Long QT syndrome

Should we treat all asymptomatic patients?

Venice Arrhythmia 2015
Arthur A.M. Wilde
NO CONFLICT OF INTEREST TO DECLARE
Long QT Syndrome(s)

- Autosomal dominant/autosomal rec.
- Genetically heterogeneous
- 16 genes (LQTS$_{1-16}$)
- $\geq 60\%$ genotyped ($\geq 90\%$ in families)
- Gene-specific features
Before puberty LQT1 (males), after puberty LQT2 (females)?

Risk of syncope/ACA/SCD in LQTS population: (age 1 through 75 yrs)

Moss and Goldenberg JACC 2008
Established risk factors

- Aborted sudden death
- Syncope
- Congenital deafness (JLN)
- Torsades de Pointes, T-wave alternans
- Prolonged QT (> 500ms)
- Family history of (a)SCD not
Congenital LQTS
Symptomatology
Long QT syndrome, risk stratification

Established risk factors

- Aborted sudden death
- Syncope
- Congenital deafness (JLN)
- Torsades de Pointes, T-wave alternans
- Prolonged QT (> 500ms)
- Family history of (a)SCD not
Heart Centre

Long QT syndrome, risk stratification

Established risk factors, **Asymptomatic pts**

- Aborted sudden death
- Syncope
- congenital deafness (JLN)
- Torsades de Pointes, T-wave alternans
- Prolonged QT (> 500ms)
- Family history of (a)SCD not
A patient at risk

Neonate, prenatal bradycardia, hydrops, syndactyly.

Courtesy Dr Nico Blom
Jervell Lange-Nielsen Syndrome

Female 6y old, syncopal attacks, sensorinal bilateral deafness
Long QT syndrome, risk stratification

\( QT_c \) Quartiles:
1: \( \leq 446 \text{ ms} \)
2: 447 - 468 ms
3: 469 - 498 ms
4: \( \geq 499 \text{ ms} \)
Long QT syndrome, role of genetics

Genetic ‘real estate’:
♥ Transmembrane LQTS2 mutations
♥ Missense LQTS1 mutations
♥ Specific LQTS1 mutations (e.g. A341V)
♥ Large variation in LQT3
Risk for Life-Threatening Cardiac Events in Patients With Genotype-Confirmed Long-QT Syndrome and Normal-Range Corrected QT Intervals

Ilan Goldenberg, MD,* Samuel Horr, MA,* Arthur J. Moss, MD,* Coeli M. Lopes, PhD,†
Alon Barsheshet, MD,* Scott McNitt, MS,* Wojciech Zareba, MD, PhD,* Mark L. Andrews, BBA,*
Jennifer L. Robinson, MS,* Emanuela H. Locati, MD,§ Michael J. Ackerman, MD, PhD,¶
Jesaia Benhorin, MD,|| Elizabeth S. Kaufman, MD,# Carlo Napolitano, MD,**††
Pyotr G. Platonov, MD, PhD, §§ Silvia G. Priori, MD, PhD,**†† Ming Qi, MD,‡
Peter J. Schwartz, MD, §§ Wataru Shimizu, MD, PhD,|| Jeffrey A. Towbin, MD,¶¶
G. Michael Vincent, MD,*** Arthur A. M. Wilde, MD, PhD,**# Li Zhang, MD***

Rochester and New York, New York; Milan and Parvia, Italy; Tel Aviv, Israel; Rochester, Minnesota; Cleveland, Ohio;
Lund, Sweden; Suita, Japan; Houston, Texas; Amsterdam, the Netherlands; and Salt Lake City, Utah
Table 1. Baseline and follow-up characteristics of the study population by genotype-phenotype

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Unaffected Family Members (n=1525)</th>
<th>LQTS with Normal-Range QTc (n=469)</th>
<th>LQTS with Prolonged QTc (n=1392)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>52%</td>
<td>48%</td>
<td>61%*†</td>
</tr>
<tr>
<td>Family history of SCD</td>
<td>8%</td>
<td>12%</td>
<td>19%*†</td>
</tr>
<tr>
<td>QTc (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>412 ± 22</td>
<td>419 ±20</td>
<td>501 ± 48</td>
</tr>
<tr>
<td>Median (IQ range)</td>
<td>420 (400-430)</td>
<td>420 (410-440)</td>
<td>490 (470-520)</td>
</tr>
<tr>
<td>Proband</td>
<td>8%</td>
<td>8%</td>
<td>29%*†</td>
</tr>
<tr>
<td>RR (msec)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>793 ±221</td>
<td>888 ±236</td>
<td>848 ±214 **†</td>
</tr>
<tr>
<td>Median (IQ range)</td>
<td>800 (640-930)</td>
<td>900 (740-1040)</td>
<td>840 (700-1000) **†</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LQT1</td>
<td>NA</td>
<td>40%</td>
<td>39%</td>
</tr>
<tr>
<td>LQT2</td>
<td>NA</td>
<td>45%</td>
<td>47%</td>
</tr>
<tr>
<td>LQT3</td>
<td>NA</td>
<td>16%</td>
<td>14%</td>
</tr>
<tr>
<td>Mutation: TM-MS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>NA</td>
<td>35%</td>
<td>43%</td>
</tr>
<tr>
<td>LQT1</td>
<td>NA</td>
<td>45%</td>
<td>61%</td>
</tr>
<tr>
<td>LQT2</td>
<td>NA</td>
<td>16%</td>
<td>29%*†</td>
</tr>
<tr>
<td>LQT3</td>
<td>NA</td>
<td>64%</td>
<td>31%*†</td>
</tr>
<tr>
<td>Therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>beta-blockers</td>
<td>6.2%</td>
<td>38%</td>
<td>54%*†</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>0.3%</td>
<td>0.6%</td>
<td>5%*†</td>
</tr>
<tr>
<td>LCSD</td>
<td>0.1%</td>
<td>0.2%</td>
<td>1.4%*†</td>
</tr>
<tr>
<td>ICD</td>
<td>0.6%</td>
<td>6%</td>
<td>14%*†</td>
</tr>
</tbody>
</table>
QTc $\leq$ 440ms

QTc $>$ 441ms
### Class ICD Recommendations

<table>
<thead>
<tr>
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<th>ICD Recommendations</th>
</tr>
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<tbody>
<tr>
<td>Class I</td>
<td>ICD implantation <strong>is recommended</strong> for patients with a diagnosis of LQTS who are survivors of a cardiac arrest</td>
</tr>
<tr>
<td>Class IIa</td>
<td>ICD implantation <strong>can be useful</strong> in patients with a diagnosis of LQTS who experience recurrent syncopal events while on beta-blocker therapy.</td>
</tr>
<tr>
<td>Class III</td>
<td>Except under special circumstances, ICD implantation <strong>is not indicated</strong> in asymptomatic LQTS patients who have not been tried on beta-blocker therapy</td>
</tr>
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</table>

**Family history is NOT a risk factor**
Long QT syndrome, asymptomatic pt

When should an ICD be considered?

♥ JLNS patient with a long QTc (>500msec)
♥ LQT2 pt with QTc > 550
♥ LQT3 pt with QTc > 500
♥ Torsades de Pointes, T-wave alternans
♥ rarely LQT1!
♥ Family history of (a)SCD is not a riskfactor
### Beta-blocker Recommendations

<table>
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<th>Class</th>
<th>Description</th>
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| Class I| Beta-blockers **are recommended** for patients with a diagnosis of LQTS who are:  
  - Asymptomatic with QTc ≥ 470 ms, *and/or*  
  - Symptomatic for syncope or documented VT/VF. |
| Class IIa| Beta-blockers **can be useful** in patients with a diagnosis of LQTS who are asymptomatic with QTc ≤ 470ms |

**But in who treatment is not needed?**
Long QT syndrome, focus on LQT1

Cumulative Probability of Cardiac Event

Years of Age

No. of Subjects

LQT1 group  72  36  27  19
LQT2 group  56  29  16  11
LQT3 group  36  24  16

The LQT registry
Long QT syndrome, focus on LQT1

Long QT syndrome, focus on LQT1

KCNQ1 A341V versus other KCNQ1 mutations

Crotti et al, Circulation 2007
Mutation dependent prognosis (LQTS2)
### Class I
Beta-blockers are recommended for patients with a diagnosis of LQTS who are:
- Asymptomatic with QTc ≥ 470 ms, and/or
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### Class IIa
Beta-blockers can be useful in patients with a diagnosis of LQTS who are asymptomatic with QTc ≤ 470ms

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**Low risk: asymptomatic LQT1 adult (QTc < 500?)**
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Low risk: asymptomatic LQT1 adult (QTc < 500?)
Risk Factors for Aborted Cardiac Arrest and Sudden Cardiac Death in Children With the Congenital Long-QT Syndrome

Ilan Goldenberg, MD; Arthur J. Moss, MD; Derick R. Peterson, PhD; Scott McNitt, MS; Wojciech Zareba, MD, PhD; Mark L. Andrews, BBA; Jennifer L. Robinson, MS; Emanuela H. Locati, MD; Michael J. Ackerman, MD, PhD; Jesaia Benhorin, MD; Elizabeth S. Kaufman, MD; Carlo Napolitano, MD; Silvia G. Priori, MD, PhD; Ming Qi, MD; Peter J. Schwartz, MD; Jeffrey A. Towbin, MD; G. Michael Vincent, MD; Li Zhang, MD

(Circulation 2008;117:2184-2191)
Figure 1. Kaplan–Meier estimates of the probability of ACA or SCD by gender (values in parentheses are event rates).

Figure 2. Kaplan–Meier estimates of the probability of ACA or SCD by gender and QTc subgroups (values in parentheses are event rates).


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Beta-Blocker Efficacy in High-Risk Patients With the Congenital Long-QT Syndrome Types 1 and 2: Implications for Patient Management

ILAN GOLDENBERG, M.D., JAMES BRADLEY, M.D., M.P.H., ARTHUR MOSS, M.D., SCOTT McNITT, M.S., SLAVA POLONSKY, M.S., JENNIFER L. ROBINSON, M.S., MARK ANDREWS, B.B.A., WOJCIECH ZAREBA, M.D., Ph.D., on behalf of the International LQTS Registry Investigators*

From the Cardiology Division, Department of Medicine, University of Rochester Medical Center, Rochester, New York, USA

β-Blockers for LQTS Types 1 and 2. Background: Beta-blockers are the mainstay therapy in patients with the congenital long-QT syndrome (LQTS) types 1 and 2. However, limited data exist regarding the efficacy and limitations of this form of medical management within high-risk subsets of these populations.

Methods and Results: Multivariate analysis was carried out to identify age-related gender- and genotype-specific risk factors for cardiac events (comprising syncope, aborted cardiac arrest [ACA] or sudden cardiac death [SCD]) from birth through age 40 years among 971 LQT1 (n = 549) and LQT2 (n = 422) patients from the International LQTS Registry. Risk factors for cardiac events included the LQT1 genotype (HR = 1.49, P = 0.003) and male gender (HR = 1.31, P = 0.04) in the 0–14 years age group; and the LQT2 genotype (HR = 1.67, P < 0.001) and female gender (HR = 2.58, P < 0.001) in the 15–40 years age group. Gender-genotype subset analysis showed enhanced risk among LQT1 males (HR = 1.93, P < 0.001) and LQT2 females (HR = 3.28, P < 0.001) in the respective age groups. Beta-blocker therapy was associated with a significant risk-reduction in high-risk patients, including a 67% reduction (P = 0.02) in LQT1 males and a 71% reduction (P < 0.001) in LQT2 females. Life-threatening events (ACA/SCD) rarely occurred as a presenting symptom among beta-blocker-treated patients. However, high-risk patients who experienced syncope during beta-blocker therapy had a relatively high rate of subsequent ACA/SCD (>1 event per 100 patient-years).

Conclusions: The present findings suggest that beta-blocker therapy should be routinely administered to all high-risk LQT1 and LQT2 patients without contraindications as a first line measure, whereas primary defibrillator therapy should be recommended for those who experience syncope during medical therapy. (J Cardiovasc Electrophysiol, Vol. 21, pp. 893-901, August 2010)
Proposed Management Strategy in LQT1 and LQT2 patients

LQT1 and LQT2 Subjects 0-40 yrs

High-Risk Pts
One or more of the following:
- Prior syncope without BB
- QTc ≥ 500 msec
- LQT1 male 0-14 yrs
- LQT2 female 15-40 yrs

Rx
Lifestyle modifications*
Routine BB therapy
Consider ICD on individual basis or if low BB compliance/intolerance

Syncope on BB therapy

Rx
ICD + BB therapy
Consider LCSD in LQT1 pts

Secondary Prevention Pts
Prior ACA

Rx
ICD + BB therapy
Proposed Management Strategy in LQT1 and LQT2 patients

LQT1 and LQT2 Subjects 0-40 yrs

Low-Risk pts
No prior syncope and QTc < 500 msec and one of the following:
- LQT1 female 0-14 yrs
- LQT2 male and female 0-14 yrs
- LQT1 male and female 15-40 yrs
- LQT2 male 15-40 yrs

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One or more of the following:
- Prior syncope without BB
- QTc ≥ 500 msec
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Prior ACA

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- **Low-Risk pts**
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  - and one of the following:
    - LQT1 female 0-14 yrs
    - LQT2: male and female 0-14 yrs
    - LQT1 male and female 15-40 yrs
    - LQT2 male 15-40 yrs

  - **Rx**
    - Lifestyle modifications
    - Consider BB on individual basis

- **High-Risk Pts**
  - One or more of the following:
    - Prior syncope without BB
    - QTc ≥ 500 msec
    - LQT1 male 0-14 yrs
    - LQT2 female 15-40 yrs

  - **Rx**
    - Lifestyle modifications
    - Routine BB therapy
    - Consider ICD on individual basis or if low BB compliance/intolerance

  - Syncope on BB therapy
    - **Rx**
      - ICD + BB therapy
      - Consider LCSD in LQT1 pts

- **Secondary Prevention Pts**
  - Prior ACA

  - **Rx**
    - ICD + BB therapy
Proposed Management Strategy in LQT1 and LQT2 patients

LQT1 and LQT2 Subjects 0-40 yrs

Low-Risk pts
- No prior syncope and QTc < 500 msec and one of the following:
  - LQT1 female 0-14 yrs
  - LQT2 :male and female 0-14 yrs
  - LQT1 male and female 15-40 yrs
  - LQT2 male 15-40 yrs

Rx
- Lifestyle modifications
- Consider BB on individual basis

High-Risk Pts
- One or more of the following:
  - Prior syncope without BB
  - QTc ≥ 500 msec
  - LQT1 male 0-14 yrs
  - LQT2 female 15-40 yrs

Rx
- Lifestyle modifications
- Consider ICD on individual basis or if low BB compliance/intolerance

Secondary Prevention Pts
- Prior ACA

Rx
- ICD + BB therapy

Syncope and/or increase in QTc to > 500 msec during follow-up

Rx
- Initiate BB therapy

Syncope on BB therapy

Rx
- ICD + BB therapy
  - Consider LCSD in LQT1 pts
Amsterdam, the Netherlands
December 4th 2015

For information and registration see www.20yrsCG.nl

Organising committee:
Karin Y. van Spaendonck
J. Peter van Tintelen
Arthur Wilde

www.20yrsCG.nl
Thank you
Mutations sites in the KCNQ1 gene

Risk of Aborted Cardiac Arrest or Sudden Cardiac Death During Adolescence in the Long-QT Syndrome

Jenny B. Hobbs, MD
Derick R. Peterson, PhD
Arthur J. Moss, MD

Context Analysis of predictors of cardiac events in hereditary long-QT syndrome (LQTS) has primarily considered syncope as the predominant end point. Risk factors specific for aborted cardiac arrest and sudden cardiac death have not been investigated.
Risk during adolescence (10-20y)

♥ 2772 children followed between 10 and 20y
♥ 81 ACA and 45 SCD (4.5%)
♥ risk factors: syncope, QTc and gender (10-12)

JAMA 2006;296:1249-1254
**Table 2. Time-Dependent Multivariable Cox Model: Risk of Aborted Cardiac Arrest or Sudden Cardiac Death (Ages 10-20 Years)**

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of Events</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent syncope vs no syncope in past 10 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Syncopal event in past 2-10 y and no events within 2 y</td>
<td>9</td>
<td>2.7 (1.3-5.7)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>≥2 Syncopal events in past 2-10 y and no events within 2 y</td>
<td>29</td>
<td>5.8 (3.6-9.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1 Syncopal event in past 2 y</td>
<td>26</td>
<td>11.7 (7.0-19.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥2 Syncopal events in past 2 y</td>
<td>20</td>
<td>18.1 (10.4-31.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>QTc ≥530 ms</td>
<td>51</td>
<td>2.3 (1.6-3.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Males aged 10-12 y vs age-matched females*</td>
<td>19</td>
<td>4.0 (1.8-9.2)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Time-dependent β-blocker therapy for those with recent syncope†</td>
<td>10</td>
<td>0.36 (0.2-0.7)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

*Between the ages of 13 and 20 years, there was no significant difference in risk between the sexes.
†β-Blocker therapy was significant only among those who had experienced syncope in the past 2 years.
Does the genotype matter?