New Management of LQTS: Gene-Specific Therapies, Cardiac Denervation, and Sports Participation Issues

Michael J. Ackerman, MD, PhD, FACC

Windland Smith Rice Cardiovascular Genomics Research Professor
Professor of Medicine, Pediatrics, and Pharmacology
Director, Long QT Syndrome Clinic and the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory
President, Sudden Arrhythmia Death Syndromes (SADS) Foundation

2015 SADS Foundation International Meeting
New York City, NY
May 29, 2015
Learning Objectives to Disclose:
• To **ASSESS** the currently available treatment options for LQTS in general and LQT3 in particular
• To **CRITIQUE** the ICD and left cardiac sympathetic denervation (LCSD) therapy and their role in the treatment of LQTS
• To **EXAMINE** whether an athlete with LQTS can remain an athlete

Conflicts of Interest to Disclose:
• Consultant – Boston Scientific, Gilead Sciences, Medtronic, St. Jude Medical, and Transgenomic/FAMILION
• Royalties – Transgenomic/FAMILION
Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes

Silvia G. Priori, (HRS Chairperson)¹, Arthur A. Wilde, (EHRA Chairperson)², Minoru Horie, (APHRS Chairperson)³, Yongkeun Cho, (APHRS Chairperson)⁴, Elijah R. Behr⁵, Charles Berul⁶, Nico Blom⁷*, Josep Brugada⁸, Chern-En Chiang⁹, Heikki Huikuri¹⁰, Prince Kannankeril¹¹‡, Andrew Krahn¹², Antoine Leenhardt¹³, Arthur Moss¹⁴, Peter J. Schwartz¹⁵, Wataru Shimizu¹⁶, Gordon Tomaselli¹⁷†, Cynthia Tracy%¹⁸

Document Reviewers: Michael Ackerman (USA), Bernard Belhassen (Israel), N. A. Mark Estes III (USA), Diane Fatkin (Australia), Jonathan Kalman (Australia), Elizabeth Kaufman (USA), Paulus Kirchhof (UK and Germany), Eric Schulze-Bahr (Germany), Christian Wolpert (Germany), Jitendra Vohra (Australia), Marwan Refaat (USA), Susan P. Etheridge (USA), Robert M. Campbell (USA), Edward T. Martin (USA), Swee Chye Quek (Singapore)
Congenital Long QT Syndrome

- Normal QT interval
- Prolonged QT

1. Syncope
2. Seizures
3. Sudden death

Torsades de pointes
Your 17-year-old female athlete fainted while running on a treadmill. Subsequently, you diagnose LQTS and genetically confirm as LQT1. Her QTc is 503 ms.

You recommend an ICD and disqualify her from competitive sports.

1. YES
2. NO
Long QT Syndrome Recommendations

Class I Recommendations

The following lifestyle changes are recommended in all patients with a diagnosis of LQTS:

- Avoidance of QT prolonging drugs (www.qtdrugs.org)
- Identification and correction of electrolyte abnormalities that may occur during diarrhea, vomiting, metabolic conditions or imbalanced diets for weight loss.

Beta-blockers are recommended for patients with a diagnosis of LQTS who are:

- Asymptomatic with QTc \geq 470$ ms, \textit{and/or}
- Symptomatic for syncope or documented VT/VF.

Left cardiac sympathetic denervation (LCSD) is recommended for high-risk patients with a diagnosis of LQTS in whom:

- ICD therapy is contraindicated or refused, \textit{and/or}
- Beta-blockers are either not effective in preventing syncope/arrhythmias, not tolerated, not accepted or contraindicated.

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

All LQTS patients who wish to engage in competitive sports should be referred to a clinical expert for evaluation of risk.
Efficacy of Beta Blocker Therapy

Villain et al. *European Heart Journal* 25:1405-1411, 2004
Ackerman, Priori, Schwartz, Vincent, Wilde. Personal LQTS Clinics, 2013
Treatment Options for LQTS

LQTS ≠ LCSD

Beta-Blocker Therapy
Treatment Options for LQTS

No Active Therapy Necessary If:
- Asymptomatic male
- > 40 years old
- QTc < 460 ms
- Haploinsufficient, LQT1-causing C-terminal missense mutation

Treatment Options for LQTS

Nadolol – 1-1.5 mg/kg/day or 50 mg/m²/day – QD or BID
or
Propranolol – 3-4 mg/kg/day (BID, LA, TID for the liquid)

Caution w/ Using Atenolol and Metoprolol!
Chatrath, Bell, Ackerman. *Pediatr Cardiol* 25:459-465, 2004
Chockalingam … Wilde. *JACC* 2012

Propranolol and/or Mexiletine/Ranolazine (LQT3)
Treatment Options for LQTS

Chatrath, Bell, Ackerman. Pediatr Cardiol 25:459-465, 2004

Chockalingam … Wilde. JACC 2012

% of symptomatic patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>51</td>
<td>8</td>
</tr>
<tr>
<td>Nadolol</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>35</td>
<td>29</td>
</tr>
</tbody>
</table>

p = 0.9

n = 51

n = 15

n = 35
Treatment Options for LQTS

Chockalingam…Wilde. JACC 2012

Cumulative event-free survival

Time (months)

Patients at risk
Propranolol/Nadolol  66  23  7  5  2
Metoprolol      35  17  9  1  0

Beta-Blocker Therapy

p=0.02

Propranolol / Nadolol

Metoprolol
LQT3-Specific Pharmacotherapy

Targeting the Late Sodium Current
Mexiletine, Flecainide, Ranolazine, and Propranolol

- Improve, shorten, normalize the QTc
- Survival benefit??

Kapplinger ... Ackerman. *Heart Rhythm* 2009
Rationale for Development of GS-6615 in LQT3

- LQT3 pathophysiology:
  - Gain-of-function mutation(s) in SCN5A
  - Result in increase in late $I_{Na}$
    - Prolongation of APD
    - QT prolongation

- GS-6615:
  - Selective and potent inhibitor of late $I_{Na}$
  - Expected to shorten QT interval

Slide courtesy of Arthur Wilde
Average QTcF change in Lead V5 between 4-12 hrs after GS-6615 (Day 1 vs. Day -1)

Dose of GS-6615

<table>
<thead>
<tr>
<th>Doses</th>
<th>10 mg (n=3)</th>
<th>20 mg (n=3)</th>
<th>30 mg (n=3)</th>
<th>60 mg (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Cmax (ng/mL)</td>
<td>119</td>
<td>237</td>
<td>300</td>
<td>638</td>
</tr>
</tbody>
</table>

Zareba et al. HRS 2014

Slide courtesy of Arthur Wilde
Multiple Doses: GS-6615 Shortens QTc

Slide courtesy of Arthur Wilde
### Long QT Syndrome Recommendations


<table>
<thead>
<tr>
<th>Class IIa Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-blockers</strong> can be useful in patients with a diagnosis of LQTS who are asymptomatic with QTc ≤ 470ms</td>
</tr>
<tr>
<td><strong>ICD implantation</strong> can be useful in patients with a diagnosis of LQTS who experience recurrent syncopal events while on beta-blocker therapy.</td>
</tr>
<tr>
<td><strong>LCSD</strong> can be useful in patients with a diagnosis of LQTS who experience breakthrough events while on therapy with beta-blockers/ICD.</td>
</tr>
<tr>
<td><strong>Sodium channel blockers</strong> can be useful, as add-on therapy, for LQT3 patients with a QTc &gt; 500 ms who shorten their QTc by &gt; 40 ms following an acute oral drug test with one of these compounds.</td>
</tr>
</tbody>
</table>
Class III Recommendation

Except under special circumstances, ICD implantation is not indicated in asymptomatic LQTS patients who have not been tried on beta-blocker therapy.
Treatment Options for LQTS

LQTS ≠ X

< 15%  > 75%

LQTS CsOE

©2002 Mayo Clinic
Indications for ICD Therapy

Secondary Prevention

- Aborted cardiac arrest
- Rx intolerance or breakthrough
Indications for ICD Therapy

Primary Prevention

- QTc > 550 ms and not LQT1
- LQT2 women, QTc > 500 ms, +/- Sx
- Infants with 2:1 AV block?
- JLNS (LQTS w/ deafness)?
- +ve FHx of SCD (=1, >1, >2)?
- LQT3?
Treatment Options for LQTS

- Beta Blocker Rx (LQTS)
- ICD
- LCSD

©2002 Mayo Clinic
### Left Cardiac Sympathetic Denervation

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1916</td>
<td>First left stellectomy for angina</td>
<td>Jonnesco</td>
</tr>
<tr>
<td>1961</td>
<td>First bilateral sympathectomy for VT</td>
<td>Estes and Izlar</td>
</tr>
<tr>
<td>1968</td>
<td>First LCSD for VT</td>
<td>Zipes et al.</td>
</tr>
<tr>
<td>1970</td>
<td>First LCSD for LQTS</td>
<td>Moss and McDonald</td>
</tr>
<tr>
<td>2003</td>
<td>First reported videoscopic LCSD for LQTS</td>
<td>Li et al.</td>
</tr>
<tr>
<td>2009</td>
<td>Largest series of videoscopic LCSD</td>
<td>Mayo Clinic</td>
</tr>
</tbody>
</table>

*LCSD = Denervation of lower half of the left stellate ganglion (T1) and the sympathetic chain from T2 - T4*
Anti-Fibrillatory Effect of LCSD

CA n=22
CA/SD n=8/1

-59%

CER CLUSTER
- > 0.17 CER/month
- >0.04 -0.17 CER/month
- 0 -0.04 CER/month

<table>
<thead>
<tr>
<th>Cardiac event rate/month</th>
<th>PRE-LCSD</th>
<th>POST-LCSD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.86</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>0.01</td>
<td>0.005</td>
</tr>
</tbody>
</table>

(mean CER 0.32±0.64) (mean CER 0.07±0.27)

-78%

Left Cardiac Sympathetic Denervation

- LCSD has a potent anti-fibrillatory effect in LQTS
  
  Schwartz et al. Circulation 2004

LCSD’s anti-fibrillatory effects caused by:

- “Norepinephrine ablation”
- Improved repolarization as evidenced by a decrease in QTc in ~30%
Left Cardiac Sympathetic Denervation

Videoscopic Denervation Therapy at Mayo

- N = 149 LCSDs from November 2005 to present
- Average age: 20 ± 17 years
  (4 weeks of age to 85 years)
- LQTS (105, LQT1 in 62, LQT2 in 26, LQT3 in 9); CPVT (24); IVF (11); Cardiomyopathy (9)
- LQTS: QTc = 497 ± 67 ms
## Demographics of LQTS Cohort (N=52)

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>24/28</td>
</tr>
<tr>
<td>Age at Diagnosis (years)</td>
<td>10.0 ± 10</td>
</tr>
<tr>
<td>Age at LCSD (years)</td>
<td>14.1 ± 10</td>
</tr>
<tr>
<td>Baseline QTc (ms)</td>
<td>528 ± 74</td>
</tr>
<tr>
<td>Genotype Positive</td>
<td>92%</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>98%</td>
</tr>
<tr>
<td>ICD pre-LCSD</td>
<td>31%</td>
</tr>
<tr>
<td>ICD shocks pre-LCSD</td>
<td>36%</td>
</tr>
</tbody>
</table>

Bos...Ackerman. *Circulation Arrhythmia & EP* 2013
LQTS Genotypes in LCSD Cohort

- LQT1 (23)
- LQT3 (4)
- LQT2 (9)
- JLNS (3)
- Multiple (9)
- G-/P+ (4)

Bos...Ackerman. Circulation Arrhythmia & EP 2013
Left Cardiac Sympathetic Denervation

- High Risk
- Breakthroughs
- ICD Shocks

βBL Intolerant

Bos...Ackerman. Circulation Arrhythmia & EP 2013
LCSD in LQTS

<table>
<thead>
<tr>
<th>Number of Cardiac Events</th>
<th># of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before LCSD</td>
<td>After LCSD</td>
</tr>
<tr>
<td>&gt;10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>6-10</td>
<td>6-10</td>
</tr>
<tr>
<td>1-5</td>
<td>1-5</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Bos…Ackerman. *Circulation Arrhythmia & EP 2013*
LCSD in LQTS

"LCSD is NOT a cure!"
Current LCSD Indications at Mayo Clinic

- History of appropriate ICD therapy
- Rx intolerance or breakthrough
- High risk phenotype but not ideal for ICD – “bridge to ICD”
- High risk patients in developing countries without access to an ICD

Collura, Johnson, Moir, Ackerman. *Heart Rhythm* 6:752-759, 2009
What Can I Do?
Can I Play?
Summary of Bethesda Conference #26 (1994)

Unless your heart is perfect, NO COMPETITIVE SPORTS PERIOD!!!
Unless your heart is perfect or the syndrome is confined to just your genome, NO COMPETITIVE SPORTS except perhaps class IA sports!!!

So, what are class IA sports anyway? Please tell me there is something good in there!!
<table>
<thead>
<tr>
<th>Increasing Static Component</th>
<th>III. High (&gt;50% MVC)</th>
<th>II. Moderate (20-50% MVC)</th>
<th>I. Low (&lt;20% MVC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bobsledding/Luge†, Field events (throwing), Gymnastics†, Martial arts*, Sailing, Sport climbing, Water skiing†, Weight lifting†, Windsurfing†</td>
<td>Body building†, Downhill skiing†, Skateboarding†, Snowboarding†, Wrestling*</td>
<td>Boxing*, Canoeing/Kayaking, Cycling†, Decathlon, Rowing, Speed-skating†, Triathlon†</td>
</tr>
<tr>
<td></td>
<td>Archery, Auto racing†, Diving†, Equestrian†, Motorcycling†</td>
<td>American football*, Field events (jumping), Figure skating*, Rodeoing†, Rugby*, Running (sprint), Surfing†, Synchronized swimming†</td>
<td>Basketball*, Ice hockey*, Cross-country skiing (skating technique), Lacrosse*, Running (middle distance), Swimming, Team handball</td>
</tr>
<tr>
<td></td>
<td>Billiards, Bowling, Cricket, Curling, Golf, Riflery</td>
<td>Baseball/Softball*, Fencing, Table tennis, Volleyball</td>
<td>Badminton, Cross-country skiing (classic technique), Field hockey*, Orienteering, Race walking, Racquetball/Squash, Running (long distance), Soccer*, Tennis</td>
</tr>
</tbody>
</table>

**Task Force 8**

**Increasing Dynamic Component**

**A. Low (<40% Max O₂)**

**B. Moderate (40-70% Max O₂)**

**C. High (>70% Max O₂)**
ESC Guidelines

Advised disqualification from all competitive sports for any LQTS patient:

Either symptomatic or asymptomatic

ECG with QTc > 440 ms (males) or > 460 ms (females)
Recommended genetic testing for confirmation

Genotype positive/Phenotype negative patients **NOT** OK to play

Pelliccia et al. *EHJ* 26:1422-1445, 2005
Unless your heart is perfect or the syndrome is confined to just your genome and you live west of the Atlantic Ocean, NO COMPETITIVE SPORTS except perhaps class IA sports!!!
Congenital Long QT Syndrome

Normal QT interval

Prolonged QT

1. Syncope
2. Seizures
3. Sudden death

Bethesda Conference #36:
Patients with concealed LQTS may be allowed to participate in sports!!!

Torsades de pointes
Congenital Long QT Syndrome

Normal QT interval

Prolonged QT

1. Syncope
2. Seizures
3. Sudden death

European Society of Cardiology

FORGET ABOUT IT!
MANIFEST OR CONCEALED – YOU ARE DONE!
“GENE CARRIERS” – YOU ARE DONE!

Syncope
Seizures
Sudden death

Torsades de pointes
Genetic Discrimination
Mayo Clinic’s LQTS Clinic Philosophy

Respect Patient/Family Autonomy and their Right to Make a Well Informed Decision
Sports Participation and LQTS

Total Cohort (N = 353)
6 - 40 year olds with LQT1-3

Non-Athlete
N = 196
Chose Disqualification
N = 27

Athlete
N = 157
Chose to Remain an Athlete
N = 130

Johnson and Ackerman. JAMA 308:764-765, 2012
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (Male/Female)</strong></td>
<td>70/60</td>
</tr>
<tr>
<td><strong>Age at Diagnosis (years)</strong></td>
<td>11 ± 7</td>
</tr>
<tr>
<td><strong>QTc (ms)</strong></td>
<td>471 ± 46</td>
</tr>
<tr>
<td><strong>Symptoms Prior to Diagnosis</strong></td>
<td>29 (22%)</td>
</tr>
<tr>
<td><strong>Beta-Blockers</strong></td>
<td>112 (87%)</td>
</tr>
<tr>
<td><strong>ICD</strong></td>
<td>20 (15%)</td>
</tr>
<tr>
<td><strong>Follow-Up (years)</strong></td>
<td>5.1 ± 2.9</td>
</tr>
</tbody>
</table>

Johnson and Ackerman. *JAMA* 308:764-765, 2012
Sports Participation and LQTS

Genotypes within the Athlete Cohort
(N=130)

LQT1 (57%)

LQT2 (32%)

LQT3 (8%)

Multiple (3%)
<table>
<thead>
<tr>
<th>Increasing Static Component</th>
<th>Increasing Dynamic Component</th>
<th>A. Low (&lt;40% Max O₂)</th>
<th>B. Moderate (40-70% Max O₂)</th>
<th>C. High (&gt;70% Max O₂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>III. High (&gt;50% MVC)</td>
<td><strong>25</strong></td>
<td><strong>4</strong></td>
<td><strong>0</strong></td>
<td></td>
</tr>
<tr>
<td>II. Moderate (20-50% MVC)</td>
<td><strong>0</strong></td>
<td><strong>14</strong></td>
<td><strong>34</strong></td>
<td></td>
</tr>
<tr>
<td>I. Low (&lt;20% MVC)</td>
<td><strong>3</strong></td>
<td><strong>22</strong></td>
<td><strong>28</strong></td>
<td></td>
</tr>
</tbody>
</table>

- Bobsledding/Luge*, Field events (throwing), Gymnastics*, Martial arts*, Sailing, Water skiing*, Weight lifting*, Wrestling*
- Body building*, Downhill skiing*, Skateboarding*, Snowboarding*, Wrestling*
- Boxing*, Canoeing/Kayaking, Cycling*, Decathlon, Rowing, Sport climbing*, Triathlon*
- Archery, Auto racing*, Diving*, Equestrian*, Motorcycling
- American football*, Field events (jumping), Figure skating*, Rugby*, Running (sprint), Surfing*, Synchro swimmin
- Basketball*, Ice hockey*, Cross-country skiing (skating), Lacrosse*, Long distance running, Team handball
- Billiards, Bowling, Cricket, Curling, Golf, Rifle
- Baseball/Softball*, Fencing, Table tennis, Volleyball
- Badminton, Cross-country skiing (classic technique), Field hockey*, Orienteering, Race walking, Racquetball, Running (distance), Soccer*, Tennis
Results

<table>
<thead>
<tr>
<th>Level</th>
<th># of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; College</td>
<td>8</td>
</tr>
<tr>
<td>High School</td>
<td>32</td>
</tr>
<tr>
<td>&lt; 14 Year Old Travel, City, Little League</td>
<td>90</td>
</tr>
</tbody>
</table>

49/130 (38%) were involved in multiple sports
Sports Participation and LQTS

1 LQTS Athlete with 2 Events in 650+ Athlete-Years

11-year-old boy with LQT1, QTc 560 ms, and prior out-of-hospital cardiac arrest who has received 2 VF-terminating ICD shocks while warming up to play soccer and baseball.

Johnson and Ackerman. JAMA 308:764-765, 2012
EXERCISE IN GENETIC CARDIOVASCULAR DISEASE
Aka - LIVE-LQTS

Aim 1: Incidence of Arrhythmic Events over 3 Years
Comparison moderate or vigorous exercisers vs sedentary

Aim 2: Quality of Life
Comparison moderate or vigorous exercisers vs sedentary

Age 8-50 years, with OR without ICD
- Any level exercise; Pts are equipped with a FitBit -
Can enroll directly through coordinating center; All questionnaires, interviews over phone and internet
→ No geographic constraints to participation

For more information: 866-207-9813
live.hcm@yale.edu or live.lqts@yale.edu

NIH R01 HL125918-01, PIs Lampert, Ackerman, Day
## Class I Recommendations

The following lifestyle changes are recommended in all patients with a diagnosis of LQTS:
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**ICD implantation** is recommended for patients with a diagnosis of LQTS who are survivors of a cardiac arrest.

**All LQTS patients** who wish to engage in competitive sports should be referred to a clinical expert for evaluation of risk.
Take Home Points

1. Tailoring of therapy is not only possible but is essential as most do not need and should not receive an ICD.

2. Beta Blockers (BBs) for most but all BBs may not be created equal. Caution w/ atenolol and metoprolol. At minimum, avoid once a day dosing of A & M.

3. Stay tuned regarding GS-6615 and LQT3

4. Remember denervation therapy for those malignant cases. Don’t just let the ICD keep firing!

5. Athletes with LQTS – Don’t just kick them out, refer them to an expert!
“The challenge is NOT preventing their sudden death.”

“The challenge is helping them to LIVE and THRIVE despite their diagnosis!”
WINDLAND SMITH RICE

Sudden Death Genomics Laboratory

In memory of

Windland Smith Rice

1970-2005

Beloved daughter, sister, wife and mother

August 2006

“To heal the sick and advance the science”

Dr. Charles W. Mayo
If you feel you have benefitted from this presentation, please make a donation now.

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