Management of Inherited Sudden Death Syndromes: Current and Emerging Therapies

Neil Seller
Emerging...

• Become apparent or prominent
  • Not novel ...
Sudden Death Syndromes

• Inherited Arrhythmia syndromes
  • LQTS
  • CPVT
  • BrS
  • ERS
  • SQTS

• Cardiomyopathies
  • HCM
  • RCM
  • ARVC/D
LQTS
KCNJ5 KCNE2
KCNE1 AKAP9
CAV3 SCN4B
SNTA1

BrS
GPD1L FCF12
HCN4 HEY2
KCND2 KCND3
RANGRF PKP2
KCNE3 KCNE5
SCN10A SCN2B
SEMA3A TRPM4
SCN3B SLMAP

ERS
KCNJ8 ABCC9
SCN10A
CACNA1C
Cacna2d1
CACNB2

SQTS

LQTS
KCNJ5 KCNE2
KCNE1 AKAP9
CAV3 SCN4B
SNTA1

CPVT
ANK2 CALM1 CALM2 CALM3
TRDN RYR2

BrS
GPD1L FCF12
HCN4 HEY2
KCND2 KCND3
RANGRF PKP2
KCNE3 KCNE5
SCN10A SCN2B
SEMA3A TRPM4
SCN3B SLMAP

ERS
KCNJ8 ABCC9
SCN10A
Cacna2d1
CACNB2
Therapy

Chronology, Priority, or Intensity

Intent

Composition

Levels of Care

Lines of Therapy

Therapy

Pharmacotherapy

Biological therapy

Implantable device therapy

by matter

by energy

by human interaction

by by animal interaction

by meditation

by creativity

by sleeping and waking

Counseling

Cognitive behaviour therapy

Family therapy

Education

Physical/occupation therapy

Lifestyle modifications

Lifestyle

Coaching

Physical/occupation therapy

Curative

Definitive

Destination

Palliative

Preventative

Abortive

Bridge

Consolidation

Supportive

Stepdown

Systemic

Gold standard

Investigational

Maintenance

Emperic

Primary care

Secondary care

Tertiary care

End-of-life care

First-line

Second-line

Third-line

Pharmacotherapy

Implantable device therapy

Biological therapy

by matter

by energy

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Primary care

Secondary care

Tertiary care

End-of-life care

First-line

Second-line

Third-line
Outline of discussion

• Lifestyle modification
• Pharmacotherapy
• Surgical therapy
• Device therapy
Long QT syndrome

- Lifestyle modifications

**Summary of the major AHA and ESC exercise recommendations**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Patients are generally not advised, or strongly discouraged from participating in activities that involve burst exertion, activities in which loss of consciousness carries additional risks of traumatic injury, extreme sports, swimming (particularly in LQT1) and abrupt loud noises (particularly in LQT2), whilst low intensity activities that are permitted. Most other activities should be assessed on an individual basis. In competitive athletes, restriction from all competitive sports is recommended, except those of low intensity. C+P— patients may be allowed to participate in competitive sports.</td>
<td>In athletes with symptomatic or electrophysiologically manifesting LQTS, competitive sports participation may be considered following expert consultation, initiation of treatment, appropriate precautionary measures and the athlete has been asymptomatic for at least 3 months (level of evidence C).</td>
<td>No competitive sports and avoidance of burst sports and specific triggers Light to moderate leisure time sports in low-risk patients</td>
</tr>
</tbody>
</table>
Long QT Syndrome

- β blockers
  - All patients
  - Genotype-dependent response
- Mexiletine
- LQT3 β blocker refractory patients
Long QT syndrome

• Sympathectomy
  • Current guidelines
    • High risk patients in whom:
      • ICD contraindicated or refused and/or
      • β blockers ineffective/not tolerated/not accepted/contraindicated

Practical recommendations, LQTS patients who either:
1. experience LQTS-triggered breakthrough cardiac events despite adequate β-blockade
2. cannot tolerate β-blocker therapy secondary to undesirable side effects or absolute contraindications such as asthma
3. experience >1 appropriate ventricular fibrillation-terminating ICD shock(s) or electrical storms
4. require a so-called “bridge to ICD” due to young age and particularly malignant/high risk LQTS genotype/phenotype.
Long QT syndrome

• Device therapy
  • Current guidelines:
    • Class I: survivors of cardiac arrest
    • Class IIa: Recurrent syncope on β blocker therapy
  
  Practical recommendations, ICD should be considered for those LQTS patients who:
    1. Survived a cardiac arrest despite adequate β-blockade or LCSD,
    2. Survived a cardiac arrest off therapy, except when a reversible/preventable cause such as QT-prolonging medications or electrolyte abnormalities are identified
    3. Suffer from recurrent LQTS-triggered syncope despite adequate β-blockade when LCSD is not a viable option
    4. Suffer from recurrent LQTS-triggered syncope despite adequate β-blockade and LCSD, and
    5. in rare extenuating circumstances such as asymptomatic patients with a QTc ≥ 550 ms with overt signs of electrical instability (e.g. T-wave alternans) on ECG and or additional objective evidence of being high risk (e.g. postpubertal LQT2 women) despite adequate β-blockade and LCSD
Long QT syndrome

• Wearable cardiac defibrillators

• can be considered in patients with LQTS deemed to be at high risk for SCA

1. while up-titrating beta blockers, considering ICD therapy, or
2. when navigating short term periods of increased SCA-risk, like the post-partum period in LQT2 women, ICD revision or temporary inactivation,
3. or during short term administration of known QT prolonging medications.
Long QT syndrome

• Cardiac Transplant

Cardiac transplantation in children and adolescents with long QT syndrome.

Kolle AM¹, Bos JM², Etheridge SP³, Cannon BC⁴, Bryant RM⁵, Johnson JN⁶, Ackerman MJ⁶.
Long QT syndrome

• Minor Long QT genes
  • IKs (AKAP9-LQTS and KCNE1-LQTS) ≈ LQT1
  • IKr (KCNE2-LQTS) ≈ LQT2
  • INa (CAV3-LQTS, SCN4B-LQTS, and SNTA1-LQTS) ≈ LQT3
Long QT syndrome

- Multisystem diseases
  - Ankyrin B Syndrome
  - Jervell and Lange-Nielsen syndrome
  - Andersen-Tawil syndrome
  - Timothy syndrome
  - Calmodulinopathy
Long QT syndrome
CPVT

- **Lifestyle modifications**

Summary of the major AHA and ESC exercise recommendations

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<td>Patients are generally not advised, or strongly discouraged from participating in sports which carry additional risk of traumatic injury in patients at risk of impaired consciousness. Most low-moderate intensity activities are probably permitted. In athletes, restriction to participation in low-intensity sports is advisable.</td>
<td>No changes since 2004 guidelines (level of evidence C)</td>
<td>Only competitive sports with low cardiovascular demand. Recreational sport with moderate cardiovascular demand. Avoid hyperthermia and electrolyte disturbances</td>
</tr>
</tbody>
</table>
Table 1: Clinical Studies of Patients With Catecholaminergic Polymorphic Ventricular Tachycardia Treated With Flecainide

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Number of patients</th>
<th>Female</th>
<th>RVR2 mutation/ CASQ2 mutation/ no mutation identified/ genetic testing not performed</th>
<th>Age at start of flecainide (years*)</th>
<th>Combined with β blocker</th>
<th>Daily flecainide dosage</th>
<th>Follow-up*</th>
<th>Cardiac events</th>
<th>Compliant</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watanabe et al. 2009</td>
<td>Case report</td>
<td>2</td>
<td>1 (50 %)</td>
<td>1/0/0</td>
<td>36 and 12</td>
<td>1 (50 %)</td>
<td>3 mg/kg, NR</td>
<td>12 weeks</td>
<td>0</td>
<td>No</td>
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</tr>
<tr>
<td>Bernabei et al. 2010</td>
<td>Case report</td>
<td>1</td>
<td>1 (100 %)</td>
<td>NR</td>
<td>32</td>
<td>1 (100 %)</td>
<td>100 mg</td>
<td>3 months</td>
<td>0</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Van der Wiel et al. 2011</td>
<td>Retrospective cohort study</td>
<td>33</td>
<td>24 (73 %)</td>
<td>32/1/0</td>
<td>25 (7–66)</td>
<td>31 (94 %)</td>
<td>150 mg (100–300); 1 kg/4 % myocardium</td>
<td>20 months (12–40)</td>
<td>1/0 (3 %)</td>
<td>No</td>
<td>6 (18 %)</td>
</tr>
</tbody>
</table>

C

- Change baseline vs flecainide arms
  - NSVT (n = 3)
  - Flecainide first

- Change baseline vs placebo arms
  - NSVT (n = 4)

- NVST (n = 2)

- PVCs (n = 4)

**Efficacy of ivabradine to control ventricular arrhythmias in catecholaminergic polymorphic ventricular tachycardia.**

Volkmar G1, Klug D2.

CPVT

• Sympathectomy
  • Class IIb:
    May be considered in patients who experience syncope/VT/ICD shocks on β blockers
    or
    Patients intolerant or with contraindication to beta-blockers
CPVT

- Device therapy
- Current guidelines
- I: Cardiac arrest, recurrent syncope or VT despite optimal medical management, and/or LCSD

### Table:

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Recruitment period (yrs)</th>
<th>Inclusion criteria</th>
<th>Total N</th>
<th>Number with ICD n (%)</th>
<th>Primary prevention (%)</th>
<th>≥1 inappropriate shock (%)</th>
<th>≥1 inappropriate shock (%)</th>
<th>Electrical storm (%)</th>
<th>Other complications (%)</th>
<th>OAT (%)</th>
<th>Death despite ICD (%)</th>
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<tbody>
<tr>
<td>Mayachi 2005</td>
<td>Retro</td>
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<tr>
<td>TOTAL</td>
<td></td>
<td></td>
<td></td>
<td>750</td>
<td>330 (44)</td>
<td>158 (48)</td>
<td>126 (38)</td>
<td>66 (20)</td>
<td>39 (19)</td>
<td>21 (20)</td>
<td>6 (2)</td>
<td>0</td>
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Brugada Syndrome

- **Lifestyle modification**

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Brugada Syndrome

• Pharmacotherapy
  • Hydroquinidine

Impact of clinical and genetic findings on the management of young patients with Brugada syndrome.


• Currently only advocated as treatment for electrical storm or adjunctive therapy with ICD
Brugada Syndrome

• Alternative pharmacotherapeutic agents
  • Isoproterenol
  • Propranolol
  • Disopyramide
  • Quinine sulphate
  • Phosphodiesterase III inhibitors
  • Bepridil
Brugada Syndrome

• Device therapy
  • Current guidelines
    • Class I: recommended in patients with BrS who:
      • Are survivors of Cardiac arrest and/or
      • Documented spontaneous sustained VT
    • Class IIa: can be useful in patients with spontaneous type I ECG who have a history of syncope judged to be likely caused by ventricular arrhythmias
    • Class IIb: may be considered in patients with a diagnosis of BrS who develop VF during programmed electrical stimulation
Brugada Syndrome

Type 1 Brugada pattern

- Avoid drugs that may induce or aggravate ST segment elevation in right precordial leads (www.BrugadaDrugs.org)
- Avoid cocaine and excessive alcohol intake
- Immediately treat fever with antipyretic drugs. (Class I)

Symptomatic
- Electrical storm
- Prior cardiac arrest sustained VT
- Syncope seizure NAR

Presumably arrhythmic origin
- Isoproterenol +/- quinidine (Class Ila)

ICD (Class I)

ICD (Class Ila)

Quinidine (Class Ila)
RVOT ablation (Class Iib)
Cilostazol

Repeated appropriate shocks

ICD (Class I)

ICD (Class Ila)

Close follow-up

Quinidine

ICD (Class I)

ICD (Class Ila)

Quinidine, if ICD indicated but refused or contraindicated (Class Ila)

Asymptomatic
- Spontaneous and fever-induced type 1 Brugada pattern

Based on patient and ECG characteristics (Age, Gender, Jp amplitude, QRS fragmentation, ...)

Inducible VT/VF with up to 2 ES

Close follow-up

Type 1 Brugada pattern induced by sodium channel blocker

Close follow-up

+ +
SQTS

- Lifestyle modifications

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<tr>
<td>Restriction from competitive sports with the possible exception of low intensity activities until phenotype is better understood</td>
</tr>
</tbody>
</table>
SQTS

- Pharmacotherapy
  - Hydroxyquinidine
  - Sotalol
SQTS

• Device therapy
  • Current guidelines:
    • Class I: Recommended in symptomatic patients who
      1. Are survivors of cardiac arrest
      2. Documented spontaneous VT (with or without syncope)
    • Class IIb: may be considered in
      • Asymptomatic patients with SQTS with family history of sudden death
ERS

- Lifestyle modifications
  - Generally as for Brugada Syndrome

---

Summary of the major AHA and ESC exercise recommendations

|------------------------|------------------------|------------|
| Patients are generally not advised, or strongly discouraged from participating in sports which carry additional risk of traumatic injury in patients at risk of impaired consciousness. Most low-moderate intensity activities are probably permitted. In athletes, restriction to participation in low-intensity sports is advisable. | No changes since 2004 guidelines (level of evidence C) | Only competitive sports with low cardiovascular demand
Recreational sport with moderate cardiovascular demand
Avoid hyperthermia and electrolyte disturbances |
ERS

- Pharmacotherapy
  - Hydroxyquinidine
    - Only recommended in addition to ICD
  - Other
    - Isoproterenol
    - Cilostazol (Milrinone)
ERS

• Device therapy
  • Class I: Recommended in ERS patients who are survivors of cardiac arrest
  • Class IIb: May be considered in
    1. Symptomatic family members of ERS patients with ST elevation in ≥ 2 inferior or lateral leads
    2. Asymptomatic patients with high risk ER pattern (high J wave amplitude, horizontal/descending ST segment) with strong family history of juvenile sudden death
ERS pattern

ER pattern
>0.1 mV in at least 2 contiguous infero-lateral leads

Symptomatic

Electrical storm

Prior cardiac arrest sustained VT

Isoproterenol (Class Ila) +/- quinidine

ICD (Class I)
If ICD refused or contraindicated Quinidine

Repeate appropriate shocks

ICD (Class Iib)
Close follow-up without ILR

Quinidine (Class Ila) cilostazol

Asymptomatic

Syncope, seizure NAR and strong family history of sudden death at young age

Presumably arrhythmic origin

High-risk ER ECG pattern (prominent J-waves, horizontal/descending ST-segment, high dynamicity) and strong family history of unexplained sudden death at young age

Yes

ICD (Class Iib)
Close follow-up

No

ICD (Class Iib)
Close follow-up