

A PK/PD meta-analysis to assess inter-study variability and translational value of preclinical exposure-QTc relationships

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Background

- Drug-induced QTc-interval prolongation (Δ QTc) is systematically assessed in preclinical cardiovascular (CV) safety studies as a surrogate for pro-arrhythmic risk in human.
- Such studies in conscious telemetered dogs (4-8 animals) can be based on varying designs (e.g. dose range, number of doses, route of administration, study duration, PK/PD sampling in same animals or a satellite group, no PK assessment).

Methods & Results

- The work-flow of this meta-analysis is shown below, followed by an illustration of main results.
- For moxifloxacin, inter-study variability (ISV) was additionally assessed in a hierarchical random-effects model¹.

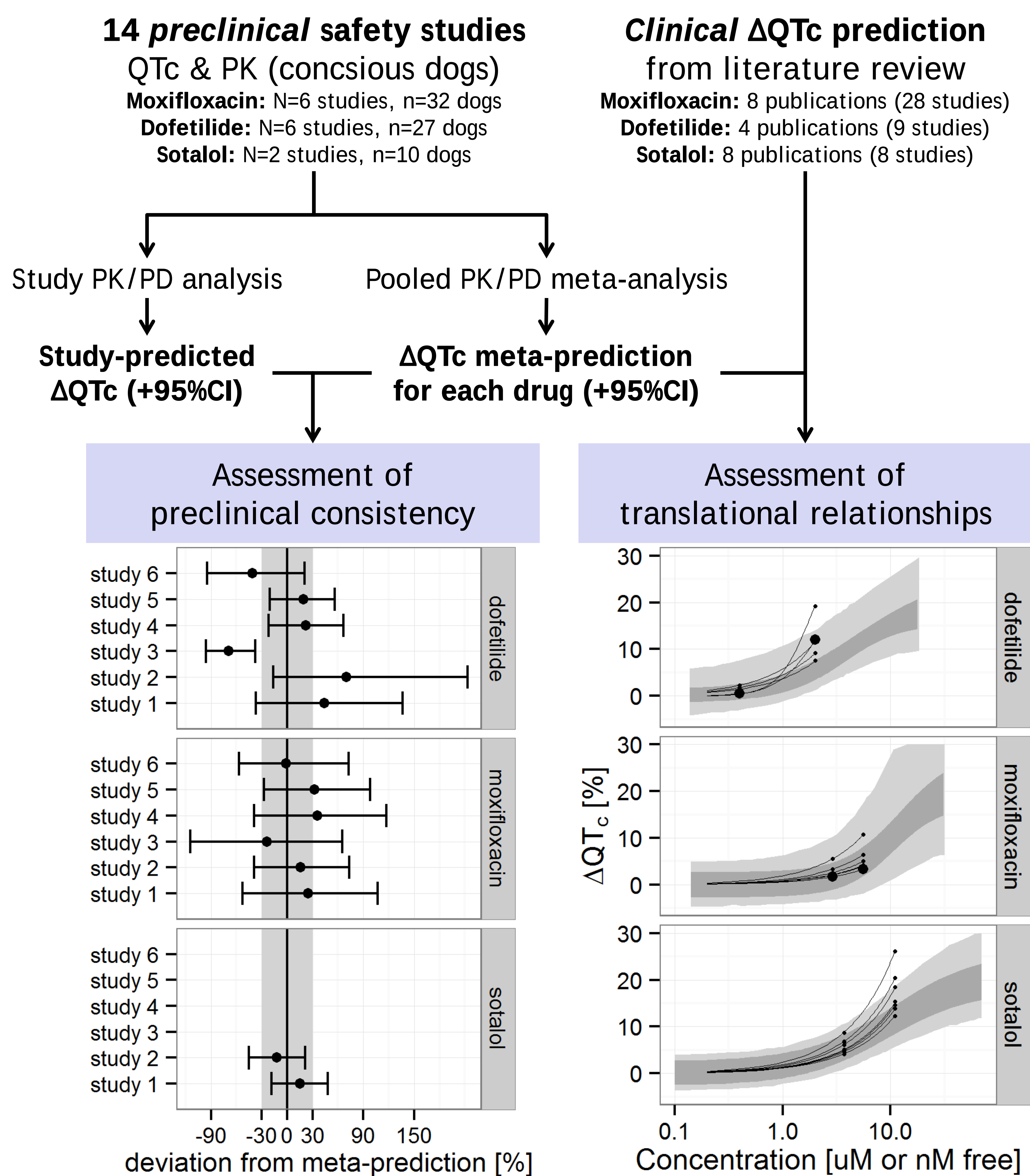


Fig.1: Consistency of predictions at upper therapeutic exposure.

Deviation of individual study-predicted Δ QTc from Δ QTc meta-predictions at upper therapeutic exposure. Vertical shaded area: $\pm 30\%$ = overall mean deviation (ISV). Error bars: 95%CI, 13/14 studies comprise the meta-prediction and can be considered unbiased & consistent.

Fig.2: Pharmacodynamics and translation.

Pharmacodynamics in the conscious dog (shaded area, dark/light grey: 95%CI/90% prediction interval of meta-predictions) is overlapping with clinical Δ QTc (lines) at lower and upper level of therapeutic exposure (dots; clinical meta-predictions are indicated with larger dots).

Objective

To assess pharmacodynamic (PD) relationships derived from varying preclinical studies with respect to their:

- quantitative consistency of preclinical Δ QTc prediction (inter-study variability)
- correlation of preclinical Δ QTc with clinical effects (translational relationship)

Consistency of Δ QTc-predictions at upper therapeutic exposure (Fig.1):

- The 95%CIs of 13/14 (93%) study-predictions comprised the meta-prediction, despite varying structural models.
- Inter-study variability (ISV) of Δ QTc-predictions was 30% (range: 1-69%).

Model-based assessment of ISV (moxifloxacin):

- Including an ISV-level in the meta-model decreased between-subject variability (BSV) in PD by 10-26%, most on the hill coefficient.
- Estimated ISV (24-39%, RSE>100%) did not exceed BSV (28-37%).

Pharmacodynamic characterization (Fig.2):

The preclinical PDs of all 3 drugs was best characterized by E_{max} -meta-models (Δ QTc_{max}=50-55ms or 20-22% from baseline).

Preclinical Δ QTc meta-predictions

(therapeutic range):

- Moxifloxacin: 4-12 ms (2.9-5.6 μ M, EC_{50} :11.6 μ M)
- Dofetilide: 4-18 ms (0.4-2 nM, EC_{50} : 4.2 nM)
- Sotalol: 14-19 ms (3.7-11 μ M, EC_{50} : 10.1 μ M)

Translation: clinical Δ QTc predictions

- Expressed as %change from baseline, clinical & pre-clinical Δ QTc effects we overlapping

Summary & Conclusions

This first quantitative assessment suggests that consistent Δ QTc predictions can be obtained from highly varying preclinical studies by systematic PK/PD analysis

→ suitable for translational purpose

A 10% Δ QTc in the dog seems to correspond to an almost half-maximal effect (and ≥ 35 ms Δ QTc in human)

→ 10% effect² is an unsatisfying study sensitivity target

→ PK/PD analysis can improve the detection of small preclinical Δ QTc³