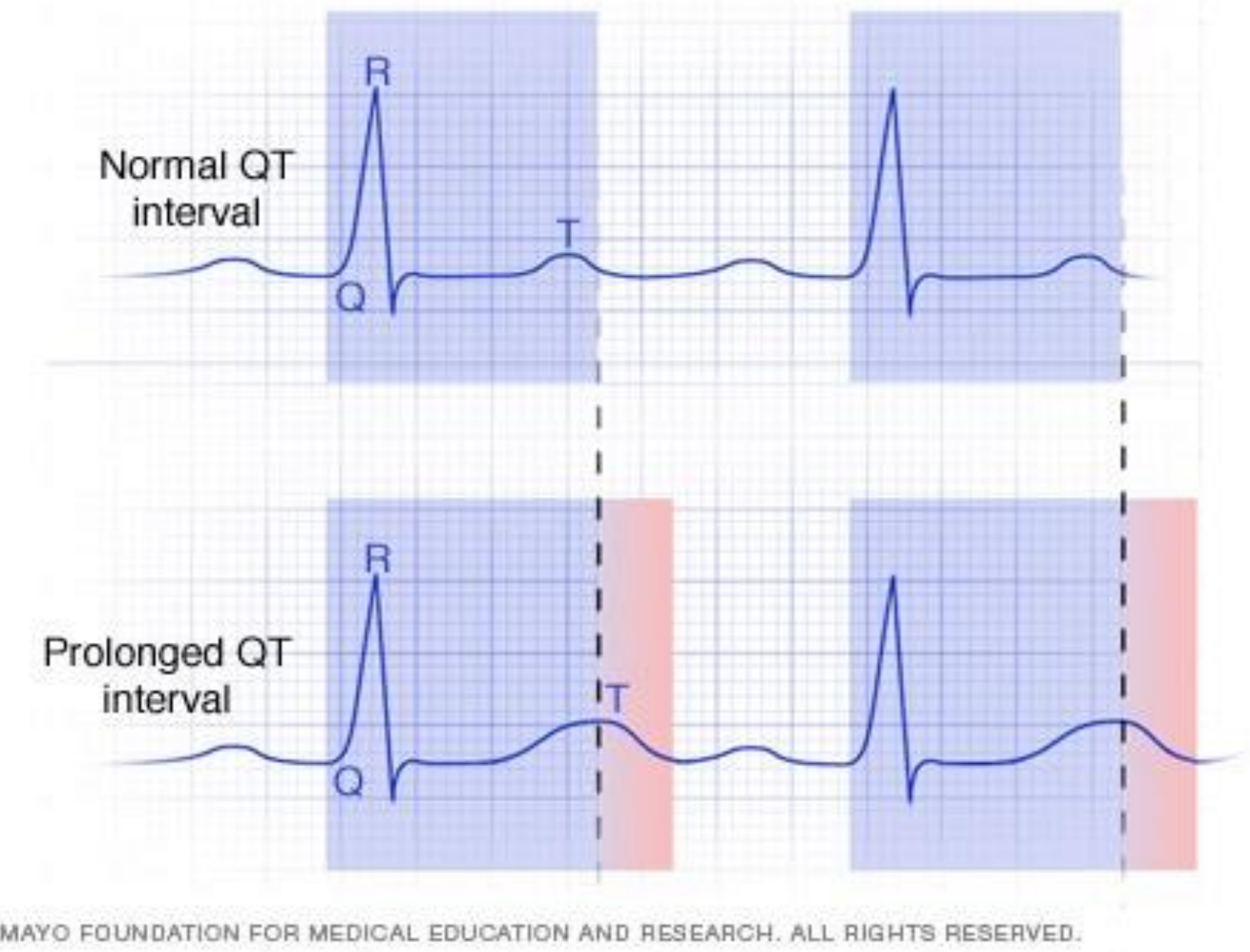
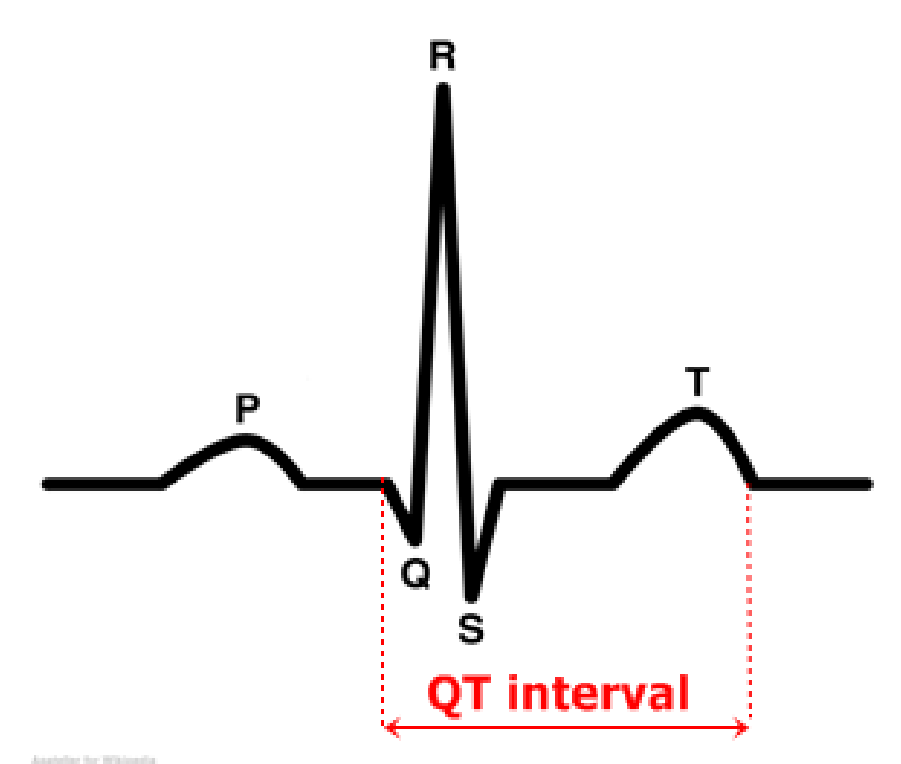


Number of ECG Replicates Influences the Estimated QT Prolonging Effect of a Drug

H.E.C. van der Wall^{1,3}, P. Gal¹, M.J.B. Kemme^{1,2}, G.J.P. van Westen³, J. Burggraaf^{*,1,3,4}

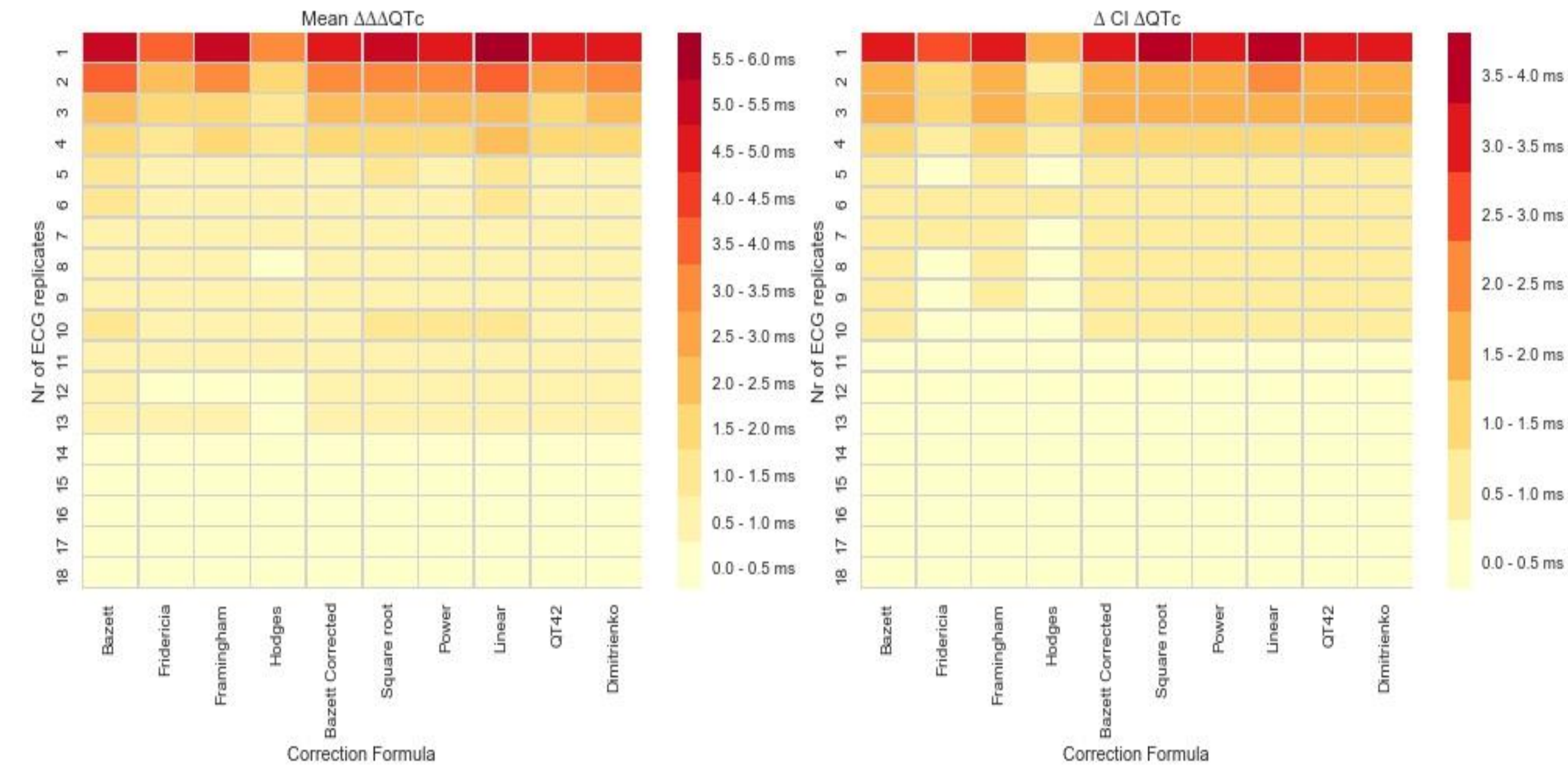
1: Centre for Human Drug Research, Leiden, the Netherlands, 2: VU Medical center, Department of Cardiology, Amsterdam, the Netherlands, 3: Leiden Academic Centre for Drug Research, Leiden, the Netherlands, 4: Leiden University Medical Center, Leiden, the Netherlands



© MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH. ALL RIGHTS RESERVED.

Methods

- 100 healthy volunteers, who received a compound prolonging the QT interval, divided in 10 cohorts
- $\Delta\Delta QT_c$ of 18 ECG replicates per subject averaged for each replicate count (1-18)
- 10 different correction formulas
- For each replicate count and correction formula, calculation of:
 - $\Delta_{18 \text{ replicates}} \Delta_{\text{placebo}} \Delta_{\text{baseline}} QT_c$
 - $\Delta_{18 \text{ replicates}} 90\% CI \Delta_{\text{baseline}} QT_c$



Introduction

Drugs can cause QT prolongation, which can lead to:

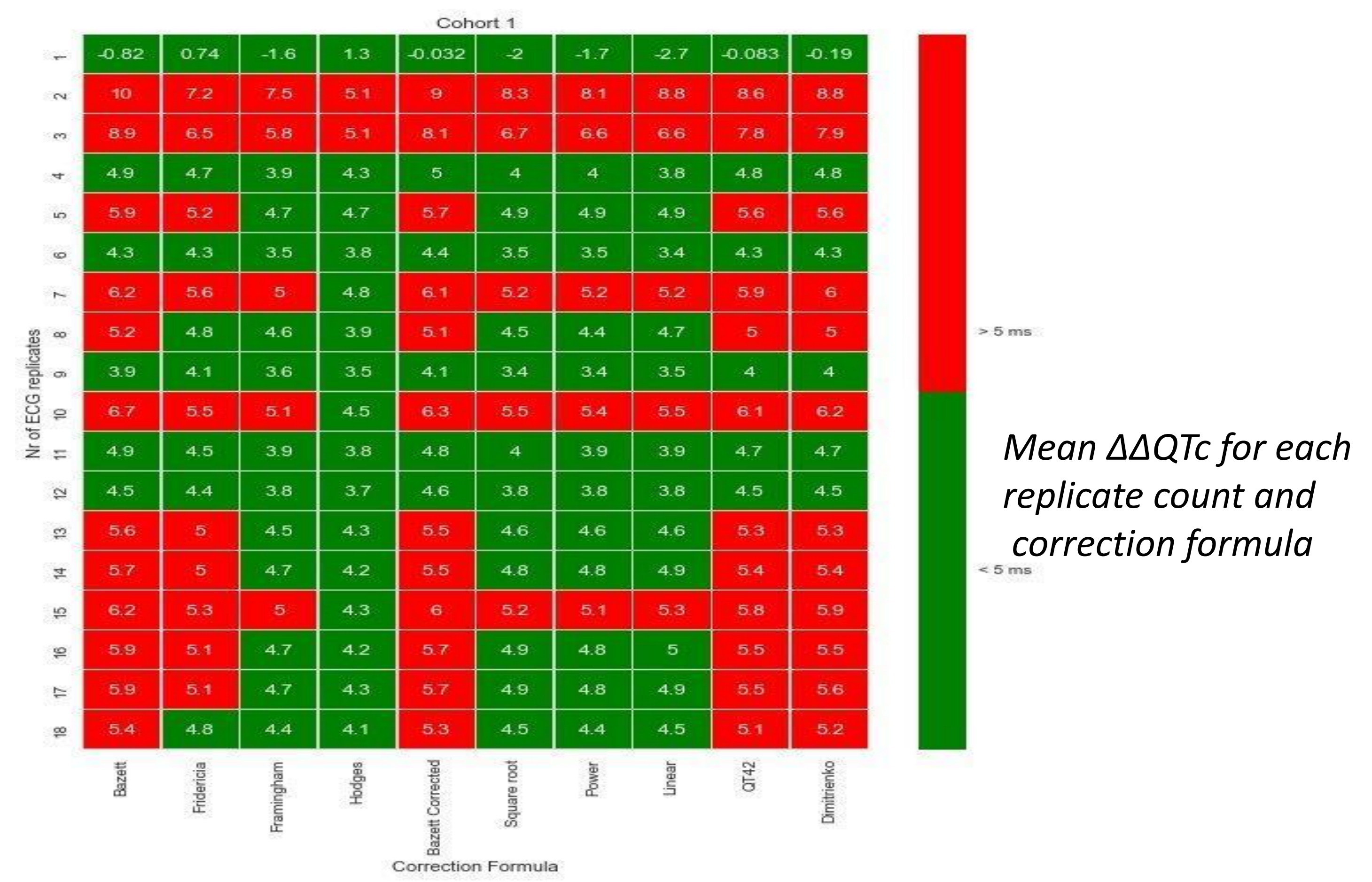
- Fainting
- Seizures
- Sudden death

To identify these drugs, the ICH has set guidelines:

- Triplicate ECGs
- Mean QT prolongation corrected for both baseline and placebo ($\Delta\Delta QT_c$) must not exceed 5 ms
- Upper limit of 90% confidence interval of $\Delta\Delta QT_c$ prolongation must not exceed 10 ms

AIM

The present analysis addressed the effect of the number of ECG replicates extracted from a continuous ECG on estimated QT interval prolongation for different QT correction formulas.



Results

The mean prolongation difference was >4 ms for single and > 2 ms for triplicate ECG measurements compared to the 18 ECG replicate mean value. The difference was <0.5ms after 14 replicates. In contrast, concentration-effect analysis was independent of replicate count and also of QT correction formula.

Concentration-Effect analysis

Decile	Estimated mean \pm SD investigational medicinal compound concentration (ng/mL)	Mean \pm SD QT prolongation (ms) using 3 ECG replicates	Mean \pm SD QT prolongation (ms) using 5 ECG replicates	Mean \pm SD QT prolongation (ms) using 18 ECG replicates
1	7.6 \pm 2.5	6.51 \pm 16.59	5.21 \pm 12.47	4.84 \pm 11.54
2	23.2 \pm 3.1	6.08 \pm 7.13	8.37 \pm 5.63	7.31 \pm 5.2
3	59.6 \pm 10.7	-1.04 \pm 10.79	0.45 \pm 14.15	0.83 \pm 13.11
4	119.6 \pm 18.8	5.93 \pm 11.59	8.78 \pm 10.08	6.53 \pm 9.6
5	181.3 \pm 12.8	0.81 \pm 9.06	2.82 \pm 6.54	3.55 \pm 7.93
6	238.5 \pm 22.7	9.74 \pm 13.30	9.01 \pm 11.84	9.28 \pm 12.15
7	335.3 \pm 30.2	16.61 \pm 13.63	15.65 \pm 12.52	15.11 \pm 11.96
8	397.9 \pm 16.2	16.12 \pm 18.56	14.56 \pm 13.02	15.42 \pm 12.72
9	485.3 \pm 32.0	5.06 \pm 13.22	7.46 \pm 13.38	6.77 \pm 13.71
10	616.1 \pm 55.5	19.40 \pm 13.37	20.17 \pm 9.01	19.78 \pm 10.98
Slope (ml * ng ⁻¹ * ms)		0.022492	0.021380	0.022055
R ²		0.462857	0.539141	0.583485
p-value		0.030387	0.015601	0.010115

Conclusions

- The number of ECG replicates impacted the estimated QT interval prolongation for all deployed QT correction formulas.
- However, concentration-effect analysis was independent of both the replicate number and correction formula.

