Investigating the Ethnic Differences between the Effects of Moxifloxacin on Cardiac Conduction in Japanese and Caucasians

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RICHMOND Pharmacology

Overview

1. Is there literature suggesting ethnic differences in QTc responses to medicines?
2. The results from our own work so far (published and pending publication)
3. Outlook and further work proposed/planned

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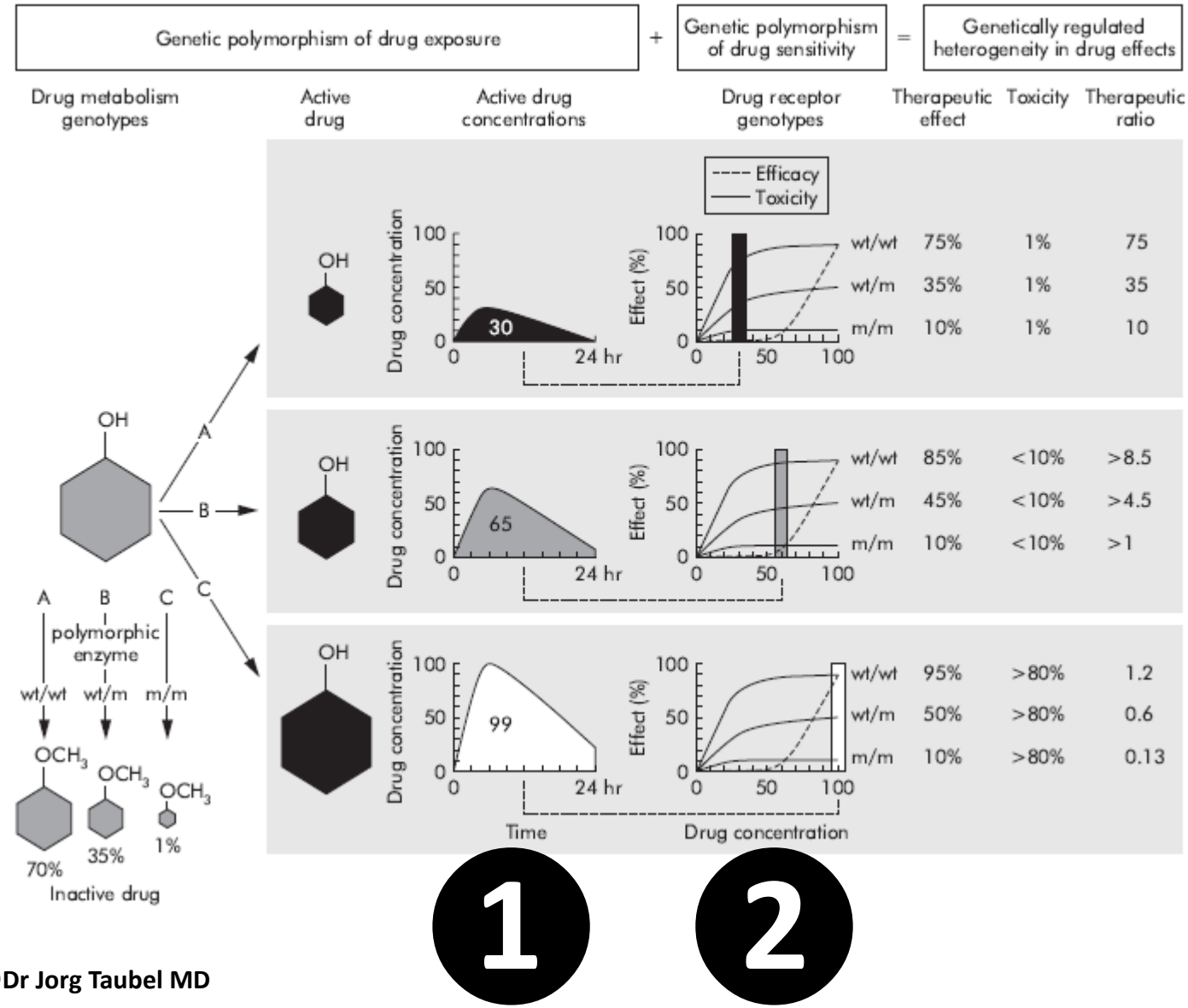
Genetic Polymorphism



1. PK effects
2. PD effects

Figure 1 Polygenetic determinants of drug response (reproduced with the publisher's permission, from Evans and Johnson, *Annu Rev Genomics Hum Genet* 2001;**2**:9–39).

PK and PD Effects

- There are significant inter-ethnic differences in the frequency of variant alleles of genes (e.g. *CYP2D6*, *CYP2C19*, *CYP2C9*) resulting in inter-ethnic differences in metabolism of their substrates.
- Highly polymorphic CYP2D6 and the frequency of variant alleles of CYP2D6 that result in impaired drug metabolism (increased plasma concentrations) is **higher among white Caucasians** compared with their Oriental counterparts.
- There are marked inter-ethnic differences in the frequency of variant alleles of genes, encoding for cardiac ion channels, with some alleles being **population-specific**. The frequency of variant *KCNH2* alleles that results in sensitivity to drug-induced QT interval prolongation is **higher among White Caucasians**.

Shah RR.
Drug-induced QT interval prolongation: does ethnicity of the thorough QT study population matter?
Br J Clin Pharmacol. 2013 Feb;75(2):347-58.

Published FDA Data on Moxifloxacin

- Pooled analysis of 20 TQT studies
- A subset of 60 Asian (Indian, Japanese and Chinese) subjects from 4 studies contributing 3, 9, 20 and 28 subjects each was compared to 788 Caucasian subjects
- C_{max} exposure in Asians was +6% compared to Caucasians
- No significant race effects were detected

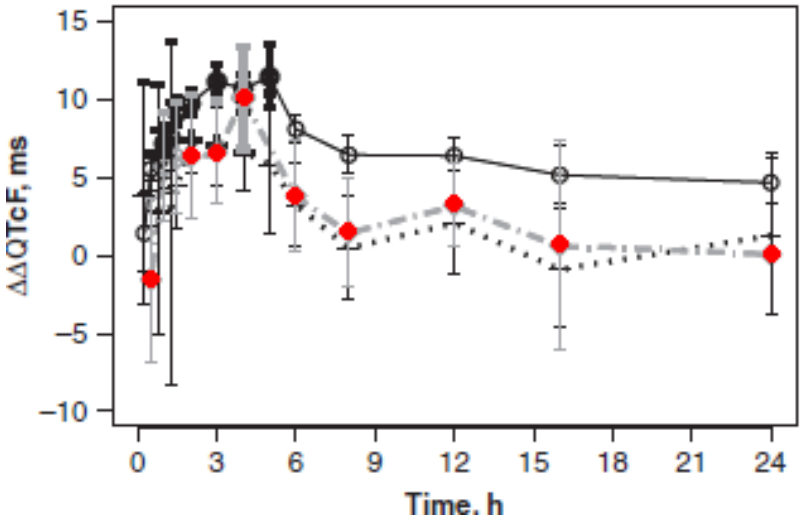


*Figure 1. Summary ΔΔQTcF versus time plots for the 20 pooled TQT studies divided by … race category (…Caucasian [n = 788], solid, circles; black [n = 105], dotted, plus symbols; **Asian [n = 72], dash-dot, diamonds**). … quantile means ± 90% confidence interval. …*

Florian JA et al.
Population Pharmacokinetic and Concentration–QTc Models for Moxifloxacin: Pooled Analysis of 20 Thorough QT Studies. J Clin Pharmacol. 2011 Aug;51(8):1152-62.

Quinidine in American and Korean

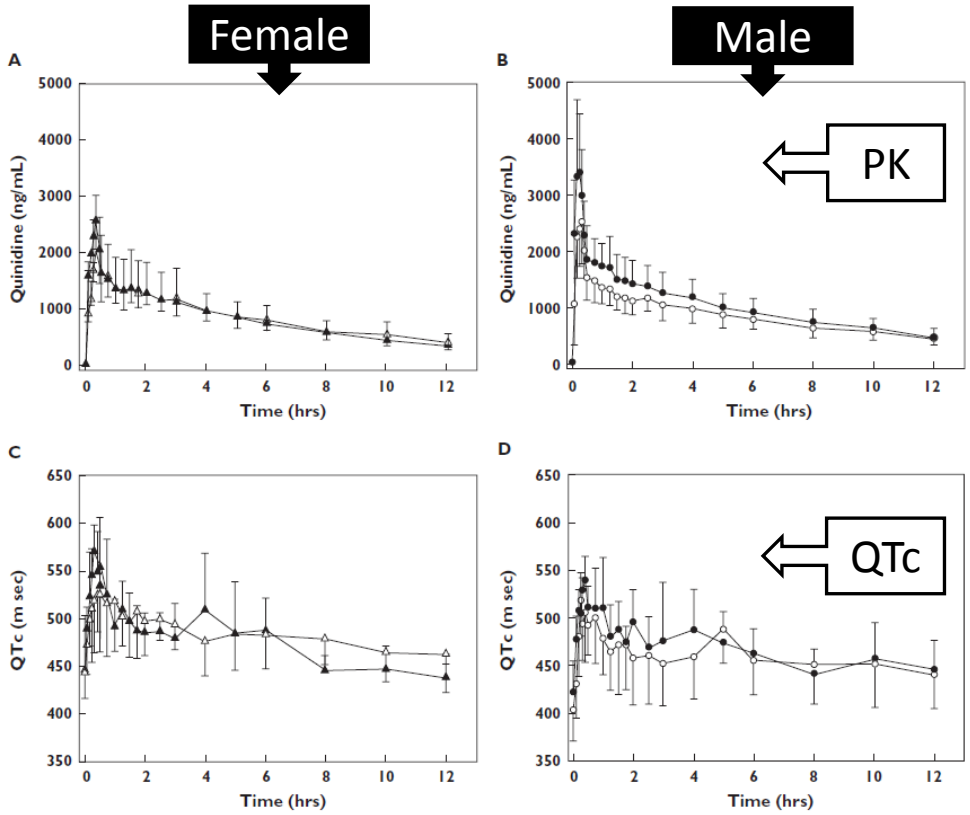


Figure 1
Mean plasma quinidine concentration-time profiles and the time course of QTc interval after a 20 min infusion of quinidine (4 mg kg^{-1}) in 24 healthy Korean subjects (open symbol) and 13 healthy Caucasian subjects (closed symbol). (A) and (B) Mean plasma quinidine concentration-time curve in female and male subjects, respectively. (C) and (D) Mean QTc interval-time curve in female and male subjects, respectively. Each point indicates mean ± SD

infusion of quinidine (4 mg kg^{-1}) for 20 min

N=37	Korean	Caucasian
Male	12	7
Female	12	6
Total	**24**	**13**

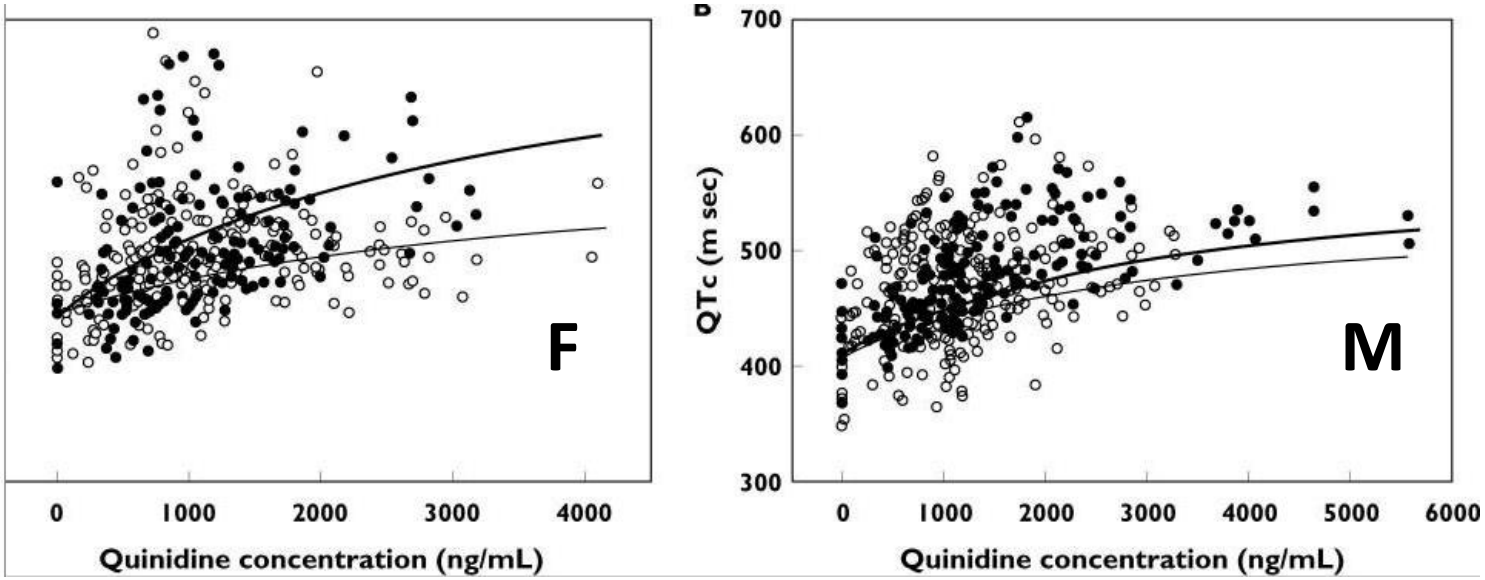
Significant QTc prolongation ~75-100ms

Caucasian ●Korean ◌

Flockhart DA et al.
Possible interethnic differences in quinidine-induced QT prolongation between healthy Caucasian and Korean subjects.
Br J Clin Pharmacol. 2007 Feb;63(2):206-15.

Shin & Flockhart; BJCP 2006

PK-PD Study in Korean ◌ and Caucasian ●



Limitations:

- QTcB
- HR effects not described (HR effect, use dependent block)
- Study in two sites
- No ECG baseline day/baselines >450msec
- Placebo data not presented
- Paper ECG, different equipment in sites
- ECG over-reading

Investigating Ethnic differences

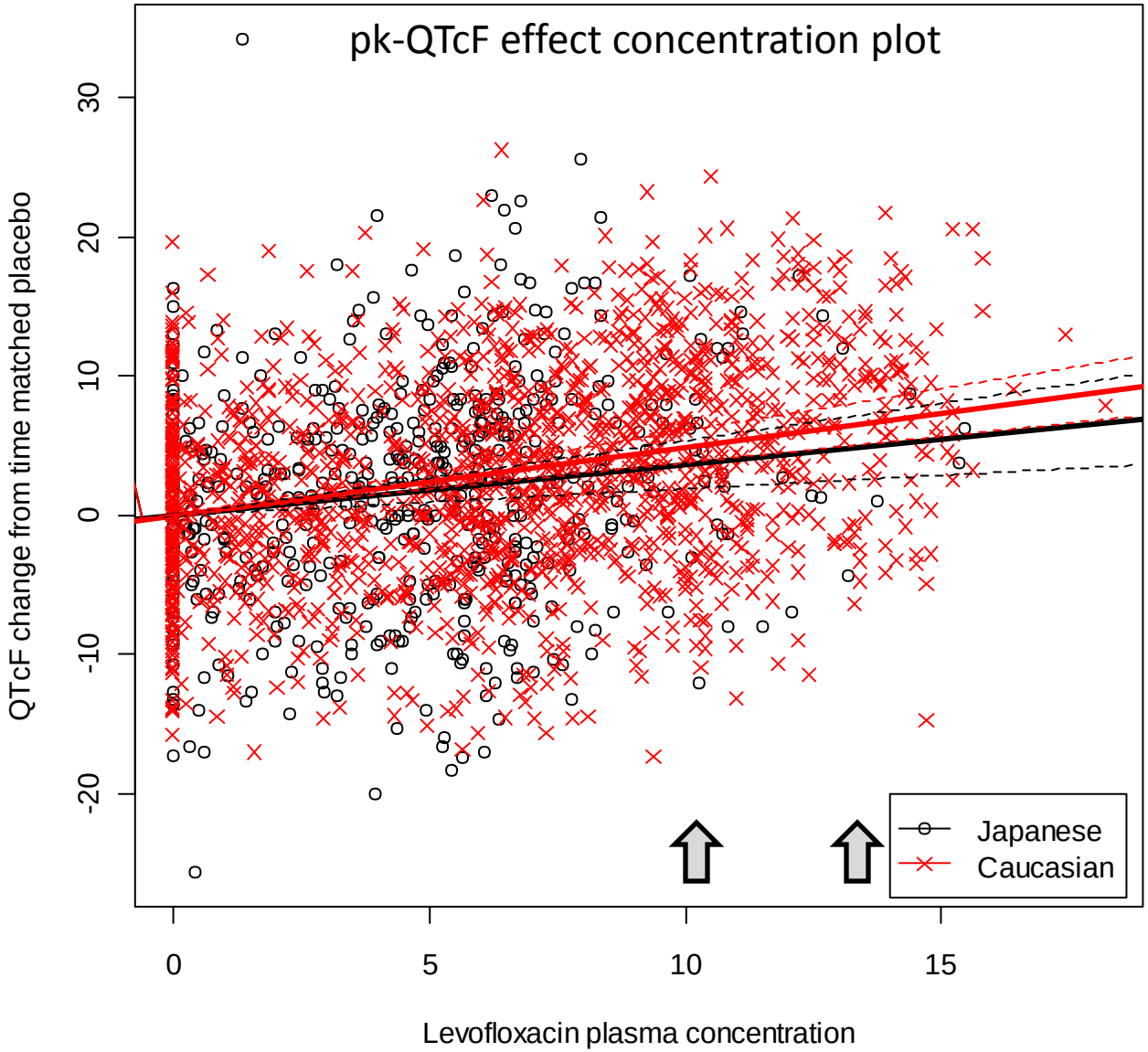
QT studies involving Japanese
Moxifloxacin
Antipsychotic (marketed)
H1 Antagonist (marketed)
Levofloxacin

QT studies investigating physiological effects involving Japanese
Insulin
C-Peptide
Glucose

With reasonable sample sizes, moxifloxacin control and high precision ECG acquisition *and* high precision measurements all of these studies showed either no difference between ethnicities or minuscule differences which in all instances were not statistically significant.

That does not mean clinically differences cannot exist, but we certainly have not seen any evidence for differences in sensitivity so far.

Levofloxacin post hoc analysis

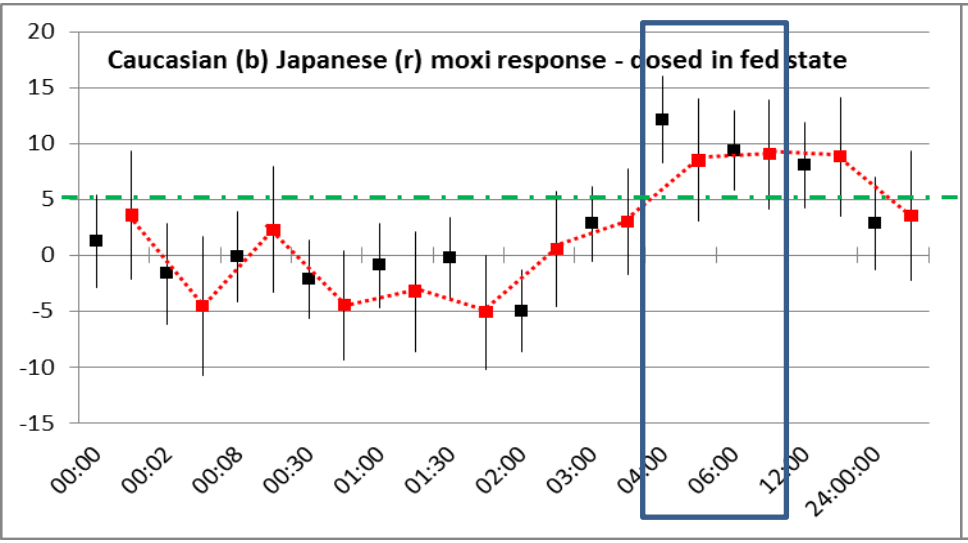


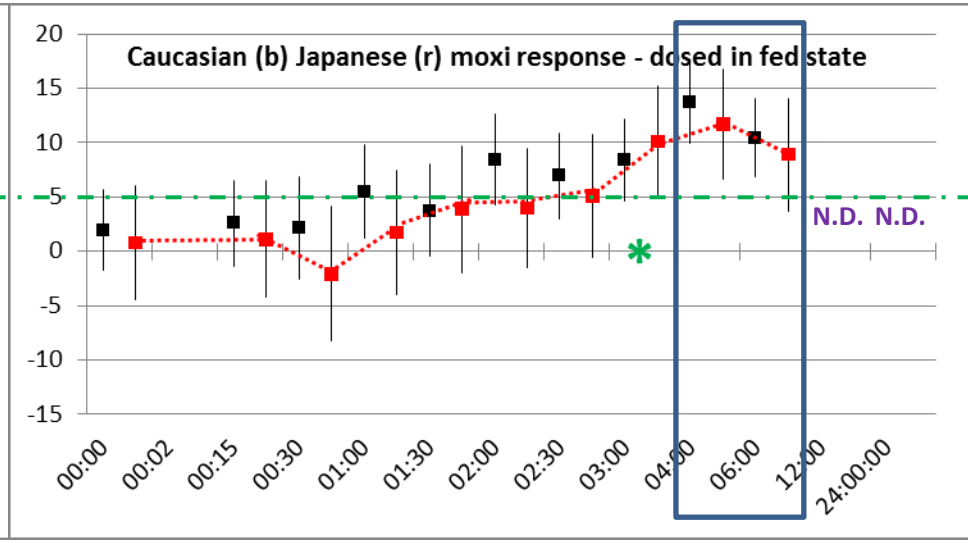
- ❑ Japanese subjects show the extremes of QTc shortening/lengthening
- ❑ Caucasians have the highest plasma concentrations
- ❑ The slope indicates the QTc prolonging properties of Levofloxacin
- ❑ The slope for the Japanese subjects is flatter, that of the Caucasians steeper
- ❑ The confidence intervals overlap
- ❑ No significant differences

Sugiyama et al.
Br J Clin Pharmacol 2011

400mg oral Moxifloxacin *after* a meal

Design: 4-way cross-over studies, single dose. Study 1: N= 42 /Study 2: N= 32
All subjects received 400mg oral moxifloxacin 10 minutes after completing a breakfast Placebo baseline day preceded all treatment days; oral placebo after breakfast only





RED: Japanese, BLACK: Caucasian

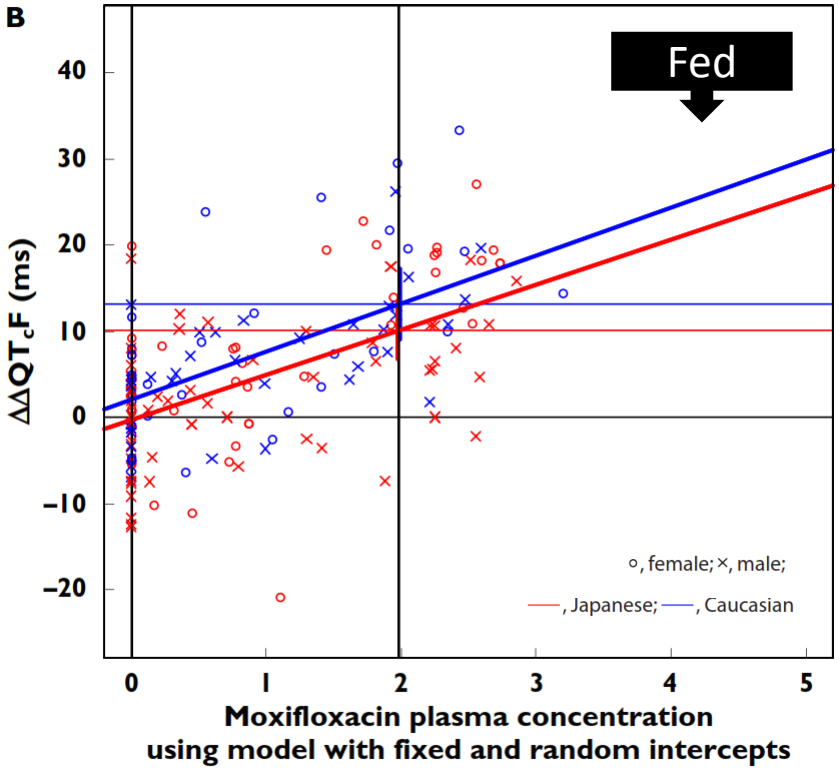
STUDY 1 [N=42]

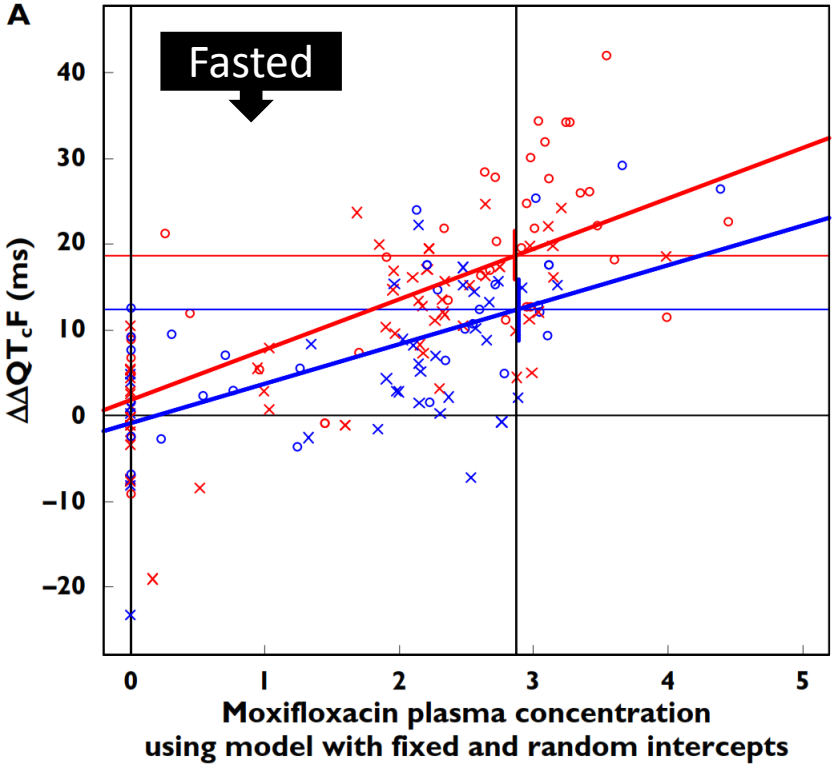
STUDY 2 [N=32]

Note the -- largely PK driven -- delay in QTc response.

400mg oral Moxifloxacin *after* a meal

Concentration effect modelling (CEM):





STUDY 2 [N=32]

Note we found a reverse relationship in fasting condition in Study 2 (published)

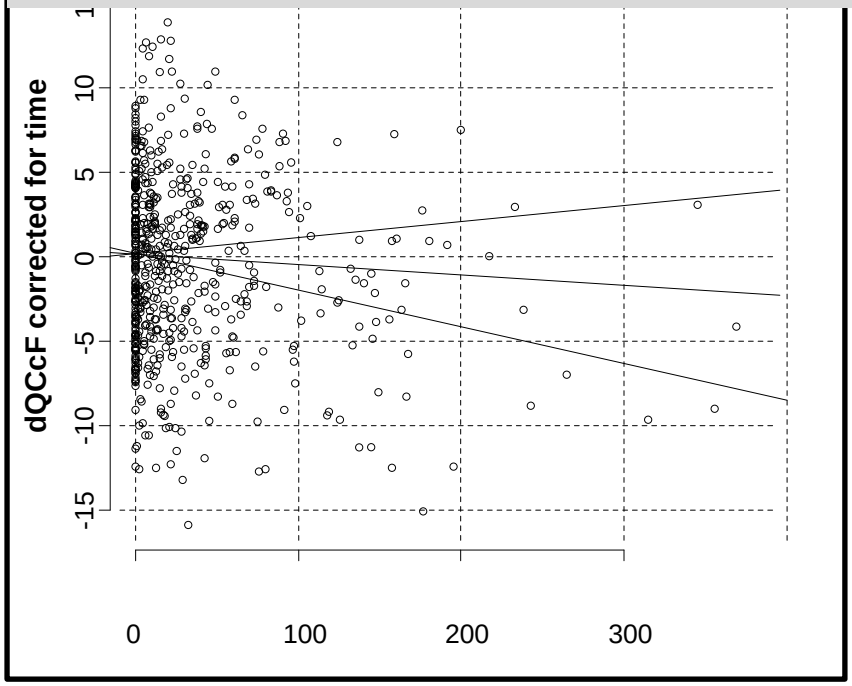
Combining TQT with Ethnic PK Bridging

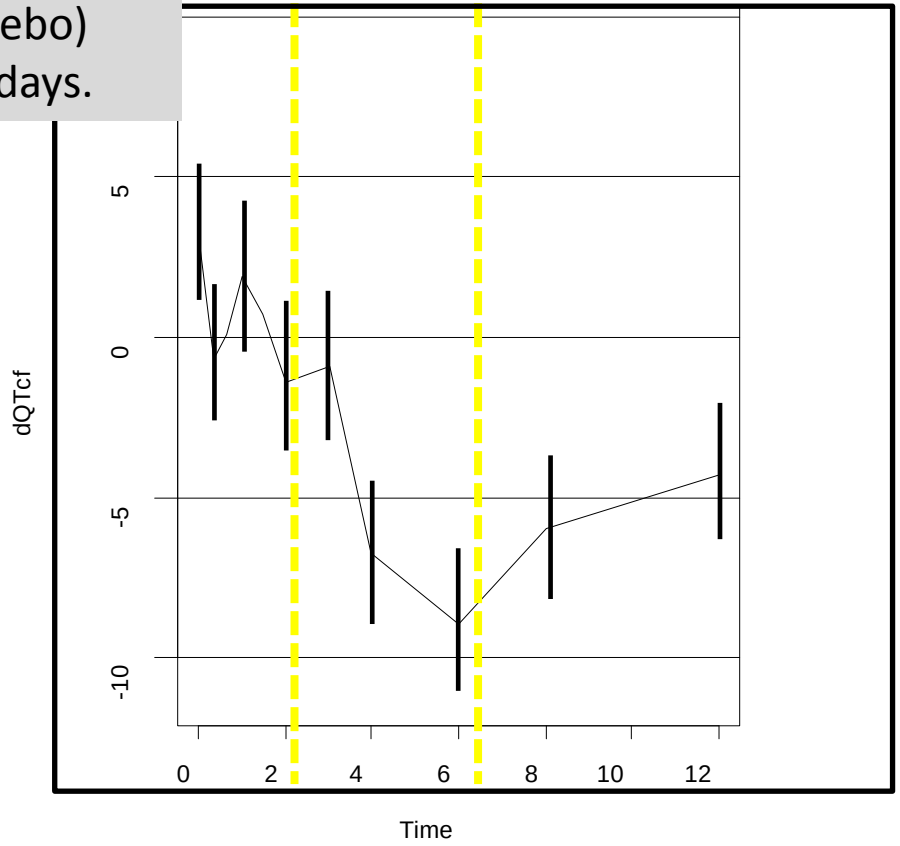
- Where Ethnic PK Bridging is intended and the moxifloxacin arm in a "TQT" study is *not* mandatory:
  This may be easily combined with thorough ECG assessments during that study to
  - Provide further PK-PD data on cardiac safety
  - Allow head-on ethnic comparisons in the same study
  - Can be used in a combined analysis where a TQT study has already been done in another ethnicity
- Two studies in one -- save time and cost.

TQT in Japanese PK Bridging

Design:
SAD study in 3 cohorts of N=9 (6 active, 3 placebo)
Placebo baseline day preceding all treatment days.

Meals at 2 and 6 hours post dose





PK-PD Analysis

Time Course Analysis

(meal effect confirming ECG sensitivity)

Food produces a consistent QT effect

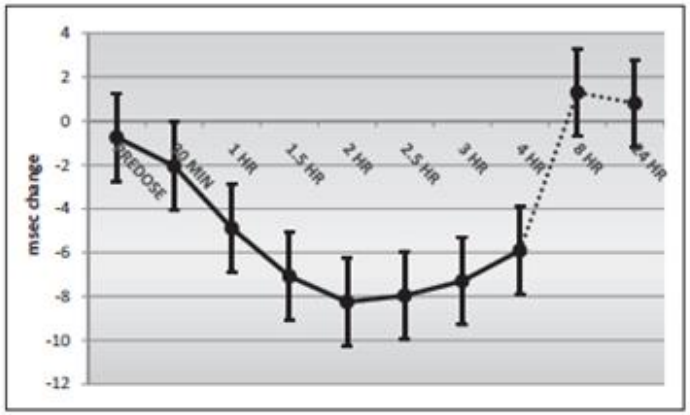


Figure 3. Food effect on QTcF with confidence interval of 95%.

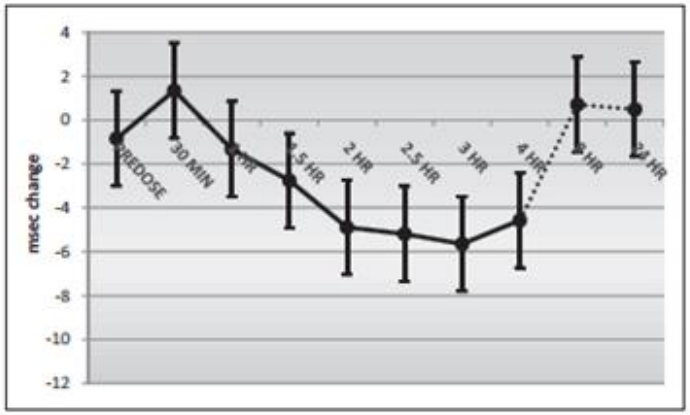


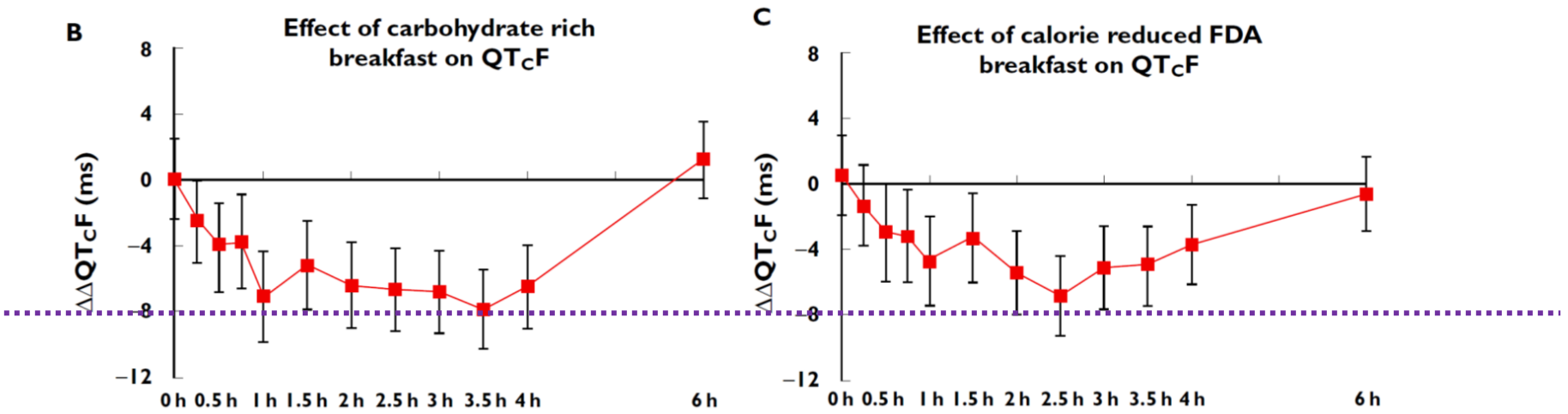
Figure 4. Food effect on QTcIP with confidence interval of 95%.

- Smart + simple method
- Physiological response
- Reliable and reproducible
- Described by others

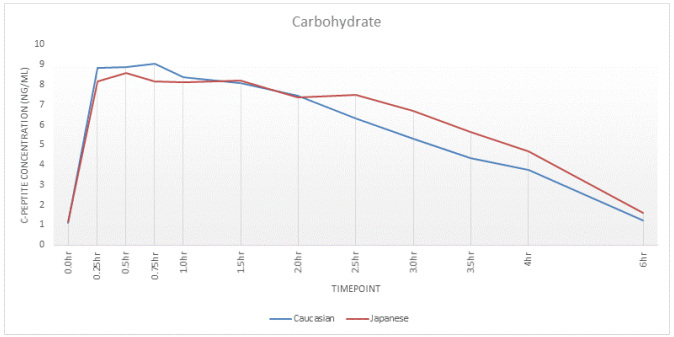
1. **Shortening of the QT interval after food can be used to demonstrate assay sensitivity in thorough QT studies**
   J Taubel, AH Wong, A Naseem, G Ferber, AJ Camm;
   The Journal of Clinical Pharmacology 52 (10), 1558-1565, 2012
2. **Insulin at normal physiological levels does not prolong QTc interval in thorough QT studies performed in healthy volunteers**
   J Taubel, U Lorch, G Ferber, J Singh, VN Batchvarov, I Savelieva, AJ Camm
   British Journal of Clinical Pharmacology 75 (2), 392-403
3. **Concentration-effect modelling based on change from baseline to assess the prolonging effect of drugs on QTc together with an estimate of the circadian time course.**
   Ferber G et al.
   J Clin Pharmacol. 2014. DOI: 10.1002/jcph.347
4. **Acute hyperglycaemia disturbs cardiac repolarization in type 1 diabetes.**
   Gordin D et al.
   Diabet Med. 2008; 25(1): 101-5.

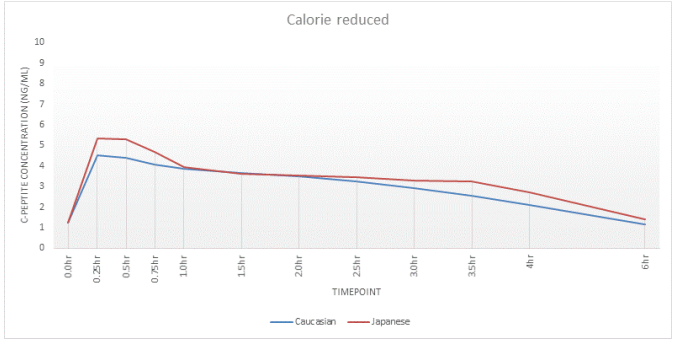
Physiological Effects

The effect is similar with different types of meals; although a fatty meal (containing less carbohydrate) leads to a slightly smaller effect (AUC).



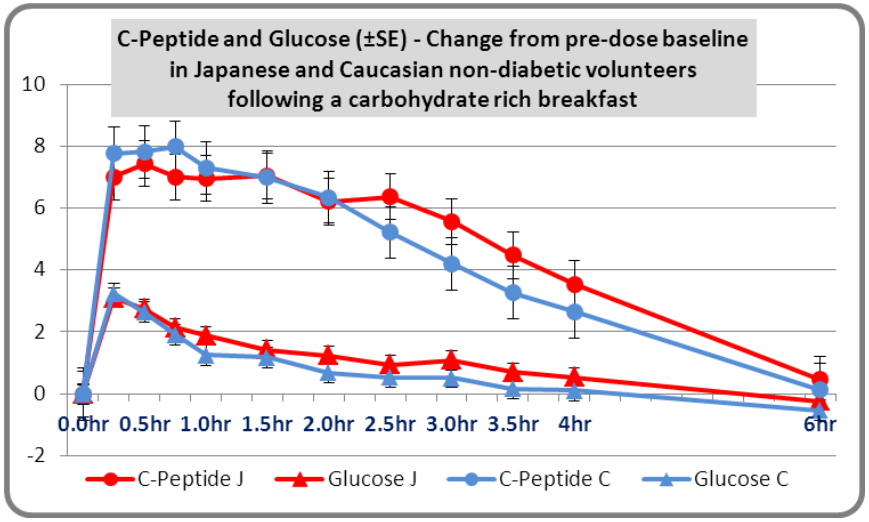
C-Peptide Concentration

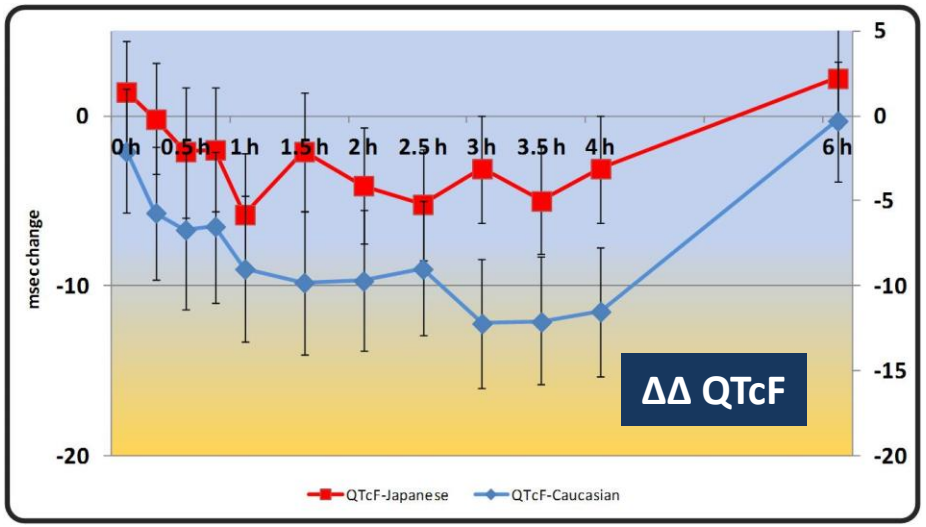




Taubel J et al.
Insulin at normal physiological levels does not prolong QT(c) interval in thorough QT studies performed in healthy volunteers. Br J Clin Pharmacol. 2013 Feb;75(2):392-403.

high carbohydrate breakfast on QTcF





<u>2-4 hours after meal</u>

Glucose: J>C

C-Peptide: J>C (lower at start)

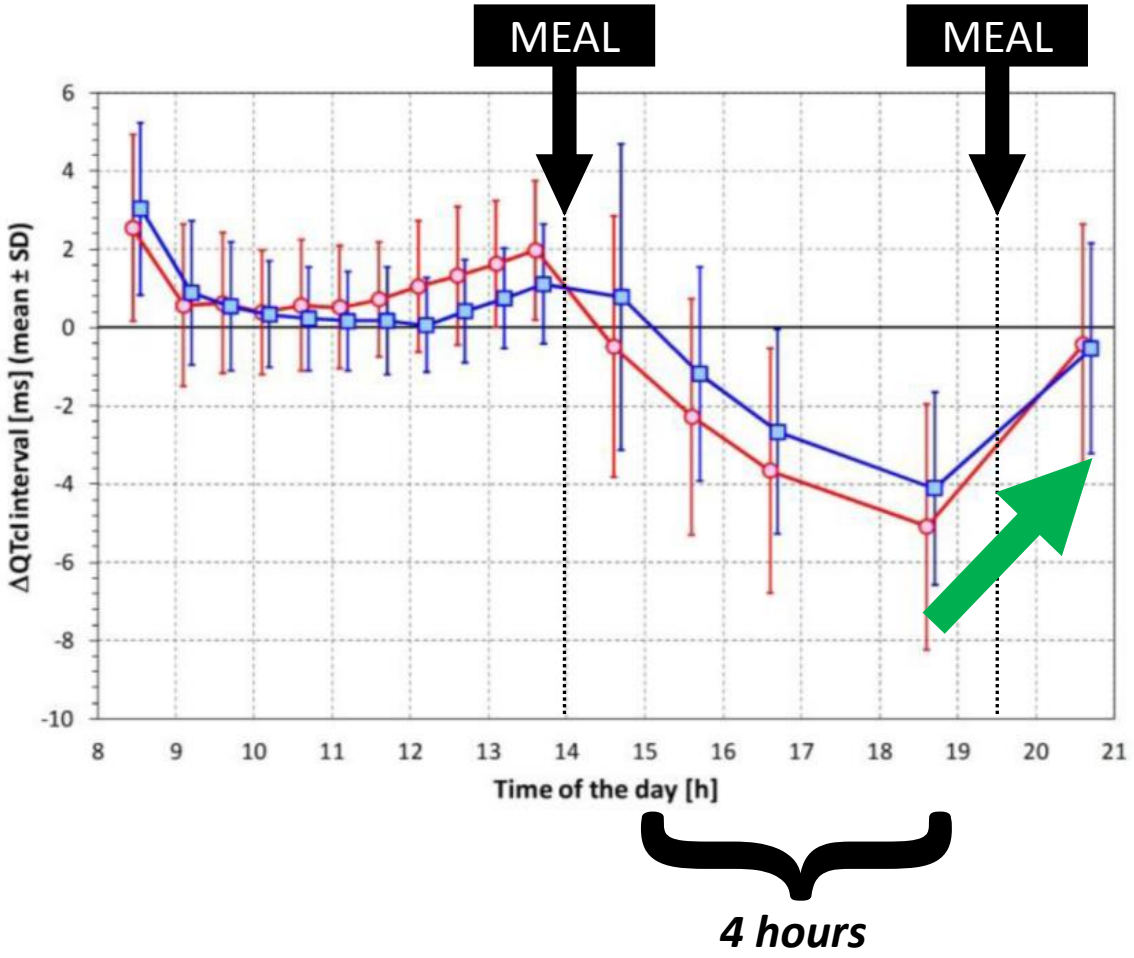
QTcF shortening: J<C

BY ETHNICITY

	Japanese	Caucasian
Emax	1 hour	3 hours
mean change QTcF [90%CI] msec	**-5.8 [-9.4, -2.3]**	**-12.2 [-16.0 , -8.4]**

Corona E et al. Analysis of the Genetic Basis of Disease in the Context of Worldwide Human Relationships and Migration PLOS GENETICS 2013

Meal effect on ECG published by others



The effect after the second meal is described as

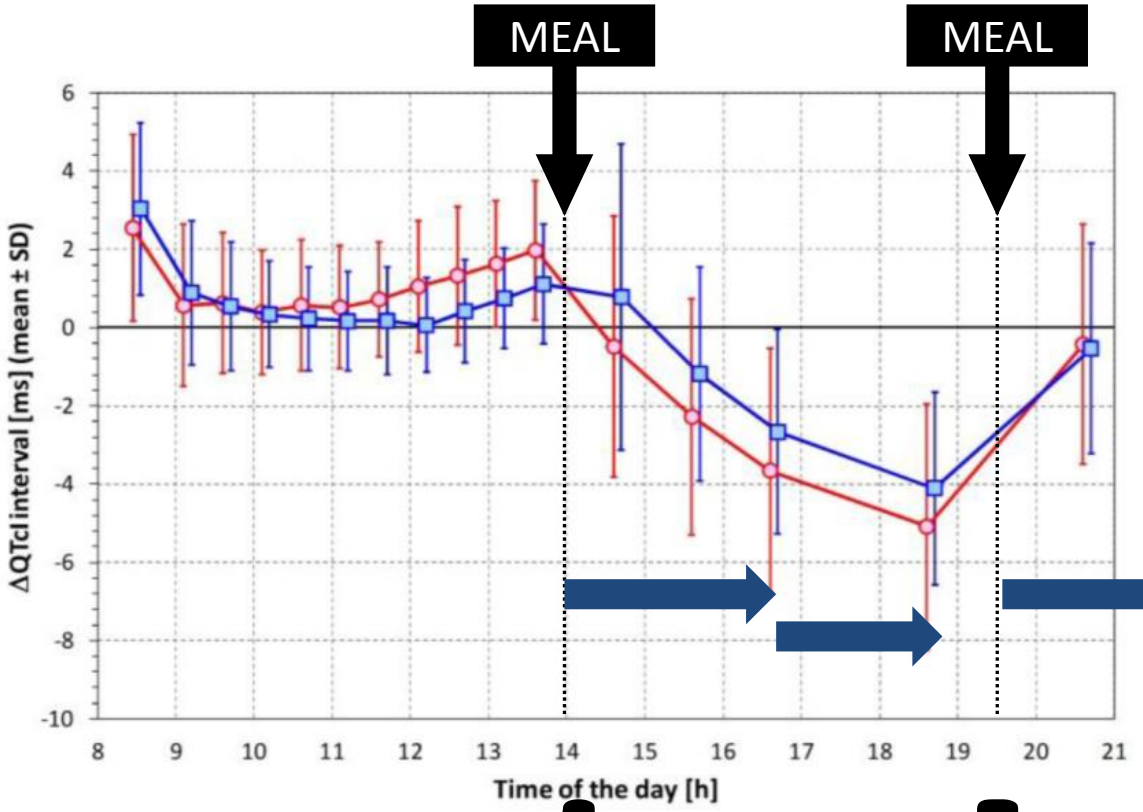
"QTc prolongation"

whereas this merely is a **return to baseline** and *no effect* at a time where no effect *is to be expected*

Figure 2

Hnatkova K et al.
QTc Changes after Meal Intake: Sex Differences and Correlates.
J Electrocardiol. 2014 Aug 2. pii: S0022-0736(14)00300-8. doi: 10.1016/j.jelectrocard.2014.07.026. [Epub ahead of print]

Results are simple to interpret



For the second meal,
no samples were taken at
appropriate time points:

?
?

Whatever the effect of the second meal, it was quite simply missed.

4 hours ***4 hours***

Hnatkova K et al.
QTc Changes after Meal Intake: Sex Differences and Correlates.
J Electrocardiol. 2014 Aug 2. pii: S0022-0736(14)00300-8. doi: 10.1016/j.jelectrocard.2014.07.026. [Epub ahead of print]

Conclusions

1. Currently there is no evidence for clinically significant ethnic differences in QTc response for a number of medicines so far
2. Similarity in physiological response to a meal, but c-peptide PK-PD may be different?
3. We can further improve our studies by enhancing specificity and reducing cost.
   - For example by combining PK Bridging PK studies with ECG assessments

Acknowledgements

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- Dr Ulrike Lorch (clinical work)
- Professor John Camm (encouragement!)

Thank you

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