Πρόληψη αιφνιδίου καρδιακού θανάτου σε ασθενή με καναλοπάθεια

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Ιατρικό Κέντρο Αθηνών
Disclosures

• Nothing to disclose
Overview

• Long QT
• Short QT
• Catecholaminergic Polymorphic VT
• Brugada Syndrome
• +/- Early Repolarization Syndrome
Overview

• Long QT
• Short QT
• Catecholaminergic Polymorphic VT
• Brugada Syndrome
Key Genes in Long QT syndrome

- Mutations in 13 genes associated with LQTS.
- Pathogenic mutations identified in 75% of cases.
- Three main genes account for 90% of genotyped cases.

### Long QT Syndrome (LQTS)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Protein</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNQ1</td>
<td>11p15.5</td>
<td>potassium channel alpha subunit (Kv7.1)</td>
<td>30-35%</td>
</tr>
<tr>
<td>KCNH2</td>
<td>7q35-q36</td>
<td>potassium channel alpha subunit (Kv11.1)</td>
<td>25-40%</td>
</tr>
<tr>
<td>SCN5A</td>
<td>3p21</td>
<td>cardiac sodium channel alpha subunit (NaV1.5)</td>
<td>5-10%</td>
</tr>
</tbody>
</table>
### Diagnosis of Long QT Syndrome (in the absence of syncope or QT prolongation)

**Recommendations**

<table>
<thead>
<tr>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

LQTS is diagnosed in either:
- QTc ≥ 480 ms in repeated 12-lead ECGs OR
- LQTS risk score ≥ 3

LQTS is diagnosed in the presence of a confirmed pathogenic LQTS mutation, irrespective of the QT duration.

ECG diagnosis of LQTS should be considered in the presence of a 460 ms < QTc < 480 ms in repeated 12-lead ECGs in patients with an unexplained syncopal episode or documented ventricular tachycardia/fibrillation in the absence of heart disease.

**QTc ≥ 480 ms in Asymptomatic Individuals**

**Mutation Carriers**

**QTc > 460 ms in Patients with Syncope**

**Priori SG, Eur Heart J 2015;36:2793-867**
The Pillars for Risk Assessment

Original Article

Risk Stratification in the Long-QT Syndrome

Silvia G. Priori, M.D., Ph.D., Peter J. Schwartz, M.D., Carlo Napolitano, M.D., Ph.D., Raffaella Bloise, M.D., Elena Ronchetti, Ph.D., Massimiliano Grillo, M.D., Alessandro Vicentini, M.D., Carla Spazzolini, M.V., Janni Nastoli, B.S., Georgia Bottelli, B.S., Roberta Folli, B.S., and Donata Cappelletti, B.S.
Survival is modified by Genotype
...and by the QTc interval

Priori et al. NEJM 2003
Interplay Between Genetic Substrate, QTc Duration, and Arrhythmia Risk in Patients With Long QT Syndrome

Andrea Mazzanti, MD, Riccardo Maragna, MD, Gaetano Vacanti, MD, Nicola Monteforte, MD, Raffaella Blosse, MD, Maira Marino, RN, Lorenzo Braghieri, MD, Patrick Gambelli, BSc, Mirella Memmi, BSc, Elena Pagan, MSc, Massimo Morini, DEng, Alberto Malovini, BSc, Martin Ortiz, MD, Luciana Sacilotto, MD, Riccardo Bellazzi, PhD, Lorenzo Monserrat, MD, PhD, Carlo Napolitano, MD, PhD, Vincenzo Bagnardi, PhD, Silvia G. Priori, MD, PhD
Clinical Predictors

- Aborted Cardiac Death HR 2.6
- History of Syncope HR 2.5
- Female Gender HR 1.7

Mazzanti et al. JACC 2018
Genotype and QTc Duration

**TABLE 2** Effect of QTc Duration on Risk of Experiencing LAEs at 5 Years Off Beta-Blockers Stratified by genotype

<table>
<thead>
<tr>
<th>QTC Duration, ms</th>
<th>n</th>
<th>Risk (95% CI)</th>
<th>Risk (95% CI)</th>
<th>n</th>
<th>Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>461-470</td>
<td>78</td>
<td>1.3 (0.3-2.3)</td>
<td>44</td>
<td>3.0 (0.8-5.2)</td>
<td>18</td>
</tr>
<tr>
<td>471-480</td>
<td>63</td>
<td>1.5 (0.3-2.7)</td>
<td>26</td>
<td>3.4 (1.0-5.8)</td>
<td>16</td>
</tr>
<tr>
<td>481-490</td>
<td>50</td>
<td>1.7 (0.4-3.0)</td>
<td>39</td>
<td>3.9 (1.3-6.5)</td>
<td>15</td>
</tr>
<tr>
<td>491-500</td>
<td>22</td>
<td>2.0 (0.5-3.5)</td>
<td>21</td>
<td>4.5 (1.5-7.4)</td>
<td>7</td>
</tr>
<tr>
<td>501-510</td>
<td>5</td>
<td>3.6 (1.4-9.9)</td>
<td>2</td>
<td>12.6 (4.1-17.9)</td>
<td>7</td>
</tr>
<tr>
<td>511-520</td>
<td>3</td>
<td>3.6 (1.4-9.9)</td>
<td>2</td>
<td>12.6 (4.1-17.9)</td>
<td>7</td>
</tr>
<tr>
<td>521-530</td>
<td>5</td>
<td>4.4 (0.8-7.9)</td>
<td>5</td>
<td>9.9 (3.7-15.7)</td>
<td>3</td>
</tr>
<tr>
<td>531-540</td>
<td>5</td>
<td>4.4 (0.8-7.9)</td>
<td>5</td>
<td>9.9 (3.7-15.7)</td>
<td>3</td>
</tr>
<tr>
<td>541-550</td>
<td>2</td>
<td>4.4 (0.8-7.9)</td>
<td>5</td>
<td>9.9 (3.7-15.7)</td>
<td>3</td>
</tr>
<tr>
<td>551-560</td>
<td>4</td>
<td>4.4 (0.8-7.9)</td>
<td>5</td>
<td>9.9 (3.7-15.7)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;560</td>
<td>14</td>
<td>5.1 (0.8-9.1)</td>
<td>22</td>
<td>11.3 (4.1-17.9)</td>
<td>7</td>
</tr>
</tbody>
</table>

- **LQT2** -> Risk 130% vs. LQT1
- **LQT3** -> Risk 157% vs. LQT1

15% increase in Risk every 10 ms QTc increase

*Mazzanti et al. JACC 2018*
Calculated 5 year Risk

Mazzanti et al. JACC 2018
LQT is a treatable disorder
Lifestyle modifications

LQTS: Lifestyle modifications for all patients (class I)

- Avoidance of QT prolonging drugs...

  www.crediblemeds.org

- Correction of electrolyte abnormalities:

- Avoidance of genotype-specific triggers for arrhythmias:

  LQT1

  LQT2
Pharmacological Therapy

**Beta-blockers for all patients?**

<table>
<thead>
<tr>
<th>Beta-blockers are recommended in patients with a clinical diagnosis of LQTS.</th>
<th>I</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers should be considered in carriers of a causative LQTS mutation and normal QT interval.</td>
<td>Ila</td>
<td>B</td>
</tr>
</tbody>
</table>


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**Cardiac Event Rate Before / After BB**

<table>
<thead>
<tr>
<th>Cardiac Events/patient/year</th>
<th>Before BB</th>
<th>After BB</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1 (n=69)</td>
<td>0.375</td>
<td>0.125</td>
</tr>
<tr>
<td>LQT2 (n=42)</td>
<td>0.375</td>
<td>0.25</td>
</tr>
<tr>
<td>LQT3 (n=28)</td>
<td>0.375</td>
<td>0.125</td>
</tr>
</tbody>
</table>

p<0.001  
p=NS

Moss et al Circulation 2000
Arrhythmic Events on β blockers

Priori et al. JAMA 2004
Sodium Channel Blockers

Sodium channel blockers (mexiletine, flecainide, or ranolazine) may be considered as add-on therapy to shorten QT interval in LQT3 patients with a QTc >500 ms.

Before mexiletine

QTc 542 ms

After mexiletine

QTc 427 ms
ICD

ICD?

Survivors of CA

ICD implantation with the use of beta-blockers is recommended in LQTS patients with previous cardiac arrest.

ICD implantation in addition to beta-blockers should be considered in LQTS patients who experienced syncope and/or VT while receiving an adequate dose of beta-blockers.

Syncope during BB Therapy

Implant of an ICD may be considered in a beta-blocker therapy in asymptomatic carriers of a pathogenic mutation in KCNH2 or SCN5A when QTc is >500 ms.

Asymptomatic with QTc > 500 ms and LQT2 or LQT3
Case 1

- Γυναίκα 39 ετών
- Τραυματική συγκοπή Χ 4 τις τελευταίες 48 ώρες (2 ΤΕΠ)
- Κακοήθεις χαρακτήρες συγκοπής (ύπτια θέση)
- 3ος μήνας από τη γέννηση του 2ου παιδιού
- Χωρίς χρήση φαρμάκων τους τελευταίους 3 μήνες
Case 1

Χωρίς ηλεκτρολυτικές διαταραχές
Case 1
Overview

• Long QT
• Short QT
• Catecholaminergic Polymorphic VT
• Brugada Syndrome
ICD in Short QT

### Asymptomatic

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>1. In asymptomatic patients with a short QTc interval, observation without treatment is recommended (S7.9.1.5-1,S7.9.1.5-2).</td>
</tr>
<tr>
<td>I</td>
<td>B-NR</td>
<td>2. In patients with short QT syndrome who have a cardiac arrest or sustained VA, an ICD is recommended if meaningful survival greater than 1 year is expected (S7.9.1.5-3–S7.9.1.5-5).</td>
</tr>
</tbody>
</table>

### Survivors of CA
Risk Stratification

• Markedly shortened QTc values <300 ms are associated with increased risk of SCD
  • especially during sleep or rest, in young persons, in whom the median QTc was 285 ms

• Clinical score including
  • QTc duration,
  • clinical history of documented polymorphic VT or VF,
  • unexplained syncope,
  • Family history of autopsy-negative SCD or sudden infant death syndrome,
  • positive genotype results (SQT1), KCNQ1 (SQT2), and KCNJ2 (SQT3)
Overview

• Long QT
• Short QT
• Catecholaminergic Polymorphic VT
• Brugada Syndrome
### b blocker

<table>
<thead>
<tr>
<th>COR</th>
<th>LOP</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td><strong>1.</strong> In patients with catecholaminergic polymorphic ventricular tachycardia, a beta blocker is recommended (S7.9.1.2-1, S7.9.1.2-2).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>I</th>
<th>B-NR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2.</strong> 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 (S7.9.1.2-2—S7.9.1.2-6).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IIa</th>
<th>B-NR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.</strong> In patients with catecholaminergic polymorphic ventricular tachycardia and with clinical VT or exertional syncope, genetic counseling and genetic testing are reasonable (S7.9.1.2-7).</td>
<td></td>
</tr>
</tbody>
</table>

### Genetic testing

### Recurrent VA or Syncope: bb + flecainide, LCD, ICD
Overview

• Long QT
• Short QT
• Catecholaminergic Polymorphic VT
• Brugada Syndrome
Figure 4. Patients 7 and 8. Electrocardiograms during sinus rhythm.
Paper speed = 25 mm/s. Abbreviations as in Figure 1.
Right Bundle Branch Block, Persistent ST Segment Elevation and Sudden Cardiac Death: A Distinct Clinical and Electrocardiographic Syndrome

A Multicenter Report

PEDRO BRUGADA, MD, JOSEP BRUGADA, MD
Aalst, Belgium and Barcelona, Spain

Objectives. The objectives of this study were to present data on eight patients with recurrent episodes of aborted sudden death unexplainable by currently known diseases whose common clinical and electrocardiographic (ECG) features define them as having a distinct syndrome different from idiopathic ventricular fibrillation.

Background. Among patients with ventricular arrhythmias who have no structural heart disease, several subgroups have been defined. The present patients constitute an additional subgroup with these findings.

Methods. The study group consisted of eight patients, six male and two female, with recurrent episodes of aborted sudden death. Clinical and laboratory data and results of electrocardiography, electrophysiology, echocardiography, angiography, histologic study and exercise testing were available in most cases.

Results. The ECG during sinus rhythm showed right bundle branch block, normal QT interval and persistent ST segment elevation in precordial leads V1 to V4 and 3 not explainable by electrolyte disturbances, ischemia or structural heart disease. No histologic abnormalities were found in the four patients in whom ventricular biopsies were performed. The arrhythmia leading to (aborted) sudden death was a rapid polymorphic ventricular tachycardia initiating after a short coupled ventricular extrasystole. A similar arrhythmia was initiated by two to three ventricular extrastimuli in four of the seven patients studied by programmed electrical stimulation. Four patients had a prolonged HV interval during sinus rhythm. One patient receiving amiodarone died suddenly during implantation of a demand ventricular pacemaker. The arrhythmia of two patients was controlled with a beta-adrenergic blocking agent. Four patients received an implantable defibrillator that was subsequently used by one of them, and all four are alive. The remaining patient received a demand ventricular pacemaker and his arrhythmia is controlled with amiodarone and diphenylhydantoin.

Conclusions. Common clinical and ECG features define a distinct syndrome in this group of patients. Its causes remain unknown.

(I Am Coll Cardiol 1992;20:1391-6)
Special Article

Brugada Syndrome: Update 2009

Pedro Brugada, Begoña Benito, Ramon Brugada, Josep Brugada

The Ramon Brugada Sr. Foundation, the Universities of Barcelona (Fundacio Clinic), Girona (Spain) and Brussels, Belgium (UZ Brussels-VUB)
Consensus documents on BrS

Proposed Diagnostic Criteria for the Brugada Syndrome
Consensus Report

Arthur A.M. Wilde, MD, PhD; Charles Antzelevitch, PhD; Martin Borggrefe, MD, PhD; Josep Brugada, MD; Ramón Brugada, MD; Pedro Brugada, MD, PhD; Domenico Corrado, MD; Richard N.W. Hauer, MD, PhD; Robert S. Kass, MD; Koonlawee Nademane, MD; Silvia G. Priori, MD, PhD; Jeffrey A. Towbin, MD; for the Study Group on the Molecular Basis of Arrhythmias of the European Society of Cardiology

Brugada Syndrome
Report of the Second Consensus Conference
Endorsed by the Heart Rhythm Society and the European Heart Rhythm Association

Charles Antzelevitch, PhD; Pedro Brugada, MD, PhD; Martin Borggrefe, MD, PhD; Josep Brugada, MD; Ramon Brugada, MD; Domenico Corrado, MD, PhD; Ihor Gussak, MD, PhD; Herve LeMarec, MD; Koonlawee Nademane, MD; Andres Ricardo Perez Riera, MD; Wataru Shimizu, MD, PhD; Eric Schulze-Bahr, MD; Hanno Tan, MD, PhD; Arthur Wilde, MD, PhD
Consensus documents on BrS

J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge

2016

Charles Antzelevitch, PhD, FHRS, Gan-Xin Yan, MD, PhD, Michael J. Ackerman, MD, PhD, Martin Borggreve, MD, Domenico Corrado, MD, PhD, Jihong Guo, MD, Ihor Gussak, MD, PhD, Can Hasdemir, MD, Minoru Horie, MD, Heikki Huikuri, MD, Changsheng Ma, MD, Hiroshi Morita, MD, PhD, Gi-Byoung Nam, MD, PhD, Frederic Sacher, MD, PhD, Wataru Shimizu, MD, PhD, Sami Viskin, MD, Arthur A.M. Wilde, MD, PhD, FHRS
Update on the diagnosis of BrS

<table>
<thead>
<tr>
<th>I. ECG (12-Lead/Ambulatory)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Spontaneous type 1 Brugada ECG pattern at nominal or high leads</td>
<td>3.5</td>
</tr>
<tr>
<td>B. Fever-induced type 1 Brugada ECG pattern at nominal or high leads</td>
<td>3</td>
</tr>
<tr>
<td>C. Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge</td>
<td>2</td>
</tr>
</tbody>
</table>

*Only award points once for highest score within this category. One item from this category must apply.

II. Clinical History*

| A. Unexplained cardiac arrest or documented VF/polymorphic VT | 3 |
| B. Nocturnal agonal respirations | 2 |
| C. Suspected arrhythmic syncope | 2 |
| D. Syncope of unclear mechanism/unclear etiology | 1 |
| E. Atrial flutter/fibrillation in patients <30 years without alternative etiology | 0.5 |

*Only award points once for highest score within this category.

III. Family History

| A. First- or second-degree relative with definite BrS | 2 |
| B. Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first- or second-degree relative | 1 |
| C. Unexplained SCD <45 years in first- or second-degree relative with negative autopsy | 0.5 |

*Only award points once for highest score within this category.

IV. Genetic Test Result

A. Probable pathogenic mutation in BrS susceptibility gene | 0.5

Score (requires at least 1 ECG finding)

- ≥3.5 points: Probable/definite BrS
- 2–3 points: Possible BrS
- <2 points: Nondiagnostic
Risk Stratification

- Aborted SCD
- Syncope
- Asymptomatic Patients
  - Age + Gender
  - Familial and Genetic Background
  - Spontaneous vs provoked type 1
  - EP study
  - ECG indices
Risk Stratification

• Aborted SCD
• Syncope
• Asymptomatic Patients
  • Age + Gender
  • Familial and Genetic Background
  • Spontaneous vs provoked type 1
  • EP study
  • ECG indices
Aborted SCD

Risk of recurrent VF among patients presenting with cardiac arrest:

- 35% at 4 years
- 44% at 7 years
- 48% at 10 years

Syncope

• 1/3 of contemporary BrS cohorts present with syncope
• 4 times higher vs asymptomatic patients
• 4 times lower vs aSCD
• Arrhythmic vs vagal syncope
Asymptomatic Patients

- Fortunately, only a minority of patients diagnosed with BrS today have a history of cardiac arrest:
  - 6% in Europe
  - 18% in Japan
- Asymptomatic patients represent a majority (~63%) of newly diagnosed BrS.
- Their risk of developing symptoms is relatively low (0.5% per year).
- Unfortunately, for most the first symptom is cardiac arrest/SCD.
- Lethal/Non Lethal Events: 8/10 in BrS vs 8/60 in LQTS.
Risk Stratification

• Aborted SCD
• Syncope

• Asymptomatic Patients
  • Age + Gender
  • Familial and Genetic Background
  • Spontaneous vs provoked type 1
  • EP study
  • ECG indices
Age and Gender

- **Mean age** at the time of cardiac arrest is **39–48 years**
- **First symptoms** between **20 and 65** years of age.
- **Asymptomatic elderly patients with BrS** are thought to be at **relatively low risk** for future cardiac events.
- In all age series, **64%–94%** of patients with BrS who presented with **cardiac arrest** were **male**
- Males are also at increased risk for displaying a spontaneous type I Brugada ECG and for having inducible VF during EP studies.
- Nevertheless, because the **majority of asymptomatic patients are also male**, gender is not an independent predictor of arrhythmic events.
Risk Stratification

• Aborted SCD
• Syncope

• **Asymptomatic Patients**
  • Age + Gender
  • **Familial and Genetic Background**
  • Spontaneous vs provoked type 1
  • EP study
  • ECG indices
Familial and Genetic Background

- Neither **family history of SCD**
- Nor **mutation** (of any type) in the **SCN5A** gene
- to be of value in risk stratification

*Circulation 2010. FINGER Registry*
Familial Background

- The study was conducted at 26 institutions across Japan
- Prospectively followed up for more than 12 months
- Probands
- With either coved or saddle back type

Genes in BrS

<table>
<thead>
<tr>
<th>Locus</th>
<th>Gene/protein</th>
<th>Ion channel</th>
<th>Percent of probands</th>
</tr>
</thead>
<tbody>
<tr>
<td>BrS1</td>
<td>3p21, SCN5A, Na\textsubscript{v}1.5</td>
<td>↓ I\textsubscript{Na}</td>
<td>11%–28%</td>
</tr>
<tr>
<td>BrS2</td>
<td>3p24, GPD1L</td>
<td>↓ I\textsubscript{Na}</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS3</td>
<td>12p13.3, CACNA1C, Ca\textsubscript{v}1.2</td>
<td>↓ I\textsubscript{Ca}</td>
<td>6.6%</td>
</tr>
<tr>
<td>BrS4</td>
<td>10p12.33, CACNB2b, Ca\textsubscript{v}2b</td>
<td>↓ I\textsubscript{Ca}</td>
<td>4.8%</td>
</tr>
<tr>
<td>BrS5</td>
<td>19q13.1, SCN1B, Na\textsubscript{v}1</td>
<td>↓ I\textsubscript{Na}</td>
<td>1.1%</td>
</tr>
<tr>
<td>BrS6</td>
<td>11q13-14, KCNE3, MiRP2</td>
<td>↑ I\textsubscript{to}</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS7</td>
<td>11q23.3, SCN3B, Na\textsubscript{v}3</td>
<td>↑ I\textsubscript{Na}</td>
<td>Rare</td>
</tr>
</tbody>
</table>

7. In patients with suspected or established Brugada syndrome, genetic counseling and genetic testing may be useful to facilitate cascade screening of relatives (S7.9.1.3-18–S7.9.1.3-20).

<table>
<thead>
<tr>
<th>Locus</th>
<th>Gene/protein</th>
<th>Ion channel</th>
<th>Percent of probands</th>
</tr>
</thead>
<tbody>
<tr>
<td>BrS11</td>
<td>17p13.1, RANGRF, MOG1</td>
<td>↓ I\textsubscript{Na}</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS12</td>
<td>3p21.2-p14.3, SLMAP</td>
<td>↓ I\textsubscript{Na}</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS13</td>
<td>12p12.1, ABCC9, SUR2A</td>
<td>↑ I\textsubscript{K-ATP}</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS14</td>
<td>11q23, SCN2B, Na\textsubscript{v}2</td>
<td>↓ I\textsubscript{Na}</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS15</td>
<td>12p11, PKP2, Plakophilin-2</td>
<td>↓ I\textsubscript{Na}</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS16</td>
<td>3q28, FGF12, FHAF1</td>
<td>↓ I\textsubscript{Na}</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS17</td>
<td>3p22.2, SCN10A, Na\textsubscript{v}1.8</td>
<td>↓ I\textsubscript{Na}</td>
<td>5%–16.7%</td>
</tr>
<tr>
<td>BrS18</td>
<td>6q, HEY2 (transcriptional factor)</td>
<td>↑ I\textsubscript{Na}</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Listed in chronologic order of their discovery.
Risk Stratification

- Aborted SCD
- Syncope

**Asymptomatic Patients**
- Age + Gender
- Familial and Genetic Background
- **Spontaneous vs provoked type 1**
- EP study
- ECG indices
Spontaneous vs drug-induced type I BrS
Spontaneous vs drug-induced type I BrS

- Spontaneous type 1 ECG not predictive (event rate per year, 0.8% versus 0.4%; HR, 2.0; CI, 0.5 to 7.4; P 0.26)

- Shorter time to the first arrhythmic event during follow-up.

- Indicating the dynamic nature of ECG pattern

So, repeated ECGs and ECG during fever to reveal spontaneous type 1 during fup
## Drug Challenge

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajmaline</td>
<td>1 mg/kg over 10 minutes</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Flecainide</td>
<td>2 mg/kg over 10 minutes</td>
<td>Intravenous</td>
</tr>
<tr>
<td></td>
<td>200–300 mg</td>
<td>Oral (&gt;1 hour)</td>
</tr>
<tr>
<td>Procainamide</td>
<td>10 mg/kg over 10 minutes</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Pilsicainide</td>
<td>1 mg/kg over 10 minutes</td>
<td>Intravenous</td>
</tr>
</tbody>
</table>
Risk Stratification

- Aborted SCD
- Syncope

- Asymptomatic Patients
  - Age + Gender
  - Familial and Genetic Background
  - Spontaneous vs provoked type 1
  - EP study
  - ECG indices
EP study

Brugada et al. Circulation 2003
Risk Stratification in Brugada Syndrome

Results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) Registry

A

Entire Cohort

Arrhythmia-free survival (%)

Follow up (months)

VTs/VF Inducible (n = 126)
VTs/VF Not inducible (n = 182)

Number at risk

Not inducible 182 172 153 111 71 37
Inducible 126 116 100 77 46 25

p = 0.67

B

1 or 2 Extras

Arrhythmia-free survival (%)

Follow up (months)

VTs/VF Inducible (n = 63)
VTs/VF Not inducible (n = 245)

Number at risk

Not inducible 245 232 205 149 98 52
Inducible 63 56 48 48 37 25

p = 0.89

• EP study
Risk Stratification in Brugada Syndrome

Results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) Registry

- EP study
Risk Stratification in Brugada Syndrome

Results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) Registry

Table 4: Cox Multivariate Models

<table>
<thead>
<tr>
<th></th>
<th>p Value</th>
<th>HR</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inducibility</td>
<td>0.559</td>
<td>0.721</td>
<td>0.241</td>
<td>2.159</td>
</tr>
<tr>
<td>Spontaneous type 1 and syncpe</td>
<td>0.001</td>
<td>6.406</td>
<td>2.211</td>
<td>18.658</td>
</tr>
<tr>
<td>Inducibility</td>
<td>0.835</td>
<td>0.890</td>
<td>0.288</td>
<td>2.661</td>
</tr>
<tr>
<td>Ventricular refractory period</td>
<td>0.008</td>
<td>5.666</td>
<td>1.578</td>
<td>20.345</td>
</tr>
<tr>
<td>Inducibility</td>
<td>0.972</td>
<td>1.020</td>
<td>0.337</td>
<td>3.091</td>
</tr>
<tr>
<td>QRS-fragmentation</td>
<td>0.000</td>
<td>8.888</td>
<td>3.040</td>
<td>26.033</td>
</tr>
</tbody>
</table>

Backward elimination—likelihood ratio

Step 1
- Spontaneous type 1 and syncpe: 0.012, 4.158, 1.378, 12.783
- QRS-fragmentation: 0.007, 4.926, 1.540, 15.775
- Ventricular refractory period: 0.045, 3.908, 1.090, 14.821
- Inducibility: 0.959, 1.030, 0.336, 3.355

Step 2
- Spontaneous type 1 and syncpe: 0.011, 4.205, 1.382, 12.791
- QRS-fragmentation: 0.007, 4.902, 1.560, 15.402
- Ventricular refractory period: 0.045, 3.903, 1.030, 14.783
Circulation

ACC/AHA/HRS SYSTEMATIC REVIEW

Systematic Review for the 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society
Risk Stratification

- Aborted SCD
- Syncope

- **Asymptomatic Patients**
  - Age + Gender
  - Familial and Genetic Background
  - Spontaneous vs provoked type 1
  - EP study
  - **ECG indices**
Electrocardiographic Parameters and Fatal Arrhythmic Events in Patients With Brugada Syndrome
Combination of Depolarization and Repolarization Abnormalities

Tokioka et al. JACC 2014
Electrocardiographic Parameters and Fatal Arrhythmic Events in Patients With Brugada Syndrome
Combination of Depolarization and Repolarization Abnormalities

Tokioka et al. JACC 2014
• ECG

Electrocardiographic Parameters and Fatal Arrhythmic Events in Patients With Brugada Syndrome
Combination of Depolarization and Repolarization Abnormalities

Tokioka et al. JACC 2014
Prevalence of early repolarization pattern in inferolateral leads in patients with Brugada syndrome

Konstantinos P. Letsas MD •, Frédéric Sacher MD †, Vincent Probst MD, PhD ‡, Reinhold Weber MD •, Sébastien Knecht MD †, Dietrich Kalusche MD •, Michel Haissaguerre MD †, Thomas Arentz MD •
• **ECG**

  • QRS fragmentation
  • concomitant finding of ERP
  • **Late potentials** recorded using signal-averaged ECG
  • T-wave alternans
  • increased **QRS width**
  • **Prominent R wave** in aVR
  • **Augmented ST-segment elevation** of a type 1 Brugada pattern during the recovery phase of an exercise test
  • Prolonged Tpeak-Tend
Use of implantable loop recorders in patients with Brugada syndrome and suspected risk of ventricular arrhythmia

Maciej Kubala*, Linda Aïssou, Sarah Traullé, Anne-Lise Gugenheim, and Jean-Sylvain Hermida

Europace 2011

Aims
Implantable cardioverter defibrillator (ICD) therapy is recommended in patients with Brugada syndrome (BS) who experienced aborted sudden cardiac death (SCD) or syncope while the risk stratification of ventricular arrhythmias is a difficult step in patients with atypical symptoms. Implantable loop recorder (ILR) use has been proposed to study patients with unexplained recurrent syncope events, but its usefulness remains to be defined in patients with BS. In this retrospective study we aimed to investigate the effectiveness of ILR as a diagnostic tool in BS patients suspected of low or moderate risk of SCD.

Methods and results
We gathered data from 11 ILR recipients with supposed risk of ventricular arrhythmia, issue of Amiens registry of 204 patients with BS. We reported clinical events before and after implant, electrocardiogram (ECG) characteristics, ILR findings, and its limitations as well as to try to specify ILR utility in diagnosis approach and its consequent contribution to guide the optimal therapy. Within the 11 patients (8 men, 3 women), 9 were symptomatic, and 5 had a spontaneous Type 1 ECG pattern. During mean follow-up period of 33 months, 11 patients had a recurrence of symptoms with a mean delay of 9 months after implant. Bradycardia (two atrioventricular blocks and two sinus bradycardia) was detected in four out of eight patients (50%), and there was no ventricular arrhythmia in any patient during symptomatic events which included six syncopal syncope and two epileptic seizures. Two initially asymptomatic patients did not experience any symptoms after ILR implant and their ILR recordings did not reveal any arrhythmias.

Conclusion
The ILR contributed to the exclusion of a ventricular arrhythmia as a mechanism of an atypical syncpe in patients with electrocardiographic BS and the suspension of the ICD implant. Episodes of transient symptomatic bradycardia were the most common findings suggesting the vagal mechanism of symptoms. The use of ILR should be considered in selected patients with atypical syncope and spontaneous or transient Type 1 ECG pattern.

Keywords
Brugada syndrome • Implantable loop recorder • Syncope • Ventricular arrhythmia
“Treatment starts with diagnosis”

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class(^a)</th>
<th>Level(^b)</th>
<th>Ref.(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The following lifestyle changes are recommended in all patients with a diagnosis of Brugada syndrome:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Avoidance of drugs that may induce ST-segment elevation in right precordial leads (<a href="http://www.brugadadrugs.org">http://www.brugadadrugs.org</a>)</td>
<td>I</td>
<td>C</td>
<td>This panel of experts</td>
</tr>
<tr>
<td>(b) Avoidance of excessive alcohol intake and large meals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) Prompt treatment of any fever with antipyretic drugs.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Patient letter

We advise our patients to give the following letter, listing all the drugs on this website, to all of their health care professionals (including their general practitioner, dentist and pharmacist). Although the most appropriate treatment of Brugada syndrome is under discussion, avoidance of potentially proarrhythmic drugs and treatment of fever (which is a well-known trigger of cardiac events in Brugada syndrome) are generally accepted to be an important part of (prophylactic) treatment. However, some patients may (only) be appropriately treated with an implantable cardioverter-defibrillator. Some drugs may have an antiarrhythmic effect and may be used favorably in the acute or chronic setting (see potential antiarrhythmic drugs).
Case 2

• Άνδρας 35 ετών

• Ιστορικό PAF από 5ετίας με περιστασιακή χρήση φλεκαϊνίδης

• Αποτραπέντας ΑΚΘ

• Χωρίς ιστορικό συγκοπής

• Χωρίς οικογενειακό ιστορικό ΑΚΘ
Baseline (V.42, Lead 2 Intercostal)
Prevalence, Clinical Characteristics and Management of Atrial Fibrillation in Patients With Brugada Syndrome

Moisés Rodríguez-Mañero, MD, Mehdi Namdar, MD, Andrea Sarkozy, MD, PhD, Rubén Casado-Arroyo, MD, Danilo Ricciardi, MD, Carlo de Asmundis, MD, PhD, Gian-Battista Chierchia, MD, Kristel Wauters, MD, Jayakeerthi Y. Rao, MD, Fatih Bayrak, MD, Sophie Van Malderen, MD, Pedro Brugada, MD, PhD

Heart Rhythm Management Center, Universitair Ziekenhuis Brussels – Vrije Universiteit Brussel, Brussels, Belgium

Atrial fibrillation (AF) can be the first manifestation of latent Brugada syndrome (BS). The aim of our study was to assess the prevalence of AF as the first clinical diagnosis in patients with BS and their demographic and clinical characteristics and diagnosis management in a large cohort of patients. The patient group consisted of 611 patients with BS. The data from those with a diagnosis of AF previous to the identification of BS were analyzed (n = 35). Eleven cases were unmasked after the initiation of a class I antiarrhythmic drug and one during the establishment of general anesthesia. In the remaining population, BS was diagnosed using an ajmaline test performed mainly because of younger age in patients with lone AF (n = 13), previous syncope or sudden cardiac death (n = 3), or a clinical history of sudden cardiac death in the family (n = 5). The mean patient age was 49 ± 15 years, 21 were male patients, 14 had a family history of sudden death, 15 had had previous syncope, and 4 had survived cardiac arrest. Concomitant electrical disorder was found in 13 patients. Remarkably, 21 patients had normal findings on the baseline electrocardiogram. In conclusion, AF could be one of the first clinical manifestations of latent BS in a considerable number of patients. This identification is crucial because the treatment of these patients is subject to relevant changes. The ajmaline test plays an essential role, mainly in young patients with a family history of sudden death, despite having normal findings on a baseline electrocardiogram.
Case 3

• Άνδρας 39 ετών
• Αίσθημα παλμών και καταγραφή βραχέων ριπών SVT επί συμπτώματος
• Φλεκαϊνίδη 100 x2
• Χωρίς ιστορικό συγκοπής, σπασπών, ANR (gasping)
• Χωρίς οικογενειακό ιστορικό ΑΚΘ
• Απουσία εμφανούς δομικής καρδιοπάθειας
40 mg flecainide (day × 2)

Unconfirmed Diagnosis.
**CONSIDER ACUTE STEMI**

- Atrial fibrillation
- Demand pacing
- Lead(s) unsuitable for analysis: I V3 V5 V6
- Interpretation: made without knowing patient's gender/age
- Left ventricular hypertrophy by voltage only
- Septal ST-elevation: CONSIDER ACUTE INFARCT
- Inferior and anterior ST-T abnormality may be due to the hypertrophy and/or ischemia
- Low QRS voltages in limb leads

Abnormal ECG

Unconfirmed Diagnosis.
Sinus rhythm
- Interpretation needs without knowing patient's gender/age
  - rSR'(V1) - probably normal variant
- Normal ECG

Unconfirmed Diagnosis.
Η καρδιακή κυκλοφορία μεταφέρεται (εμπίπτει εμπρός)
3/4 τελικώς 84 με 86 δευτερόλεπτα.
Key messages

• Η διάγνωση μπαίνει με το ΗΚΓ

• Χρειάζεται όμως και κλινική υποψία (AF, Syncope, NAR)

• Η διάγνωση μέρος της θεραπείας