

# Not-In-Trial Simulations: A Tool for Mitigating Cardiovascular Safety Risks

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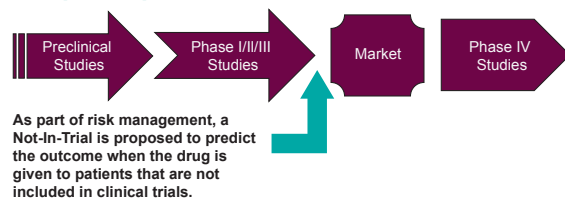
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## Background & Objective

QT/QTc-interval prolongation continues to be a concern in drug development today. More effort is needed to explain the discrepancies between trial outcomes and real-life data from epidemiological studies. The objective of this study is to better translate clinical findings to real-life situations and resolve the discrepancies in pre- vs. post-market estimates of QTc-interval prolongation.

**Figure 1. Diagram proposing when Not-In-Trial simulation would be beneficial in the drug development process**



## Methods

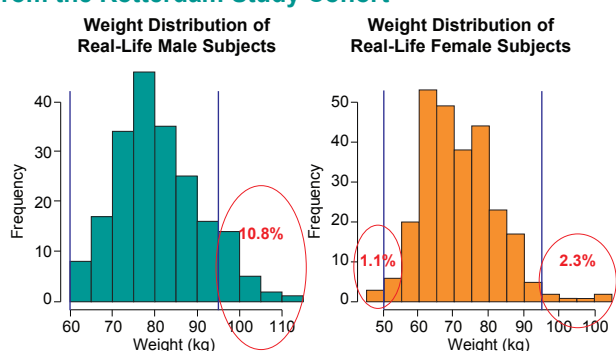
Using *d,l*-sotalol as a paradigm compound, the gap between clinical trial outcomes and epidemiological observations was identified by simulating the drug-induced effects of a population with the same demographic properties as real-life users. Any additional effects were evaluated by calculating the absolute differences in QTc prolongation between taking the drug alone and in conjunction with co-medications and comorbidities using the Rotterdam Study Cohort as the reference population. A new mechanism-based tool was developed: QTc (real-life population) = baseline + circadian rhythm + drug exposure + effects of co-medications and comorbidity conditions. Distribution of simulated and observed values were then compared non-parametrically. Finally, the approach was validated with the compound, cisapride.

## Results

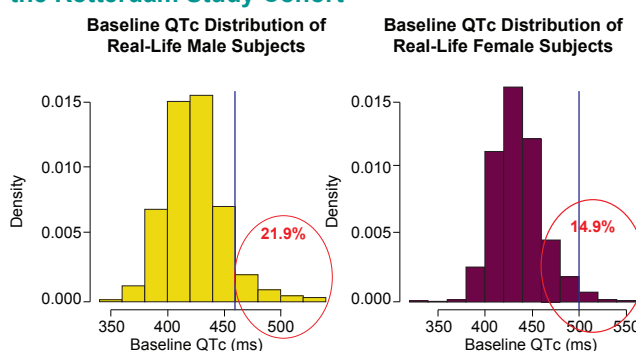
### Problem

Drug exposure is only one of the explanatory variables for QTc prolongation in real life. Trial design also contributes to the bias in drug induced effects. In **Figures 2 and 3**, it is shown that a portion of the real-life population (circled in histograms) would not be represented in a clinical trial due to inclusion/exclusion criteria. When applying a real-life weight distribution to the clinical model, there is a clear mismatch between the model-simulated values and the observed QTc from the Rotterdam Cohort.

**Figure 2. Weight distribution of real-life sotalol users from the Rotterdam Study Cohort**

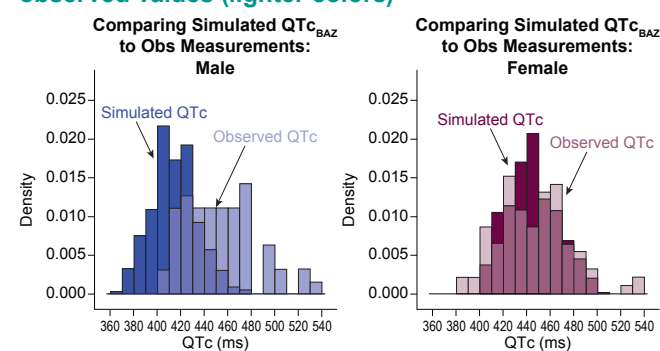


**Figure 3. Baseline distribution of sotalol users from the Rotterdam Study Cohort**



Inclusion and exclusion criteria is bounded by the vertical bars

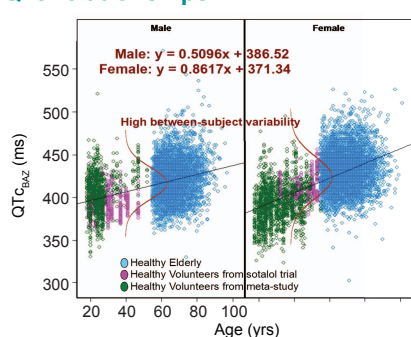
**Figure 4. Comparing simulated QTc (darker colors) to observed values (lighter colors)**



### Solution

To resolve the discrepancies between predicted drug-induced QTc values and actual observed values in real-life population, the approach of QTc (observed) = age, sex-dependent baseline (**Figure 5**) + contribution of comorbidities and co-medications (**Table 1**) + drug effects (**Figure 6**) is tested. The final simulations showed that the novel approach can adequately describe the observed data within the inter-individual variability boundary (**Figure 7**).

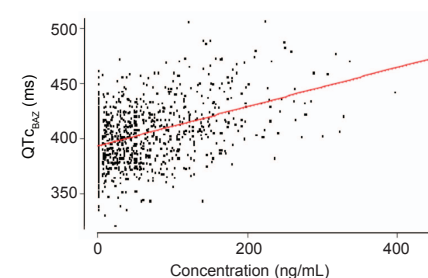
**Figure 5. Cross-sectional age and sex-dependent baseline QTc relationships**



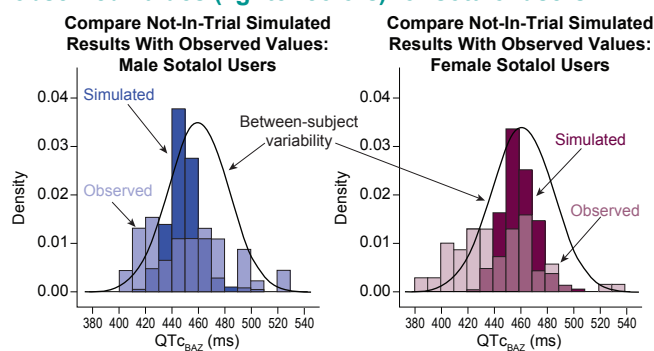
**Table 1. Contribution of comorbidities and co-medications on QTc interval prolongation found using linear regression**

Heart Failure	5.8 (±3.49) for female, 7.7 (±4.02) for male
Myocardial Infarction	3.2 (±2.11) for female, 3.0 (±2.31) for male
Arrhythmia	3.0 (±2.0) for female, 5.4 (±2.28) for male
Diabetes	20.4 (±9.51) for female, 18.5 (±9.21) for male

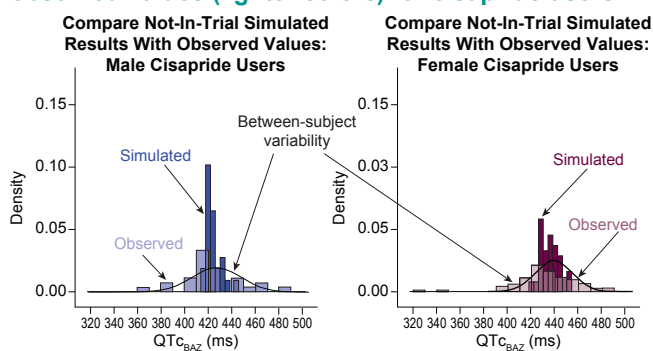
**Figure 6. A typical drug effect relationship between concentration and QTc**



**Figure 7. Comparing simulated QTc (darker colors) to observed values (lighter colors) for sotalol users**



**Figure 8. Comparing simulated QTc (darker colors) to observed values (lighter colors) for cisapride users**



### Validation

Using the same approach, simulations were done to cisapride users. The distribution of the observed QTc values (lighter color) once again fell within the simulated distribution (darker color) (**Figure 8**).

## Conclusions

The underlying assumption in conducting clinical trials is that findings about drug effect are generalizable to the real-life population. However, in the case of *d,l*-sotalol, our results showed that *only part* of the observed QTc distribution in the real-life population could be attributed to the drug effect. The new approach demonstrated and validated here enabled better estimation of the true risk that could mitigate future drug withdrawal due to cardiovascular safety.

## Data

### Clinical Trial Population

- Standard inclusion/exclusion criteria
- Male or female subjects between 18-55 years of age, inclusive
- Body mass index between 19-30 kg/m<sup>2</sup>, with weight between 50-95 kg, inclusive

### Real-Life Population - Rotterdam Study Cohort

- Subjects ≥55 years of age
- Longitudinal data of maximum 4 visits

