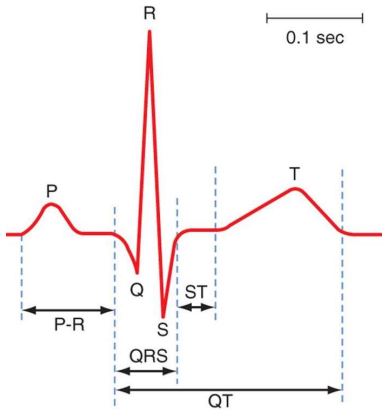
# Take it to Heart with the QT: A Prolonged Understanding of QTc Management

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## Conflicts of Interest

I have no conflicts of interest to disclose

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## Learning Objectives

- Describe the pathophysiology of QT interval prolongation along with associated risk factors
- Review available primary literature for proper assessment and calculation of the QT interval
- Discuss various strategies for mitigation risk factors with QT prolongation to provide safe and effective patient care
- Evaluate resources for evidence-based decision making in the setting of a prolonged QT interval

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## 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.

High

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 |

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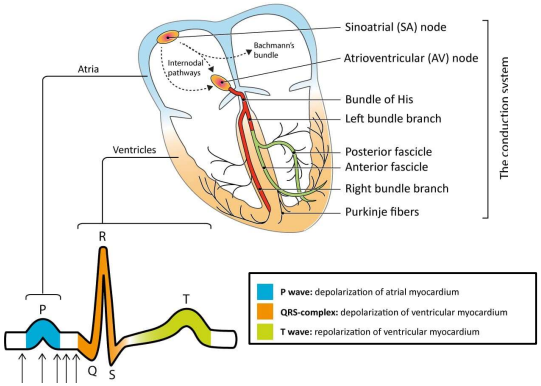
## Cardiac Electrophysiology




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

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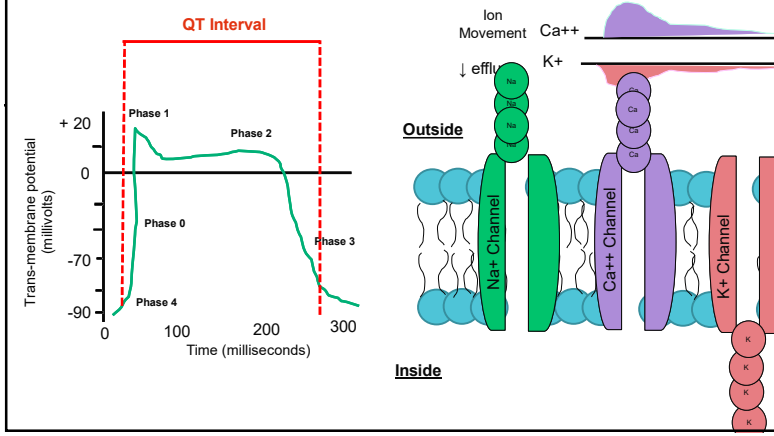
## Cardiac Electrophysiology

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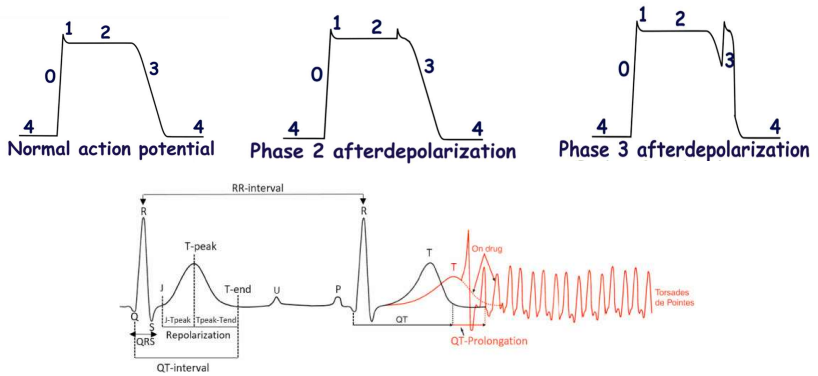
## Pathophysiology: Early Afterdepolarizations

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## 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<br>6% of cardiac arrests over two-month period |
| >90% of patients with TdP have ≥1 identifiable risk factor | |

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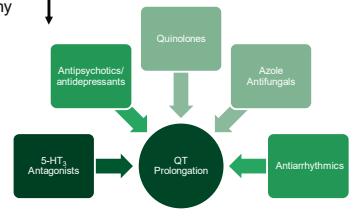
## Risk Factors for QTc Prolongation

**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.

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## QTc Common Cutoffs

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## 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.

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## 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.

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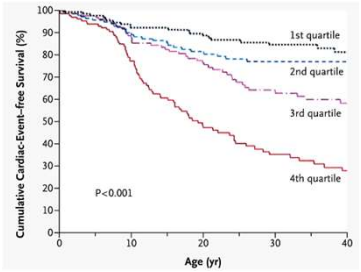
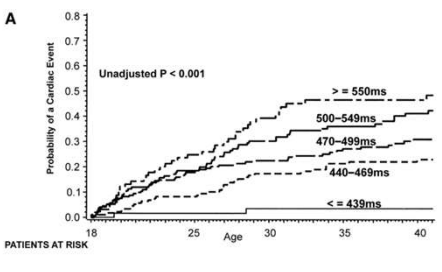
## Established Cutoffs Cont'd




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.

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## Downfall of Cutoff Selection

- Cutoffs largely based on QTc Bazett
- Most data is stratified from patients with congenital long QT syndrome
- No absolute correlations of prolonged QTc's and risks for TdP
- Use of different QT correction formulas in pharmaceutical industries

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## Appropriate Measurement of a QT Interval

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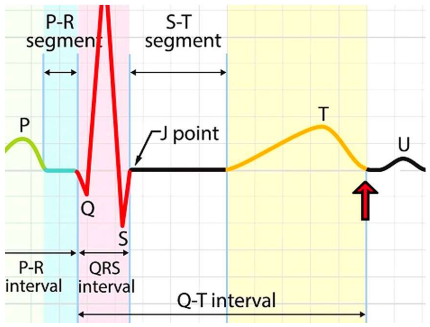
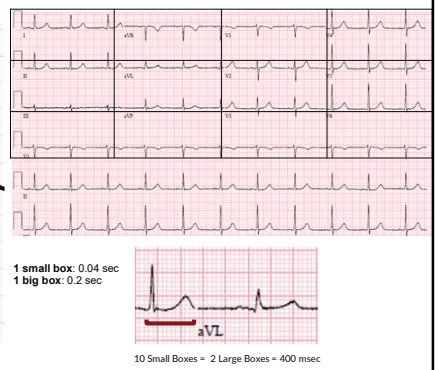
## Manual QT Interval Measurement

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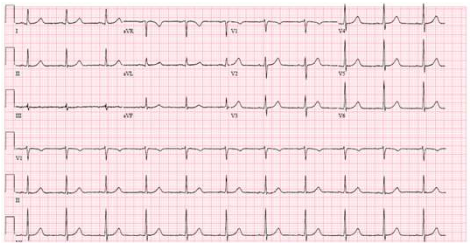
## Automated QT Interval Measurement

| | | |
|---|---|---|
| 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



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

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

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## 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

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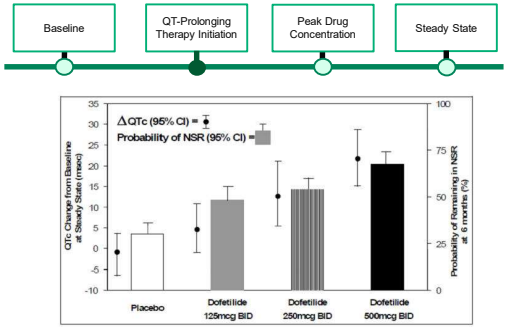
## Timing of QT Interval Measurement




**QT prolongation is generally a concentration-dependent phenomenon**

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

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## 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**

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# Appropriate Correction of a QT Interval

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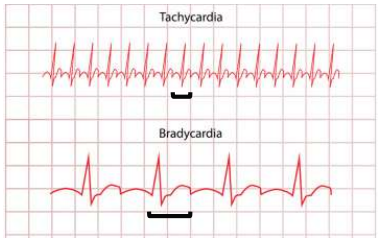
## QT Interval Correction




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

| | |
|---|---|
| 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 | $\frac{QT\ \times\ (120 + HR)}{180}$ |

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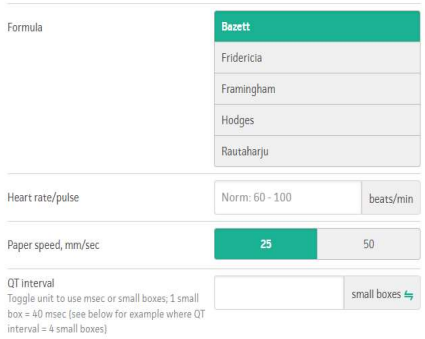
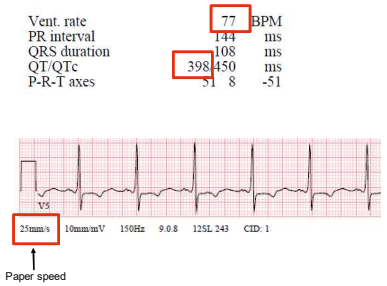
## MD Calc QTc Calculation

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## QTc Variability

| Name | Formula | QTC | CF's EKG Findings |
|---|---|---|---|
| QTc Bazett | $\frac{QT}{\sqrt{RR}}$ | 528 | Ventricular Rate 106 BPM<br>QT Interval 390 msec<br>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?**

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## 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

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## 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

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## Conclusion:

**QTc Bazett**
Over exaggerated the amount of patients with true QTc prolongation regardless of patient's heart rate

**Clinical Results**
Withholding critical first choice medications

**Guideline Recommendations**
AHA/ACCF/HRS recommend use of linear regression functions instead of Bazett's formula for QT rate correction

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

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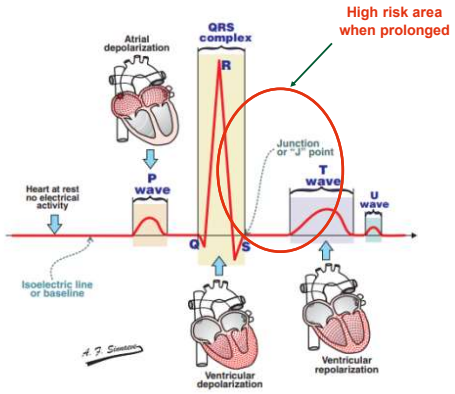
## Electrical Activity Conduction

REMINDER

Normal QRS Value:

80-100 msec

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## JT Interval

**USE:**

**Represents the time for ventricular repolarization in the setting of ventricular conduction abnormalities**

**In patients with a QRS > 120 msec, the QT/QTc interval reflects prolonged depolarization rather than repolarization. The JT/JTc interval is a better reflection of repolarization alone**

- **Ventricular pacing**
- **Left bundle branch block**
- **Right bundle branch block**
- **Other ventricular conduction delays with QRS > 120**

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.

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## JT Interval Calculation

**Normal**

**< 330 msec***

**Abnormal**

**> 430 msec**

**Calculation:**
**JTc = QTc - QRS**

*based on sotalolol package insert

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## 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.

High

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

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# Mitigating Risks of QTc Prolongation

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## Mitigating QT Prolongation Risk

**Modifiable Risk Factors**

- QT Prolonging Medications
- Electrolyte Abnormalities

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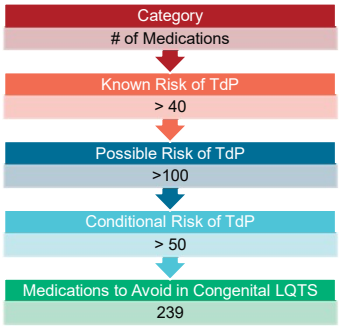
## QT-Prolonging Medications




| 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.

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## 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

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## 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

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## 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**

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## Amiodarone and QTc Prolongation

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

**DESIGN**

Systematic review of published literature identifying amiodarone-associated proarrhythmic events

**Primary objective**: occurrence of torsade de pointes during amiodarone administration

**Secondary objective**: effects of amiodarone in patients with previously documented drug-induced torsade de pointes.

**RESULTS**

A total of 65 case reports, 17 uncontrolled studies, and 7 controlled studies were identified

TdP incidence overall of 0.7% (17 out of 2878 patients)

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.

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## Amiodarone and QTc Prolongation Cont'd

**Theories for Decreased Risk of TdP with Amiodarone**

1. Uniformly delays repolarization in all layers of the myocardial wall → Results in QT prolongation and no transmural heterogeneity of repolarization (necessary for the development of a reentrant arrhythmias)
2. Amiodarone inhibition of sodium currents responsible for producing arrhythmias → Protection against irregular rhythms

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

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## 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 |

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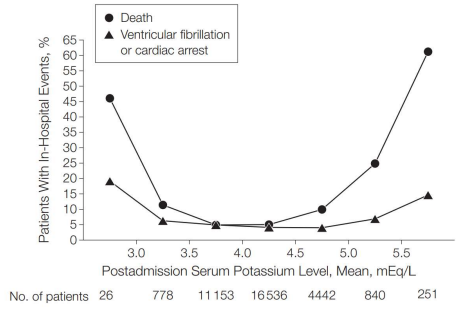
## Potassium Disturbances and Adverse Cardiac Events




| 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.

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## 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

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## Tools for Risk Stratification

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## 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

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## 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<br>Potassium should be potassium determined closest to EKG timing | No 0 | Yes +2 |
| Admission QTc ≥450 msec<br>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<br>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 |

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## 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?

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

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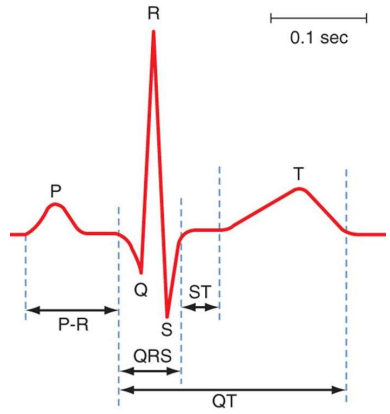


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