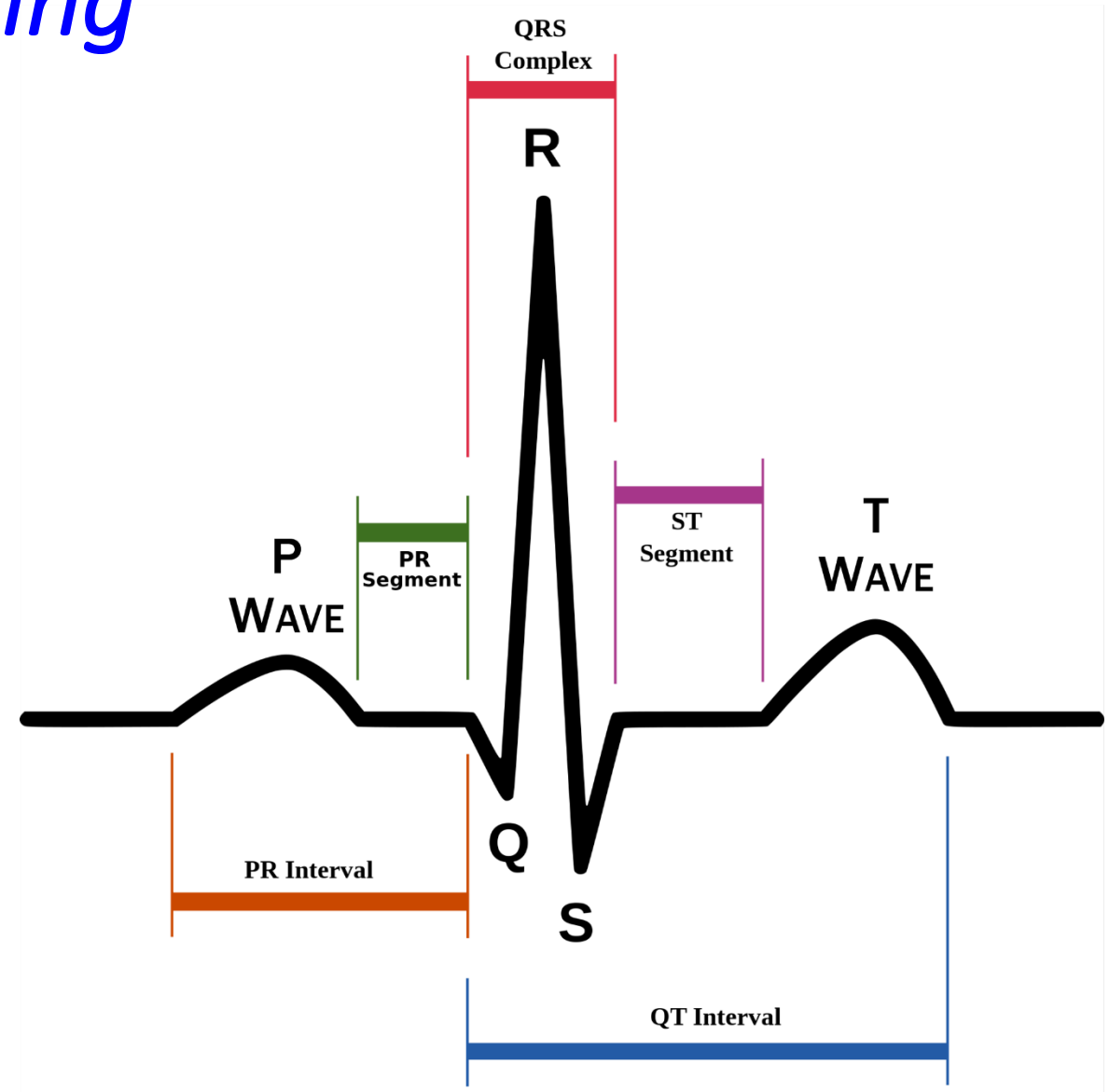
The QT Interval– Safety Endpoint for DR-TB trials

Kelly Dooley & Gary Maartens

(Disclaimer: I know very little cardiac electrophysiology)

The ECG tracing

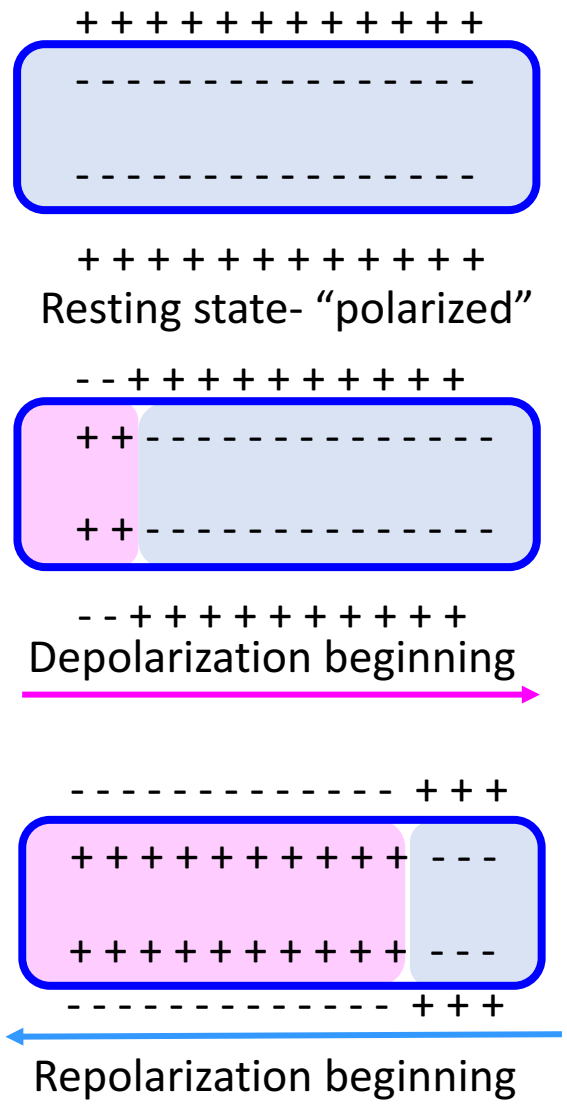


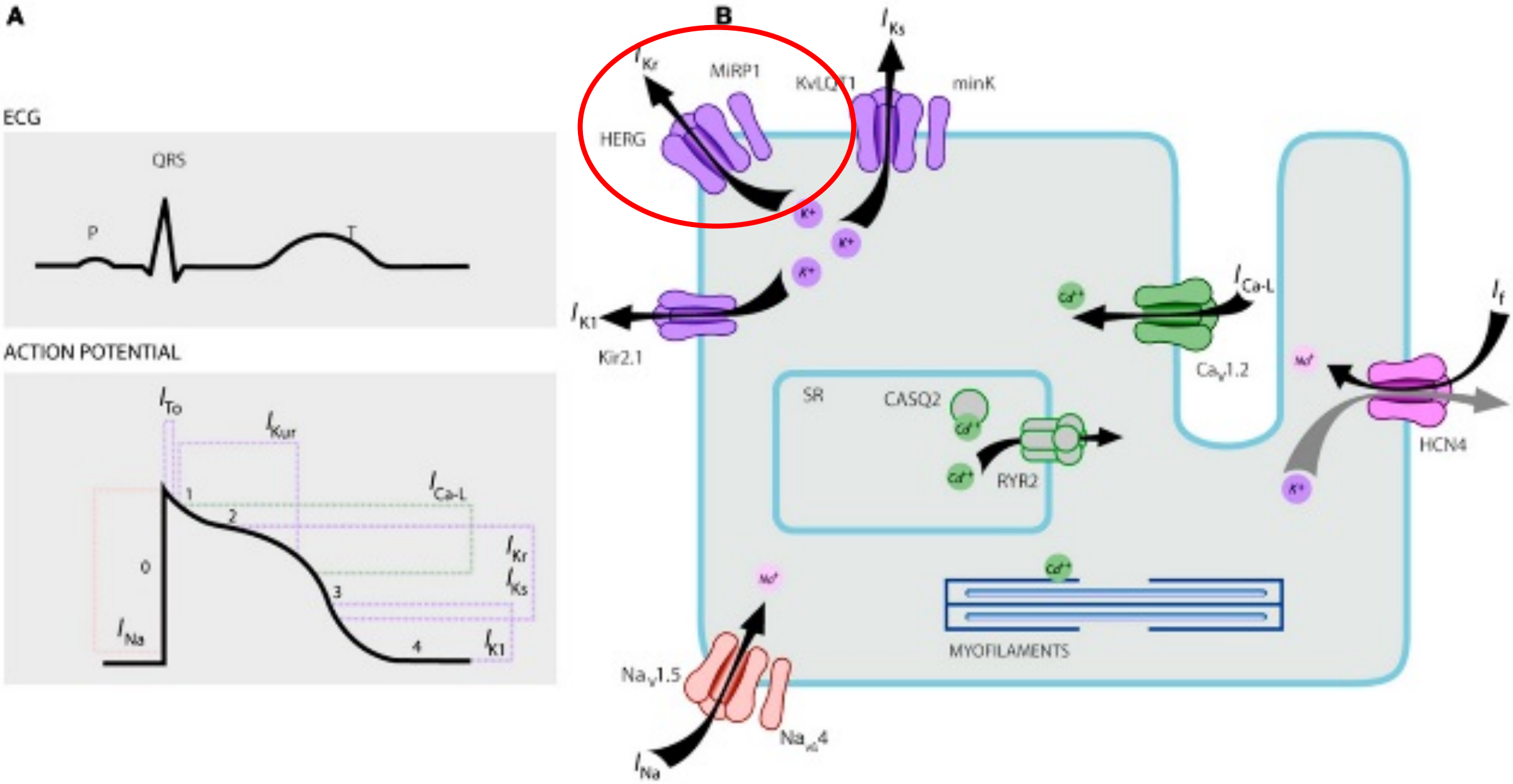
Physiology of a cardiac myocyte

Flow of ions (Na^+, Ca^{2+}, K^+) across the cell membrane constitutes a flow of electricity

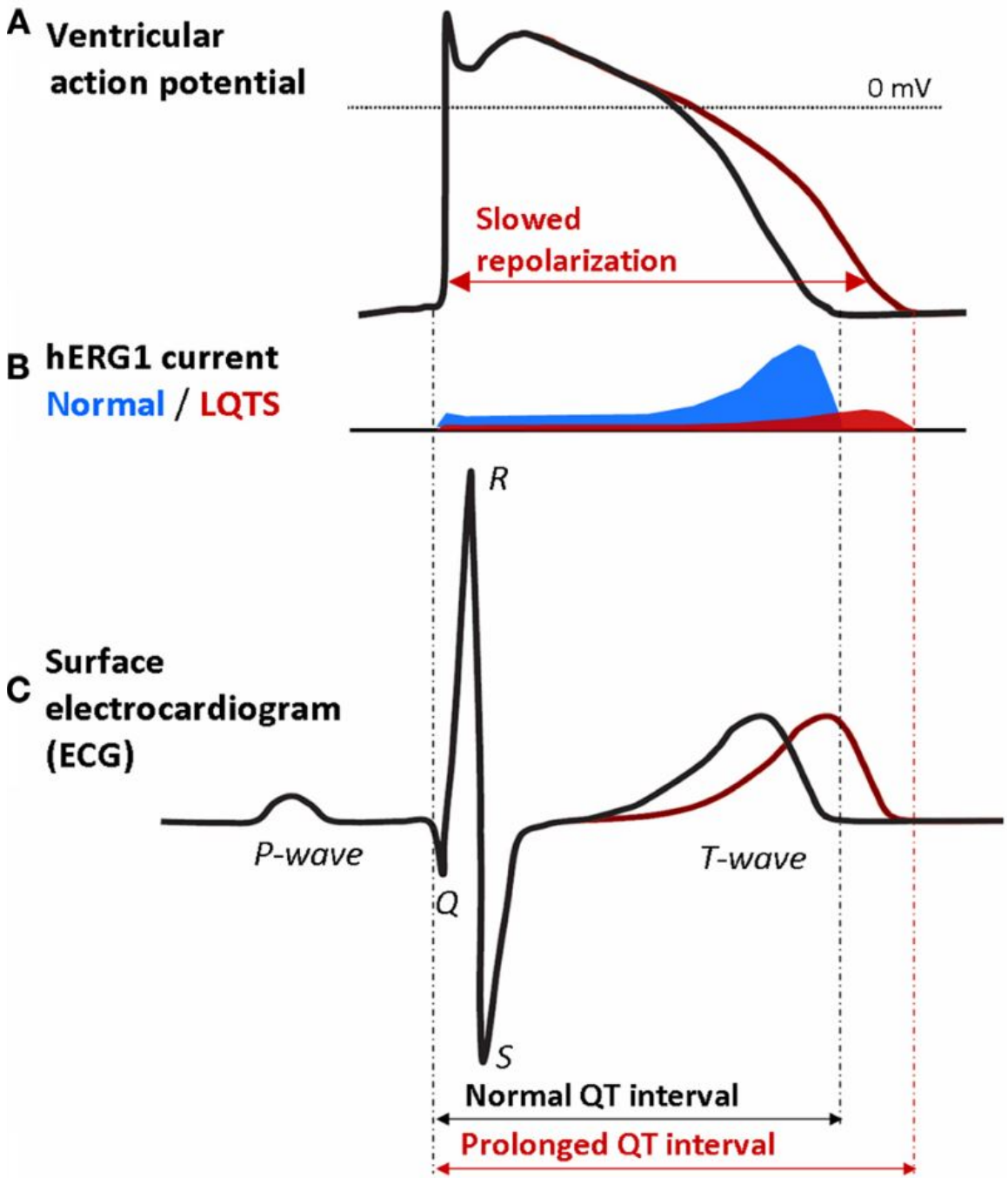
- Resting state: Inside of cell membrane negatively charged, outside of cell membrane positively charged
- Depolarization: Inside of cell membrane becomes positively charged relative to outside of cell membrane
- Repolarization: Return to resting state
- Excitability: electrical impulse starts at one end of cardiac cell, rapidly propagates to the other end
- Conductivity: cardiac cell transfers impulse to neighboring cell

The QT interval represents Ventricular depolarization and repolarization



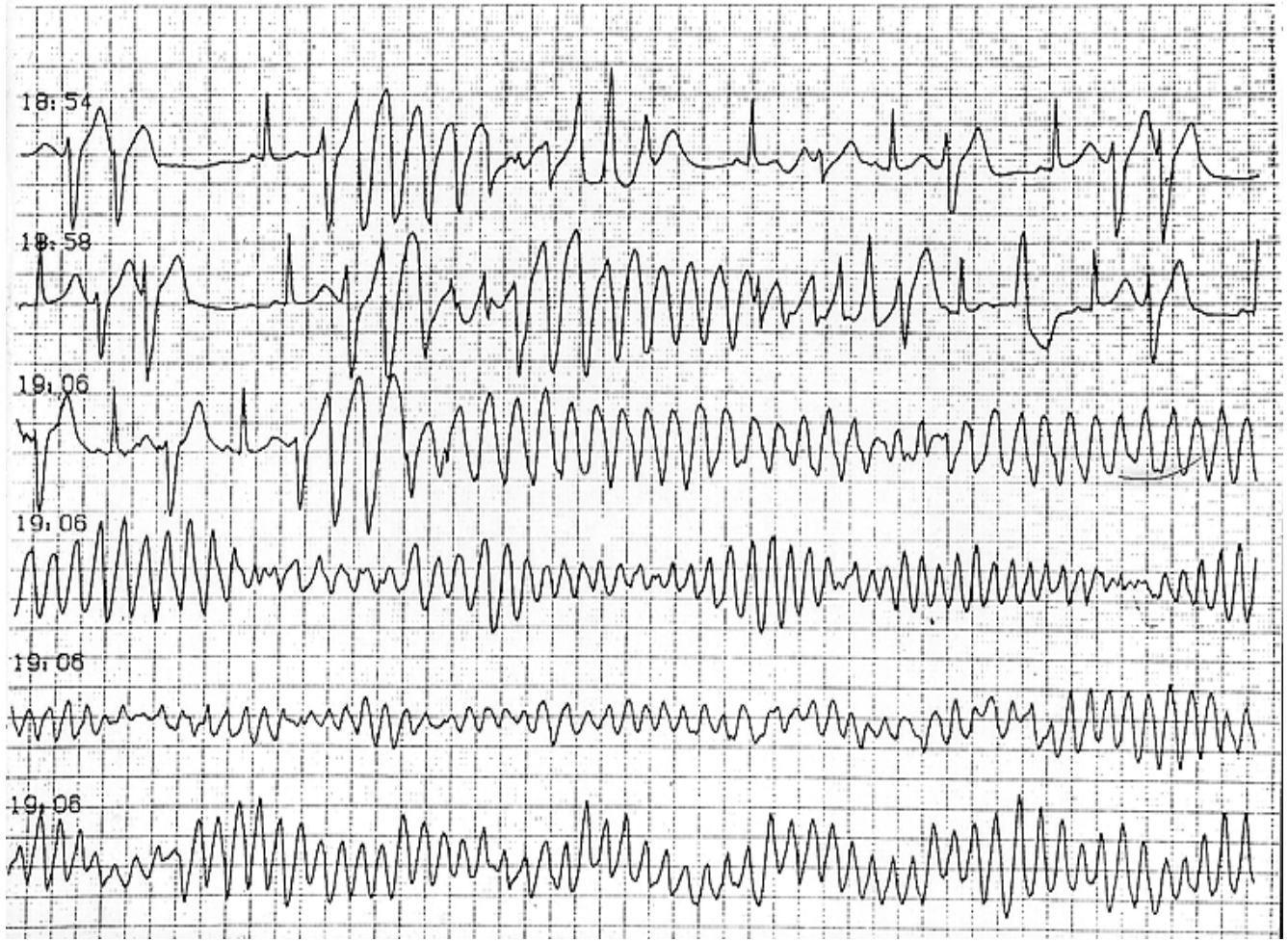


http://www.frontiersin.org/files/Articles/72177/fped-01-00039-HTML/image_m/fped-01-00039-g001.jpg



http://journal.frontiersin.org/article/10.3389/fphar.2010.00137/full

Why care about the QT interval?



Torsades de Pointes:

“twisting of the spikes”

Life-threatening

Things that prolong the QT interval

- Electrolyte Abnormalities especially **Magnesium and Potassium (often reduced by aminoglycosides)**
- Bradycardia/ Sino Atrial Blocks
- Myocardial Ischemia/Infarction
- Congestive Heart Failure, Hypoxia
- Central nervous system disorders
- Endocrinopathy: **Hypothyroidism (often caused by ethionamide/PAS)**
- Congenital Long QT Syndrome
- **Drugs**

QT as a surrogate for risk of torsades

QT prolongation is a poor surrogate for torsades, but **all drugs that produce torsades prolong QT**

Torsades is rare

- Terfenadine – incidence of torsade 1/50,000
  - *Unacceptable for a medicine for hay fever*
- Quinidine – incidence of torsade 1-2%

Drug-induced Torsades

Susceptible host (prolonged QT due to cardiac disease, long QT, etc)

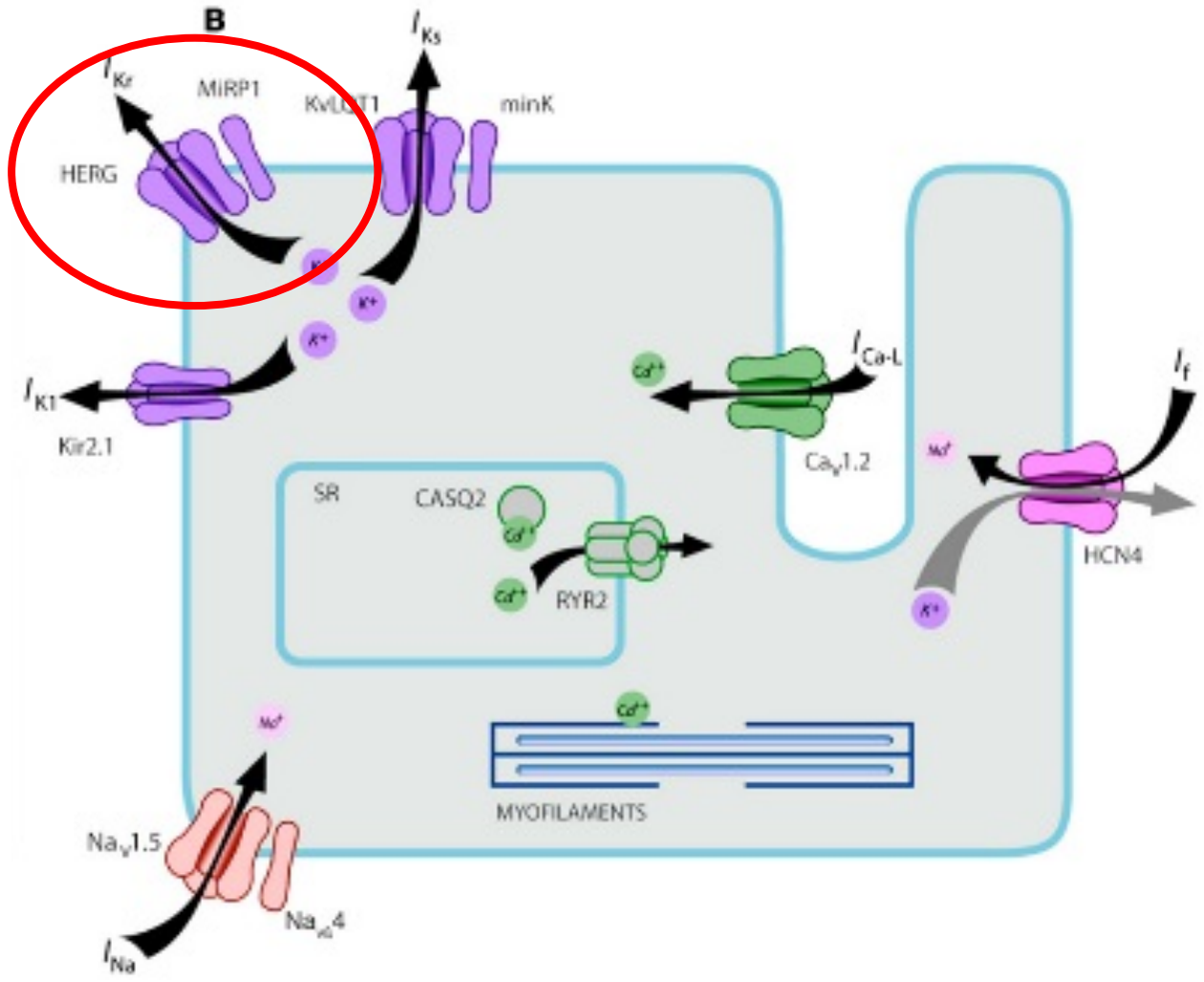
Multiple QT-prolonging drugs e.g.:

- Bedaquiline
- Clofazimine
- Delamanid
- Moxifloxacin
- Efavirenz

QT-prolonging drug with drug that inhibits its metabolism

How do drugs prolong the QT interval?

- Direct blocking of I_{kr} channel (HERG)
- Indirectly, by effects on surface expression of the ion channel
- May affect trafficking of other ion channels
- 40% of direct hERG blockers also have effects on hERG trafficking



Pre-clinical QT Safety Studies

Screens:

- In vivo HERG studies
- Animal models

How relevant are pre-clinical QT studies?

- Effects in vitro may not be seen in vivo & vice versa
- Metabolites may vary significantly between animals and humans (e.g. metabolites of bedaquiline & delamanid drive QT effects)
- Animal models don’t reliably predict human effects

Typical paces drug is put through to assess cardiac risk

Clinical: ICH E14 TET (Thorough ECG Trial)

- All new drugs with systemic bioavailability should have a thorough QTc/QT trial performed irrespective of preclinical profile
- The trial needs to define a ***5 ms effect with a one sided 95% CI that excludes a 10 ms effect using time matched methods***

The exception: Drugs that cannot be given to healthy subjects

Design:

- Normal healthy subjects
- Typically 4 arms: placebo, therapeutic dose, supratherapeutic dose, active comparator (moxifloxacin)
- Can be cross-over or parallel design, depending on drug characteristics

Thorough QT study - soon to be replaced?

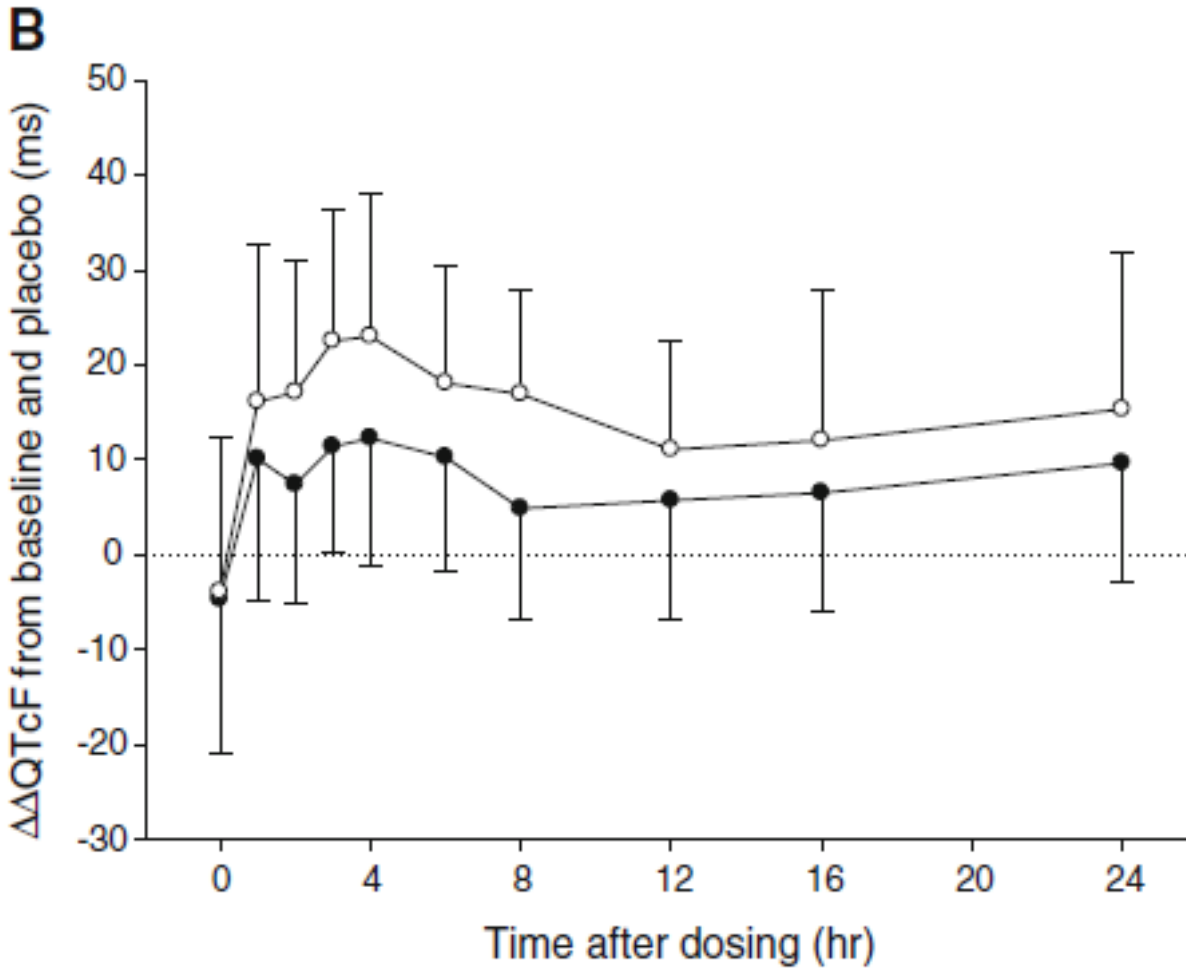
Results From the IQ-CSRC Prospective Study Support Replacement of the Thorough QT Study by QT Assessment in the Early Clinical Phase

B Darpo[1,2*], C Benson[3†], C Dota[4*], G Ferber[5], C Garnett[6*], CL Green[7], V Jarugula[8†], L Johannesen[9], J Keirns[10†], K Krudys[11], J Liu[11], C Ortemann-Renon[12*], S Riley[13], N Sarapa[14†], B Smith[2], RR Stoltz[15], M Zhou[2] and N Stockbridge[16]

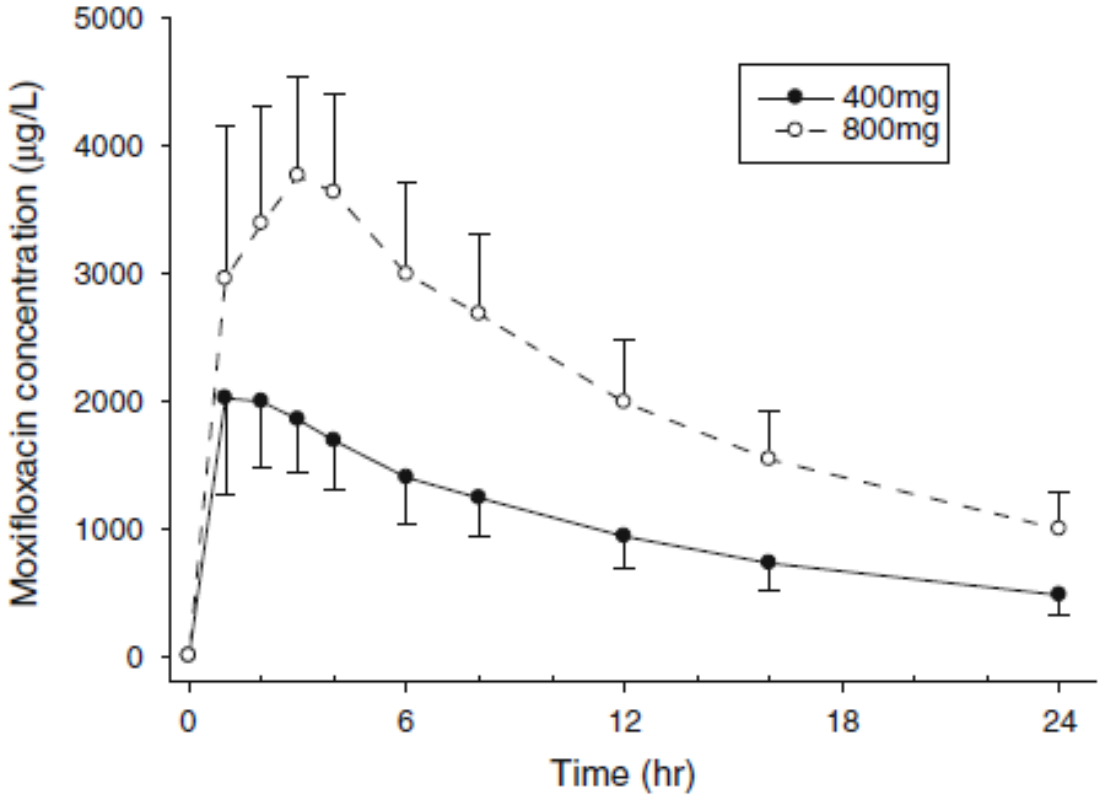
The QT effects of five "QT-positive" and one negative drug were tested to evaluate whether exposure–response analysis can detect QT effects in a small study with healthy subjects. Each drug was given to nine subjects (six for placebo) in two dose levels; positive drugs were chosen to cause 10 to 12 ms and 15 to 20 ms QTcF prolongation. The slope of the concentration/ΔQTc effect was significantly positive for ondansetron, quinine, dolasetron, moxifloxacin, and dofetilide. For the lower dose, an effect above 10 ms could not be excluded, i.e., the upper bound of the confidence interval for the predicted mean ΔΔQTcF effect was above 10 ms. For the negative drug, levocetirizine, a ΔΔQTcF effect above 10 ms was excluded at 6-fold the therapeutic dose. The study provides evidence that robust QT assessment in early-phase clinical studies can replace the thorough QT study.

Cardiac Safety Research Consortium (CSRC) study, CPT 97: 326

QT study mirrors PK: 400 vs 800 mg Moxifloxacin



Baseline- and placebo-controlled changes in QTcF with MOX 400 mg (•) and MOX 800 mg (o)



Plasma concentrations of MOX when given at a dose of 400 mg (•) and 800 mg (o)

Moon *et al.* Drugs RD (2014) 14: 63

What magnitude of QTc prolongation is dangerous?

E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

"In clinical trials, a prolongation of QTc > 500 ms during therapy has been a threshold of particular concern."

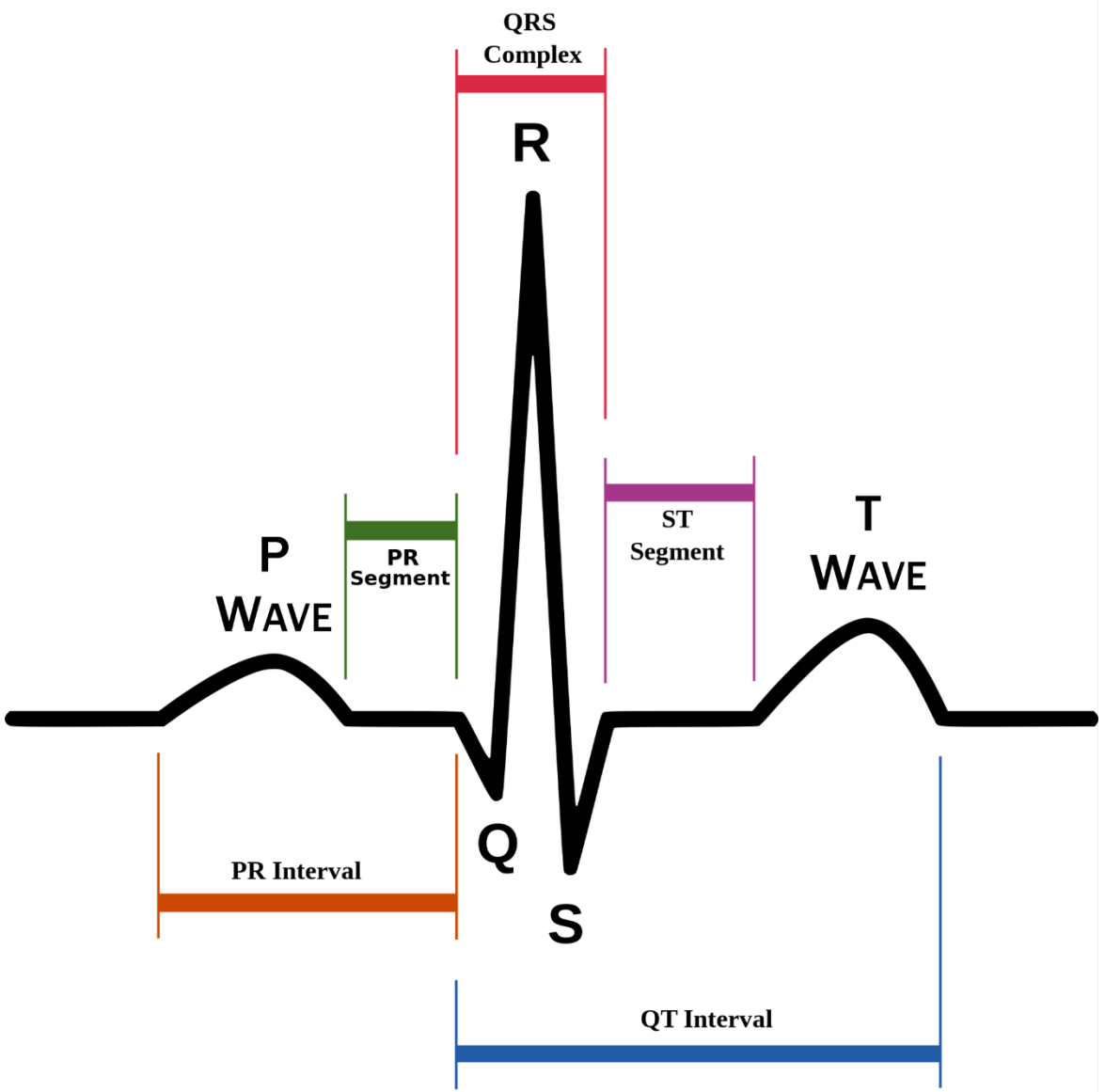
Measuring the QT

Machine vs. manual measurement

- Artefact, end of T wave

Correction factors

- As heart rate increases, QT must shorten to allow for next beat
- Fridericia's correction (QTcF):
  - $QTcF = QT/\sqrt[3]{RR}$
  - Note RR= 60/heart rate
- Bazett's correction (QTcB) not recommended:
  - QTcB overcorrects at high heart rates→ false impression of a large QTc increase



http://a-fib.com/wp-content/uploads/2012/08/Schematic-diagram-of-normal-sinus-rhythm-for-a-human-heart-as-seen-on-ECG-Wikipedia-free-to-use.png

Central reading is essential

Inaccurate electrocardiographic interpretation of long QT: The majority of physicians cannot recognize a long QT when they see one

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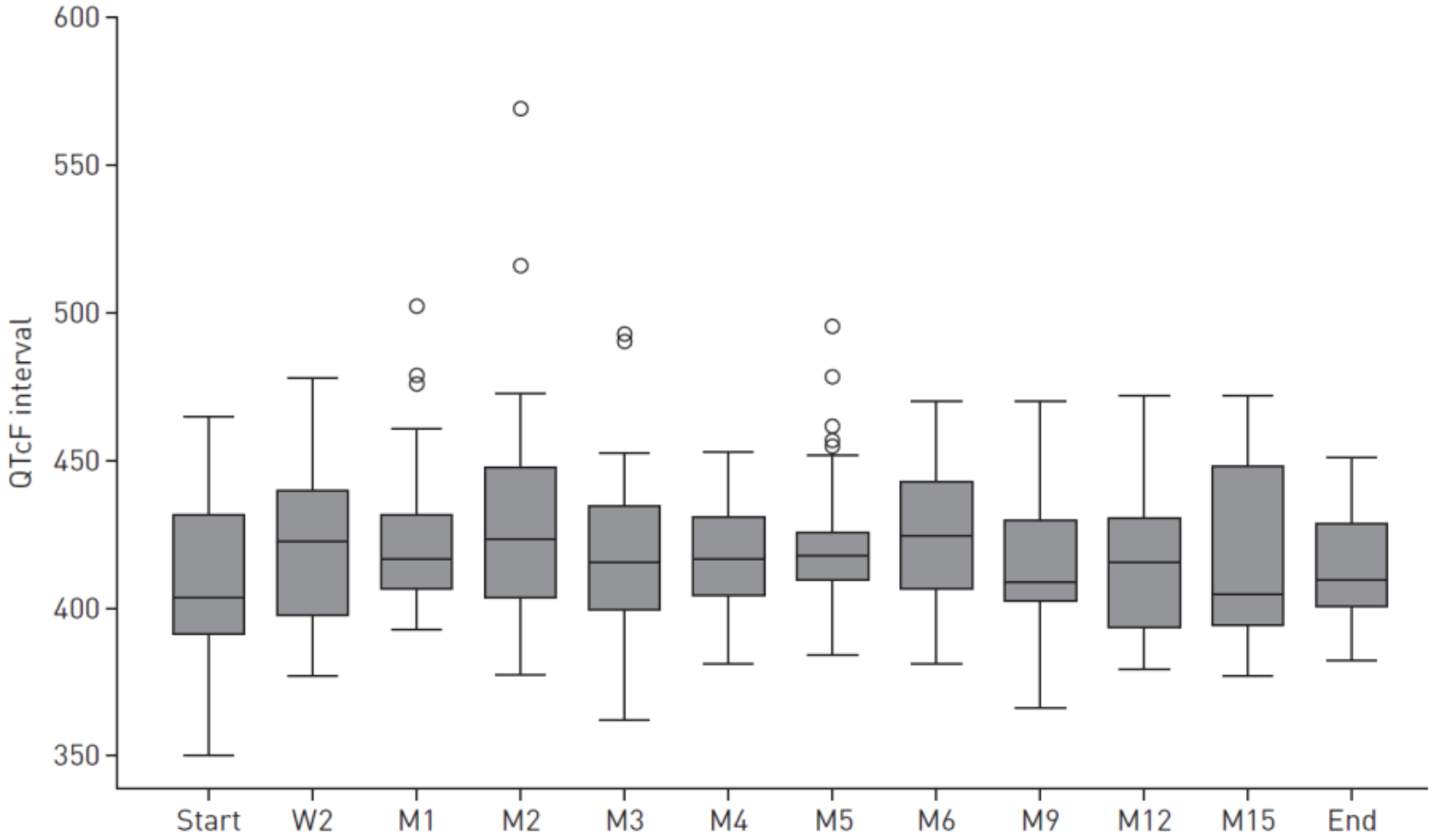
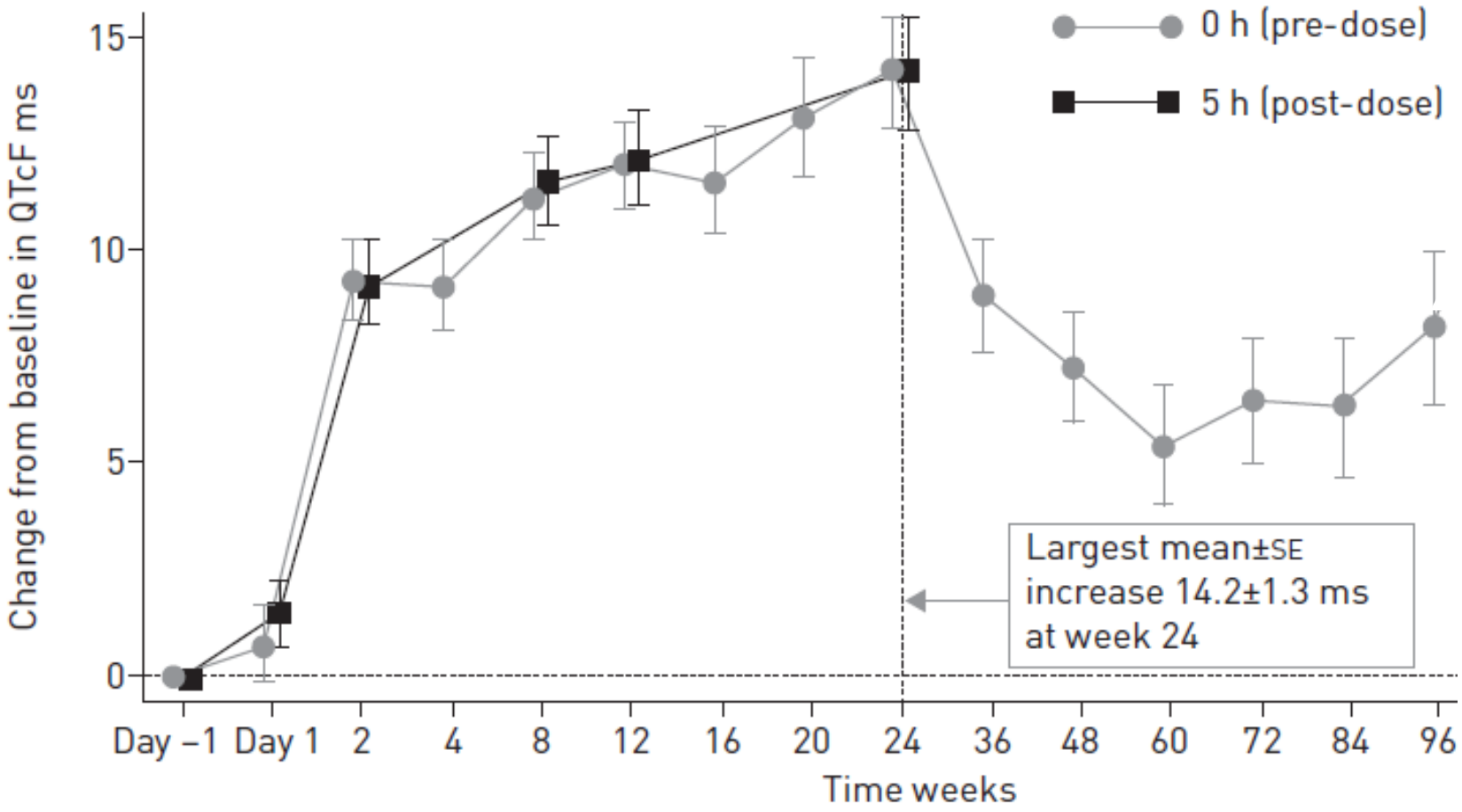
Heart Rhythm Vol. 2 June 2005

Prolonged BDQ, QTc change over time: observational n=43; 11 QTcF >500 ms



Eur Respir J 2017; 49: 1601799

BDQ QTc change over time RCT, central read



N=228

Eur Resp J 2016;47:564

QT variability

- Normal QTc: ≤450 in men, ≤470 in women
- QTc variation in an individual is *expected* (up to 75 ms during 24 hours)
- Difficult to tell if changes in QTc are drug related or are due to usual QTc variation with time

Get replicate ECGs!

- **Sources of variability**
  - Sex (Females have longer QTs)
  - Age (QT increases with age)
  - Heart rate
  - Position
  - Autonomic tone
  - Meals
  - Menstrual cycle
  - Time of day
  - Illness
  - Technical Issues

Practical points for QT study design

- ECGs done in triplicate, resting, 5-10 minutes apart
- Ideally do ECGs at similar time of day, approximating Tmax
- Sites must read ECGs & react to their interpretation of grade 3/4 QTc prolongation, but central reads recorded for database – training of site clinicians important
- SOP for grade 3/4 QTc should include measuring K & Mg, with aggressive replacement if low
- List of RELEVANT QT prolonging concomitant meds (CredibleMeds.org)

COMBINED LIST OF DRUGS THAT PROLONG QT AND/OR CAUSE TORSADES DE POINTES (TDP)

CredibleMeds® has reviewed available evidence for the drugs on the following list and place them in one of three designated categories: Known Risk of TdP (KR), Possible Risk of TdP (PR) or have a Conditional Risk of TdP (CR). The full description of these categories can be found on the CredibleMeds.org website.

Generic Name	Brand Name
Alfuzosin (PR)	Uroxatral
Amantadine (CR)	Symmetrel and others
Amiodarone (KR)	Cordarone and others
Amisulpride (CR)	Solian and others
Amitriptyline (CR)	Elavil (Discontinued 6/13) and others

Generic Name	Brand Name
Citalopram (KR)	Celexa and others
Clarithromycin (KR)	Biaxin and others
Clomipramine (PR)	Anafranil
Clozapine (PR)	Clozaril and others
Cocaine (KR)	Cocaine
Crizotinib (PR)	Xalkori

Generic Name	Brand Name
Flecainide (KR)	Tambocor and others
Fluconazole (KR)	Diflucan and others
Fluoxetine (CR)	Prozac and others
Flupentixol (PR)	Depixol and others
Fluvoxamine (CR)	Faverin and others
Foscarnet (PR)	Foscavir

https://www.crediblemeds.org/