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ESC Classification of Cardiomyopathies (morphological)

Channelopathies / Inherited arrhythmia syndromes / Primary electrical heart diseases ...

... are not ‘cardiomyopathies’. 

The heart is (mostly) structurally normal using routine cardiac imaging techniques.
## Cardiac Ion Channel Disorders
(Primary Electrical Heart Diseases)

<table>
<thead>
<tr>
<th>Ventricular</th>
<th>Supraventricular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-QT syndrome (LQTS)</td>
<td>Sinus node dysfunction*</td>
</tr>
<tr>
<td>Short-QT syndrome (SQTS)</td>
<td>Atrial fibrillation*</td>
</tr>
<tr>
<td>Brugada syndrome*</td>
<td>AV block*</td>
</tr>
<tr>
<td>Polymorphic VT/VF (CPVT)</td>
<td>RBBB, LBBB, …*</td>
</tr>
<tr>
<td>Early Repolarisation (ERS)*</td>
<td>WPW (+HCM)</td>
</tr>
</tbody>
</table>

(Idiopathic VF)
(drug-induced LQTS)
(SIDS, SUDS/SADS, drowning/sport victims, …)

*: exclude phenocopies (mimicking conditions), consider genetics if familial or unexplained/idiopathic case
DGK / DGPK Expert Consensus Statement
Molecular Diagnostics of Cardiovascular Diseases
Arrhythmias

- Long-QT syndrome (LQTS)
- Catecholam. polymorphic VT (CPVT)
- Syndromic: JLNS, Timothy, Andersen

Brugada syndrome (BrS)

- Others: IVF, early repolarisation, Short-QT (SQTS), drug-induced forms, ...  

SNPs / Polymorphisms

- Diagnostics
- Therapy
- Prognosis

Schulze-Bahr et al. (2015) Kardiol. online
Pocket guidelines
International version in prep.
DGK / DGPK Expert Consensus Statement
Molecular Diagnostics of Cardiovascular Diseases
Indications for Molecular Diagnostics

1. **Disease**: Sensitivity >30%
   **Gene**: Sensitivity >10%

2A. **Disease**: Sensitivity 10-30%
   **Gene**: Sensitivity 1-10%

2B. **Disease**: Sensitivity <10%
   **Gene**: Sensitivity <1%

3. Disease w/o genetic basis
   Gene w/o known relation with disease

- Diagnostics
- Therapy
- Prognosis

Schulze-Bahr et al. (2015) Kardiol. online
Pocket guidelines
International version in prep.
currents

Na\(^+\) current

Ca\(^{2+}\) current

\(I_{To}\) current

IKs current

IKr current

channels

Na\(_{v}1.5\), sodium

Ca\(_{v}1.2\), calcium

K\(_{v}4.3\) potassium

KCNQ1 – K\(_{v}7.1\) potassium

hERG – K\(_{v}11.1\) potassium

genes

SCN5A

CACNA1C

KCND3

KCNQ1

KCNH2
Heart-rate corrected QT Interval (QTc; Bazett’s method)

- QTc Female: 360 – 460 ms
- QTc Male: 350 – 450 ms

**QT scale.**

- **Very long QT.**
  - LQTS even if asymptomatic. Exclude II° causes

- **Long QT.**
  - LQTS when supported by symptoms, family history or additional tests.*

- **Long QT possible.**

- **Normal QT.**
- **Short QT.**
  - SQTS when supported by symptoms or family history.
  - Additional tests: Repeated ECG, Holter, T-wave morphology (?), electrophysiologic studies (?)

- **Very short QT.**
  - SQTS even if asymptomatic. Exclude II° causes

LQTS
K⁺-Channel-Type
(LQT 1, 2, 5-7
[Andersen])
LQTS
Na⁺-Channel-Type
(LQT3, 9, 10)
LQTS
Ca\textsuperscript{2+}-Channel-Type
(LQT8, Timothy)
LQTS Genotype (+):
Normal baseline QT Interval (at rest)

25% n=469
419 ± 20 ms

n=1,392
501 ± 48 ms

Non-LQTS:
n=1,525
412 ± 22 ms

Syncope
40% 21% (10%)

ACA/SCD
11% 2.3% (0.8%)

Goldenberg et al. (2011) JACC. 57: 51-59
“Finding the missing heritability of complex diseases”

- **Rare** alleles causing Mendelian disease
  - High effect
  - Very rare

- **Low-frequency** variants with intermediate effect
  - Intermediate effect
  - Rare

- **Common** variants implicated in common disease by GWA
  - Modest effect
  - Low frequency

- Few examples of high-effect common variants influencing common disease
  - Low

SCN5A Gene Alterations: Phenotype vs. Common Variation

- A180G
- V528I
- V120I
- R552G
- H558R
- H987Q
- P1090L
- S1103Y
- Q1027R
- K1500N
- R34C
- V728I
- H558R
- R1193Q
- V1951L

Legend:
- Long QT Syndrome
- Conduction Defect / Sinus node disease
- Brugada Syndrome
- Mixed Phenotype
- Dilated Cardiomyopathy
ECG Parameters - Quantitative Traits
(GWAS; H²: heritability estimates)

**TBX5, SCN10A**
6p21, 10q21
Effect: 5-7%

H²: 0-36%

**SCN10A, SCN5A**
CAV1-CAV2, NKX2-5, SOX5, WNT11, MEIS1, TBX5, -3
Effect: 1-3 ms
SCN10A
Effect: 1-3 ms

H²: ~34%

**CYP2D6 *4/*4 PMs + Betablocker treatment:**
Effect HR -8.5/min

MYH6
Effect 5.7% of HR

H²: 29-77%

**NOSAP1-rs10494366, NOSAP1-rs2880058**
Effect: 3-7 ms

KCNH2 K897T (LQT2)
Effect: 3-4 ms

<1% of variance explained
H²: 29-77%

**ANK-B (LQT4)**
2-3 ms

SCN10A
Effect: 1-3 ms

6p21, 10q21

Effect: 5-7%

H²: 0-36%

**KCNE1_D85N (LQT5)**
Effect: ~10 ms

**TBX5, SCN10A**
6p21, 10q21
Effect: 5-7%

H²: 0-36%
KCNH2
K897T

0.84/0.16
Fins \((n=415)\)
Ratus norvegicus (c)

0.76/0.24
Caucasians
\((n=1030)\)
Mus musculus
(c) Oryctolagus cuniculus (c) Canis familiaris (nc, R)

#
Twins
\((n=236)\)
alQTS
\((n=1)\)

LQT1-Fins \((n=261)\)

0.87/0.13
US citizens \((n=90)\)

#

LQT1-Fins \((n=261)\)

Different ethnic populations

0.98/0.02
Japanese \((n=50)\)

0.84/0.16
Caucasians \((n=100)\)

0.76/0.24
US-Caucasians \((n=100)\)

0.96/0.04
African Americans \((n=100)\)

897T: female carriers had ↑ repolarization parameters; no isoform-associated effect in males

897T: ↑ current activation (−7 mV shift) and deactivation (HEK 293), ↑ \(I_{Kr}\) current.

897T carriers \((n=58)\) had a shorter QT interval than 897K carriers (females>males, twins: males> females)

897T: \(I_{Kr}\) currents comparable with wild-type (+MIRP) (Xenopus oocytes)

897T: no gender-related differences in baseline QTc, but increased QTc during exercise.

897T: \(I_{Kr}\) channel activation comparable with wild type, reduced protein level (Western), ↓ deactivation and inactivation, hyperpolarizing shift in steady-state inactivation, decrease of \(I_{Kr}\) (HEK 293)

Allele frequencies: alQTS \((n=98)\) ~ controls

897T: changes in \(I_{Kr}\) channel kinetics, PKA modulation similar to wild-type: ↓ \(I_{Kr}\) current density, ↓ deactivation time constants, ↓ inactivation (HEK 293). LQT1 (589D)+ 897T carriers \((n=39)\) had a longer QT interval than 897K carriers.

Heterozygous genotype: 8.2% US-Blacks \((n=305\) total), 33.1% US-Caucasians \((n=187)\), 7.5% US-Asians \((n=134)\), 6.8% Hispanics \((n=118)\) n.d.

897T: ↓ \(I_{Kr}\) current density, −5 mV shift of activation, ↑ inactivation and recovery; normal protein levels (Western)
Disease Severity: Balancing the Protein between Normal and Mutant ?!

- Concept of ‘Genomic Convergence’
- Disease expression of a (mutant) haplotype $M^{*-G-A-A}$ depends on the second allele
- Wild-type N-$x-x-x$ haplotype might have a different, intrinsic allele expression

(adapted from Amin et al., EHJ 2012)
Evidence of Polymorphic Sites within the 3′-UTR of LQT-1 (KCNQ1)

... KCNQ1

Ancestral haplotype:
G A A

QTc  N
430  26
440  1
450  31
470  17
520  3

ECG of a young female

“Asymptomatic“, National Team Player (Basketball)
Channels regulated by sympathetic nervous system (cAMP)
Imaging of Myocardial Innervation
Radioactive Tracer Activity

Sympathetic System

L-Tyrosine → NE → NE → NE → NE

[11C]HED
[123I]MIBG

MYOCYTE

α1: [11C]-GB67
β1: [11C]-CGP
β2: 12177

Parasympathetic System

Choline → ACh → Ch

[11C]MQNB

MYOCYTE

ACh

m2
Sympathetic cardiac innervation: 28 symptomatic LQTS pts. (MIBG-SPECT)


| Controls | All Long QT | Long QT-1 | Long QT-2 | Long QT$_X$
|----------|------------|-----------|-----------|-----------
| N: 10    | 28         | 7         | 12        | 9         |
| QTc (ms) | 501±69     | 481±69    | 508±81    | 508±54    |

Abnormal MIBG: 17
Segm. with tracer ↓: 5

MIBG-SPECT and QT Prolongation: 28 symptomatic LQTS pts.

<table>
<thead>
<tr>
<th>Controls</th>
<th>QTC ≤ 500 ms</th>
<th>QTC ≥ 500 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>N: 28</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>QTc (ms) 501±69</td>
<td>468</td>
<td>543</td>
</tr>
<tr>
<td>Syncope/VF 18/10</td>
<td>7/0</td>
<td>5/7</td>
</tr>
</tbody>
</table>

Abnormal MIBG: 17 (61%) 10 (56%) 7 (70%)
Therapy LQTS

- Depends on symptoms and QTc duration
  
  (i) BB
  (ii) BB and ICD, if BB is not tolerated
       or QTc $\uparrow \uparrow$
       or symptoms during BB
  (iii) ICD for secondary prophylaxis (or class IIB)
  (iv) class IB antiarrhythmics for LQT3

- Avoid QT-prolonging agents, serum $\downarrow$ K+

- Avoid genotype-specific triggers, modify life style to genotype
Strategies to Restore Ion Channel Dysfunction

Class 1: Abnormal protein synthesis (altered transcription or translation)
Class 2: Defective protein processing/trafficking.
Class 3: Abnormal gating/kinetics
Class 4: Altered or no permeability

Increase number of functional (WT) channels

Modulate dysfunctional channels
Loss of Functional HERG Channels: Key Mechanism for LQT-2 ($I_{Kr}$ ↓)

Anderson et al. (2006) Circulation 113: 365-373

Missense mutations were trafficking-deficient" (Western blot: 135 kDa)

4/6 Missense mutations (R328C, P347S, T436M, R922W) had wild-type like $I_{Kr}$

155 kDa: Mature HERG protein
135 kDa: Immature HERG protein

HEK293
Ranolazine Effects on Ventricular Repolarisation (rabbit hearts, in vivo)

Reduction of
• APD and TDR in M and Purkinje cells (lower HR) at the ventricular level

Table 1  Summary of ranolazine potency in inhibiting cardiac ion channel currents in canine left ventricular myocytes

<table>
<thead>
<tr>
<th>Ion currents</th>
<th>IC$_{50}$ values (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Inward</td>
<td></td>
</tr>
<tr>
<td>Peak $I_{Na}$</td>
<td>294</td>
</tr>
<tr>
<td>Late $I_{Na}$</td>
<td>5.9</td>
</tr>
<tr>
<td>Peak $I_{Ca,L}$</td>
<td>296</td>
</tr>
<tr>
<td>$I_{Na-Ca}$</td>
<td>91</td>
</tr>
<tr>
<td>B. Outward</td>
<td></td>
</tr>
<tr>
<td>$I_{K}$</td>
<td>11.5</td>
</tr>
<tr>
<td>$I_{K1}$</td>
<td>17% at 30 µM</td>
</tr>
<tr>
<td>$I_{K1}$</td>
<td>No effect</td>
</tr>
<tr>
<td>$I_{K}$</td>
<td>No effect</td>
</tr>
</tbody>
</table>

All data from Antzelevitch et al., except peak $I_{Na}$, which is from Undrovinas et al.

Note: The magnitude of effect of ranolazine on peak and late $I_{Na}$ is voltage, frequency, and tissue dependent (see text for details).

IC$_{50}$ = concentration of ranolazine that causes 50% inhibition (potency).

Antzelevitch et al. (2011) Heart Rhythm 8: 1281-90
Late I(Na) current: A substrate to maintain repolarization

p-, phosphorylated
o-, oxidized

Cardiac-like Myocytes (from human induced, pluripotent stem cells; hiPSCs, LQT-2)

Modelling the long QT syndrome with induced pluripotent stem cell
Izhaki et al. Nature Feb. 2010 epub

FPD: field potential duration

EAD suppression with nifedipin (I(Ca2+) block),
Pinacidil (I(K-ATP) opener), ranolazine (I(Na(Kr) block)
Repolarisation:
Respect also the short (SQTS).
Heart-rate corrected QT Interval (QTc; Bazett‘s method)

**QT scale.**

- **Very long QT.**
  LQTS even if asymptomatic. Exclude II° causes

- **Long QT.**
  LQTS when supported by symptoms, family history or additional tests.*

- **Long QT possible.**
  Additional tests when indicated:* Repeated ECG, Holter, T-wave morphology, exercise, epinephrine-challenge, adenosine-challenge.

- **Normal QT.**

- **Short QT.**
  SQTS when supported by symptoms or family history. Additional tests: Repeated ECG, Holter, T-wave morphology (?), electrophysiologic studies (?)

- **Very short QT.**
  SQTS even if asymptomatic. Exclude II° causes

Proband:
QT: 300 ms
QTc: 335 ms
QTp: 78%

Brother:
QT: 300 ms
QTc: 335 ms
QTp: 80%
(Short) QT Intervals: The Range
(Japan, >110,000 In-hospitals)

A. Total
- 421 ±25ms

B. Male
- 418 ±25ms

C. Female
- 424 ±25ms

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>380.0</td>
<td>387.0</td>
</tr>
<tr>
<td>2.0</td>
<td>378.0</td>
<td>386.0</td>
</tr>
<tr>
<td>1.0</td>
<td>373.0</td>
<td>381.0</td>
</tr>
<tr>
<td>0.5</td>
<td>369.0</td>
<td>376.0</td>
</tr>
<tr>
<td>0.15</td>
<td>362.0</td>
<td>369.0</td>
</tr>
<tr>
<td>0.1</td>
<td>361.0</td>
<td>367.0</td>
</tr>
<tr>
<td>0.0</td>
<td>331.0</td>
<td>329.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
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<tr>
<td>10-19</td>
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<tr>
<td>20-29</td>
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<td>30-39</td>
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<td>40-49</td>
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<td>50-59</td>
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<td>60-69</td>
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<tr>
<td>70-79</td>
<td></td>
</tr>
<tr>
<td>80-89</td>
<td></td>
</tr>
<tr>
<td>90-99</td>
<td></td>
</tr>
</tbody>
</table>

Heart Rhythm (2012) 9: 66-72
Shortened AP/Repolarization and K+ Currents ($I_K$): SQT1-3
SQTS
Ca\(^{2+}\)-Channel Types

\(\text{CACNB2b}^{n=1+BrS},\)  
\(\text{CACNA1c}^{n=4+BrS}\)  
\(\text{CACND2d}^{n=4}\)
**Expert Consensus Recommendations on Short QT Syndrome Therapeutic Interventions**

<table>
<thead>
<tr>
<th>Class</th>
<th>Recommendation</th>
<th>Details</th>
</tr>
</thead>
</table>
| Class I | 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 | 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.  
  4. Sotalol *may be considered* in asymptomatic patients with a diagnosis of SQTS and a family history of SCD. |

(... disopyramide, flecainide, ibutilide, nifekalant, ...)

Heart Rhythm (2013), in press (ePUB)  
Europace (2013), in press
Brugada Syndrome
(BRGDA / BrS)
Brugada Syndrome (BrS): Indicative ECGs

- **BrS Type 1-ECG** only diagnostic at rest, after provocation, after conversion of BrS Type 2/3
- J-point / ST ↑ of more than 2 mm in two or more right precordial leads
- Exclusion of other causes (phenocopying conditions)

**Number of indicative leads (e.g., one)**
- **‘Best’ lead (e.g., V2)**
- **Leads at atypical sites (e.g., 2nd ICR)**

![ECG Tracings](image)
Brugada Syndrome (BrS): Epicardial APD Prolongation

Epicardial vs. Endocardial MAPs:
- Patients: +15 ms
- Control: -11 ms

+ Pilsicainide:
- Patients: +34 ms
- Control: -14 ms

Figure 2: Example of Surface Electrocardiograms (II, V2, and V5) and Intracardiac Unipolar Electrogram at the RVOT

Activation-recovery interval (ARI), repolarization time (RT), and activation time (AT) were measured at the right ventricular outflow tract (RVOT).

Nagase et al. (2008) JACC 51: 1154-1160v
Cardiac Sodium Channelopathies ($I_{Na}$)

- LQT-3
- BrS-1; PCCD
- LQT-10, SIDS
- LQT-12, SIDS
- LQT-9, SIDS
- IVF, AF, SIDS
- BrS-7
- BrS-5, AF, PCCD
- BrS-2, SIDS
- AF

In average, 21% SCN5A+ 
All mutations are 'private', no gene hot spots.
Brugada Syndrome (BrS):
The decrease in $I(\text{Na})$ peak current


Shift of voltage dependence of steady-state activation towards more depolarized membrane potentials

Hyperpolarizing shift of the voltage dependence of steady-state inactivation curve will lead to fewer sodium channels at RMP.

Slower recovery from channel inactivation has also been described for BrS-associated SCN5A mutations.

Expert Consensus Recommendations on Brugada Syndrome Therapeutic Interventions

Class I

1. 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 (for example, visit 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.
## Expert Consensus Statement: Brugada

### Class IIA

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:
   a) Who 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 1 ECG.

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

### Class III

10. ICD Implantation *is not indicated* in asymptomatic BrS patients with a drug induced type 1 ECG and on the basis of a family history of SCD alone.

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Heart Rhythm (2013), in press (ePUB)
Europace (2013), in press
Brugada Models (cor.-art. perf. RV canine wedge) and Effect of Quinidine

Pilsicainide or Pinacidil: 12.5 or 2 µmol/L
(I(to) agonist NS-5806 5 µmol/L)

Verapamil (I(Ca) block) 5 µmol/L

Pilsicainide/Pinacidil + Quinidine 5 µmol/L
(blocks: I(Na_TTX+), I(to), I(Ks), I(Kr), I(K1), I(K-ATP))

Reduced epicardial dispersion of repolarisation
Reduced TDR (epi-endocardial)
Restored epicardial notch

Morita et al. (2010) Heart Rhythm 7: 820-828
(Non-) Availability of quinidine:

- **Green** = available
- **Red** = not available
- **Yellow** = available with restrictions
- **White** = no data

JACC (2013) 61: 2383-2387
Novel Approaches in Brugada syndrome Models

- PDE-III inhibitors (2-10 µmol/L): Milrinone, Cilastazol > cAMP ↑, I(L-Ca) ↑
- I(to) blockers/regulators: 4-AP (4’ aminopyridine) Semaphorin / SEMA3A CRIP (cold-inducible RNA-binding protein for I(to))

Terfenadine (blocks: I(Na) and I(Ca))

Szel et al. (2013) Heart Rhythm 10: 1720–1727
Boczek at al. (2014) Circ Res.115: 460-469
Long-term Suppression of J-wave in Brugada syndrome

C: Cilostazole 200 mg/d (24 months)
B: Clopidogrel (acute phase)

C: Quinidine 200 mg/d (24 months)

Szel et al. (2013) Heart Rhythm 10: 1720–1727
Boczek et al. (2014) Circ Res.115: 460-469
Figure. Computational modeling of impact of cold-inducible RNA-binding protein (CIRP) $I_{to}$ downregulation in rat and human cardiomyocytes. A, Schematic of CIRP regulation in the rat cardiomyocyte (left), where the absence of CIRP leads to greater $I_{to}$ density and a shortened action potential (AP) duration (right). B, Computational modeling of human AP waveforms in ventricular (left) and atrial (right) myocytes reveals expected tissue-specific effects when increasing $I_{to}$ current density.
CPVT
(catecholaminergic polymorphic ventricular tachycardia)
CPVT: Treatment Options

- Due to severe clinical course, treatment is considered a priori in 'affected' individuals.

- **Suggestive indicators** for therapeutic effectiveness are the reduction of VES/VT and symptoms.

- Treatment options include:
  - **Life style modification**!
  - Drugs (BB +/- verapamil +/- flecainide)
  - ICD implantation
  - Left sympathetic cardiac denervation (LSCD)
CPVT: First and Second Focus

n=27 CPVT pts.
81% Single focus
19% Double focus

RVOT: n=15
RVA: n=6
LVOT: n=1
LVA: n=1

Sumitomo et al. (2003) Heart 89: 66-70
Flecainide  ? RYR2 blockade by luminal/cytoplasmic binding
KN-93 (1µM)  CamKII inhibition – less phosphorylation
Dantrolene  RYR2 binding (effective in MHH/RYR1)
Ranolazine (10µM)  reduces P_0 of RYR2 receptors
Fig. 4. Einthoven’s first ECG tracings. Recording of an ECG with A, B, C and D wave using a capillary electrometer (upper registration). The lower ECG registration is Einthoven’s first published electrocardiographic tracing using a string galvanometer and a different nomenclature with P, Q, R, S, and T wave.
Eric Schulze-Bahr

Institute for Genetics of Heart Diseases
Department for Cardiology and Angiology
University Hospital Münster (Germany)
Uses of Genetic Testing in Cardiovascular Diseases

- Diagnostic and/or predictive testing (for monogenic traits)
- Pharmacogenomic testing (CYP450, e.g. -2C9, -2D6)
- Postmortem testing (‘Molecular Autopsy‘)

- Risk prediction testing, uses genome information (QTLs) from GWAS to assess individual relative risk for common cardiovascular disorders

- Direct-to-consumer testing, commercial service without professional medical consultation
- Pre-implantation testing (selection during fertilization)