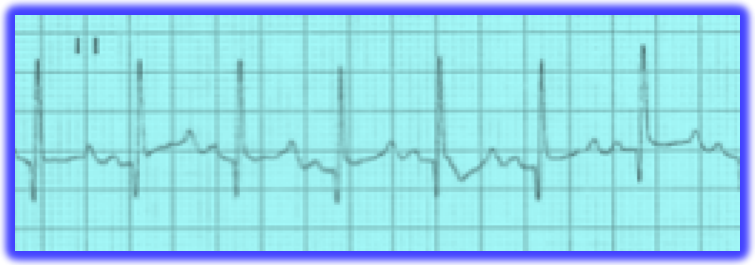
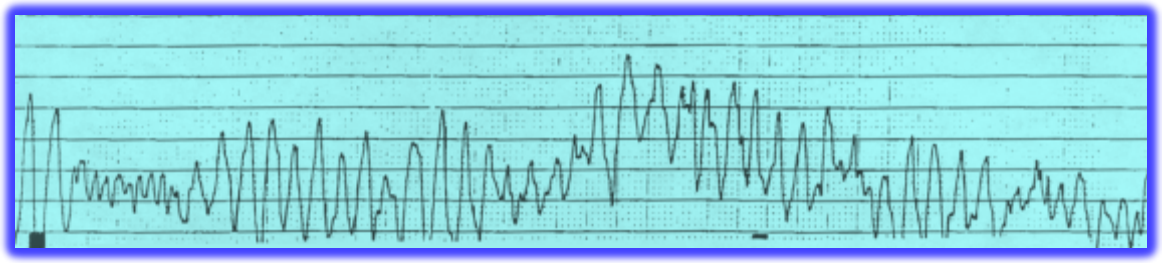
# Management of Arrhythmia Syndromes in the Newborn and Very Young Child:
# Unique Risks & Barriers in this Age Population






## Mitchell Cohen, MD FACC FHRS

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SADS FOUNDATION
SUDDEN ARRHYTHMIA DEATH SYNDROMES


9th Annual International SADS Foundation Conference
Putting it Together: From the Genome to the Phenotype

# Disclosures: None

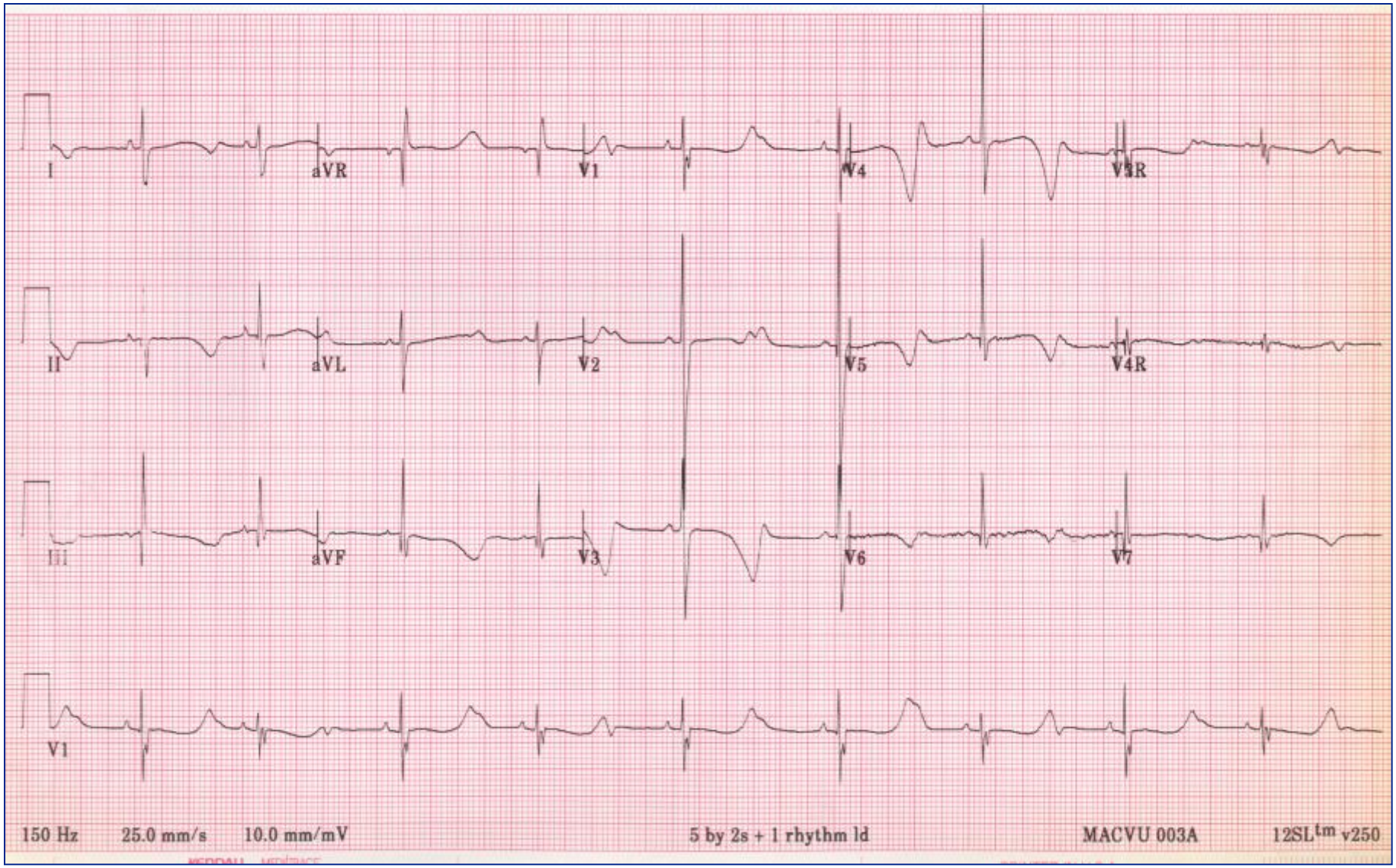
# Channelopathies in the Young

- Long QT Syndrome
- Catecholamine Polymorphic VT
- Brugada Syndrome
- Short QT

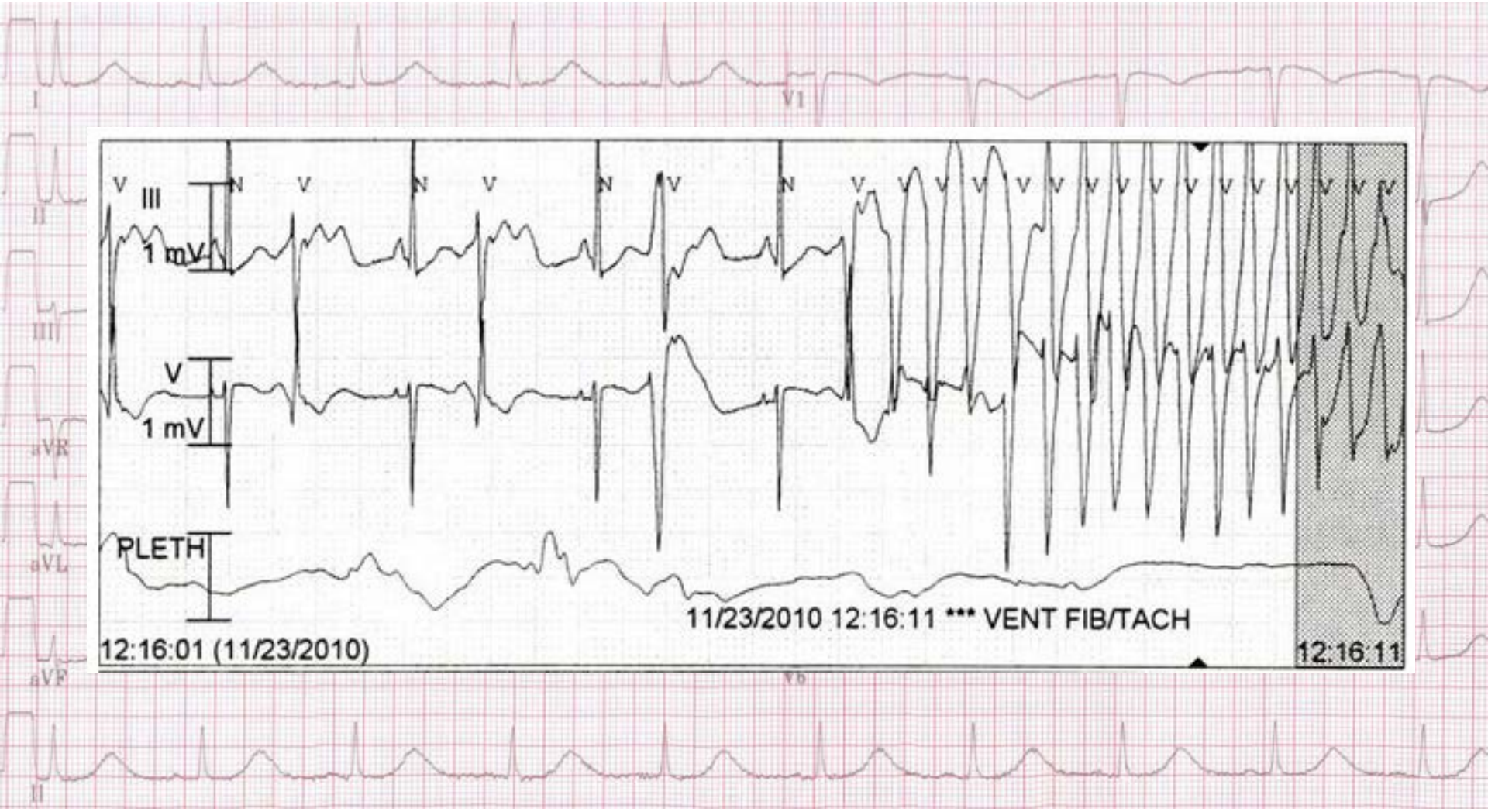
# Arrhythmia Syndromes in the VERY Young

- Challenges in diagnosing channelopathy conditions in newborns
- Management of neonatal channelopathies is a serious problem
- Generates major anxiety to families and physicians
- Treatment ranges from conservative management to more aggressive and invasive approaches

# LONG QT SYNDROME



# Diagnosing LQT is easy, when..



# Challenges in Diagnosing LQTS

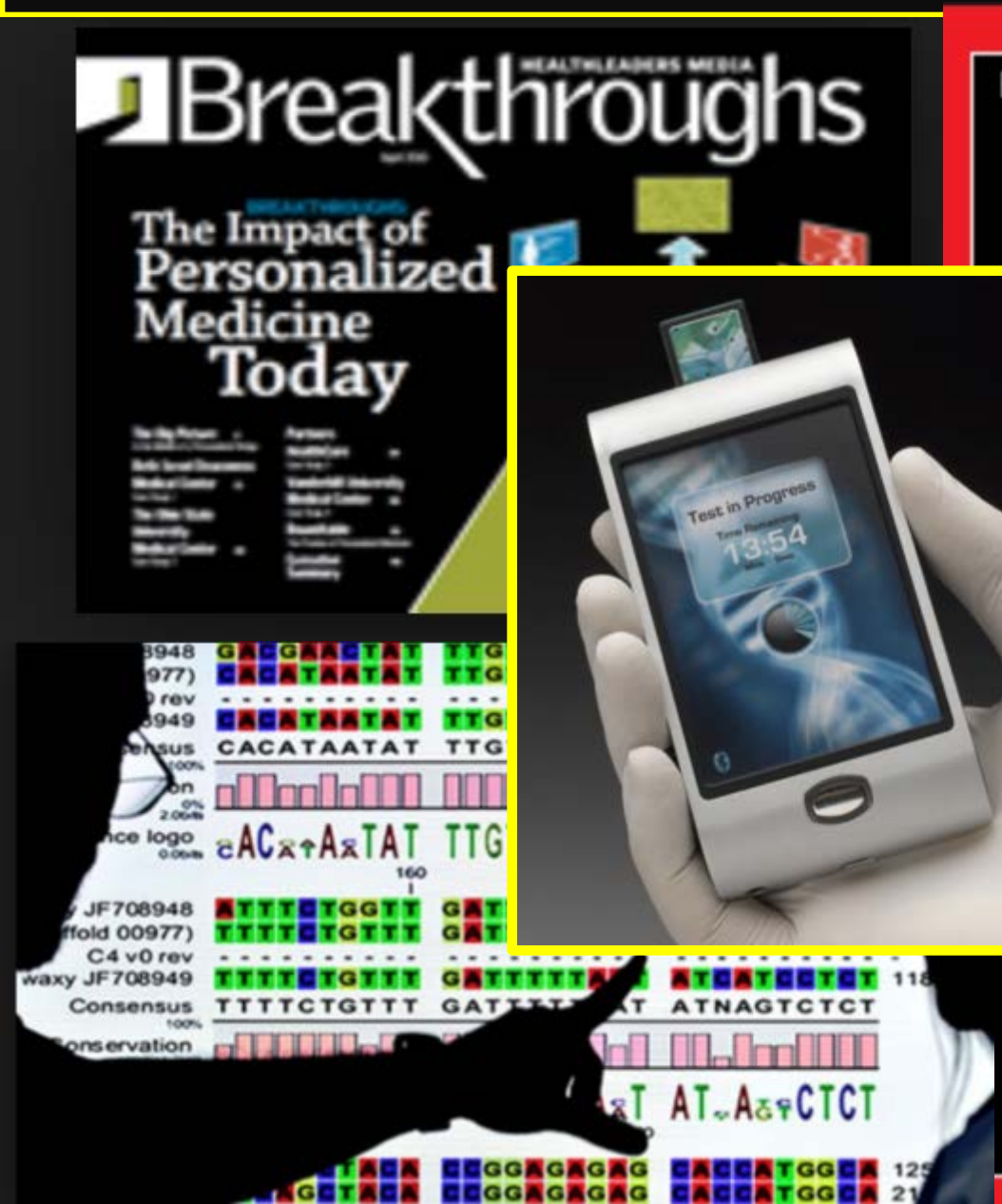
- **Electrocardiogram Variability**
  - 30% of patients with gene-positive LQT mutations have a QTc that overlaps-normal healthy children.
  - 10-15% of healthy individuals have a QTc above a value of 440 msec
  - **Difficult to make EKG diagnosis before DOL #4**

A QTc >500 msec diagnosis is easy, the challenges often occur in the QTc 460-480 msec > moving beyond the EKG

# Challenges in Diagnosing LQTS

- **Disease Variability**
  - Approximately 30% of patients with LQT mutations will never have a symptom.
  - Clinical signs, symptoms, and ECG characteristics do not adequately differentiate subtypes of LQTS.
  - Differentiating LQTS subtype may help risk prediction & aid in treatment options.

# genotype patients ≈ 75%




# LQT Outcomes in the 1st Year of Life

Journal of the American College of Cardiology
© 2009 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 54, No. 9, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.05.029

QUARTERLY FOCUS ISSUE: HEART RHYTHM DISORDERS

## Clinical Implications for Patients With Long QT Syndrome Who Experience a Cardiac Event During Infancy

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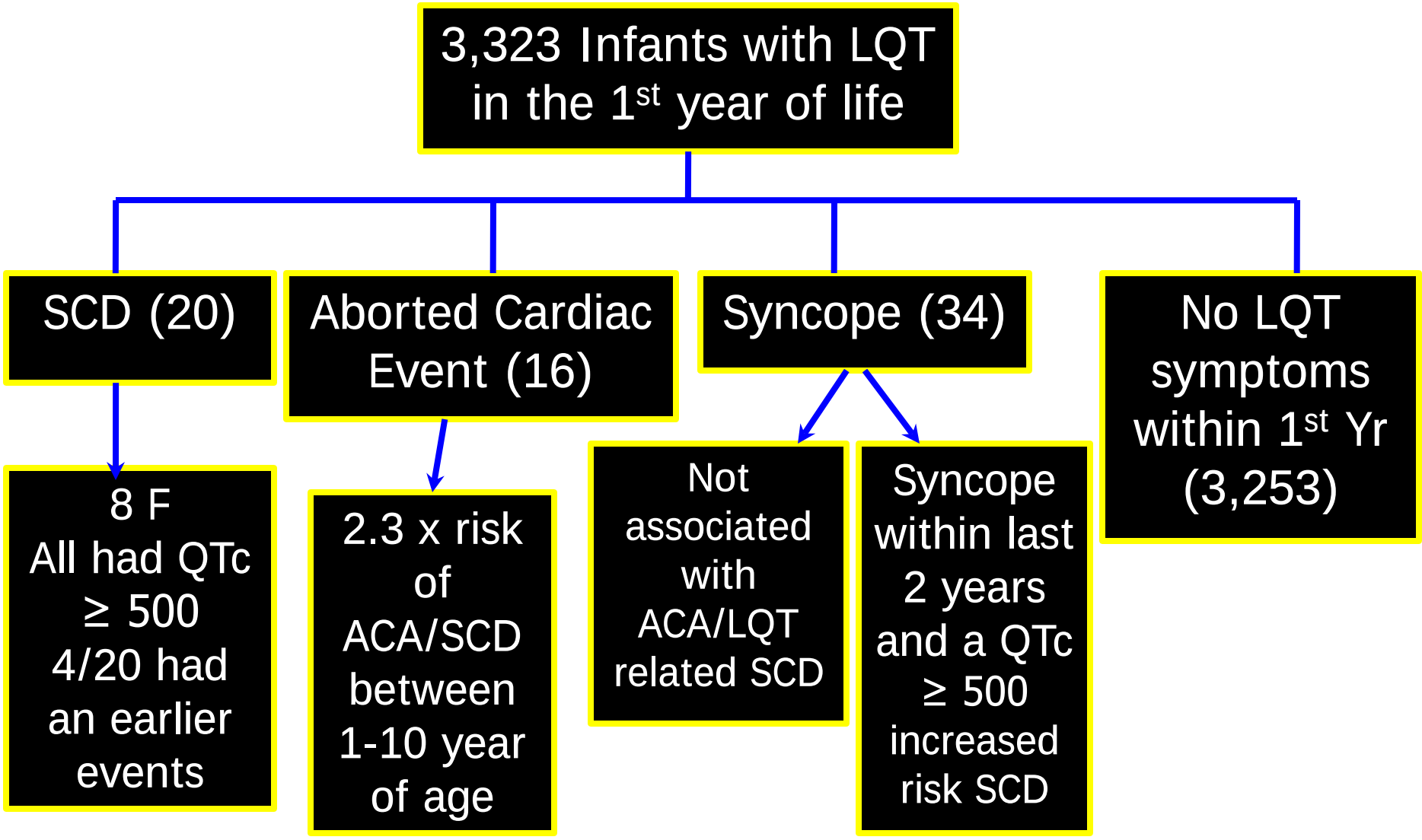
*Pavia and Milan, Italy; Rochester, New York; Rochester, Minnesota; Jerusalem, Israel; Cleveland and Cincinnati, Ohio; and Salt Lake City, Utah*

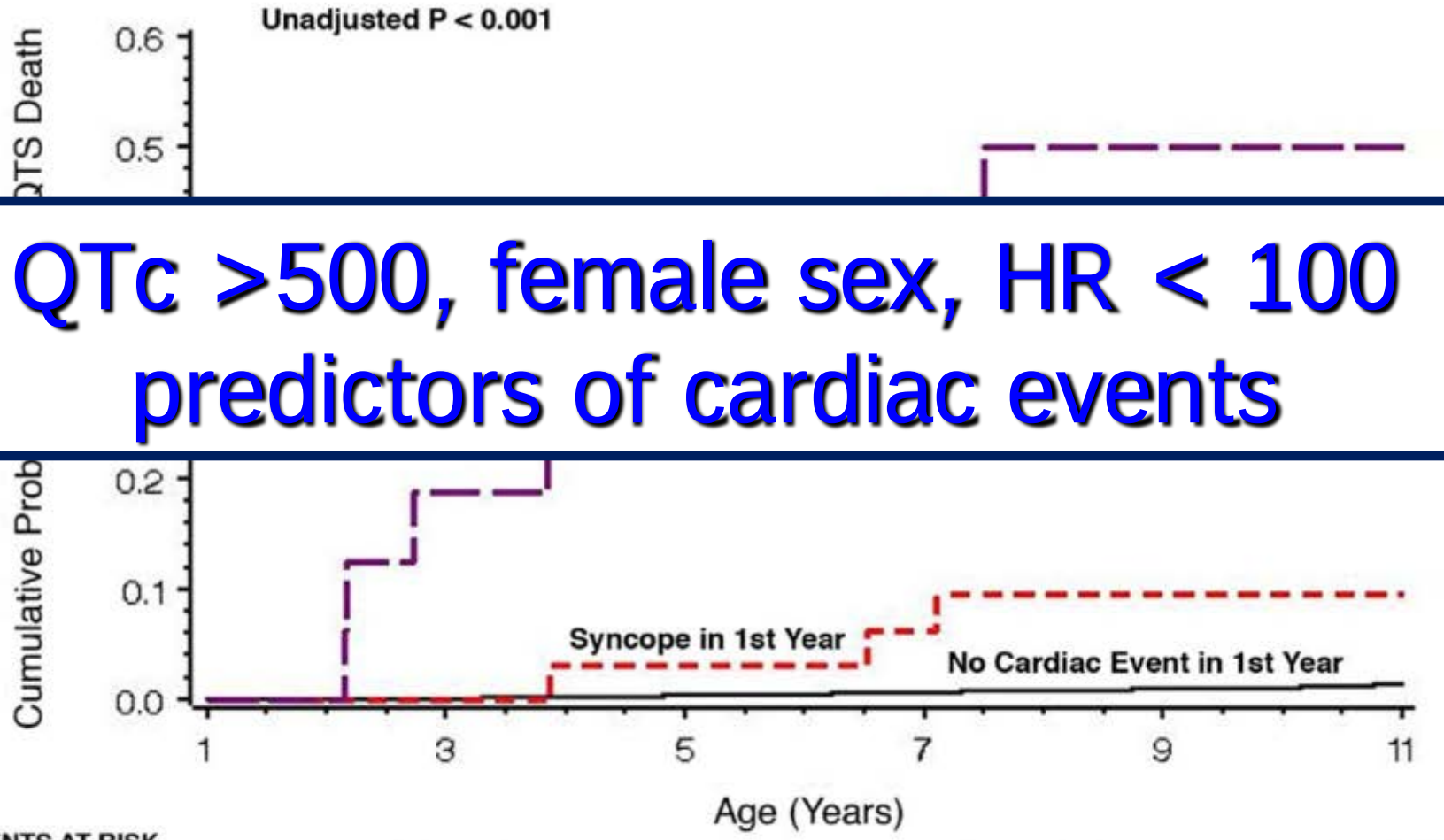



Beta-blockers risk reduction of >65% in this sub-cohort

Beta-blockers should be first line of therapy

Beta blockers are not ALWAYS effective in the young

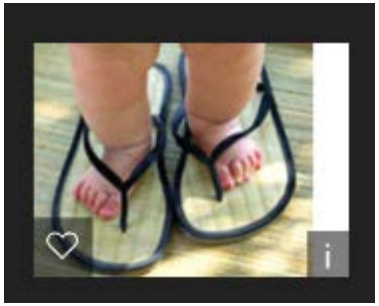
# Cumulative Probability of ACA/LQT Related Death




**QTc >500, female sex, HR < 100 predictors of cardiac events**

| PATIENTS AT RISK | | | | | | |
|---|---|---|---|---|---|---|
| No CE in 1st Year | 3253 | 3240 (0) | 3198 (0) | 3141 (0.01) | 3077 (0.01) | 3014 (0.01) |
| Syncope in 1st Year | 34 | 33 (0) | 31 (0.03) | 29 (0.06) | 25 (0.09) | 22 (0.09) |
| ACA in 1st Year | 16 | 13 (0.19) | 11 (0.31) | 9 (0.44) | 8 (0.50) | 7 (0.50) |

# Infants are Unique



- Children are not small adults
- Infants are not small children

- Symptomatic infants with LQT are HIGH RISK
- Tend to be sicker and can't vocalize symptoms
- Beta-blockers are not uniformly 100% protective
- ICDs are a challenge to implant
- LCSD may be reasonable, but the infant is in a state of rapidly evolving autonomic development
  - (sleep cycle, sleep position, barorecpetors)

# Scenario #1: My Pragmatic Approach to Diagnosing and Managing LQT in the Young Child

A parent has a **known LQT diagnosis** *(genotype known)*

↓

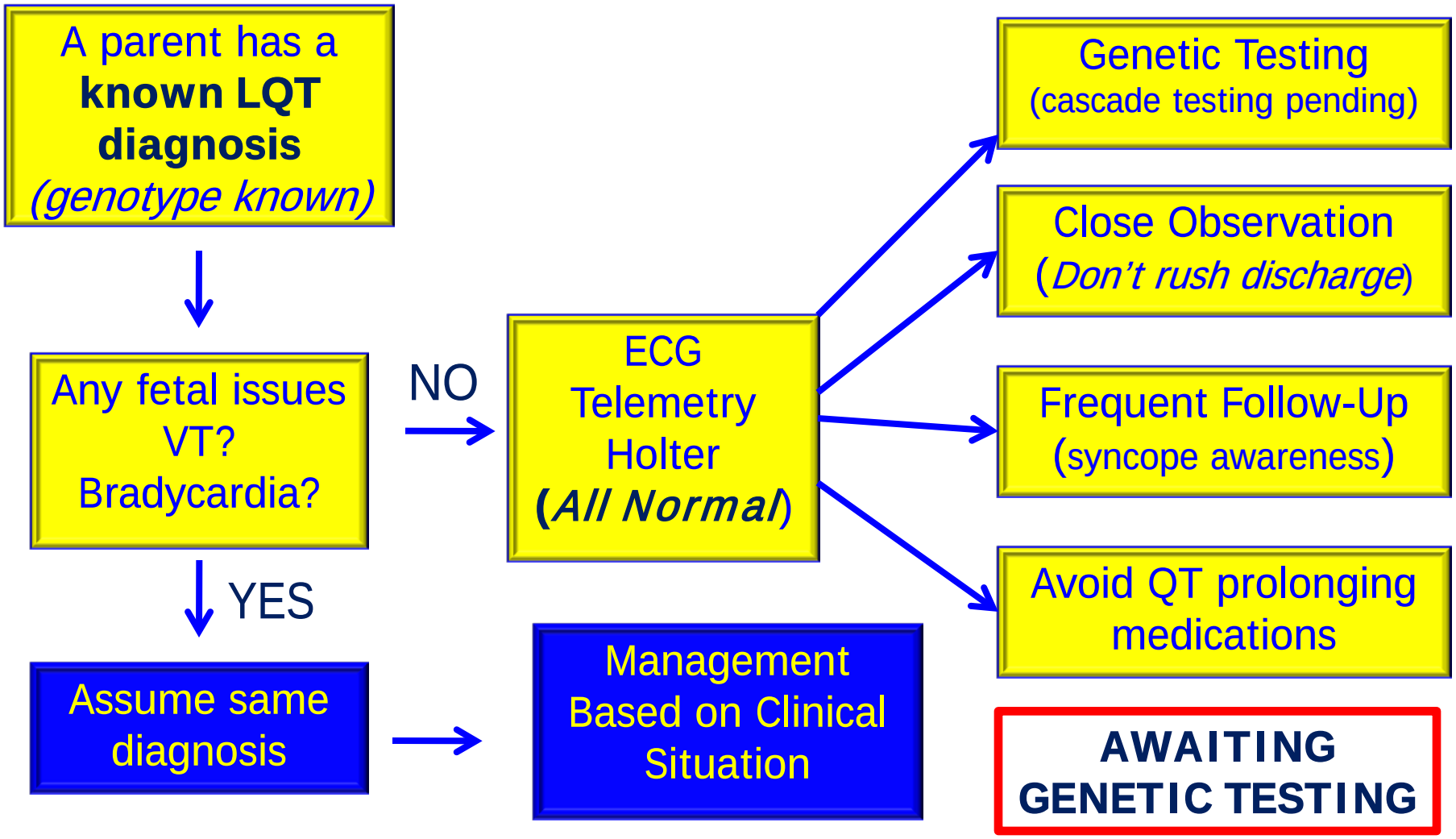
Any fetal issues
VT?
Bradycardia?

↓ **YES**

Assume same diagnosis → Management Based on Clinical Situation

**AWAITING GENETIC TESTING CONFIRMATION**

# Scenario #1: My Pragmatic Approach to Diagnosing and Managing LQT in the Young Child



# The Nursery "stable management" – Anticipatory Questions & Guidance

- What is the QT interval?
- What is the heart rate?
- Is the patient having any significant bradycardia?
- Is the patient having any ventricular arrhythmias?
- How long to watch in the nursery/NICU?
- What is the disposition (how far do they live)?
- What medications to start?
- CPR training for the parents?
- Who will be giving the meds?
- Dose adjustment for weight gain?
- How is the baby feeding (breast?)
- Medications to avoid
- What to tell the pediatrician

# Scenario #1: My Pragmatic Approach to Diagnosing and Managing LQT in the Young Child

A parent has a **known LQT diagnosis** *(genotype known)*

↓

Any fetal issues
VT?
Bradycardia?

NO →

ECG
Telemetry
Holter
**Abnormal Findings**

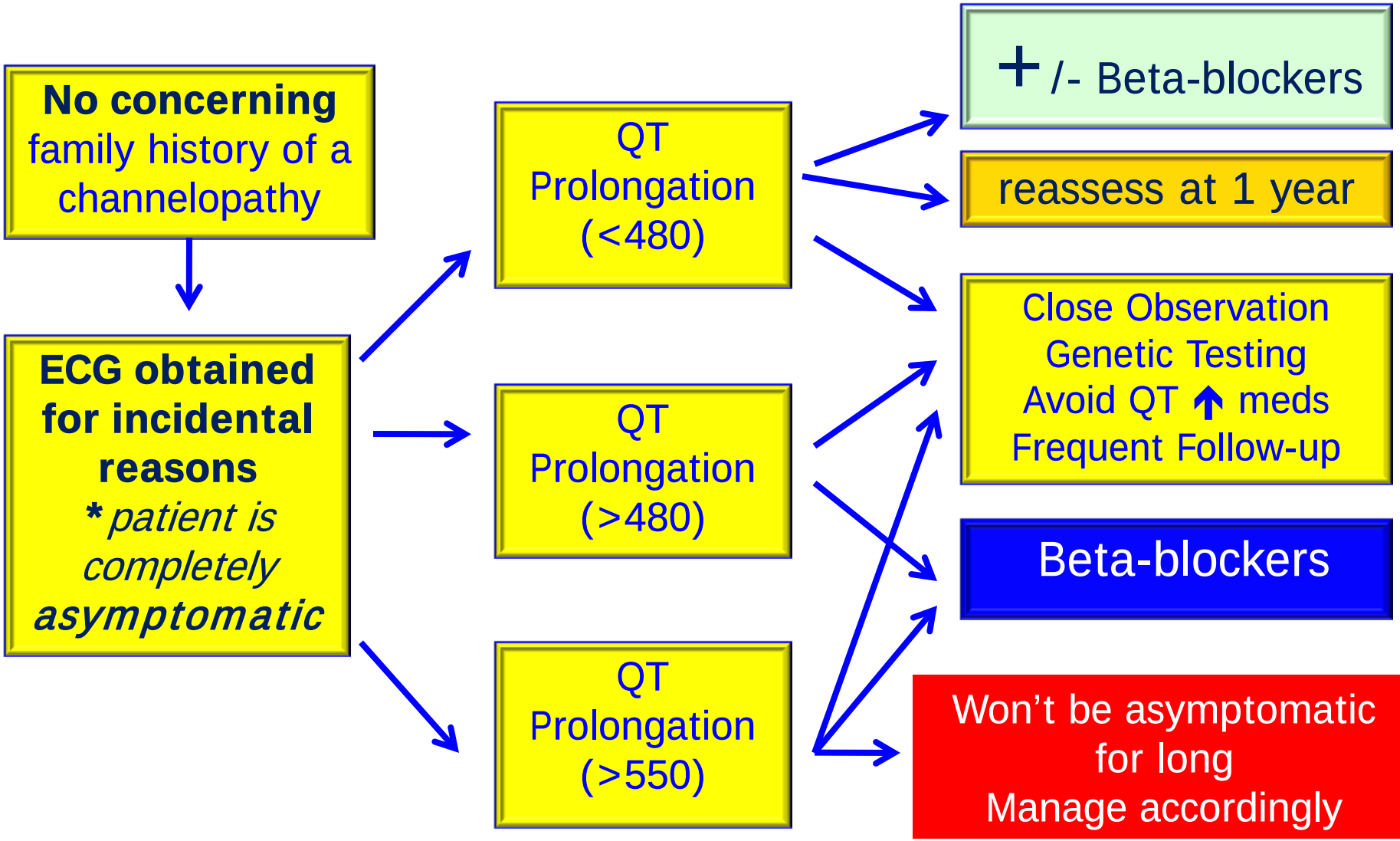
↓

Management Based on Clinical Situation

- Beta-blockers
- Pacemaker
- ICD
- LCSD
- Lido/Mexilitine
- Magnesium
- Observation

**AWAITING GENETIC TESTING**

# Scenario #2: My Pragmatic Approach to Diagnosing and Managing LQT in the Young Child



# Scenario #3: My Pragmatic Approach to Diagnosing and Managing LQT in the Young Child

**No concerning** family history of a channelopathy → **Normal fetal course** → ECG obtained because someone noticed:
*Bradycardia*
*AV block*
*Non-sustained VT*

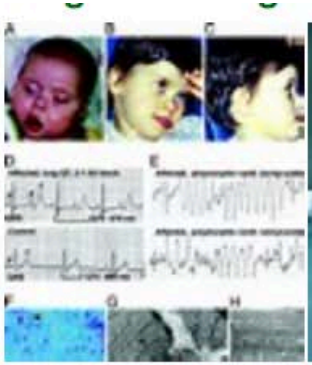
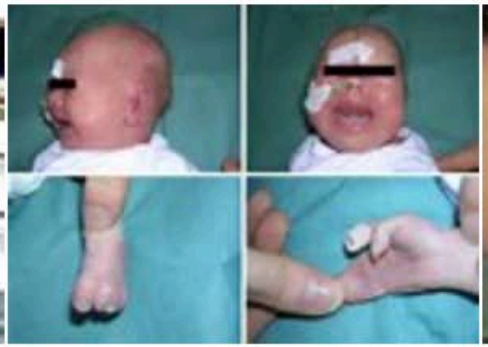
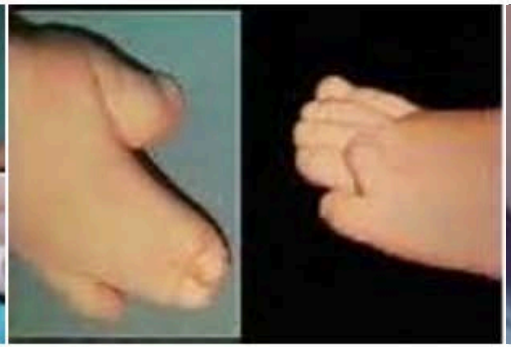
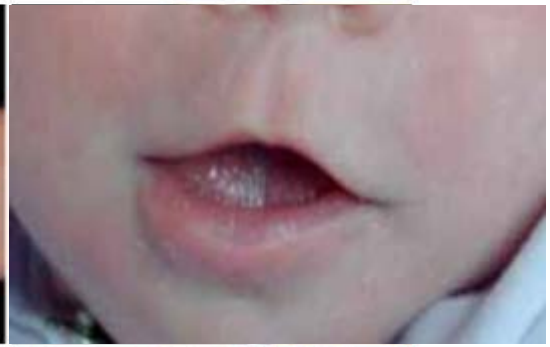
QT prolonged  Bizarre T waves  Non-sustained VT (TdP)

- Beta-blockers
- Pacemaker
- ICD
- Left cardiac sympathetic denervation
- Lido/Mexilitine
- Magnesium

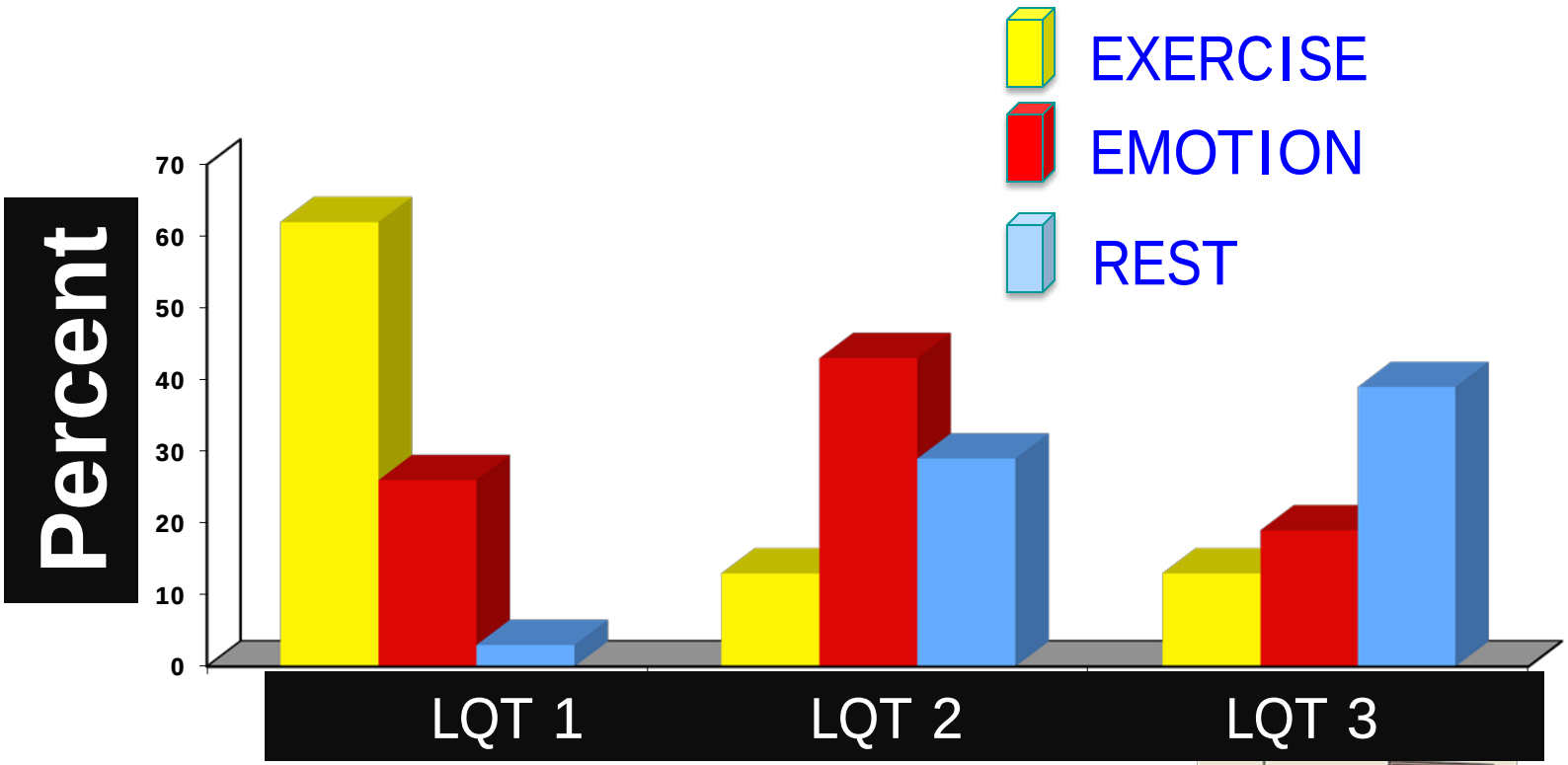
# Don't Forget to Do a Physical Exam

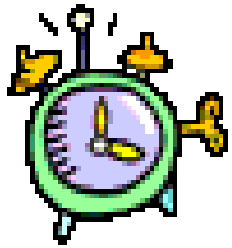
## Timothy Syndrome

- Spontaneous mutation in CACNA1C.
- QT prolongation
- Fingers and toes syndactyly
- Thin upper lip
- Autism, developmental delay

# Occurrence of Gene-Specific Triggers



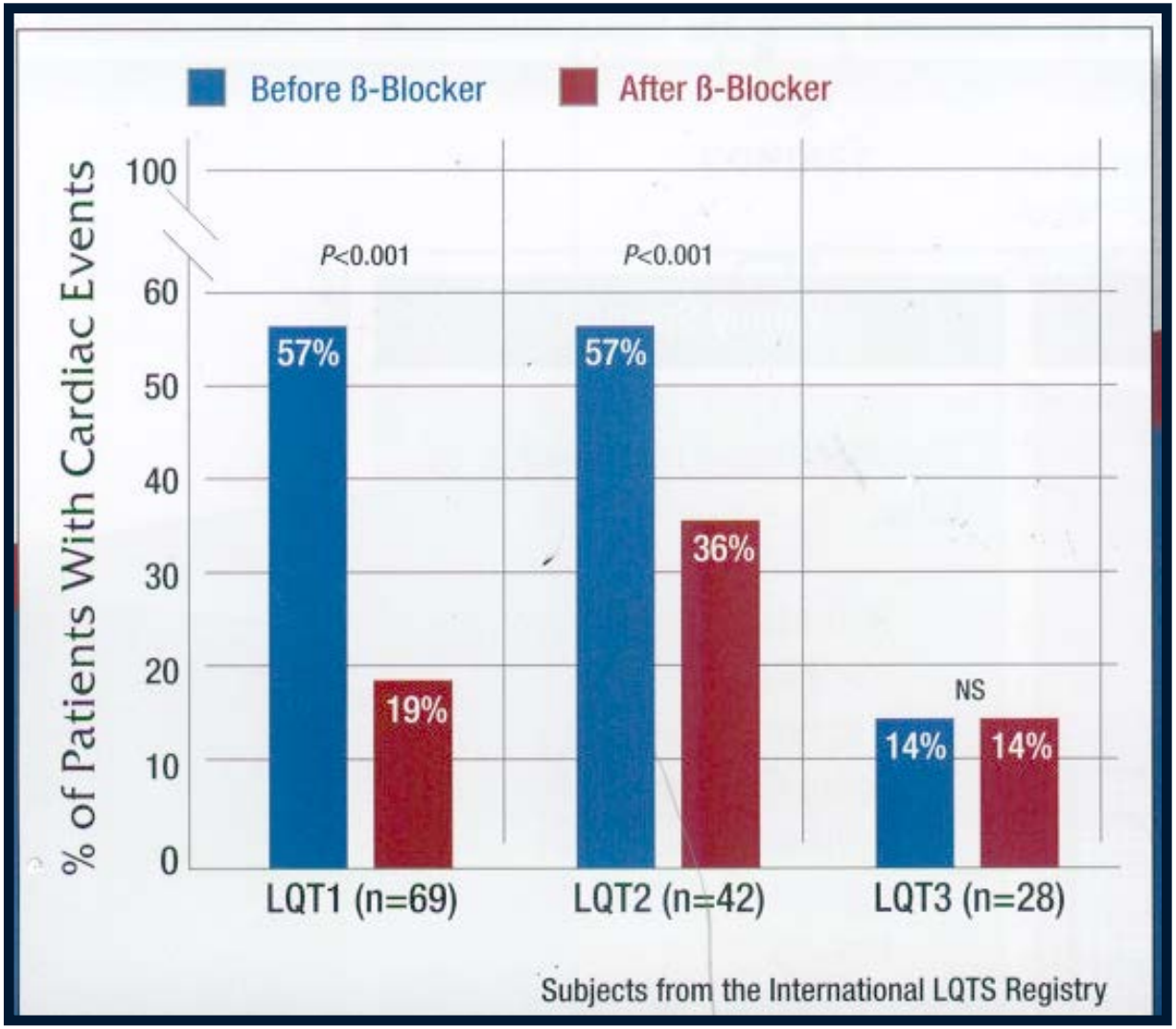
Circ 2001;103:89-95

Emotion

No Sleep

Stress

# Approach to the Asymptomatic Young Patient with LQT



# Not All Beta-Blockers Are Equal

## Efficacy of Different Beta-Blockers in the Treatment of Long QT Syndrome

Abeer Abu-Zeitone, BS PHARM, MS, PHD,* Derick R. Peterson, PHD,† Bronislava Polonsky, MS,* Scott McNitt, MS,* Arthur J. Moss, MD*

**ABSTRACT**

**BACKGROUND** In LQTS, β-blocker therapy is effective in reducing the risk of cardiac events (syncope, aborted cardiac arrest, sudden cardiac death). Limited studies have compared the efficacy of different β-blockers.

**OBJECTIVES** The goal of this study was to compare the efficacy of different β-blockers in long QT syndrome (LQTS) and in genotype-positive patients with LQT1 and LQT2.

**METHODS** The study included 1,530 patients from the Rochester, New York–based LQTS Registry who were prescribed

Atenolol, Nadolol, Metoprolol, Propanolol

LQT2: Nadolol only BB significant risk-reduction in 1st cardiac event

LQT1: no difference in 1st-cardiac event amongst 4 BB

Propanolol the least effective against recurrent cardiac events

**CONCLUSIONS** Although the 4 β-blockers are equally effective in reducing the risk of a first cardiac event in LQTS, their efficacy differed by genotype; nadolol was the only β-blocker associated with a significant risk reduction in patients with LQT2. Patients experiencing cardiac events during β-blocker therapy are at high risk for subsequent cardiac events, and propranolol is the least effective drug in this high-risk group. (J Am Coll Cardiol 2014;64:1352–8) © 2014 by the American College of Cardiology Foundation.

# Not All Beta-Blockers Are Equal

Published by Elsevier Inc.

http://dx.doi.org/10.1016/j.jacc.2012.07.046



## Not All Beta-Blockers Are Equal in the Management of Long QT Syndrome Types 1 and 2

Higher Recurrence of Events Under Metoprolol

[author block]

## Nadolol, Metoprolol, Propanolol

Evaluated only LQT 1 & 2 Patients

Excluded anyone on BB < 1 year of age

Propanolol had the greatest effect on QTc shortening

Propanolol & Nadolol equally effective

Metroprolol should NOT be used for symptomatic LQT 1 or LQT 2

# Management: Drug Avoidance in Long QT

- **AVOID**: Certain drugs may provoke life-threatening arrhythmias in patients with LQT **(www.QTdrugs.org)**
  - **Anti-arrhythmics**
    - procainamide, amiodarone, sotalol
  - **Anti-histamine**
    - astemizole, terfenedine
  - **Anti-fungal & anti-microbial**
    - ketoconazole
    - trimetheprim/sulfa
  - **Psychotropic medications**
    - haloperidol, tricyclics
- Avoid nonessential OTC medications in LQT

# Long QT3 (gain function Na channel)

- Most of what we have talked about regarding BB has related to LQT 1 & 2.
- **Long QT is NOT one disease entity**
- Genotype & phenotype differences (age/sex)
- Tends to cause more bradycardia, BB OK?

- Multicenter Study:406 LQT3 pts (Wilde A Circ 2016)
- Followed LQT3 patients after 1 year
- 12 patients symptomatic in 1st year-of-life
  - 7 syncope
  - 6 had ACA (4 died)

Symptomatic LQT3 in year 1 very concerning

# Approach to the Symptomatic Young Patient with LQT

Are we dealing with bradycardia?

Sinus bradycardia?

2:1 AV block?

Are we dealing with VT?

Pause-dependent?

How bad is the QT?

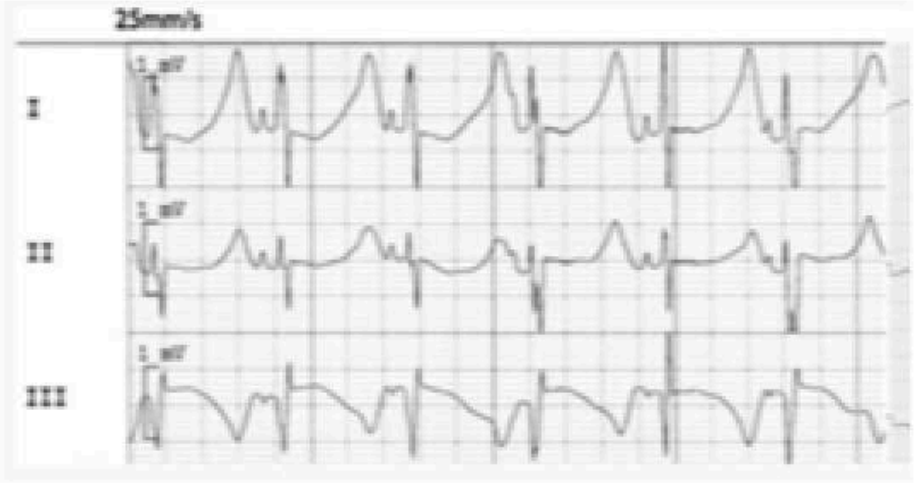
>500 msec?

>600 msec?

# Challenging Case #1

- Term newborn at 48 hours noted to have bradycardia (85 bpm) and some respiratory distress. Also noted by the OB to have some bradycardia at 30 weeks gestation.

- No family history of syncope or SCD

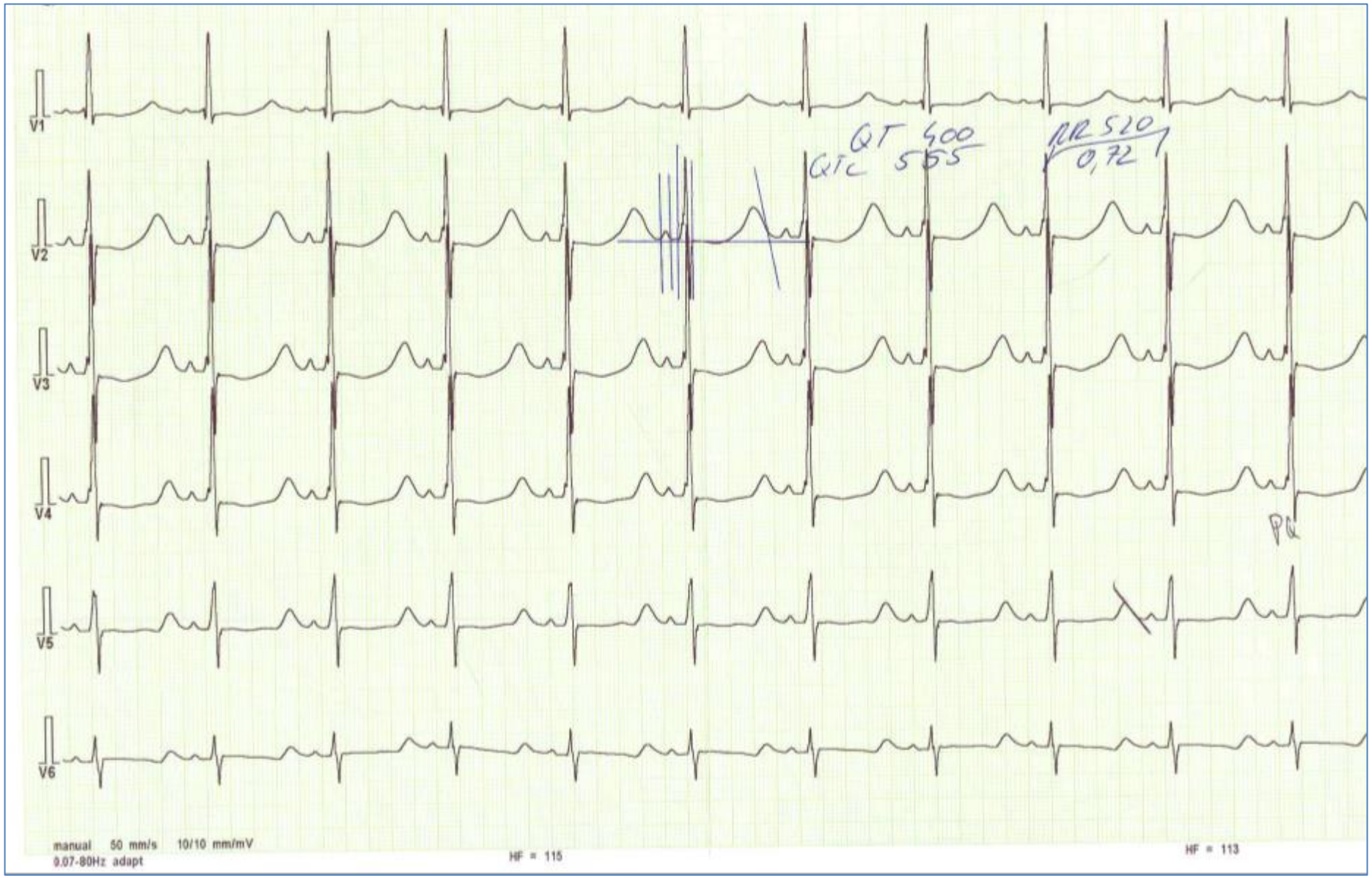



*Courtesy Roman Gebauer*

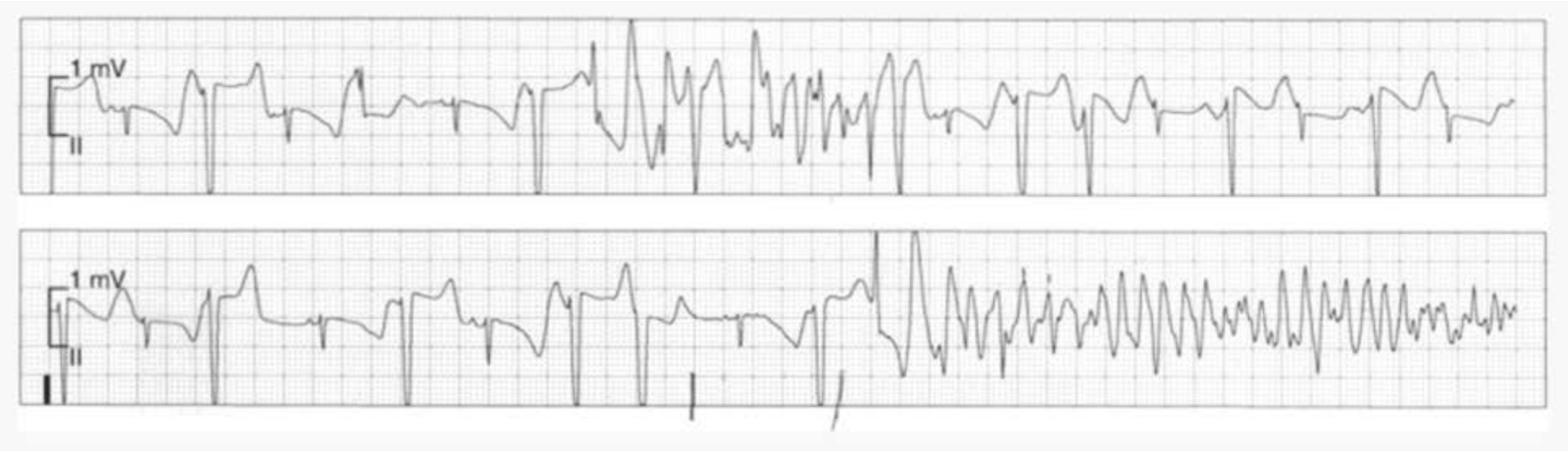
Normal ECHO

QTc 730 msec

Occasional single PVCs


V1
V2
V3
V4
V5
V6
QT 400
QTc 565
RR 520
0,72
manual 50 mm/s 10/10 mm/mV
0.07-80Hz adapt
HF = 115
HF = 113

# 30 minute after arrival in ICU




Defibrillation
Intubation
Chest compressions (brief)

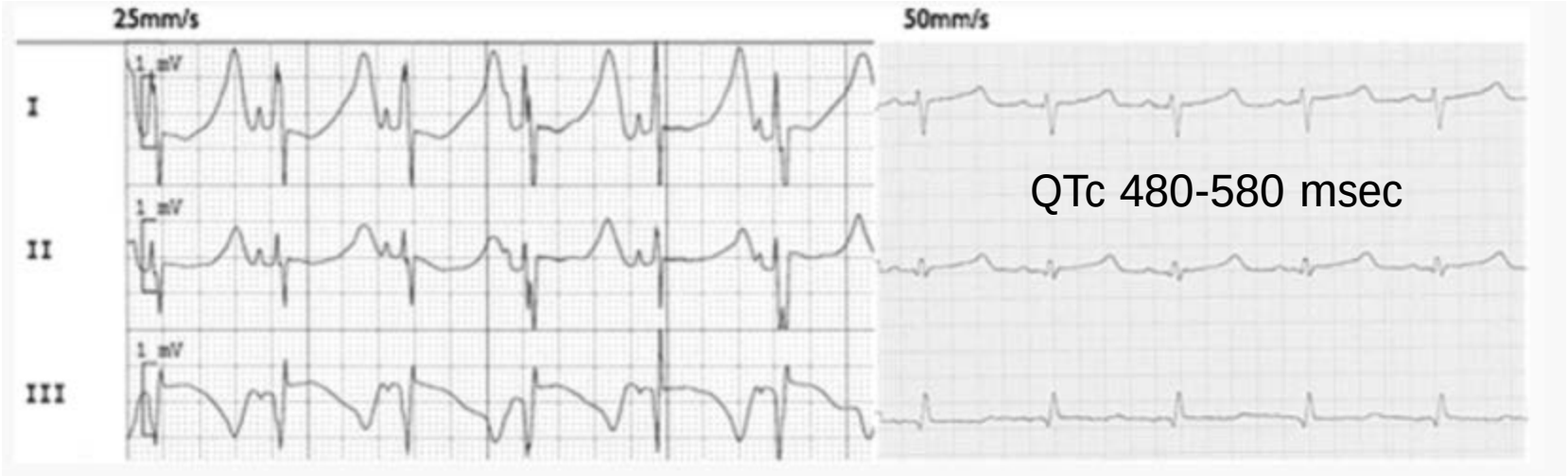
# Options

- Beta-blockers
- Mexilitine
- Beta-blockers and Mexilitine
- Beta-blockers and pacemaker
- Pacemaker only
- Left sympathetic denervation
- ICD
- Combination of the above
- All of the above

# Clinical Course

- IV beta-blockers (Esmolol 100ug/kg/min)
- No further episodes of TdP
- IV lidocaine given (? shortening of QT)
- Suspicious this was LQT 3
- Mexiltine added to propanolol

# Follow-Up EKG – SCN5A 9c.5314C>G




Stayed in hospital for 1 month
No further episodes
Doing well

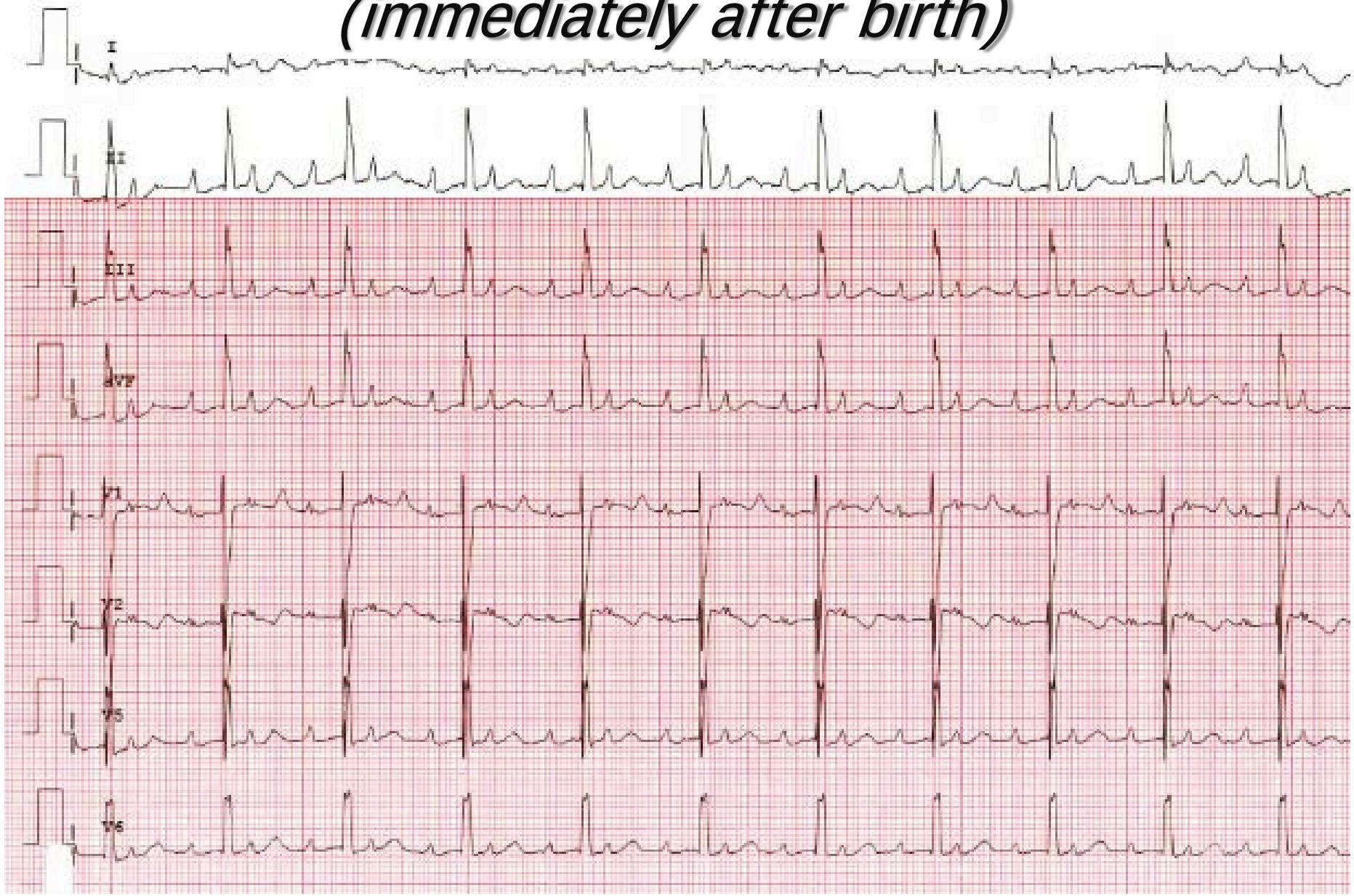
# Challenging Case #2

- Called from a remote clinic with a 37 week 2.7 kg baby born via emergent c/s secondary to bradycardia.

- Bradycardia lasted for about 90 min and now the HR has returned to 130 bpm (regular) and the neonate appears well with a normal cardiovascular examination.

- Baby is transferred to the NICU at the children's hospital –clinically remains well- no further bradycardia over a period of 3 days

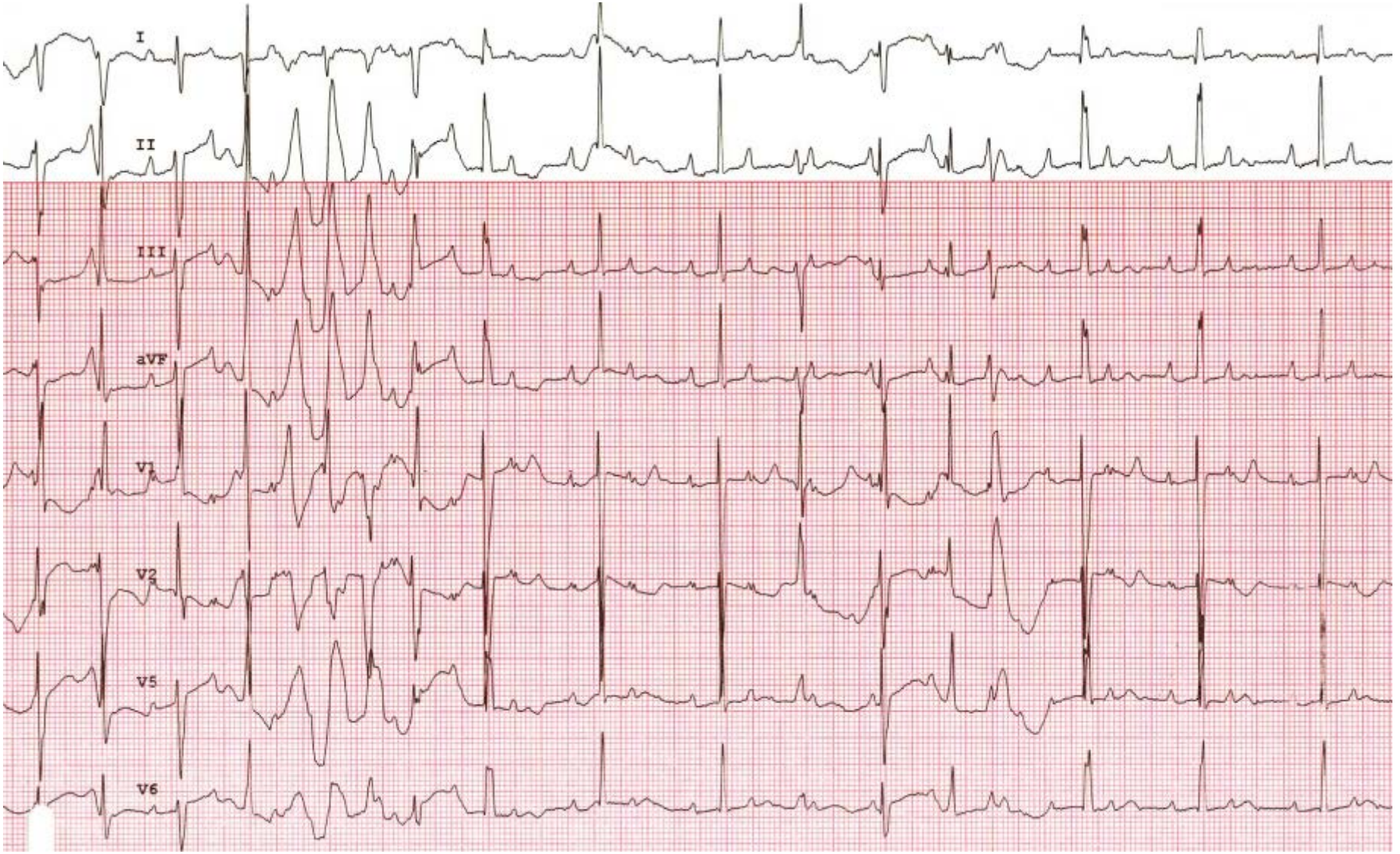
# Electrocardiogram
## (immediately after birth)

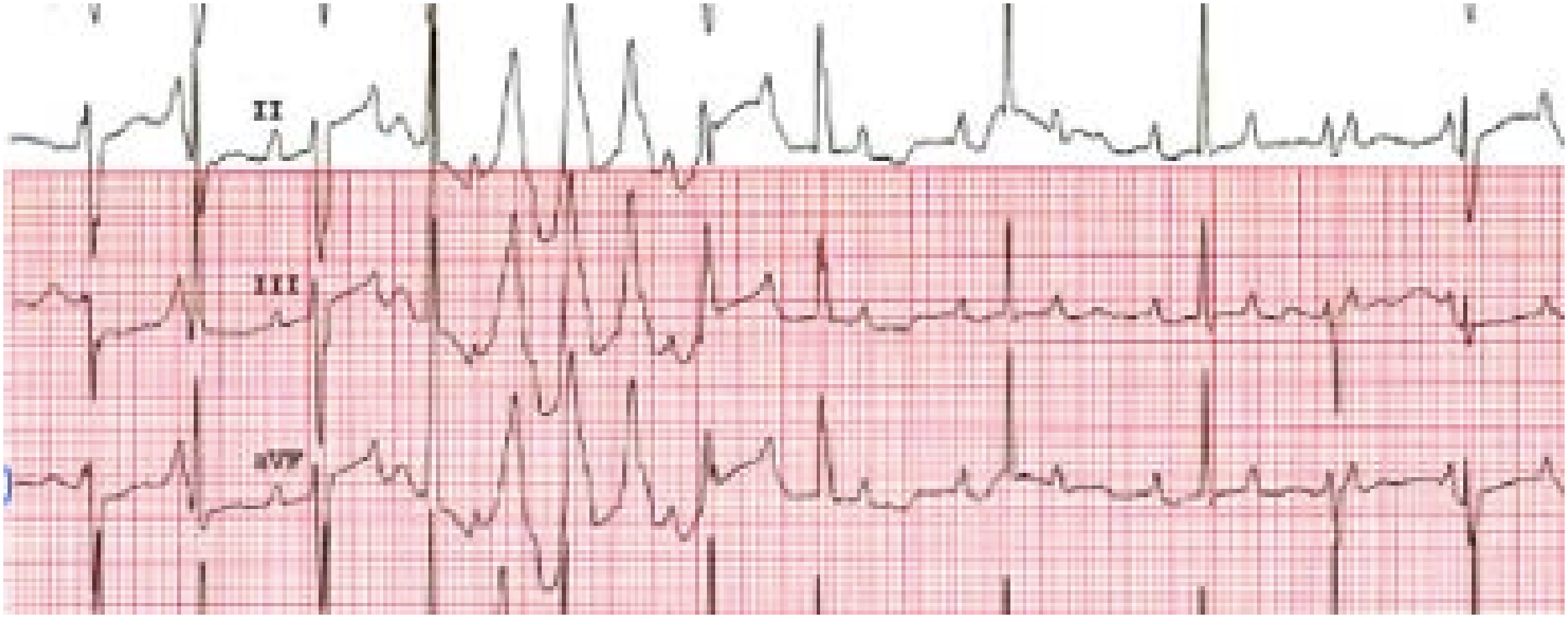


- **Family History: 2 older sisters both healthy, mom has a history of "vagal-like" events a number of years ago and a seizure when she was 16. No other family history of syncope, seizures, sudden cardiac death.**

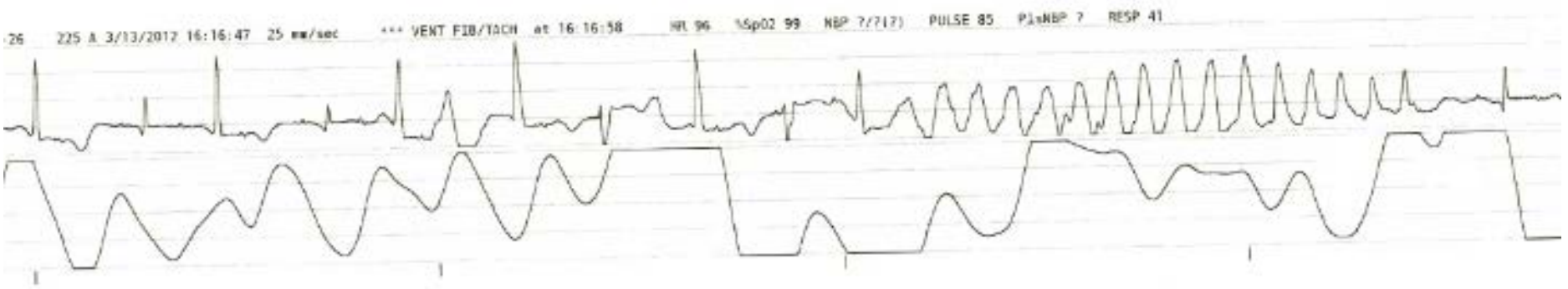
- Physical Examination: 2.7 kg, HR 138, BP 62/38
  - Normal examination
- Echocardiogram: structurally normal heart; excellent bi-ventricular function.
- Laboratory Studies:
  - Electrolytes Normal

# While getting a rhythm strip.....



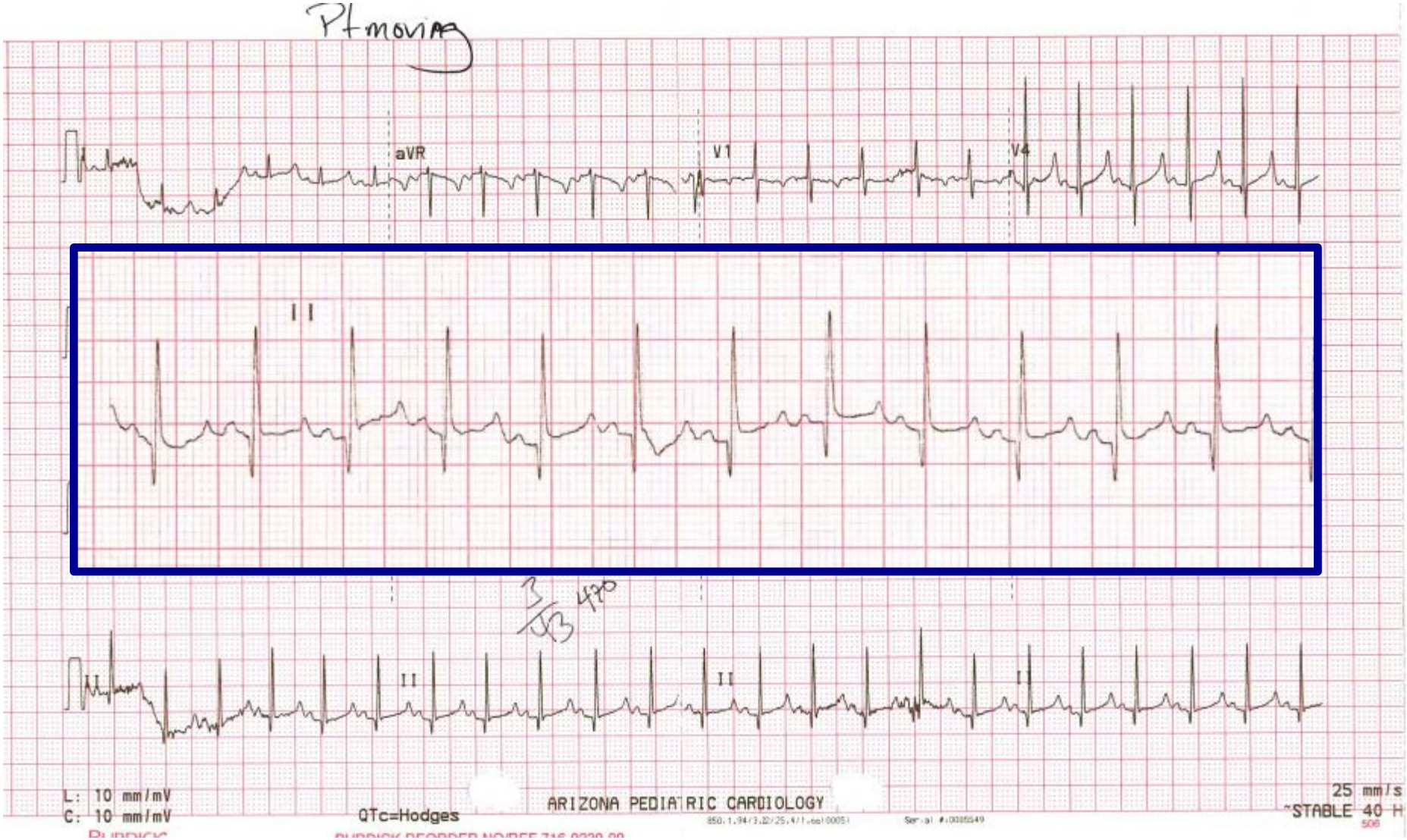

II
III
aVF

# D.O.L #4 while on telemetry.....




that was it –never happened again
Heart rate maybe a little slower,
but not necessarily true pause-dependent TdP
Started IV Esmolol

# Electrocardiogram (DOL #5)



# Options

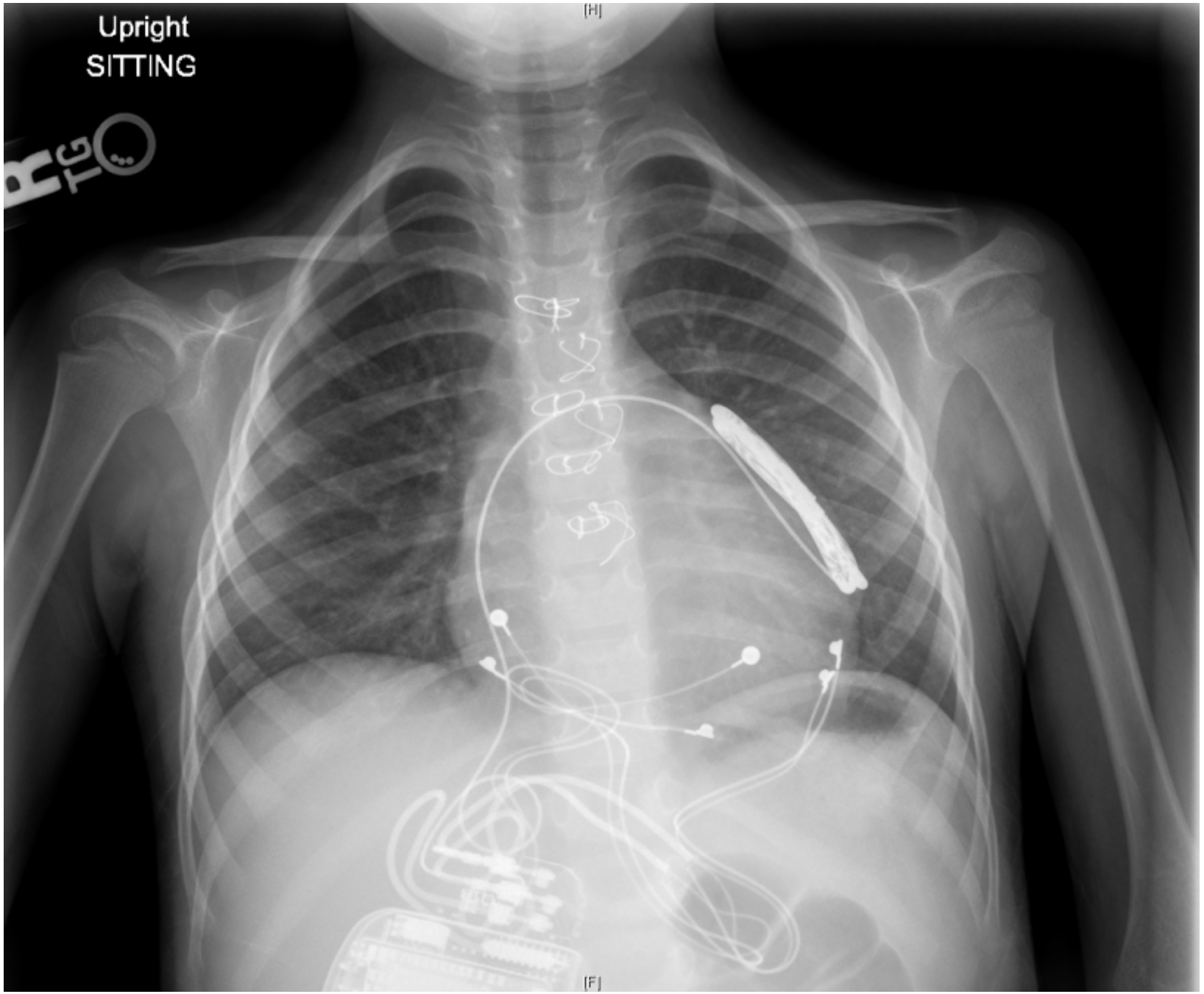
- ☐ Beta-blockers
- ☐ Beta-blockers and Mexilitine
- ☐ Beta-blockers and pacemaker
- ☐ Pacemaker only
- ☐ Left sympathetic denervation
- ☐ ICD
- ☐ Combination of the above
- ☐ All of the above
- ☐ Pray your week of service ends today

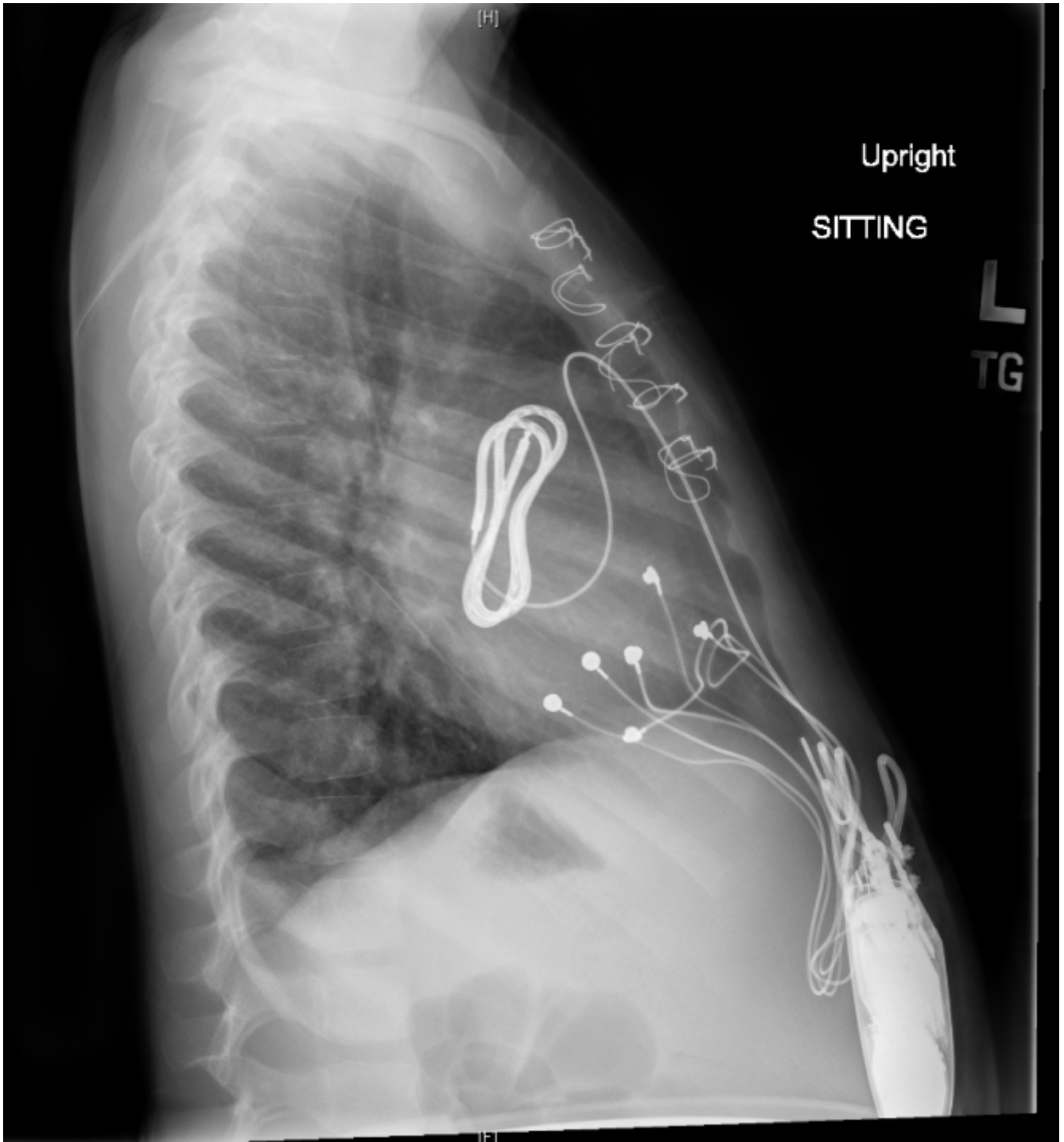
# Options

- ☐ Beta-blockers
- ☐ Beta-blockers and Mexilitine
- ☑ **Beta-blockers and pacemaker**
- ☐ Pacemaker only
- ☑ **Left sympathetic denervation**
- ☐ ICD
- ☐ Combination of the above
- ☐ All of the above
- ☐ Pray your week of service ends today

# Gene Test: KCNH2 (LQT 2)

- Continue on propanolol 4mg/kg/day
- Left AAI paced at 80-90 bpm
- At age 4 years (still asymptomatic) routine interrogation of her PM early ventricular couplets noted.
- Underwent PM removal, addition of an epicardial coil, ICD system
- Changed to nadolol
- No events in the last year


Upright
SITTING
[H]
[F]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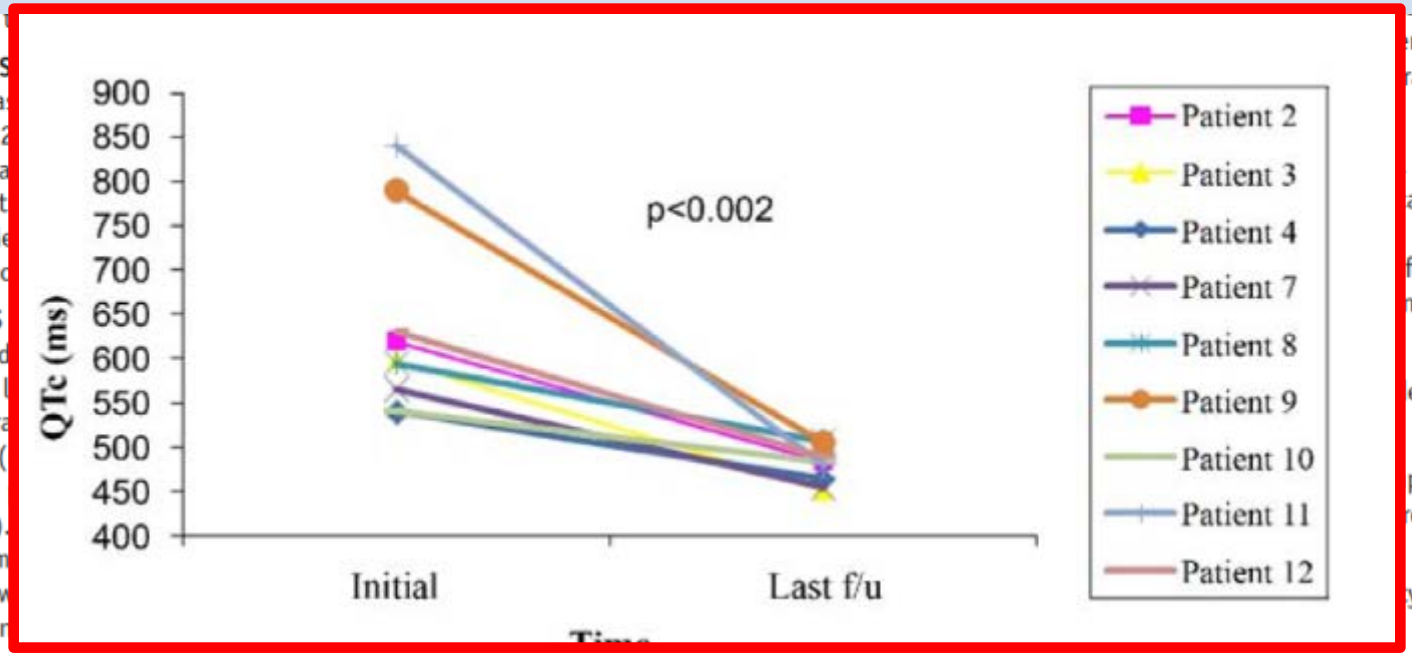
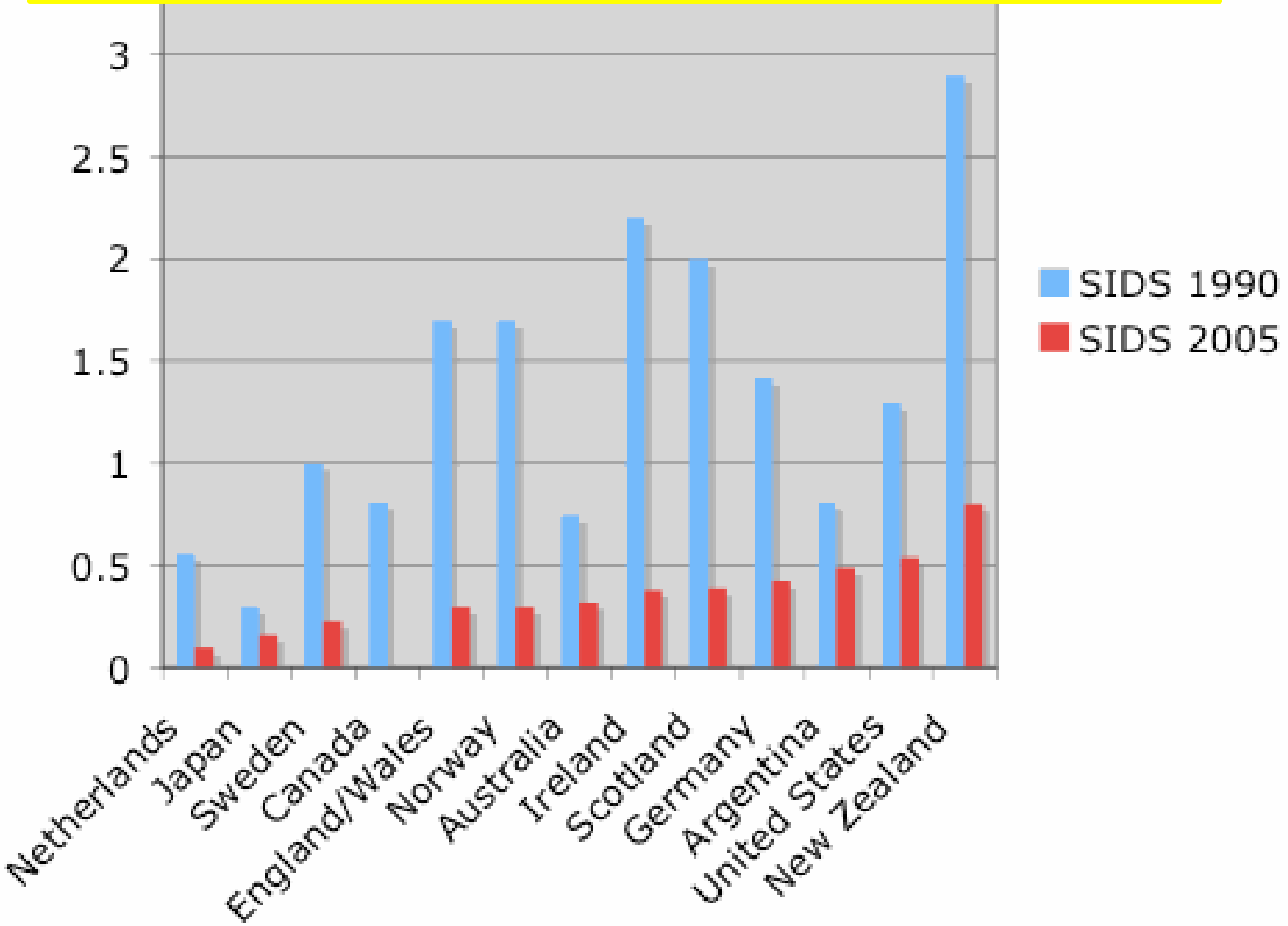
# Congenital long QT syndrome and 2:1 atrioventricular block: An optimistic outcome in the current era

- Long QT with 2:1 AV block is rare
- 4.5% of congenital LQT diagnosis
- 12 patients diagnosed DOL #1 (QTc range 531-840 msec)
- N=8 (67%) received a permanent pacemaker
- N=3 (25%) received ICD for TdP while on beta-blockers
- No mortality
- QTc shortens overtime even in initially high-risk patients

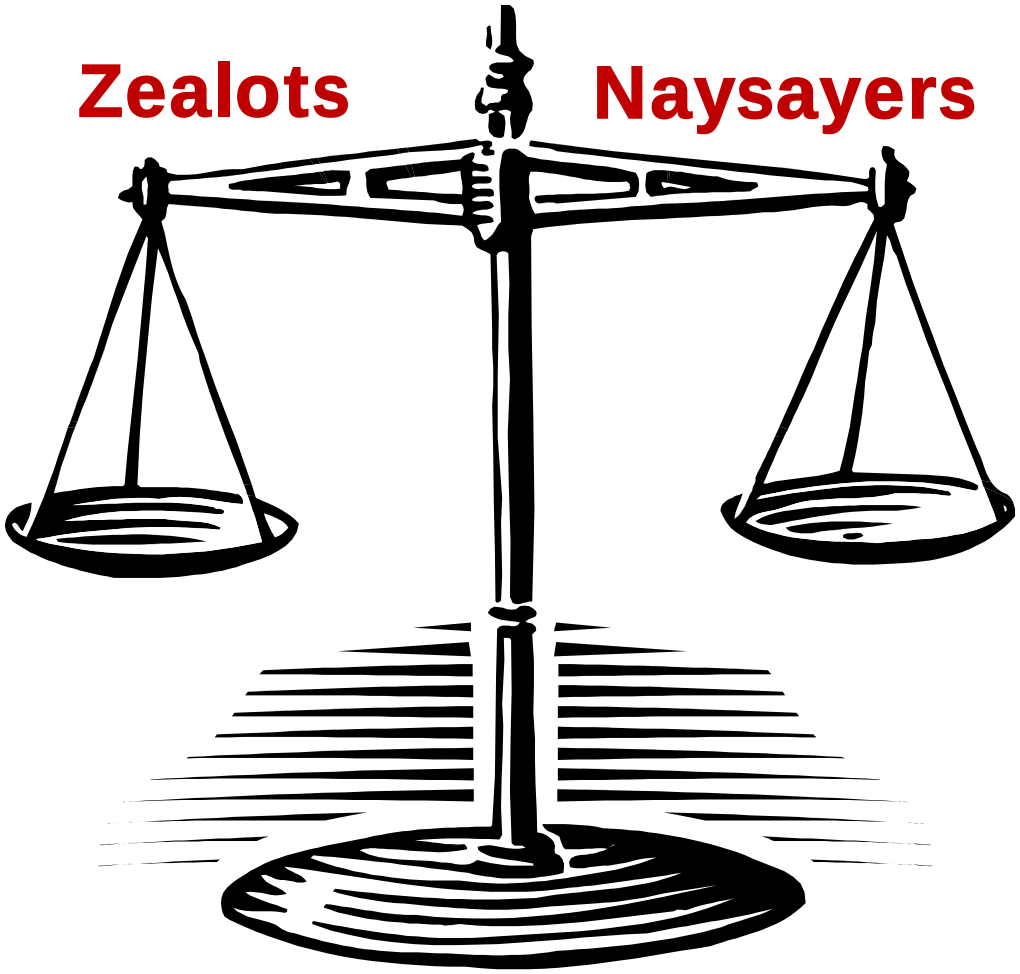


# Can we go from Sudden Cardiac Death to Sudden Infant Death?

# Despite the drastic reduction still the 3rd most common cause of infant mortality in the US



# Sudden Infant Death Syndrome and Long QT Syndrome



# Physiological Factors

## Quiet sleep prolongs the QT interval

Pediatr Res 1979;13:139-41

### Effect of Position on Sleep, Heart Rate Variability, and QT Interval in Preterm Infants at 1 and 3 Months' Corrected Age

Ronald L. Ariagno, MD*, Majid Mirmiran, MD*§, Marian M. Adams, MD*, Anna G. Saporito, MS*, Anne M. Dubin, MD‡, Roger B. Baldwin, MA*

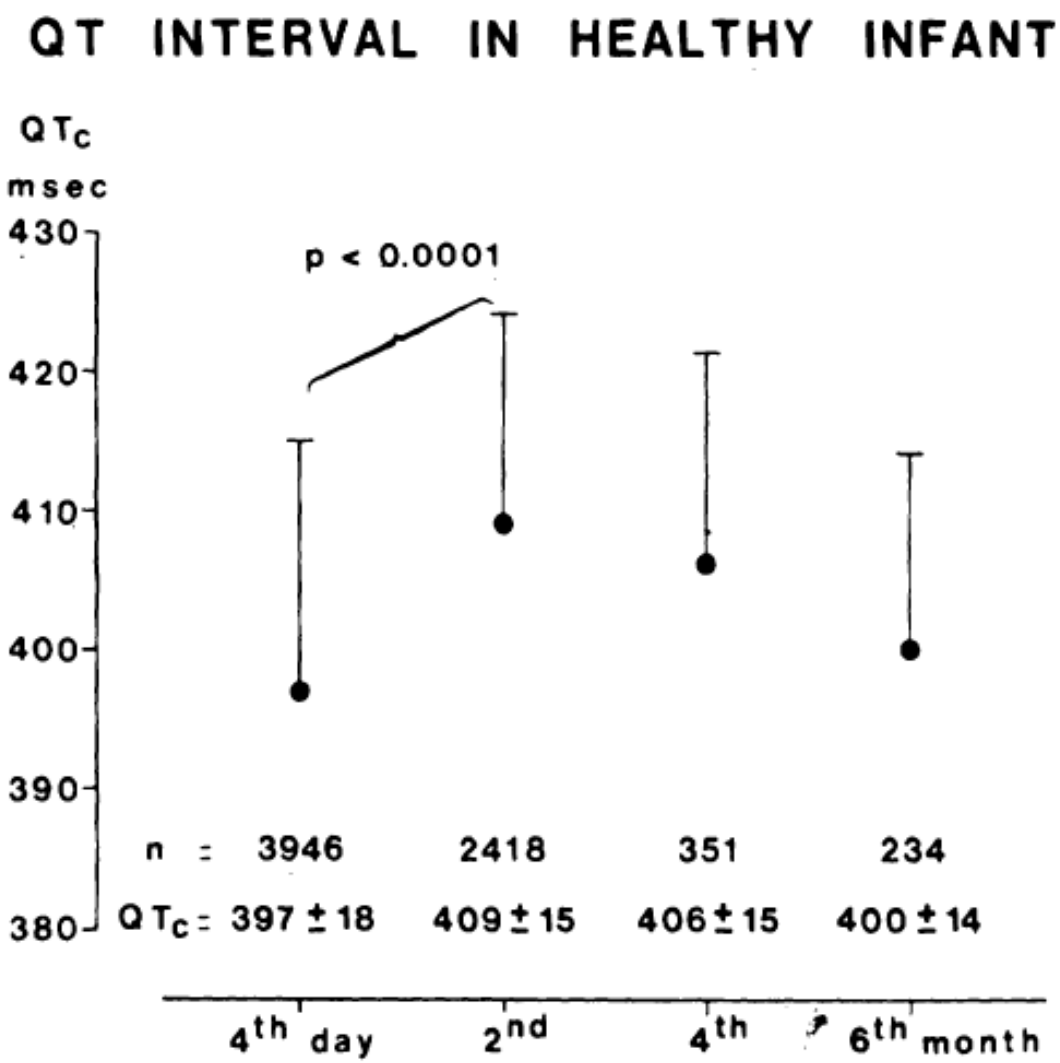
TABLE 4. QT and JT Intervals Compared With Sleep Position

QTc significantly shortens during quiet sleep supine but not prone

| | | | |
|---|---|---|---|
| $QT_c$ average, 1 mo | 0.451 (0.023) | 0.443 (0.025) | .03 |
| $QT_c$ average, 3 mo | 0.418 (0.019) | 0.422 (0.018) | NS |

Pediatrics 2003

# Peak Incidence SIDS @2-3 months




Circ 1982

# Physical & Emotional Stress Can Prolong the QT

# clinical retrospective Link between SIDS & LQT

## Potential Role of QT Interval Prolongation in Sudden Infant Death Syndrome

BARRY J. MARON, M.D., CHESTER E. CLARK, M.D.,
ROBERT E. GOLDSTEIN, M.D., AND STEPHEN E. EPSTEIN, M.D.

- 42 sets of parents with at least one infant with SIDS
- QT prolongation was present in at least one member of 11 (26%).
- In families where a parent had prolongation of QT interval, 36% of siblings also had QT prolongation

# clinical prospective link between SIDS & LQT

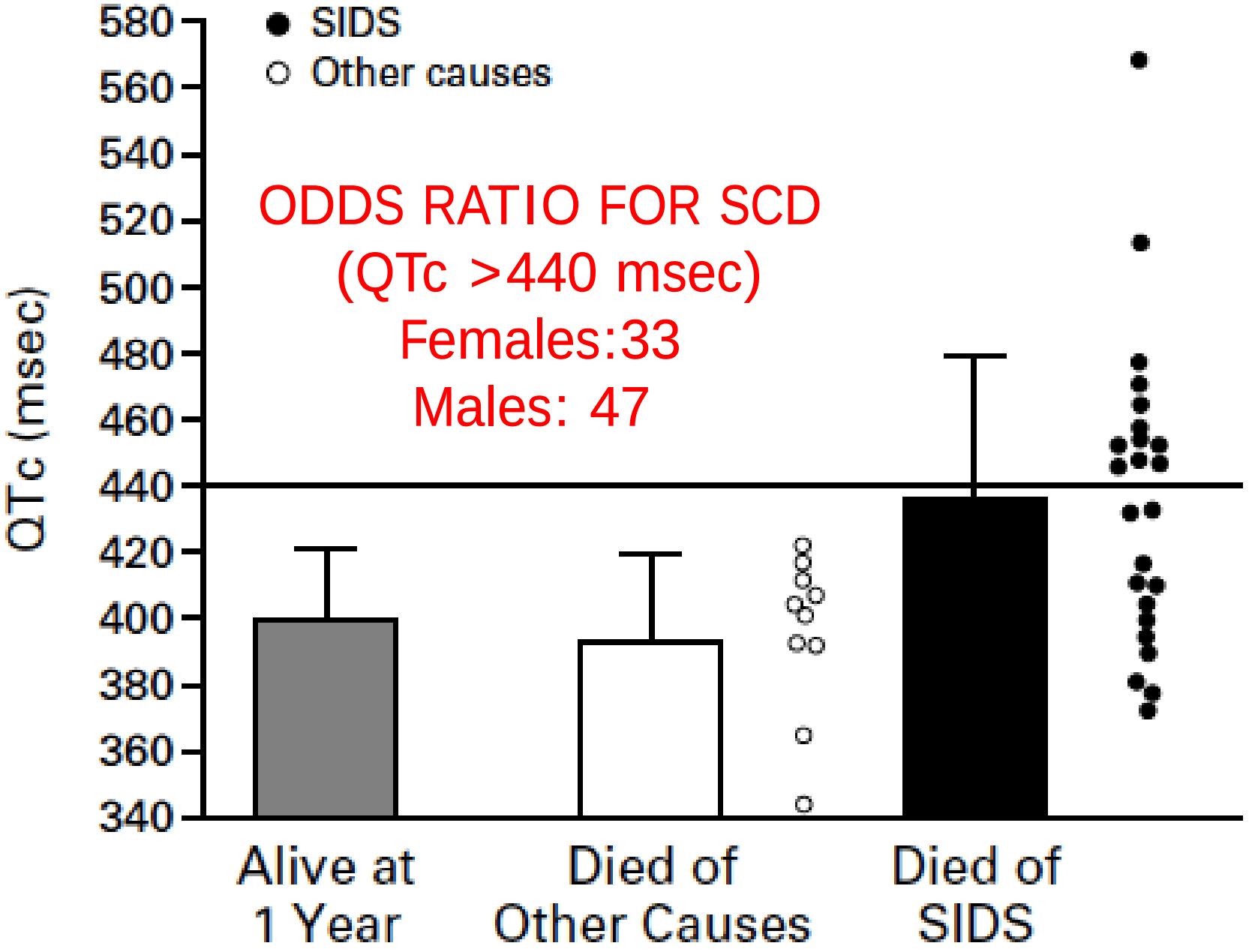
The New England Journal of Medicine



VOLUME 338 JUNE 11, 1998 NUMBER 24

## PROLONGATION OF THE QT INTERVAL AND THE SUDDEN INFANT DEATH SYNDROME

PETER JOHN SCHWARTZ, M.D., MARCO STRAMBA-BADIALE, M.D., PH.D., ALESSANDRO SEGANTINI, M.D., PAOLA AUSTONI, M.D., GIULIANO BOSI, M.D., ROBERTO GIORGETTI, M.D., FABIO GRANCINI, M.D., ERNESTO DIEGO MARNI, M.D., FRANCESCO PERTICONE, M.D., DARIO ROSTI, M.D., AND PATRIZIA SALICE, M.D.*


SIDS
Other causes
ODDS RATIO FOR SCD
(QTc >440 msec)
Females:33
Males: 47
QTc (msec)
580
560
540
520
500
480
460
440
420
400
380
360
340
Alive at 1 Year
Died of Other Causes
Died of SIDS

# Postmortem Molecular Analysis of *SCN5A* Defects in Sudden Infant Death Syndrome

Michael J. Ackerman, MD, PhD
Benjamin L. Siu, MD
William Q. Sturner, MD
David J. Tester, BS
Carmen R. Valdivia, MD

**Context** Fatal arrhythmias from occult long QT syndrome may be responsible for some cases of sudden infant death syndrome (SIDS). Because patients who have long QT syndrome with sodium channel gene (*SCN5A*) defects have an increased frequency of cardiac events during sleep, and a recent case is reported of a sporadic *SCN5A* mutation in an infant with near SIDS, *SCN5A* has emerged as the leading candidate ion channel gene for SIDS.

**Objective** To determine the prevalence and functional properties of *SCN5A* muta-

- Postmortem molecular analysis of 93 SIDS victims
- Searched for SCN5A ONLY
- 2 mutations
- 4 week-old and 6 week old
- SIDS attributable to 2% mutations in SCN5A

first year of life. In 1998, the rate of SIDS was 0.64 per 1000 live births in the United States.[3] Thus, SIDS still claims more than 2500 infants each year and accounts for approximately 9% of the more than 28000 infants who die be-

with an R1826H mutation in exon 28. These 2 distinct mutations occurred in highly conserved regions of the sodium channel and were absent in 400 control patients (800 alleles). Functionally, the A997S and R1826H mutant channels expressed a sodium current characterized by slower decay and a 2- to 3-fold increase in late sodium current.

**Conclusion** Approximately 2% of this prospective, population-based cohort of SIDS cases had an identifiable *SCN5A* channel defect, suggesting that mutations in cardiac

# Guthrie Cards

Heart Rhythm. 2010 Apr;7(4):481-6. Epub 2010 Jan 4.

**Posthumous diagnosis of long QT syndrome from neonatal screening cards.**

Gladding PA, Evans CA, Crawford J, Chung SK, Vaughan A, Webster D, Neas K, Love DR, Rees MI, Shelling AN, Skinner JR.

Cardiac Inherited Diseases Group, Auckland City Hospital/Starship Children's Hospital, Auckland, New Zealand.

Abstract

N=19 cases of SCD in New Zealand
6/19 (31%) identified as having a channelopathy

EUROPEAN SOCIETY OF CARDIOLOGY®

Europace (2014) **16**, 1706–1713
doi:10.1093/europace/euu037

REVIEW

# Sudden unexplained death in infants and children: the role of undiagnosed inherited cardiac conditions

**Table 1** Genes with mutations associated with SIDS and SADS

| Disease | Gene | Encoded protein | Frequency in SADS (%) | Frequency in SIDS (%) |
|---|---|---|---|---|
| LQT1 | KCNQ1 | Kv7.1 potassium channel α-subunit | 6.4[29] | 1.0[30–32] |
| LQT2 | KCNH2/HERG | Kv11.1 potassium channel α-subunit | 3.5[29] | 0.5[30] |
| LQT3/BrS1 | SCN5A | Nav1.5 sodium channel α-subunit | 3.5[29] | 4.8[30–34] |
| LQT6 | KCNE2 | MiRP1 potassium channel β-subunit | 1.2[29] | 0.5[30] |
| LQT9 | CAV3 | Caveolin 3 | | 1.5[30,35] |
| LQT10 | SCN4B | Navβ4 sodium channel β-subunit | | 0.3[36] |
| LQT12 | SNTA1 | Alpha-1-syntrophin | | 1.0[37] |
| CPVT1 | RYR2 | Cardiac ryanodine receptor | 11.6[29] | 1.5[38] |
| BrS2 | GPD1-L | Glycerol-3-phosphate dehydrogenase 1-like sodium channel interacting protein | | 0.9[39] |
| BrS7 | SCN3B | Navβ3 sodium channel β-subunit | | 0.7[36] |
| BrS8 | KCNJ8 | Kir6.1 potassium channel α-subunit | | 0.7[40] |
| | GJA1 | Cx43 gap junction protein | | 0.3[41] |
| HCM | MYBPC3 | Cardiac myosin-binding protein C | | 0.6[42] |
| HCM | TNNI3 | Cardiac troponin I | | 0.3[42] |

# Meta-Analysis

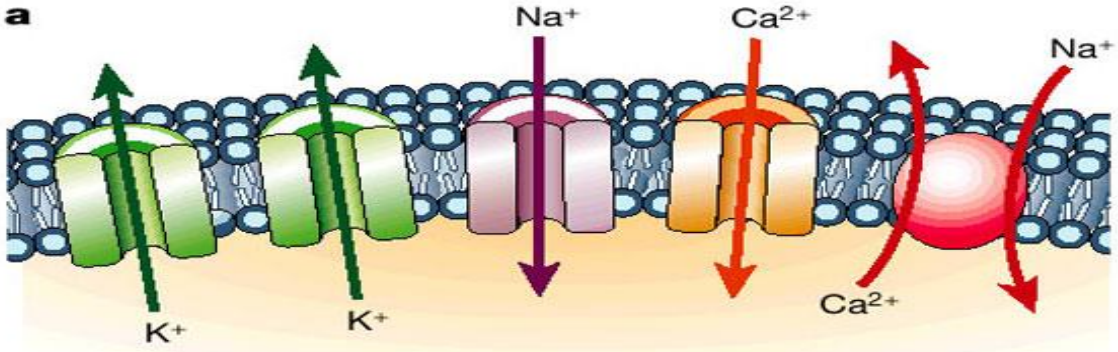
Review

## Cardiac ion channel mutations in the sudden infant death syndrome

Eva C. Klaver, G. Marja Versluijs, Ronald Wilders *,1

*Heart Failure Research Center, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*

close to 1,000 molecular autopsy SIDS cases




- 1 in 5 SIDS victims caries a mutation of a cardiac related ion-channel gene defect
- Genetic analysis should be performed in cases of sudden infant death syndrome and sudden cardiac death

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