PKPD-Modelling of QT Prolongation Following Deliberate Self-Poisonings with Citalopram

Lena Friberg[1], Geoffrey Isbister[2], Peter Hackett[3] and Stephen Duffull[1]

[1] School of Pharmacy, University of Queensland, Australia

[2] Clinical Toxicology and Pharmacology, Newcastle Mater Hospital and Tropical Toxinology Unit, Charles Darwin University, Australia

[3] Clinical Pharmacology and Toxicology, Western Australian Centre for Pathology and Medical Research, Australia

PKPD studies in clinical toxicology

- No controlled studies
  - Uncertainty in dosing history
- Co-ingested drugs
- Decontamination procedures
  - Activated charcoal
  - Vomiting
- Sparse sampling
  - Few samples in absorption phase

Analysing PK and PD data from overdoses

- Population PKPD analysis
- Fully Bayesian methodology
  - Prior information

Posterior distribution | Prior distribution | Likelihood distribution

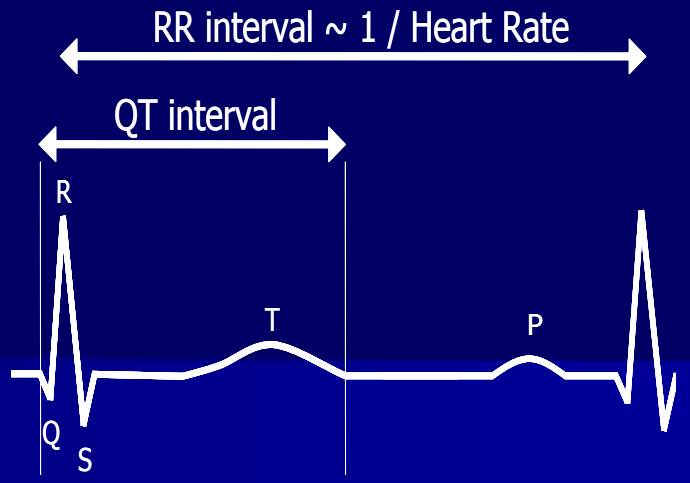
$$p(\theta|y) \propto p(\theta) \cdot p(y|\theta)$$

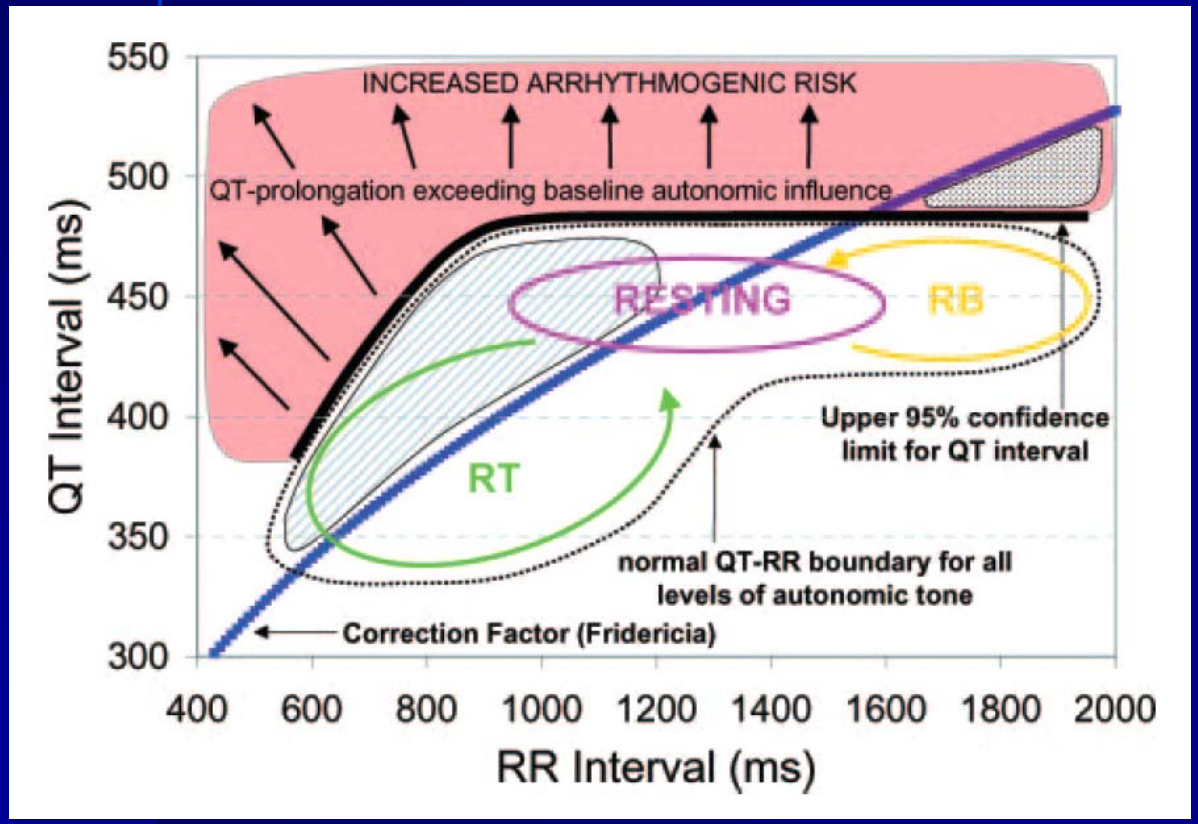
  - Uncertainty in dose and time

Citalopram in overdose

- Antidepressant – SSRI
- QT prolongation in a larger frequency than other SSRIs
  (Isbister et al, 2004)
- Documented cases of Torsade de Pointes (TdP)
  (Tarabar et al, 2003; Meuleman et al, 2001)
- Several fatal cases described
  (Öström et al, 1996; Jonasson and Saldeen, 2002)

QT-RR





Fossa et al. J Pharmacol Exp Ther, 2005

Aim

- To develop a PKPD-model describing the time course of QT prolongation for citalopram
- To evaluate the effect of charcoal administration on the relative risk of TdP after citalopram overdose

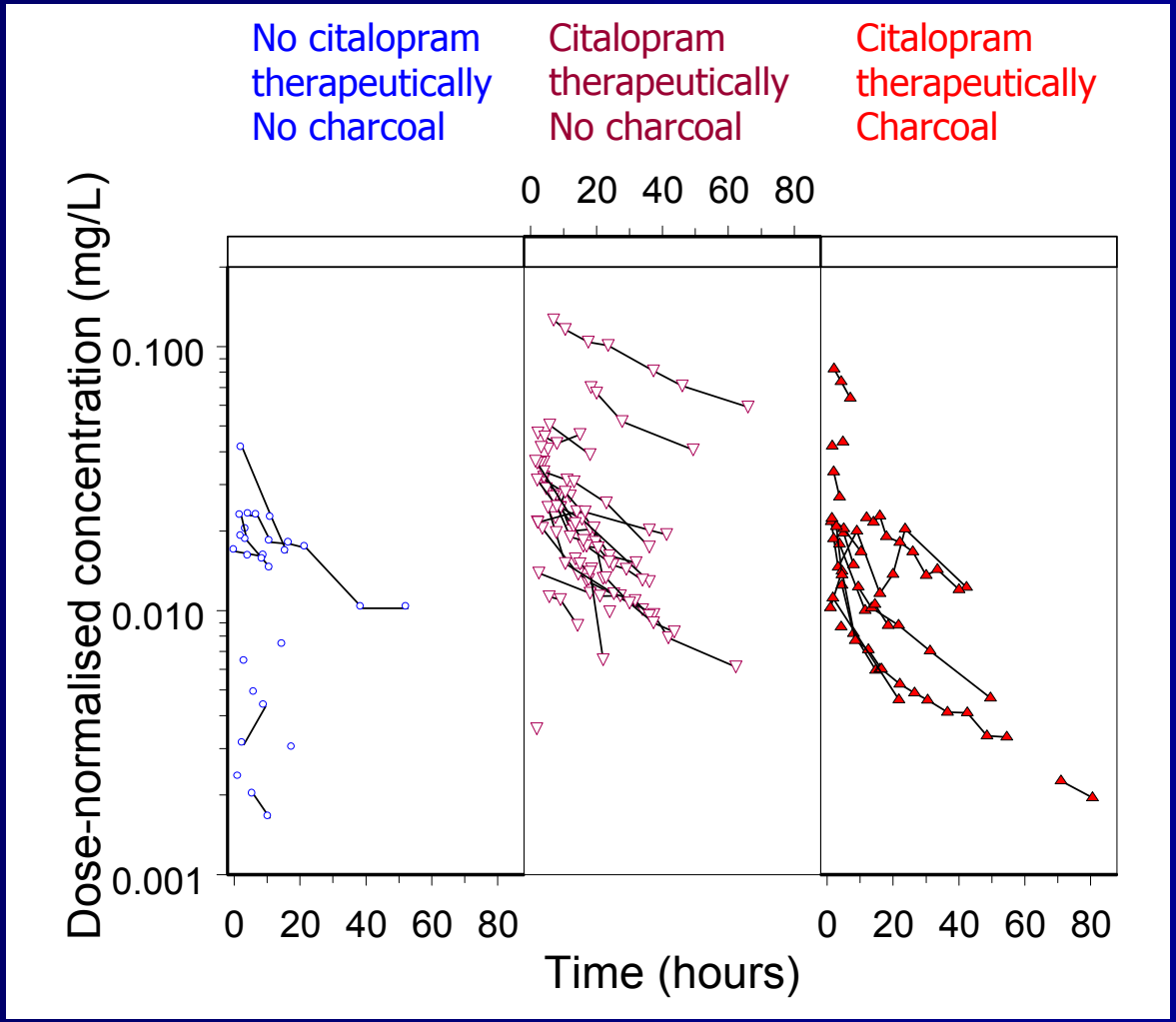
Data set

- 53 patients who had taken citalopram in an overdose event
  - 63 events
  - 36 females (68%)
  - 13-72 years (median 30 years)
  - Reported dose: 20-1700 mg (1 – 85 tablets)
  - Single dose activated charcoal on 17 events (0.5-4 hours after the overdose)
  - 39 patients were taking citalopram therapeutically
  - No case of TdP

Veracity grade of dosing history

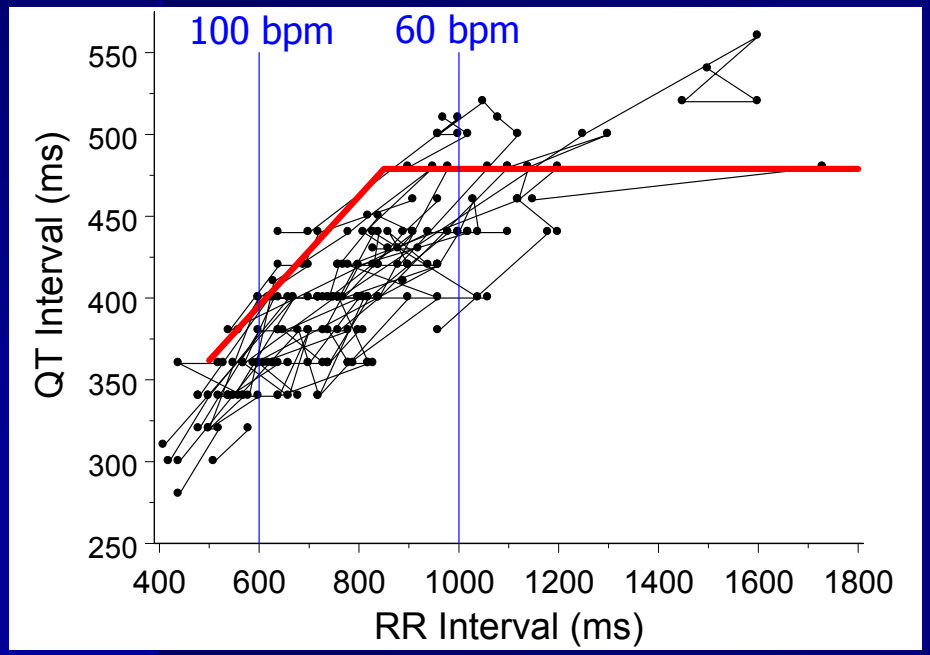
Veracity grade	Description	# of events
0	Excellent history	0
1	Good history	21
2	Less reliable history	15
3	Poor history	27
4	Very poor history	0

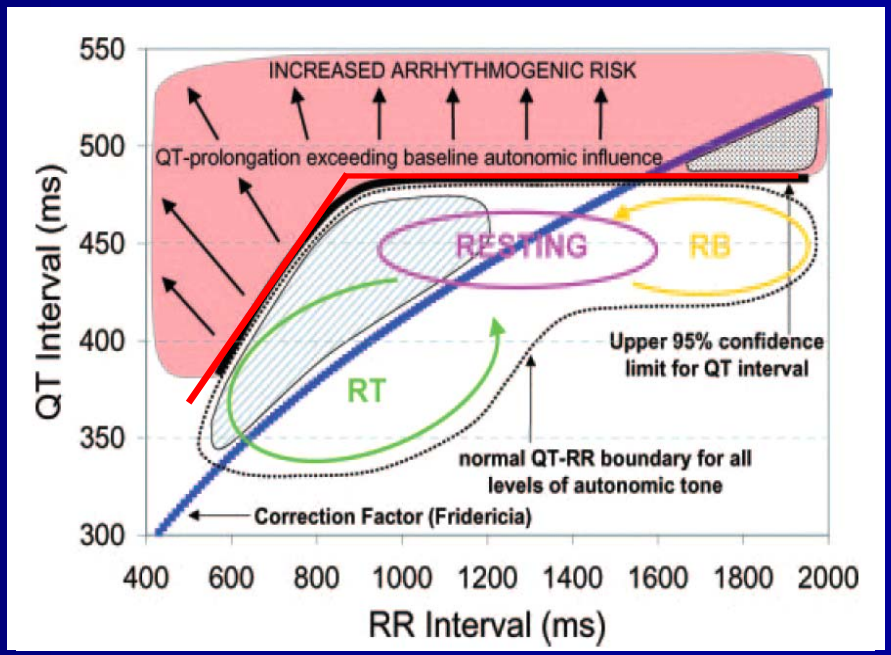
Dose-normalised (30 mg) concentrations vs. time (n=189)



Observed QT-RR intervals

- 167 QT and RR combinations
  - 33 combinations at "increased risk"





Data analysis

- WinBUGS v. 1.4
- Prior information
  - PK Informative
    - 14 PK studies on citalopram taken in therapeutic doses
  - PD Low-information
    - Biologically plausible

Final PK model

Uncertainty in dose ~ veracity grade

F

Ka

1-compartment

CL

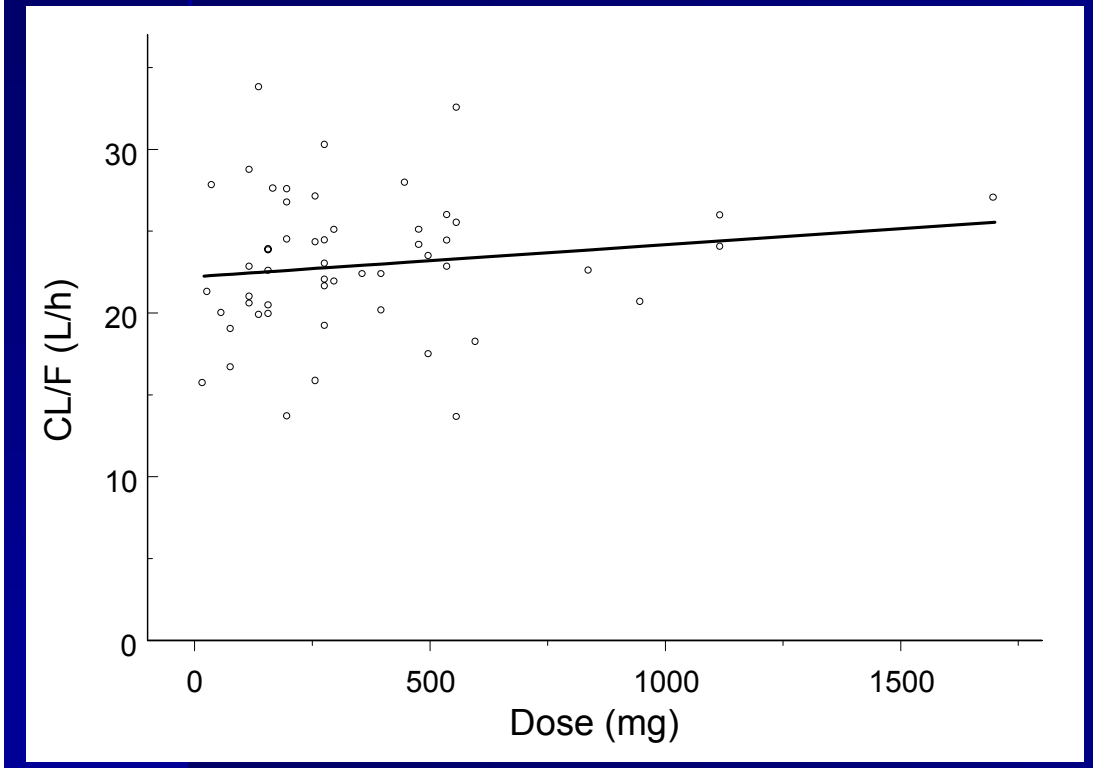
Reduced F by 22%

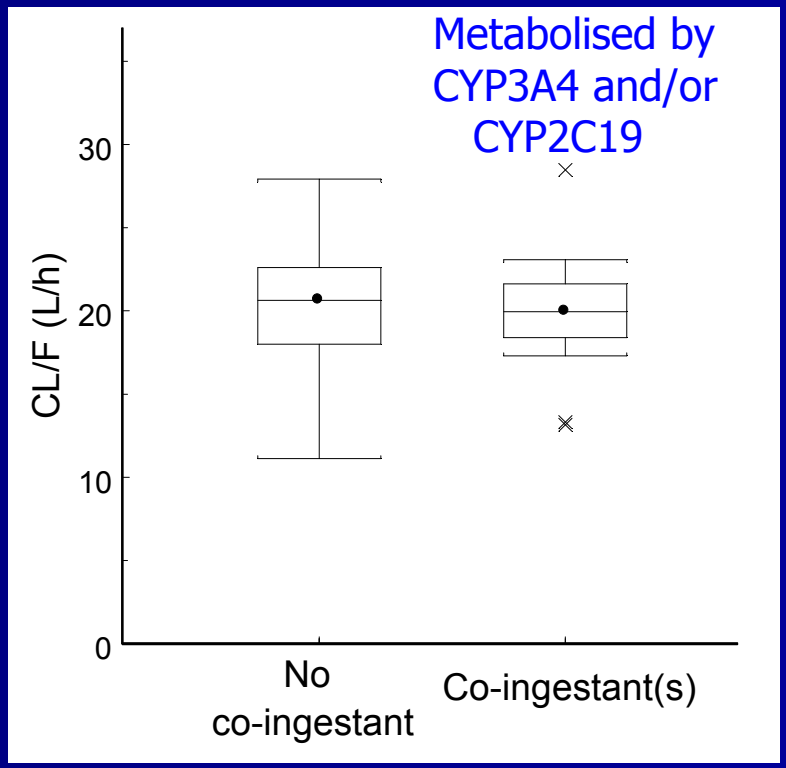
Activated charcoal

Increased CL by 72%

Uncertainty in time of ingestion

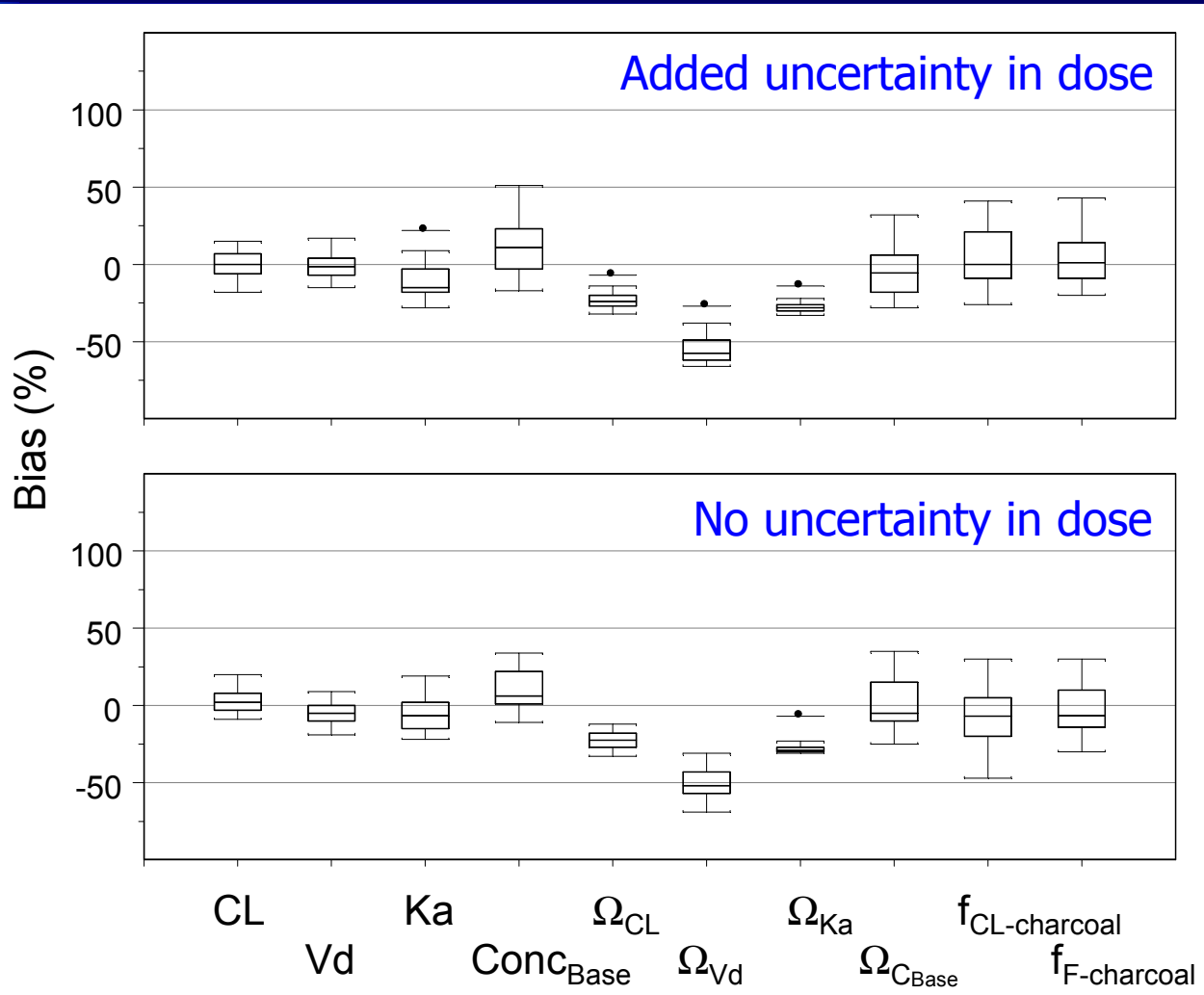
Dose-dependent clearance? Interactions with co-ingestants?





Simulation study

Bias in PK parameters in 30 data sets with the same "design"

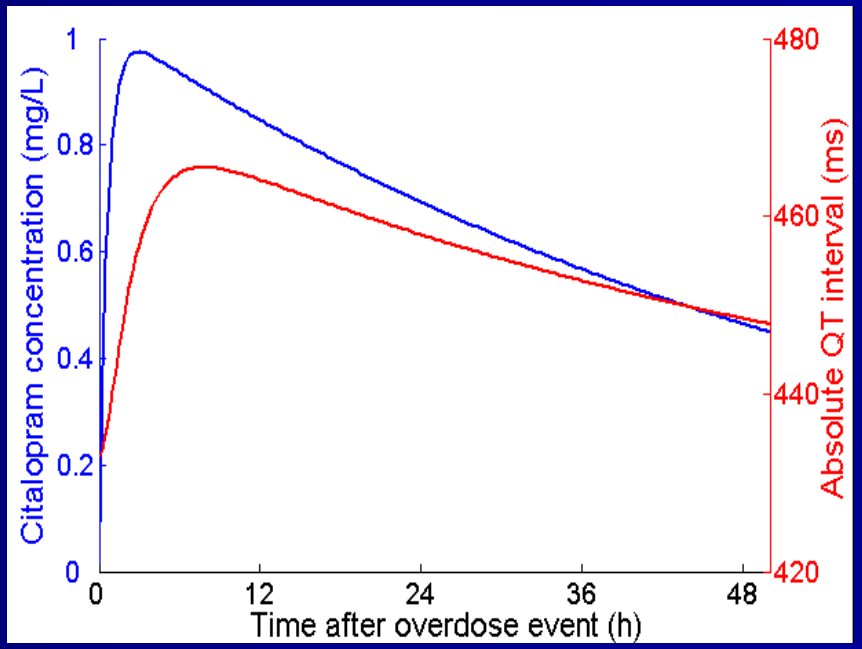


PKPD model of QT interval prolongation

$$QT_{ij} = QTc_{ij} \cdot RR_{ij}^{\alpha_i}$$

$$QTc_{ij} = QTc_{i,0} + Slope_i \cdot Ce_{ij} + \Delta QTc_{i,co-ingestant\ drugs}$$

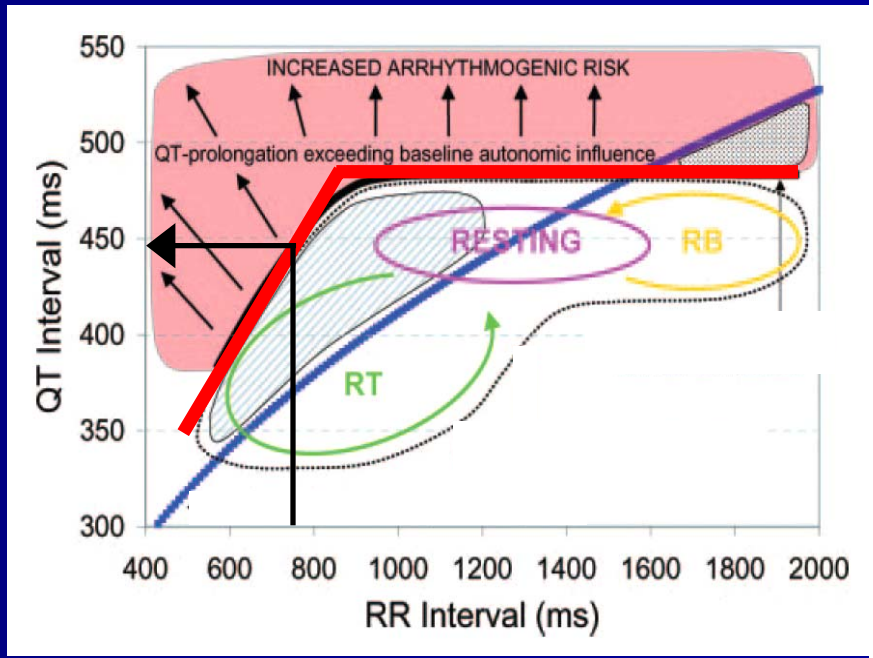
- t_{eq} = 1.4 h
- α = 0.36
- Slope = 40 L·ms/mg
- $QTc_{i,0}$
  - 9 ms higher in women
  - increased with age
- $\Delta QTc_{i,co\text{-}ingestant\ drugs}$ < 5 ms



Simulation of probability for risk of TdP from PKPD model

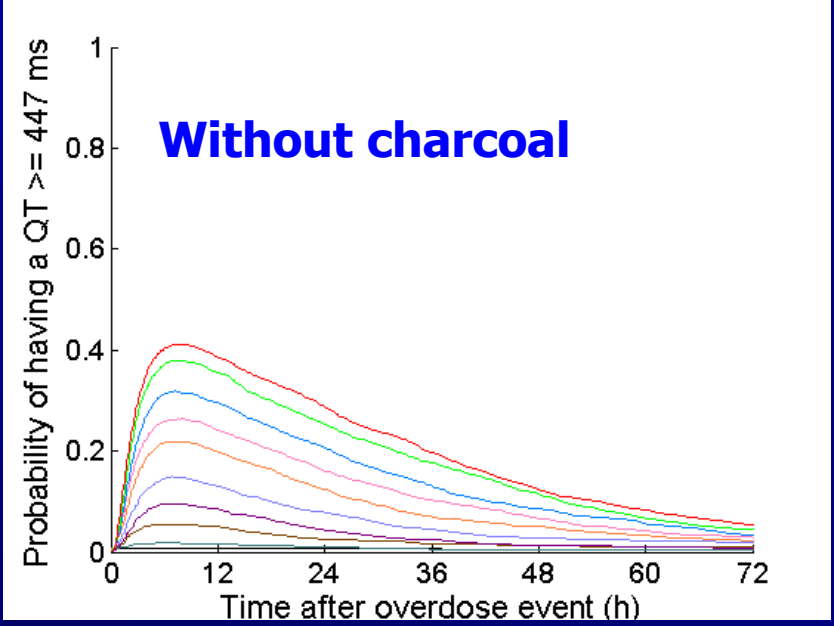
- 2000 patients
  - 10 dose levels: 5-90 x DDD (Defined Daily Dose; 20 mg)
- Median of observed RR intervals (760 ms)

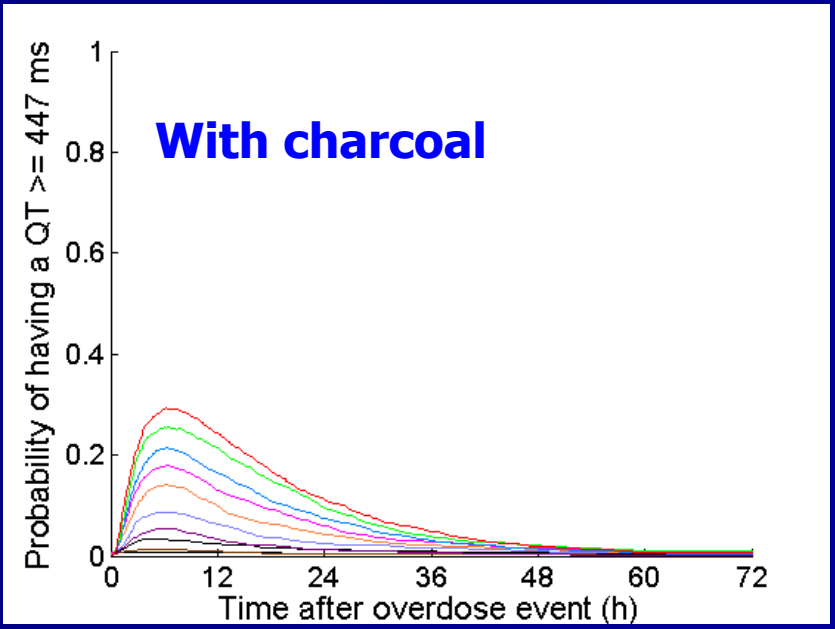
  $\Rightarrow$ QT interval with increased risk of TdP (447 ms)



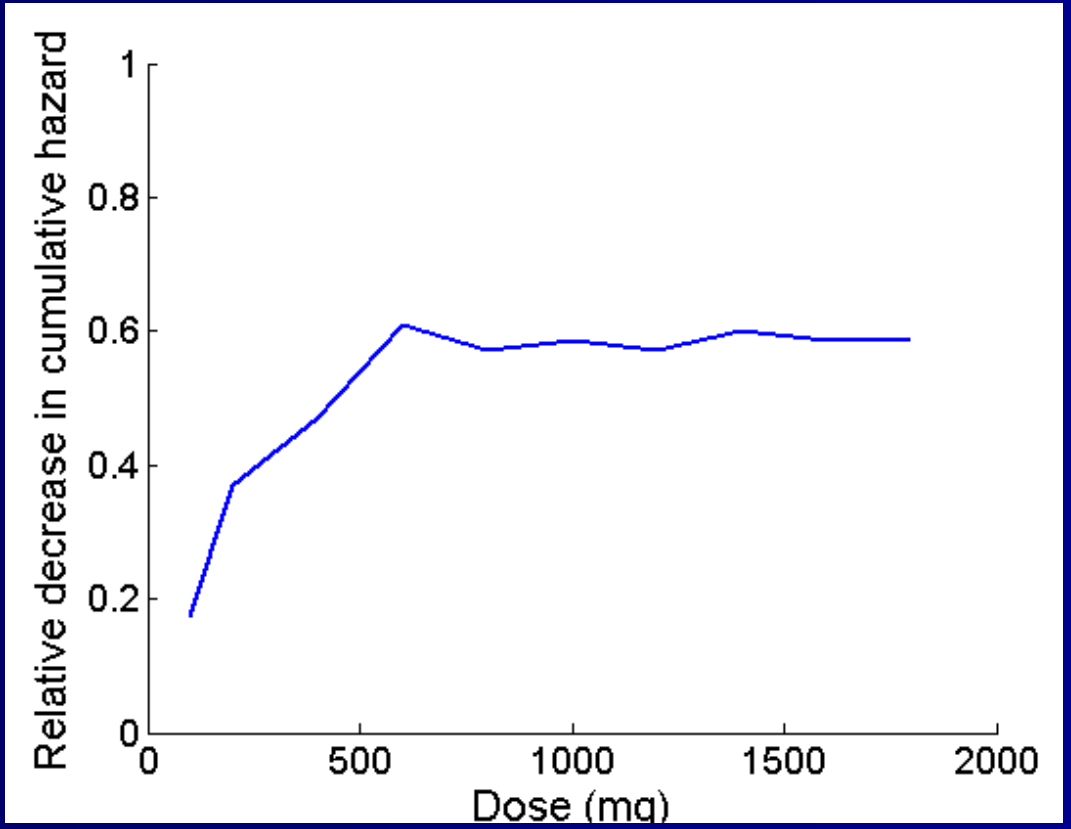
Probability of risk for TdP with and without activated charcoal

RR = 80 bpm (= 760 ms)





Relative reduction in hazard/risk for TdP by charcoal



Conclusions

- Informative priors and veracity judgements on dosing history could be used for developing a PKPD model from overdose data
- Activated charcoal reduced F and increased CL after citalopram overdoses
- QT prolongation was delayed relative to C_{max} of citalopram
- Administration of activated charcoal reduced the risk for TdP by approximately 60%

Acknowledgements

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