



The Risk of QTc Interval Prolongation with Psychotropics

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Disclosure: Christopher Celano, MD

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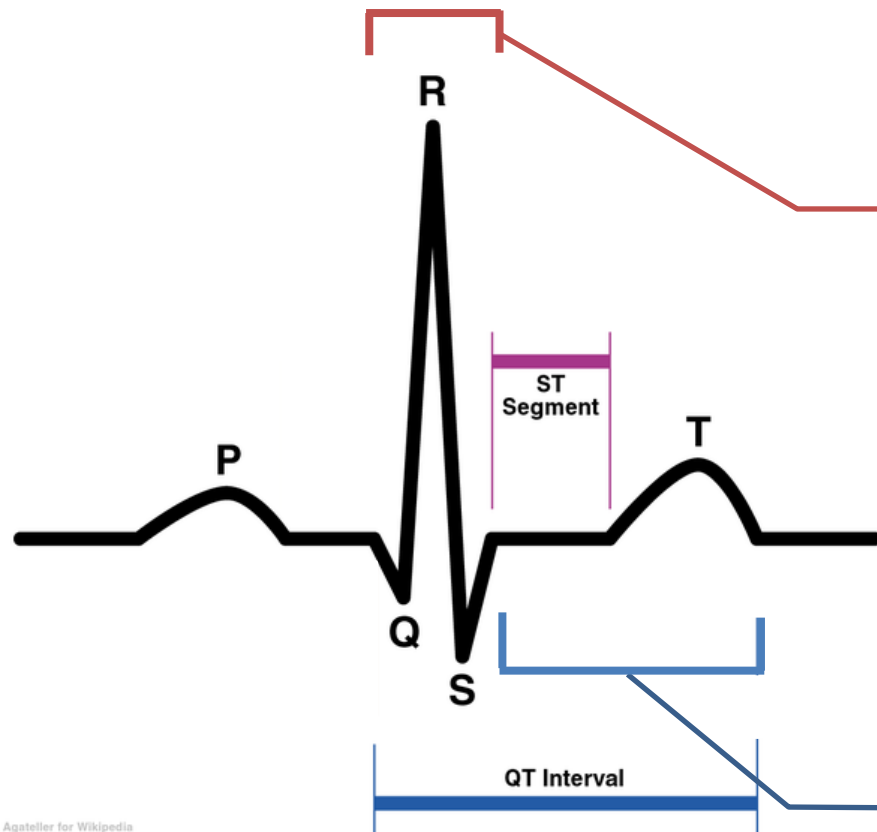
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Topics for Discussion

- QTc interval and its measurement
- Risk factors for QTc prolongation
- Relationships between psychiatric medications and QTc prolongation
- QTc monitoring in clinical practice

What is the QT interval?



QRS Complex =
ventricular depolarization

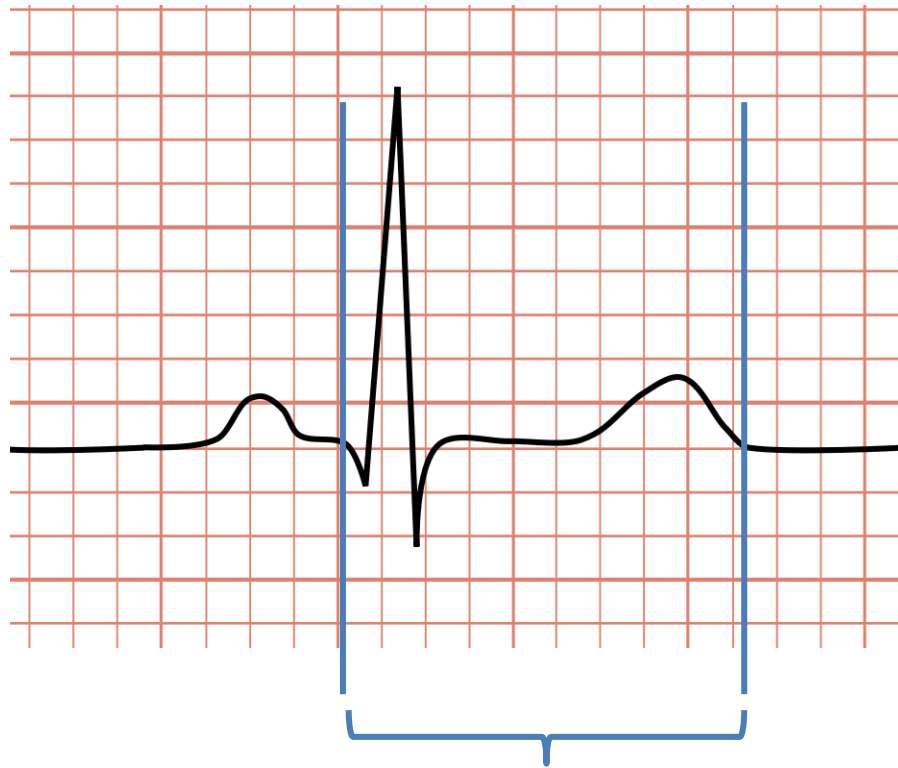
ST segment + T wave =
ventricular repolarization

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How to Measure QTc

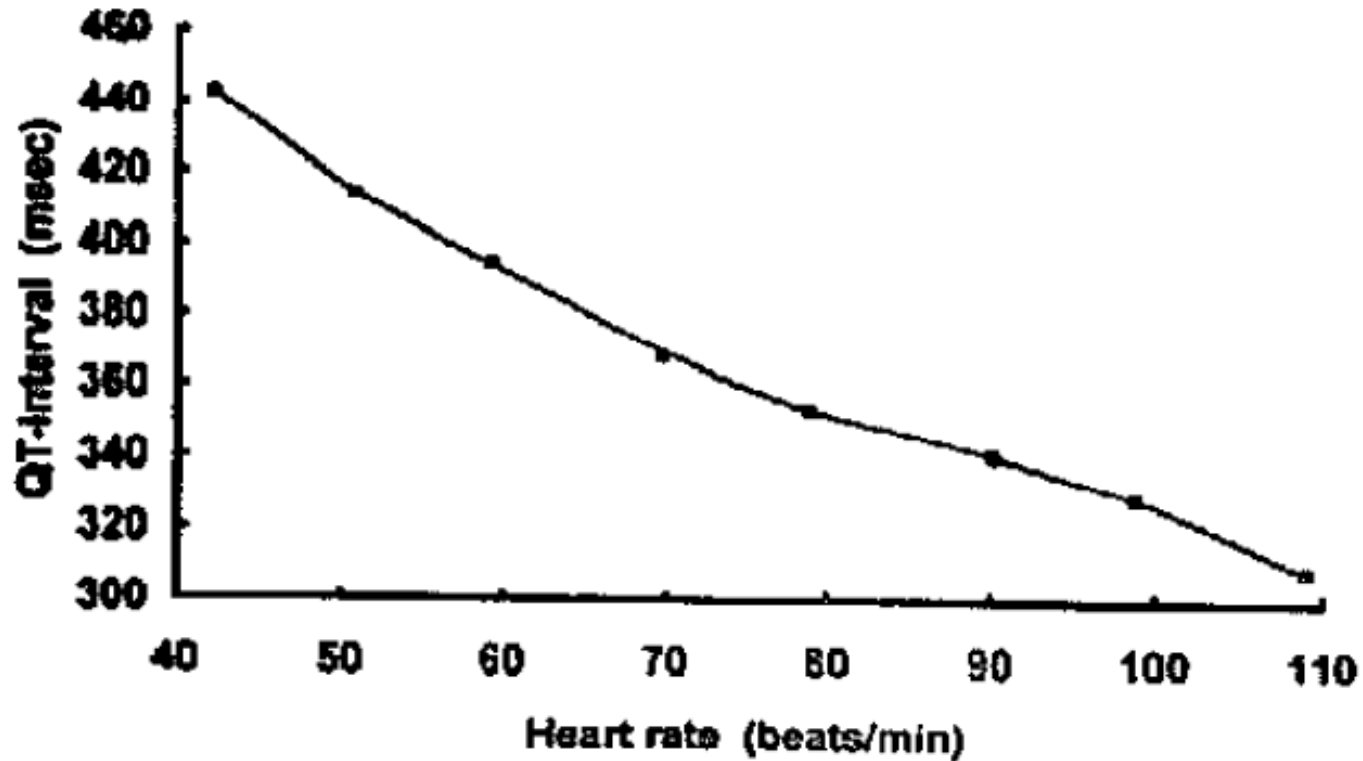
- Pick an appropriate lead on the ECG.
 - Usually II, V2, or V3.
- Measure the QT interval.
- Measure the heart rate or RR interval.
- Calculate the QTc.

Measure the QT interval



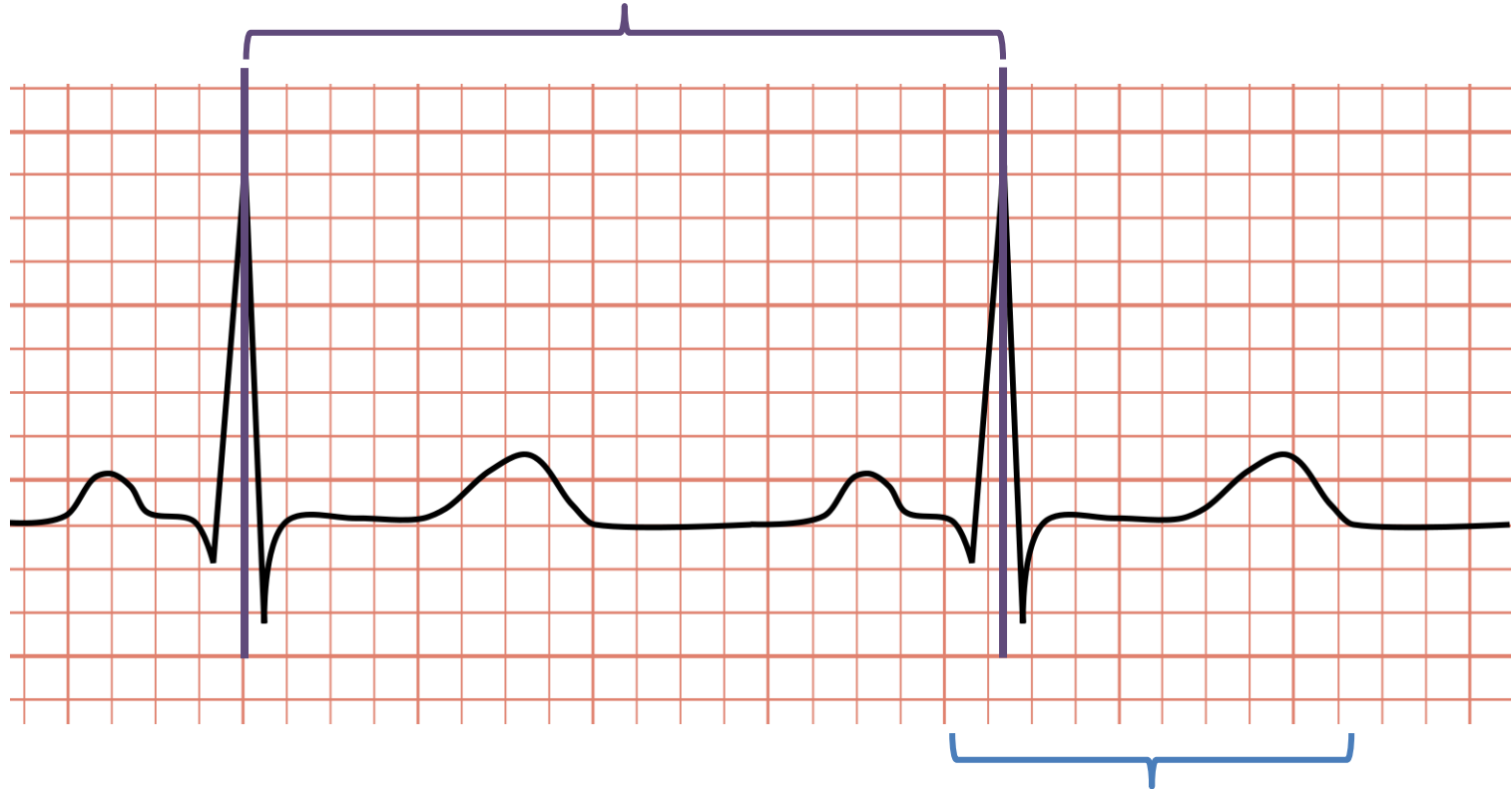
9 boxes + 10 msec
QT = 370 msec

QT intervals are HR-dependent



Measure the RR interval

17 boxes + 10 msec
RR = 690 msec
HR = 87 beats/minute



QT = 370 msec

Correction Formulae

| Method | Formula |
|------------|--------------------------------|
| Bazett | $QTc = QT / \sqrt{RR}$ |
| Fridericia | $QTc = QT / \sqrt[3]{RR}$ |
| Framingham | $QTc = QT + 0.154 (1000 - RR)$ |
| Hodges | $QTc = QT + 1.75(HR - 60)$ |

Bazett:

$$QTc = 0.370 / \sqrt{0.690}$$

$$QTc = 0.445$$

$$QTc = 445 \text{ msec}$$

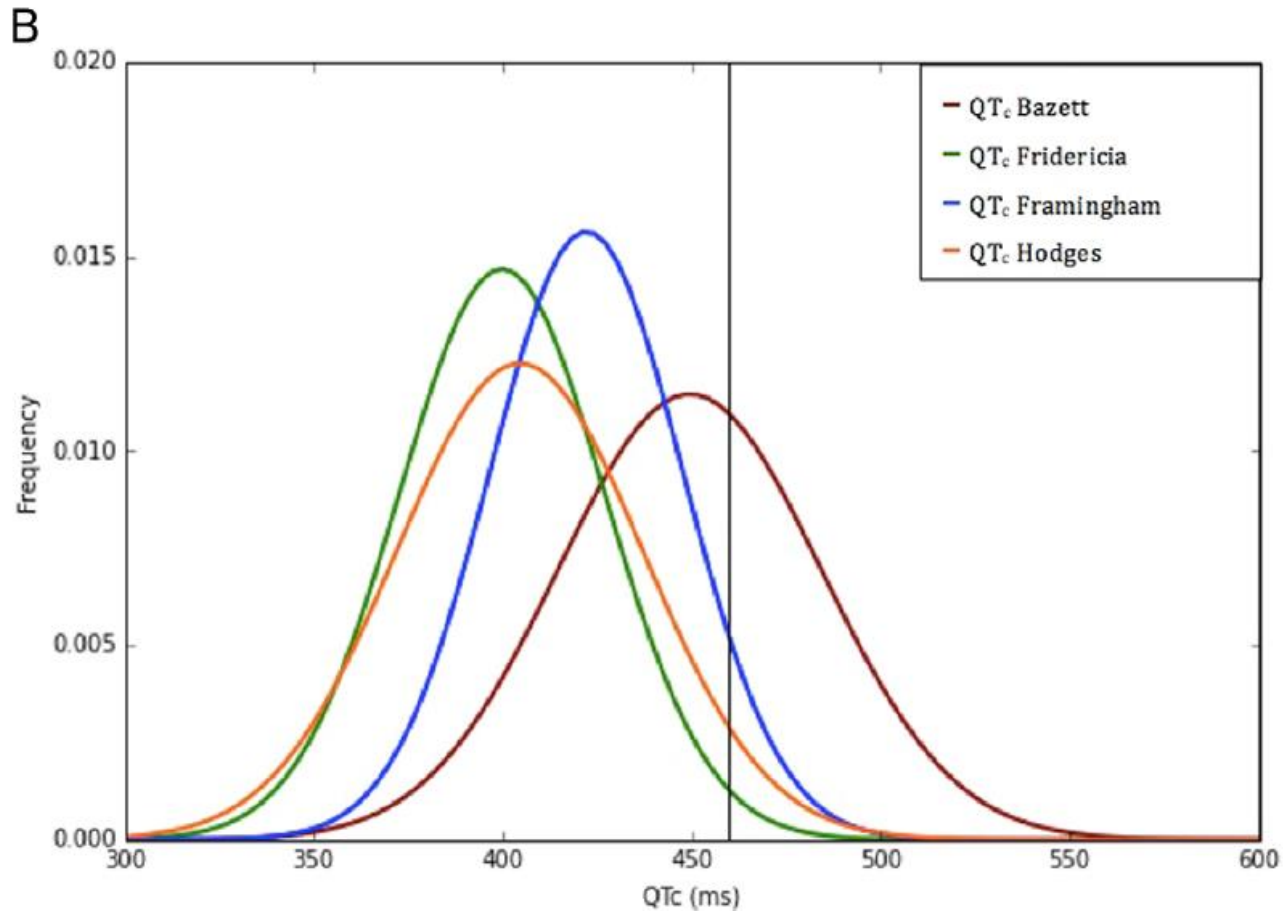
Hodges:

$$QTc = 370 + 1.75 (87-60)$$

$$QTc = 370 + 47.25$$

$$QTc = 417 \text{ msec}$$

QTc Correction Methods



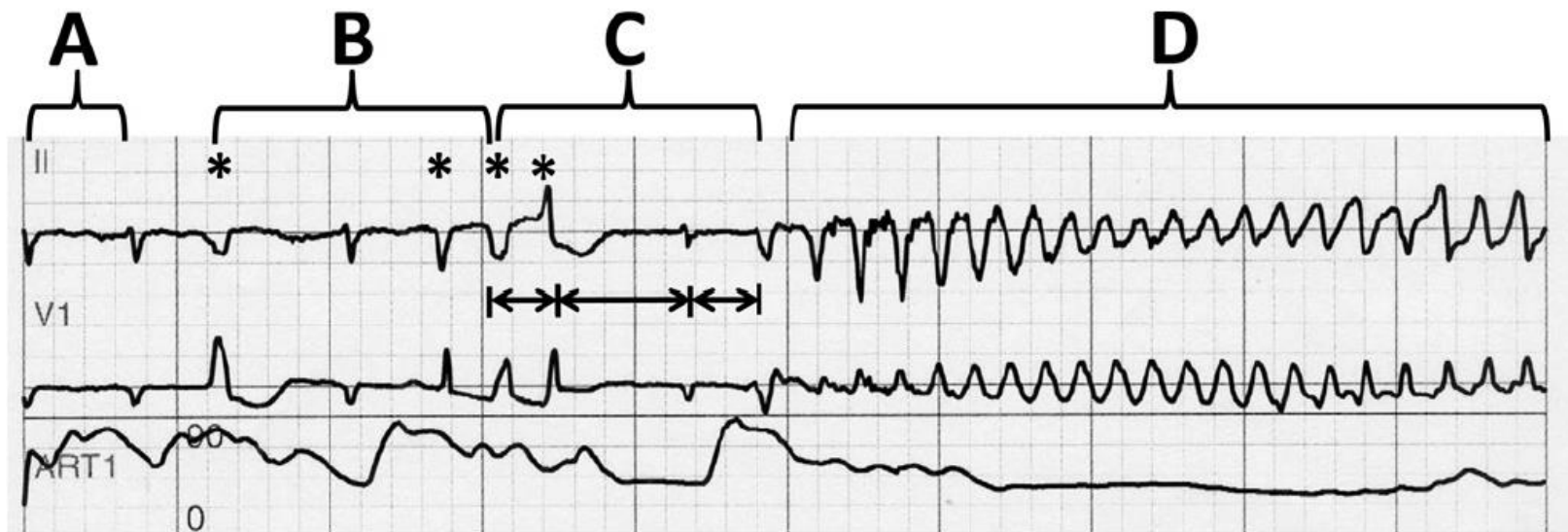
Normal Ranges

| Rating | Adult Men | Adult Women |
|------------|--------------|--------------|
| Normal | < 430 msec | < 450 msec |
| Borderline | 431-450 msec | 451-470 msec |
| Prolonged | > 450 msec | > 470 msec |

However, we generally become more concerned if QTc > 500 msec.

Why do we worry about QTc prolongation?

- Torsades de pointes (TdP)
 - “Twisting of the points”
 - May lead to sudden syncope or dizziness



Risk Factors for QTc Prolongation

- Female gender
- Increased age
- Congenital Long QT Syndrome
- Structural Cardiovascular Disease
- COVID-19 and its treatments*
- Electrolyte abnormalities
- Hepatic dysfunction
- Other medications that prolong QTc
- Metabolic inhibitors

Psychiatric Medications and QTc

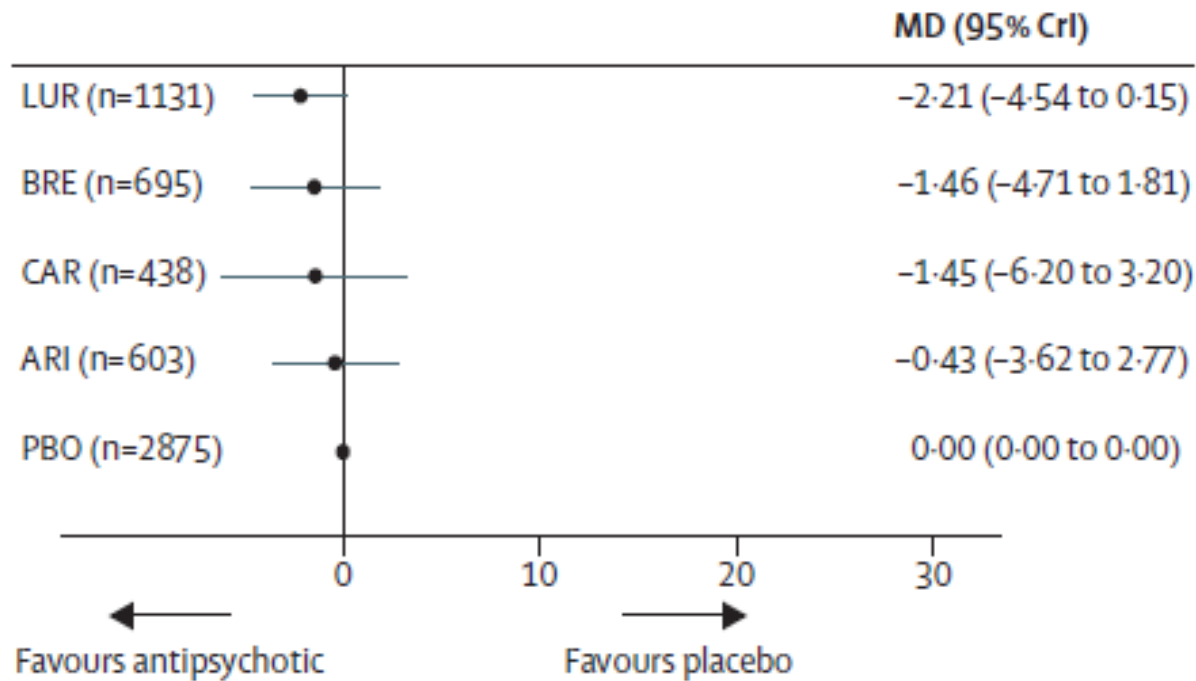
- Antipsychotic Medications
 - First Generation
 - Second Generation
- Antidepressants
 - SSRIs
 - Tricyclic Antidepressants
 - Atypical Antidepressants
- Other psychiatric medications

Antipsychotic medications

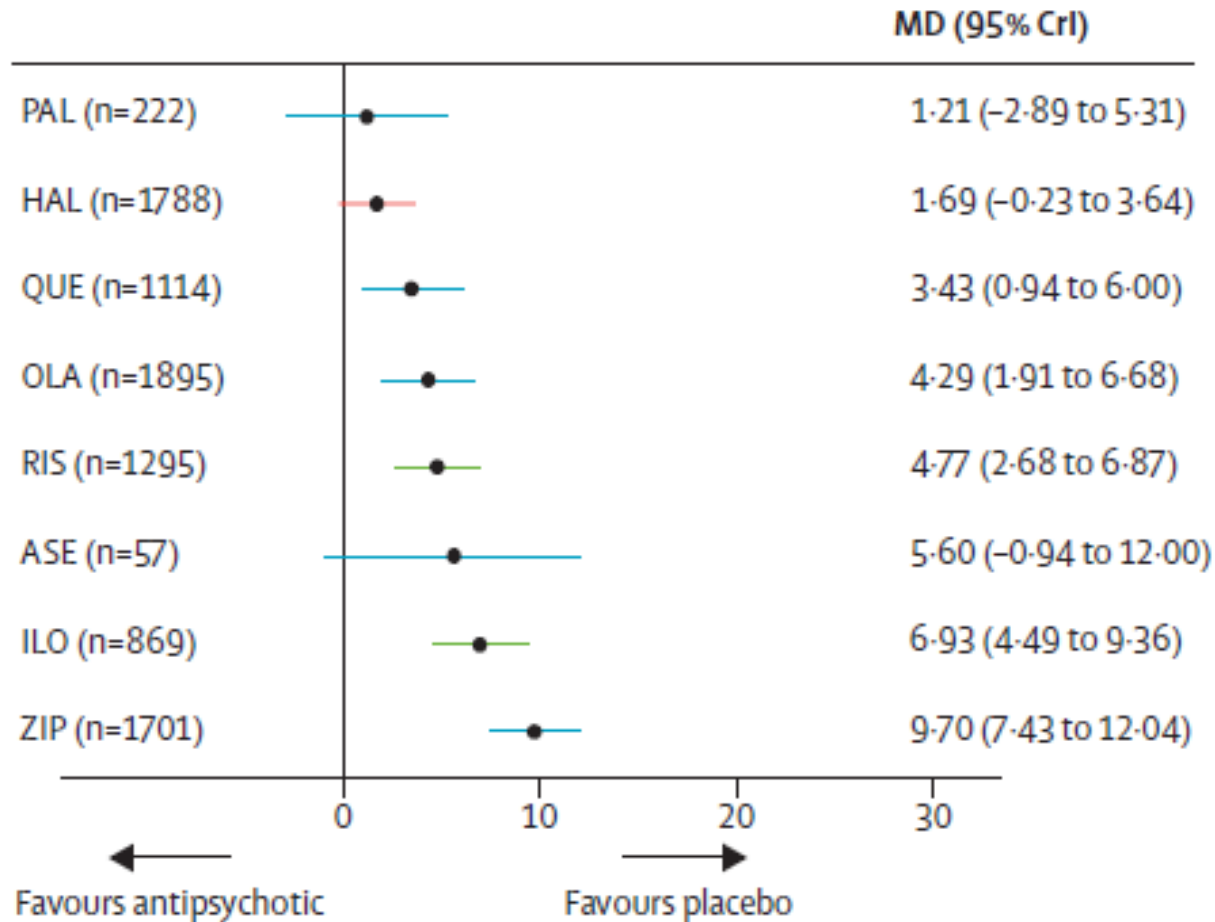
- Nearly all antipsychotics prolong QTc, but the degree of prolongation differs substantially among agents.
- Haloperidol
 - In oral form, haloperidol leads to QT prolongation that is similar to aripiprazole, quetiapine, and asenapine.
 - Intravenous form may lead to higher risk of QTc prolongation, with some caveats.
 - FDA recommends cardiac monitoring for patients receiving intravenous haloperidol.

Antipsychotic Medications

- Second generation antipsychotics



Antipsychotic Medications



Antipsychotic Medications

- Second generation antipsychotics
 - Highest risk: ziprasidone and iloperidone
 - Lowest risk: aripiprazole and lurasidone
 - FDA warnings
 - Ziprasidone (black box)
 - Quetiapine
 - Intravenous haloperidol
 - There may be a dose-response relationship for antipsychotics and QTc, but evidence is mixed.

Antipsychotic Medications and Mortality

- Both first- and second-generation antipsychotics have been linked to ventricular arrhythmias or sudden cardiac death.
 - Case-crossover study (N=17,718)
 - OR=1.53
 - Haloperidol, prochlorperazine, thioridazine, quetiapine, and risperidone were associated with increased risk.
- FDA black box warning for second-generation antipsychotics in elderly patients with dementia.

Antidepressants and QTc

- SSRIs
 - Initially thought to be quite safe
 - SADHART, ENRICHED, CREATE
 - FDA warnings:
 - Initial
 - Citalopram should not be prescribed at doses greater than 40mg
 - Citalopram should not be used at doses >20mg in those with liver dysfunction or over age 60
 - Revision
 - Citalopram is not recommended at doses greater than 40mg
 - Citalopram should be discontinued in anyone with QTc>500 ms

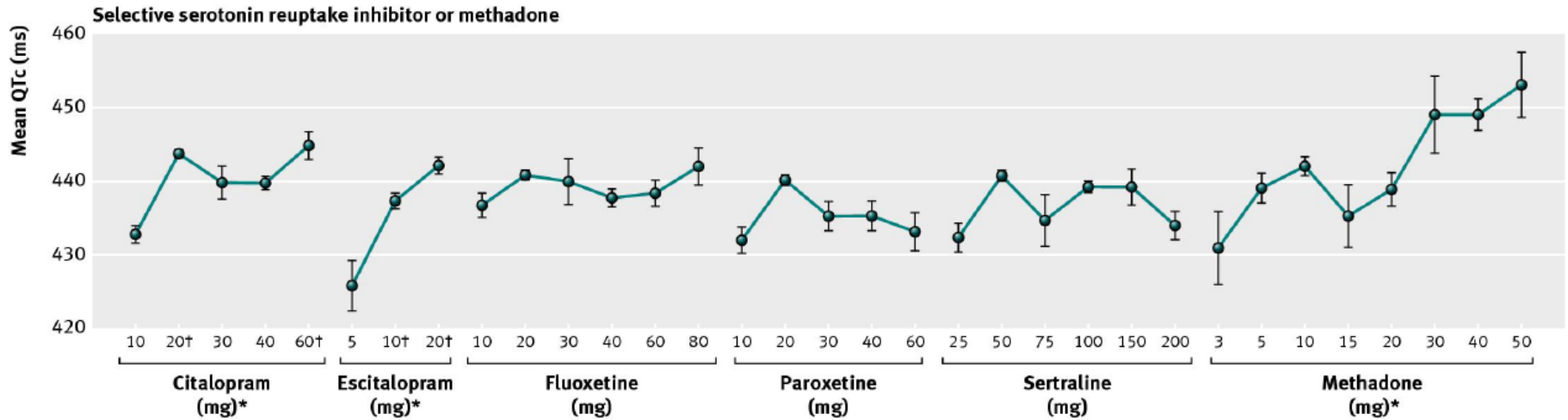
Citalopram and QTc

| Medication and dose | QT prolongation (95% CI) |
|--------------------------|--------------------------|
| Citalopram 20mg daily | 8.5 (6.2, 10.8) |
| Citalopram 40mg daily | 12.6 (10.9, 14.3) |
| Citalopram 60mg daily | 18.5 (16.0, 21.0) |
| Moxifloxacin 400mg daily | 13.4 (10.9, 15.9) |

Escitalopram and QTc

| Medication and dose | QT prolongation (95% CI) |
|--------------------------|--------------------------|
| Escitalopram 10mg daily | 4.5 (2.5, 6.4) |
| Escitalopram 20mg daily | 6.6 (5.3, 7.9) |
| Escitalopram 30mg daily | 10.7 (8.7, 12.7) |
| Moxifloxacin 400mg daily | 9.0 (7.3, 10.8) |

Effects of SSRIs on QTc

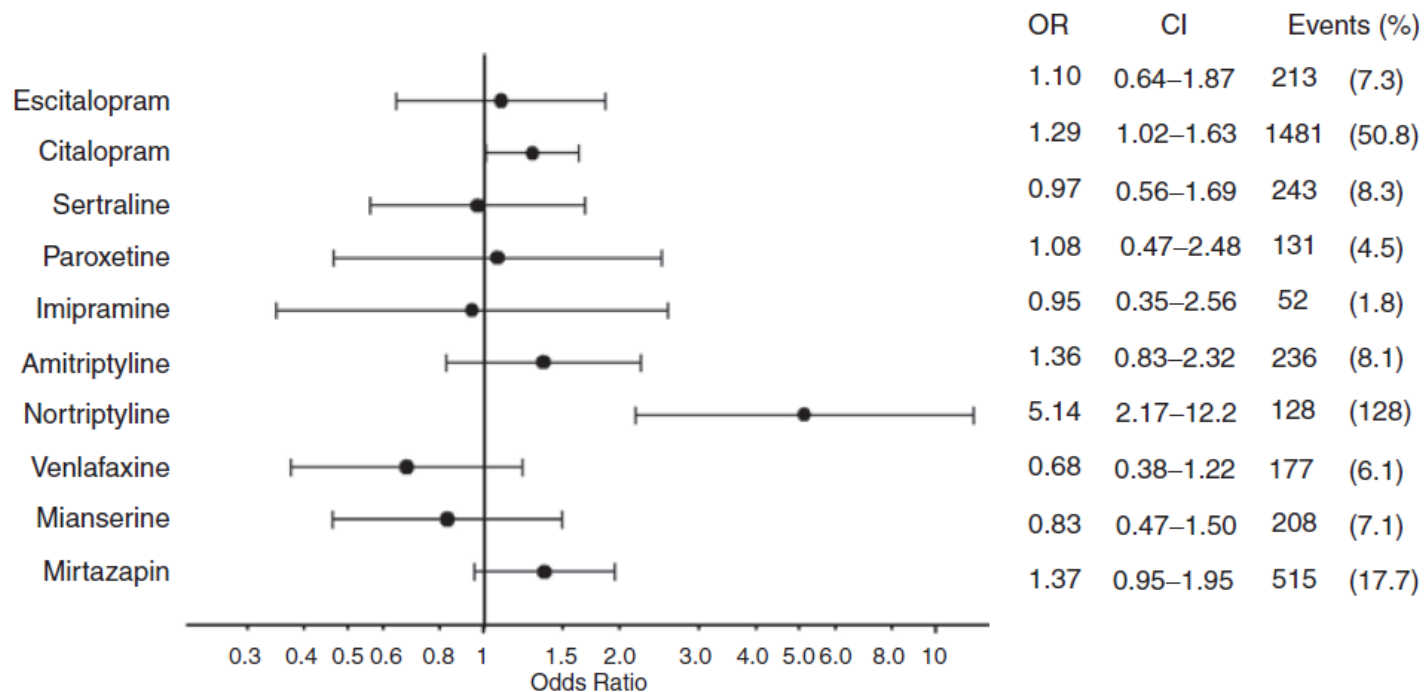


Effects of Antidepressants on QTc

| Medication | N | Difference in QTc (ms) | p-value |
|--------------|-------|------------------------|---------|
| Citalopram | 696 | 10.58 | .002 |
| Escitalopram | 360 | 7.27 | <.0001 |
| Fluoxetine | 135 | 4.50 | .32 |
| Fluvoxamine | 27 | -5.00 | <.0001 |
| Paroxetine | 1486 | -1.04 | .67 |
| Sertraline | 369 | 3.00 | <.0001 |
| SSRIs | 3,079 | 6.10 | <.001 |
| TCAs | 1,587 | 10.01 | <.001 |

SSRIs and Ventricular Arrhythmias

- Evidence is less clear
 - Danish case-time-control study



SSRIs and Ventricular Arrhythmias

- Tennessee Medicaid Cohort Study
 - Retrospective cohort study of 54,220 patients receiving high dose citalopram (>40mg daily) or escitalopram (>20mg daily) or equivalent doses of other SSRIs.
 - Neither citalopram nor escitalopram had higher risks of sudden unexpected death or all-cause mortality than other SSRIs.
- Patient-level meta-analysis for escitalopram
 - Escitalopram led to mild 3.5msec increases in QTc, compared to placebo.
 - Rates of cardiovascular side effects were similar between escitalopram and placebo.

Tricyclic Antidepressants and QTc

- Tricyclic antidepressants
 - Affect sodium, calcium, and potassium channels
 - Generally are considered to be higher risk for QTc prolongation than SSRIs
 - Have other cardiovascular side effects as well

Atypical Antidepressants and QTc

- Venlafaxine
 - Minimal risk at therapeutic doses (1 case report), low risk in overdose (1%).
- Bupropion
 - Associated with QTc prolongation in overdose; possibly confounded by tachycardia
- Trazodone
 - Associated with mild QTc prolongation in overdose
- Mirtazapine
 - No clear QTc prolongation risk, though it has been associated with a higher risk of SCD or ventricular arrhythmias than paroxetine in one study
- Newest antidepressants (duloxetine, vilazodone, vortioxetine, levomilnacipran, desvenlafaxine, brexpiprazole)
 - Not associated with clinically meaningful QT prolongation

Other Psychiatric Medications and QTc

- Lithium
 - Can cause QTc prolongation at levels > 1.2 mmol/L
- Anticonvulsants
 - Not associated with QTc prolongation
- Stimulants
 - Not associated with QTc prolongation
- Benzodiazepines
 - Not associated with QTc prolongation

Other Psychiatric Medications and QTc

- Acetylcholinesterase Inhibitors
 - Donepezil has been linked to QT prolongation in a cross-sectional study and case reports, though data are mixed.
 - Galantamine and rivastigmine have been noted in rare case reports.
 - Memantine has been linked to QT prolongation in rare case reports but not in an observational study.
- Antihistamines
 - Diphenhydramine and hydroxyzine have been linked to QT prolongation and TdP in case reports and pharmacovigilance studies, typically at toxic doses or with other risk factors.

Kuwahata 2021, Malone 2020, Park 2021, Takehara 2015, Kajitani 2016, Ali 2020, Ali 2021, Shah 2015, Schlit 2017, Vigne 2015

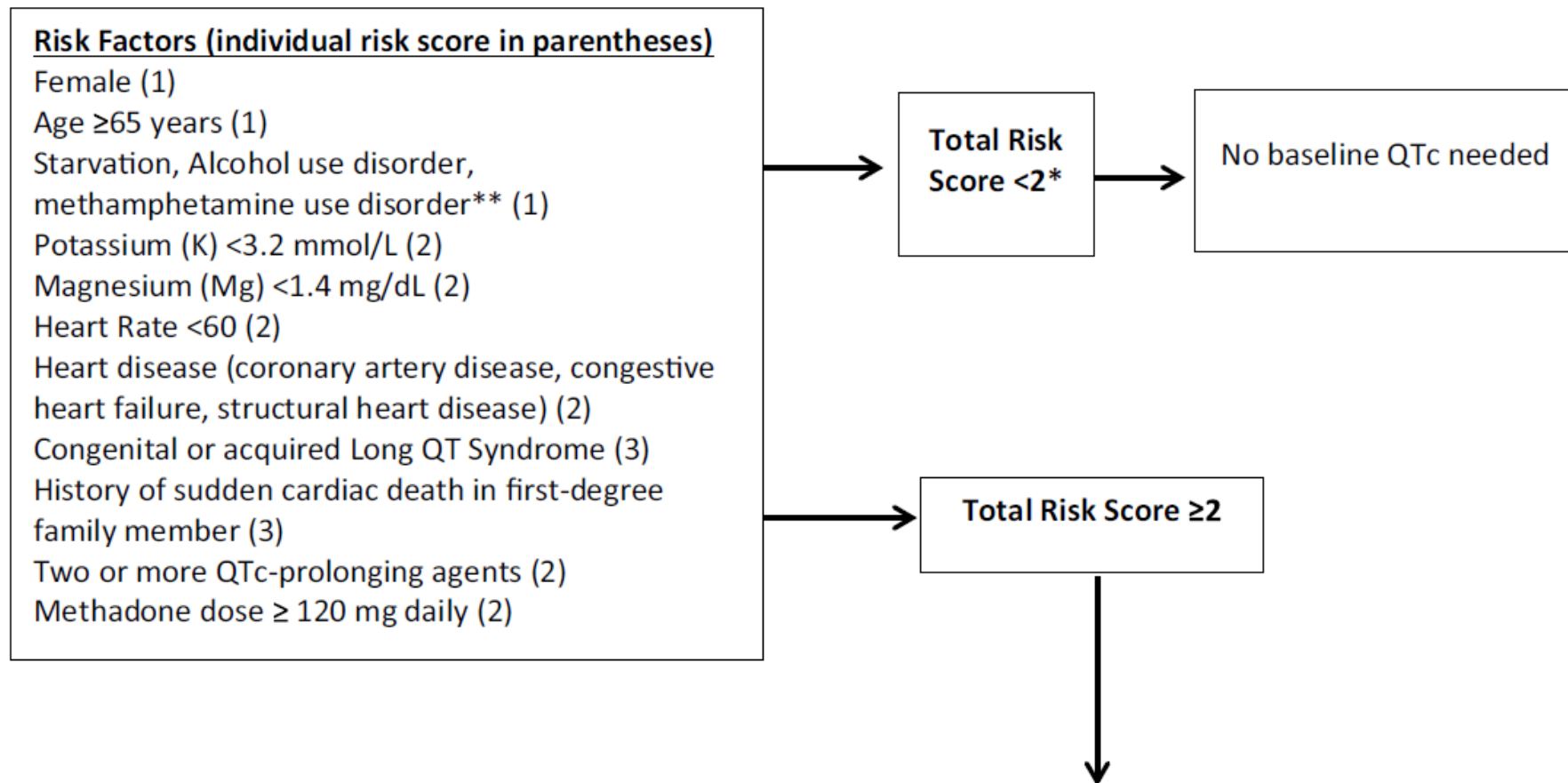
Skills for QTc Monitoring in Practice

- Know how to calculate a QTc on an ECG.
 - Do not rely on the QTc measured by the machine.
 - Use the Fridericia or Hodge's formula to correct for heart rate.
- Know the risk factors for QTc prolongation.
- Know which medications are higher-risk.
 - Antipsychotics: thioridazine, ziprasidone, possibly iloperidone
 - Antidepressants: citalopram, escitalopram, tricyclic antidepressants

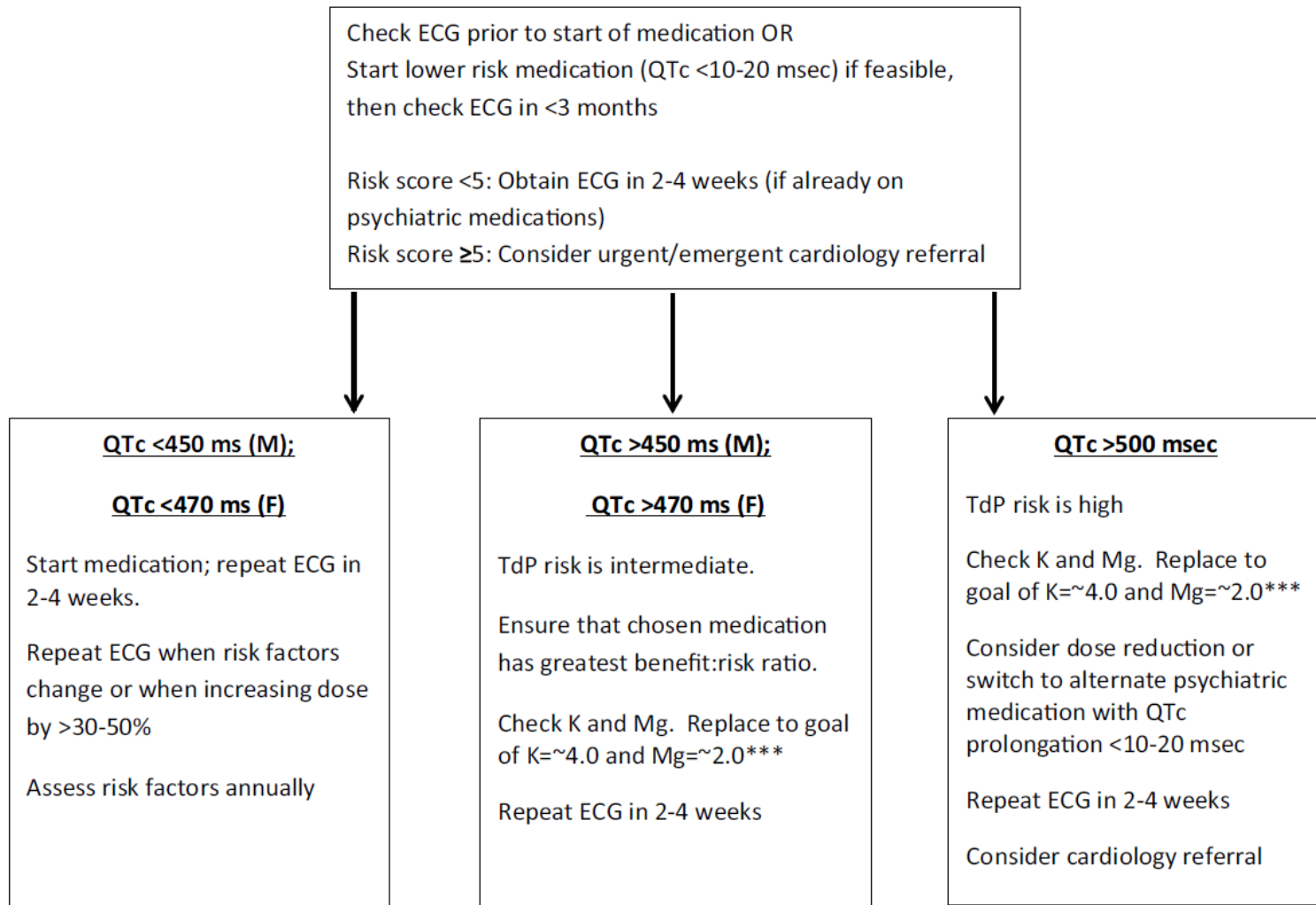
When to monitor QTc

- Know when to monitor QTc.
 - For patients without significant risk factors and on lower-risk medications, no monitoring is needed.
 - For patients with significant risk factors or on a higher-risk medication, check QTc at baseline, then again at steady-state or when risk factors change (e.g., change in dose).

Association of Medicine and Psychiatry Algorithm



Association of Medicine and Psychiatry Algorithm



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