

# ALTERNATIVE METHODS FOR THE CONFIRMATION OF ASSAY SENSITIVITY IN THOROUGH QT STUDIES

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## Introduction

Moxifloxacin is most commonly used as a positive control to confirm assay sensitivity as mandated by ICH E14 guidelines<sup>1, 2, 3</sup>. Moxifloxacin is well established in producing on average QT prolongation (QTcF) of 10 msec or greater<sup>4, 5</sup> following an oral 400 mg single dose. This larger than originally anticipated effect is addressed in the ICH E14 implementation group Questions and Answers document<sup>6</sup> and to the requirement of at least one of the lower bounds of the confidence intervals being greater than 5 msec<sup>4</sup> to confirm assay sensitivity in a thorough QT study.

Therefore, an alternative method of confirming assay sensitivity which is able to detect small changes around the regulatory threshold of 5 msec has been proposed<sup>5</sup>.

More recently a study has demonstrated that a carbohydrate rich meal shortens the QTc which may warrant its use as a non pharmacological method of confirming assay sensitivity. QTcF values for Caucasians were shortened for at least 4 hours after a carbohydrate rich meal and this has since been confirmed in further studies<sup>7</sup>.

## Aims

In this paper, the effect of a carbohydrate rich meal on HR, QT and QTcF in Japanese subjects under the conditions of a Thorough QT (TQT) study was investigated. The intention was to confirm if there is any difference compared Caucasians and to previous published Caucasian data.

## Methods

The data presented originates from an open-label, randomised, placebo-controlled, crossover study that evaluated the effect of different food content on the QT/QTc interval of the ECG using a single 400 mg dose of moxifloxacin as a positive control. This TQT study was compliant with International Conference on Harmonization (ICH) E14 guideline and the study design was consistent with previous studies<sup>7</sup>.

### Subject numbers

32 subjects were included in the study (19 Japanese and 13 Caucasian) and all subjects completed all arms of the study:

Japanese: 8 females and 11 males

Caucasian: 6 females and 7 males

### Food content

Subjects were given a high carbohydrate breakfast (>70% carbohydrate) 30 minutes prior to anticipated dosing time with placebo and consumed 10 minutes before anticipated dosing.

The choice of breakfast was chosen since it has been used in previous studies<sup>8</sup> to maintain consistency. The carbohydrate content of the breakfast was as follows:

High carbohydrate = 134g (536kcal) – 81% of total content

The sensitivity of the study was confirmed by moxifloxacin 400 mg (single dose) showing a QTcF prolongation of 14.5 msec.

### Data Analysis & Statistical Methods

The digital ECG recordings were transmitted electronically to the ECG core laboratory for computer based, manually verified, digital calliper measurement of conduction intervals (RR, PR, QRS and QT) using a threshold method assessing a computer derived global beat using the MUSE Interval Editor (GE Healthcare). All ECGs for a given subject were read by the same person and in blinded fashion.

### Safety Assessment

Adverse events were recorded from first treatment until follow-up.

## Results

### Effect of high carbohydrate content breakfast on HR

Mean HR was found to increase when subjects received high carbohydrate breakfast compared with placebo. The greatest effect was observed at 0.25 hours (Japanese) and 1.5 hours (Caucasian) post ingestion (Figure 1).

- mean change heart rate [90%CI]: 7.4 [5.5, 9.3] bpm (Japanese)
- mean change heart rate [90%CI]: 10.0 [7.0, 13.0] bpm (Caucasian)

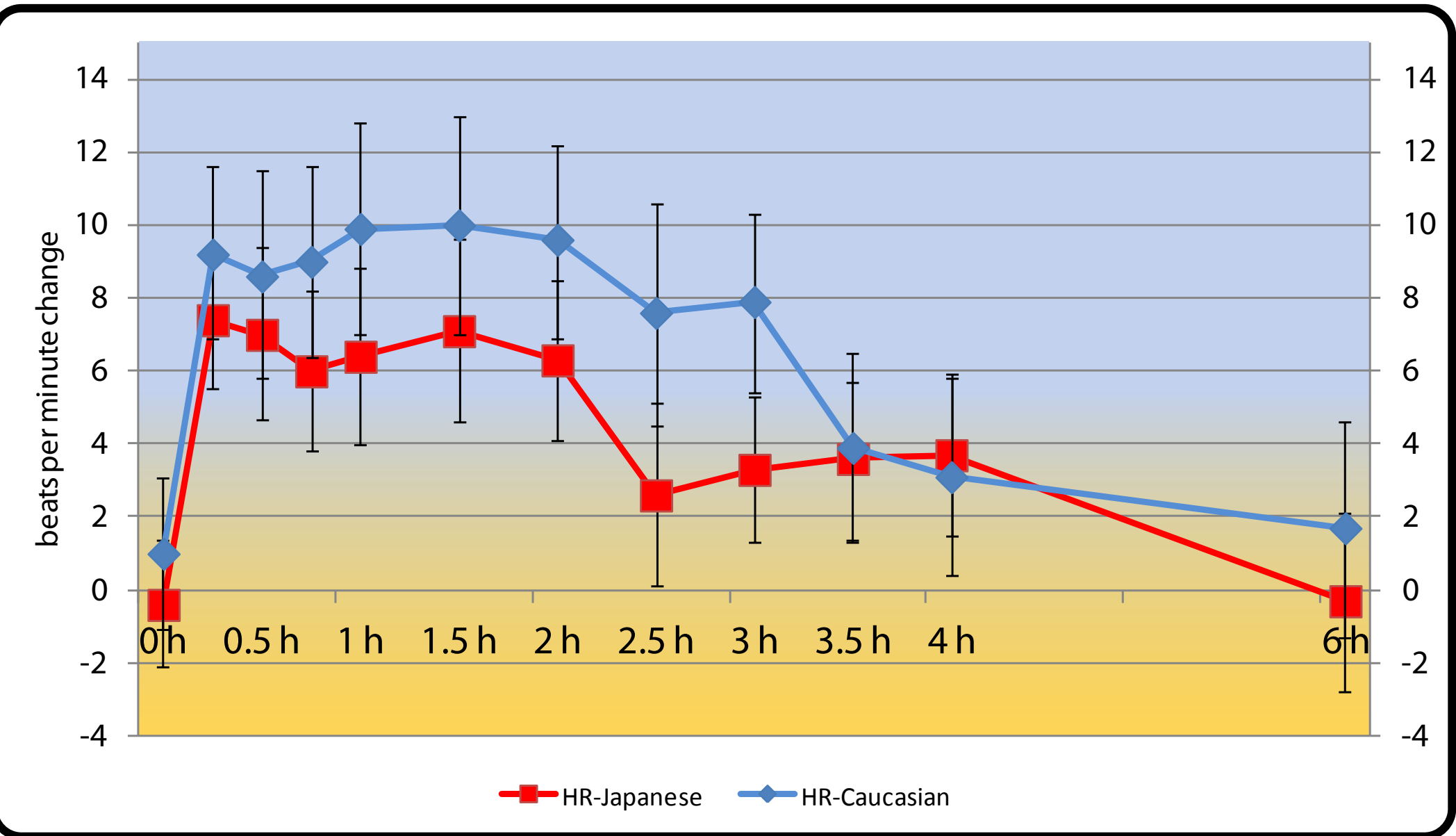


Figure 1 Effect of a carbohydrate rich breakfast on heart rate with confidence interval of 90%

### Effect of high carbohydrate content breakfast on QT

Mean QT was shortened in subjects receiving high carbohydrate breakfast compared with placebo. The greatest effect was observed at 1 hour (Japanese) and 1.5 hours (Caucasian) post ingestion (Figure 2).

- mean change QT [90%CI]: -20.7 [-26.4, -15] msec (Japanese)
- mean change QT [90%CI]: -34.3 [-41.8, -27] msec (Caucasian)

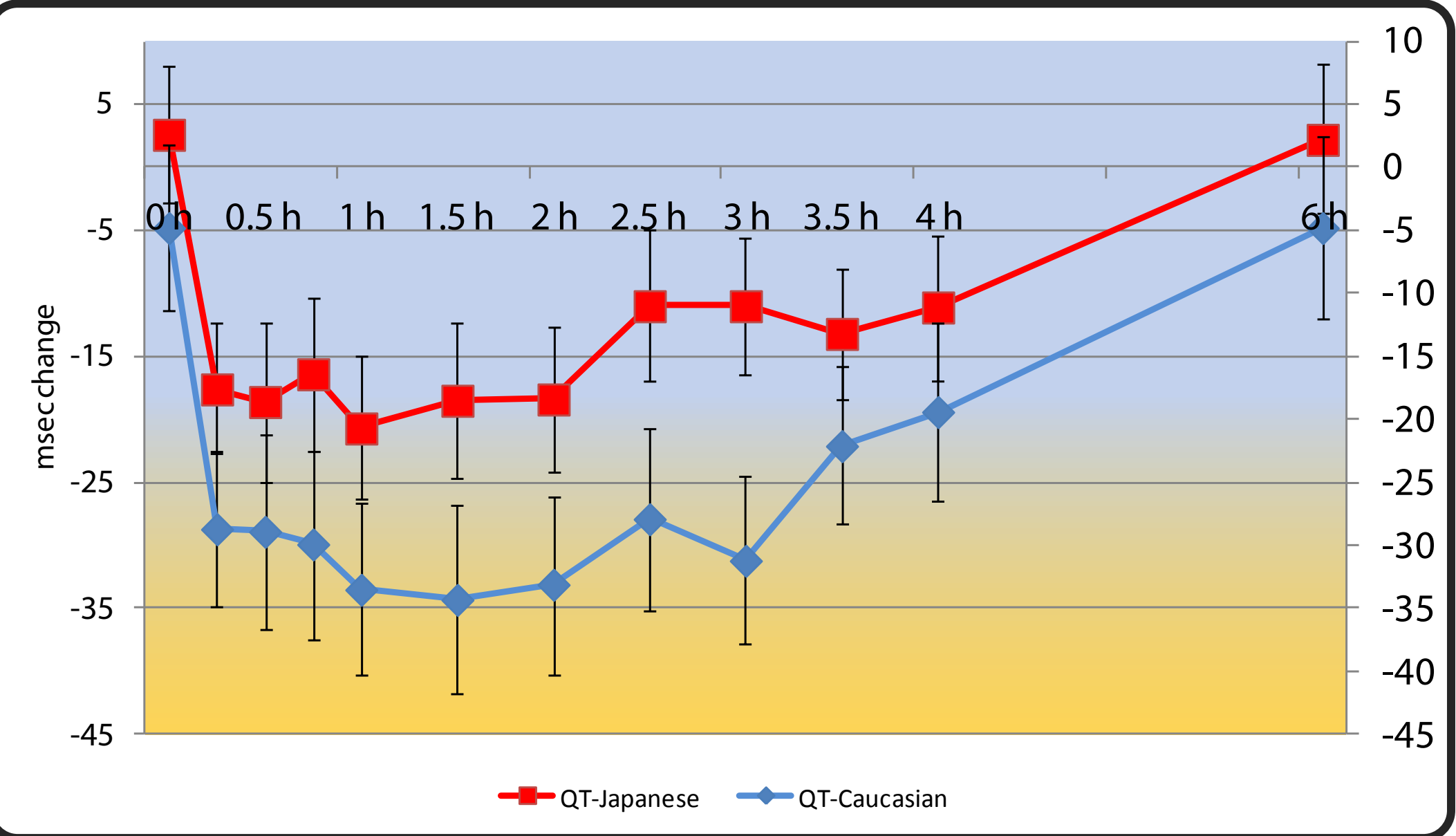


Figure 2 Effect of a carbohydrate rich breakfast on ΔQT with confidence interval of 90%

### Effect of high carbohydrate content breakfast on QTcF

Mean QTcF was shortened in subjects receiving high carbohydrate breakfast compared with placebo. The greatest effect was observed at 1 hour (Japanese) and 3 hours (Caucasian) post ingestion (Figure 3).

- mean change QTcF [90%CI]: -5.8 [-9.4, -2.3] msec (Japanese)
- mean change QTcF [90%CI]: -12.2 [-16.0, -8.4] msec (Caucasian)

## Discussion and Conclusion

Meals of high carbohydrate content have been associated with transient endogenous physiological insulinaemia<sup>8</sup>. If postprandial insulinaemia plays a significant role in the observed effects of food on ECG, then meals with high levels of carbohydrates would be expected to show a greater effect.

In this study, a steep increase in heart rate was observed for both races with a greater increase in Caucasian subjects which gradually returned to baseline. A parallel reduction in QT interval was observed which was inversely related to the change in HR. Greater QT shortening was observed in Caucasian subjects compared to Japanese subjects. When corrected using Fridericia's correction, Caucasian subjects showed greater QTcF shortening compared to Japanese subjects.

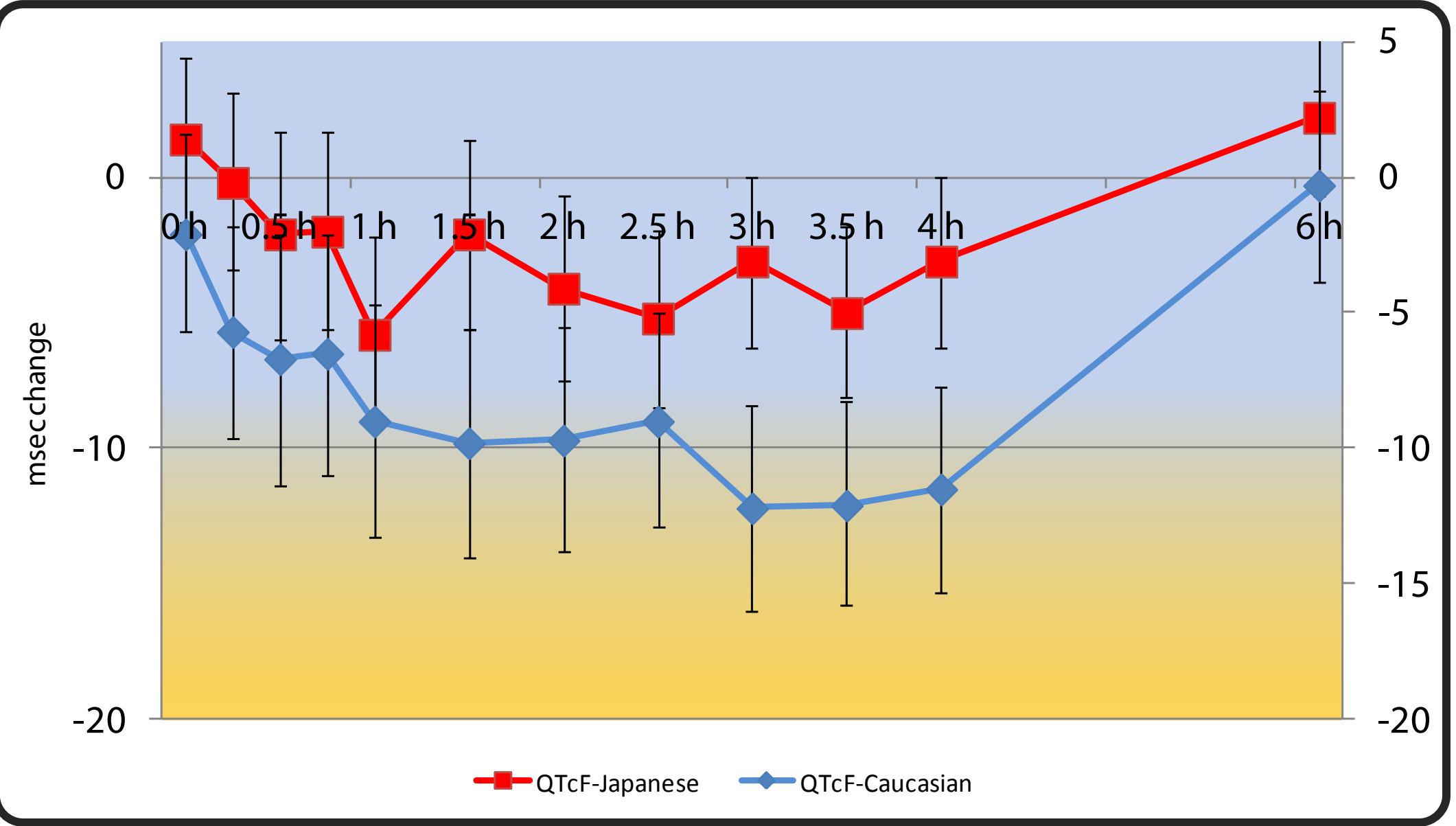


Figure 3 Effect of a carbohydrate rich breakfast on ΔQTcF with confidence interval of 90%

The results show significant difference between the races for QTcF between 1.5 hours and 4 hours (except 2.5 hours) post ingestion (Figure 3). The findings in Caucasians are in agreement with previous data which have shown a QTcF shortening of 8.2 msec (95% CI: 6-10 msec) in Caucasian subjects<sup>7</sup> and with other studies using high carbohydrate content meals<sup>9, 10</sup>.

It should be noted that, given the difference in weight between the races and the relative higher food to weight ratio for Japanese subjects, an equal or even greater response would have been anticipated for Japanese subjects than the observed findings. This may be interesting considering the standard diet for the Japanese is different to Caucasians with higher carbohydrate/protein content and less fat, therefore, Japanese subjects may be more used to the high carbohydrate content of meals. Furthermore, the excretion of insulin and C-peptide may differ between the races and have an important role in QT/QTc effects following ingestion. This concept will require further investigation.

Even though the observed changes are negative (QTcF shortening of 5.8 and 12.2 msec) the direction of the effect is not important when considering that the assay control is used to confirm that the study is capable of detecting small changes. This study shows that a standardised food arm could be used as an alternative method to demonstrate assay sensitivity in Japanese. However, more work will have to be done to explain the difference in response.

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