

# Characterizing associations of nocturnal glycemic control with QTc interval in children with type 1 diabetes – a model-based analysis

Verena Gotta (1), Sara Bachmann (2), Marc Pfister (1), Birgit Donner (3)

(1) Pediatric Pharmacology and Pharmacometrics, (2) Pediatric Endocrinology and Diabetology,  
(3) Pediatric Cardiology, University of Basel Children's Hospital, Basel, Switzerland

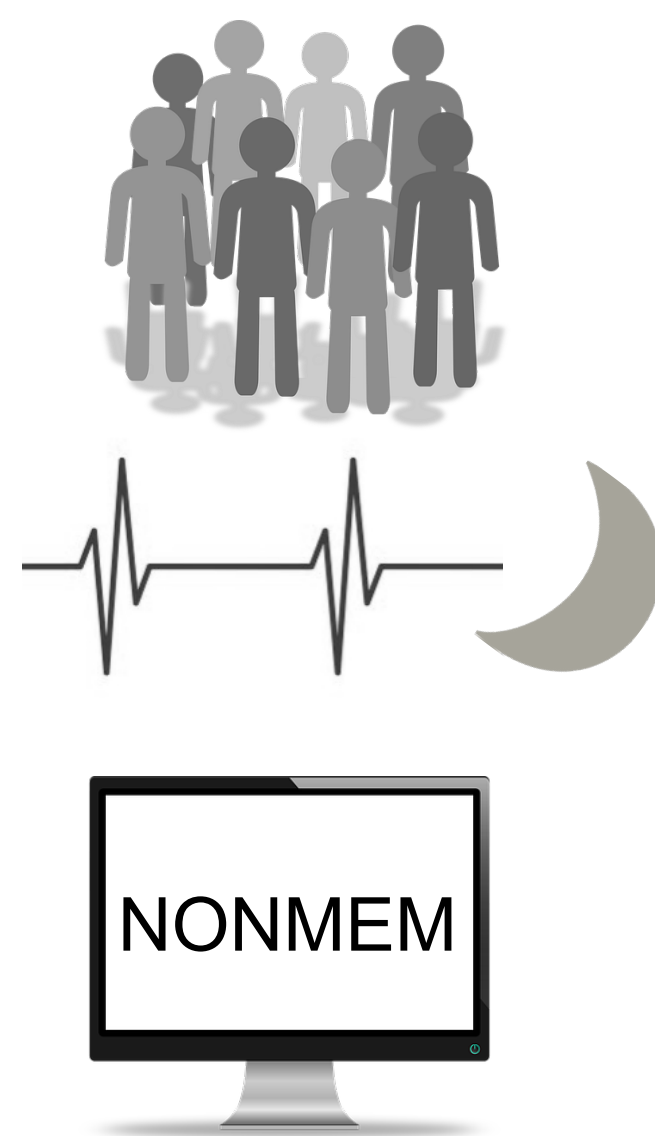
## Introduction

- The heart-rate corrected QT (QTc) interval is subject to significant inter- and intra-individual variability. QTc lengthening is associated with increased risk of ventricular arrhythmia & sudden cardiac death.
- In children with type 1 diabetes (T1D) an **association between nocturnal hypoglycemia (<3.7mmol/l) and QTc lengthening (QTcB: heart-rate correction using Bazett equation)** of 7 ms compared to euglycemia has previously been observed[1].

→ **Objective:** To increase the quantitative understanding of this association, and to quantify other sources of QTc variability in the pediatric diabetic population

## Methods

- Data from prospective observational study in 25 cardiac healthy children with T1D (home setting) [1]
  - age range: 8.1-17.6 years
  - duration of T1D: 0.5-13.3 years
- Continuous subcutaneous glucose and Holter electrocardiogram measurements (5 consecutive nights) averaged over 5 min for analysis
- Analysis: non-linear mixed effect modelling



QTcB/QTc  
Base models



Covariate model



Variability in  
sensitivity to  
QTc-lengthening

- Comparison of Bazett versus individual heart-rate correction (QTcB vs QTcI)
- Quantification of random QTc variability (between-subject, inter-night, residual intra-individual variability: BSV, INV, RV)
- Adjustment for known effects on QTc:
  - circadian variation
  - age and gender
- Investigation of glucose-QTc relationship (univariable + adjusted analysis)
- Investigation of factors that may modify sensitivity to QTc-lengthening, in particular:
  - duration of diabetes
  - HbA1c
  - time in hypoglycemia
  - glucose variability
  - pre-study magnesium serum level

## Results

### QTcB/QTcI Base models

- Random variability was reduced in the QTcI compared to the QTcB Base model (and further in the covariate model: Table 1, Fig 1 & 2)

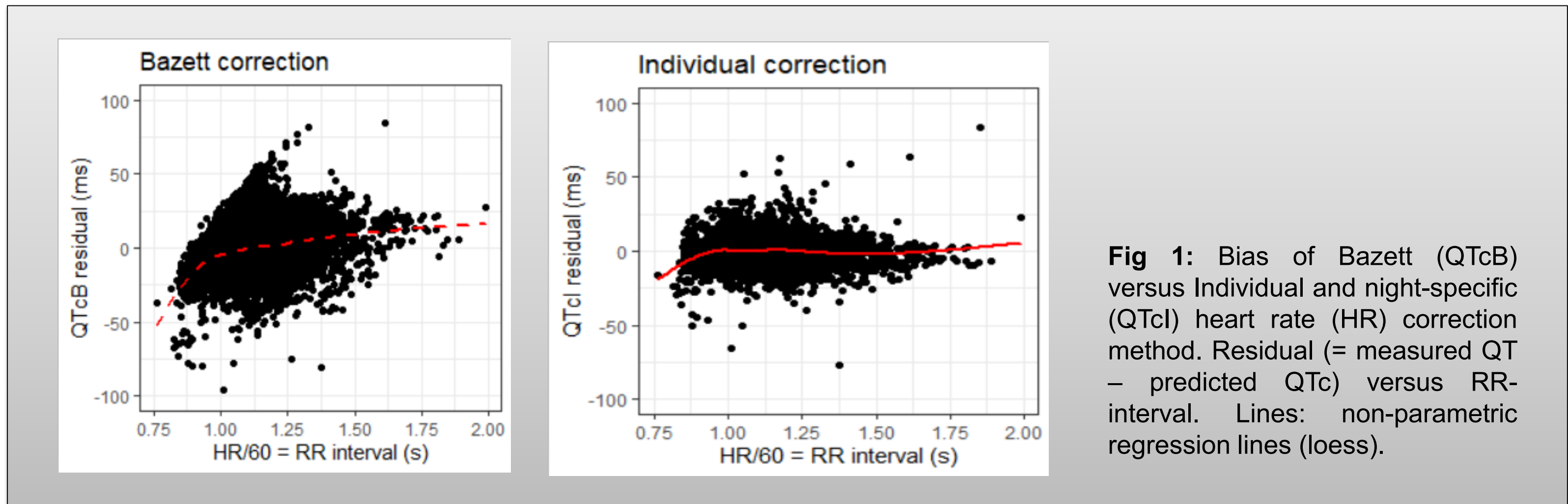


Fig 1: Bias of Bazett (QTcB) versus Individual and night-specific (QTcI) heart rate (HR) correction method. Residual (= measured QT – predicted QTc) versus RR-interval. Lines: non-parametric regression lines (loess).

### Covariate model

- This model accounted for significantly ( $P < 0.01$ ) shortened QTc in adolescent boys, circadian variation (cosine function) and a linear glucose-QTc relationship (strongest association assuming a delayed effect, e.g. through sympatho-adrenergic stimulation) (Table 1, Fig. 2)
- A linear glucose-QTc relationship was visually and statistically (lower AIC) preferred over alternative relationships, including categorical stratification (estimating 1.75 ms longer QTc in hypo- versus euglycemia; relative standard error, RSE: 27%).

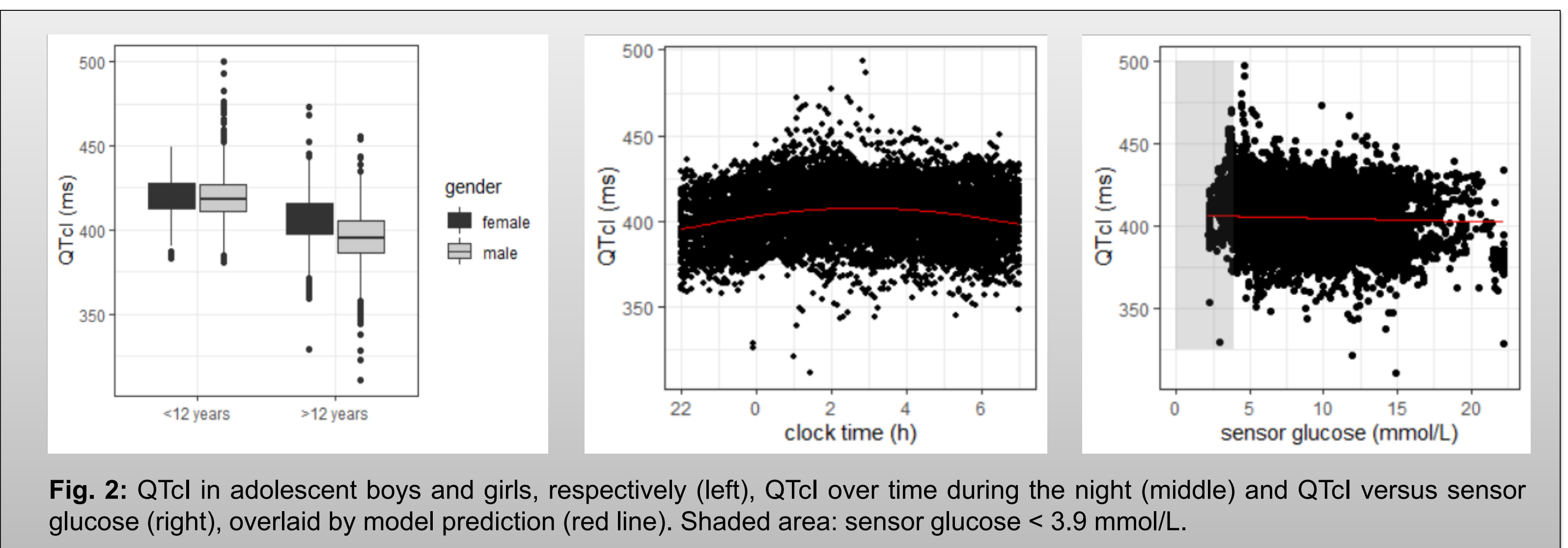


Fig. 2: QTcI in adolescent boys and girls, respectively (left), QTcI over time during the night (middle) and QTcI versus sensor glucose (right), overlaid by model prediction (red line). Shaded area: sensor glucose < 3.9 mmol/L.

Table 1: Comparison of variability and parameter estimates from base models (QTcB: Bazett-correction, QTcI: individual and night-specific heart rate correction) and the developed adjusted covariate model

| Parameter                             | QTcB<br>Base model | QTcI<br>Base model | QTcI<br>Covariate model |
|---------------------------------------|--------------------|--------------------|-------------------------|
| <b>Fixed effects</b>                  |                    |                    |                         |
| QTc <sub>ref</sub> (ms)               | 408 (0.9%)         | 406 (0.7%)         | 399 (0.7%)              |
| heart-rate correction factor          | -0.5 (fixed)       | -0.43 (3.1%)       | -0.40 (3.8%)            |
|                                       |                    | BSV: 11% (28%)     | BSV: 15% (22%)          |
|                                       |                    | INV: 20% (9.8%)    | INV: 20% (9.7%)         |
| effect <sub>Male, &lt;12 y</sub> (ms) |                    |                    | -14.6 (29.1%)           |
| amplitude (fraction)                  |                    |                    | 0.048 (3.0%)            |
| shift (h)                             |                    |                    | 2.89 (1.2%)             |
| slope glucose-QTc (ms/mmol/L)         |                    |                    | -0.76 (6.2%)            |
| delay rate constant (1/h)             |                    |                    | 0.56 (9.5%)             |
| <b>Random variability in QTc</b>      |                    |                    |                         |
| Between-subject, BSV (ms)             | ±14.1 (15.3%)      | ±12.6 (15.6%)      | ±9.7 (16.4%)            |
| Inter-night, INV (ms)                 | ±7.8 (8.2%)        | ±7.5 (8.8%)        | ±6.5 (8.8%)             |
| Residual (ms)                         | ±8.5 (0.8%)        | ±8.0 (0.8%)        | ±7.4 (0.8%)             |

### Variability in sensitivity to QTc-lengthening

- Adding BSV and INV on the slope parameter quantified relevant random variability ( $\pm 1$ -2 ms per 1 mmol/L), however with the typical mean slope estimate approximating 0 (large RSE >100%), i.e. predicting both positive and negative glucose-QTcI associations, even within the same patient (→ not retained, unphysiological); no significant correlation with patient characteristics were identified.
- When not including BSV/INV on the slope, significantly different sensitivity was estimated according to HbA1c ( $>/<7.5\%$ ), duration of diabetes ( $>/<5.2$  years) and time in hypoglycaemia ( $>/<3.6\%$ /nighttime), but not glucose variability ( $>/<36\%$ ) or magnesium levels ( $>/<0.8$  mmol/L).

## Conclusions

- A **clinically mild association** of nocturnal hypoglycemia with longer QTc intervals could be **confirmed** in this model-based analysis.
- Relevant circadian variation quantified in this study, with **longest QTc around 03:00 AM, may contribute to higher risk of sudden unexpected overnight death** in the pediatric diabetic population.
- In analogy to a thorough QT study, conduct of a controlled study design comparing several experimental controlled glucose levels is warranted to further characterize underlying relationships between hypoglycemic events and QTc interval in children with T1D.