Pediatric ECG evaluation for MDR-TB trials

Pediatric MDR-TB Training for PHOENIx, P1108 and 2005
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Adolescent AIDS Clinical Trials Network

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Why is a cardiologist presenting……..?

“Key Points” - Summary of evidence BDQ and DLM - MDR-TB treatment

		Bedaquiline	Delamanid
Safety	• SAEs (including mortality)[5]	• Increased mortality observed, QT prolongation	• No increased risk of mortality observed, QT prolongation
	• AEs	• Most common (>10% of cases): headache, nausea, arthralgia	• Most common (>10% of cases): nausea, vomiting, dizziness
	• Absolute medical contraindications	• Severe cardiac disease or QTc >500 ms	• Severe cardiac disease or QTc >500 ms, albumin less than 2.8 g/dL
	• Drug–drug interactions	• Significant interactions with drugs that inhibit or induce the CYP3A4 enzymes. Additive cardiotoxicity with drugs that prolong the QT interval (moxifloxacin, clofazimine, efavirenz, lopinavir/ritonavir are not recommended in concomitant use with Bdq). Prolonged terminal elimination half-life (about 5.5 months).	• Significant interactions only with drugs that strongly inhibit or induce the CYP3A4 enzymes. Additive cardiotoxicity with drugs that prolong the QT interval (data available showing QT prolongation when Dlm is administered with Lfx, but no data available on concomitant use with Mfx and Cfz; no DDI with efavirenz, tenofovir, lopinavir/ritonavir for Dlm dosed at 100 mg BD).

WHO - Companion handbook MDR-TB 2014, Annex 4.3

Update on BDQ/LQT - Review Published Jan. 2017

- UDWADIA et al. [2013-15?]:
  - 20pts, mean QTcF increased by 50msec, 3 with QTcF >500msec.
  - Mfx and Clz

- GUGLIELMETTI [2015?]:
  - 45pts, 11% with QTcF>500msec
  - 2 “unexplained” deaths

- SKRAHINA [DATES?]:
  - 197pts, *“...41% experienced cardiac disorders - e.g. abnormal electrocardiogram and arrhythmia”*
  - 2 deaths

Pontali E, et al. Eur Respir J 2017; 49: 1700146

Objectives

- Better understand the cardiac physiology of prolonged QT and Torade de Pointes (TdP)
- Examine (critique) the current approach
- Estimating arrhythmogenic risk with MD-TB drugs
- Can we reduce arrhythmogenic risk?

Background - “Torsadogenic Drugs”

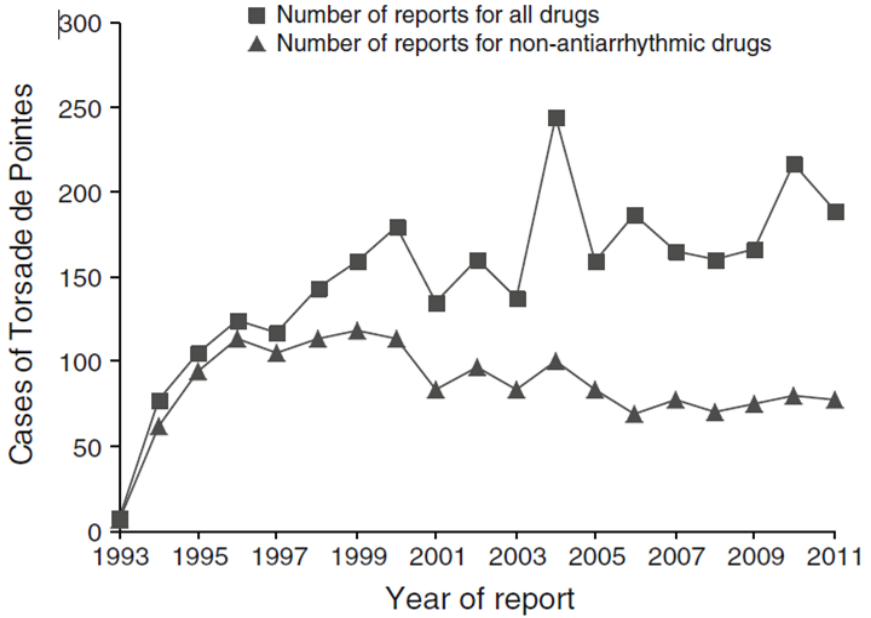


Fig. 1 Annual number of spontaneous reports of Torsade de Pointes received by the US FDA Adverse Event Reporting System

History:

- 1990’s - non-cardiac drugs found to cause life threating TdP
- This lead to multiple drugs pulled from market
- hERG=KCNH2 (gene) encoding a K-channel protein was identified in mid-1990’s as the culprit site

N. Stockbridge et al. Drug Saf (2013) 36:167–182.

Background - “Torsadogenic Drugs”

Table 1 Drugs withdrawn from the market as a result of their potential for QT prolongation and/or TdP (adapted from Shah [12])

Drug	Year of introduction	Therapeutic class	Year of withdrawal
Prenylamine	1960s	Antianginal	1988
Lidoflazine[a]	1979	Antianginal	1989
Terodiline	1986	Antianginal/urinary incontinence	1991
Terfenadine	1982	Antihistamine	1998
Sertindole[b]	1996	Antipsychotic	1998
Astemizole	1986	Antihistamine	1999
Grepafloxacin	1997	Antibiotic	1999
Cisapride	1988	Gastric prokinetic	2000
Droperidol	1960s	Tranquilizer/analgesic	2001
Levacetylmethadol	1997	Methadone substitution	2001
Dofetilide[a]	1999	Class III drug for atrial fibrillation	2004
Thioridazine	1958	Antipsychotic	2005
Clobutinol	1960s	Antitussive	2007
Dextropropoxyphene [c]	1960s	Opioid analgesic	2009

[a] Not commercialized

[b] Re-introduced later following re-evaluation of benefit-risk

[c] In addition to QT-liability, safety in overdose was also an issue

TdP Torsade de pointes

N. Stockbridge et al. Drug Safe (2013) 36:167–182.

Background - “Torsadogenic Drugs” - antibiotics

Erthromycin (TdP reported)
Clarithromycin (TdP reported)
Ketoconazole
Pentamidine (TdP reported)
Quinine
Chloroquine (TdP reported)
Halofantrine (TdP reported)
Amantadine (TdP reported)
Sparfloxacin
Grepafloxacin (TdP reported, withdrawn in UK and USA)
Moxifloxacin
Pentavalent antimonial meglumine

Yap, YG. Heart. 2003 Nov; 89(11): 1363–1372.

Background - “Torsadogenic Drugs” + cytochrome P450

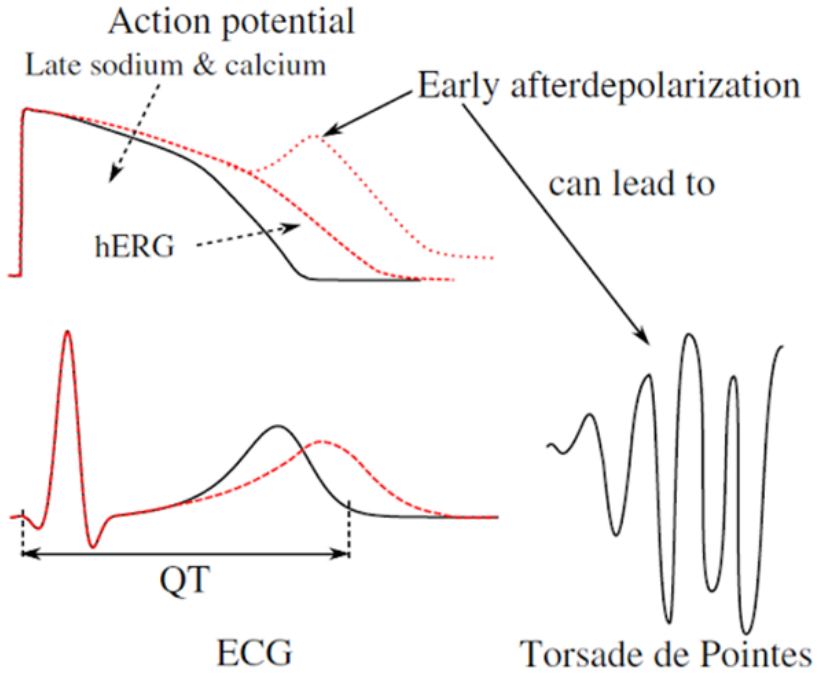
Multiple QT prolonging drugs and/or DD-interactions is usually the culprit

- Ketoconazole prolongs QTc - blocks hERG (KCNH2) channel
- Inhibit the hepatic cytochrome P450 CYP3A4 isoenzyme.
- Ketoconazole + terfenadine (also P450) = dangerously prolonged QT interval - TdP

Yap, YG. Heart. 2003 Nov; 89(11): 1363–1372.

Is QTc prolongation in and of itself dangerous?

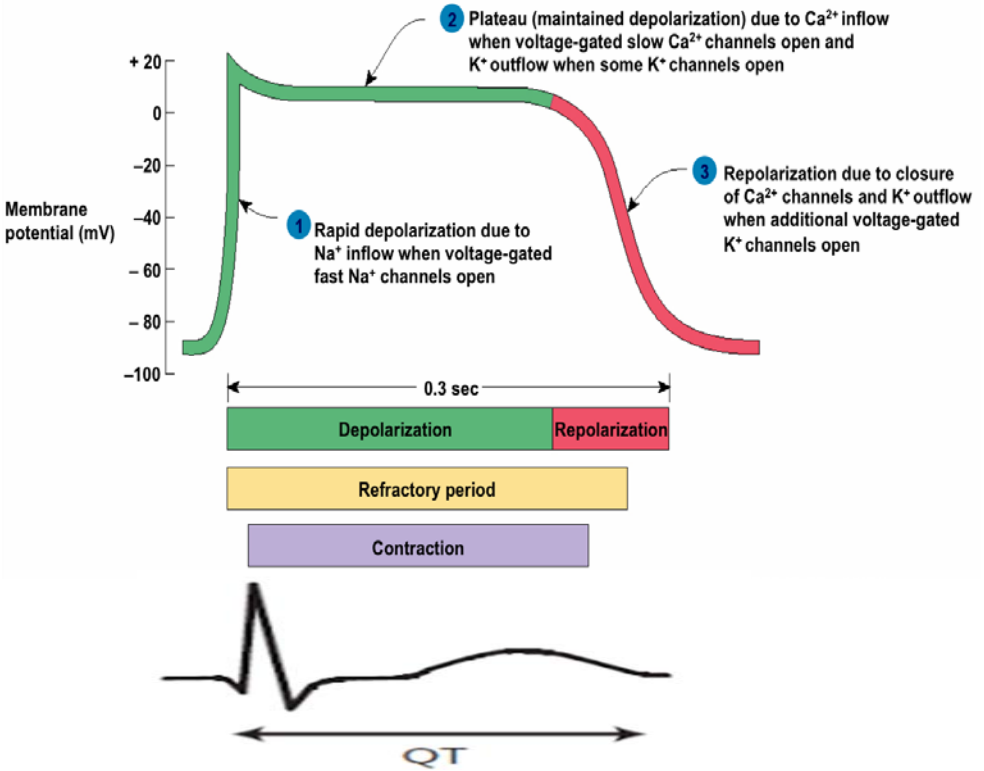
From QTc to Danger……



Roden DM. NEJM (2004); 350:1013-22.

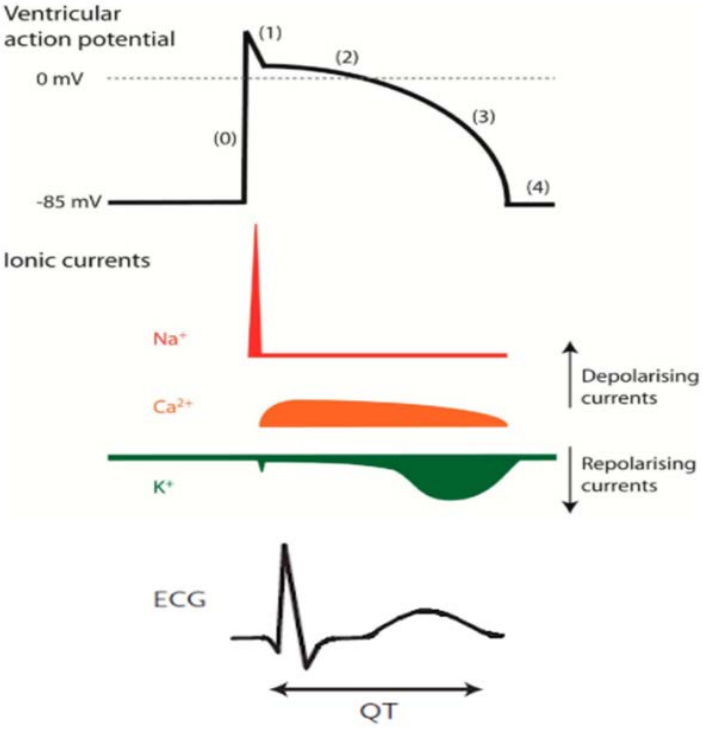
Electrophysiology of the Heart - vocabulary check

Electrophysiology of the Heart - “vocabulary check”



- Action Potential
- Depolarization
- Repolarization
- Phase 3 of Repolarization
- iKr = RAPID potassium current
- hERG (KCNH2) = potassium channel protein
- QTc = interval from Q, to T, corrected for HR
- Friderica (QTcF) = preferred correction method
- Torsades de Pointes = specific type of ventricular tachycardia from prolonged QTc

From QTc to Danger……



- REPOLARIZATION resets the cells current - “ready for the next beat”
- This repolarization segment of the action potential is due primarily to K+ OUTFLOW via hERG (KCNH2) protein K-channel
- Drug-induced arrhythmia is mediated through this REPOLARIZATION segment
- Prolongation increases risk for TdP

http://what-when-how.com/wp-content/uploads/2012/05/tmp2C4.jpg

From QTc to Danger……

Substrate for Torsades de Pointes (TdP)

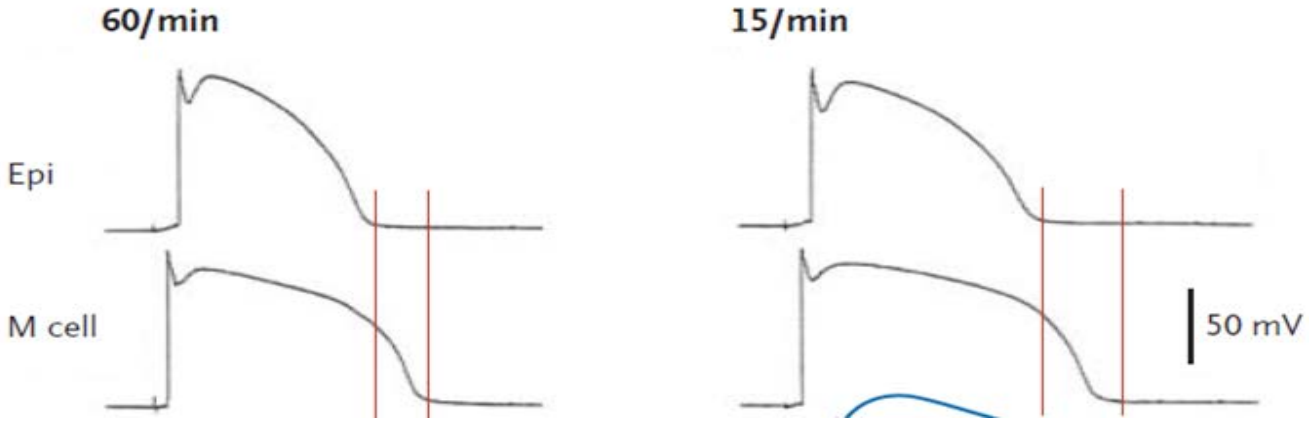
1. Prolonged Phase 3 repolarization
2. QT Dispersion
3. Early After Depolarization (EAD) beats

From QTc to Danger…… 2. QT Dispersion

- Dispersion - regional myocardial differences in repolarization = thus QTc differences
- Normal Physiology = minimal dispersion present
- Dispersion can be:
  - Transmural
  - LV-RV
  - Apex-Base

From QTc to Danger…… 2. QT Dispersion

- **<u>Repolarization Heterogeneity - QT Dispersion</u>**
  - Exposed myocardial cells to hERG (KCNH2) block - then bradycardia
  - EPI cells are at one potential = shorter QT
  - M-cells are still repolarizing = longer QT



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From QTc to Danger…… 3. Early After Depolarization (EAD)

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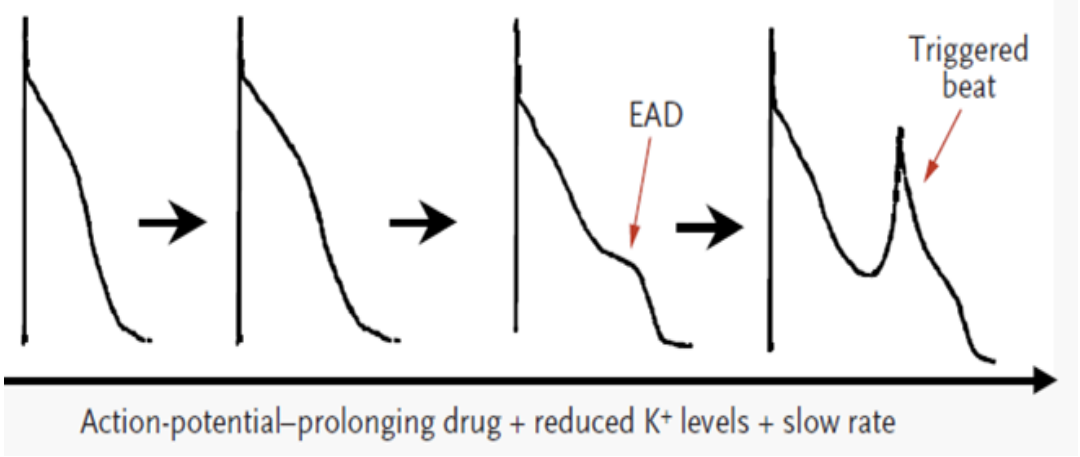

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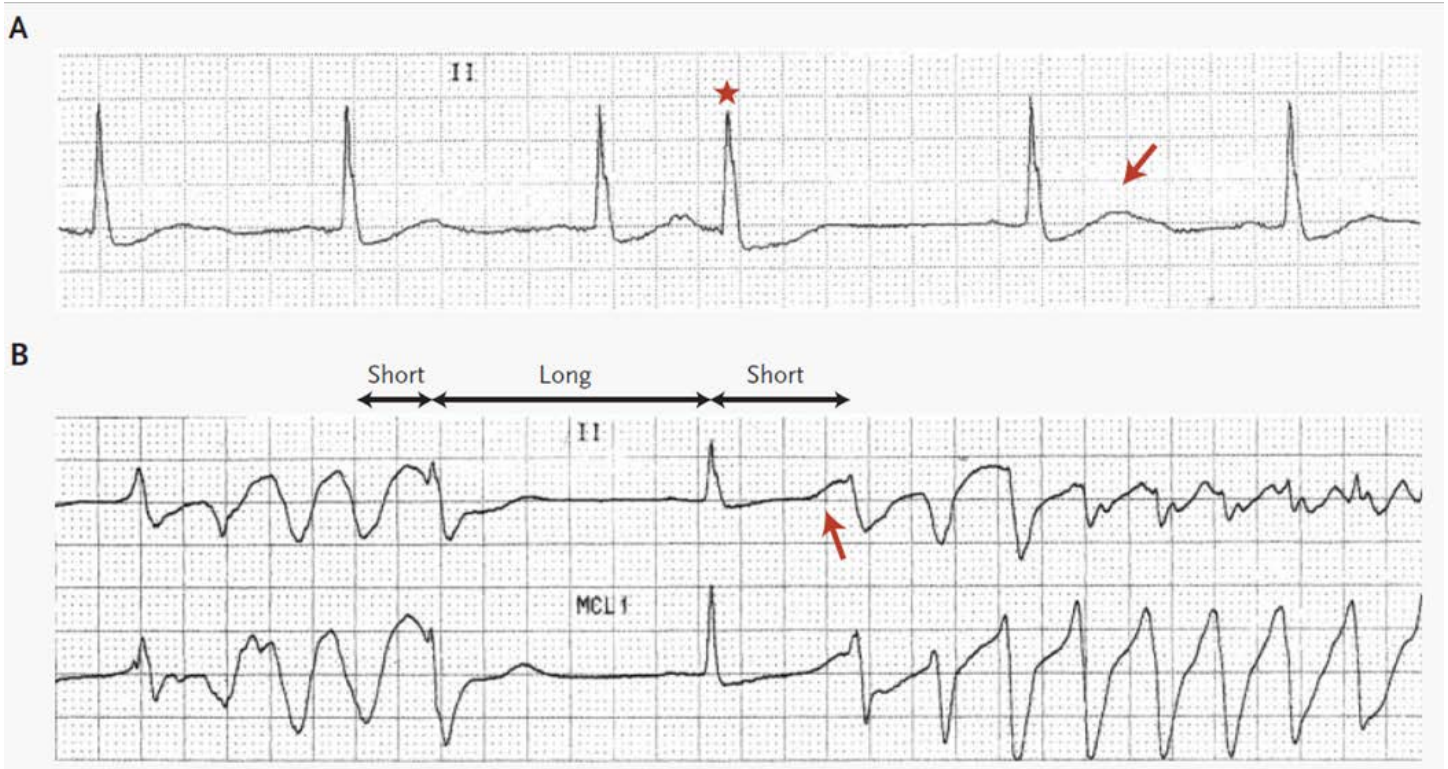
From QTc to Danger…… Torsades de Pointes (TdP)



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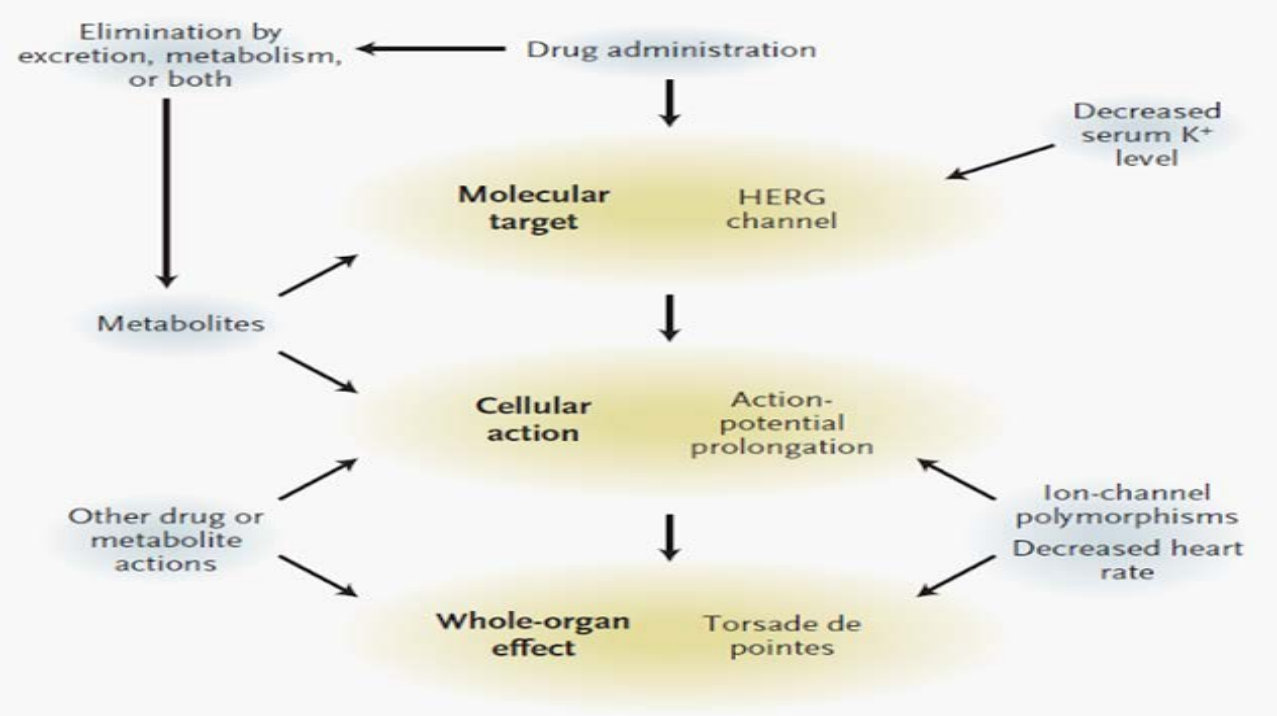
From QTc to Danger…… Torsades de Pointes (TdP)

- “Symptomatic TdP”
  - Hospital based drug induced
  - Congenital LQTS patients
- Slower than V-FIB
- One can have “runs” of TdP
    - FREQUENTLY Self resolves = palps, dizziness, syncope
    - ...but can degenerate into V-fib = sudden death
    - Opportunity to identify signal - “patient with palpitations / dizziness”

Schwartz and Ackerman. Eur Heart J (2013) 34 (40): 3109-3116. Kannankeril and Roden. Pharmacol Rev, 62 (2010);760–781.

From QTc to Danger…… Torsades de Pointes (TdP)



Roden DM. NEJM (2004); 350:1013-22.

“Reduced Repolarization Reserve”

A unifying framework to understand Drug Induced LQT is the concept of “reduced repolarization reserve”

- Idea of that multiple often-redundant mechanisms maintain normal repolarization, so minor alterations in function may not be obvious at baseline.
  - Minor polymorphism in channel gene leads to small decrease function - near normal QT
    - Add Drug
    - Add low K, low Mg
    - Add bradycardia
  - ……..then you markedly increase risk for TdP

Kannankeril and Roden. Pharmacol Rev, 62 (2010), pp. 760–781.

Risk Factors for Torsades de Pointes

- Female sex, 2-3:1 increased risk
- Bradycardia, typically <60 BPM
- Hypokalemia, especially <3.5 mg/dl
- Hypomagnesemia, especially <1.5mg/dl
- Subclinical Congenital LQTS (<10% of all cLQTS)
- Ion Channel polymorphisms

Kannankeril and Roden. Pharmacol Rev, 62 (2010), pp. 760–781.

Current Approach: BDQ (p1108) DLM (p2005) Protocols

- Exclusions
  - Cardiac disease (subject); family history of LQTS
  - QTcF>460msec
- Monitoring
  - Frequent high quality ECGs for reproducible QTcF data
    - ~30ECGs/subject x 72subjects over 40 (BDQ) 28 (DLM) weeks = ~2,200
    - Digital QTcF reads, physician over-reads
  - Low K, Low Mg, Low Ca - identify and treat
  - Low Alb (for DLM)
  - Drug-Drug (DD) Interactions

Limit DD-Interactions - BDQ (p1108) DLM (p2005) Protocols

- Prohibited MEDS:
  - Neuroleptics: phenothiazines thioridazine, haloperidol, chlorpromazine, trifluoperazine, pericycline, prochlorperazine, fluphenazine, sertindole, and pimozide
  - Quinolone antimalarials (e.g. chloroquine and quinacrine)
  - Moxifloxacin, gatifloxacin, and sparfloxacin
  - Tricyclics: amitriptyline, doxepin, desipramine, imipramine, and clomipramine
  - Anti-arrhythmic: quinidine, procainamide, disopyramide, encainide, flecainide, sotalol, amiodarone, digitalis
  - Clarithromycin

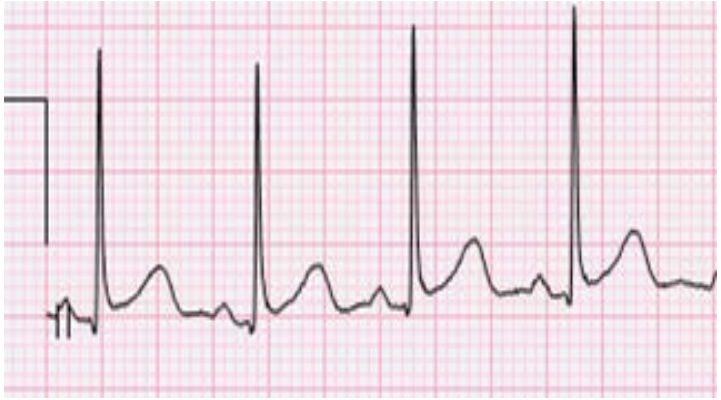
BDQ long ½ life and CYP3A4

Strong CYP3A4 Inhibitors:

- Azole antifungals: ketoconazole, fluconazole (with caution), voriconazole, itraconazole
- Ketolides such as telithromycin
- Macrolide antibiotics (other than azithromycin and clarithromycin) for more than two weeks

QT Interval: How to Measure.

- Definition = time from the start of the QRS to the end of the T-wave
- Measured in LIMB LEAD II or V5
- Correct for HR using
  - QTc = “QT-corrected”
  - QTc = $QT/\sqrt[3]{RR}$
  - Fridericia Correction
  - RR=time between “R-waves”
  - RR in SECONDS
- Upper limit of Normal Duration:
  - QTc < 455 to 460msec



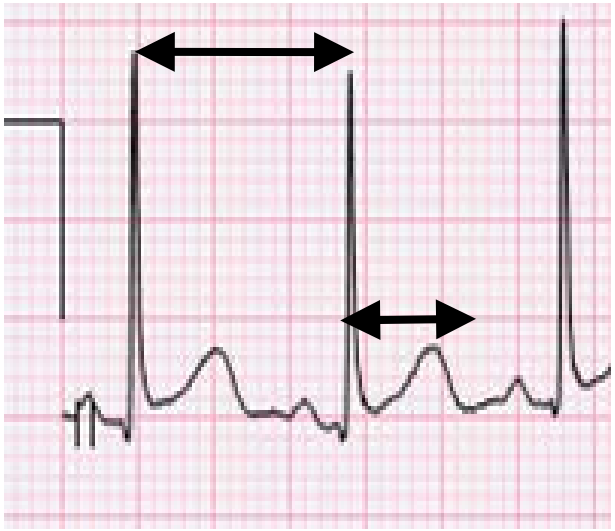
QT Interval: How to Measure.

QTc= $QT/\sqrt[3]{RR}$

- RR interval =14.5 boxes
  =14.5 x 40msec
  =580msec
  =0.58sec
  $\sqrt[3]{RR}$ =0.8339

- QT=9.5 boxes
  =380msec

- Therefore the QTc = 380/0.8339
  =456msec



ONLINE CALCULATOR

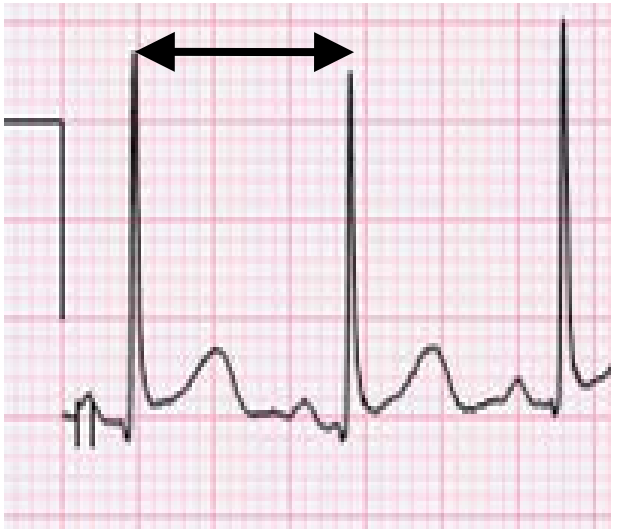
https://www.medcalc.org/clinicalc/corrected-qt-interval-qtc.php

QT Interval: HR, RR and cubed root Table

QTc = $QT/\sqrt[3]{RR}$

$\sqrt[3]{RR}$

HR	RR	cubed root of RR
50	1.20	1.06
55	1.09	1.03
60	1.00	1.00
65	0.92	0.97
70	0.86	0.95
75	0.80	0.93
80	0.75	0.91
85	0.71	0.89
90	0.67	0.87
95	0.63	0.86
100	0.60	0.84
105	0.57	0.83
110	0.55	0.82
115	0.52	0.81
120	0.50	0.79
125	0.48	0.78
130	0.46	0.77



Current Clinical Approach: QTcF Thresholds

P1108 BDQ and P2005 DLM: Exclusion of >460msec, WHY HIGHER?

- 440msec is exceeded by approximately 15% of the population
- 450msec males, 460msec female is the 95% (healthy post-puberty)
- 470msec males, 480msec females is the 99th% (healthy post-puberty)
- Pediatric QTc are slightly longer
  - QTc shortens after puberty in MALES
  - QTc “fails to shorten” after puberty in FEMALES = stays “LONG”

Schwartz and Ackerman. Eur Heart J (2013) 34 (40): 3109-3116. DOI: https://doi.org/10.1093/eurheartj/eht089

Adverse Event Grading: Appendix V - TOX TABLE

	Grade 1	Grade 2	Grade 3	Grade 4
ECG Criteria: corrected QTc interval Note: QT corrected based on Frederica method (QTc=QT/cubed root of RR interval).	QTc ≥460msec, but <480msec	QTc >=480msec, but <500msec	QTc ≥500msec OR QT > 60 msec greater than baseline AND QT>=480 ms	Life-threatening consequences (Torsades de pointes, other serious ventricular dysrhythmias)
Cardiac Clinical Criteria	Any one of the following clinical symptoms (one event, without clear evidence of non-cardiac etiology): ⇒ syncope ⇒ chest pain ⇒ palpitations ⇒ dizziness	Recurrence/ongoing clinical symptoms (without clear evidence of non-cardiac etiology): ⇒ syncope ⇒ chest pain ⇒ palpitations ⇒ dizziness	Recurrence/ongoing clinical symptoms - *with evidence of ventricular tachycardia** ⇒ syncope ⇒ chest pain ⇒ palpitations ⇒ dizziness * Note that this presence of Ventricular Tachycardia (VT) *is the adverse outcome* to be avoided/identified; the symptoms are surrogates for "possible" VT, but if VT is demonstrated, then BDQ is permanently discontinued irrespective of QTc or symptoms.	

Cardiac Toxicity Management: Appendix VI

ECG-determined or clinical cardiac toxicity		
SEVERITY	**STUDY DRUG USE**	**FOLLOW-UP AND MANAGEMENT**
Grade 1	Continue BDQ	Repeat ECG and clinical evaluation of symptoms within 72 hours
Grade 2	Continue BDQ	Repeat ECG and clinical evaluation of symptoms within 48 hours
Grade 3 (ECG)	Hold Fluoroquinolone (FQ) and BDQ	If repeat ECG and clinical evaluation of symptoms within 72 hours continues to show Grade 3, hold the FQ and hold study drug (= Grade 4). Check K+, Mg +2 and Ca +2 (corrected for albumin) and correct as necessary Contact the study team and indicate in the participant line: "Grade 3 ECG."
Grade 3/4 (*Cardiac Clinical Criteria*)	Hold FQ and Permanently discontinue BDQ if not other explanation; e.g., lab abnormality Note: STUDY DRUG USE for *Cardiac Clinical Criteria* meeting Grade 3 or Grade 4 are equivalent – that is *permanently discontinue BDQ*	Check K+, Mg +2 and Ca +2 (corrected for albumin) and correct as necessary Contact the study team and indicate in the participant line: "Grade 3/4 Cardiac." Discuss with the team the permanent discontinuation of study drug.
Grade 4 (ECG)	Hold FQ and Permanently discontinue BDQ if not other explanation; e.g., lab abnormality	Check K+, Mg +2 and Ca +2 (corrected for albumin) and correct as necessary Contact the study team and indicate in the participant line: "Grade 4 ECG." Discuss with the team the permanent discontinuation of study drug.

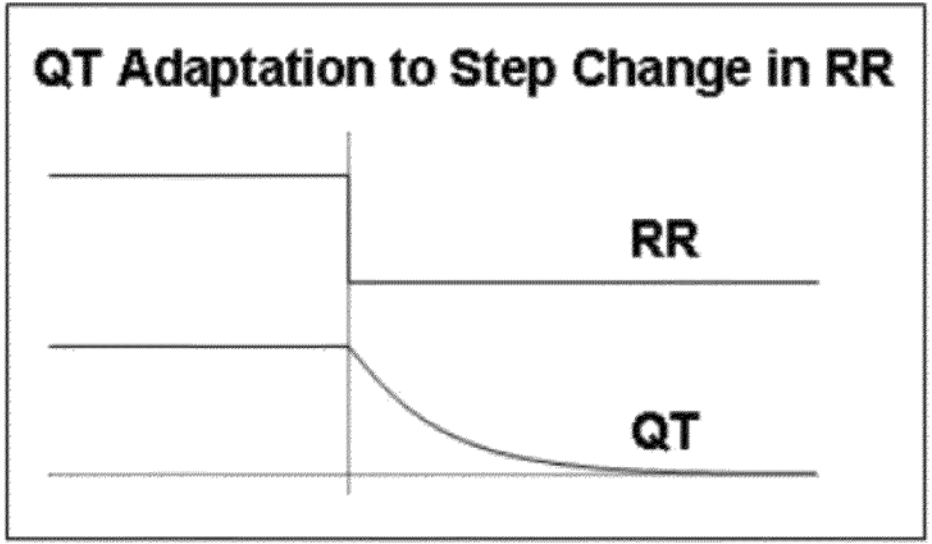
Outliers = Adverse Events - examine closely

- Congenital LQTS
  - Prevalence 1:2000-1:7500
  - Incomplete pentrance
- Genotype carriers with “normal” phenotype = normal QTc at baseline, but with increased sensitivity to drugs that affect REPOL
- Polymorphisms in ion channels - not a “disease”, but perhaps underlies unexplained prolonged QTc
- New, yet to be identified DD-interactions?

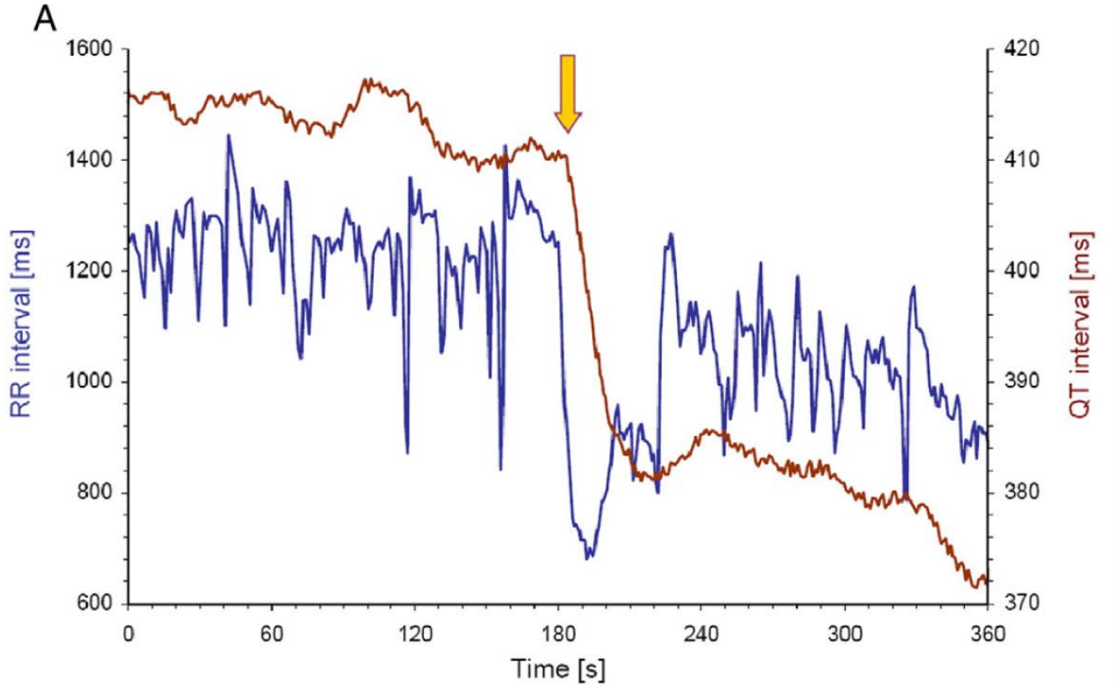
Critique: Are we sampling accurately and adequately for risk?

- QT - Physiologic Determinants are Complex
  - Circadian
  - Sex, female
  - Parasympathetic/Autonomic Tone
  - Posture (orthostasis, recovery)
    - RR mediated
    - and autonomic mediated
  - Meals
  - Recording/Measurement “Noise” – correctly pinpointing Q, R, Tend
  - Hysteresis

QT RR Hysteresis



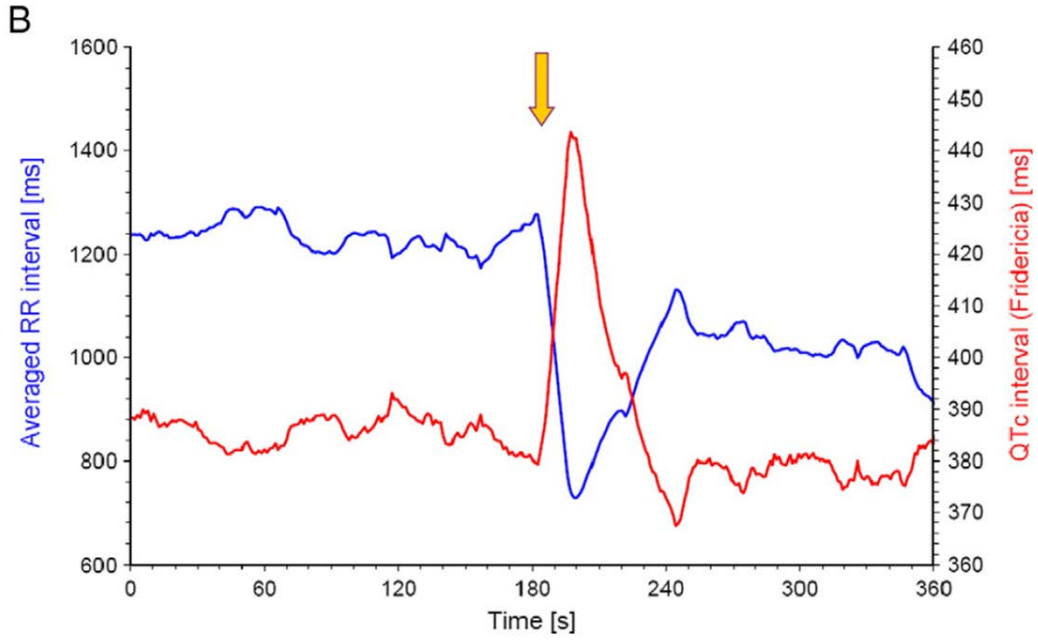
QT RR Hysteresis



- At the ARROW, the subject STANDS UP
- HR goes up (RR time shortens)
- QT interval shortens
- Note the delay… the HR increases faster than the QT shortens

Garnett CE et al. CSRC White Paper. Am Heart J 2012;163:912-30

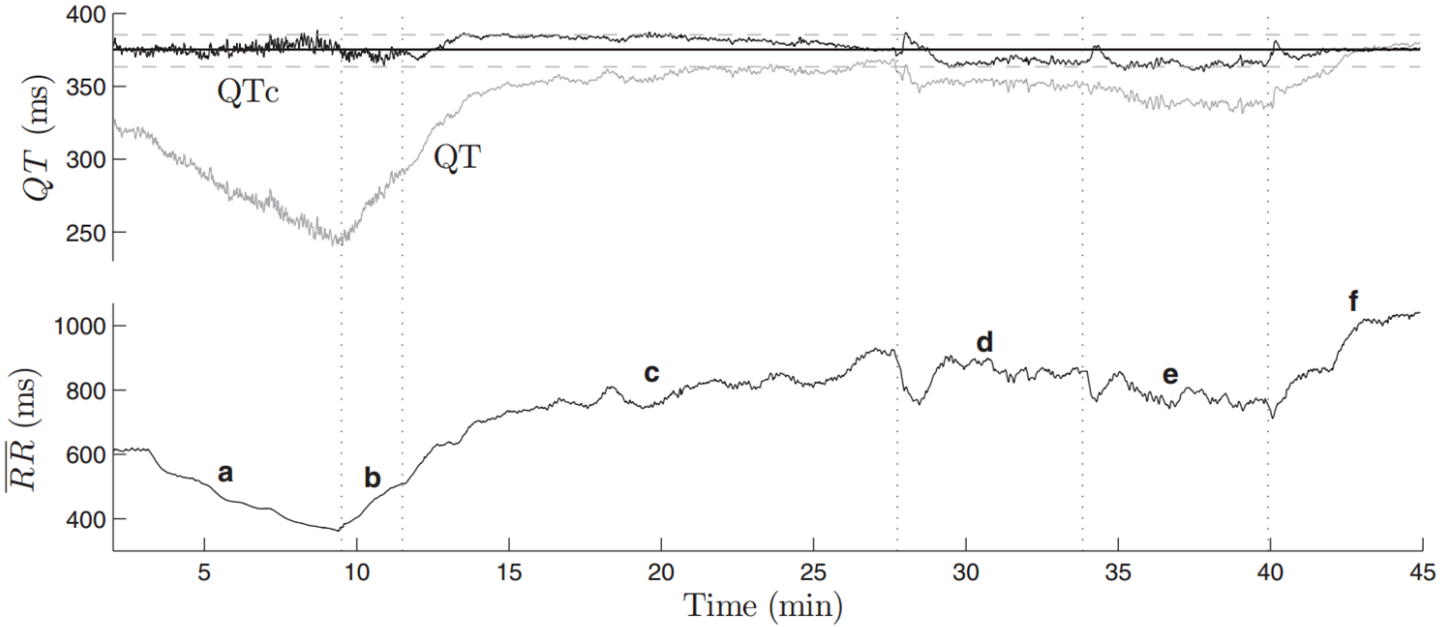
QT RR Hysteresis



- Graph QTc and RR versus time
- The “corrected” QT is erronously too long (=red spike)
- After 1-2 mins RR-QT relation resets to an accurate level
- Hysteresis is “electrical memory” - the QT changes more slowly with rapid HR changes - both during acceleration and deceleration of the HR

Garnett CE et al. CSRC White Paper. Am Heart J 2012;163:912-30

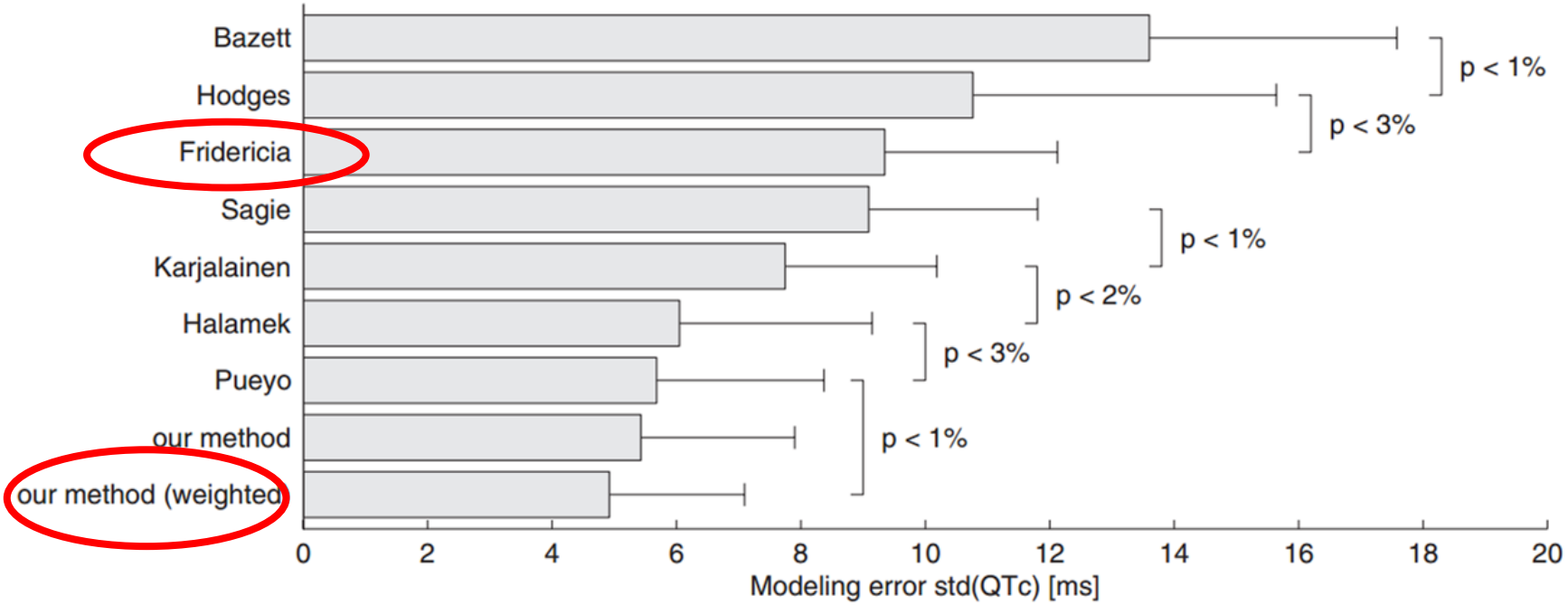
QT-RR - Subject-Specific rate Correction



a = Running
b = Walking
c = Lying in bed
d = Sitting Up
e = Standing
f = Lying in bed

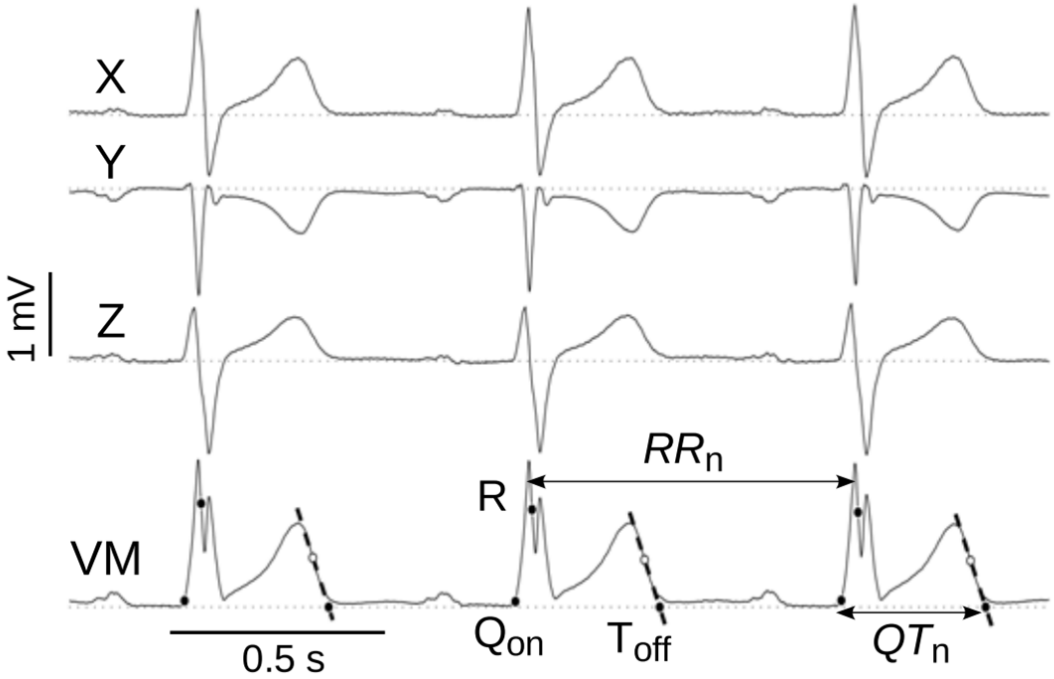
Jacquemet et al. Physiol. Meas. 32 (2011) 619–635. doi:10.1088/0967-3334/32/6/001

QTc Correction Methods



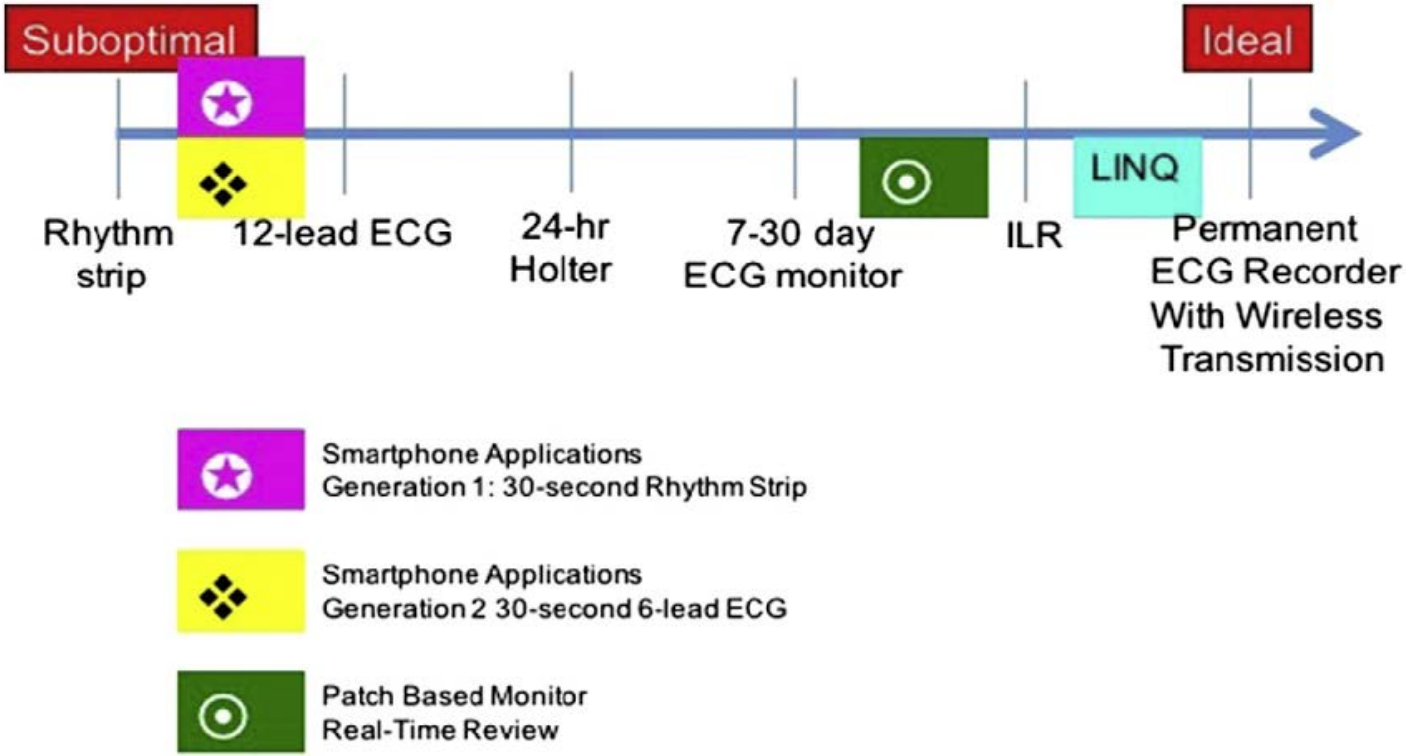
Jacquemet et al. Physiol. Meas. 32 (2011) 619–635. doi:10.1088/0967-3334/32/6/001

QTc Correction Methods - mean “Vectorgram”



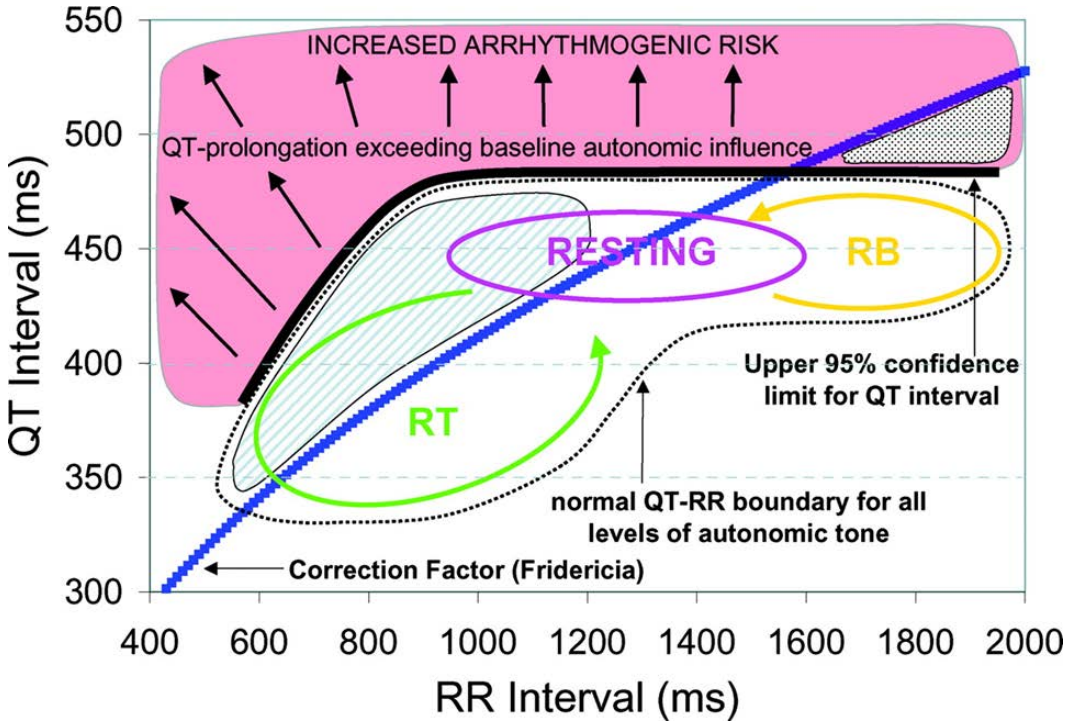
Jacquemet et al. Physiol. Meas. 32 (2011) 619–635. doi:10.1088/0967-3334/32/6/001

ECG Recorders with Wireless Transmissions



Piccini JP. et al. Am Heart J (2017);187:156-69.

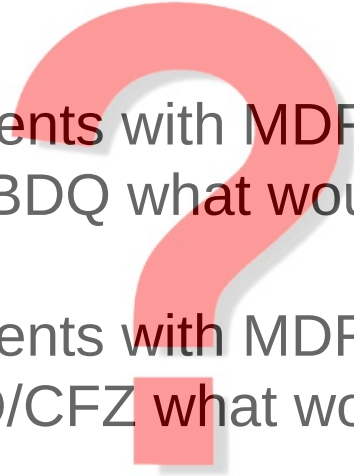
“False” Positive/Negative QTc



…..Can potentially be overcome by dynamic beat to beat modeling of QT-RR.

Fossa AA et al. J Pharmacol Exp Ther. 2005 Jan;312(1):1-11. Epub 2004 Aug 11.

Prolonged QT: How Dangerous is it?



- If ALL pediatric patients with MDR-TB were exposed to a 26 weeks of DLM OR BDQ what would be the estimate of TdP risk?
- If ALL pediatric patients with MDR-TB were exposed to a 26 weeks of DLM/BDQ/CFZ what would be the estimate of TdP risk?

Prolonged QT: How Dangerous is it?

DLM/BDQ both prolong the QTc by 10-15msec

- Can we quantify the danger of QTc prolongation?
  - Data available - reasonable estimates of risk
- What are the thresholds of QTc that correlate with TdP?
  - 500msec
- Can a drug prolong the QTc and NOT increase risk of TdP?
  - YES! - Confounds these critical questions.

Lessons Learned from Congenital LQTS - TYPE 2

- CLQTS is a “surrogate” disease for Drug Induced LQT
- 10msec increase in QTc 5-7% increase risk of TdP
- From 440 to 540msec = 85% higher risk of TdP
- QTc>500msec x2-3 risk of TdP

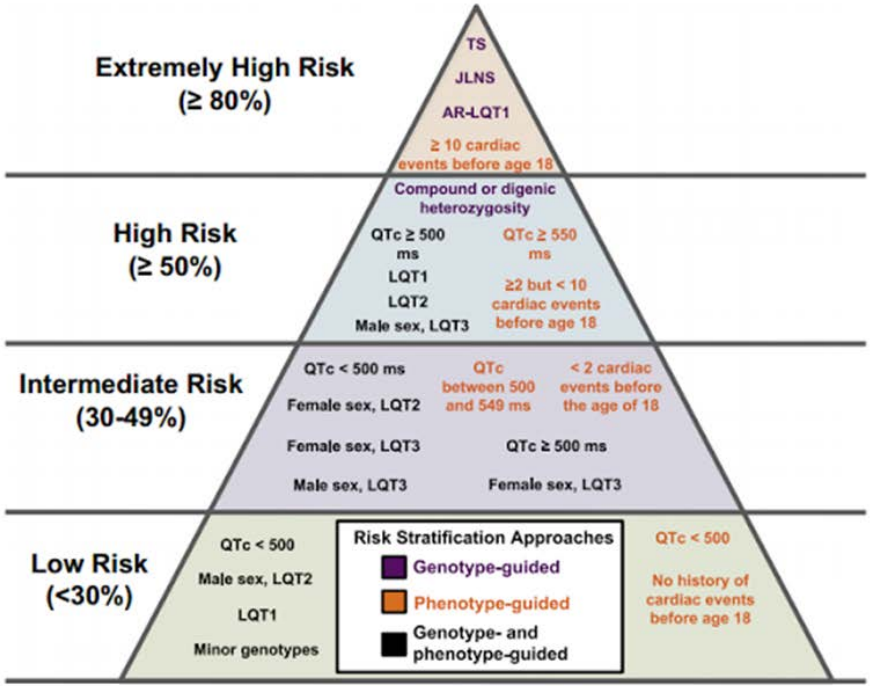
Schwartz and Ackerman. Eur Heart J (2013) 34 (40): 3109-3116. DOI: https://doi.org/10.1093/eurheartj/eht089

Lessons Learned from Congenital LQTS - TYPE 2

- Overall Mortality of 1-2% in 800-1000 patients with treated Congenital LQTS
- Less than 20% of individuals with LQTS should have ICDs placed
- Prognosis in LQTS TYPE 2
  - “Low risk” = QTc<500msec
  - <30% incidence of life threatening events over 40 years

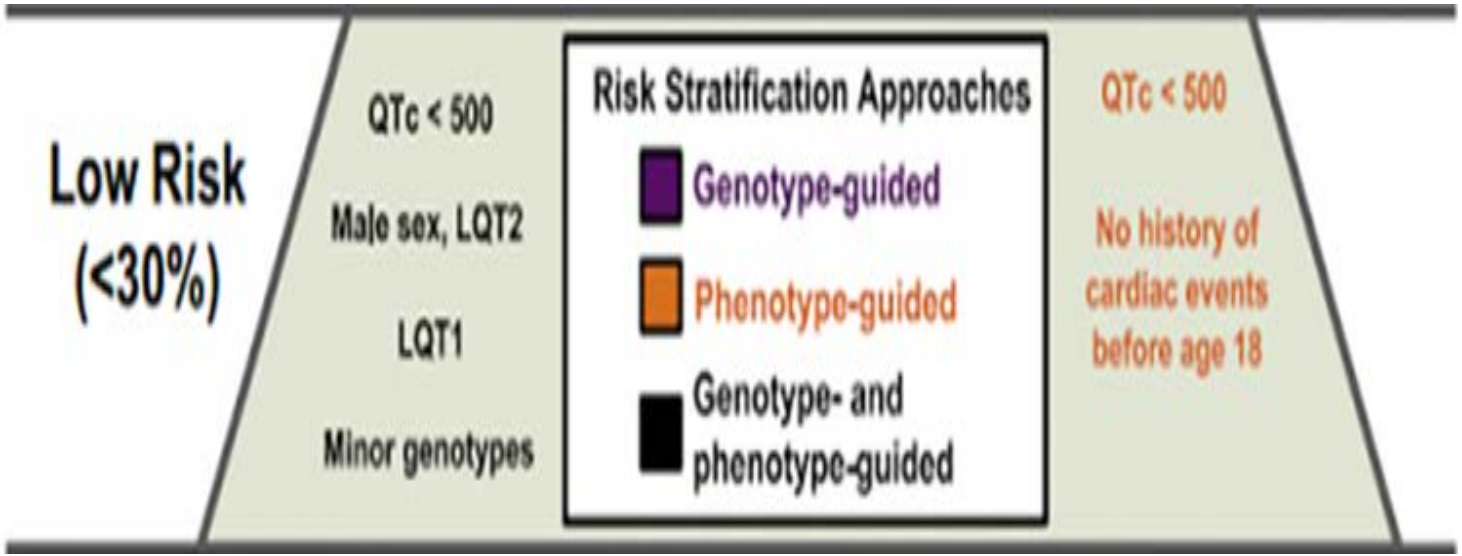
Schwartz and Ackerman. Eur Heart J (2013) 34 (40): 3109-3116. DOI: https://doi.org/10.1093/eurheartj/eht089

Lessons Learned from Congenital LQTS - TYPE 2



Schwartz and Ackerman. Eur Heart J (2013) 34 (40): 3109-3116. DOI: https://doi.org/10.1093/eurheartj/eht089

Lessons Learned from Congenital LQTS - TYPE 2



Schwartz and Ackerman. Eur Heart J (2013) 34 (40): 3109-3116. DOI: https://doi.org/10.1093/eurheartj/eht089

Lessons Learned from Congenital LQTS - TYPE 2

“Low risk” = QTc<500msec, there is a <30% incidence of life threatening events over 40 years

- So, IF drug induced K-channel block is similar to LQTS TYPE 2 - (there is modest evidence for this), THEN:
  - The incidence of life threatening events over 26 WEEKS of drug exposure with QTc<500msec could be estimated:

RISK of an “EVENT” would be = 0.5/40 x 30% = 0.4% during Rx

Schwartz and Ackerman. Eur Heart J (2013) 34 (40): 3109-3116. DOI: https://doi.org/10.1093/eurheartj/eht089

Lessons Learned - All Drugs - TdP

- Cisapride
  - TdP incidence 1:120,000
- Moxifloxacin
  - QTc 5-10msec, always <30msec
  - TdP incidence 1:1,000,000
- Terfenadine
  - Alone QTc 6msec
  - Add erythromycine or ketoconazole = 80-100msec
  - 100,000,000 scripts filled prior to rare cases of TdP recognized
  - Most cases inhibit CYP3A4 from liver disease, or DDI - ketoconazole/erythromycin

Yap, YG; Kannankeril and Roden; Drew BD. Circ 2010 March 2;121(8):1047-60.

Lessons Learned - Antiarrhythmic Drugs - TdP

- Sotolol
  - The mean effect on QTc =10–40 ms at clinically used doses
  - 0.3% incidence of TdP with 80mg daily dose
  - 3.8% incidence of TdP with 680mg daily dose
- General risk of TdP in antiarrhythmic drugs that prolonged QTc
  - 1 to 3% risk of TdP over 1 to 2 years of exposure
- Complex, yet to be fully defined, relationship between K channel block, degree of QT prolongation and risk for TdP
  - Example:
    - Amiodarone prolongs QTc
    - Widely used
    - TdP is exceedingly rare

Kannankeril and Roden. Pharmacol Rev, 62 (2010), pp. 760–781.

Future?

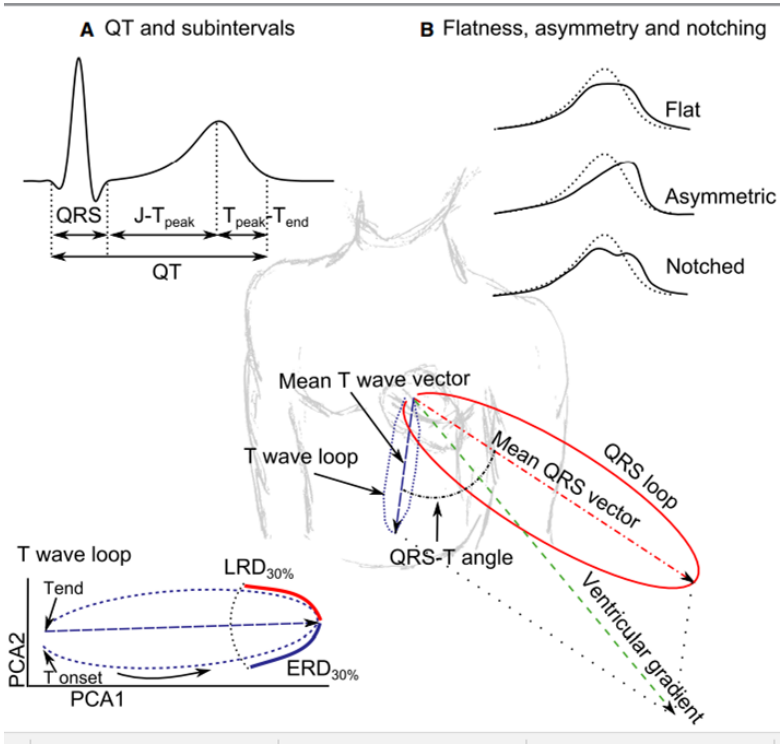
- Develop continuous monitoring:
  - wearable/subcutaneous?
  - wireless transmission
- Accurate, reproducible QT-RR patient specific correction
  - automated
- “Beyond QT”
  - T-wave analysis, automated
- Continuous Alarm thresholds - better define
- “Protective” meds for those at risk?

Future - Predictors of Risk - Beyond the QTc

Animal models:
TdP correlates with **temporal instability of the action potential** more tightly than it does with prolongation of the QT interval

Kannankeril and Roden. Pharmacol Rev, 62 (2010);760–781.

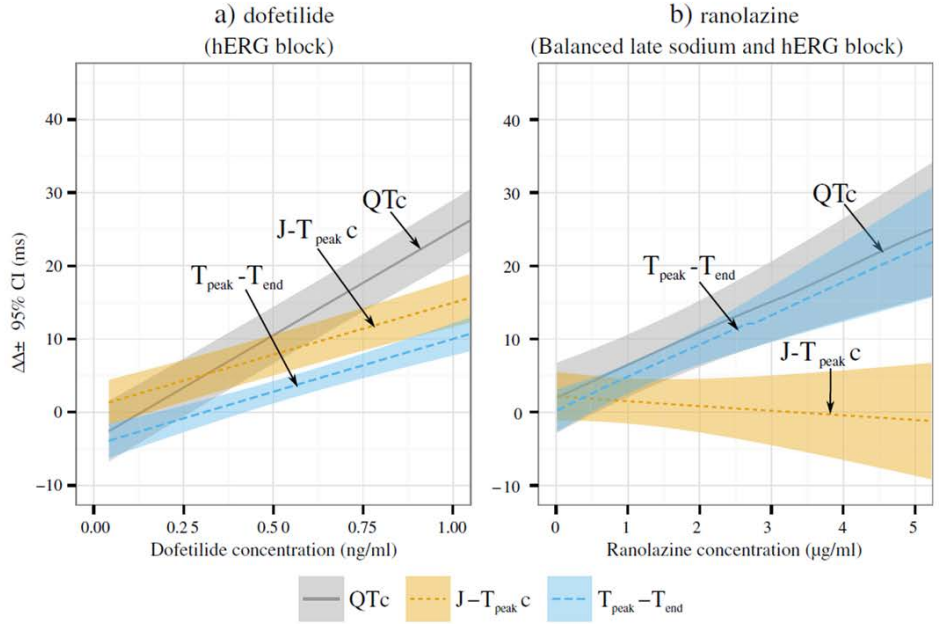
Future - Predictors of Risk - Beyond the QTc



TdP risk via… "combined approach of assessing multiple ion channels, subintervals of the QT (eg, J-Tpeak and Tpeak-Tend) and T wave morphology"

Kannankeril and Roden. Pharmacol Rev, 62 (2010);760–781. Vincente J. et al. J Am Heart Assoc. 2015;4: e001615.

Future - follow J-Tpeak and Tpeak-Tend?



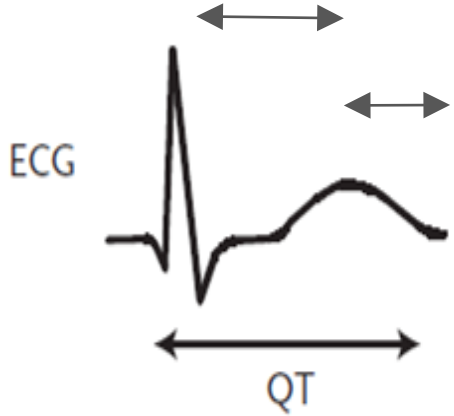
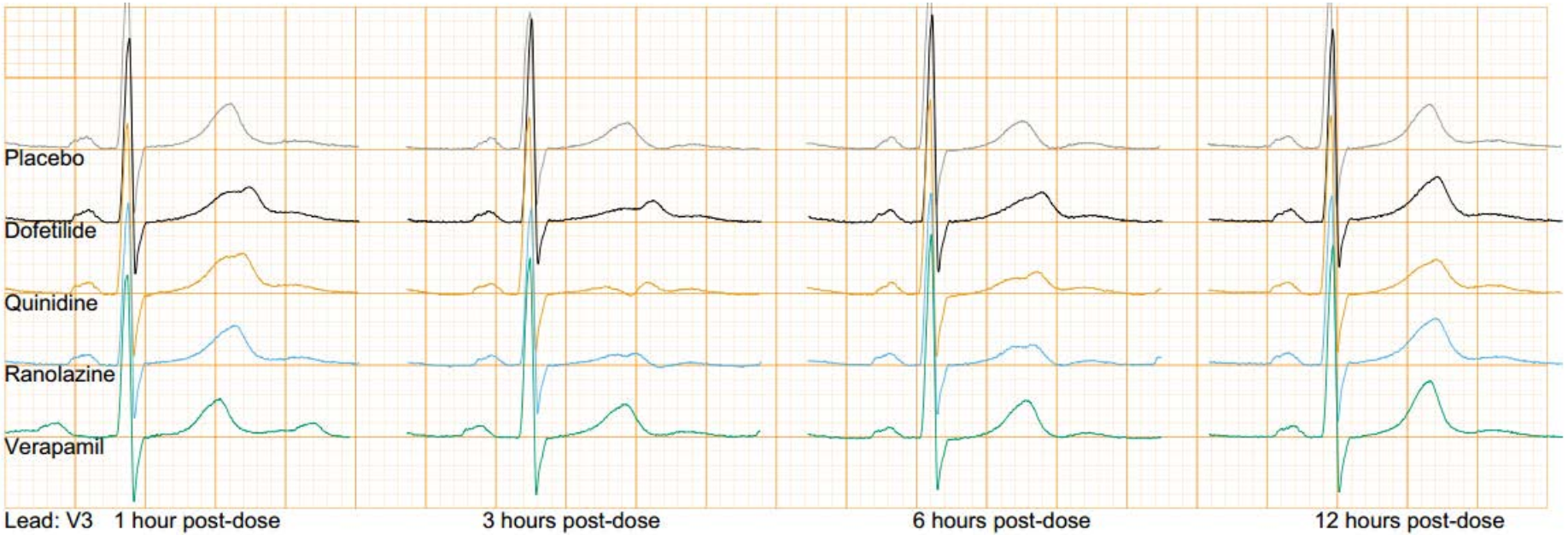


Fig. 3. ECG signatures of selective hERG potassium channel block (dofetilide, left) and balanced late sodium and hERG block (ranolazine, right) in exposure response models for QTc, J–T_{peak}c and T_{peak}–T_{end}. Selective hERG block prolongs QTc by prolonging both J–T_{peak}c and T_{peak}–T_{end}, while balanced multichannel block prolongs QTc by prolonging T_{peak}–T_{end} with no effect on J–T_{peak}c. Adapted from Johannesen et al. [25].

Vicente J. et al. J. Electro (2016); 49:837-842.

Future - ECG Predictors of Risk - T-wave morphology



Vincente J. et al. J Am Heart Assoc. 2015;4: e001615.

END