ΤΙ ΠΡΕΠΕΙ ΝΑ ΓΝΩΡΙΖΕΙ ΟΓΕΝΙΚΟΣ ΚΑΡΔΙΟΛΟΓΟΣ ΓΙΑ ΤΙΣ ΔΙΑΥΛΟΠΑΘΕΙΕΣ

ΣΤΕΛΙΟΣ ΠΑΡΑΣΚΕΥΑΪΔΗΣ
ΔΙΕΥΘΥΝΤΗΣ ΕΣΥ

Α΄ Καρδιολογική Κλινική ΑΠΘ,
Νοσοκομείο ΑΧΕΠΑ, Θεσσαλονίκη
NO CONFLICT OF INTEREST
Sudden Cardiac Death (SCD)  
Aborted Cardiac Arrest (ACA)

- USA: 350,000 - 400,000 /year

**channelopathies:** 10%–15% of cases of unexplained SCD in young adults and children
ΔΙΑΥΛΟΠΑΘΕΙΕΣ

- Long QT syndrome
- Short QT syndrome
- Brugada syndrome
- Catecholaminergic polymorphic ventricular tachycardia (CPVT)
- Early repolarisation syndrome
Long QT Syndrome

- Genetic disorder: 1/2,000
- ECG evidence: QTc interval prolonged
  - > 450 ms in males
  - > 470 ms in females
- Hallmark arrhythmia: Torsade de pointes VT, or polymorphic VT
- Primary presenting symptom: Syncope
- SCD in children or young adults
- SCD: 13% first manifestation of LQTS
<table>
<thead>
<tr>
<th>LQT1</th>
<th>LQT2</th>
<th>LQT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Χρωμόσωμα 11</td>
<td>Χρωμόσωμα 7</td>
<td>Χρωμόσωμα 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II</th>
<th>aVF</th>
<th>V5</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="II график" /></td>
<td><img src="image2" alt="aVF график" /></td>
<td><img src="image3" alt="V5 график" /></td>
</tr>
</tbody>
</table>

- Πρώιμα εμφανιζόμενα ευρέα κύματα Τ
- Χαμηλού δυναμικού κύματα Τ
- Όψιμα κύματα Τ

T wave alternans

noticed T waves
LQTS (15 genes, > 500 mutations)

| LQTS subtype | Culprit gene | Protein | Functional effect of mutation | Frequency of cases (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>KCNQ1</td>
<td>Alpha-subunit of $I_{Ks}$</td>
<td>Loss-of-function, reduced $I_{Ks}$</td>
<td>30–35</td>
</tr>
<tr>
<td>LQT2</td>
<td>KCNH2</td>
<td>Alpha-subunit of $I_{Kr}$</td>
<td>Loss-of-function, reduced $I_{Kr}$</td>
<td>25–30</td>
</tr>
<tr>
<td>LQT3</td>
<td>SCN5A</td>
<td>Alpha-subunit of $I_{Na}$</td>
<td>Gain-of-function, increased late $I_{Na}$ inward current</td>
<td>5–10</td>
</tr>
<tr>
<td>LQT4</td>
<td>ANK2</td>
<td>Ankyrin-B; links membrane proteins with underlying cytoskeleton</td>
<td>Loss-of-function, disrupts multiple ion channels</td>
<td>&lt;1</td>
</tr>
<tr>
<td>LQT5</td>
<td>KCNE1</td>
<td>Beta-subunit of $I_{Ks}$</td>
<td>Loss-of-function, reduced $I_{Ks}$</td>
<td>&lt;1</td>
</tr>
<tr>
<td>LQT6</td>
<td>KCNE2</td>
<td>Beta-subunit of $I_{Kr}$</td>
<td>Loss-of-function, reduced $I_{Kr}$</td>
<td>&lt;1</td>
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<tr>
<td>LQT7</td>
<td>KCNJ2</td>
<td>Alpha-subunit of $I_{K1}$</td>
<td>Loss-of-function, reduced $I_{K1}$</td>
<td>&lt;1</td>
</tr>
<tr>
<td>LQT8</td>
<td>CACNA1 c</td>
<td>Alpha-subunit of $I_{Ca,l}$</td>
<td>Gain-of-function, increased $I_{Ca,l}$</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT9</td>
<td>CAV3</td>
<td>Caveolin-3; a scaffolding protein in caveolae</td>
<td>Increased late $I_{Na}$ inward current</td>
<td>&lt;1</td>
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<tr>
<td>LQT10</td>
<td>SCN4B</td>
<td>Beta 4-subunit of $I_{Na}$</td>
<td>Gain-of-function, increased late $I_{Na}$ inward current</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT11</td>
<td>AKAP9</td>
<td>A kinase-anchor protein-9; sympathetic $I_{Ks}$ activation</td>
<td>Loss-of-function, reduced $I_{Ks}$</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT12</td>
<td>SNTA1</td>
<td>Alphal-syntrophin; regulation of $I_{Na}$</td>
<td>Increased late $I_{Na}$ inward current</td>
<td>Rare</td>
</tr>
<tr>
<td>LQT13</td>
<td>KCNJ5</td>
<td>Kir 3.4</td>
<td>Loss-of-function, reduced $I_{K,Ac,h}$</td>
<td>Rare</td>
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<tr>
<td>LQT14</td>
<td>CALM1</td>
<td>Calmodulin-1</td>
<td>Altered calcium signaling</td>
<td>&lt;1</td>
</tr>
<tr>
<td>LQT15</td>
<td>CALM2</td>
<td>Calmodulin-2</td>
<td>Altered calcium signaling</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

LQT1, LQT2, LQT3: 95% of genotype-positive LQTS
75% of all LQTS
QT measurement
leads II, V5 or V6: longest value
Distribution of QTc intervals in carriers (LQTS) and noncarriers (control)
Holter ECG Recording in LQTS Patient with Syncope
(representative strips of ECG recording, part 2 of 2)
Risk-Stratification Scheme for ACA or SCD in LQTS Patients

- **Very High Risk (Secondary Prevention):**
  - Post-CPR or Spontaneous TDP
  - QTc > 500 msec, syncope
  - 14%

- **High Risk (Primary Prevention):**
  - Either one or more:
    - QTc > 500 msec
    - Prior syncope
  - 3%

- **Low Risk:**
  - QTc < 500 msec, no syncope
  - 0.5%

- Secondary prevention
  - Post-CPR, spontaneous TDP

*Goldenberg I, Moss A, JACC 2008;51:2291-300*
Probability of a Cardiac Event

probability of ACA or SCD among the 4 genotyped subgroups

Probability of LQTS-Related Events by Gender

first cardiac event (syncope, ACA, SCD)

A

Probability of a first Cardiac Event from Age 1 through 75 Years by Gender

B

Probability of ACA or SCD from Age 1 through 75 Years by Gender

probability of ACA or SCD by QTc category

probability of ACA or death in genotyped patients

# LQTS diagnostic (SCHWARTZ) criteria 1993–2012

<table>
<thead>
<tr>
<th>Electrocardiographic findings&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>QTc&lt;sup&gt;b&lt;/sup&gt;</td>
<td>≥480 ms</td>
<td>3</td>
<td>460–479 ms</td>
<td>2</td>
</tr>
<tr>
<td>B</td>
<td>QTc&lt;sup&gt;b&lt;/sup&gt; 4th minute of recovery from exercise stress test ≥480 ms</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Torsade de pointes&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>T-wave alternans</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>Notched T-wave in three leads</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>Low heart rate for age&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Syncope&lt;sup&gt;e&lt;/sup&gt; With stress</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Without stress</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Congenital deafness</td>
<td></td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Family members with definite LQTS&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Unexplained sudden cardiac death below age 30 among immediate family members&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SCORE:**
- ≤ 1 point: low probability of LQTS
- 1.5–3 points: intermediate probability of LQTS
- ≥ 3.5 points: high probability

Schwartz P, Ackerman M EHJ 2013

sensitivity: 19%  
specificity: 99%
Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes

Expert Consensus Recommendations on LQTS Diagnosis

1. LQTS is diagnosed:
   a. In the presence of an LQTS risk score $\geq 3.5$ in the absence of a secondary cause for QT prolongation and/or
   b. In the presence of an unequivocally pathogenic mutation in one of the LQTS genes or
   c. In the presence of a corrected QT interval for heart rate using Bazett’s formula (QTc) $\geq 500$ ms in repeated 12-lead electrocardiogram (ECG) and in the absence of a secondary cause for QT prolongation.

2. LQTS can be diagnosed in the presence of a QTc between 480 and 499 ms in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation.
Expert Consensus Recommendations on LQTS Therapeutic Interventions

Class I

1. The following lifestyle changes are recommended in all patients with a diagnosis of LQTS:
   a. Avoidance of QT-prolonging drugs (www.qtdrugs.org)
   b. Identification and correction of electrolyte abnormalities that may occur during diarrhea, vomiting, metabolic conditions, or imbalanced diets for weight loss

2. Beta-blockers are recommended in patients with a diagnosis of LQTS who are:
   a. Asymptomatic with QTc ≥ 470 ms and/or
   b. Symptomatic for syncope or documented ventricular tachycardia/ventricular fibrillation (VT/VF).
3. Left cardiac sympathetic denervation (LCSD) is recommended in high-risk patients with a diagnosis of LQTS in whom:
   a. Implantable cardioverter-defibrillator (ICD) therapy is contraindicated or refused and/or
   b. Beta-blockers are either not effective in preventing syncope/arrhythmias, not tolerated, not accepted or contraindicated.

4. ICD implantation is recommended in patients with a diagnosis of LQTS who are survivors of a cardiac arrest.

5. All LQTS patients who wish to engage in competitive sports should be referred to a clinical expert for the evaluation of risk.
6. **Beta-blockers can be useful** in patients with a diagnosis of LQTS who are asymptomatic with QTc $\leq 470$ ms.

7. **ICD implantation can be useful** in patients with a diagnosis of LQTS who experience recurrent syncopal events while on beta-blocker therapy.

8. **LCSD can be useful** in patients with a diagnosis of LQTS who experience breakthrough events while on therapy with beta-blockers/ICD.

9. **Sodium channel blockers can be useful**, as add-on therapy, for LQT3 patients with a QTc $\geq 500$ ms who shorten their QTc by $40$ ms following an acute oral drug test with one of these compounds: mexiletine, flecainide or ranolazine.
Consensus recommendations for ICDs in long QT syndrome

Legend

- Class I
- Class IIa
- Class IIb
- Class III

1. Prior cardiac arrest? Yes → ICD recommended
2. No → Recurrent syncope while on beta blocker?
   - Yes → ICD can be useful
   - No → Asymptomatic not treated with beta blockers
     - Yes → ICD is not indicated*

*Except under special circumstances, ICD implantation is not indicated in asymptomatic patients who have not been tried on beta-blocker therapy.
## Lifestyle Modifications Recommendations for LQTS Patients

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LQTS1</th>
<th>LQTS2</th>
<th>LQTS3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid competitive sport activity</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Avoid swimming without supervision</td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Avoid emotional stress</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Avoid exposure to acoustic stimuli mostly during sleep</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Avoid drugs that may prolong QT interval</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Avoid drugs that may deplete potassium/magnesium</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
</tbody>
</table>
LQTS (LQT1-3) genetic testing recommendations

Class I

- when a strong clinical index of suspicion for LQTS. Schwartz score > 3.5

- for any asymptomatic patient with QTc > 480 ms (prepuberty) or > 500 ms (adults) on serial 12-lead ECGs

Ackerman M et al. Europace 2011;13:1077–1109
LQTS genetic testing recommendations

Class I
Mutation-specific genetic testing is recommended for family members and other appropriate relatives subsequently following the identification of the LQTS-causative mutation in an index case.

Class IIb
for any asymptomatic patient with otherwise idiopathic QTc values > 460 ms (prepuberty) or
> 480 ms (adults) on serial 12-lead

Genetic tests: diagnostics in 75-80%
Short QT Syndrome (SQTS)

QTc : < 330 msec

or QTc : 360 ms and one or more of the following:
- a pathogenic mutation
- family history of SQTS
- family history of sudden death ≤ 40 yr
- survival of a VT/ VF episode in the absence of heart disease.

PQ segment depression : frequent

Male: 75%
SCD: 33%
A FIB: 18%

### Short QT Syndrome-Diagnostic score

**Diagnostic parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QTC</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;370</td>
<td>1</td>
</tr>
<tr>
<td>&lt;350</td>
<td>2</td>
</tr>
<tr>
<td>&lt;330</td>
<td>3</td>
</tr>
<tr>
<td><strong>J point–T peak interval</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;120 msec</td>
<td>1</td>
</tr>
<tr>
<td><strong>Clinical history</strong>*</td>
<td></td>
</tr>
<tr>
<td>History of sudden cardiac arrest</td>
<td>2</td>
</tr>
<tr>
<td>Documented polymorphic VT or VF</td>
<td>2</td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td>1</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
</tr>
<tr>
<td><strong>Family history</strong>*</td>
<td></td>
</tr>
<tr>
<td>First-degree or second-degree relative with high probability of SQTS</td>
<td>2</td>
</tr>
<tr>
<td>First-degree or second-degree relative with unexplained cardiac arrest</td>
<td>1</td>
</tr>
<tr>
<td>Sudden infant death syndrome</td>
<td>1</td>
</tr>
<tr>
<td><strong>Genotype</strong>*</td>
<td></td>
</tr>
<tr>
<td>Genotype-positive</td>
<td>2</td>
</tr>
<tr>
<td>Variant of unknown significance in a culprit gene</td>
<td>1</td>
</tr>
</tbody>
</table>

**Probability**

- **High**: ≥ 4
- **Intermediate**: 3
- **Low**: ≥ 2

*Spears D, Gollob M. The Application of Clinical Genetics 2015:8; 215-232*
Short QT syndrome - genetic subtype

<table>
<thead>
<tr>
<th>SQTS subtype</th>
<th>Culprit gene</th>
<th>Protein</th>
<th>Functional effect of mutation</th>
<th>Frequency of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SQTS1</td>
<td>KCNH2</td>
<td>Alpha-subunit of $I_{K_r}$</td>
<td>Loss-of-function, reduced $I_{K_r}$</td>
<td>18–33</td>
</tr>
<tr>
<td>SQTS2</td>
<td>KCNQ1</td>
<td>Alpha-subunit of $I_{K_s}$</td>
<td>Loss-of-function, reduced $I_{K_s}$</td>
<td>&lt;5</td>
</tr>
<tr>
<td>SQTS3</td>
<td>KCNJ2</td>
<td>Alpha-subunit of $I_{K_1}$</td>
<td>Loss-of-function, reduced $I_{K_1}$</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Genetic testing in SQTS: positive 18-40%
SQTS MANAGEMENT
Class I

1. ICD implantation *is recommended* in symptomatic patients with a diagnosis of SQTS who:
   
a. Are survivors of a cardiac arrest *and/or*
   
b. Have documented spontaneous sustained VT with or without syncope.

Class IIb

2. ICD implantation *may be considered* in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.

3. Quinidine *may be considered* in asymptomatic patients with a diagnosis of SQTS and a family history of SCD. (SQTS1)

4. Sotalol *may be considered* in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.
Brugada syndrome (BRS) is diagnosed in patients with ST-segment elevation with type 1 morphology ≥ 2 mm in ≥ 1 lead among the right precordial leads V₁, V₂ positioned in the 2nd, 3rd, or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs.

BrS is diagnosed in patients with type 2 or type 3 ST-segment elevation in ≥ 1 lead among the right precordial leads V₁, V₂ positioned in the 2nd, 3rd, or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type I ECG morphology.
# Brugada syndrome (BRS)

(SCN5A, K, Ca)

<table>
<thead>
<tr>
<th>BrS subtype</th>
<th>Culprit gene</th>
<th>Protein</th>
<th>Functional effect of mutation</th>
<th>Frequency of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BrS1</td>
<td>SCN5A</td>
<td>Alpha-subunit of $i_{Na}$</td>
<td>Gain-of-function, reduced $I_{Na}$</td>
<td>11–28</td>
</tr>
<tr>
<td>BrS2</td>
<td>GPD1L</td>
<td>Glycerol-3-phosphate dehydrogenase</td>
<td>Loss-of-function, reduced $I_{Na}$</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS3</td>
<td>CACNA1C</td>
<td>Alpha-subunit of $i_{CaL}$</td>
<td>Loss-of-function, reduced $I_{CaL}$</td>
<td>6–7</td>
</tr>
<tr>
<td>BrS4</td>
<td>CACNB2</td>
<td>Beta-subunit of $i_{CaL}$</td>
<td>Loss-of-function, reduced $I_{CaL}$</td>
<td>4–5</td>
</tr>
<tr>
<td>BrS5</td>
<td>SCN1B</td>
<td>Beta-subunit of $i_{Na}$</td>
<td>Loss-of-function, reduced $I_{Na}$</td>
<td>1–2</td>
</tr>
<tr>
<td>BrS6</td>
<td>KCNE3</td>
<td>Beta-subunit of $i_{to}$</td>
<td>Gain-of-function, increased $I_{to}$</td>
<td>&lt;1</td>
</tr>
<tr>
<td>BrS7</td>
<td>SCN3B</td>
<td>Beta-subunit of $i_{Na}$</td>
<td>Loss-of-function, reduced $I_{Na}$</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS8</td>
<td>HCN4</td>
<td>Alpha-subunit of $i_{i}$</td>
<td>Loss-of-function, reduced $I_{i}$</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Genetic testing in BRS: positive 25-40%
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajmaline</td>
<td>1 mg/kg over 5 min</td>
<td>IV</td>
</tr>
<tr>
<td>Flecainide</td>
<td>2 mg/kg over 10 min</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>400 mg</td>
<td>PO</td>
</tr>
<tr>
<td>Procainamide</td>
<td>10 mg/kg over 10 min</td>
<td>IV</td>
</tr>
<tr>
<td>Pilsicainide</td>
<td>1 mg/kg over 10 min</td>
<td>IV</td>
</tr>
</tbody>
</table>
spontaneous type I ECG, syncope, ventricular refractory period (VRP) < 200 ms, and QRS fragmentation seem useful to identify candidates for prophylactic ICD implantation. VT/ VF inducibility : NS

Priori S et al. JACC 2012; 59:37-45
The following lifestyle changes are recommended in all patients with diagnosis of BrS:

a. Avoidance of drugs that may induce or aggravate ST-segment elevation in right precordial leads (e.g., Brugadadrugs.org)

b. Avoidance of excessive alcohol intake

c. Immediate treatment of fever with antipyretic drugs.

2. ICD implantation is recommended in patients with a diagnosis of BrS who:

a. Are survivors of a cardiac arrest and/or

b. Have documented spontaneous sustained VT with or without syncope.
3. ICD implantation *can be useful* in patients with a spontaneous diagnostic type I ECG who have a history of syncope judged to be likely caused by ventricular arrhythmias.

4. **Quinidine** *can be useful* in patients with a diagnosis of BrS and history of arrhythmic storms defined as more than two episodes of VT/VF in 24 hours.

5. **Quinidine** *can be useful* in patients with a diagnosis of BrS who:
   a. Qualify for an ICD but present a contraindication to the ICD or refuse it *and/or*
   b. Have a history of documented supraventricular arrhythmias that require treatment.

6. **Isoproterenol infusion** *can be useful* in suppressing arrhythmic storms in BrS patients.
Class IIb

7. ICD implantation *may be considered* in patients with a diagnosis of BrS who develop VF during programmed electrical stimulation (inducible patients).

8. Quinidine *may be considered* in asymptomatic patients with a diagnosis of BrS with a spontaneous type I ECG.

9. Catheter ablation *may be considered* in patients with a diagnosis of BrS and history of arrhythmic storms or repeated appropriate ICD shocks.

- EP study: IIb indication
ICDs in Brugada syndrome

Class I
- Prior cardiac arrest or Sustained VT?
  - Yes: ICD recommended
  - No

Class IIa
- Spontaneous Type I ECG and hx of syncope judged to be caused by vent arrhythmias?
  - Yes: ICD can be useful
  - No

Class IIb
- Inducible VF on EP Study?
  - Yes: ICD may be considered
  - No or No EP Study

Class III
- Asymptomatic with drug induced Type I ECG and family history of SCD?
  - Yes: ICD is not indicated
Man, 40 yrs, syncope during sleep
ECG on admission (type 2 BRS)
Procainamide Test
18 Months later – Electrical storm (3 shocks-ICD) during fever
ECG post electrical storm (type 1 BRS)
ECG on admission (type 1 BRS)
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

**Prevalence:** 1:10,000

- mortality (untreated): 50% by the age of 30 years
- mutations in the gene encoding cardiac ryanodine receptor (*RyR2*) or calsequestrin (*CASQ2*)
CPVT-DIAGNOSIS

1. CPVT *is diagnosed* in the presence of a structurally normal heart, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic ventricular premature beats (VPBs) or VT in an individual younger than <40 years.

2. CPVT *is diagnosed* in patients (index case or family member) who have a pathogenic mutation.

3. CPVT *is diagnosed* in family members of a CPVT index case with a normal heart who manifest exercise-induced premature ventricular contractions or bidirectional/polyformic VT.

4. CPVT *can be diagnosed* in the presence of a structurally normal heart and coronary arteries, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic VPBs or VT in an individual older than >40 years.
RISK STRATIFICATION

HIGH RISK

• occurrence of cardiac arrest (not syncope) before diagnosis
• diagnosis in childhood
• after diagnosis, the lack of beta-blocker therapy and the use of beta-blockers other than nadolol
• persistence of complex ectopy in exercise tests
## CPVT-genetic subtype

<table>
<thead>
<tr>
<th>CPVT subtype</th>
<th>Culprit gene</th>
<th>Protein</th>
<th>Functional effect of mutation</th>
<th>Frequency of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPVT1</td>
<td>RyR2</td>
<td>Cardiac ryanodine receptor</td>
<td>Gain-of-function</td>
<td>60</td>
</tr>
<tr>
<td>CPVT2</td>
<td>CASQ2</td>
<td>Calsequestrin-2</td>
<td>Loss-of-function</td>
<td>1-2</td>
</tr>
<tr>
<td>CPVT3</td>
<td>Locus at 7p22-p14 (homozygous)</td>
<td>Not known</td>
<td>Not known</td>
<td>Rare</td>
</tr>
<tr>
<td>CPVT4</td>
<td>CALM1</td>
<td>Calmodulin</td>
<td>Loss-of-function</td>
<td>Rare</td>
</tr>
<tr>
<td>CPVT5</td>
<td>TRDN</td>
<td>Triadin</td>
<td>Loss-of-function</td>
<td>Rare</td>
</tr>
</tbody>
</table>

### Genetic testing in CPVT:
- positive 60%

### Genetic testing is recommended:
- in pts with exercise or emotional stress induced bidirectional VT or polymorphic VT
- after identification of a pathogenic mutation: to first-degree relatives
Management  CPVT
Class I

1. The following **lifestyle changes** are **recommended** in all patients with a diagnosis of CPVT:
   a. Limit/avoid competitive sports
   b. Limit/avoid strenuous exercise
   c. Limit exposure to stressful environments.

2. Beta-blockers are **recommended** in all symptomatic patients with a diagnosis of CPVT. **Nadolol, propranolol**

3. ICD implantation is **recommended** in patients with a diagnosis of CPVT who experience cardiac arrest, recurrent syncope or polymorphic/bidirectional VT despite optimal medical management, and/or LCSD.
4. Flecainide *can be a useful* addition to beta-blockers in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT while on beta-blockers.

5. Beta-blockers *can be useful* in carriers of a pathogenic CPVT mutation without clinical manifestations of CPVT (*concealed mutation-positive* patients).
6. LCSD may be considered in patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT/several appropriate ICD shocks while on beta-blockers and in patients who are intolerant or with contraindication to beta-blockers.

Class III

7. ICD as a stand-alone therapy is not indicated in an asymptomatic patient with a diagnosis of CPVT.

8. Programmed electrical stimulation is not indicated in CPVT patients.
Early repolarization

- prevalence: 1-13% (6-24%) in general population
- male: 75%
- 40% of healthy athletes (series including 1000 athletes)

- idiopathic VF (IVF): 15-70%
Early Repolarization Syndrome (ERS)

1. **ERS syndrome is diagnosed** in the presence of J-point elevation $\geq 1$ mm in $\geq 2$ contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/polymorphic VT.

2. **ERS syndrome can be diagnosed** in a SCD victim with a negative autopsy and medical chart review, with a previous ECG demonstrating J-point elevation $\geq 1$ mm in $\geq 2$ contiguous inferior and/or lateral leads of a standard 12-lead ECG.

3. **ERS pattern can be diagnosed** in the presence of J-point elevation $\geq 1$ mm in $\geq 2$ contiguous inferior and/or lateral leads of a standard 12-lead ECG.
Early repolarization

"benign"

"malignant"
Distinguishing “benign” from “malignant early repolarization”: The value of the ST-segment morphology

Raphael Rosso, MD,*‡ Eran Glikson,*‡ Bernard Belhassen, MD,∗ Amos Katz, MD,† Amir Halkin, MD,* Arie Steinvil, MD,* Sami Viskin, MD*

n= 45 with VF

Rapidly ascending ST segment (benign)  
Horizontal/descending ST segment (malignant)

J wave
Management of ERS

Class I

1. **ICD implantation** is **recommended** in patients with a diagnosis of ER syndrome who have survived a cardiac arrest.

Class IIa

2. **Isoproterenol** infusion **can be useful** in suppressing electrical storms in patients with a diagnosis of ER syndrome.

3. **Quinidine** in addition to an ICD **can be useful** for secondary prevention of VF in patients with a diagnosis of ER syndrome.
Class IIb

4. ICD implantation may be considered in symptomatic family members of ER syndrome patients with a history of syncope in the presence of ST-segment elevation $\geq 1$ mm in two or more inferior or lateral leads.

5. ICD implantation may be considered in asymptomatic individuals who demonstrate a high-risk ER ECG pattern (high J-wave amplitude, horizontal/descending ST-segment) in the presence of a strong family history of juvenile unexplained sudden death with or without a pathogenic mutation.

Class III

6. ICD implantation is not recommended in asymptomatic patients with an isolated ER ECG pattern.
MALE, 35 yrs - SYNCOPE

QTc = 416 msec
ECG
ECG-Early repolarization

interpolated PVC, coupling interval: < 200 ms
HOLTER

16 sec

echo, stress test, coronary angio : normal

ICD IMPLANTATION
CONCLUSION
απαραίτητος ισχυρός δείκτης κλινικής υποψίας

Inherited Arrhythmia Clinics

Patients (probands) and first-degree relatives with a diagnosed or suspected inherited cardiovascular disease as a potential cause of SCD (SUDS/SUDI) should be evaluated in a dedicated clinic with appropriately trained staff.
ΕΥΧΑΡΙΣΤΩ για την προσοχή σας
Prevention of Ventricular Fibrillation Episodes in Brugada Syndrome by Catheter Ablation Over the Anterior Right Ventricular Outflow Tract Epicardium

substrate ablation

Nademane K et al. Circulation 2011;123:1270-1279
Sudden Cardiac Arrest Associated with Early Repolarization

Michel Haïssaguerre, M.D., Nicolas Derval, M.D., Frederic Sacher, M.D.,

Propability of no VF recurrence

n=206 VF
ER: 31% in VF vs 5% control