Prevention and Management of Drug-Induced QT Interval Prolongation and Torsades de Pointes

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Disclosures

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LEARNING OBJECTIVES

• Given a patient with drug-induced torsades de pointes (TdP), distinguish risk factors for drug-induced QTc interval prolongation and TdP and their contribution to the occurrence of TdP.
• Given a patient with drug-induced TdP, describe how this arrhythmia could have been prevented.
• Assess the influence of emerging predictive analytics (validated QT interval prolongation risk scores, clinical decision support systems) on the risk of drug-induced QT interval prolongation.
• Given a patient with drug-induced TdP, develop a patient-specific treatment regimen.
Drug-Induced QT Interval Prolongation and Torsades de Pointes — Culprits, Risk Factors, and Consequences

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Skaggs School of Pharmacy and Pharmaceutical Sciences
School of Medicine
University of Colorado
QT Interval Prolongation

Bazett’s Formula:

\[ QT_c = \frac{QT}{\sqrt{RR}} \]
QTc Interval Prolongation

- QTc interval prolongation
  -> 480 ms for females
  -> 470 ms for males

- Increased risk of TdP
  - QTc $\geq$ 500 ms
  - QTc increases $\geq$ 60 ms
  - 5-7% for every 10 ms increase

Circ. 2010;121:1047-60
QT Interval Prolongation and TdP

• Congenital long QT syndrome
  – 1 in 2000 births

• 22% of admissions have prolonged QT intervals
  – 51% prescribed QT prolonging drugs

• ~13,000 TdP events in the US annually

Can Pharm J (Ott). 2016;149:139-52
Eur Heart J Supplements 2001; 3 (Suppl K): K70–K80
TdP

• Rare outcome
  – Big data needed
  – Rely on QT interval prolongation

• Most often studied in hospitalized patients
Self-Assessment
Ernie is a 52 YOF admitted for heart failure who develops TdP

**PMH**: Heart failure with reduced ejection fraction, chronic back pain, hypertension, GERD, generalized anxiety

**Current meds**: Omeprazole, citalopram, lisinopril, tramadol, bisoprolol

Which of the following accurately describes her risk factors for QT interval prolongation?

- **A** Age, citalopram, hypertension
- **B** Hypertension, omeprazole, tramadol
- **C** Bisoprolol, citalopram, heart failure
- **D** Tramadol, heart failure, female
Risk Factors
Risk Factors

• Mechanisms
  – Delayed rectifier potassium current inhibition ($I_{KR}$)
  – Late sodium current enhancement ($I_{NaL}$)

• Modifiable and non-modifiable
Cardiovascular Disease

- Bradycardia
- Stress-related cardiomyopathy
- Acute MI
- Stroke
- Heart failure and reduced ejection fraction
Electrolytes

- Hypokalemia
- Hypomagnesemia
- Hypocalcemia
- Excess licorice
- Apheresis
- Gitelman Syndrome
Endocrine

• Hypothyroidism
• Panhypopituitarism
Autonomic Nervous System

• Pheochromocytoma
• Head-up tilt
• Pure autonomic failure
Emerging Risk Factors

• Environmental
  – Hypothermia

• Inflammatory/Immunity
  – Celiac disease
  – Mechanism
    • CRP, TNF-alpha, IL-6, IL-1

Heart. 2017; 103:1821-9
PloS One. 2014;9:e95994
Other Risk Factors

• Female sex
• Older age
• Genetic
• Propionic acidemia
• Liquid protein diet
• Sickle cell disease
• Drugs
QT Prolonging Drugs

• > 130
• 23% of all outpatients
  – 55% of geriatrics
• 3-fold increased risk of sudden cardiac death

Eur Heart J. 2005;26:2007-12
# Crediblemeds Risk Categories

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Defined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known</td>
<td>Prolong QT <strong>AND</strong> Known TdP risk</td>
</tr>
<tr>
<td>Possible</td>
<td>Prolong QT <strong>BUT</strong> Lack evidence for TdP risk when taken as recommended</td>
</tr>
<tr>
<td>Conditional</td>
<td>Known TdP risk <strong>BUT</strong> Only under certain conditions <strong>OR</strong> By creating conditions that increase TdP risk</td>
</tr>
<tr>
<td>Avoid in LQTS</td>
<td>High TdP risk for congenital LQTS <strong>Includes all categories above plus drugs that do not prolong QT but have special risk because of other actions</strong></td>
</tr>
</tbody>
</table>
Newer Drugs of Concern

- Tramadol
- Memantine
- Cimetidine
- Aclarubicin
- Apalutamide
- Abarelix
- Amsacrine

- Maprotiline
- Zuclopenthixol
- Clotiapine
- Lacidipine
- Metolazone
- Propafenone
- Eperisone
Increased Risk of Drug-Induced TdP

- Higher serum concentrations
  - IV administration
  - Inadequate renal dose adjustment
  - Drug interactions
- > 1 QT interval prolonging drug
- Presence of other risk factors

Can Pharm J (Ott). 2016;149:139-52
Drug Induced TdP

• Review of 249 drug-induced TdP events
  – ~100% ≥ 1 risk factor
  – 71% ≥ 2 risk factors

Medicine. 2003;82:282-90
## Weighing the Risk

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Change in QTc Interval (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inpatients</td>
</tr>
<tr>
<td>Baseline QT interval &gt;450ms</td>
<td>N/A</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>14.7-24.1</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>8.1-20.4</td>
</tr>
<tr>
<td>Female sex</td>
<td>13.9</td>
</tr>
<tr>
<td>QT prolonging drug</td>
<td>11.1</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>10.1</td>
</tr>
<tr>
<td>Older age</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>

Number of Risk Factors Increases TdP Risk

- 0 Risk Factors: Odds Ratio (95% CI) = 0
- 1 Risk Factor: Odds Ratio (95% CI) = 3.2 (2.1-5.1)
- 2 Risk Factors: Odds Ratio (95% CI) = 7.3 (4.6-11.7)
- ≥3 Risk Factors: Odds Ratio (95% CI) = 9.2 (4.9-17.4)

J Electrocardiol. 2010;43:572-6
Case Study
Betty is a 52 YOF admitted for heart failure who develops TdP

PMH: Heart failure with reduced ejection fraction, chronic back pain, hypertension, GERD, generalized anxiety

Current meds: Omeprazole, citalopram, lisinopril, tramadol, bisoprolol

Which of the following accurately describes her risk factors for QT interval prolongation?

A. Age, citalopram, hypertension
B. Hypertension, omeprazole, tramadol
C. Bisoprolol, citalopram, heart failure
D. Tramadol, heart failure, female
Which of the following could have decreased the risk of Betty developing TdP?

- A. Give potassium prophylactically on admission
- B. Use alternatives to citalopram and tramadol
- C. Use pantoprazole instead of omeprazole
- D. Use ranitidine instead of omeprazole
After Discharge: Primary Care Considerations

• Does GERD require a PPI?
• Are alternative PPIs affordable?
• Benefit vs risk of switching/stopping antidepressant?
• Alternatives to tramadol?
KEY TAKEAWAYS

1) **KEY TAKEAWAY**
There are many known and emerging risk factors for drug-induced TdP

2) **KEY TAKEAWAY**
Some drugs and risk factors convey greater risk of TdP than others

3) **KEY TAKEAWAY**
Nearly all instances of drug-induced TdP are associated with at least one other risk factor and the risk can often be mitigated
Reducing the Risk of Drug-Induced QT Interval Prolongation and Torsades de Pointes

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Professor, Purdue University, College of Pharmacy
and
Adjunct Professor, Indiana University, School of Medicine
Financial Relationships and Disclosures

• No industry relationships or other financial disclosures
• Volunteer (unpaid) member, Advisory Board, QT Drugs list, www.crediblemeds.org
PATIENT CASE

- **Chief complaint:**
  - 65 year-old woman presents to ED with weakness, diminished urine production, and diarrhea
  - Admitted to hospital with:
    - Acute kidney injury
    - Urinary tract infection

PATIENT CASE

- **History of Present Illness:**
  - Discharged from hospital 8 days prior to this admission after receiving treatment for osteomyelitis of the left hip

- **Past Medical History:**
  - Hypertension
  - Chronic stable angina
  - Systemic lupus erythematosus

- **Allergies:**
  - Penicillin (reaction not documented)

PATIENT CASE

• Medications Prior to Admission:
  o Ciprofloxacin 500 mg orally twice daily
  o Vancomycin 1g IV every 8 hours
  o Ranitidine 150 mg orally twice daily
  o Lisinopril 40 mg orally once daily
  o Metoprolol XL 100 mg orally once daily
  o HCTZ 25 mg orally once daily
  o Fexofenadine 60 mg orally twice daily

PATIENT CASE

• Select Laboratory Values on Admission:
  o $\text{Na}^{++} = 143 \text{ mEq/L}$
  o $\text{K}^{+} = 2.9 \text{ mEq/L}$
  o $\text{Mg}^{++} = 1.4 \text{ mg/dL}$
  o Serum creatinine = 7.9 mg/dL
  o BUN = 34 mg/dL

PATIENT CASE

• Medications Initiated in the Hospital:
  o Ciprofloxacin and vancomycin discontinued
  o Potassium supplementation
  o Hydroxyzine 200 mg orally twice daily
  o Metoprolol 100 mg orally twice daily
  o Ranitidine 150 mg orally twice daily
  o Clonidine intermittently for hypertensive urgency
  o Hydroxychloroquine 200 mg orally twice daily
  o Levofloxacin 250 mg orally once daily

PATIENT CASE

• On Day #3 of Hospitalization:
  o ECG in the morning:
    ❖ QTc interval = 605 ms
  o 12:50 pm:
    ❖ Patient found unresponsive
    ❖ Placed on telemetry monitor – *Torsades de pointes*
  o Received MgSO4 2g IV:
    ❖ Arrhythmia terminated, patient regained consciousness

Which one of the following drugs is the most likely culprit in causing drug-induced torsades de pointes in this patient?

A. Clonidine
B. Levofloxacin
C. Metoprolol
D. Ranitidine
PATIENT CASE

• On Day #3 of Hospitalization:
  o 2:30 pm
    ▶ Telemetry monitor alarm sounded: Torsades de pointes
    ▶ Patient found pulseless
    ▶ TdP terminated spontaneously
    ▶ Patient was intubated and transferred to ICU

PATIENT CASE

• On Day #3 of Hospitalization:
  ○ 3:50 pm
    ✷ Telemetry monitor alarm sounded: Torsades de pointes
    ✷ Patient found pulseless
    ✷ Patient underwent defibrillation, sinus rhythm restored

Which one of the following is therapies is most likely to facilitate termination of TdP in this patient?

A. Synchronized direct current cardioversion
B. Isoproterenol 2-10 mcg/min continuous IV infusion
C. Lidocaine 1-1.5 mg/kg IV, then 3 mg/min IV infusion
D. Magnesium sulfate 1-2 g IV over 15 minutes
• On Day #3 of Hospitalization:
  o 3:55 pm
    ❖ Telemetry monitor alarm sounded: Ventricular fibrillation
    ❖ Patient underwent defibrillation x 3
    ❖ MgSO4 2g IV administered
    ❖ Sinus rhythm restored
COULD THIS CASE HAVE BEEN PREVENTED?  
COULD IT HAVE BEEN PREDICTED?

- This patient’s TdP risk factors:
  - Female
  - 65 years old
  - Hypokalemia
  - Hypomagnesemia
  - Multiple QT-prolonging drugs
    - Hydroxychloroquine
    - Hydroxyzine
    - Levofloxacin
  - Inadequate dose adjustment of levofloxacin for acute kidney injury
PREDICTIVE ANALYTICS

• Generates predictions using techniques including data mining, modeling, machine learning, and others
• Can be used to develop methods of risk quantification and prediction of QT interval prolongation and/or TdP
• Predictive analytics have also been incorporated into clinical decision support (CDS) tools to alert clinicians regarding patients at increased risk of developing QTc interval prolongation

Pharmacotherapy 2018;38:813-821.
Pro-QTC Score - Mayo Clinic

• Institution-wide computer-based QT alert system was implemented at Mayo Clinic
• System screens all ECGs and alerts clinicians if QTc interval is ≥ 500 ms
• A “pro-QTc” score was developed

## Diagnoses/Conditions Included in Mayo Clinic Pro-QTc Risk Score

<table>
<thead>
<tr>
<th>Condition</th>
<th>Condition</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndrome</td>
<td>Hypoglycemia</td>
<td>Post-syncope or seizure</td>
</tr>
<tr>
<td>Anorexia nervosa/starvation</td>
<td>Intoxication with QT-prolonging drugs</td>
<td>Stroke, SAH, head trauma</td>
</tr>
<tr>
<td>Bradycardia (HR &lt; 45 bpm)</td>
<td>Congenital long QT syndrome</td>
<td>Hypokalemia</td>
</tr>
<tr>
<td>HFrEF</td>
<td>Pheochromocytoma</td>
<td>Hypomagnesemia</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Kidney dialysis</td>
<td>Hypocalcemia</td>
</tr>
<tr>
<td>Female sex</td>
<td>Post-conversion of AF to sinus rhythm</td>
<td>$\geq 1$ drug from crediblemeds list within $\leq 7$ days</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Post-cardiac arrest</td>
<td></td>
</tr>
</tbody>
</table>

Each factor assigned a score of 1

Mayo Clinic Pro-QTc Risk Score

- 99% of n=470 patients with QTc ≥ 500 ms had ≥ 1 risk factor (excluding female sex)
- In patients with QTc ≥ 500 ms, mean pro-QTc risk score = 3.1 + 16
- Score ≥ 4 predicted mortality
  - Hazard ratio 1.72 (95% CI 1.11-2.66, p< 0.001)
- Components of the risk score significantly associated with death;
  - # of QTc-prolonging medications
  - Electrolyte abnormalities

Development and Validation of a Risk Score to Predict QT Interval Prolongation in Hospitalized Patients


• **Objective:**
  • Develop and validate a risk score to identify hospitalized patients at highest risk of QT\(_c\) interval prolongation

Development and Validation of a Risk Score to Predict QTc Interval Prolongation

- Prospective, observational study in n=1200 patient admissions to two 28-bed CCUs over a 1-year period
- Risk score developed in first 900 patients
- Validated in subsequent 300 patients

Development and Validation of a Risk Score to Predict QTc Interval Prolongation

Definition of QT Interval Prolongation

- QTc interval $\geq$ 500 ms at anytime during hospitalization
- Change in QTc interval $\geq$ 60 ms from value on admission

Independent Risk Factors for QTc Interval Prolongation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 68 years</td>
<td>1.3 (1.0-1.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.5 (1.1-2.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>1.4 (1.0-2.0)</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum K⁺ ≤ 3.5 mEq/L</td>
<td>2.1 (1.5-2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admitting QTc ≥ 450 ms</td>
<td>2.3 (1.6-3.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute MI</td>
<td>2.4 (1.6-3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 2 QTc-prolonging drugs</td>
<td>2.6 (1.9-5.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2.7 (1.5-4.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.7 (1.6-5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>One QTc-prolonging drug</td>
<td>2.8 (2.0-4.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Calculation of Risk Score for QTc Interval Prolongation

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 68 years</td>
<td>1</td>
</tr>
<tr>
<td>Female sex</td>
<td>1</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>1</td>
</tr>
<tr>
<td>Serum K+ ≤ 3.5 mEq/L</td>
<td>2</td>
</tr>
<tr>
<td>Admitting QTc ≥ 450 ms</td>
<td>2</td>
</tr>
<tr>
<td>Acute MI</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 2 QTc-prolonging drugs</td>
<td>3</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3</td>
</tr>
<tr>
<td>One QTc-prolonging drug</td>
<td>3</td>
</tr>
<tr>
<td>Maximum risk score</td>
<td>21</td>
</tr>
</tbody>
</table>

## Development and Validation of a Risk Score to Predict QTc Interval Prolongation

### QTc Interval Risk Score Stratification

<table>
<thead>
<tr>
<th>Risk score category</th>
<th>Risk score</th>
<th>QTc prolongation in derivation group</th>
<th>QTc prolongation in validation group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt; 7</td>
<td>51%</td>
<td>53%</td>
</tr>
<tr>
<td>Moderate</td>
<td>7-10</td>
<td>35%</td>
<td>34%</td>
</tr>
<tr>
<td>High</td>
<td>≥ 11</td>
<td>14%</td>
<td>13%</td>
</tr>
</tbody>
</table>

ROC AUC (c-statistic) = 0.832
## Development and Validation of a Risk Score to Predict QTc Interval Prolongation

### QTc Interval Risk Score Stratification

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+ Predictive value</th>
<th>- Predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>0.67</td>
<td>0.88</td>
<td>0.55</td>
<td>0.88</td>
</tr>
<tr>
<td>High</td>
<td>0.74</td>
<td>0.77</td>
<td>0.79</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Development and Validation of a Risk Score to Predict QTc Interval Prolongation

• A risk score using easily obtainable clinical risk factors predicts patients at highest risk for QTc interval prolongation during hospitalization
• May be useful for guiding monitoring and treatment decisions
## RISQ-PATH Score - Belgium

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>K+ &lt; 3.5 mEq/L&lt;br&gt;Baseline QTc ≥ 450 ms (males) or 470 ms (females)</td>
<td>6 points each</td>
</tr>
<tr>
<td>Age ≥ 65 years&lt;br&gt;Female sex&lt;br&gt;Smoking&lt;br&gt;Ischemic cardiomyopathy&lt;br&gt;Hypertension&lt;br&gt;Arrhythmia&lt;br&gt;Thyroid disturbances&lt;br&gt;Ca²⁺ &lt; 8.6 mg/dL&lt;br&gt;For each “list 1” crediblemeds drug</td>
<td>3 points each</td>
</tr>
<tr>
<td>BMI ≥ 30 kg/m²&lt;br&gt;Liver failure&lt;br&gt;CRP &gt; 5 mg/L</td>
<td>1 point each</td>
</tr>
<tr>
<td>Neurological disorders&lt;br&gt;Diabetes&lt;br&gt;GFR ≤ 30 mL/min&lt;br&gt;For each “list 2” crediblemeds drug</td>
<td>0.5 points each</td>
</tr>
<tr>
<td>For each “list 3” crediblemeds drug</td>
<td>0.25 points each</td>
</tr>
<tr>
<td><strong>Maximum total</strong></td>
<td>40.5 + sum QT drugs</td>
</tr>
</tbody>
</table>
## RISQ-PATH Score - Belgium

**Low risk score defined as < 10**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROC AUC</td>
<td>0.72 (95% CI 0.62-0.81)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>96.2% (78.4-99.8%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>32.9% (25.6-41.0%)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>19.7% (13.4-27.9%)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>98.0% (88.2-99.9%)</td>
</tr>
</tbody>
</table>
Genetic Variant Risk Score

- Secondary analysis of R, DB, PC crossover trial of 3 QT interval-prolonging drugs with n=15 time-matched QT and plasma drug concentrations
  - Dofetilide
  - Quinidine
  - Ranolazine
  - Placebo
- Genetic analysis of n=22 subjects was performed
- Genetic score comprised n=61 common genetic variants
- Correlated with slope of subject’s drug-induced increase in QTc vs drug concentration

Genetic Variant Risk Score

- Secondary analysis of R, DB, PC crossover trial of 3 QT interval-prolonging drugs with n=15 time-matched QT and plasma drug concentrations
  - Dofetilide
  - Quinidine
  - Ranolazine
  - Placebo
- Genetic analysis of n=22 subjects was performed
  - n=17 European descent, n=4 African descent, n=1 Asian descent
- Genetic score comprised n=61 common SNPs with previously established effects on QT interval from a large GWAS
- Correlated with slope of subject’s drug-induced increase in QTc vs drug concentration

### Genetic Variant Risk Score

**Subjects of European descent (n=17)**

<table>
<thead>
<tr>
<th></th>
<th>r (95% CI)</th>
<th>p</th>
<th>r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic score vs baseline</td>
<td>0.52 (0.05 to 0.80)</td>
<td>0.03</td>
<td>0.27</td>
</tr>
<tr>
<td>Genetic score vs dofetilide QTc slope</td>
<td>0.55 (0.09 to 0.81)</td>
<td>0.02</td>
<td>0.30</td>
</tr>
<tr>
<td>Genetic score vs quinidine QTc slope</td>
<td>0.48 (-0.03 to 0.79)</td>
<td>0.06</td>
<td>0.23</td>
</tr>
<tr>
<td>Genetic score vs ranolazine slope</td>
<td>0.52 (0.05 to 0.80)</td>
<td>0.03</td>
<td>0.27</td>
</tr>
</tbody>
</table>

## Genetic Variant Risk Score

### Subjects of African descent (n=4)

<table>
<thead>
<tr>
<th></th>
<th>r (95% CI)</th>
<th>p</th>
<th>r²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic score vs baseline</td>
<td>0.97 (0.11 to 1.00)</td>
<td>0.03</td>
<td>0.94</td>
</tr>
<tr>
<td>Genetic score vs dofetilide QTc slope</td>
<td>0.97 (0.12 to 1.00)</td>
<td>0.03</td>
<td>0.94</td>
</tr>
<tr>
<td>Genetic score vs quinidine QTc slope</td>
<td>0.18 (-0.94 to 0.97)</td>
<td>0.82</td>
<td>0.03</td>
</tr>
<tr>
<td>Genetic score vs ranolazine slope</td>
<td>0.55 (-0.87 to 0.99)</td>
<td>0.45</td>
<td>0.30</td>
</tr>
</tbody>
</table>
Genetic Variant Risk Score

- Tested risk score in:
  - n=216 patients who had experienced TdP
  - n=771 controls who had not experienced TdP
- Genetic risk score was associated with significantly increased risk of TdP
  - p=1.3 x 10^{-7}
  - r^2 = 0.12
Incorporation of Predictive Analytics into Clinical Decision Support (CDS) Tools
Incorporation of Predictive Analytics into Clinical Decision Support (CDS) Tools

• A CDS was developed incorporating our validated risk score for QT interval prolongation
• Tested in a pre-post interventional design
• n=3140 consecutive patient admissions to the 2 x 28-bed CCUs at IU Health Methodist Hospital
• Exclusion criteria:
  o Age < 18 years (n=10)
  o ECG rhythm of complete ventricular pacing (n=215)
  o Designation of outpatient in a bed or < 24 hour stay (n=524)
• After applying exclusion criteria, n=2400 patients enrolled
Computer Alert Screen Appearance

Based on the following parameters, this patient is at greater than 80% increased risk of developing QTc prolongation.

**NAME:**

**RISK SCORE:** 12.00

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Result</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk triggering medication</td>
<td>procainamide</td>
<td>2.00</td>
</tr>
<tr>
<td>Concomitant therapy with ≥ 1 higher risk QTc medication</td>
<td>IV amodarone</td>
<td>5.00</td>
</tr>
<tr>
<td>Concomitant therapy with ≥ 1 QTc medication</td>
<td>No Qualifying Orders</td>
<td>0.00</td>
</tr>
<tr>
<td>Serum K+ &lt; 3.5 mEq/L</td>
<td>4.6 mEq/L</td>
<td>0.00</td>
</tr>
<tr>
<td>Thiazide or loop diuretic active order</td>
<td>No Qualifying Orders</td>
<td>0.00</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Not applicable</td>
<td>N/A</td>
</tr>
<tr>
<td>CrCl &lt; 50 mL/min and active renally eliminated medication</td>
<td>No Active RENAL Medication Orders</td>
<td>0.00</td>
</tr>
<tr>
<td>Gender = Female</td>
<td>Male</td>
<td>0.00</td>
</tr>
<tr>
<td>Age ≥ 65</td>
<td>62</td>
<td>0.00</td>
</tr>
<tr>
<td>Troponin-I &gt; 0.2 ng/mL or diagnosis of acute MI</td>
<td>True</td>
<td>2.00</td>
</tr>
<tr>
<td>Diagnosis of Heart Failure</td>
<td>False</td>
<td>0.00</td>
</tr>
<tr>
<td>Diagnosis of Sepsis</td>
<td>False</td>
<td>0.00</td>
</tr>
<tr>
<td>Current QTc interval &gt; 450 ms</td>
<td>484 ms</td>
<td>3.00</td>
</tr>
</tbody>
</table>

Recommend the following Action Steps based on a **Risk Score** of 12.00

Score > 11 **High Risk** Evaluate all QTc interval-prolonging meds for possible DC

ADE_SYN_CK_TORSADES_RISK_A.01  WP_SYN_TORSADES_HIGH3
Primary Outcome Measures

• Odds of developing $QT_c$ prolongation following intervention
• Odds of receiving a QT prolonging medication in patients at risk for or presenting with $QT_c$ prolongation
• Odds of receiving a non-cardiac QT prolonging medication in patients at risk for or presenting with $QT_c$ prolongation
## Results

<table>
<thead>
<tr>
<th>Event</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc interval &gt; 500 ms or ≥ 60 ms change from admitting value</td>
<td>0.65 (0.56-0.89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prescribing of any QTc interval-prolonging drug</td>
<td>0.87 (0.77-1.12)</td>
<td>0.13</td>
</tr>
<tr>
<td>Prescribing of any non-cardiac QTc interval-prolonging drug</td>
<td>0.79 (0.63-0.91)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

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Limitations

• Conducted in two cardiac care units at one institution – generalizability/external validity?
• Pre-post design – can introduce temporal bias
• Influence of education phase?
Conclusions

- A computerized CDS system incorporating a validated risk score for QT interval prolongation influences the prescribing of QT-prolonging drugs and reduces the risk of QT interval prolongation in hospitalized patients with TdP risk factors.
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Mayo Clinic CDS Alert

- Notifies clinicians when patient has QTc $\geq$ 500 ms
- Alert was sent for $n=2\%$ of adult patients
  - Resulted in a 13.9% decrease in administration of QTc interval-prolonging medications
- $n=5\%$ of pediatric patients had QTc $\geq$ 500 ms
  - Identified a child with previously undiagnosed congenital LQTS
  - Prescribers changed $\sim80\%$ of QTc interval-prolonging medications after receiving the alert

J Med Syst 2017;41:161
Pediatr Cardiol 2015;36:1350-1356.
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Mayo Clinic CDS Alert

- In Emergency Department
  - Alert was activated in 1.2% of patients
  - Identified one patient with previously undiagnosed congenital LQTS
  - Mortality was higher in ED patients identified by the QT alert
    - 13.0% vs 3.7%, p<0.001

• **Outcome:**
  - Levofloxacin discontinued
  - $K^+$ and $Mg^{2+}$ replaced aggressively
  - 24 hours later:
    - $\text{QTc} = 399 \text{ ms}$
  - No additional episodes of TdP
  - Discharged to home on day 9

Management of Torsades de Pointes

Acute Management of Arrhythmias, In: Erstad B, ed. Critical Care Pharmacotherapy. ACCP 2016;1244-1281. Used with permission from the American College of Clinical Pharmacy
Reducing the Risk of Drug-Induced QT Interval Prolongation and Torsades de Pointes

- Know drugs that are associated with QT prolongation and TdP (www.crediblemeds.org)
- Monitor risk factors for QT prolongation and TdP
- Where possible, quantify risk with appropriate risk score
- Where possible – avoid QT-prolonging drugs in patients with risk factors
- Be attentive to drug interactions/dose adjustment for kidney disease where appropriate

KEY TAKEAWAYS

1) KEY TAKEAWAY
Risk of QTc interval prolongation and torsades de pointes can be quantified with published risk scores, the use of which guide monitoring and treatment decisions in patients taking QTc interval-prolonging drugs.

2) KEY TAKEAWAY
Drug-induced torsades de pointes should be managed by discontinuing QTc interval-prolonging drugs whenever possible, defibrillation (not synchronized cardioversion) for hemodynamically unstable patients, and administration of intravenous magnesium for hemodynamically stable patients.

3) KEY TAKEAWAY
Clinical decision support (CDS) tools can be developed to alert clinicians when patients are at risk for QTc interval prolongation, and implementation of CDS alerts have been shown to reduce the risk of QTc interval prolongation.
NEW
Limited time only

Chocolate & Crème and Golden Raisin & Crème Torsades
Flaky croissant with French pastry crème