QT prolongation: risks and assessment

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Background

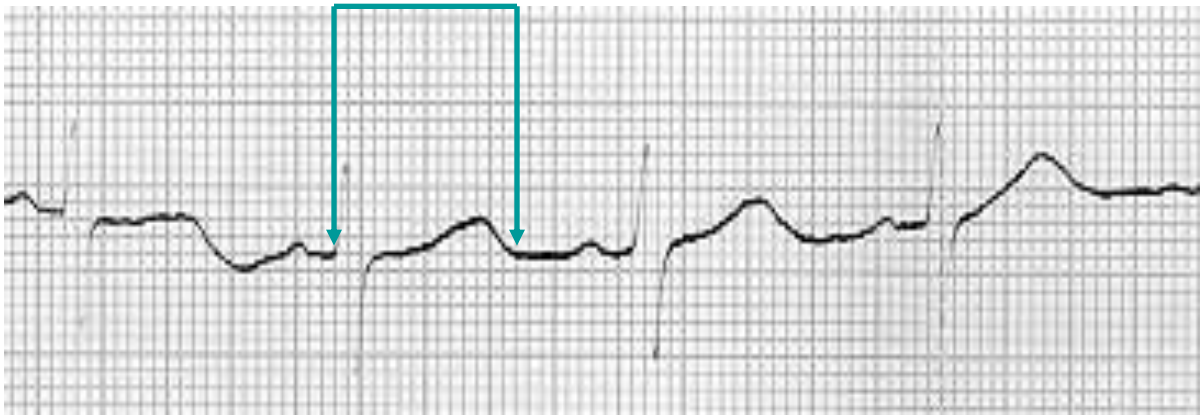
- Numerous drugs have been shown to cause QT prolongation in a dose-dependent manner
  - Post-marketing surveillance and withdrawal or warning
- QT prolongation is clearly associated with an increased risk of TdP
- No reliable criterion to identify the length of QT prolongation that is associated with a clinically significant risk of TdP
- One of the main difficulties in interpretating QT interval is its partial dependence with heart rate
- Specificities of the poisoned patient: no background ECG, how to develop risk assessment (adequate measurement of QT, heart rate correction for QT, threshold for abnormal QT)

Case observation

- 37-year-old woman, without preexisting cardiovascular disease
- Depression and chronic ethanol abuse
- Chronic treatment: fluoxetine (40 mg/day), furosemide, diazepam
- Admission after voluntary ingestion of 20 x 100 mg of trazodone
- Asymptomatic, no subjective complaints, no alteration of consciousness
- Patient was referred by the GP directly to the psychiatric unit

Case observation

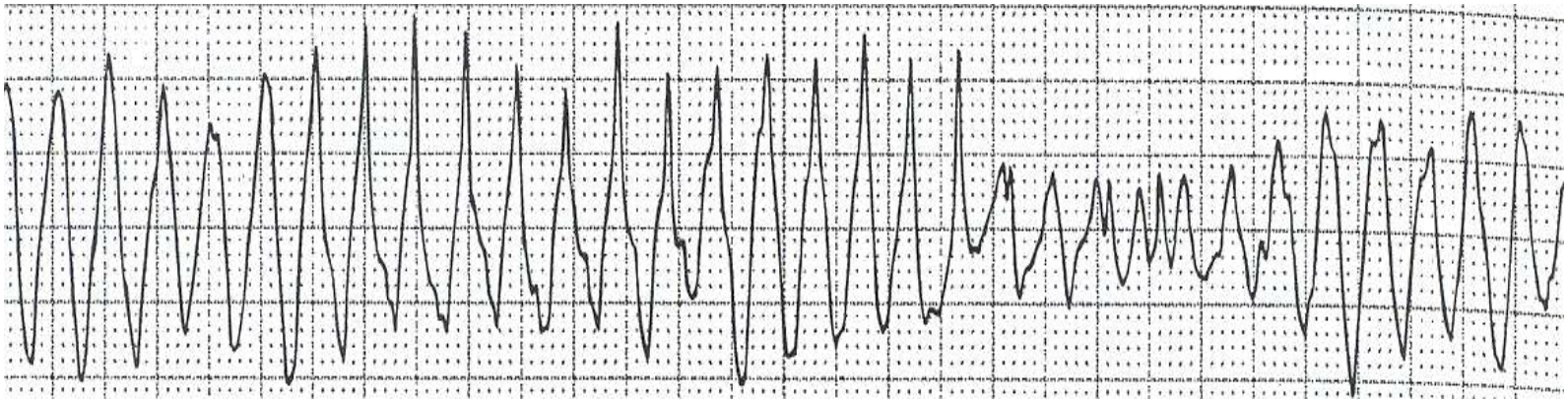
- Admission ECG:
  - Normal sinus rhythm (64 bpm) with a prolonged QT interval (QT/QTc: 520/554 msec)



- Echocardiography: normal

Case observation

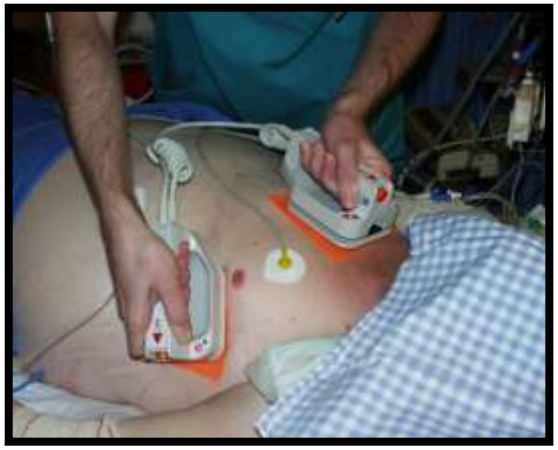
- Evolution
  - Severe hypotension (70/40 mmHg) on admission
  - First episode of *torsades de pointes* with marked hypokalaemia (2,7 mmol/L), normal magnesemia



  - Treated by external electric countershock (EEC)

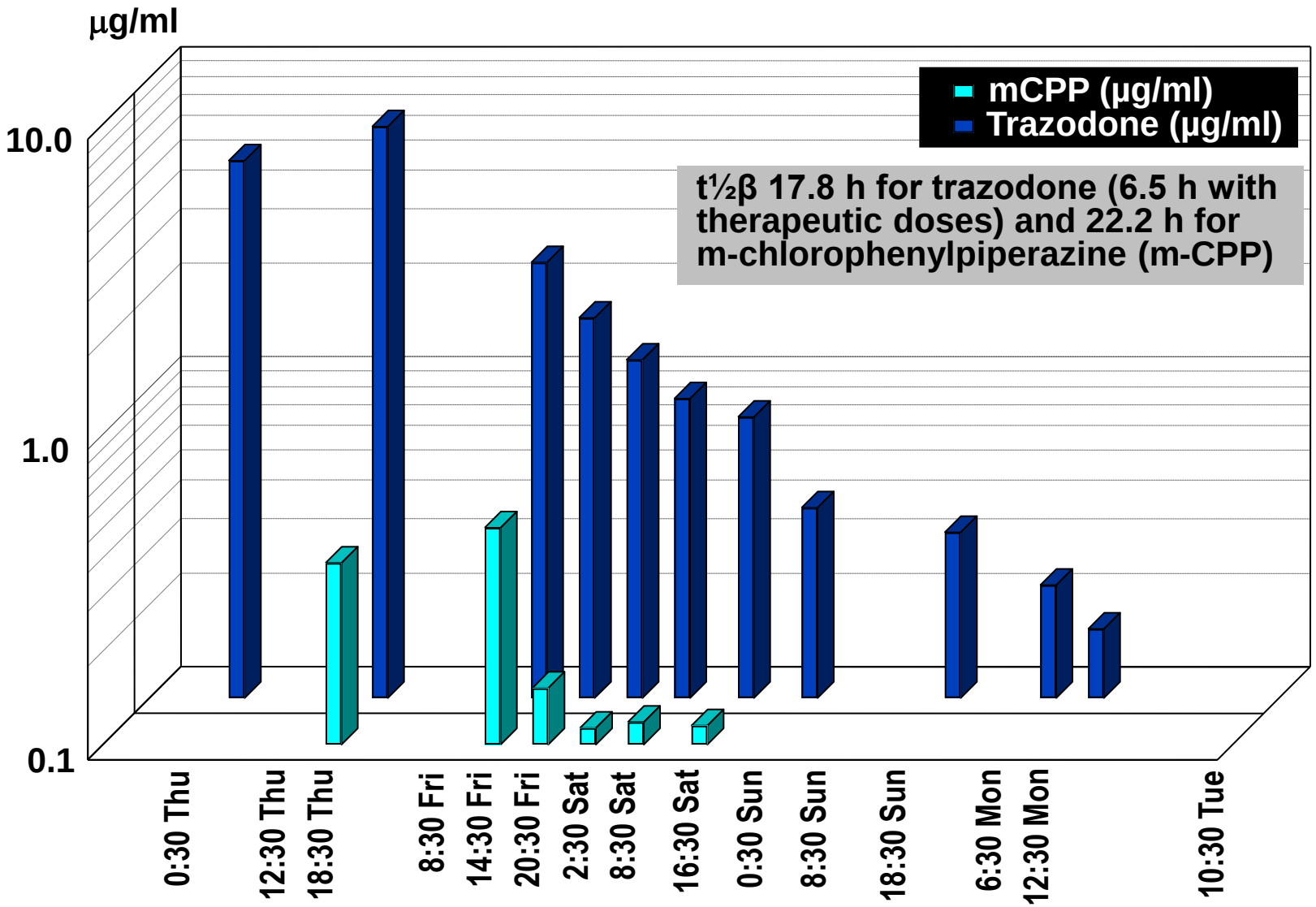
Case observation

- Evolution
  - Second episode of *torsades de pointes* with normal kalaemia treated by ECC and magnesium supplementation



  - Persistent hypotension
  - Time to ECG normalization = 6 days

Toxicokinetic data



Analysis of this case

- Risk factors related to the drug
  - Asymptomatic prolongation of the QT interval has been shown in healthy volunteers receiving trazodone, and occasionally after drug overdose. In contrast, there is no evidence that fluoxetine could modify the QT interval.
- Risk factors related to the patient
  - Female gender
  - Electrolyte disorders (HypoK ← furosemide)
  - Role of chronic ethanol abuse?
  - Role of psychological distress?
  - Concurrent medication: role of fluoxetine?
    - Influence on trazodone kinetics (and the metabolite)?
    - Influence on dynamics: biological effects have a longer duration than predicted by kinetics

Drugs and QT prolongation

Cardiac drugs	• Amiodarone • Sotalol • Disopyramide • Dofetilide • Procainamide • Quinidine
Antidepressants	• Selective serotonin re-uptake inhibitors: citalopram, escitalopram, fluoxetine • Moclobemide • Tricyclic antidepressants* • Lithium
Antipsychotics	• Amisulpride • Chlorpromazine • Haloperidol • Ziprasidone • Thioridazine
Antihistamines	• Loratadine • Astemizole • Diphenhydramine
Antimicrobials	• Ciprofloxacin, moxifloxacin, sparfloxacin • Clarithromycin, erythromycin • Fluconazole, voriconazole • Pentamidine
Other drugs	• Chloroquine • Cisapride • Dolesatron • Methadone • Arsenic

For more details,look directly at http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.cfm

Drugs commonly associated with TdP

Table 1 Twenty most commonly reported drugs associated with torsades de pointes (TdP) between 1983 and 1999[3]

Drug	TdP (n)	Fatal (n)	Total (n)	TdP/total (%)
Sotalol	130	1	2758	4.71
Cisapride	97	6	6489	1.49
Amiodarone	47	1	13725	0.34
Erythromycin	44	2	24776	0.18
Ibutilide	43	1	173	24.86
Terfenadine	41	1	10047	0.41
Quinidine	33	2	7353	0.45
Clarithromycin	33	0	17448	0.19
Haloperidol	21	6	15431	0.14
Fluoxetine	20	1	70929	0.03
Digoxin	19	0	18925	0.10
Procainamide	19	0	5867	0.32
Terodiline	19	0	2248	0.85
Fluconazole	17	0	5613	0.30
Disopyramide	16	1	3378	0.47
Bepridil	15	0	384	3.91
Furosemide	15	0	15119	0.10
Thioridazine	12	0	6565	0.18
Flecainide	11	2	3747	0.29
Loratidine	11	1	5452	0.20

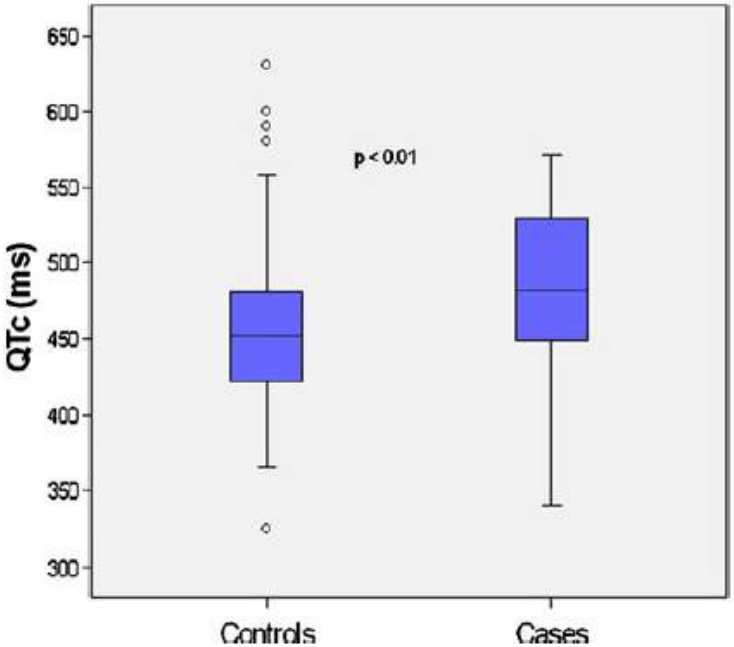
TdP (n), total number of adverse drug reaction reports which named TdP associated with this drug; Fatal (n): number of adverse drug reaction reports which named TdP with fatal outcome; Total (n): total number of adverse drug reaction reports for the drug.

Predictors of adverse cardiovascular events in suspected poisoning

- Does the occurrence of ECG abnormalities, including QTc prolongation and QT dispersion correlate with elevated risk of serious cardiac events in suspected poisoning?
  - Case control study: 34 cases compared to 101 control subjects
  - Of the 34 cases with adverse cardiovascular events
    - 19 pts with shock, 16 pts with myocardial injury, 9 pts with dysrhythmias, 15 pts with cardiac arrest
    - Toxic exposure: benzodiazepines, opioids, acetaminophen, antidepressants, antipsychotics, ethanol… with single exposure in 61%

(Manini et al., J Med Toxicol, 2010)

Predictors of adverse cardiovascular events in suspected poisoning



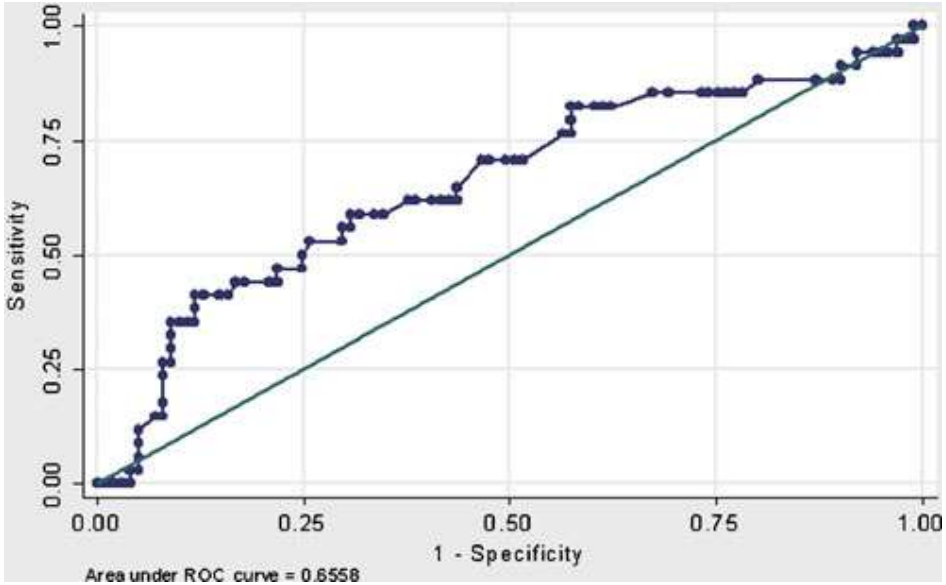
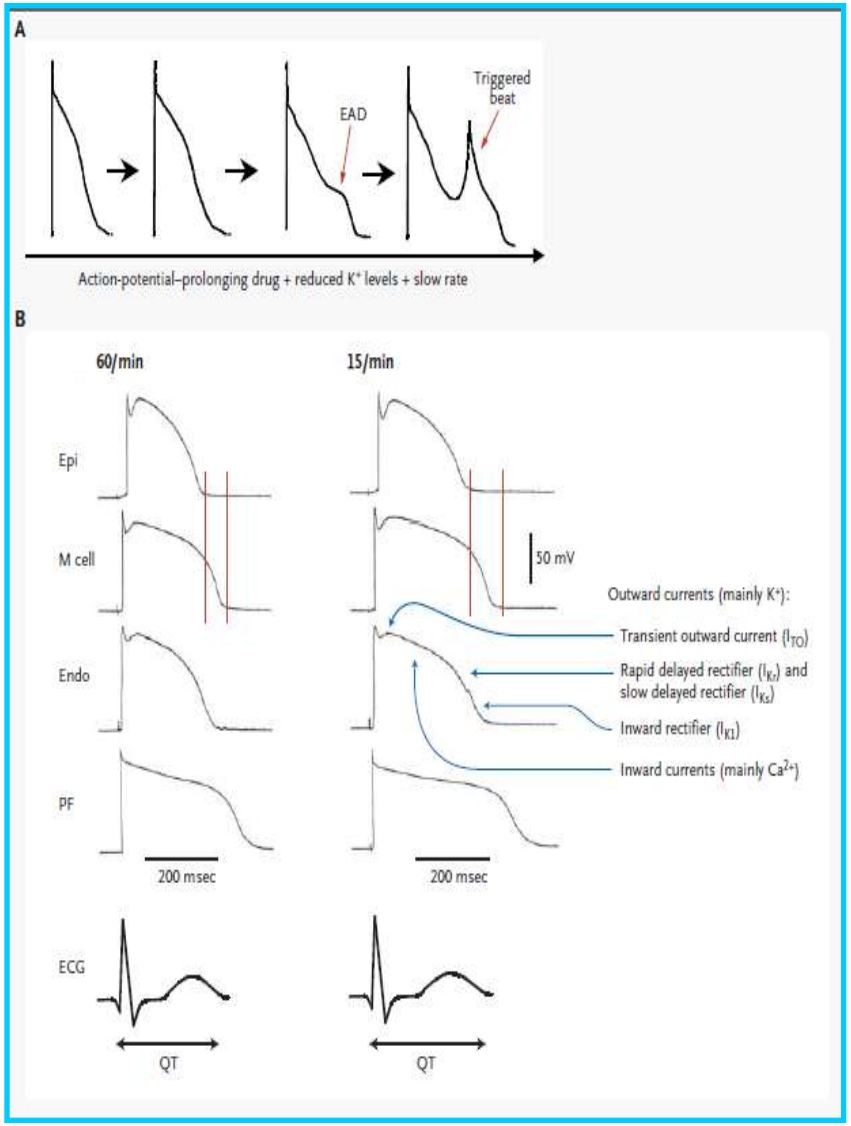


Table 5 Test characteristics of the optimal QTc and QTD cutpoints and the derived risk stratification for prediction of adverse cardiovascular events

Variable	% Sensitivity (95% CI)	% Specificity (95% CI)	% NPV (95% CI)	% PPV (95% CI)
QT analysis				
QTc cutpoint (504 ms)	41.2 (25–59)	88.1 (80–94)	81.7 (73–88)	53.8 (33–73)
QTD cutpoint (70 ms)	58.8 (41–75)	69.3 (59–78)	84.3 (75–91)	40.0 (26–55)
Risk stratification[a]				
Very low[b]	94.1 (80–99)	49.5 (39–60)	96.2 (87–100)	38.6 (28–50)
High	26.5 (13–44)	95.0 (89–98)	79.3 (71–86)	64.3 (35–87)

Mechanisms of drug-induced QT prolongation



- **Blockade of the delayed rectifier potassium channel (I_{KR}), which is coded by hERG**
- **Prolongation of the action potential, lenghtening of QT**
- **Delayed repolarization => early after depolarizations**

Focal activity

Re-entrant pathways

TdP

Non-drug risk factors and the QT interval

- Classical presentation of QT prolongation and TdP with congenital long QT syndromes
  - Romano-Ward, Jervelle, Lange-Neilsen syndrome
  - Variety of mutations in ion channel sub-units (potassium and sodium channels) and mutations in regulatory protein coding genes
- But even in « healthy » subjects, QT interval is a heritable trait and genetic variants are probably the most important factor determining the risk to develop QT prolongation after exposure to some drugs
  - These patients are likely to have normal ECG morphology and normal or near normal QT off the drug

(Isbister et al., Br J Clin Pharmacol, 2013)

Non-drug risk factors and the QT interval

- Other physiological or pathological factors
  - Female gender > 20 ms (normal range QTc?: 440 ms for men, 460 ms for women)
  - Increase of QT interval with aging
  - Diurnal variation of QT interval
  - In clinical practice, the most common pathological conditions associated with QT prolongation are electrolyte disturbances
    - HYPOKALIEMIA, HYPOCALCEMIA, HYPOMAGNESEMIA
  - Other conditions: myocardial ischemia, cardiomyopathies, hypothyroidism, obesity, hypertension….

The key issue: which are the factors increasing independently the risks for TdP in patients with prolonged QT?

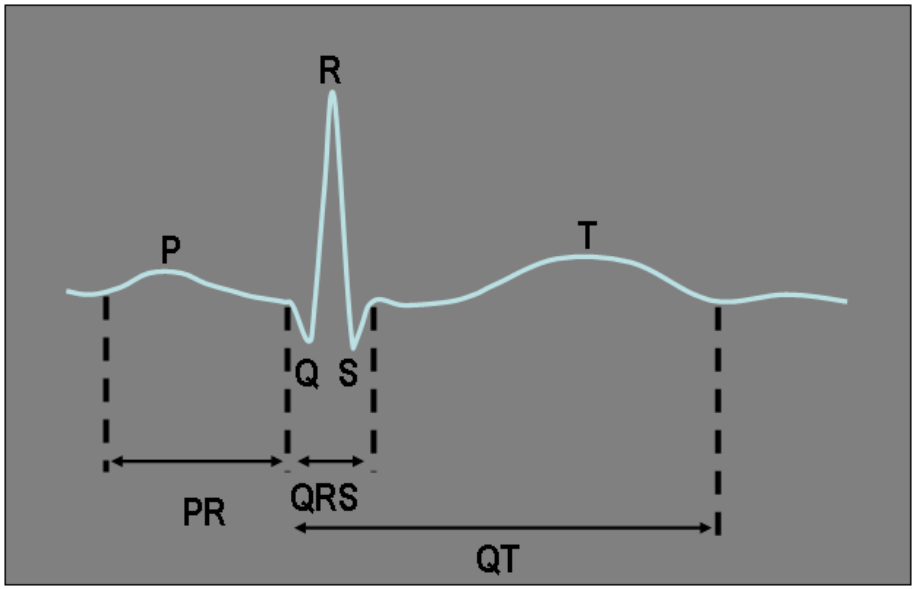
(Isbister et al., Br J Clin Pharmacol, 2013)

Medications known to inhibit CYP3A4

- Antifungals
  - Itraconazole
  - Ketoconazole
- Antidepressants
  - Nefazodone
  - Fluvoxamine
- Grapefruit juice
- Cyclosporine
- Antibiotics
  - Erythromycin
  - Clarithromycin
- Antivirals
  - Ritonavir
  - Indinavir
  - Nelfinavir
- Calcium channel blockers
  - Diltiazem

Cupp MJ, Tracy TS. Am Fam Physician. 1998;57(1):107-116.
Dresser GK, et al. Clin Pharmacokinet. 2000;38(1):41-57.

How to measure the QT interval ?

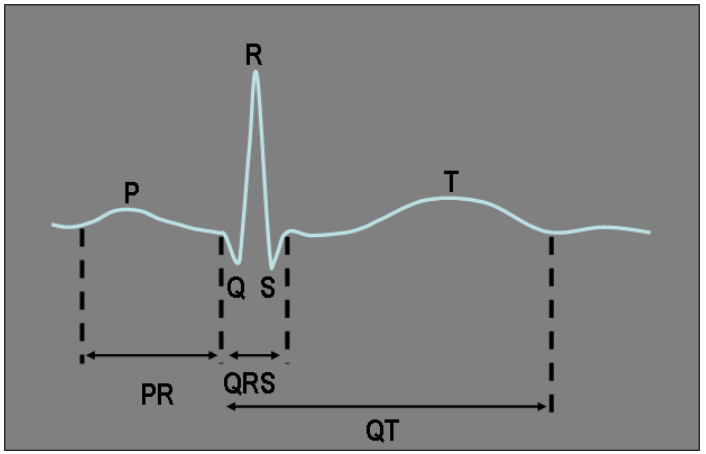


- Multiple considerations
  - Manual or automated?
  - End of the T wave?
  - Which lead? Single or multiple? Median, maximum or mean?

(Isbister et al., Br J Clin Pharmacol, 2013)

How to measure the QT interval ?

- The point where the T wave returns to the isoelectric line
- Single lead: II, longest QT about 60% of the time
- Multiple leads and median measurement
- Multiple beats, multiple leads and median
- Manual or automatic measurement?
  - Manual: accurate assessment of the end of QT
- Automatic measurement on the 12-lead ECG?
  - Not fully reliable



Simplified method

- Manual measurement of the QT interval in 6 leads, in one complex
- Visual determination of the end of T wave
- Use of median QT interval

(Isbister et al., Br J Clin Pharmacol, 2013)

Correction of QT for HR

Table 1 HR correction formulae

Name	Formula
Bazett's Correction	$QTc = \frac{QT}{RR^{0.5}}$
Fridericia's Correction	$QTc = \frac{QT}{RR^{0.33}}$
Framingham Correction	$QTc = QT + 0.156 \times (1\text{-}RR)$

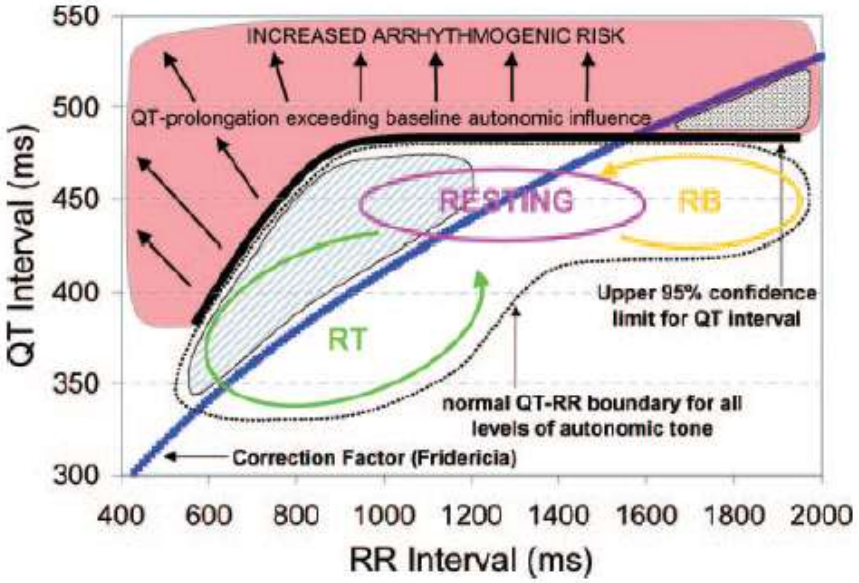
QT in ms and RR in s.

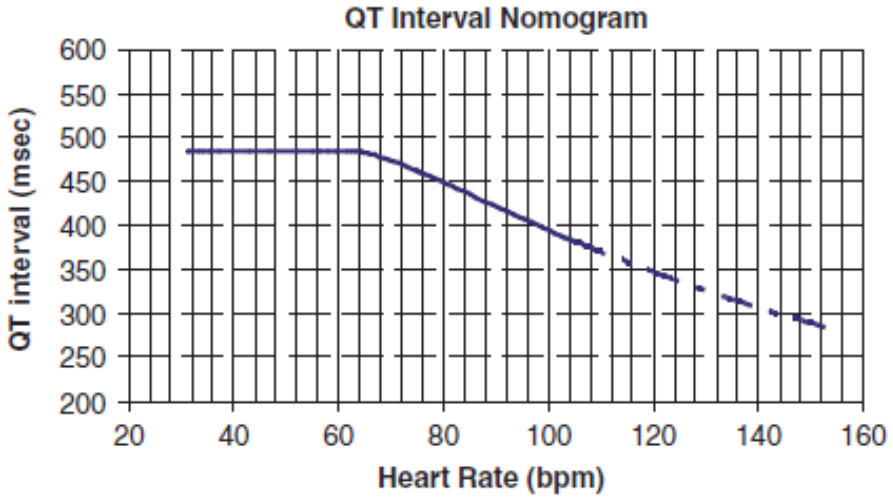
Correction of QT for HR and risk assessment

- The dependency of QT interval on heart rate is not completely resolved by the correction formulae, including Bazett's
  - Over-correction for fast HR
  - Ex: quetiapine overdose causes QTc prolongation, but no reports of TdP
- The QT/HR relationship is stable within an individual but varies significantly between individuals
- Cut-off ? 440 ms in men, 460 ms in women ?
- An absolute QT or QTc > 500 ms is often considered as a significant risk for TdP

(Isbister et al., Br J Clin Pharmacol, 2013)

What is the interest of QT nomogram?





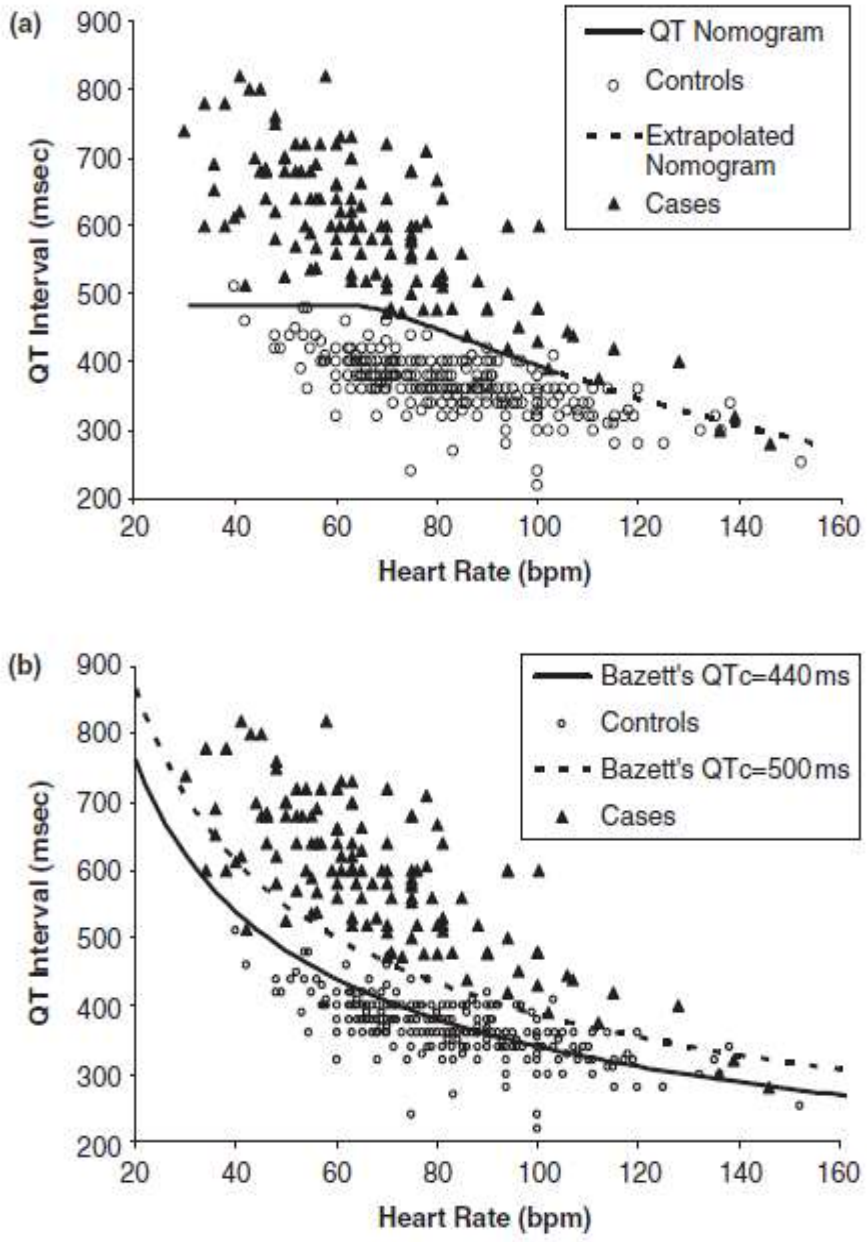
- « Cloud » diagram: plot of QT *vs* RR interval for a population
  - QT-RR plots in individuals (variability of the QT-RR relationship over a 24 h period)
  - Population « cloud » obtained by the superimposition of the individual clouds
  - QT-RR pairs outside the population « cloud » => increased risk of arrhythmia

(Fossa et al., J Pharmacol Exp Ther, 2005)

Application of the QT nomogram to a poisoned population

- Systematic review of cases of drug-induced TdP
- Controls: pts with non-cardiotoxic drugs in overdose who did not develop TdP
- Comparison between QT nomogram and curves corresponding to QTc 440 ms and QTc 500 ms
  - 139 « cases » included with a large variety of toxins, compared to 318 controls

(Chan et al., Q J Med, 2007)



- The TdP cases occurred primarily at lower HR values with longer QT interval (most of the cases with HR 30-90/min)
- The QT-HR pairs for the TdP cases fell predominantly above the QT nomogram at risk line, with some limitation for the extrapolated part of the nomogram

(Chan et al., Q J Med, 2007)

Sensitivity and specificity

Table 3 Sensitivity and specificity (95%CI) of the QT nomogram, compared to Bazett's QTc = 440 ms and QTc = 500 ms

	QT nomogram (with extrapolation)	QT nomogram (no extrapolation)*	Bazett's QTc = 440	Bazett's QTc = 500
Sensitivity	96.9% (93.9–99.9)	98.3% (96.1–100)	98.5% (96.4–100)	93.8% (89.6–98.0)
Specificity	98.7% (96.8–100)	99.3% (97.8–100)	66.7% (58.6–74.7)	97.2% (94.3–100)

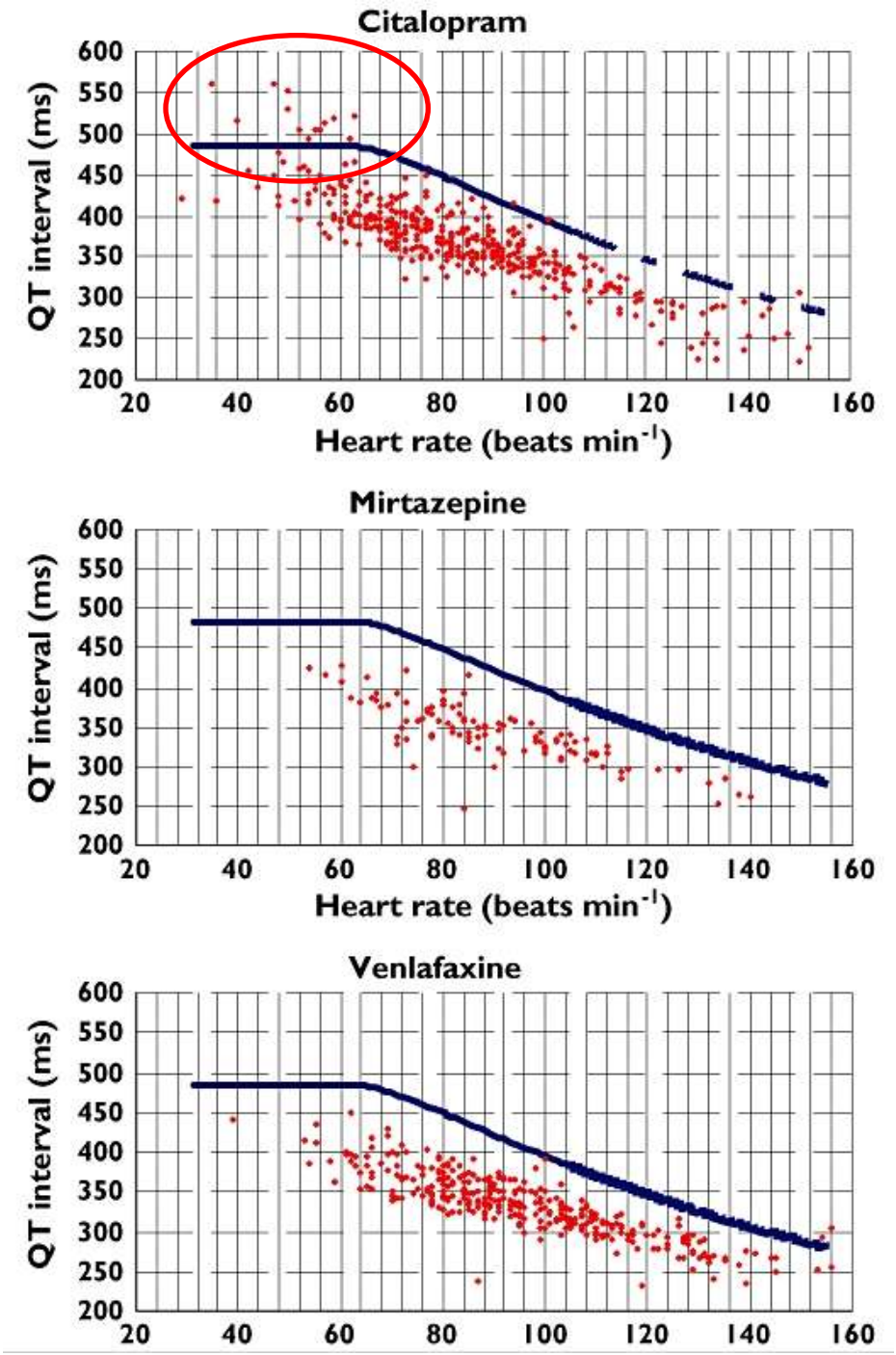
*In this analysis, all cases with HR >104 bpm were excluded from analysis, so that only the original QT nomogram was used.

- The QT nomogram has a high sensitivity and specificity for cases of drug-induced TdP
- Bazett's formula: propensity to overcorrect QT at fast heart rates (>70/min) and to undercorrect QT at slow heart rates (<50/min)
- Special interest for bradycardic pts (<60/min)
- Relative protective effect of tachycardia in the development of TdP

Evaluation of QT nomogram after antidepressant overdose

- Methods
  - Retrospective case control study of patients presenting to the hospital after overdose of citalopram, mirtazapine and venlafaxine
  - Primary outcome variable: QT higher than nomogram, compared with QTc ≥ 440 ms and ≥ 500 ms, comparison between drugs

(Waring et al., Br J Clin Pharmacol, 2010)



Results

- 858 ECG from 541 pts
- Median stated dose ingested similar in the 3 groups
- None of the pts developed TdP or significant arrhythmia
- The proportion of pts with QT ≥ nomogram was 2.4% (23.1% for QTc ≥ 440 ms and 1.1% for QTc ≥ 500 ms)
- Greater likelihood of QT ≥ nomogram with citalopram

(Waring et al., Br J Clin Pharmacol, 2010)

Evaluation of QT nomogram after antidepressant overdose

- Results
  - A higher proportion of pts in the citalopram group had QTc ≥ 440 ms

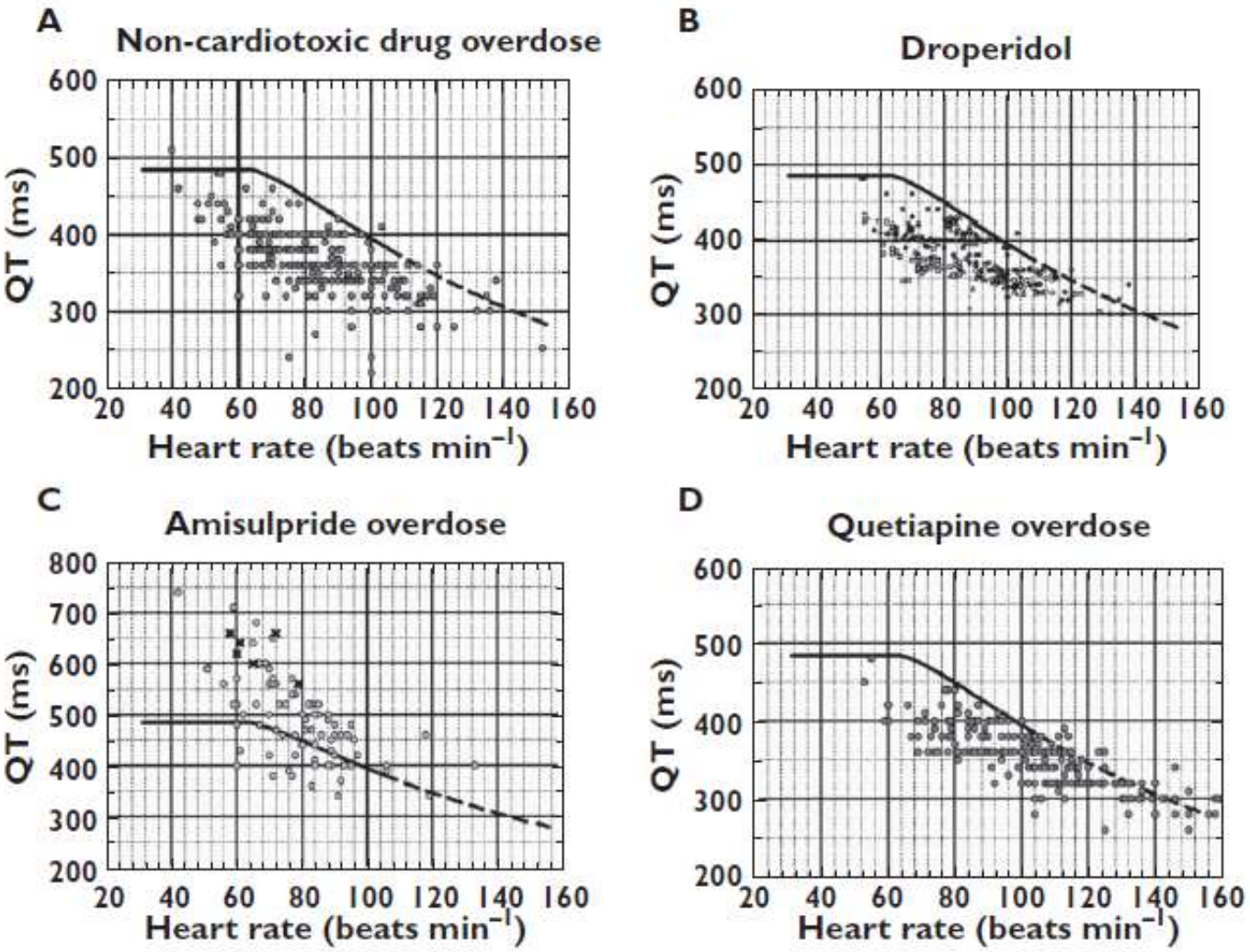
	Citalopram *n* = 215	Venlafaxine *n* = 223	Mirtazepine *n* = 103	Total *n* = 541
QT_c ≥440 ms	68 32% (26, 38%)	41 18% (14, 24%) *P* = 0.002	16 16% (10, 24%) *P* = 0.004	125 23% (20, 27%)
QT_c ≥500 ms	4 2% (1, 5%)	2 1% (0, 3%) *P* = 0.651	0 0% (0, 4%) *P* = 0.392	6 1% (1, 3%)
QT ≥ nomogram	10 5% (2, 9%)	3 1% (0, 5%) *P* = 0.075	0 0% (0, 4%) *P* = 0.060	13 2% (1, 4%)
Highest 2.5%	QT >461	QT >402	QT >421	
Highest 5%	QT >440	QT >396	QT >414	
Highest 10%	QT >423	QT >383	QT >392	

(Waring et al., Br J Clin Pharmacol, 2010)

Evaluation of QT nomogram after antidepressant overdose

- Potential advantages of the nomogram
  - Low false positive rate (2% vs 23% with cut-off 440 ms)
  - Better identification of the pts at the highest risk of significant arrhythmia
  - Nomogram more sensitive for the pts with HR 30-60/min (undercorrection of QT interval for lower HR with Bazett's formula)
  - Among a population of patients poisoned by antidepressants, identification of substances with higher risk (citalopram, amisulpride)

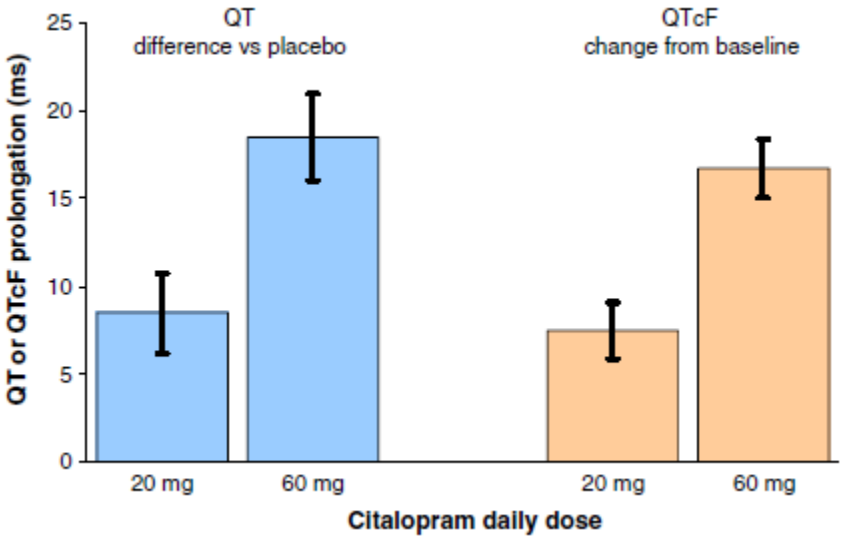
Evaluation of the QT nomogram



(Isbister et al., Br J Clin Pharmacol, 2013)

Citalopram, QT prolongation and TdP

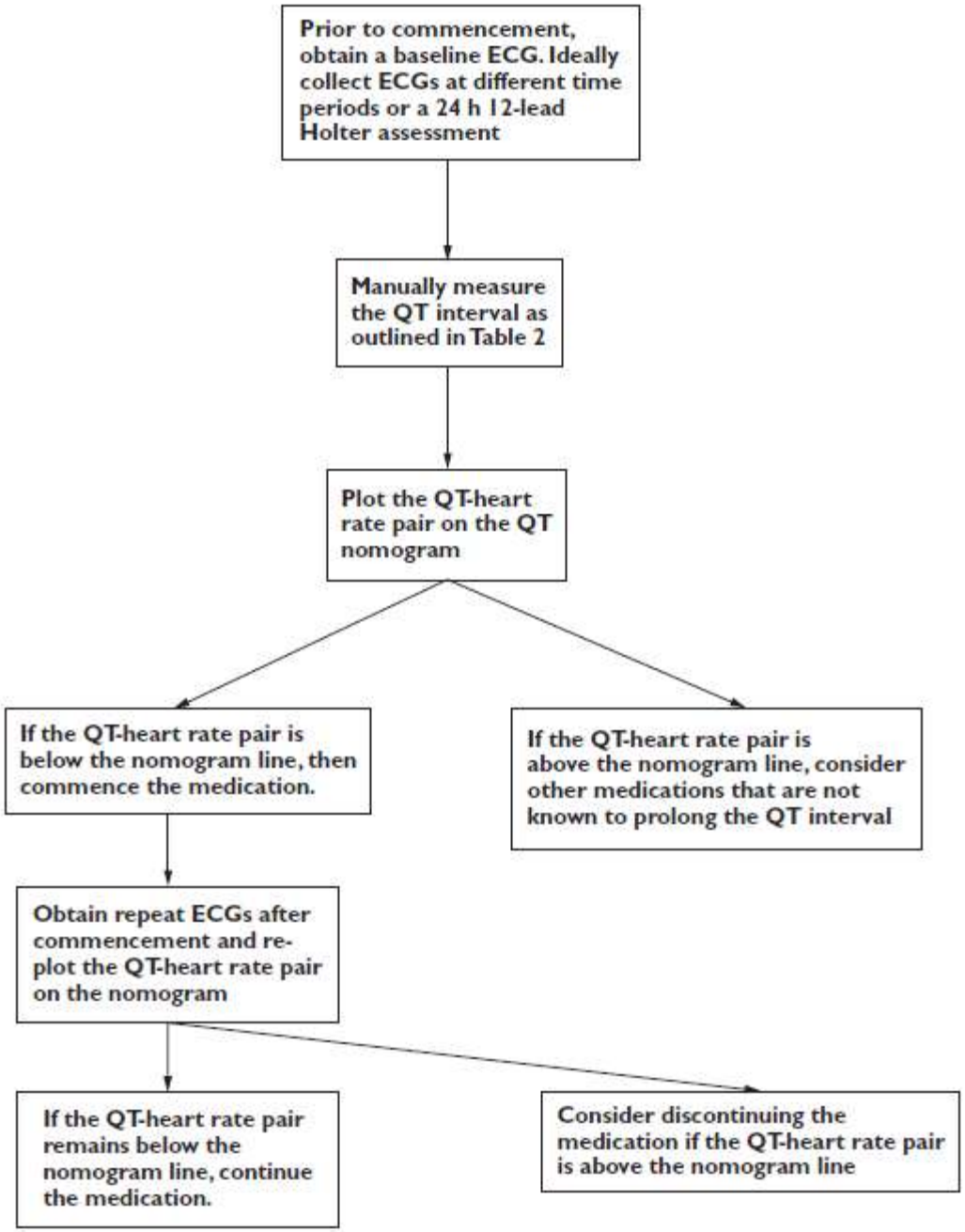
- After therapeutic doses
  - Reports of prolonged QT
  - Sweedish pharmacovigilance: citalopram in 10% cases of TdP
  - Comparison 20 mg versus 60 mg



(Cooke et al., Eur J Clin Pharmacol 2013)

Citalopram, QT prolongation and TdP

- Toxicity in the setting of citalopram overdose
  - QTc significantly higher in cases evolving citalopram than either fluoxetine, fluvoxamine, paroxetine or sertraline; 68% of citalopram overdose pts had QTc > 440 ms
  - Clear relationship between QTc prolongation and citalopram concentrations within a toxic range
  - Administration of activated charcoal may decrease the risk of QT prolongation after citalopram overdose


Prior to commencement, obtain a baseline ECG. Ideally collect ECGs at different time periods or a 24 h 12-lead Holter assessment
Manually measure the QT interval as outlined in Table 2
Plot the QT-heart rate pair on the QT nomogram
If the QT-heart rate pair is below the nomogram line, then commence the medication.
If the QT-heart rate pair is above the nomogram line, consider other medications that are not known to prolong the QT interval
Obtain repeat ECGs after commencement and re-plot the QT-heart rate pair on the nomogram
If the QT-heart rate pair remains below the nomogram line, continue the medication.
Consider discontinuing the medication if the QT-heart rate pair is above the nomogram line

Conclusions

- Many antipsychotic and antidepressant drugs are known to prolong the QTc interval in a dose-dependent manner
  - But TdP remains a rare tachyarrhythmia and the risk of TdP cannot be precisely estimated
- Importance of individual factors, electrolyte disturbances, drug interactions…
- Limitations of correction formulae for QTc: usefulness of QT nomogram
- QT nomogram does not quantify the risk or probability of TdP occurring
- Risk/benefit ratio when prescribing drugs that cause QT prolongation (methadone)