QTc Prolongation: Risk Stratification and Mitigation for Challenging Clinical Cases

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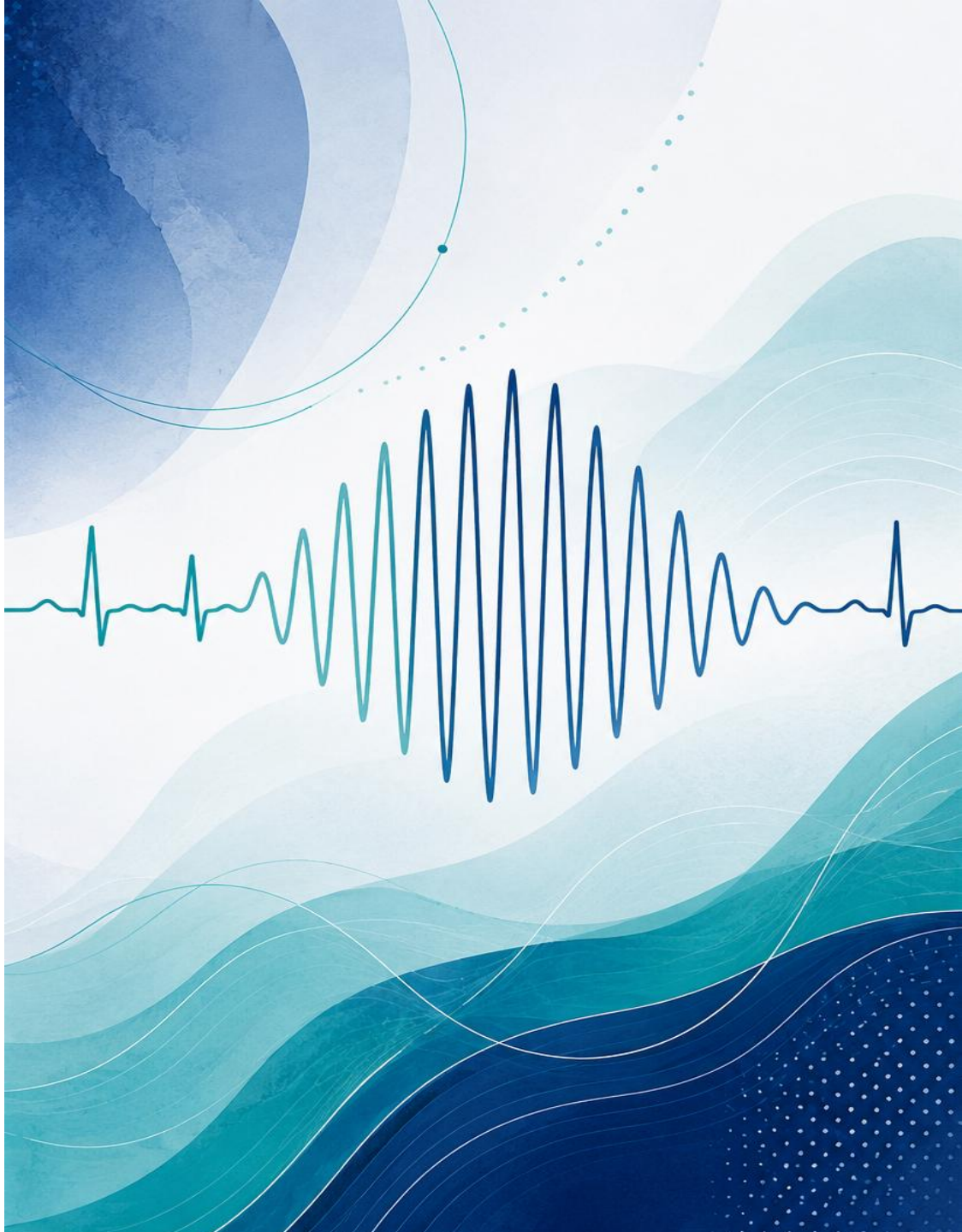
Types of Risk Mitigation

- Being comfortable measuring QTc
- Know when to adjust your approach (e.g. wide QRS from pacing or BBB)
- When to monitor
- Risk-Benefit Analysis
- Choice of medication
- Involve other experts
- Interventions for high-risk situations

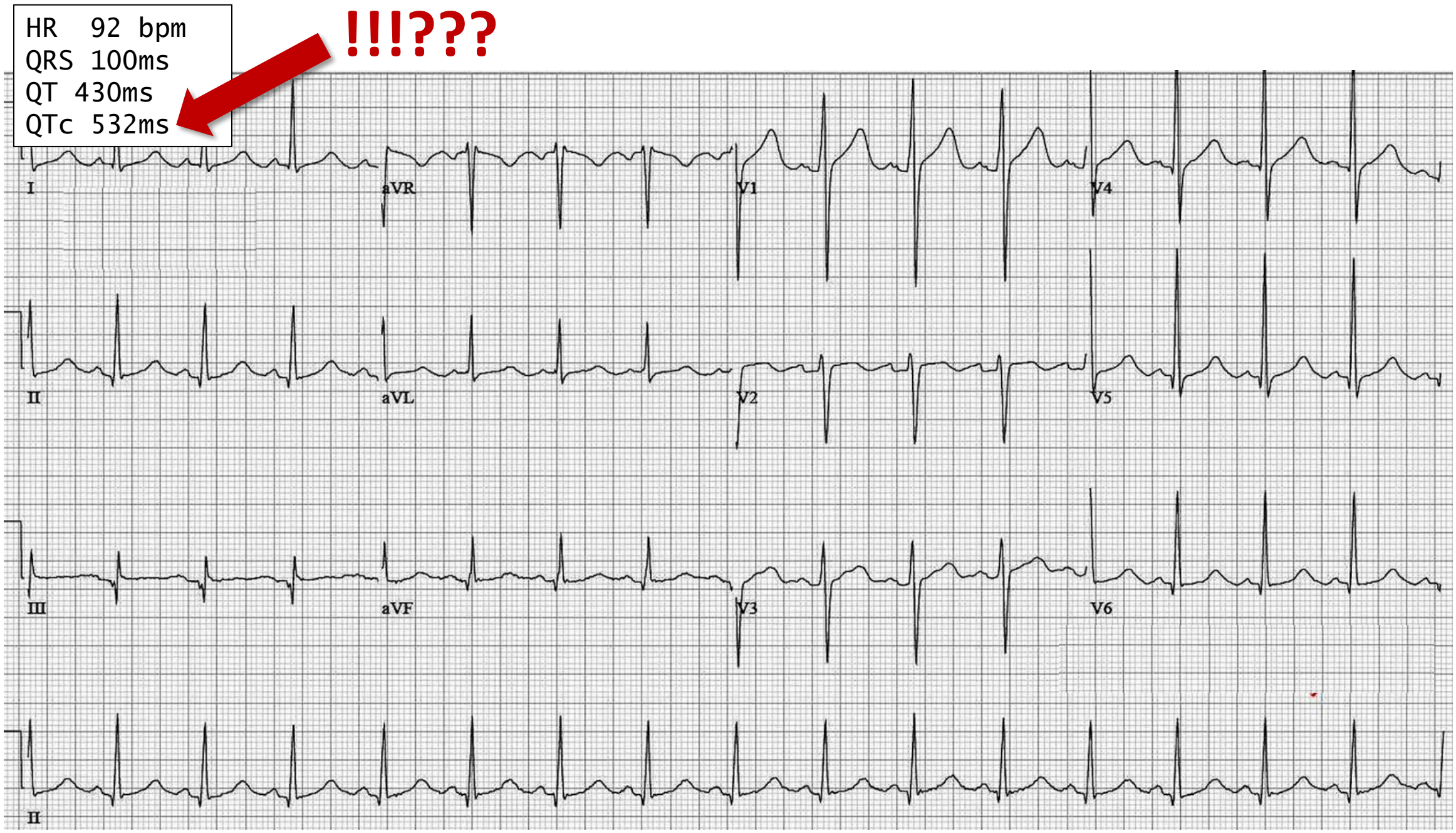


Clinical Case 1

27 y/o woman with history of GAD and social phobia, well controlled on citalopram 40mg po daily, presents to your outpatient clinic to establish care after relocating for her first job out of law school.

She has no significant past medical history, takes no other medications, has no family history of arrhythmia, cardiac arrest or sudden death. She has no suicide attempts, no inpatient psychiatric hospitalizations.

Your clinic just purchased an ECG machine, and the medical assistants were recently trained how to use the machine. While you believe her cardiac risk factors to be very low, since you have the resource available, you decide to obtain an ECG for the sake of completeness.

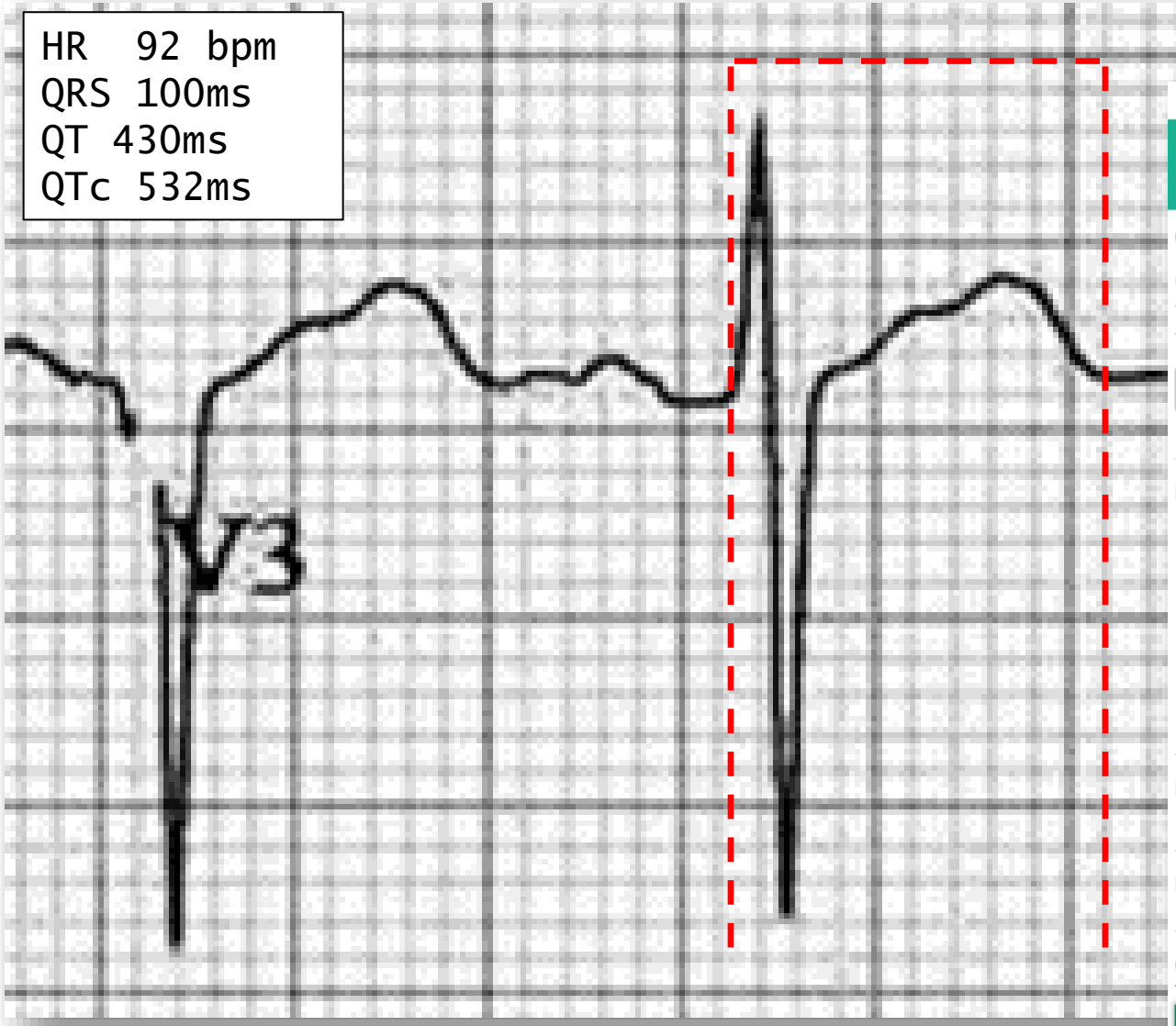

HR 92 bpm
QRS 100ms
QT 430ms
QTc 532ms
!!!???
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

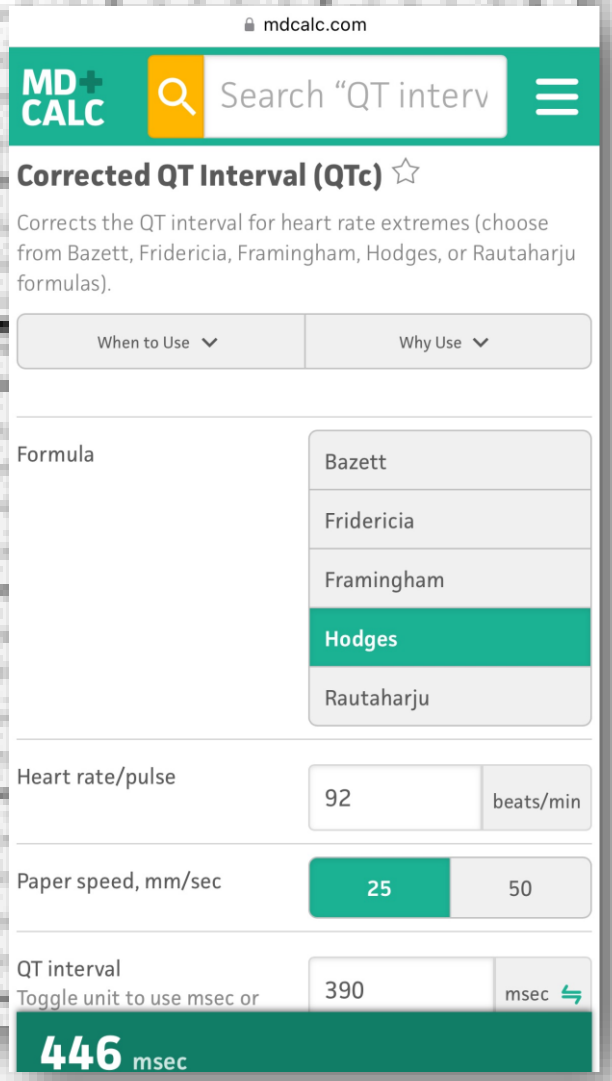
Risk Factors for TdP

Non-modifiable risk factors	Modifiable risk factors
● Female sex ● Advanced age ● Metabolizer status ● Congenital long QT syndrome ● Personal history of drug-induced QTc prolongation ● Personal history of structural or functional cardiac disease ● Family history of sudden cardiac death	● Use of ≥1 QTc prolonging drug(s) ● Pharmacokinetic drug-drug interactions ● Drug toxicity ● Severe acute illness ● Bradycardia ● Starvation ● Hepatic impairment ● Renal impairment, hemodialysis ● Risk or presence of hypokalemia, hypomagnesemia or hypocalcemia

Funk et al., 2020

QT = 390 ms





QTc (B) = 483 ms
QTc (H) = 446 ms
QTc (Fri) = 450 ms
QTc (Fra) = 444 ms

Considerations for ECG Monitoring

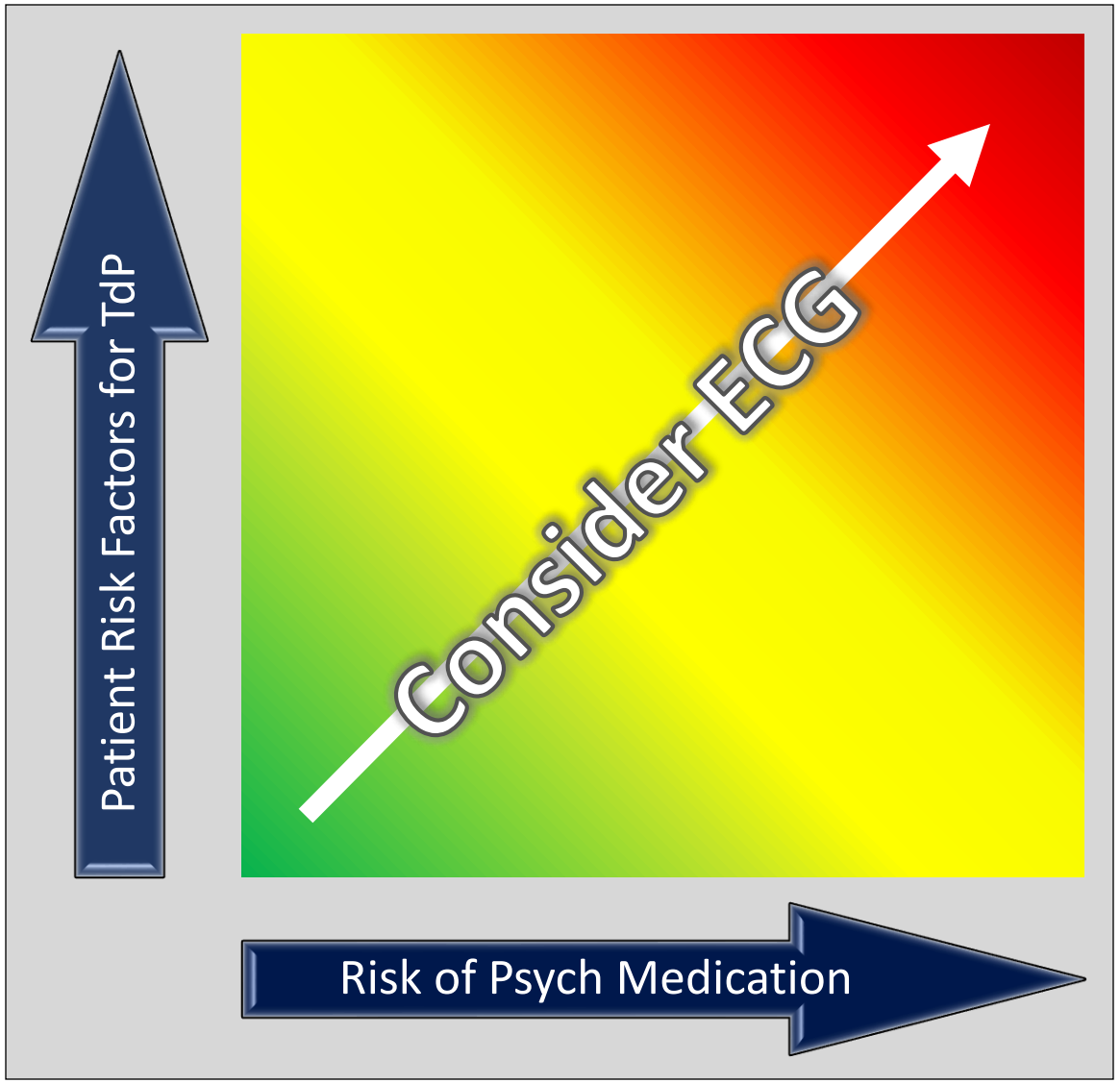
When to Obtain An Outpatient ECG?

Non-Modifiable Risk Factors For TdP

- Older Age
- Female Sex
- Functional structural heart disease
- Prior QTc prolongation or TdP
- Prior arrhythmia
- Prior cardiac arrest
- Family history arrhythmia, cardiac arrest, sudden cardiac death

Modifiable Risk Factors For TdP

- Hypokalemia
- Hypocalcemia
- Hypomagnesemia
- Bradycardia
- Renal Dysfunction
- Hemodialysis
- Liver Dysfunction
- Impaired drug metabolism
- Drug-Drug interactions
- Taking one or more QTc-prolonging drugs



Low Risk Medications

- Most SSRIs & SNRIs
- Benzodiazepines
- Valproic Acid
- Buprenorphine
- Aripiprazole
- Lurasidone

Moderate Risk Medications

- Citalopram
- Quetiapine, Risperidone, Olanzapine, Haloperidol
- Trazodone

High Risk Medication

- Methadone
- Ziprasidone
- Iloperidone
- Low -Potency Phenothiazines
- Tricyclic Antidepressants

Considerations for Outpatient ECG Monitoring

When to Obtain Baseline ECG?

No ECG Needed

No risk factors for TdP **AND**
Not prescribing High-Risk Drug

Obtain ECG

Multiple Risk Factors
for TdP **AND** Any Drug

Obtain ECG

No Risk Factors for TdP
AND High-Risk Drug

Obtain ECG AND Consider Consulting Existing Cardiologist

Risk Factors for TdP **AND** High-Risk Drug

Interpreting Baseline and Drug Steady State ECG

Proceed with Medication

QTc < 500ms **AND**
No increase of QTc by ≥ 60ms

Proceed w/ Caution: Careful Risk-Benefit Analysis

QTc > 500ms **OR** Increase of QTc ≥ 60ms

When to Consult Cardiology?

Cardiology Consultation

High-Risk Drug **AND**
QTc > 500ms **OR** Increase QTc ≥ 60ms

Immediate Cardiology (ER)

Cardiac symptoms
(dizziness, syncope, palpitations)

Methadone Safety Guidelines

Risk Factors

- Older Age
- Female Sex
- Functional structural heart dz
- Prior QTc prolongation or TdP
- Prior arrhythmia
- Prior cardiac arrest
- Family history arrhythmia, cardiac arrest, sudden cardiac death
- Hypokalemia
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Methadone Safety Guidelines

American Pain Society and Heart Rhythm Society, 2014

Baseline ECG

Obtain If:

- Risk Factors for TdP
- Prior ECG with QTc > 450ms

Consider Obtaining If:

- No risk factors for QTc prolongation/ TdP

ECG Contingencies

Consider Alternatives
when baseline QTc > 450ms <500ms

Recommend Against Use
when baseline QTc > 500ms

Considerations for All Patients

Evaluate and correct reversible causes QTc prolongation before initiation

Balance risk of TdP with risk of untreated Opioid Use Disorder

Adapted from Chou R. et al., 2014

Clinical Case 2

44 y/o man with a family history of cardiac arrest in his grandfather, father, and paternal aunt, tests positive for a genetic cardiomyopathy with high risk for sudden cardiac death. He has never had any arrhythmias or cardiac symptoms. He is implanted with a subcutaneous Implantable Cardioverter Defibrillator (ICD) for primary prevention.

His past medical and psychiatric history is notable for hyperlipidemia, recurrent sinus infections, and depression. He takes simvastatin, escitalopram, and is frequently prescribed a Z-pack (azithromycin) by his PCP.

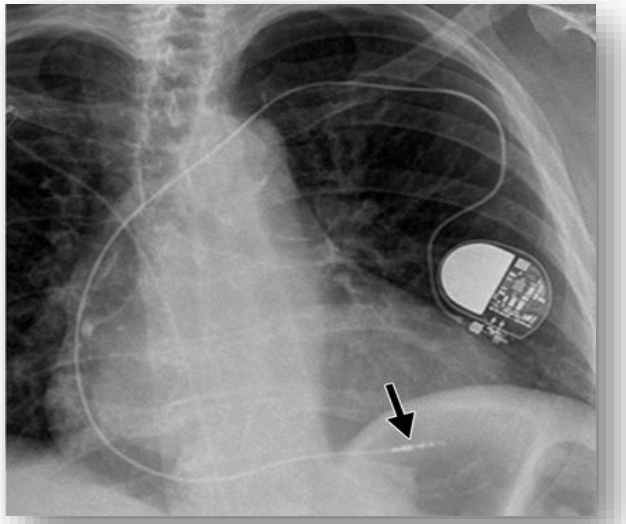
He develops a viral GI illness with multiple days of vomiting and diarrhea, not able to keep anything down. He presents to the ED for dehydration where his QTc(H) is 522ms, K+ is 2.7. The ED resident orders ondansetron for nausea. When another ED resident questions this decision due to Torsades risk, the first resident says “Don’t worry about it. He has an ICD.”

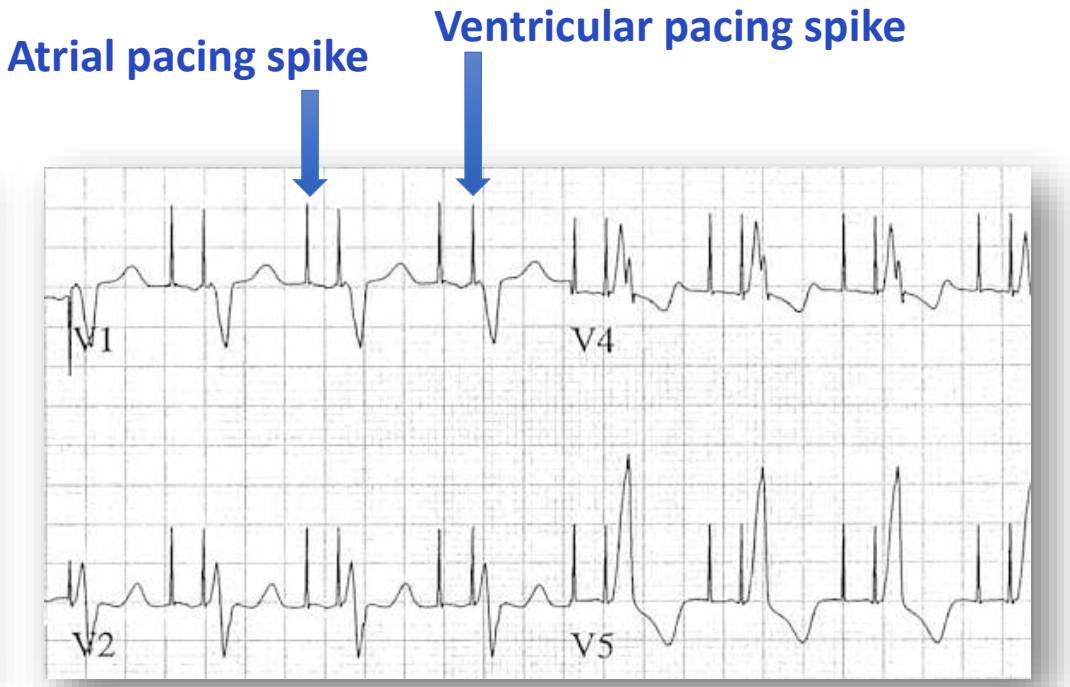
Should they worry about it?

Role of Pacemakers and Defibrillators

Permanent Pacemaker (PPM)

Indication: treatment of brady-arrhythmias
Goal: to sustain adequate HR for daily activity
How does it work? Paces the heart if the HR drops below the pacing threshold (usually 30-40 bpm)





Aguilera AL, Volokhina YV, Fisher KL. Radiographics. 2011

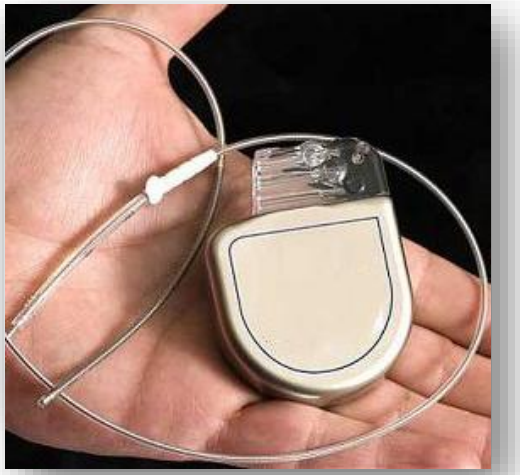
Implantable Cardioverter Defibrillator (ICD)

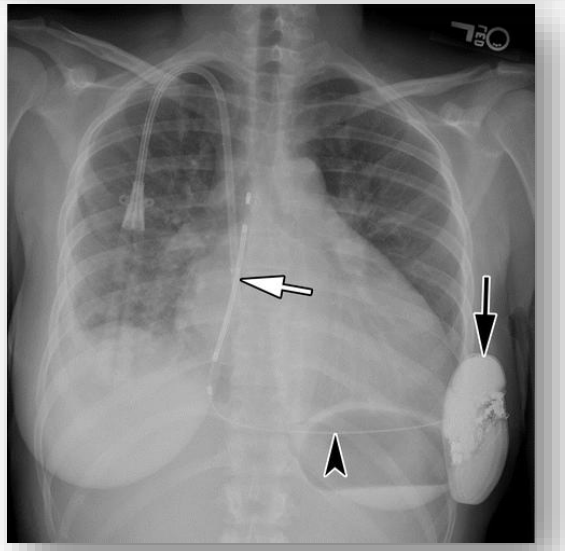
Primary Prevention:

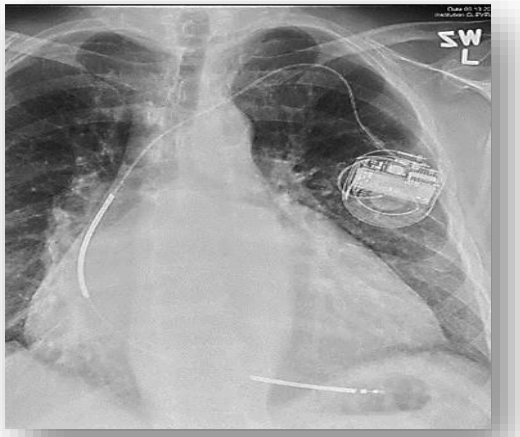
- CAD + Heart failure LVEF ≤ 35%
- Dilated Cardiomyopathy
- Certain Pathogenic Gene Mutations
- Arrhythmogenic RV Cardiomyopathy
- Congenital Long QT Syndrome
- Asymptomatic QTc > 500ms during β-Blocker
- Brugada syndrome + symptoms/ inducible AF

Secondary Prevention:

- VF sudden cardiac arrest
- sustained VT
- Hemodynamically not-tolerated VT





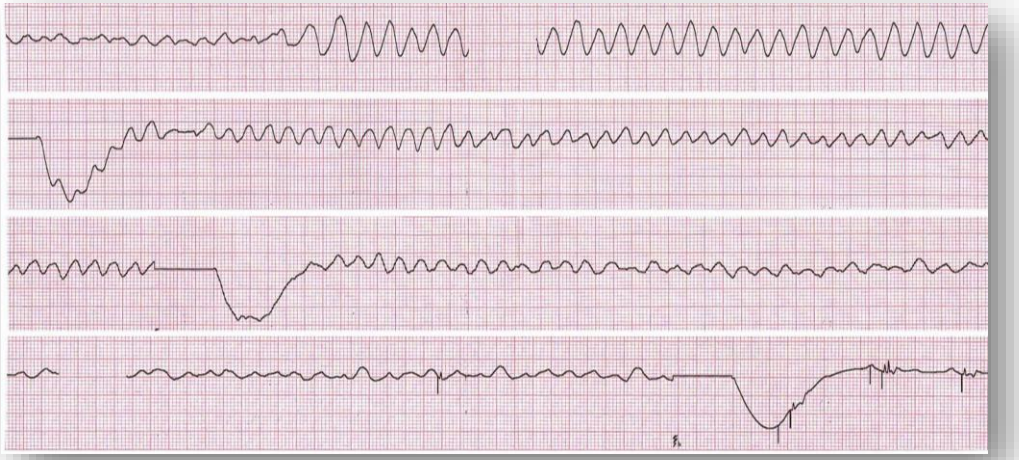


Al-Khatib. ACC/AHA/HRS 2017 Guidelines for Management of Patients with ventricular arrhythmias and the prevention of SCD.

Implantable Cardioverter Defibrillator (ICD)

ICDs can readily terminate most VT/VF effectively, but…

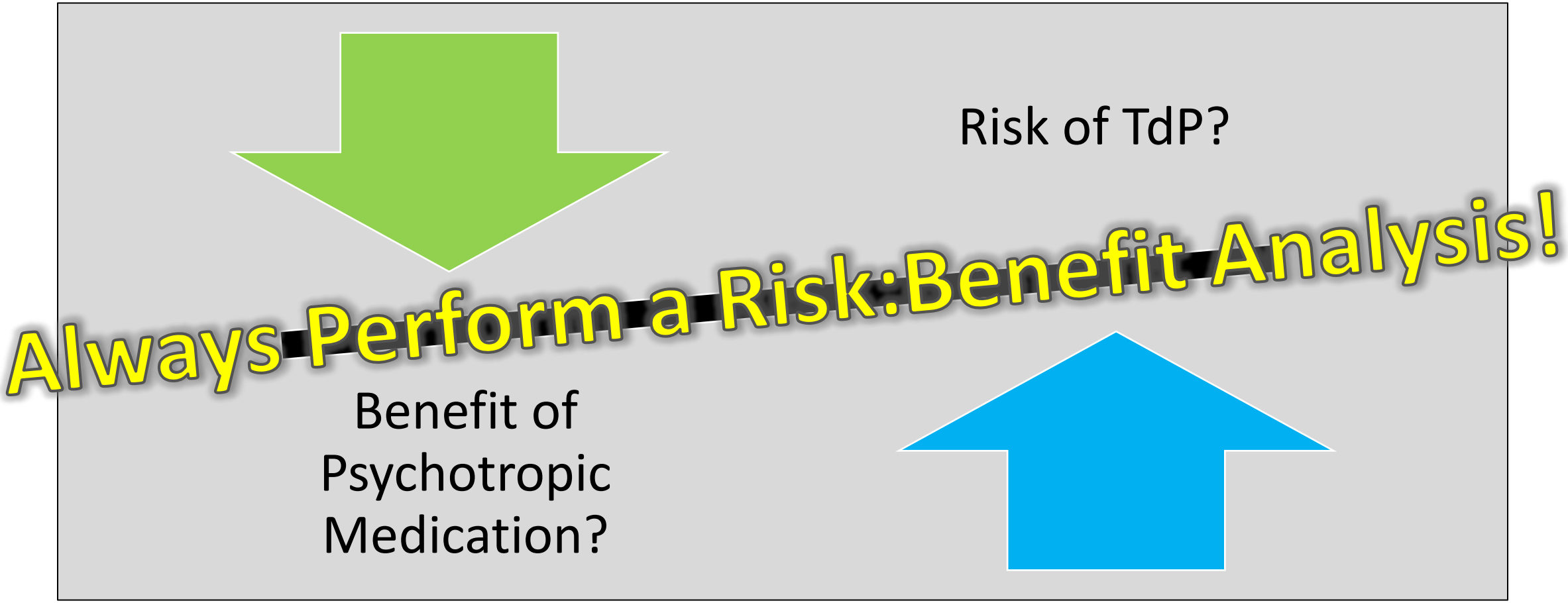
- Even appropriate shocks are independently associated with increased risks of death and worsening heart failure
- Some VT will recur if substrates are unchanged, despite “successful” shocks
- ICD “storms” are common, which lead to significant psychological morbidity (anxiety, depression, PTSD, panic)
- **A shock does not occur without morbidity!**



Risk-Benefit Analysis

Risk-Benefit Analysis

To Prescribe or Not to Prescribe?



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Should they worry about it? **YES!**

Clinical Case 2

The first ED resident keeps the ondansetron order but puts the patient on telemetry for monitoring. The patient is administered 4mg IV x 2. Forty minutes after the second dose of ondansetron, the patient suddenly yells out. Telemetry shows that he was in Torsades and shocked back to a normal sinus rhythm by his ICD.

Four minutes later, he is shocked again and in sum receives a total of 10 shocks in the span of just minutes.

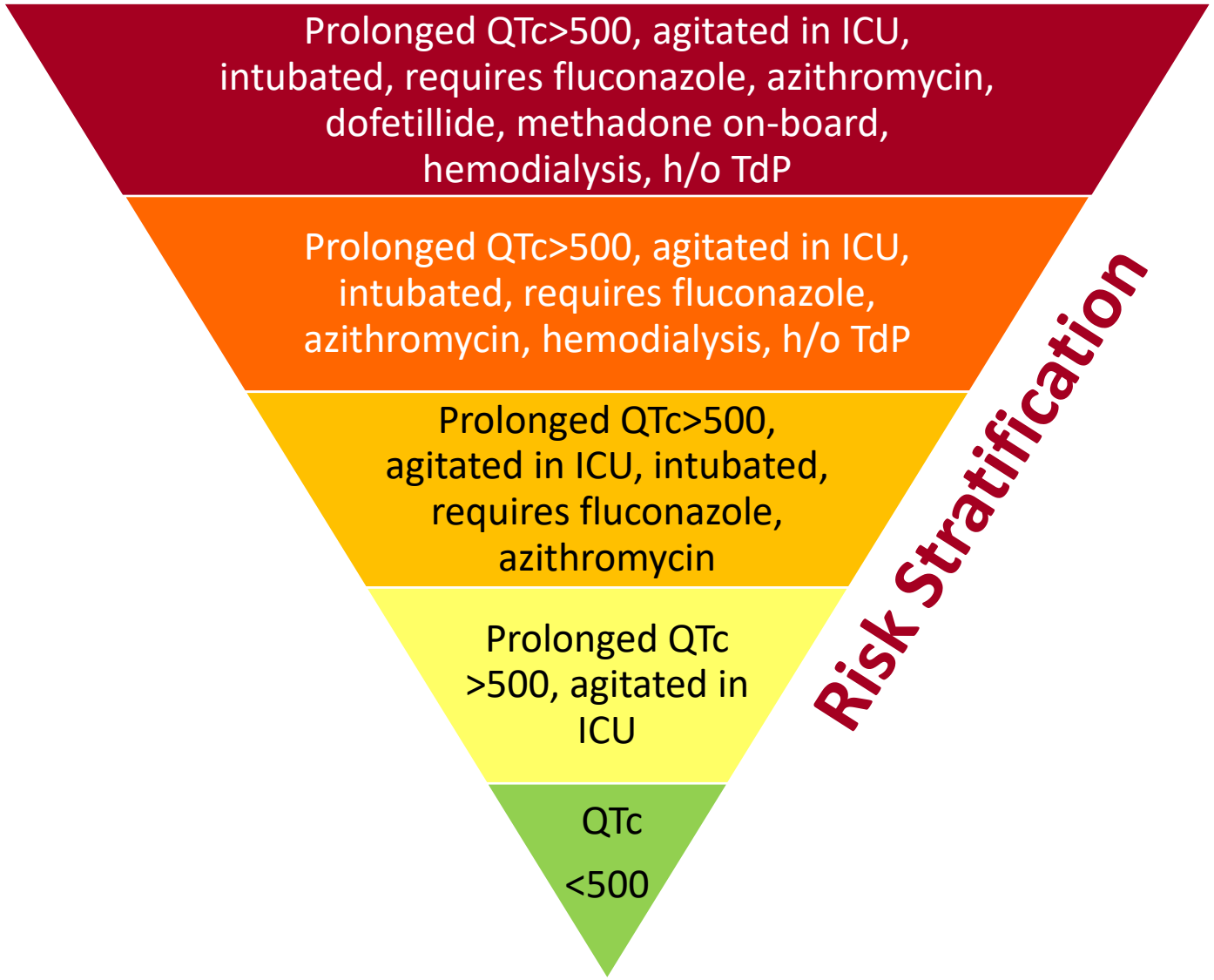
He is transferred to the CCU for further monitoring and treatment. As the psychiatry consultant, you are called later in the day for management of agitation.

Risk-Benefit Analysis: ICU Example

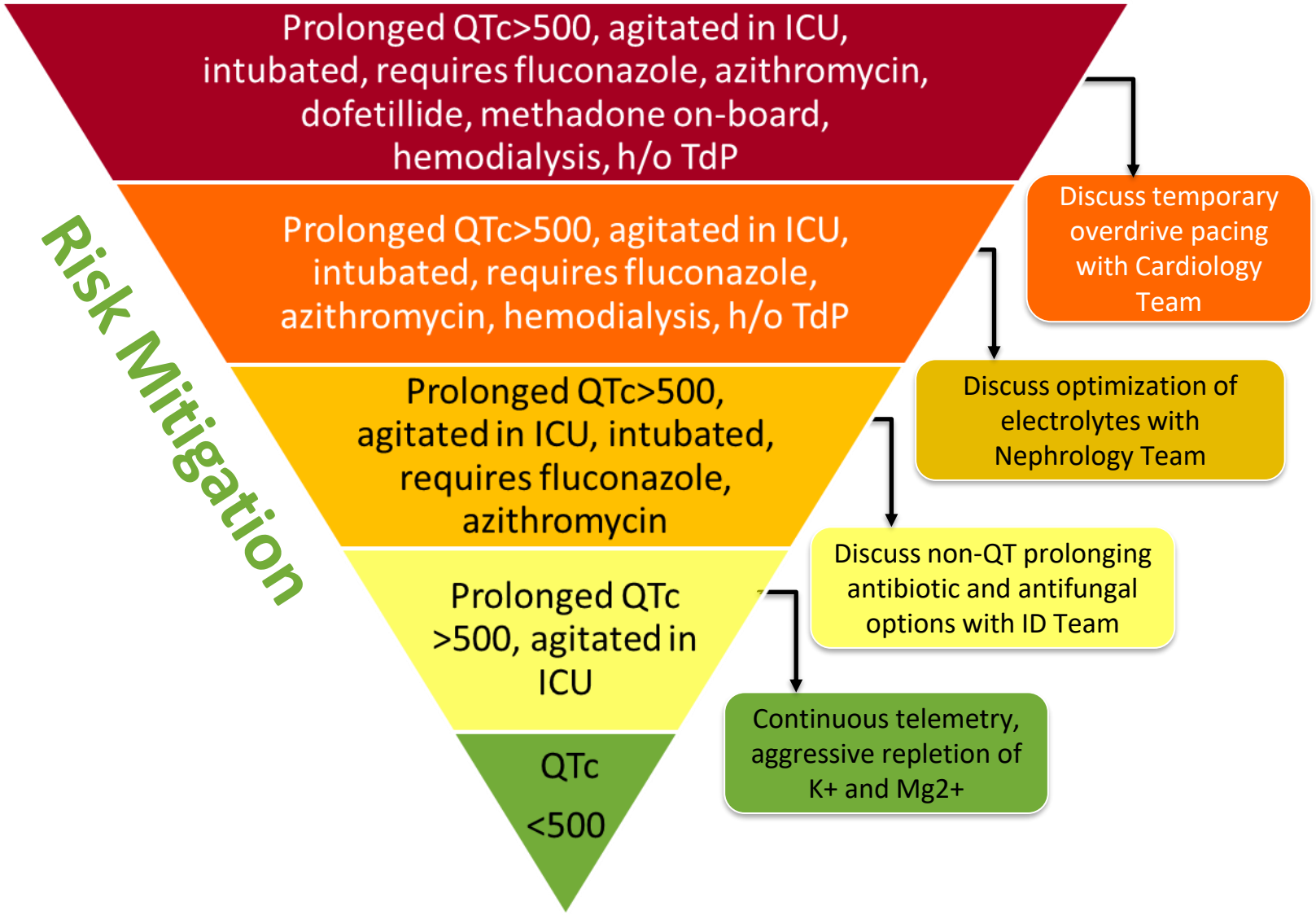
Very nature of being in ICU
Concurrent QT-prolonging medications
Parenteral administration
Susceptible to fluid shifts and electrolyte imbalance
Likely to have renal/hepatic dysfunction
Older Age

Control of Agitation
Protection of patient from injury
Protection of life-sustaining external lines/ devices
Prevent re-intubation and sedation
Prevent use of restraints

Risk Stratification & Mitigation



Risk Stratification & Mitigation

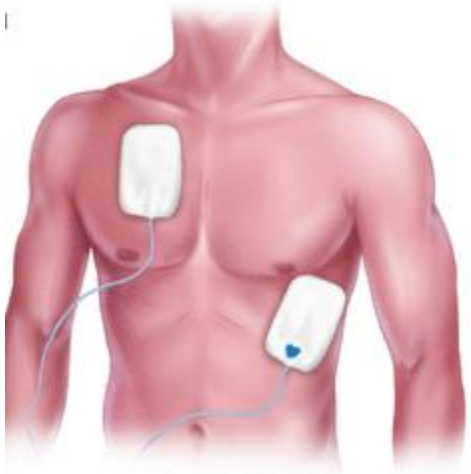


High Risk Mitigation Strategies

High-Risk Mitigation Strategies

Cardiac Overdrive Pacing

- In high-risk cases with severe bradycardia
- Overdrive pacing > 70 bpm can mitigate risk of early-after-depolarizations that can lead to a reentrant rhythm
- Nearly all cardiac implanted electronic devices have capability for overdrive pacing (except subQ ICDs)
- Pacing thresholds usually set to HR 40-50 to preserve battery-life and ventricular strain, HOWEVER pacing rates can be increased in high-risk patients
- Alternatively may consider temporary transvenous pacing or “chemical” overdrive pacing with isoproterenol (less common)

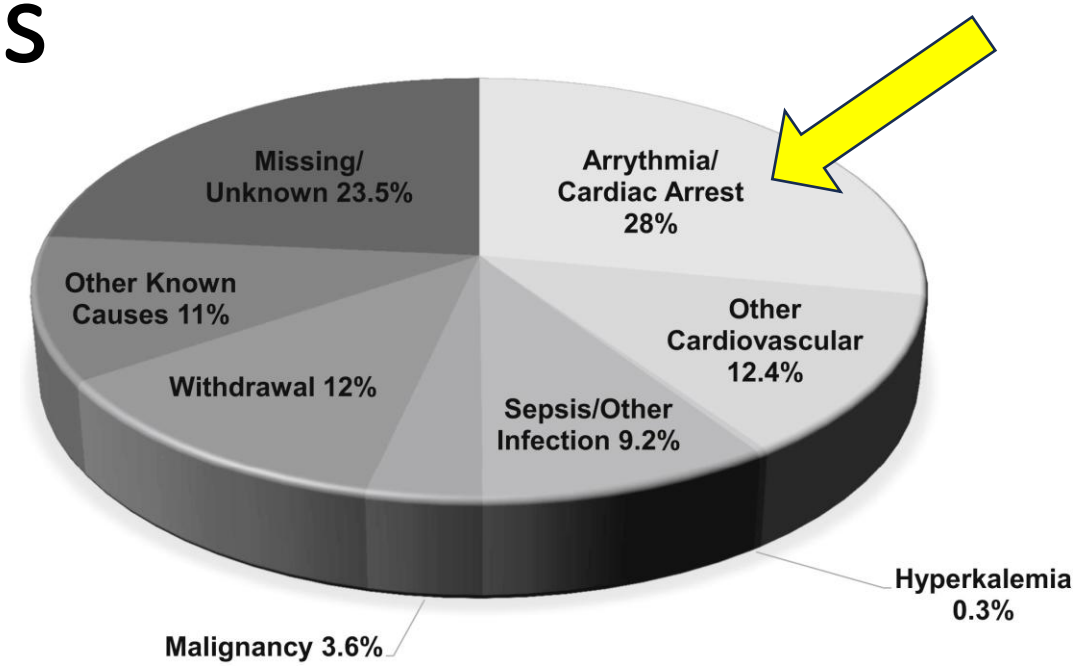


Pinski et al., 2002 Lankipalli et al., 2005

High-Risk Mitigation Strategies

Hemodialysis

- Sudden cardiac death (SCD) is leading cause of death in hemodialysis patients
- QTc prolongation very common in hemodialysis patients
- Contradicting studies regarding impact of dialysate electrolyte concentrations and serum-to-dialysate gradient measures on QTc
- Goal K+ in HD patients is 5.1
- **Work closely with nephrology in high-risk patients on HD**



Kim et al., 2019, Predictors of Arrhythmic and Cardiovascular Risk in ESRD, BMC Nephrology; Makar and Pun, 2017, AJKD

Take-Home Points

- Knowledge is power – practice ECG interpretation
- Do your own QT measurement and HR correction
- 500ms is not an absolute QTc cut-off
- Always perform a risk-benefit analysis
- Talk to your expert colleagues who can help mitigate risk

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