ATRIUM CARDIOLOGY COLLABORATIVE

@atriumrx

Don't Miss a Beat! Practical Tips on Managing Drug-Induced QTc Prolongation

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Disclosures

- Nothing to disclose

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Patient Case

TM is a 70 year old Hispanic woman who is admitted today to the hospital for a non-ST segment elevation acute coronary syndrome.

Past Medical History	Current Medications
Coronary artery disease (s/p myocardial infarction x 2 in 2010 and 2016) Heart failure with reduced ejection fraction (EF 35%) Hypertension Chronic back pain	Aspirin 81 mg daily Atorvastatin 80 mg daily, Clopidogrel 75 mg daily, Lisinopril 20 mg daily, Metoprolol succinate 100 mg daily, Spironolactone 25 mg daily, Furosemide 80 mg twice daily, Ranolazine 1000 mg twice daily Methadone 110 mg daily

What risk factors does TM have for QTc interval prolongation?

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Learning Objectives

- Identify at least two patient-related and two medication-related risk factors for QTc prolongation.
- Assess pharmacotherapy management that may cause drug-induced QTc prolongation.
- Given a patient taking concomitant medications that could prolong the QTc interval, develop a monitoring and management plan.

QTc, corrected QT interval

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Why Monitor QTc Interval Prolongation?

35%	••87 of 251 patients with QTc prolongation were given QTc-prolonging medications
42%	••70 of 166 patients with QTc interval > 500 msec were given QTc-prolonging medications
57%	••Additional QTc interval prolongation ≥ 60 msec occurred in those with QTc interval > 500 msec

Drug Saf. 2012;35:459-470.

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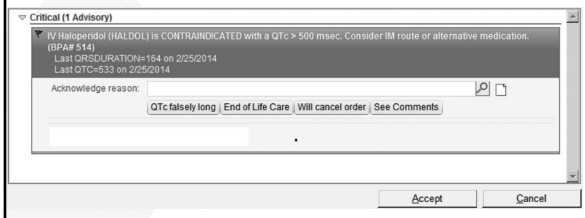
Why Should Clinicians Pay Attention?



- 483 alerts overridden with 70 different drug combinations
- Only 33% (56 patients) had an ECG within 1 month
  - 51% of these had QTc prolongation
  - 31% at high risk for Torsades de Pointes (TdP)

J Am Med Informat Assoc. 2014;21:1109-12.
Br J Clin Pharmacol. 2009;67:347–54.

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Clinical Significance of QTc Prolongation

- Sudden cardiac death
  - Most common cause of death in United States
  - Majority occur due to an arrhythmia
  - QTc interval prolongation → ↑ risk of TdP

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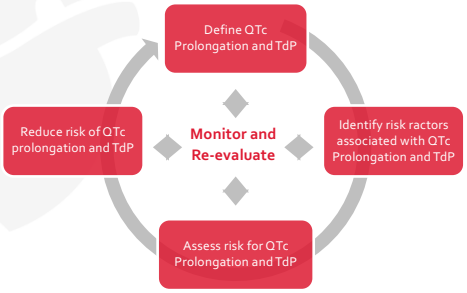
Steps for Management of Drug-Induced QTc Prolongation



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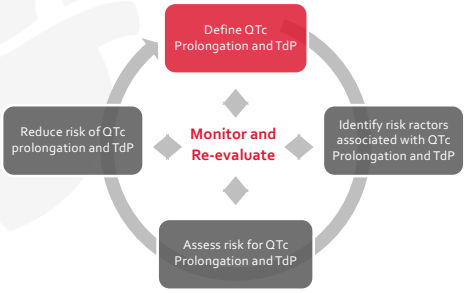

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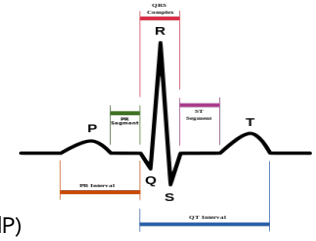
QTc Interval and Torsades de Pointes



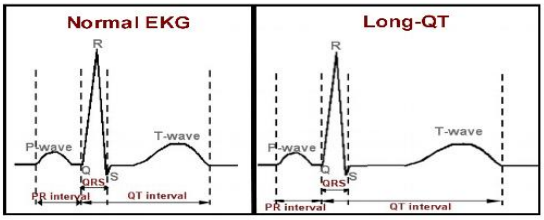
- Normal QTc
  - Men: 360-440 msec
  - Women: 360-460 msec
- Torsades de Pointes (TdP)
  - Polymorphic ventricular tachycardia
- Risk of TdP if QTc > 500 msec = 1.66-fold risk
- Risk of Torsades if QTc > 550 msec = 2.14-fold risk

https://en.wikipedia.org/wiki/QT_interval

QT vs. QTc Interval

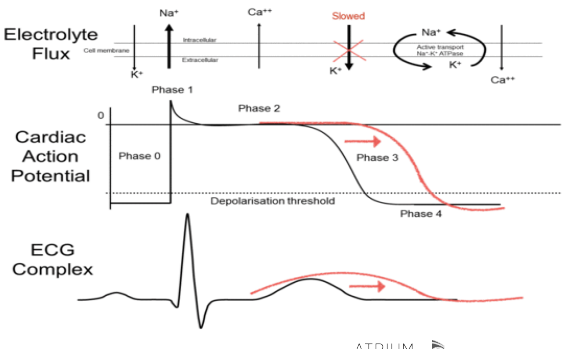
- QT interval varies as heart rate varies
- Bazett's Formula:

$$QT_c = \frac{QT}{\sqrt{RR}}$$



RR = Time from two consecutive R waves
http://www.washingtonhra.com/arrhythmias/long-qt-syndrome.php

Pathophysiology



http://curriculum.toxicology.wikispaces.net/Cardiotoxic+drugs

Etiology

- Congenital
  - 13 distinct genetic mutations
  - 1/2000 live births
- Acquired
  - Medication induced
- Risk of TdP
  - QTc > 500 msec
  - QTc prolonged > 60 msec from baseline
  - Critically ill patients

Can Pharm J (Ott). 2016;149:139-152.

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Question

Which of the following is true about QTc interval prolongation?

a) QTc interval prolongation occurs due to inhibition of calcium channel.
b) Patient often are symptomatic with QTc interval prolongation.
c) Risk of TdP is increased when QTc > 500 msec.
d) Risk of TdP is increased when QTc interval is shortened < 30 msec.
e) All of the above are true.

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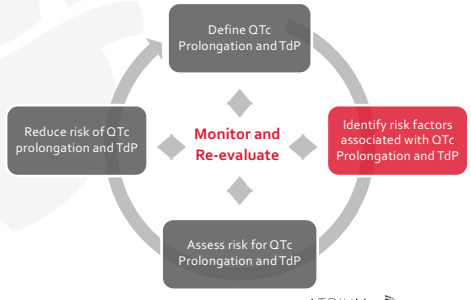
Steps for Management of Drug-Induced QTc Prolongation



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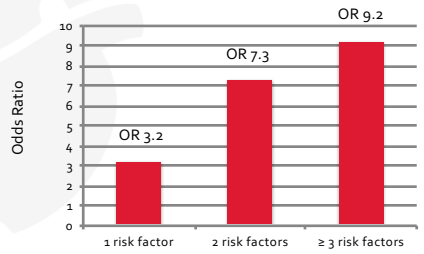
Importance of Identifying Risk Factors



J Electrocardiol. 2010;43:572-576.

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Risk Factor Evaluation

- Risk factors identified through sources:
  - Published clinical reviews
  - Clinical management guidelines
- PubMed and Medline databases
- Medications included with following criteria:
  - Primary literature to support QTc interval prolongation or TdP
  - Boxed Warning required by Food and Drug Administration
  - Frequency of patients with QTc interval prolongation ≥ 5 cases

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Risk Factor Evaluation

- Patient-related factors:
  - High-risk determined based on quality of evidence
- Data collection:
  - Dose-related effect on QTc interval prolongation
  - Frequency of patients with QTc interval prolongation and TP
  - Magnitude of QTc interval increase

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Patient-Related Risk Factors for QTc Prolongation

Patient-Related Risk Factor	Comments
Long QT syndrome (genetic)	High risk for TdP; medications that can potentially prolong QTc interval should be avoided.
QTc > 440 msec	High risk for SCD; most consistently reported threshold for QTc interval prolongation that was associated with increased risk of death
Age > 65 years	High risk for SCD
Ischemic heart disease	High risk for SCD
Female gender	Moderate risk for SCD
Heart failure (ejection fraction < 40%)	Moderate risk for SCD

SCD, sudden cardiac death
Am J Ther. 2003;10:452-457.
Circulation. 2010;121:1047-1060.

Other Patient-Related Risk Factors

Patient-Related Risk Factor
Hypokalemia
Hypomagnesemia
Hypocalcemia
Bradycardia
Treatment with diuretics
Concurrent administration of > 1 QTc interval-prolonging medications
Elevated plasma concentrations of QTc interval-prolonging medications
- Inadequate dose adjustment of renally eliminated medication
- Rapid intravenous infusion of QTc interval-prolonging medication
- Drug interaction(s)

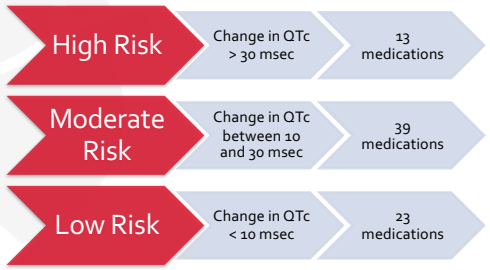
Am J Ther. 2003;10:452-457.
Circulation. 2010;121:1047-1060.

Most Common QTc-Prolonging Medications

QT-Prolonging Agent (1999)	Prescription (n = 1,097,871)
Clarithromycin	292,618 (26.7%)
Erythromycin	227,591 (20.7%)
Levofloxacin	151,448 (13.8%)
Fluoxetine	149,473 (13.6%)
Amitriptyline	115,752 (10.5%)
Sertraline	86,033 (7.8%)
Salmeterol	71,348 (6.5%)
Cisapride (no longer available)	52,218 (4.8%)
Sumatriptan	51,090 (4.7%)
Indapamide	23,505 (2.1%)
Doxepin	21,764 (2%)
Tamoxifen	20,568 (1.9%)

Am J Med. 2003;114:135-141.

QTc-Prolonging Medications: Risk Stratification



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High-Risk QTc-Prolonging Medications

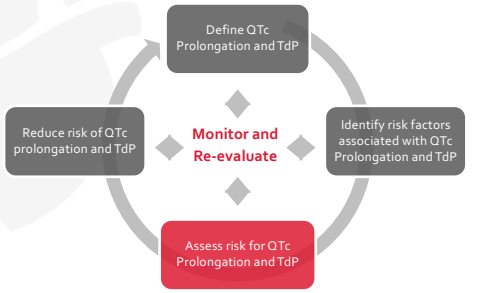
Medication	Mean Magnitude of QTc Prolongation	Dose-Related Effect?	Mean Frequency of Patients with QTc Prolongation	Mean Frequency of Patients with TdP
Amiodarone	120	Yes	7	6
Arsenic trioxide	77	Yes	21	2
Disopyramide	82	NR	5	1
Dofetilide	59	Yes	16	13
Droperidol	35	Yes	15	1
Epinephrine	67	Yes	175	0
Halofantrine	70	Yes	29	1
Ibutilide	142	Yes	205	1
Isoproterenol	67	NR	19	0
Methadone	36	Yes	9	44
Palperidone	45	Yes	207	0
Procainamide	70	No	13	2
Sotalol	70	Yes	NR	20

NR, not reported

Other Risk Categories

Low Risk of QTc Prolongation	Moderate Risk of QTc Prolongation
Chlorpromazine	Amitriptyline
Ciprofloxacin	Azithromycin
Diphenhydramine	Citalopram
Famotidine	Clozapine
Ketoconazole	Dolasetron
Nelfinavir	Erythromycin
Paroxetine	Haloperidol
Pentamidine	Ondansetron
Ritonavir	Pimozide
Rivastigmine	Quetiapine
Salmeterol	Quinidine
Trazodone	Risperidone
Voriconazole	Ziprasidone
Sertraline	Ranolazine

Steps for Management of Drug-Induced QTc Prolongation



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Risk Assessment

Risk Factor	Points
Age ≥ 68 years	1
Female gender	1
Loop diuretic	1
Serum potassium ≤ 3.5 mEq/L	2
Presenting QTc interval ≥ 450 msec	2
Acute myocardial infarction	2
Heart failure with reduced ejection fraction	3
1 QTc interval-prolonging medications	3
≥ 2 QTc interval-prolonging medications	3
Sepsis	3
Maximum Score	21

Low Risk
0 – 6

Moderate Risk
7 – 10

High Risk
11 – 21

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Circ Cardiovasc Qual Outcomes. 2013;6:479-487.

Patient Case

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- Labs: within normal limits except K 3.1 mEq/L, Mg 1.4 mg/dL
- ECG: T wave inversions, QTc 510 msec (Bazett's formula)

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Question

Using the Risk Assessment Scoring Tool, what is TM's risk score?

a) 6
b) 7
c) 12
d) 14
e) 18

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Question

How would you assess TM's risk based on the score?

a) Low risk
b) Moderate risk
c) High risk
d) Not enough information was provided

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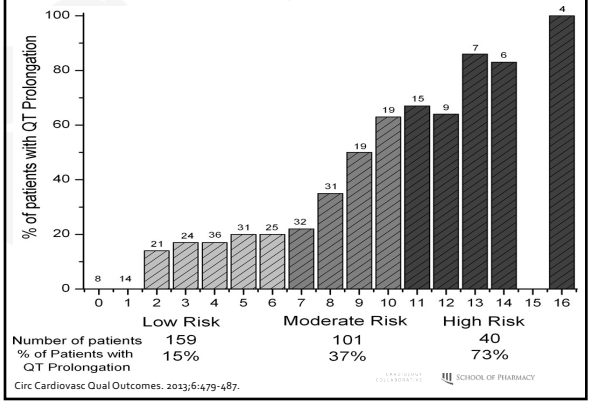
Risk Factor Tool Development and Validation



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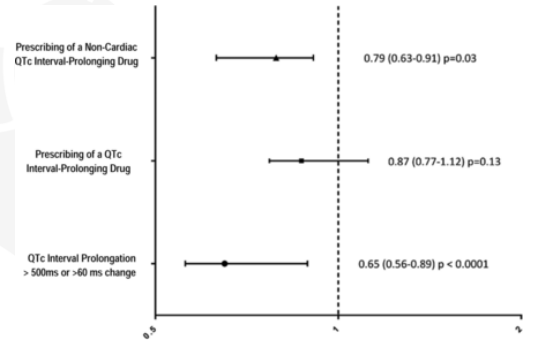
Clinical Decision Support System



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Circ Cardiovasc Qual Outcomes. 2014;7:381-390.

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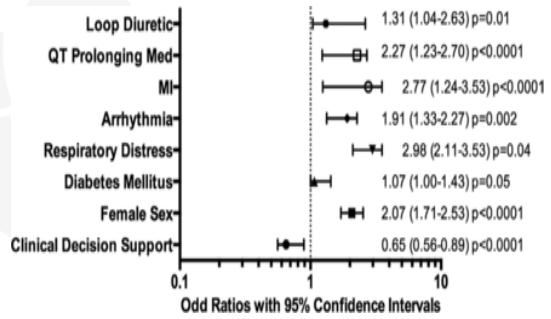

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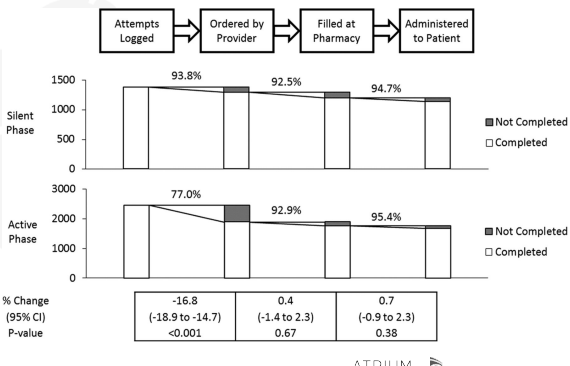
Circ Cardiovasc Qual Outcomes. 2014;7:381-390.

Computerized Physician Order Entry System



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J Am Med Informat Assoc. 2015;22:e21-e27.

Clinical Decision Support System: Overrides

Reason for Override (382/470 triggers)	n (%)
Physician-notified but ordered to continue medication	225 (59)
Patient's condition warrant drug administration	58 (15)
Therapy appropriate as ordered	48 (9)
Laboratory test to be repeated so continue treatment	20 (5)
Not applicable to formulation	6 (2)
Patient on dialysis so continue treatment as ordered	2 (1)
Reference consulted and treatment appropriate	3 (1)
Treatment plan requirement	9 (2)
Other/unknown	11 (3)

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Circ Cardiovasc Qual Outcomes. 2014;7:381-390.

Addressing Alert Fatigue

- Reduction of alerts by 53% by removing low-risk medications
- Positive predictive value: 31% before vs. 30% after
- Only 47% at risk of TdP identified using modified knowledge base

	Alert Generated (n)	No Alert Generated (n)
Patients at risk of TdP	7 (true positives)	8 (false negatives)
Patients not at risk of TdP	16 (false positives)	18 (true negatives)

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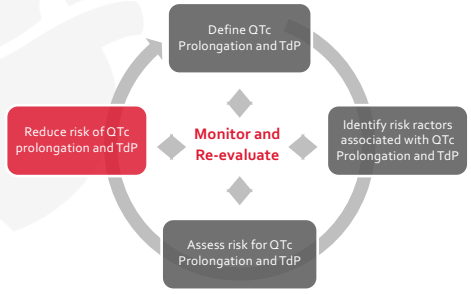
Eur J Clin Pharmacol. 2009;65:919-925.

Steps for Management of Drug-Induced QTc Prolongation



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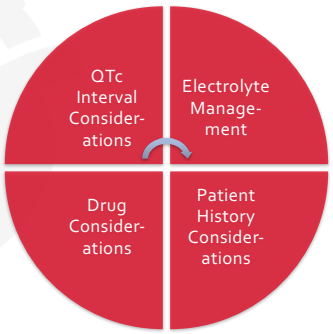
General Management Principles



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Drug-Drug Interactions

Precipitant Medication	Mechanism	QTc Interval Prolonging Medication
Antifungal Agents (e.g., itraconazole)	Inhibition of CYP3A4	Amiodarone Disopyramide Dofetilide Pimozide
Macrolide antibiotics (e.g., clarithromycin)	Inhibition of CYP3A4	
Protease Inhibitors (e.g., atazanavir, ritonavir)	Inhibition of CYP3A4	
Antidepressants (e.g., bupropion, duloxetine, fluoxetine)	Inhibition of CYP2D6	Flecainide Quinidine Thioridazine
Others: terbinafine	Inhibition of CYP2D6	

Can Pharm J (Ott). 2016;149:139-152.

QTc-Prolonging Medications Requiring Renal Dose Adjustment

- Ciprofloxacin
- Disopyramide
- Dofetilide
- Flecainide
- Fluconazole
- Levofloxacin
- Procainamide
- Sotalol
- Vandetanib

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Pharmacist Intervention

Low Risk	••Evaluate drug interactions ••Dose adjust for renal impairment
Moderate Risk	••Maintain electrolyte balance ••Monitor ECG regularly ••Also perform actions listed for low risk
High Risk	••Recommend alternative non-QTc prolonging medication if possible ••Also perform actions listed for both low and moderate risks

ECG, electrocardiogram

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Recommended Baseline ECG Monitoring

- Two or more baseline risk factors
- One or more QTc-prolonging medications
- Medication requiring close monitoring
- Concomitant use of a medication increasing concentration of a QTc-prolonging medication
- QTc-prolonging medication in presence of impaired clearance or metabolism

*Not applicable to those with congenital long-syndrome; medications known to prolong QTc interval not recommended.

Recommended Follow-Up ECG Monitoring

- Addition of any risk factors or QTc-prolonging medications
- Dose increase of QTc-prolonging medication
- Development of impaired metabolism or clearance of QTc-prolonging medication

*Not applicable to those with congenital long-syndrome; medications known to prolong QTc interval not recommended.

Follow-up ECG Monitoring: Timing

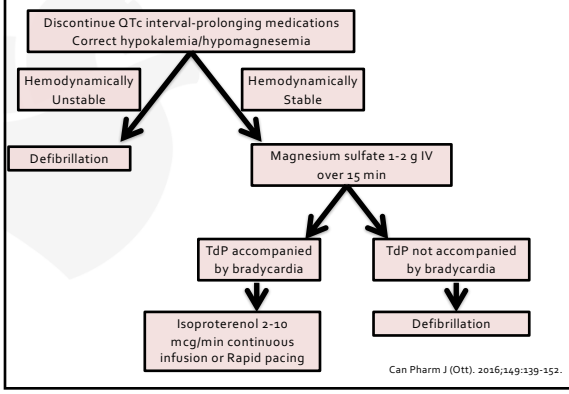
Inpatient:

- Consider 8 to 12 hours following initiation of therapy, dose increase, or overdose.
- Continue to monitor every 12-24 hours until stable.

Outpatient:

- Monitor when plasma concentration of QTc-prolonging medication is at steady state.
- Continue to monitor after 30 days and then 1-2 times/year unless changes occur or more frequent monitoring is warranted.

Management of Torsades de Pointes



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- Labs: within normal limits except K 3.1 mEq/L, Mg 1.4 mg/dL
- ECG: T wave inversions, QTc 510 msec (Bazett's formula)

Patient Case

- Assuming that the QTc interval is accurate, which of the following strategies is/are most appropriate?
  a) Decrease ranolazine to 500 mg twice daily.
  b) Administer potassium chloride and magnesium sulfate.
  c) Decrease metoprolol succinate to 25 mg once daily.
  d) A and B only
  e) All of the above

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Conclusion

- Torsades de Pointes is a life-threatening polymorphic arrhythmia and is associated with QTc > 500 msec.
- Numerous patient-related and medication risk factors can lead to QTc interval prolongation and TdP.
- Pharmacists play an important role in risk reduction:
  - Knowledge of medications associated with TdP
  - Assessment of QTc interval prolongation
  - Identification of clinically significant drug interactions
  - Renal dose adjustment of QTc-prolonging medications

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