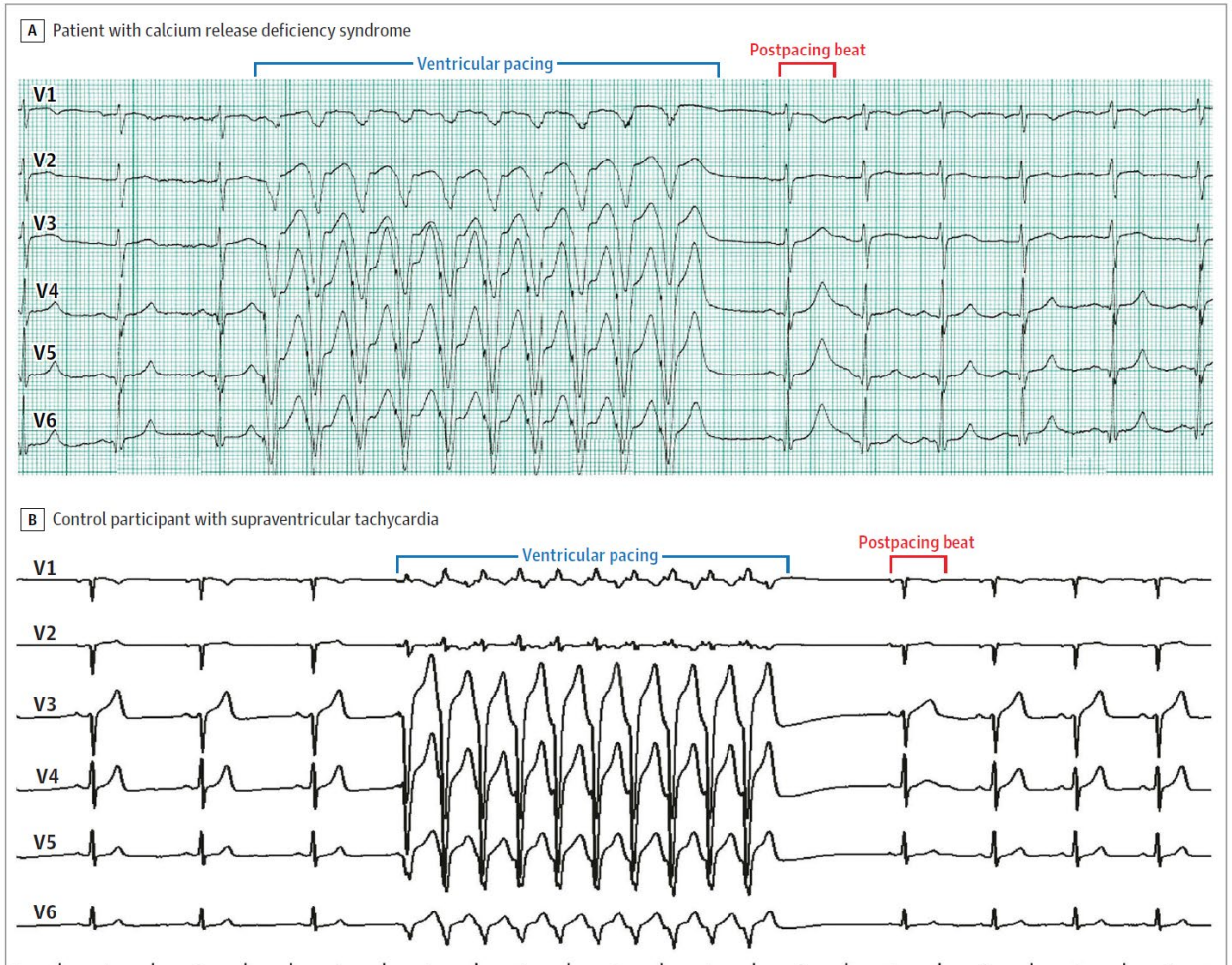
JAMA | Preliminary Communication

A Clinical Diagnostic Test for Calcium Release Deficiency Syndrome

Mingke Ni, MD; Ziv Dadon, MD; Julian O. M. Ormerod, MD, PhD; Johan Saenen, MD, PhD; Wiert F. Hoeksema, MD; Pavel Antiperovitch, MD; Rafik Tadros, MD, PhD; Morten K. Christiansen, MD, PhD; Christian Steinberg, MD; Marine Arnaud, MD; Shanshan Tian, PhD; Bo Sun, PhD; John Paul Estillore, MD; Ruiwu Wang, PhD; Habib R. Khan, MD, PhD; Thomas M. Roston, MD, PhD; Andrea Mazzanti, MD, PhD; John R. Giudicessi, MD, PhD; Konstantinos C. Siontis, MD; Aiman Alak, MD; J. Gabriel Acosta, MD; Syamkumar M. Divakara Menon, MBBS, MSc; Nigel S. Tan, MD; Christian van der Werf, MD, PhD; Babak Nazer, MD; Hari Vivekanantham, MD; Tanvi Pandya, MPH; Jennifer Cunningham; Lorne J. Gula, MD, MPH; Jorge A. Wong, MD, MPH; Guy Amit, MD; Melvin M. Scheinman, MD; Andrew D. Krahn, MD; Michael J. Ackerman, MD, PhD; Silvia G. Priori, MD, PhD; Michael H. Gollob, MD; Jeff S. Healey, MD, MS; Frederic Sacher, MD; Eyal Nof, MD; Michael Glikson, MD; Arthur A. M. Wilde, MD, PhD; Hugh Watkins, MD, PhD; Henrik K. Jensen, MD, DMSc, PhD; Pieter G. Postema, MD, PhD; Bernard Belhassen, MD; S. R. Wayne Chen, PhD; Jason D. Roberts, MD, MAS



NOVEL PHARMACOLOGICAL AGENTS: PRECISION MEDICINE APPROACH FOR TREATMENT OF CPVT

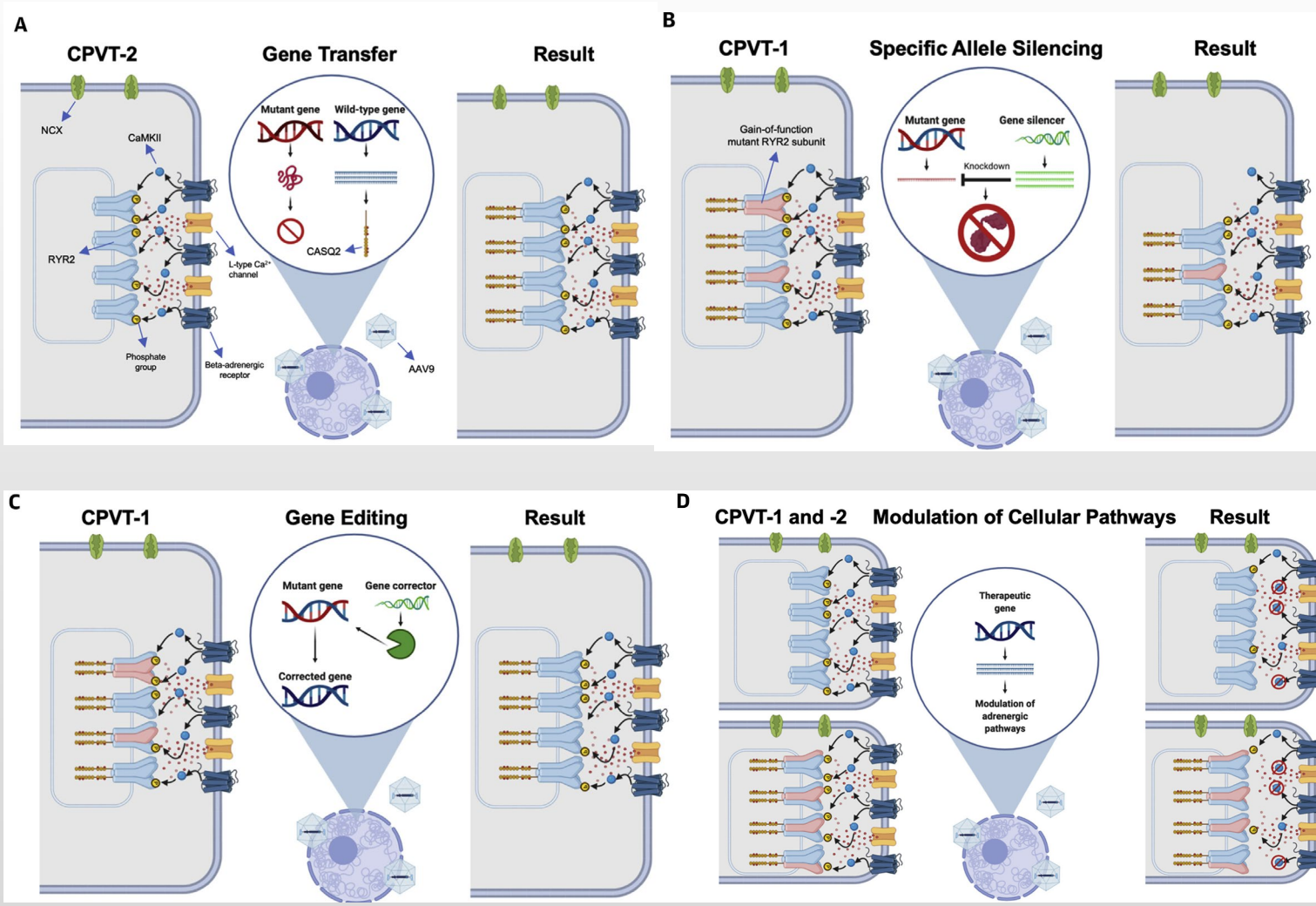
Different therapeutic strategies targeted to correct disrupted pathways that promote arrhythmogenesis have been suggested as potential novel treatments for CPVT.

- K201 - a derivative of 1,4-benzothiazepine - stabilizes Calstabin2-RYR2 binding, preventing arrhythmias
- Dantrolene - alters the interaction between the N-terminal and central domain of RYR2, thus increasing the open probability of RYR2, also corrects the defective interdomain interaction, thereby preventing VAs
- ent(+)-verticilide - derivative of the insecticide verticilide that is specific for the cardiac isoform of RYR2, inhibits DADs by selective inhibition of RYR2-mediated Ca2þ-release in intact Casq2-/- murine cardiomyocytes and suppresses arrhythmias in Casq2-/- mice

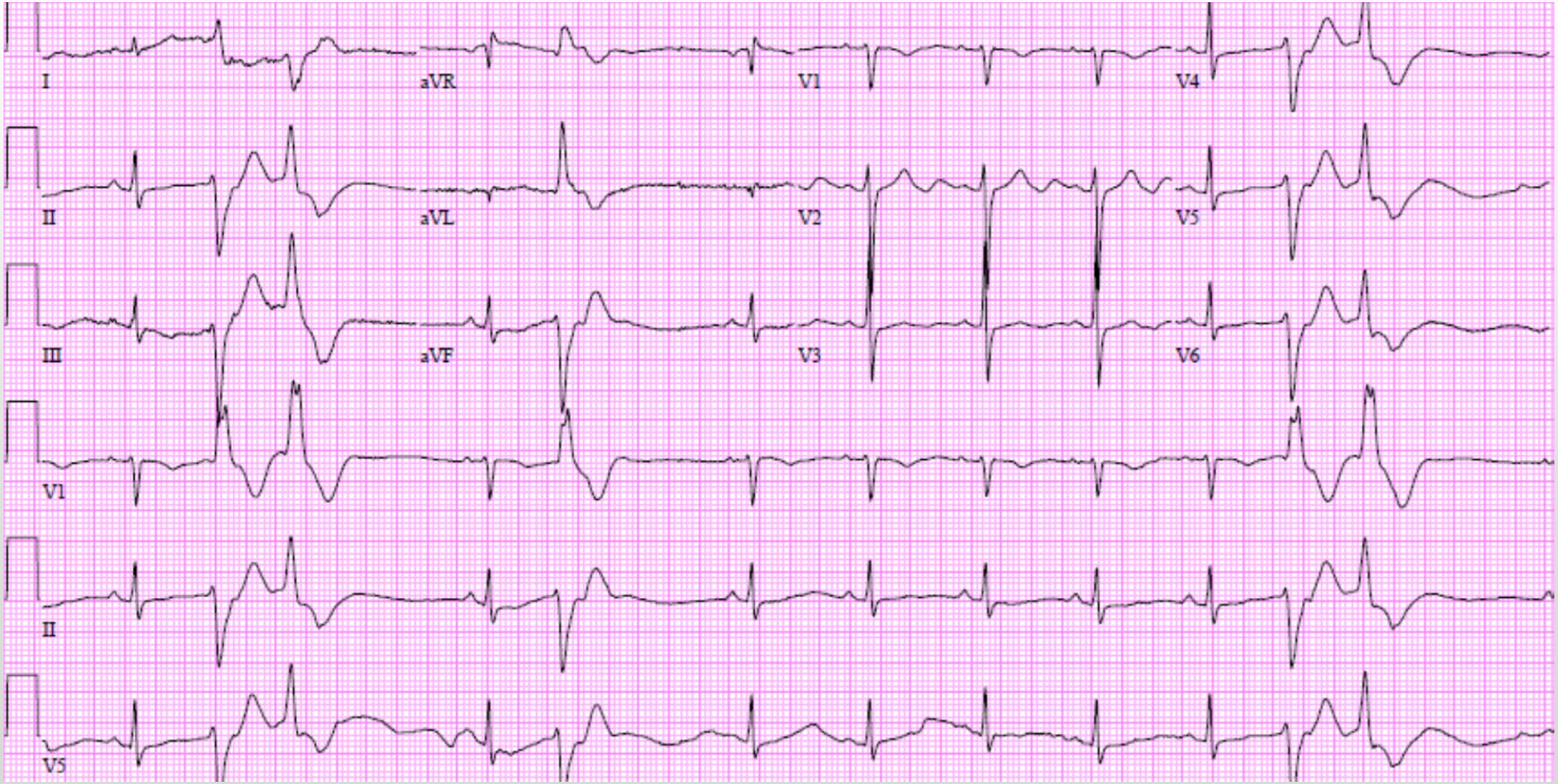
GENE THERAPY IN TYPICAL AND ATYPICAL CPVT: CURRENT POSSIBILITIES AND FUTURE PERSPECTIVES

- The most appealing future possibility is the use of gene therapy strategies to revert the molecular consequences of different causative variants.

- At present, 4 gene therapy strategies have been applied to CPVT models: 1) gene transfer, 2) allele silencing, 3) gene editing, and 4) modulation of signaling pathways



18 yo girl with recurrent syncope



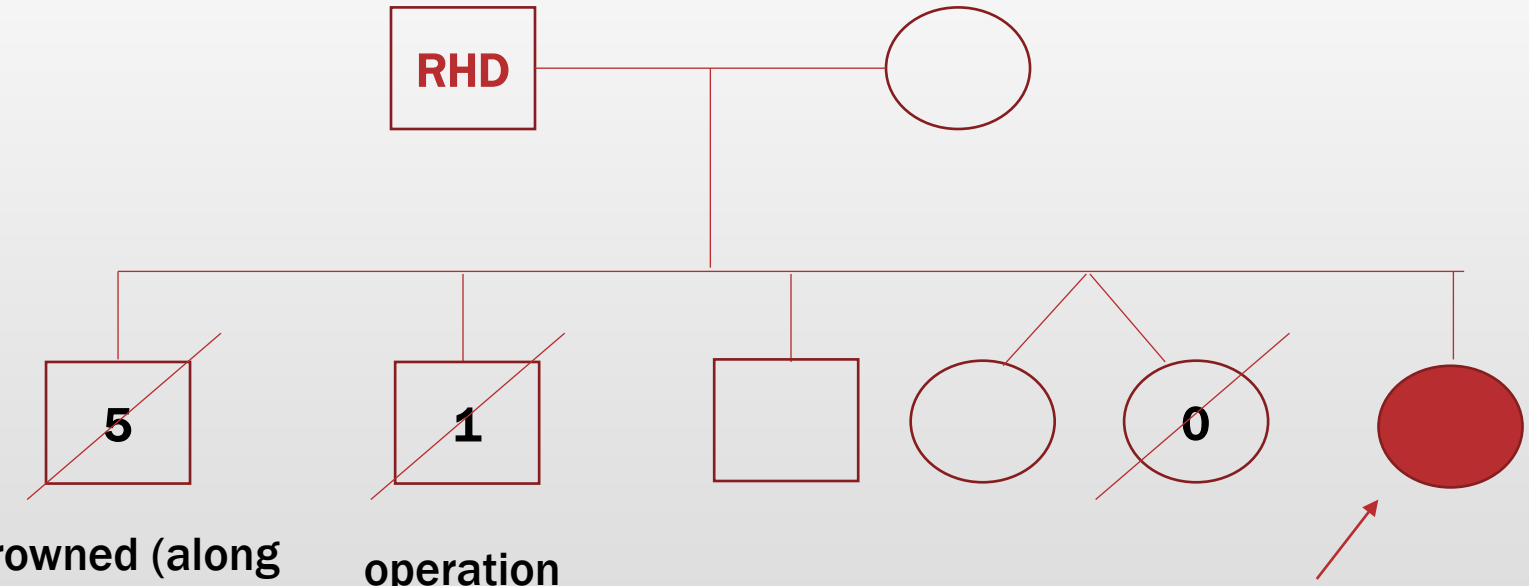
History

- Born premature at 34 weeks, healthy, no morphologic features
- At 3 years, during febrile illness, she lost consciousness. Mother describes her blue and resuscitated with DC. Diagnosis upon discharge was “febrile convulsion”.

Syncope

- First episode at 16 years while walking.
- Additional - every few months during walking, sitting or laying down.
- Describes **strong slow** heart beats, **seeing black**, and waking up after few seconds.
- Mother witnessed all – describes her **blue in face** and **cold**.
- Last episode ≈ a year ago.

Family history



drowned (along with 5 other children that got caught in the current)

operation because of “intracranial hemorrhage”

Tests performed

Underwent several tests during the past 2 years including:

- Echo, cardiac MRI – all normal
- Several Holter monitoring and exercise tests

But was never hospitalized for a thorough workup, until she arrived to our clinic at the age of 18

DD

LQTS2

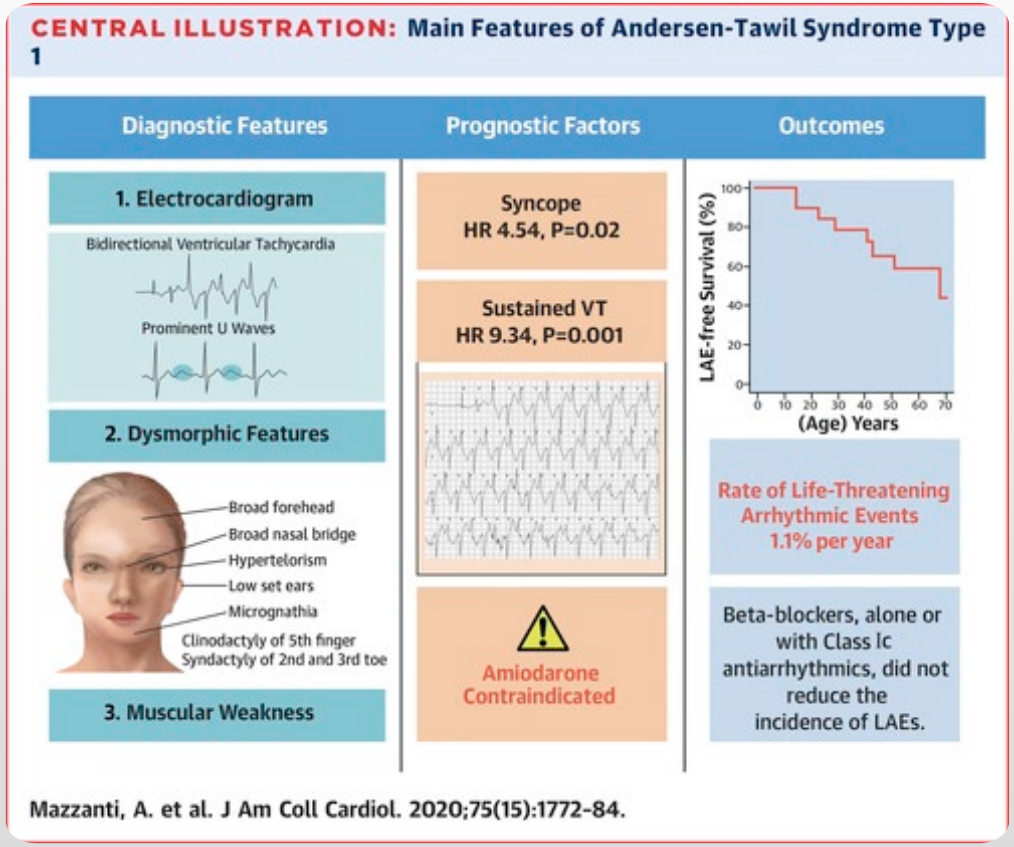
CPVT

LQTS7 (ATS)

Genetic analysis

Disease	Gene	Mutation tested	Test used	Results	Notes
Brugada syndrome	SCN5A	c. 3227 G>A, D1243N	NGS	Carrier	Rs199473599 ASJ=0.01
Andersen syndrome	KCNJ2	c. 232 G>A p.D78N	NGS	Carrier	Diseased

Andersen–Tawil syndrome (LQT7)



Rare genetic disorder (AD, 1/million) affecting several parts of the body.

Mutations in the KCNJ2 gene which encodes potassium channel protein.

The inward rectifier current (IK1) decreased by KCNJ2 loss of function mutation causes an increase in U wave amplitude rather than QT prolongation

The three predominant features:

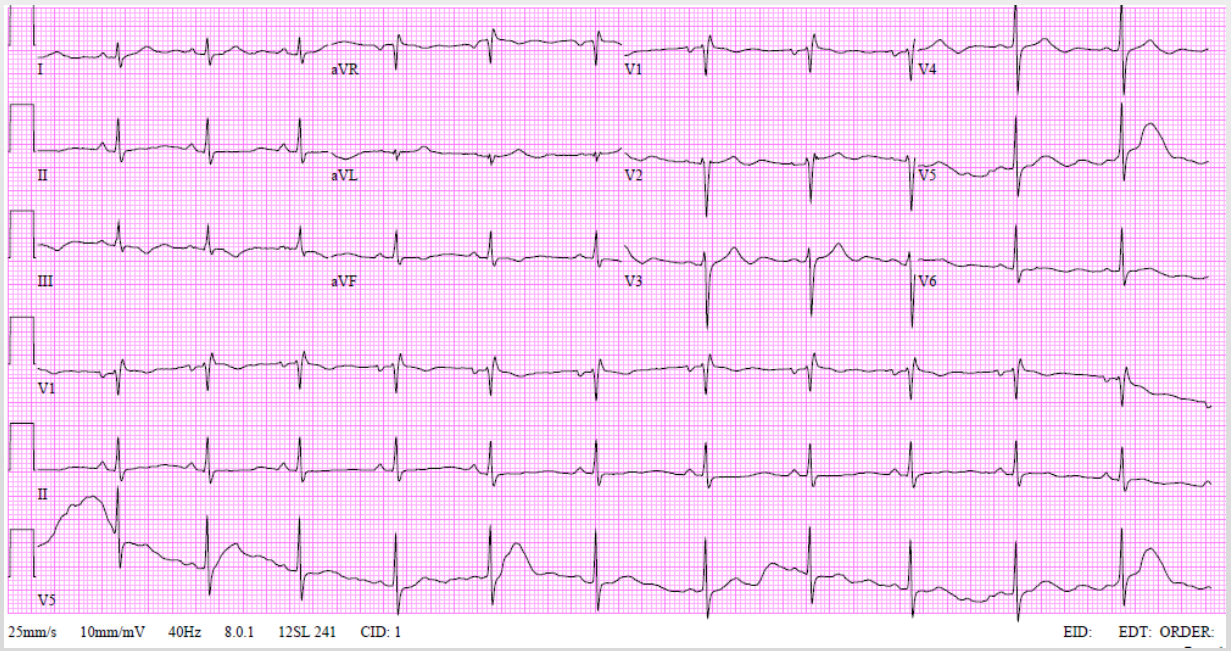
1. A long QT interval and a tendency to PVC or VT (bidirectional).
2. Physical characteristics including low-set ears and a small lower jaw.
3. Hypokalaemic periodic paralysis.

Recommendations	Class[a]	Level[b]
Diagnosis		
Genetic testing is recommended in patients with suspected Andersen–Tawil syndrome.[964,967]	I	C
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.[964,965,967,968,972]	IIa	C

Risk stratification, prevention of SCD and treatment of VA		
ICD implantation is recommended in patients with Andersen–Tawil syndrome after aborted CA or not-tolerated sustained VT.[964,967]	I	C
Beta-blockers and/or flecainide with or without acetazolamide should be considered in patients with Andersen–Tawil syndrome to treat VA.[964,970]	IIa	C
An ILR should be considered in patients with Andersen–Tawil syndrome and unexplained syncope.	IIa	C
ICD implantation may be considered in patients with Andersen–Tawil syndrome who have a history of unexplained syncope or suffer from tolerated sustained VT.[967]	IIb	C

Treatment

- Titrated with Propranolol up to 40 mg 3/day – remained with frequent PVCs
- Added flecainide slowly reaching 100 mg 2 times per day – PVCs subsided



Received ILR and NOT ICD

Thank you