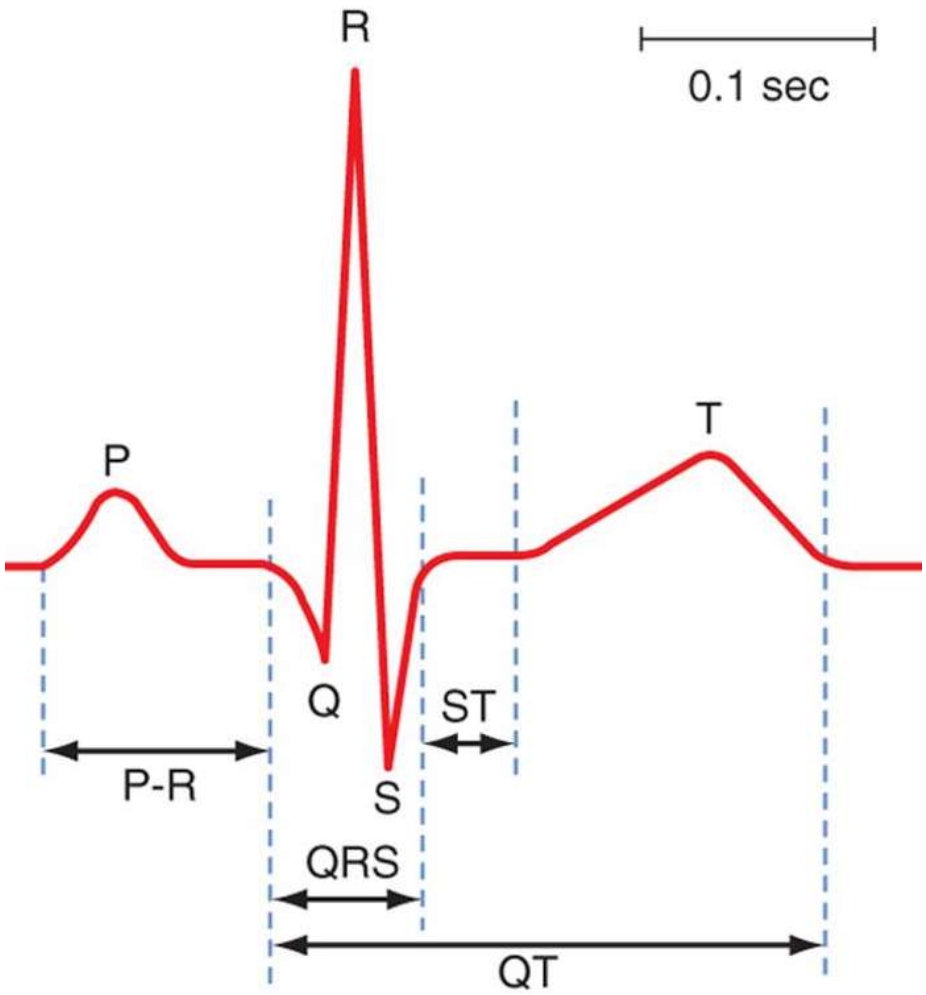
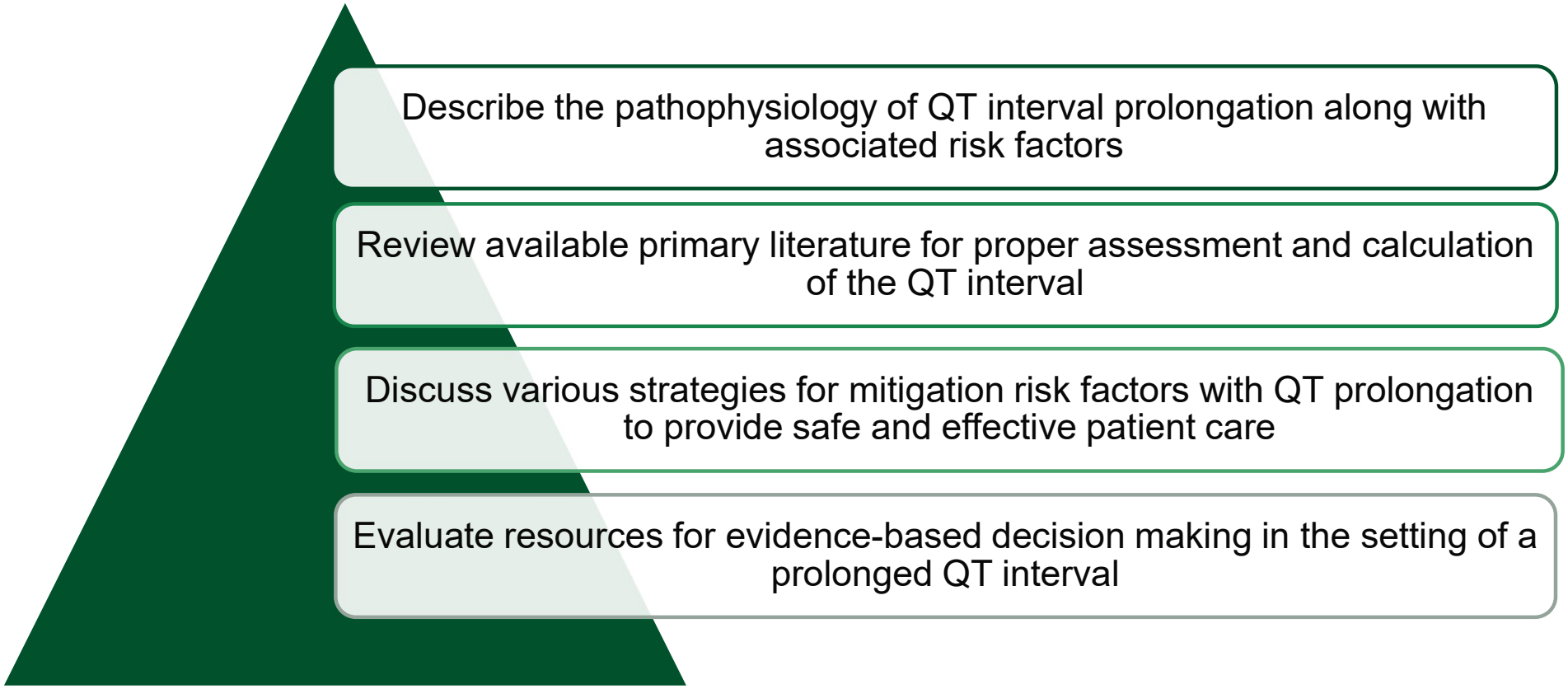
Take it to Heart with the QT: A Prolonged Understanding of QTc Management

Sally Falahat, PharmD, MPH, BCPS
Internal Medicine Clinical Specialist
Clinical Assistant Professor
UIC Retzky College of Pharmacy



Conflicts of Interest

Learning Objectives



Patient Case

CF is a 52 y/o male with a PMH of HTN, HLD and T2DM presents to the ED with 1 week history of SOB, nausea/vomiting, and fevers. Findings from the CXR reveal a possible community acquired pneumonia. Medical provider opts to start patient on azithromycin, ceftriaxone, and IV ondansetron PRN.

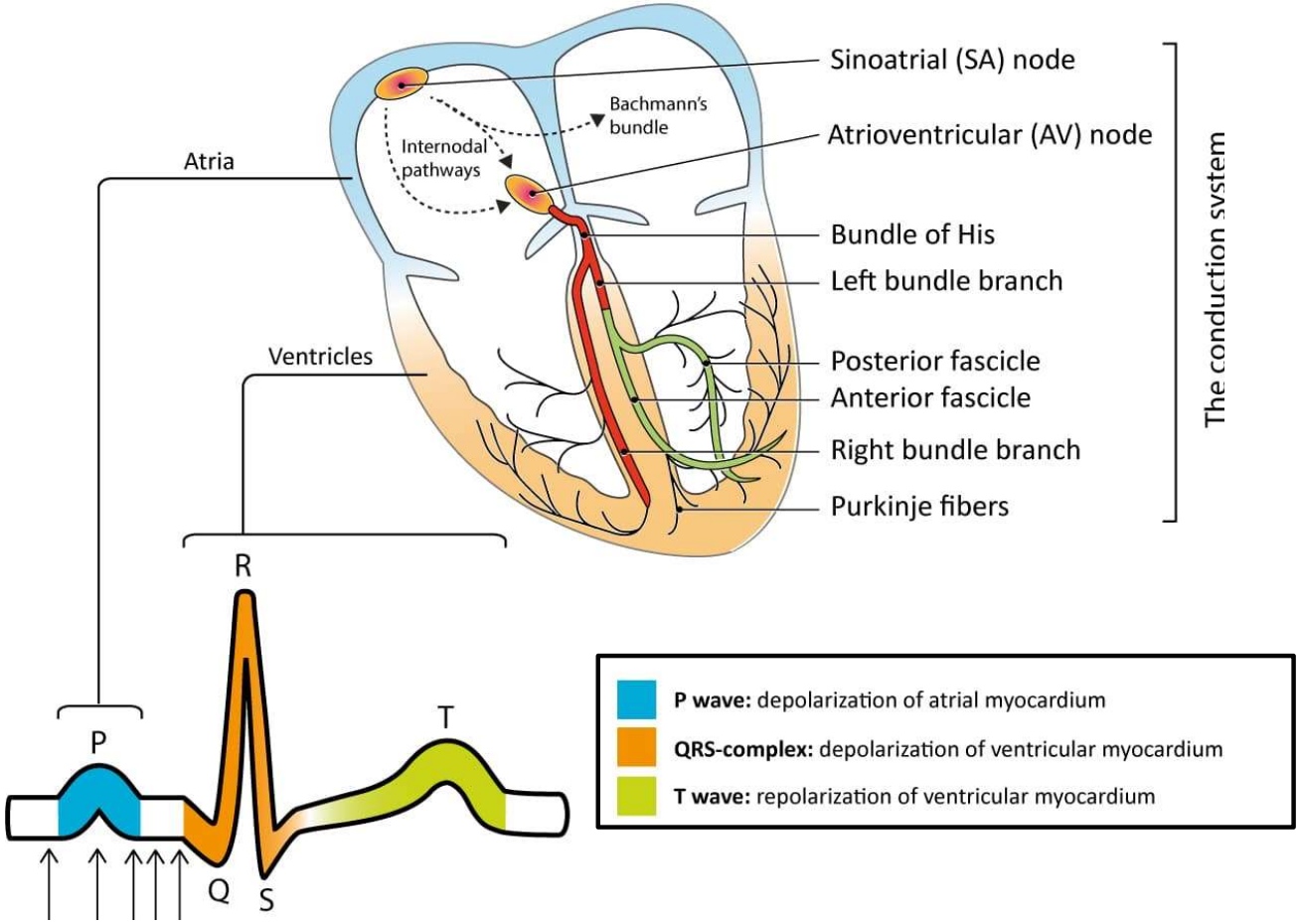
	Drug-Drug: **Azithromycin** and **Ondansetron** The concurrent use of **azithromycin** and other agents that prolong the QT interval may result in potentially life-threatening cardiac arrhythmias, including torsades de pointes

Serum Potassium	3.4 mEq/L
Serum Magnesium	2.0 mg/dL
Serum Calcium	9.2 mg/dL

EKG Findings:

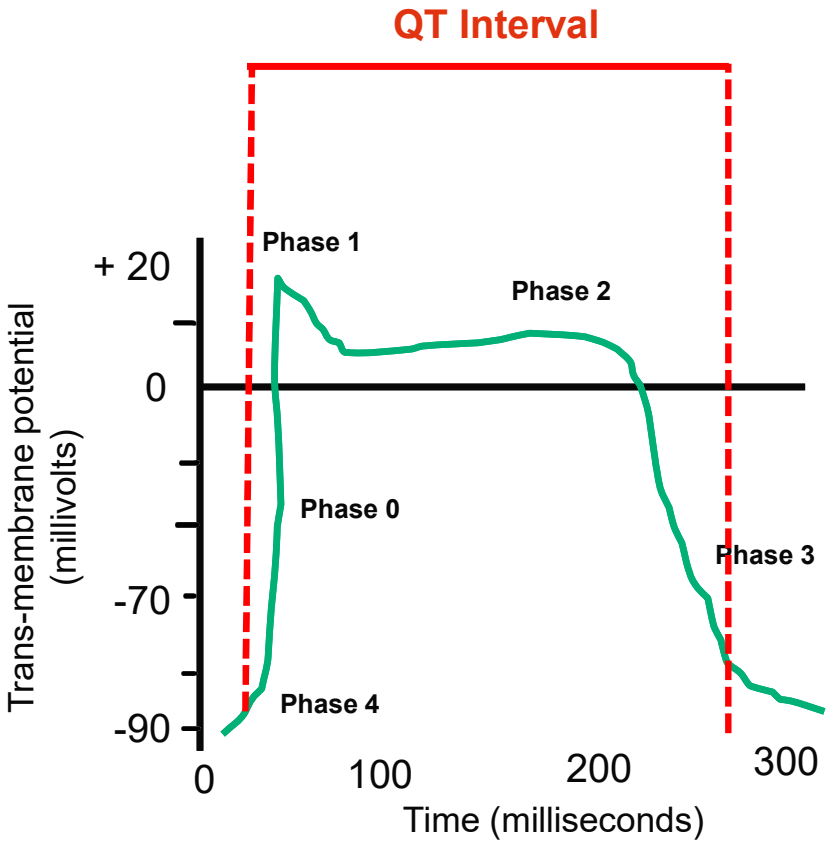
Ventricular Rate	106 BPM
QT Interval	390 msec
QTc	528 msec
QRS	118 msec

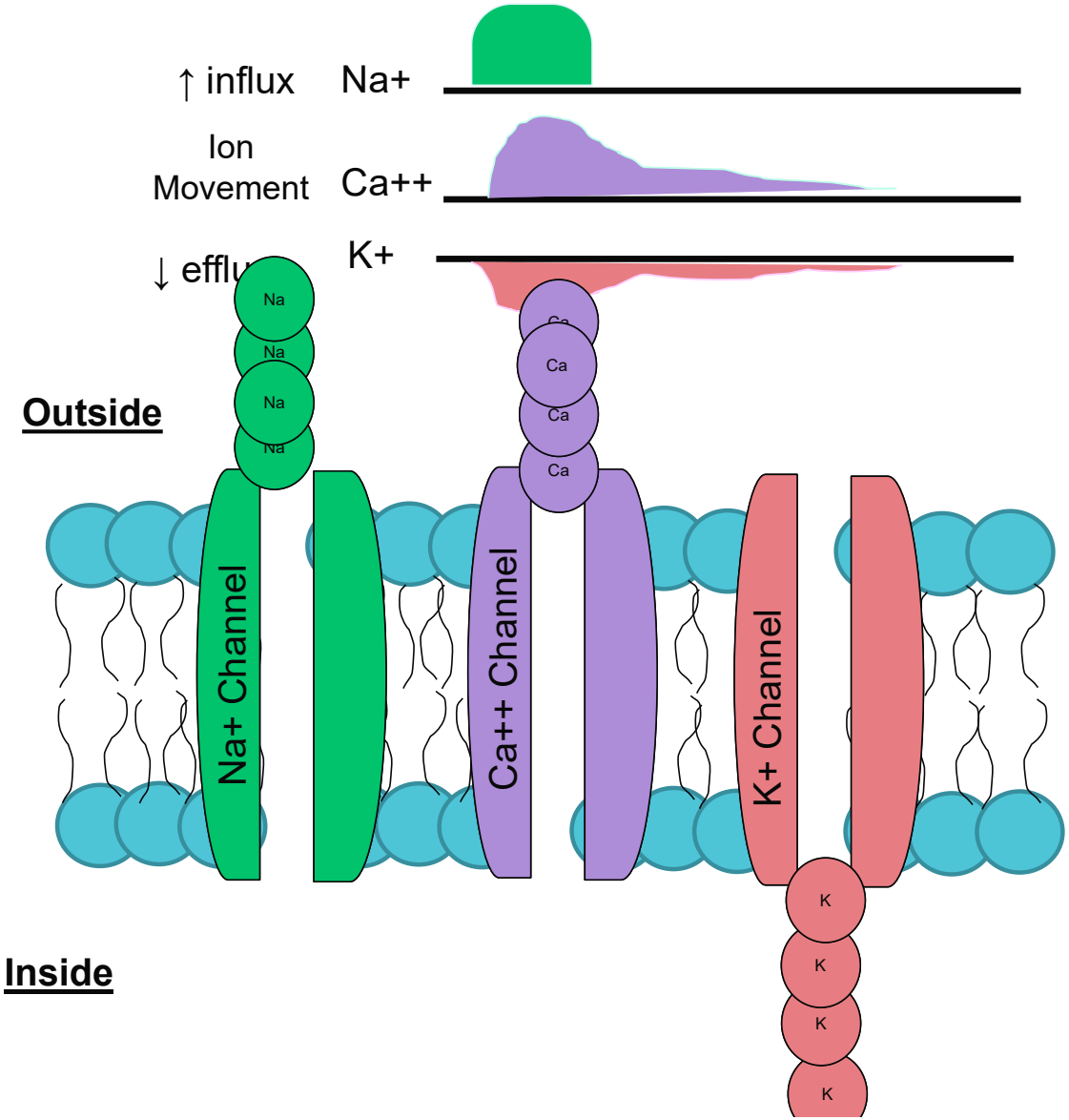
Cardiac Electrophysiology



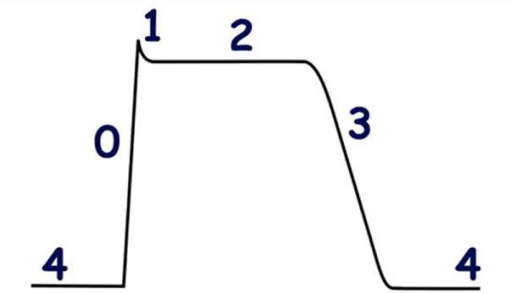
Al-Khatib SM, et al. *JAMA*. 2003;289(16):2120-2127.
Image from: https://ecgwaves.com/topic/introduction-electrocardiography-ecg-book/

Cardiac Electrophysiology

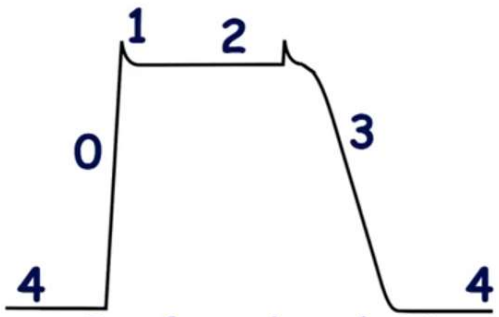




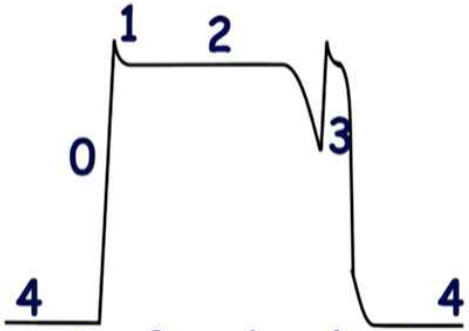
Pathophysiology: Early Afterdepolarizations



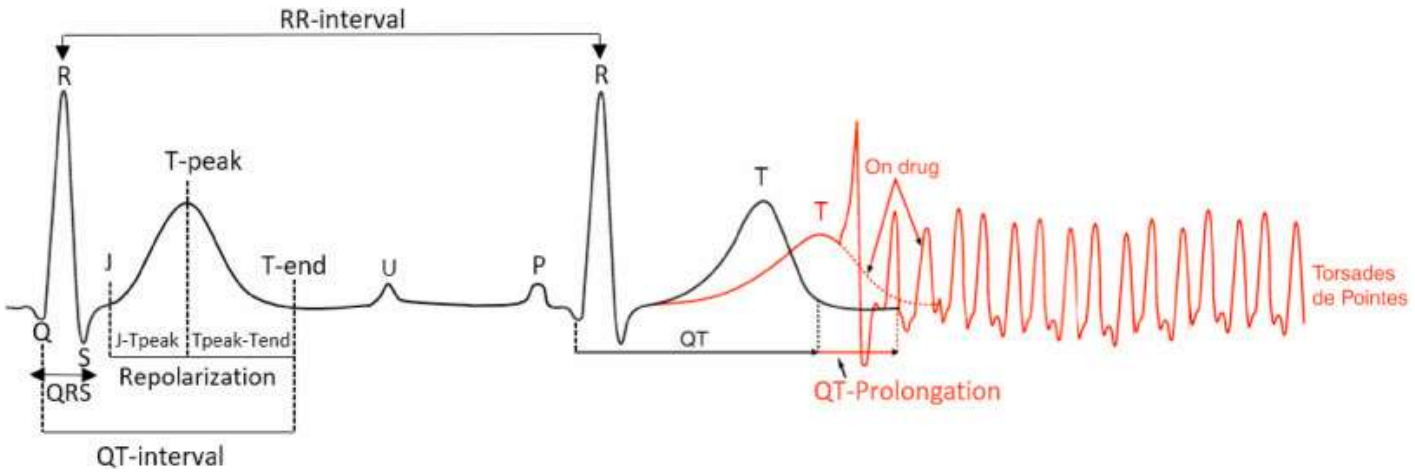
Normal action potential



Phase 2 afterdepolarization



Phase 3 afterdepolarization



Incidence of TdP

Torsades de Pointes (TdP) Incidence	
General Population	Estimated 2.5-4.5 per million per year, but may vary between populations
Intensive/Progressive Care	0.07% of all patients over two-month period 6% of cardiac arrests over two-month period
>90% of patients with TdP have ≥1 identifiable risk factor	

Risk Factors for QTc Prolongation

Cardiac

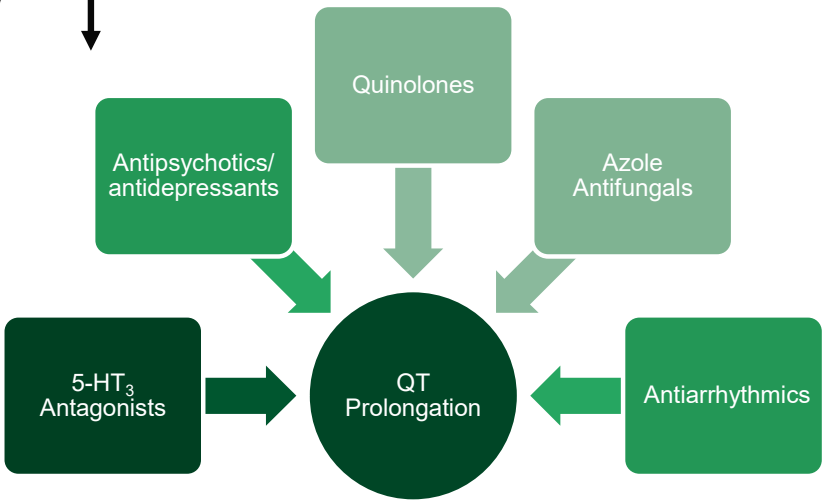
- Congenital Long QT syndrome
- History of QTc prolongation
- Bradycardia
- Ischemic heart disease
- Myocarditis
- Left ventricular hypertrophy
- Low ejection fraction

Medical Conditions

- State of shock
- Acute infection
- Systemic illness
- Starvation
- Anorexia nervosa
- Renal disease

Medication Related

- Drug toxicity
- Drug interactions
- Rapid IV infusion of QTc prolonging medications
- CYP polymorphism affect on drug metabolism



Metabolic

- Hypokalemia
- Hypomagnesemia
- Hypocalcemia

Others

- Female sex
- People of extreme age (children and elderly)

Al-Khatib SM, et al. *JAMA*. 2003;289(16):2120-2127.

QTc Common Cutoffs

Established Cutoffs for QTc Prolongation

QTc Risk Interpretation	Adult Men (msec)	Adult Women (msec)
Normal	≤ 430	≤ 450
Borderline	431-450	451-470
Prolonged	> 450	> 470

Absolute QTc Prolongation
≥500 msec

Change from Baseline QTc Prolongation
≥60 msec

Does not apply to patients with ventricular conduction abnormalities (i.e bundle branch blocks and ventricular pacing)

Rautaharju PM, et al. *Circulation*. 2009 Mar 17;119(10):e241-50.
Tisdale JE, et al.. *Circulation*. 2020;142(15):e214-e233.

Established Cutoffs

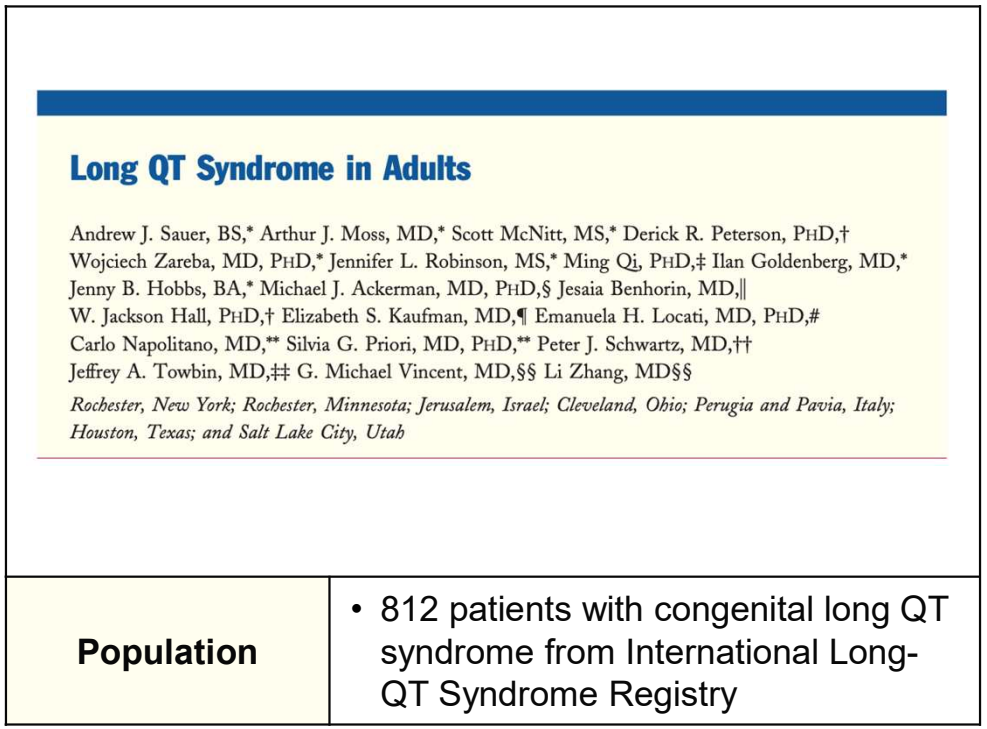
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk Stratification in the Long-QT Syndrome

Silvia G. Priori, M.D., Ph.D., Peter J. Schwartz, M.D., Carlo Napolitano, M.D., Ph.D., Raffaella Bloise, M.D., Elena Ronchetti, Ph.D., Massimiliano Grillo, M.D., Alessandro Vicentini, M.D., Carla Spazzolini, M.V., Janni Nastoli, B.S., Georgia Bottelli, B.S., Roberta Folli, B.S., and Donata Cappelletti, B.S.

Population	• Congenital long QT syndrome in 647 patients from Italy (most were families)



Long QT Syndrome in Adults

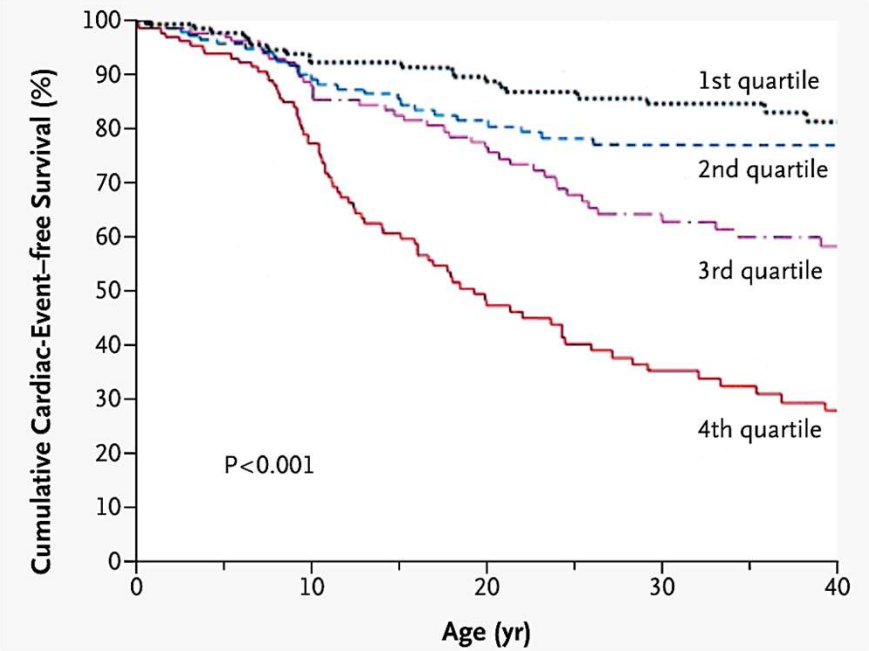
Andrew J. Sauer, BS,* Arthur J. Moss, MD,* Scott McNitt, MS,* Derick R. Peterson, PHD,† Wojciech Zareba, MD, PHD,* Jennifer L. Robinson, MS,* Ming Qi, PHD,‡ Ilan Goldenberg, MD,* Jenny B. Hobbs, BA,* Michael J. Ackerman, MD, PHD,§ Jesaia Benhorin, MD,‖ W. Jackson Hall, PHD,† Elizabeth S. Kaufman, MD,¶ Emanuela H. Locati, MD, PHD,# Carlo Napolitano, MD,** Silvia G. Priori, MD, PHD,** Peter J. Schwartz, MD,†† Jeffrey A. Towbin, MD,‡‡ G. Michael Vincent, MD,§§ Li Zhang, MD§§

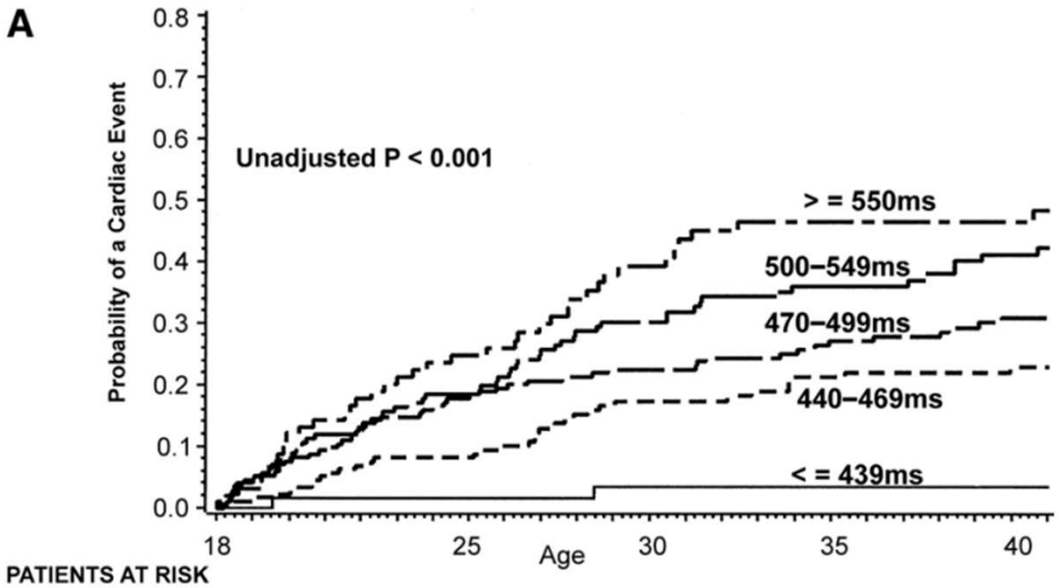
Rochester, New York; Rochester, Minnesota; Jerusalem, Israel; Cleveland, Ohio; Perugia and Pavia, Italy; Houston, Texas; and Salt Lake City, Utah

Population	• 812 patients with congenital long QT syndrome from International Long-QT Syndrome Registry

Priori SG, et al. *N Engl J Med*. 2003;348(19):1866-1874.
Sauer AJ, et al. *JACC*. 2007;49(3):329-337.

Established Cutoffs Cont'd

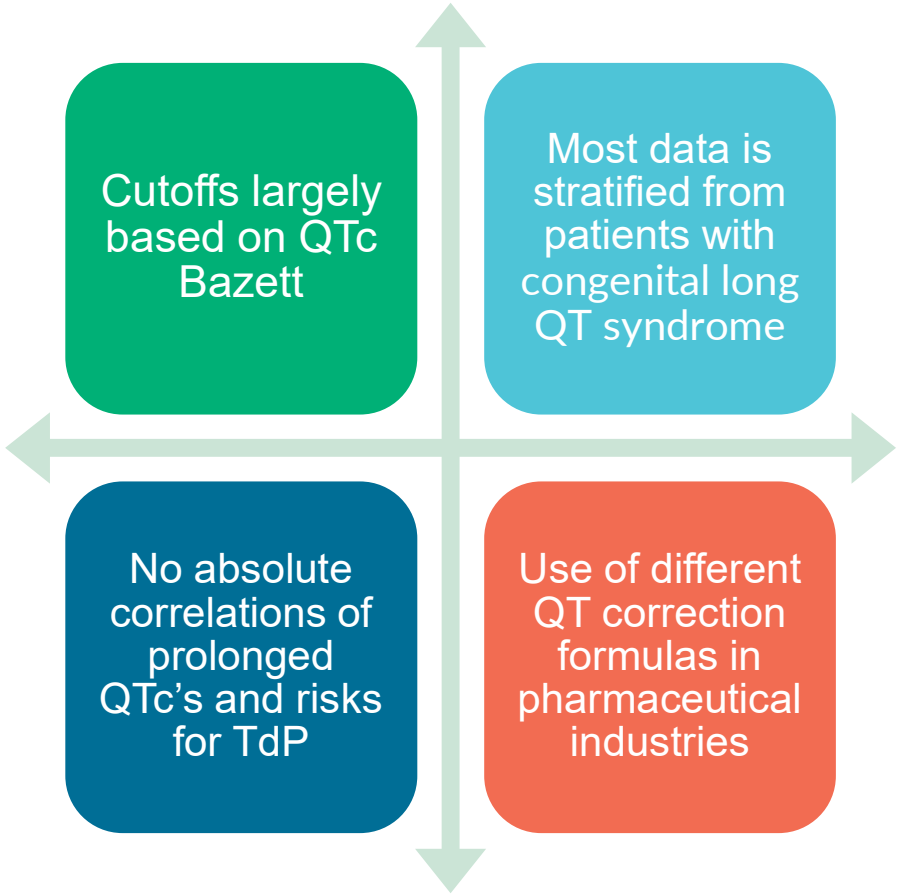




A QTc > 500 msec, using Bazett's formula, was associated with a 2-3x fold higher risk for LQTS-related events in patients with congenital LQTS

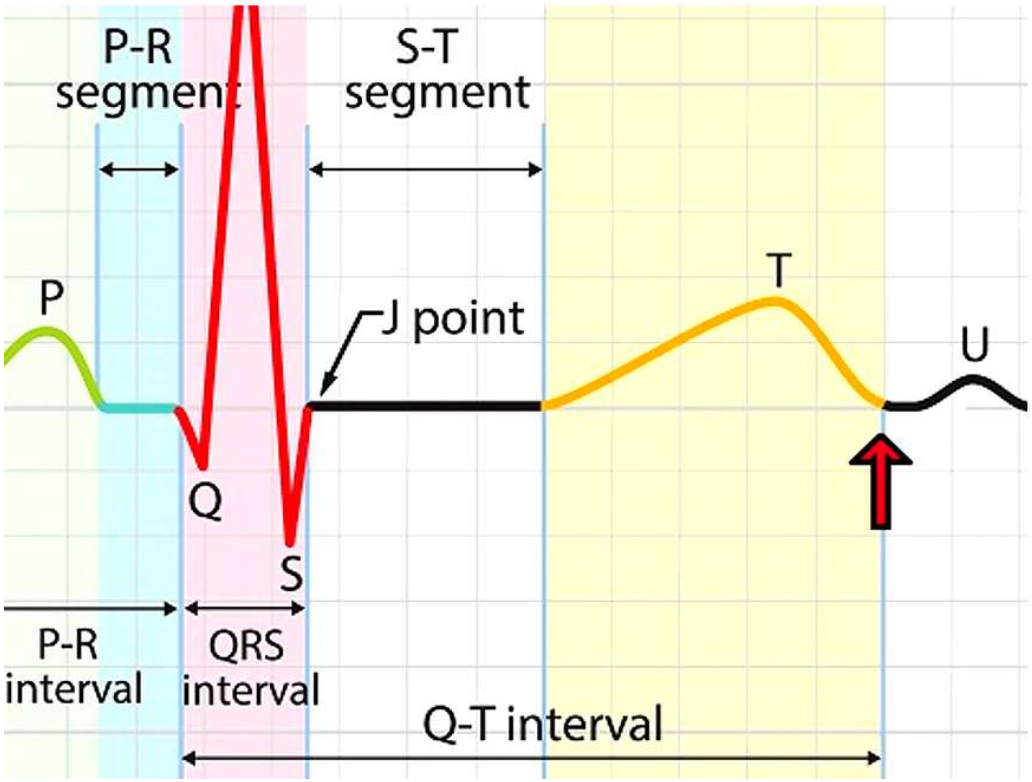
Priori SG, et al. *N Engl J Med*. 2003;348(19):1866-1874.
Sauer AJ, et al. *JACC*. 2007;49(3):329-337.

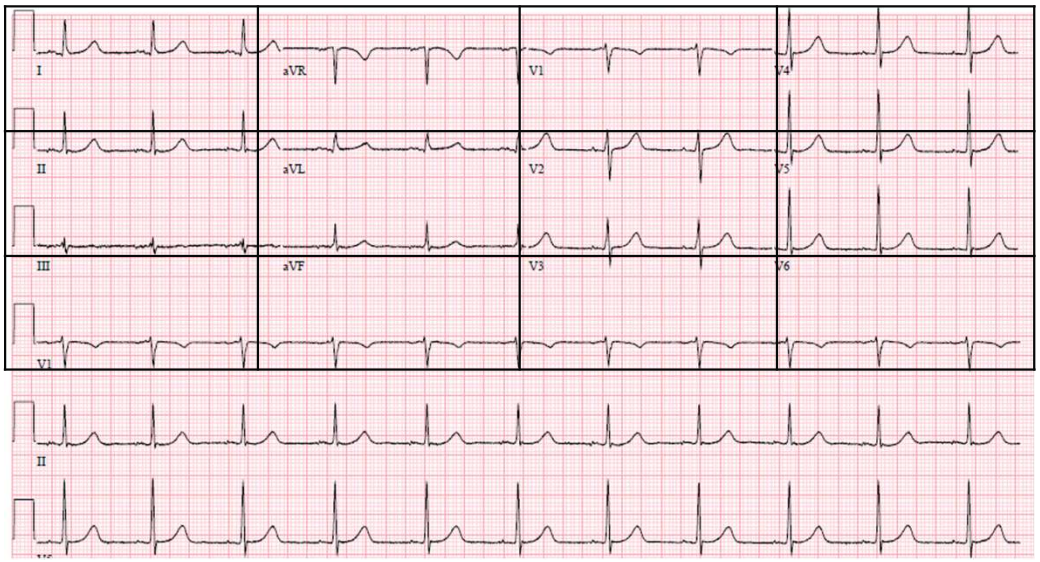
Downfall of Cutoff Selection



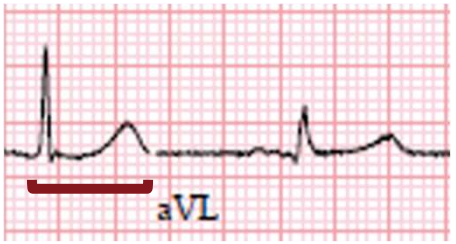
Appropriate Measurement of a QT Interval

Manual QT Interval Measurement





1 small box: 0.04 sec
1 big box: 0.2 sec



10 Small Boxes = 2 Large Boxes = 400 msec

Automated QT Interval Measurement

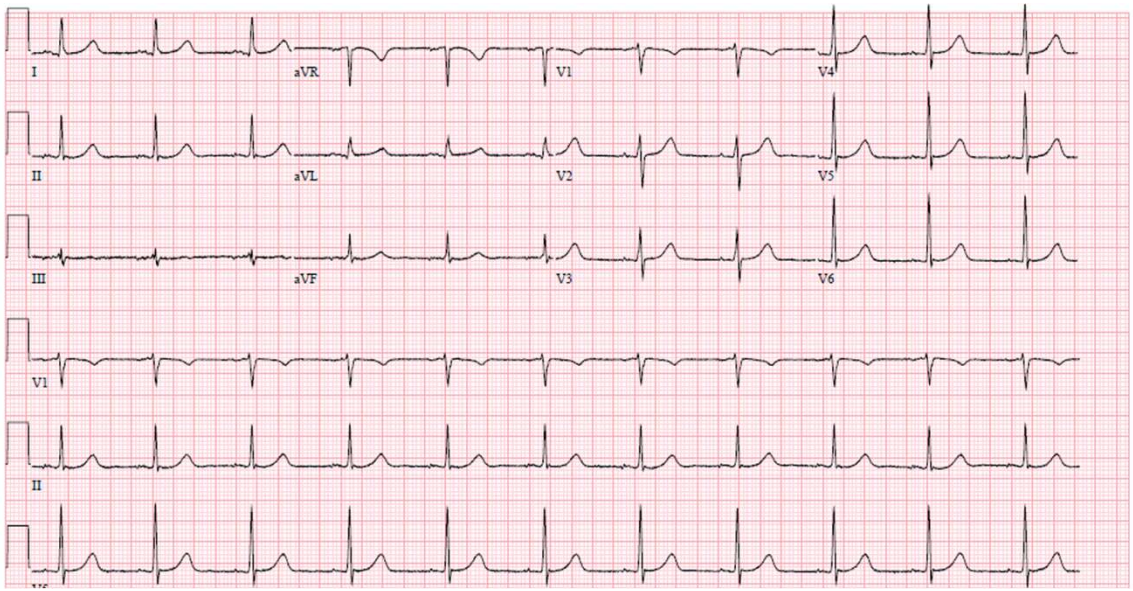
Automated calculations are less reliable in the setting of true QT prolongation and arrhythmias

Studies have shown automated algorithms to be unreliable ~50% of the time when assessing for QT prolongation

Vent. rate	65	BPM
PR interval	144	ms
QRS duration	82	ms
QT/QTc	440/457	ms
P-R-T axes	-8 32	26

Sinus rhythm
Normal ECG

Vent. rate has decreased BY 77 BPM
QRS duration has decreased



Garg A, et al. *Circ Arrhythm Electrophysiol*. 2013 Feb;6(1):76-83.
Noel ZR, et al. *Ann Pharmacother*. 2021 Jan;55(1):123-126

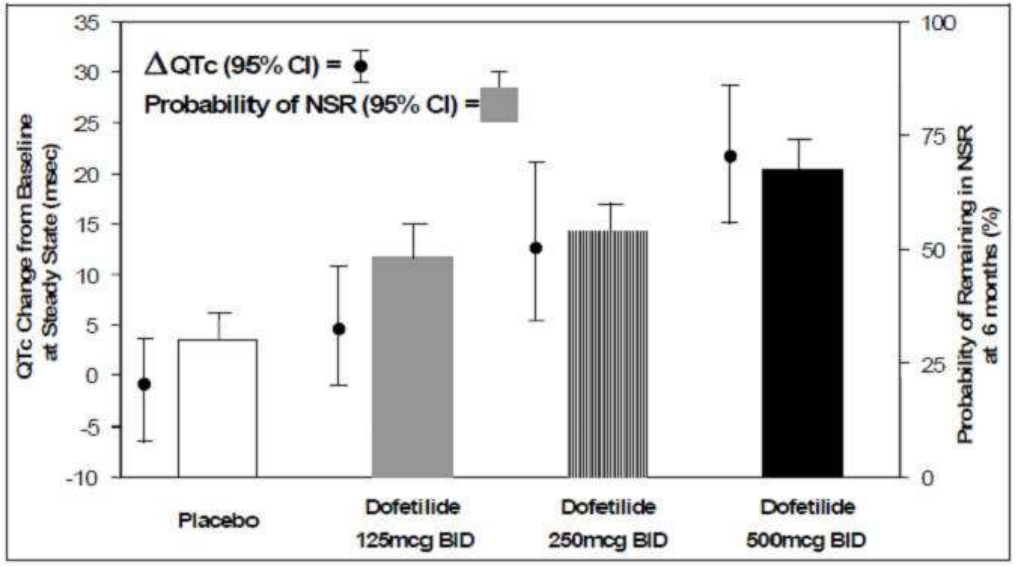
Guideline Recommendations for Best Practices in QT Measurement

AHA/ACCF/HRS recommend utilizing an experienced EKG evaluator overread when an automated QT measurement is included

The automated diagnostic statements may be able to expedite the interpretation for the EKG overreader, but should be avoided for clinical decision making

Rautaharju PM, et al. *Circulation*. 2009 Mar 17;119(10):e241-50

Timing of QT Interval Measurement



QT prolongation is generally a concentration-dependent phenomenon

Dofetilide [package insert]. New York, NY. Pfizer, inc. 2014

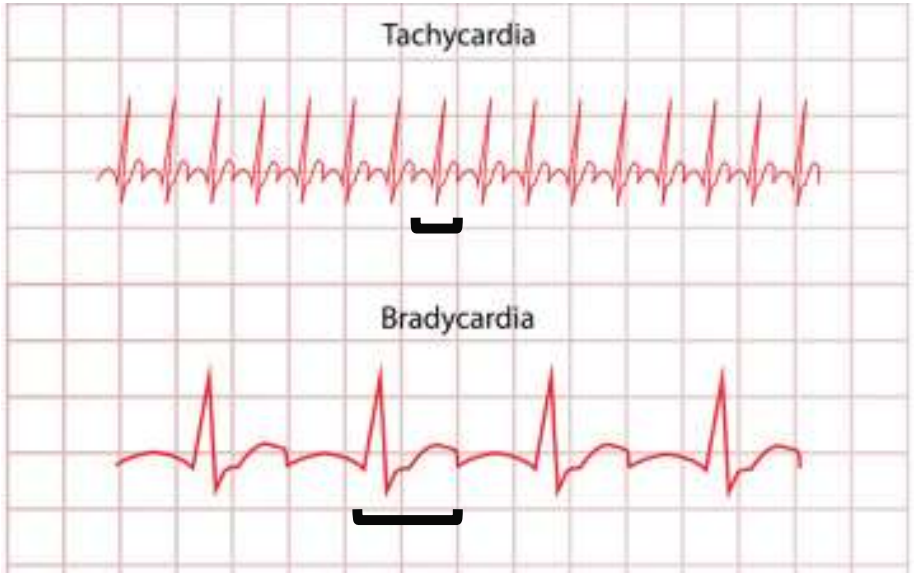
Summary of QTc Measurement

An experienced EKG evaluator overread is crucial for appropriate QTc analysis

Pharmacokinetic profile of medications should be considered for optimal EKG measurement

Appropriate Correction of a QT Interval

QT Interval Correction



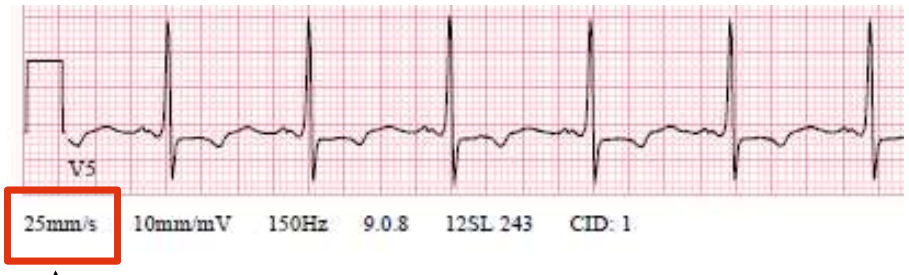
$$\textbf{Heart Rate}(\textbf{BPM}) = \frac{\mathbf{60}}{\textbf{RR Interval}\ (\textbf{sec})}$$

QTc Bazett	$\frac{QT}{\sqrt{RR}}$
QTc Fridericia	$\frac{QT}{\sqrt[3]{RR}}$
QTc Framingham	$QT + 0.154\ (1\ - RR)$
QTc Hodges	$QT + 1.75\ (HR\ - 60)$
QTc Rautaharju	$\frac{QT\ \times\ (120 + HR)}{180}$

MD Calc QTc Calculation

Formula	**Bazett**
	Fridericia
	Framingham
	Hodges
	Rautaharju
Heart rate/pulse	Norm: 60 - 100 beats/min
Paper speed, mm/sec	**25** 50
QT interval Toggle unit to use msec or small boxes; 1 small box = 40 msec (see below for example where QT interval = 4 small boxes)	small boxes ⇆

Vent. rate	77	BPM
PR interval	144	ms
QRS duration	108	ms
QT/QTc	398/450	ms
P-R-T axes	51 8	-51



Paper speed

QTc Variability

Name	Formula	QTC	CF's EKG Findings
QTc Bazett	$\frac{QT}{\sqrt{RR}}$	528	Ventricular Rate 106 BPM QT Interval 390 msec QTc 528 msec
QTc Fridericia	$\frac{QT}{\sqrt[3]{RR}}$	477	
QTc Framingham	$QT + 0.154\ (1\ - RR)$	460	
QTc Hodges	$QT + 1.75\ (HR\ - 60)$	478	
QTc Rautaharju	$\frac{QT\ \times\ (120 + HR)}{180}$	498	

Which formula should be used for QTc calculation?

Primary Literature

Which QT Correction Formula to Use for QT Monitoring?

DESIGN

Retrospective, single-center evaluation of all EKGs taken over a 2-month period at a Belgian hospital
Included 6609 hospitalized patients

QT correction performed using Bazett, Fridericia, Framingham, Hodges, and Rautaharju formulas.

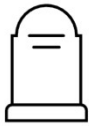
Inclusion

HR<90
QRS < 120

Exclusion

Poor quality EKGs, including missing leads, excessive noise
All but first EKG for each patient excluded

OUTCOMES



Using a multivariate cox regression analysis, Framingham (hazard ratio [HR], 7.31; 95% CI, 4.10–13.05) and Fridericia (HR, 5.95; 95% CI, 3.34–10.60) were found to be better predictors of 30-day all-cause mortality than Bazett (HR, 4.49; 95% CI, 2.31–8.74)

- Cardiac mortality: longer QRS duration = independent predictor of mortality
- Noncardiac mortality: shorter QRS duration= independent predictor of mortality

Bazett overestimated patients with potential dangerous QTc prolongation, even in NSR

LIMITATIONS

EMR review, concomitant medications not assessed, only patients with normal sinus rhythm with a narrow QRS and HR <90 BPM were included

Vandenberk B, et al. *JAHA*. 2016 5(6):e003264

Rautaharju Formula

Formula: $\frac{QT \times (120 + HR)}{180}$

validated in a study with >50,000 patients in 2014

Demonstrated higher sensitivity and specificity for TdP than Bazett formula across broad range of heart rates

Table 2. Selected cut-off point, sensitivity, specificity, and accuracy from each formula.

	Cut-off point (ms)	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	Accuracy (%)
QTcRTH	477	91.30 [86.89–94.61]	87.33 [82.96–90.92]	89.08
QT nomogram	–	91.30 [86.89–94.61]	87.33 [82.96–90.92]	89.08
QTcDMT	475	91.30 [86.89–94.61]	85.96 [81.44–89.73]	88.31
QTcFRD	473	89.13 [84.37–92.84]	88.70 [84.50–92.09]	88.89
QTcBZT	490	88.26 [83.38–92.12]	85.96 [81.44–89.73]	86.97

Othong R, *Clin Toxicol (Phila)*. 2019 Apr;57(4):234-239
Chan A, et al. *QJM*. 2007;100(10):609-615

Conclusion:

QTc Bazett	Clinical Results	Guideline Recommendations
Over exaggerated the amount of patients with true QTc prolongation regardless of patient's heart rate	Withholding critical first choice medications	AHA/ACCF/HRS recommend use of linear regression functions instead of Bazett's formula for QT rate correction

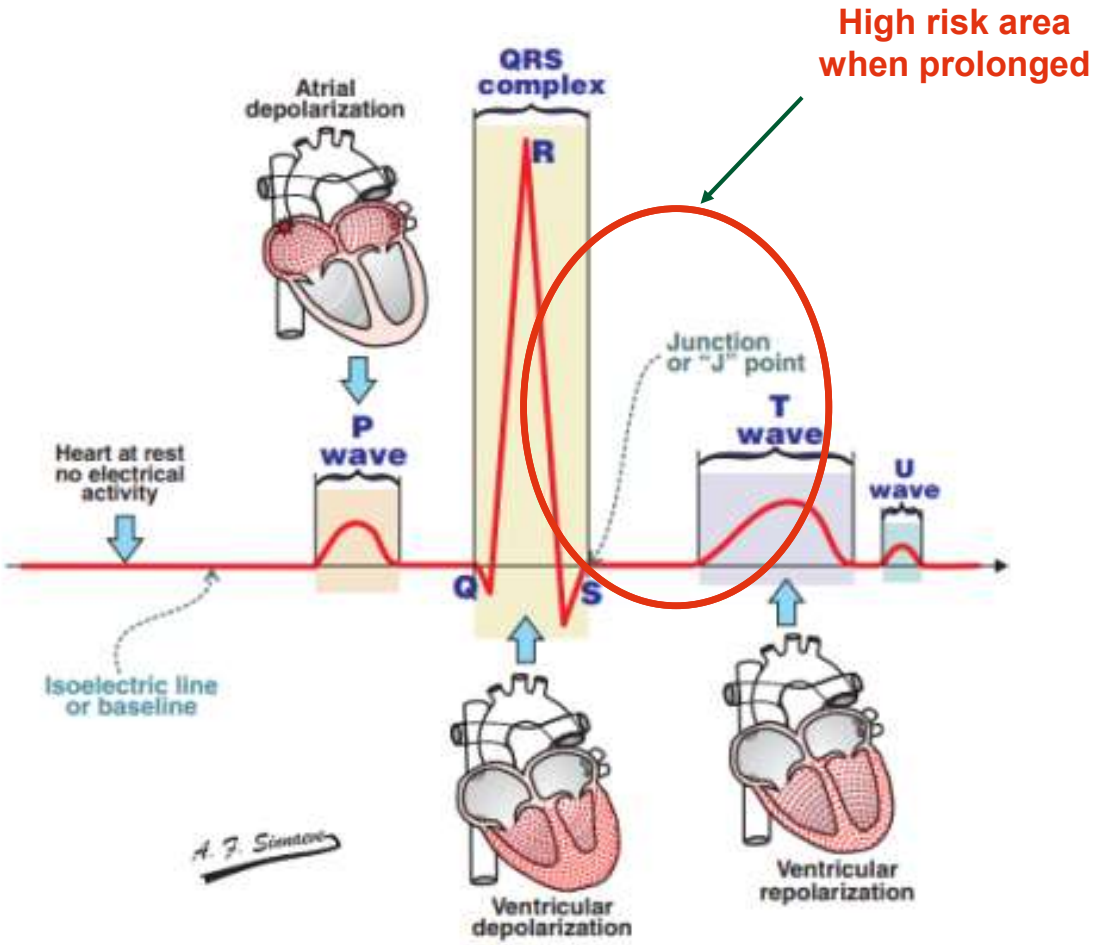
What happens if the patient has ventricular conduction abnormalities (i.e bundle branch blocks and ventricular pacing)?

Electrical Activity Conduction

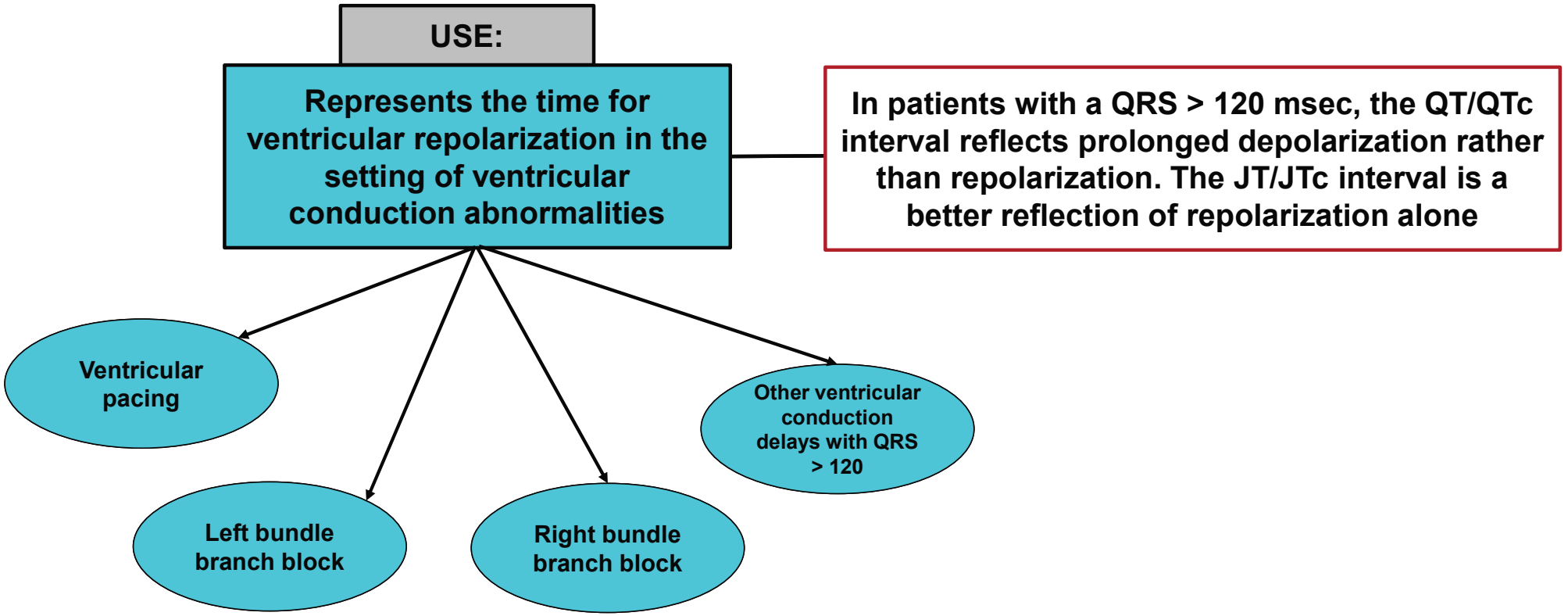
REMINDER

Normal QRS Value:

80-100 msec

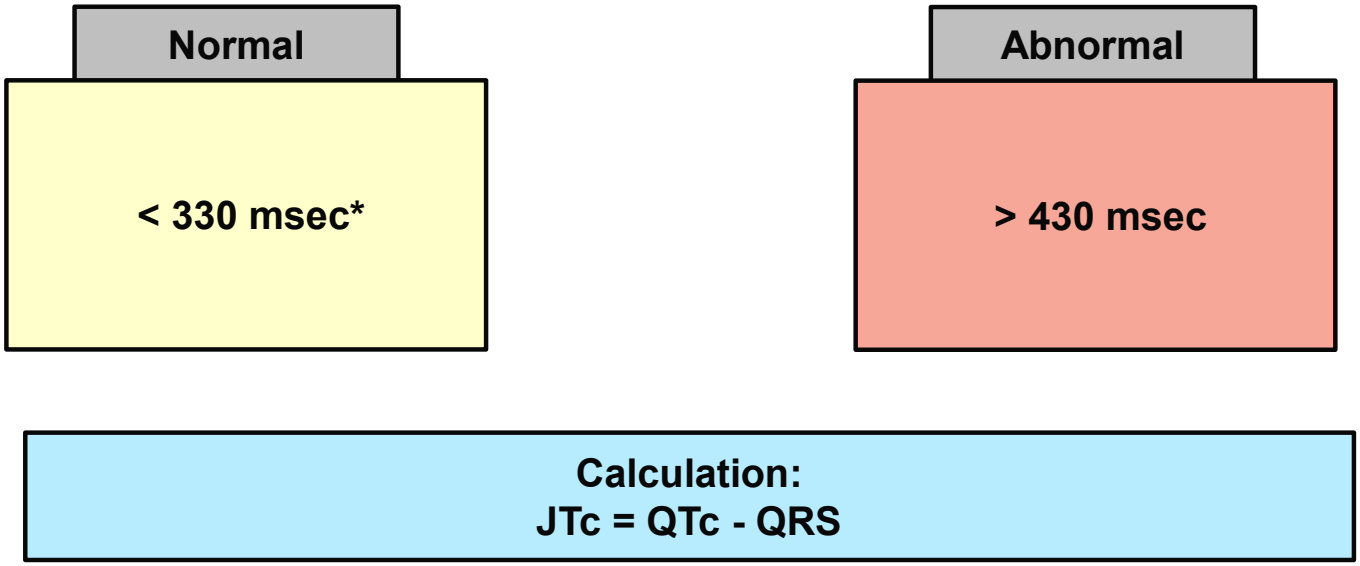


JT Interval



Duan J, et al. *Oncotarget*. 2018 May 22;9(39):25738-25749.
Zareba W, et al. *Journal of Electrocardiology*. 2017;50(6):748-751.
Zulqarnain MA, et al. *Am J Cardiol*. 2015;116(1):74-78.

JT Interval Calculation



*based on sotalolol package insert

Patient Case

CF is a 52 y/o male with a PMH of HTN, HLD,T2DM, and **a left bundle branch block** presents to the ED with 1 week history of SOB, nausea/vomiting, and fevers. Findings from the CXR reveal a possible community acquired pneumonia. MD opts to start patient on azithromycin, ceftriaxone, and IV ondansetron PRN.

	Drug-Drug: **Azithromycin** and **Ondansetron** The concurrent use of **azithromycin** and other agents that prolong the QT interval may result in potentially life-threatening cardiac arrhythmias, including torsades de pointes

Serum Potassium	3.2 mEq/L
Serum Magnesium	1.4 mg/dL
Serum Calcium	9.8 mg/dL

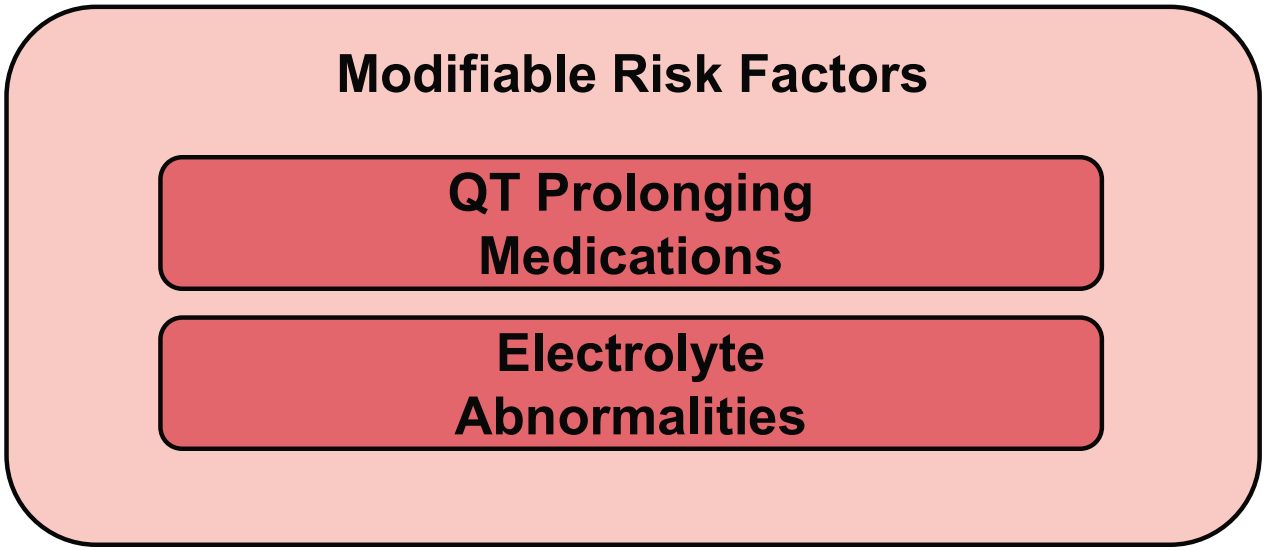
EKG Findings:

Ventricular Rate	86 BPM
QT Interval	470 msec
QTc	547 msec
QRS	157 msec

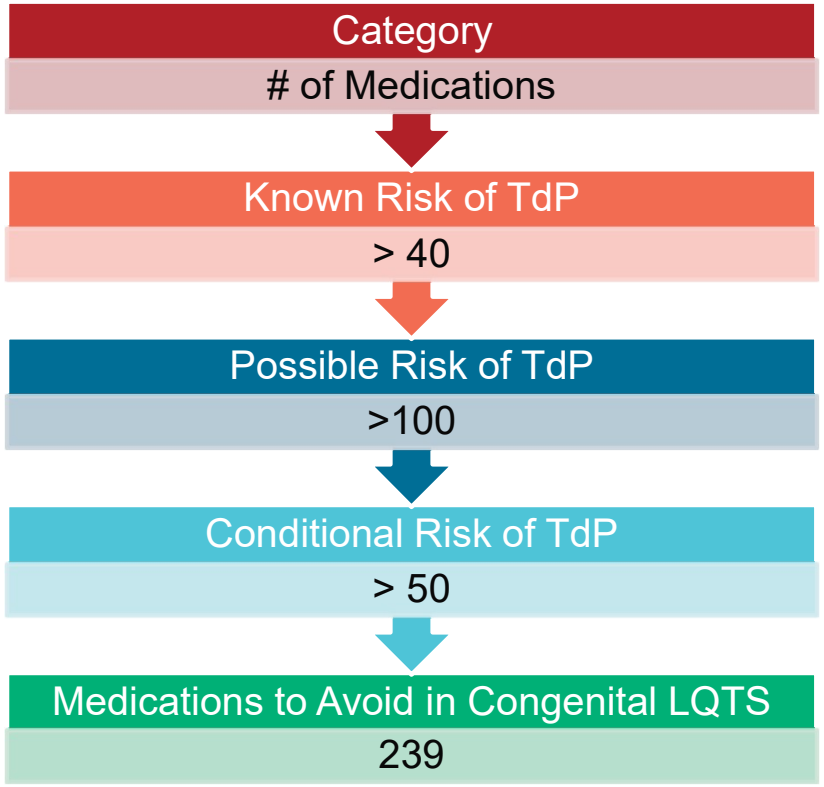
JT Interval = 390 msec; not prolonged

Mitigating Risks of QTc Prolongation

Mitigating QT Prolongation Risk



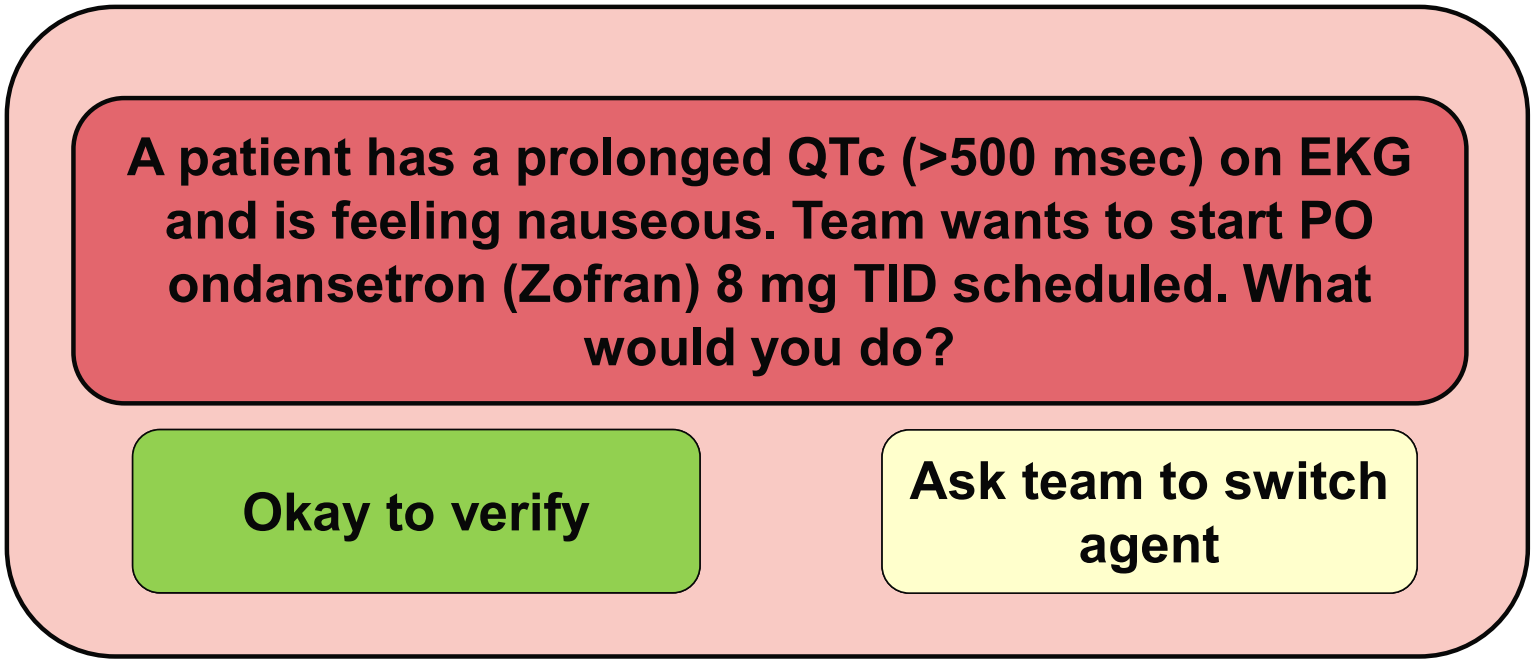
QT-Prolonging Medications



Drugs from US Most Prescribed Drugs List of 2020	
Known Risk of TdP	**Possible Risk of TdP**
Sotalol	Tizanidine
Flecainide	Lithium
Citalopram	Famotidine
Escitalopram	Mirabegron
Ondansetron	Risperidone
Fluconazole	Aripiprazole
Azithromycin	Olanzapine
Haloperidol	Quetiapine
Levofloxacin	
Dofetilide	

Drew BJ, et al. *J Am Coll Cardiol*. 2010;55(9):934-947.

Question:


A patient has a prolonged QTc (>500 msec) on EKG and is feeling nauseous. Team wants to start PO ondansetron (Zofran) 8 mg TID scheduled. What would you do?
Okay to verify
Ask team to switch agent

Ondansetron and QTc Prolongation

Ondansetron and the risk of cardiac arrhythmias: a systematic review and post marketing analysis

Systematic review of published literature identifying reported arrythmias following a single oral dose of ondansetron

Total of 18 reports describing 21 cases were identified

Primary outcome: occurrence of an arrythmia within 24 hours of a single oral administration

Primary outcome: no reports identified a single occurrence of an arrythmia

Secondary outcome: identifying all cases associating ondansetron administration to an arrythmia

Secondary outcome: 80% included IV use, 3% involved long term oral use in patient with arrythmia risk factors

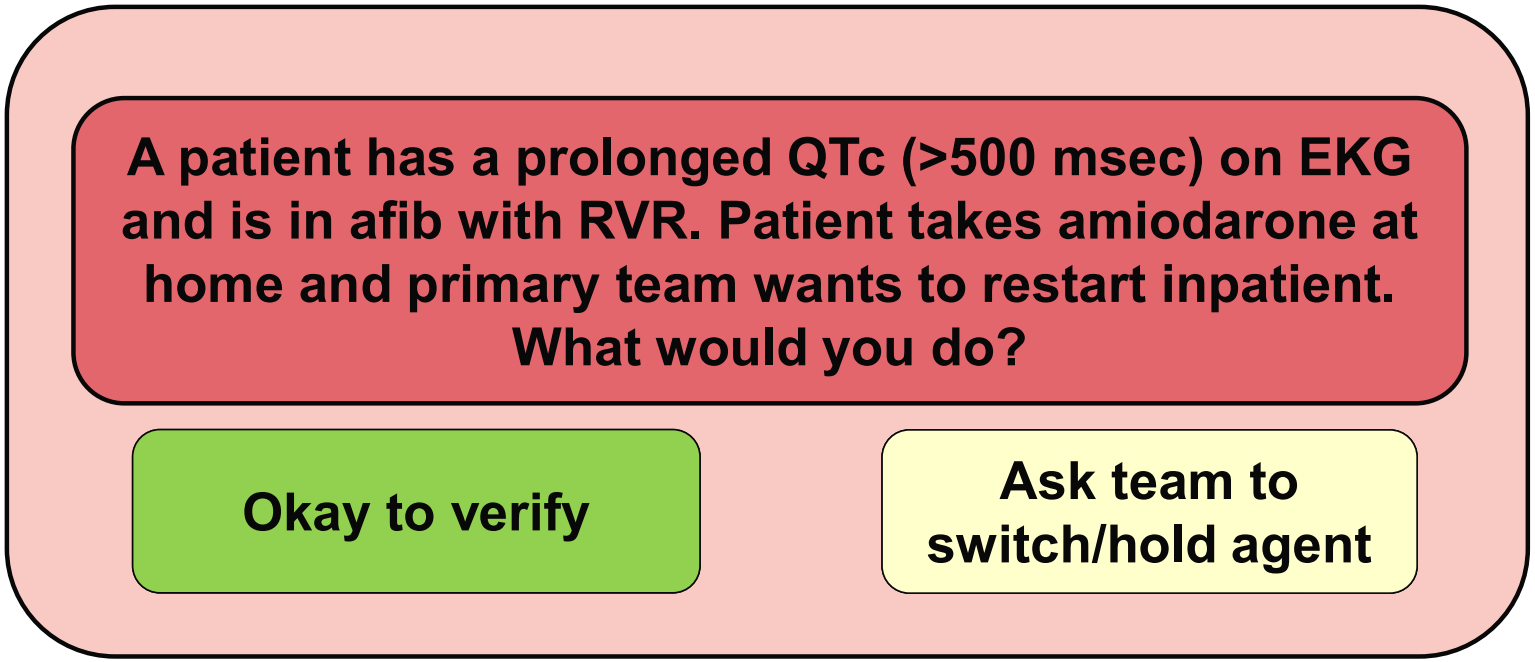
Kinetics

- **IV 32 mg dose**: 17 to 20 msec QTc prolongation
- **IV 8 mg dose**: 5.8 msec QTc prolongation
- **Oral**: no documented reports
- **Time to peak concentration after oral**: 2.3 hours
- **Time to peak concentration after IV**: 5 minutes

In June 2012, the FDA issues an update associating the risk of QT prolongation with the administration of a 32-mg intravenous dose

Freedman SB, et al. *Ann Emerg Med*. 2014;64(1):19-25.e6

Question:


A patient has a prolonged QTc (>500 msec) on EKG and is in afib with RVR. Patient takes amiodarone at home and primary team wants to restart inpatient. What would you do?
Okay to verify
Ask team to switch/hold agent

Amiodarone and QTc Prolongation

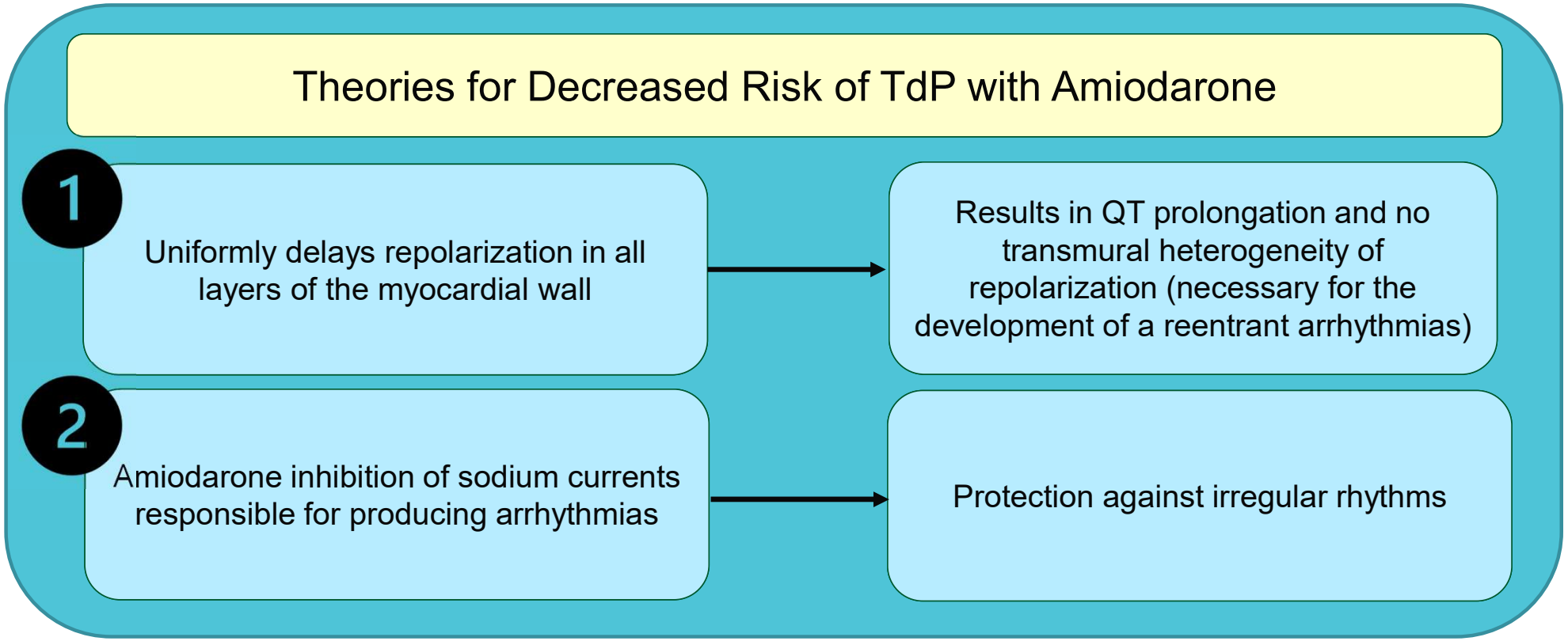
Amiodarone-associated Proarrhythmic Effects:
A Review with Special Reference to Torsade de Pointes Tachycardia

DESIGN	RESULTS
Systematic review of published literature identifying amiodarone-associated proarrhythmic events	A total of 65 case reports, 17 uncontrolled studies, and 7 controlled studies were identified
Primary objective: occurrence of torsade de pointes during amiodarone administration	TdP incidence overall of 0.7% (17 out of 2878 patients)
Secondary objective: effects of amiodarone in patients with previously documented drug-induced torsade de pointes.	31 patients with previous exposure to drug-mediated torsade de pointes were exposed to amiodarone. No incidence of TdP with amiodarone.

Patients with highest risks:
- 62% women
- 50% hypokalemia
- 20% concurrent antiarrhythmic drugs with QT prolonging risks
- 70% CAD and history of MI

Hohnloser SH, et al. *Ann Intern Med*. 1994;121(7):529-535.

Amiodarone and QTc Prolongation Cont'd

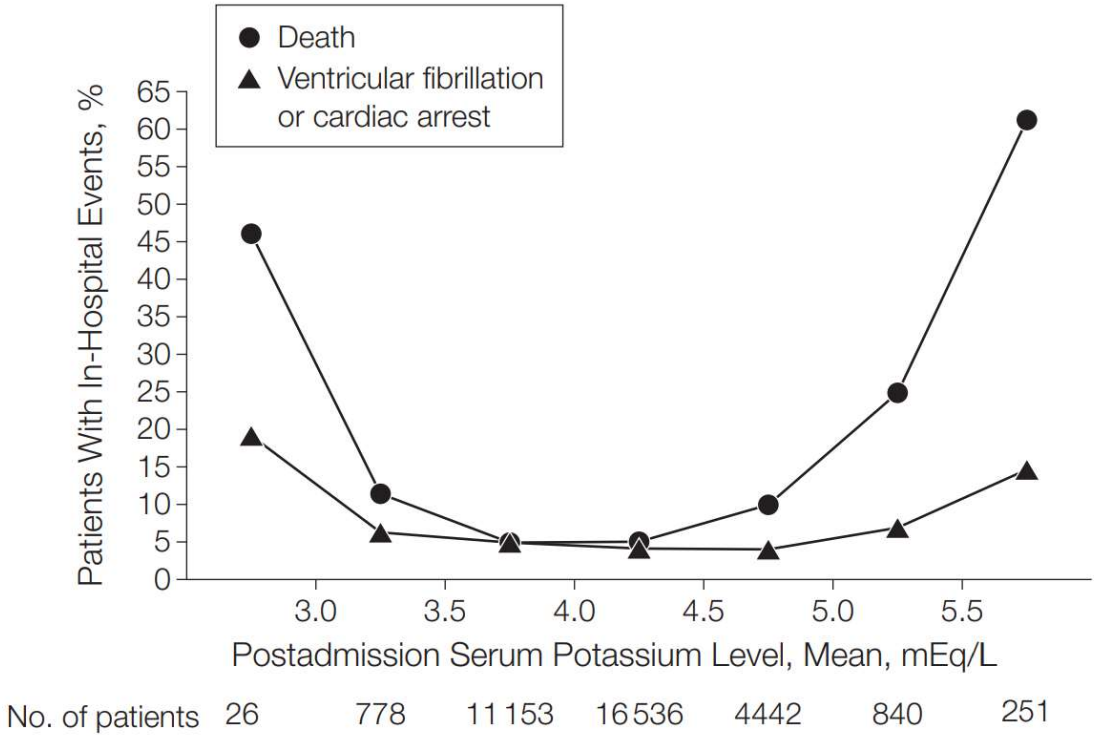


Drew BJ, et al. *J Am Coll Cardiol*. 2010;55(9):934-947.

QT Prolongation & Electrolytes Management

Electrolyte Abnormalities and Repletion Goals	
Hypokalemia	K = 4.0-5.0 mEq/L
Hypomagnesemia	Mg = 2.0-2.4 mg/dL
Hypocalcemia	Ca = 8.5-10.2 mg/dL

Potassium Disturbances and Adverse Cardiac Events



Independent Predictors	OR (95% CI)	P-Value
Potassium <3.6 mEq/L	10.6 (2.54–43.9)	<0.0001
Atrial fibrillation/flutter	6.25 (2.13–18.3)	<0.0001
QTc >480 ms	4.38 (1.19–16.1)	0.01
Coronary artery disease	2.59 (1.06–6.34)	2.59 (1.06–6.34)

Hypokalemia is one of the strongest predictors of QT prolongation, TdP, and sudden cardiac death

Maintain K+ between 4.0-5.0 mEq/L

Goyal A, et al. *JAMA*. 2012;307(2):157–164.

Other Electrolyte Abnormalities

Hypomagnesemia

- Increased rates of cardiovascular events with hypomagnesemia
- Guideline recommendations for magnesium levels ≥ 2.0 mg/dL

Hypocalcemia

- Hypocalcemia as an independent risk factor for QT prolongation
- Guideline recommendations only include maintaining calcium within normal ranges

Vandael E, et al. *Int J Clin Pharm*. 2017;39(2):424-432.
Tisdale JE, et al. *Circulation*: Cardiovascular Quality and Outcomes. 2013;6(4):479-487.
Tisdale JE, et al. *Circulation*. 2020 Oct 13;142(15):e214-e233

Tools for Risk Stratification

Risk Factors for QTc Prolongation

Development and validation of a risk score to predict QT interval prolongation in hospitalized patients

DESIGN

Prospective, observational study of 900 consecutive patients at Indiana University Health Methodist Hospital from 2008-2009

Univariate analysis of variables associated with QTc interval prolongation

Sensitivity/specificity analysis of risk scoring system developed from univariate analysis

Inclusion

Age ≥ 18 y/o
Admission to the cardiac critical care unit (CCCU)

Exclusion

Discharged from the unit in <24h
Did not receive daily EKGs or continuous telemetry
Completely paced ventricular rhythms

OUTCOMES

Variables	Points Assigned in Risk Score	Odds Ratio	95% CI (P value)
Age ≥68 years	1	1.3	1.0-1.9 (0.04)
Female Sex	1	1.5	1.1-2.0 (0.03)
Loop Diuretic	1	1.4	1.0-2.0 (0.007)
Serum K+ < 3.5 mEq/L	2	2.1	1.5-2.9 (<0.001)
Admission QTc ≥450*	2	2.3	1.6-3.2 (<0.001)
Acute MI	2	2.4	1.6-3.9 (<0.001)
On 1 QT-prolonging drug	3	2.8	2.0-4.0 (<0.001)
On ≥2 QT-prolonging drugs	3	2.6	1.9-5.6 (0.02)
Sepsis	3	2.7	1.5-4.8 (0.002)
Heart Failure	3	2.7	1.6-5.0 (<0.001)

*Later replaced with QTc Fridericia > 500 as 4 points

Tisdale JE, et al. *Circ Cardiovasc Qual Outcomes*. 2013;6(4):479-487

CF'S Risk Stratification

Age ≥68 years	No 0	Yes +1
Sex	Male 0	Female +1
Patient on loop diuretic	No 0	Yes +1
Potassium ≤3.5 mEq/L Potassium should be potassium determined closest to EKG timing	No 0	Yes +2
Admission QTc ≥450 msec Auto-calculated by EKG	No 0	Yes +2
Being admitted for acute myocardial infarction	No 0	Yes +2
Being admitted for sepsis	No 0	Yes +3
Being admitted for heart failure	No 0	Yes +3

Number of QTc-prolonging drugs given If receiving ≥2 drugs, patient receives 3 points for 1 QTc-prolonging drug as well as 3 additional points for ≥2	
None	0
1 QTc-prolonging drug	+3
≥2 QTc-prolonging drugs	+6

10 points

Tisdale Risk Score for QTc

Moderate risk

Moderate risk for QT prolongation; consider consultation with pharmacist, adjusting risk factors as much as possible

EKG should be repeated after 5 half-lives of QT prolonging drugs given to evaluate QTc

Copy Results | Next Steps

Name	QTC
QTc Bazett	528
QTc Fridericia	477
QTc Framingham	460
QTc Hodges	478
QTc Rautaharju	498

Summary: What to Consider as Pharmacists

Assess the EKG

Is the JT interval calculated for patients with ventricular conduction abnormalities?

Has an appropriate formula been used to correct for patient's heart rate (NSR vs. Afib w/ RVR)?

Assess the Prescribed Medications

How many QT prolonging medications does the patient have?

Are there any specific recommendations for QT monitoring/risks for the prescribed medications?

What are the PK/PD drug interactions?

Assess the Risk Factors

Does the patient have a history of cardiovascular disease?

Is the patient a good candidate for a risk score evaluation?

Does the patient have any modifiable risk factors?

Take it to Heart with the QT: A Prolonged Understanding of QTc Management

Sally Falahat, PharmD, MPH, BCPS
Internal Medicine Clinical Specialist
Clinical Assistant Professor
UIC Retzky College of Pharmacy