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RESEARCH ARTICLE

Characterisation of the Cardiovascular Effects of a Meal: QTcF Assessment and Further Insights into the Physiological Effects

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ABSTRACT

The electrical activity of the heart, characterised by the QT interval on an electrocardiogram (ECG), serves as a crucial parameter for evaluating cardiac health. Variations in the QT interval, particularly when corrected for heart rate using Fridericia's formula (QTcF), have long been of interest in cardiology and play a pivotal role in assessing cardiac safety in clinical trials. Understanding the influence of meals given at different times on QTcF intervals is essential for the accurate execution of Thorough QT (TQT) studies. Moreover, it has been proposed that this meal-related QT interval shortening could serve as a valuable indicator of assay sensitivity in TQT studies or even as a potential integration of TQT investigations into in Phase I/II studies.

This study explores the impact of meals on QTcF intervals, specifically in the context of pharmacodynamic studies and TQT investigations. The primary goal is to gain insights into how different meals and baseline calculations affect QTcF changes and their potential implications for cardiac health and the risk of arrhythmias. Recent research has begun shedding light on the intricate relationship between meal composition, timing, and QTcF alterations. Several studies have investigated the effects of various nutrients, such as carbohydrates, fats, and proteins, on QTcF duration, as well as the implications of postprandial changes. These investigations have unveiled the complex interplay between dietary components and the cardiovascular system, raising essential questions about how our dietary choices may influence cardiac electrophysiology.

In this comprehensive meta-analysis, we analyse data from nine studies, all conducted in accordance with Good Clinical Practice and ethical standards. These studies were approved by Ethics Committees and Regulatory authorities. Our analysis focuses on ECG assessments, involving the use of 12-lead ECGs recorded electronically and evaluated by certified cardiologists. We apply the Fridericia formula for QT correction (QTcF), as it has been shown to provide more accurate results across different heart rates compared to other correction methods.

Our findings confirm existing literature into the impact of meals on QTcF intervals. We observe a consistent shortening of QTcF following breakfast, exceeding 5 milliseconds, which aligns with the positive control requirement defined by ICH E14, thus demonstrating the validity of our approach. In contrast, the effect of lunch is consistently less than 5 milliseconds across various timepoints and studies, indicating differences in the meal-related QTcF changes.

Furthermore, our analysis incorporates gender-based assessments, showing that women exhibit a smaller effect than men, which is significant for breakfast and the fasted condition. These results suggest that the observed QTcF effect post-breakfast is a combination of the meal itself and factors unique to the initial day of a study. This insight holds potential for improving the design and interpretation of cardiac safety studies, particularly in Phase I investigations, and may offer the opportunity to explore the removal of positive control agents like Moxifloxacin, thereby reducing exposure to harmful challenge agents and contributing to the global effort to combat antimicrobial resistance (AMR).

In conclusion, this meta-analysis advances our understanding of meal-induced QTcF changes and their significance in cardiac safety assessment, offering the prospect of more efficient and patient-focused drug development practices. This not only contributes to enhanced safety but also supports the reduction of antibiotic consumption, a key element in the global fight against AMR.

Keywords: QTcF, electrocardiogram, cardiac health, TQT studies, meal-induced changes, clinical trials, meta-analysis, drug development, antimicrobial resistance, cardiac safety.

Introduction

The heart's electrical activity, as measured by the QT interval on an electrocardiogram (ECG), is a critical parameter in assessing cardiac health. Variations in the QT interval, particularly using QTcF (QT corrected for heart rate using Fridericia's formula), have long been of interest in the field of cardiology[1]. Understanding this effect is essential for the accurate execution of Thorough QT (TQT) studies and has been suggested as a method for determining assay sensitivity in particular when integrating TQT studies into Phase I/II investigations[2]. This gives the opportunity to avoid having to administer challenge agents such as Moxifloxacin, supporting global aspirations to reduce antibiotic consumption in effects to reduce antimicrobial resistance (AMR)[3,4,5]. These variations can be influenced by a multitude of factors, one of which is the type of meal consumed[6]. An "experimental component" has also been identified in that during repeated QT assessments there is an initial effect which diminishes over time, potentially due to autonomic stimuli which reduce as subjects become familiar and comfortable with the procedures[7]. It is important to decouple these two effects in order to understand how baseline calculations and different meals affect QTcF changes, which is essential for evaluating their impact on cardiac health and the potential risk of arrhythmias[8,9].

Recent research has shed light on the connection between meal composition, timing, and QTcF alterations[10]. Several studies have explored the effects of various nutrients, such as carbohydrates, fats, and proteins, on QTcF duration, as well as the implications of postprandial changes[11,12,13]. These investigations have highlighted the intricate interplay between dietary components and the cardiovascular system, raising important questions about how our dietary choices may influence cardiac electrophysiology[14].

In this article, we investigate QTcF changes associated with meals given at different times in the setting of pharmacodynamic studies, in particular Thorough QT (TQT) studies. By examining the influence of dietary factors on QTcF intervals, we aim to contribute to a better understanding of the relationship between nutrition and cardiac health[15]. Additionally, we will discuss potential clinical implications and areas for further research in this fascinating and evolving field.

It has also been proposed that understanding this meal-related QT interval shortening could serve as a valuable indicator of assay sensitivity in TQT studies, with the potential integration of TQT studies with Phase I/II investigations[16,17]. There is potential for further optimisation of clinical trial safety for volunteers by removing the needs for a QT prolonging challenge drug, i.e., Moxifoxacin, known to cause severe hepatotoxicity[18]. Given the importance of this phenomenon, a comprehensive investigation into the effect of meals on QTcF in SAD and MAD studies is warranted. In this study, we conduct a meta-analysis using drug-free data from various clinical trials to thoroughly characterise this effect.

Methods

To characterise the effect of meals on QTcF, we performed a meta-analysis using data from 9 different studies previously performed at

Richmond Pharmacology Ltd. All these studies were approved by an Ethics Committee and the Medicines and Healthcare Products Regulatory Authority and were conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All the studies included in this analysis were single-centre and compliant with the ICH E14 guideline[19].

MEASUREMENT - ECG ASSESSMENT

In all the studies, 12-lead ECGs were electronically recorded and saved using the MUSE Cardiology information system by GE Healthcare. Prior to each ECG recording, subjects were instructed to maintain a calm and uninterrupted supine resting position for a minimum of 10 minutes, refraining from any postural adjustments during the recordings. During each session, the ECGs were captured in sets of three at 1-minute intervals for a total of 3 minutes, with each individual ECG lasting 10 seconds.

Automatic ECG analysis was performed by the Marquette 12SL ECG Analysis Program. Following this automated analysis, all ECGs and their corresponding interval measurements underwent evaluation by certified cardiologists. In cases where manual adjustments to the automated measurements were required, a second cardiologist provided confirmation. Any discrepancies between the initial and secondary assessments were resolved through adjudication by a third and senior cardiologist. The specifics of this procedure have been documented elsewhere[20]. For subsequent analysis, the mean value across the triplicate ECGs was utilised.

In our studies, we employed QT correction based on the Fridericia formula (QTcF)[21]. As demonstrated by Taubel et al. (2012)[9], when compared to alternative correction methods, in particular Bazzet's correction, utilising this correction formula leads to more accurate results even at lower or higher heart rates.

Data were analysed at specific timepoints relative to the initiation of the respective meal. To ensure comparability across studies, we selected studies with consistent timepoints. The primary analysis focused on changes in QTcF from pre-prandial (pre-meal) values, specifically at timepoints 1 – 4 hours after the meal's commencement. For breakfast, we used the change from the pre-dose baseline to the relevant post-meal timepoint. For lunch, we averaged the last two pre-meal timepoints as the reference. In cases where timepoints varied across studies, we pooled data for timepoints with intervals of up to 15 minutes apart. As a control, we calculated the time course of the change from pre-dose baseline to pre-meal hours for studies where lunch was the reference meal.

Analyses were conducted by timepoint, consisting of summary statistics by study and timepoint and ANOVA models with the change from pre-prandial QTcF as the dependent variable, considering study and gender as factors. Parameter estimates, including the overall mean (LS-mean), study effects, and gender-related contrasts, were presented separately for breakfast, lunch, and the control group.

MODELLING

Specifically, for each meal (k) ∈ {Breakfast, Lunch, Control} and timepoint (i), an ANCOVA model of the form:

$$dQTcF \sim Study + bl$$

was fitted without an intercept, where the study was considered a factor, and pre-prandial baseline (bl) was used as a covariate. We derived two estimates for the effect of each meal at each timepoint: a weighted average over studies, using s_j as the estimator for study j and n_j as the number of subjects in study j, and an unweighted average across studies.

$$M_1 = \frac{1}{N}\sum s_j n_j$$

$$N = \sum n_j$$

M_2 = average (s_j)

In addition to the basic analysis, a model including gender as a factor was fitted to investigate potential gender-related differences in meal-induced QTcF changes.

Results

Studies and timepoints investigated:

STUDY 1

Study 1 was a double-blind, randomised, placebo-controlled, four-way cross-over Phase I study to investigate the pharmacokinetics, pharmacodynamics, and safety of escalating single doses in 31 healthy participants. PK samples were taken after the corresponding ECG recordings. ECG recordings were taken pre-dose and at H0.25, H0.5, H0.75, H1, H1.25, H1.5, H1.75, H2, H3, H4, H6, H8 and H12 post dose on Days -1 and 1. Meals were served on Day -1 and Day 1as follows: lunch (5 hours post-dose), dinner (9 hours post-dose) and snack (13 hours post-dose).

STUDY 2

Study 2 was a randomised, double blind, placebo- and positive-controlled, four-way, cross-over Phase I study involving 50 participants. ECG recordings were taken on D1 pre-dose and at H0.5, H1, H1.5, H2, H2.5, H3, H3.5, H4, H4.5, H5, H5.5, H6, H8, H12 and H24 post-dose. Meals were served on Day 1 as follows: breakfast (30 minutes prior to administration of IMPs to be consumed 10 minutes before dosing), lunch (7 hours post-dose), dinner (11 hours post-dose) and snack (13.5 hours post-dose).

STUDY 3

Study 3 was a randomised, placebo- and positive-controlled, cross-over study involving 32 participants. In this study the effect of meals was studied. For the present analyses the arms with a "FDA-type" breakfast and with lunch only were used. Subjects participating in the study attended for screening, two treatment periods, and a follow-up visit. On Day 1, ECG recordings were taken pre-dose and at H0.25, H0.5, H0.75, H1, H1.5, H2, H2.5, H3, H3.5, H4 and H6 post-dose. On Days 1 and 2: If breakfast was required it was served 30 minutes prior to anticipated dosing and to be consumed 10 minutes before anticipated dosing, lunch (7 hours post-dose), dinner (11 hours post-dose) and snack (13.5 hours post-dose).

STUDY 4

Study 4 was a single centre, randomised, double blind, placebo- and positive-controlled, four-way cross-over study involving 38 participants. Subjects participating in the study attended for screening, four treatment periods, and a short follow-up visit. On Day 1, ECG recordings were taken pre-dose and at 2- and 8-minutes post-dose, and also at H0.5, H1, H1.5, H2, H3, H4, H5, H6, H8 and H12 post-dose. For this study, meals were served at standard times;

breakfast was served before dosing and was of high carbohydrate content.

STUDY 5

Study 5 was an exploratory, randomised, double-blind, placebo-controlled, Phase I study which assessed the safety, tolerability, food effect, pharmacokinetics and pharmacodynamics of single (SAD) and multiple (MAD) ascending doses of oral IMP. Day 1 of Part III was used for the purpose of this meta-analysis and involved 12 participants. On Day 1 (Part III) ECG recordings were taken pre-dose and at H1, H2, H3, H4, H5, H6, H7, H8, H10, H12 and H16 post-dose. Lunch was served on Day 1 at H4 after this timepoint procedures were completed.

STUDY 6

Study 6 was a randomized, double-blind, placebo-controlled, Phase I study which assessed the safety, tolerability, food effect and pharmacokinetics of single (SAD) and multiple (MAD) ascending oral doses of the IMP in healthy post-menopausal women and pharmacodynamic effects in women of childbearing potential during menstruation. For this study, we analysed Part IIA (Day 1 breakfast) with a total of 6 participants. On Day 1 (Part IIA) ECG recordings were taken pre-dose and on H0.5, H1, H1.5, H2, H2.5, H3, H3.5, H4, H6, H7, H8 and H12 post-dose. Participants were served breakfast before study drug administration.

STUDY 7

Study 7 was a double-blind randomised, placebo-controlled, parallel group, ascending dose study and comprised participants that received a single, ascending dose (SAD) of IMP to assess its safety, tolerability, and pharmacokinetic profile. For this study, we analysed Part A (Day 1 lunch) with a total of 14 participants. ECG recordings were taken pre-dose and at H0.5, H1, H2, H4, H6, H7, H8 and H12 post-dose. Lunch was provided at 4 hours after dosing.

STUDY 8

Study 8 was an exploratory, randomised, double-blind, placebo- and active therapy-controlled, Phase I study which assessed the safety, tolerability, food effect, pharmacokinetics and pharmacodynamics of single (SAD) and multiple (MAD) ascending, oral doses of IMP. In Part I, the safety, tolerability and pharmacokinetic (PK) profile of single ascending doses of IMP was studied in healthy adult Caucasian male and female participants. For this study, we analysed Part I (Day 1 lunch) with a total of 10 participants. ECG recordings were taken pre-dose and at H0.5, H1, H1.5, H2, H2.5, H3, H4, H5, H6, H7, H8 and H12 post-dose. Lunch was served at H4 post-dose and after all procedures for this timepoint were completed.

STUDY 9

Study 9 was a randomized, double-blind, placebo controlled, parallel group study to determine the tolerability and safety of two approved malaria medications administered alone and in combination once daily for 3 days to healthy adult male and female subjects. For this study, we analysed Day 1 alone (meal of reference was breakfast) with a total of 12 participants. ECG recordings were taken pre-dose and at H1, H2, H3, H4, H5, H6, H8 and H12 post-dose. Breakfast was the first meal of Day 1 and was given at 30 minutes pre-dose.

The studies included in our analysis are described in the following table:

Table 1

		Breakfast		Lunch	
Study	Gender	n	Use	n	Use
1	Mixed			31	Day 1
2	Mixed	50	Day 1		
3[a]	Mixed	32	Day 1		
4	Mixed	38	Day 1		
5	Mixed			12	Part III, Day 1
6	Female	6	Part IIA, Day 1		
7	Male[b]			14	Part A, Day 1
8	Mixed			10	Part I, Day 1
9	Mixed	12	Day 1		
Total		138		67	

a. Study 3 included a comparison of FDA and continental breakfast; we utilised data from the continental breakfast arm. This study also had a separate arm investigating the fasted condition without any drug, and data from this arm were included in the control condition analysis.

b. Although the protocol allows women of non-childbearing potential, only males were included.

The analysis of the impact in the fasting state was also conducted for studies in which lunch was served as the first meal, meaning participants refrained from eating until lunch.

In summary, our analysis comprised data from 138 participants to assess the effect of breakfast, 67 participants to assess the effect of lunch, and 48 participants in the fasted condition. One study was excluded from the fasted condition analysis due to the absence of suitable baseline measurements under these conditions.

Figure 1 shows, for each meal, the ANCOVA-based study specific estimates of change from baseline over time. For breakfast a shortening of at least 5 ms is seen already at 1 h after start of the meal. For lunch, the onset of the effect is more subtle. In the fasted condition, a shortening compared to the pre-dose baseline can also be seen, but this effect seems more homogeneous, less dynamic and is smaller.

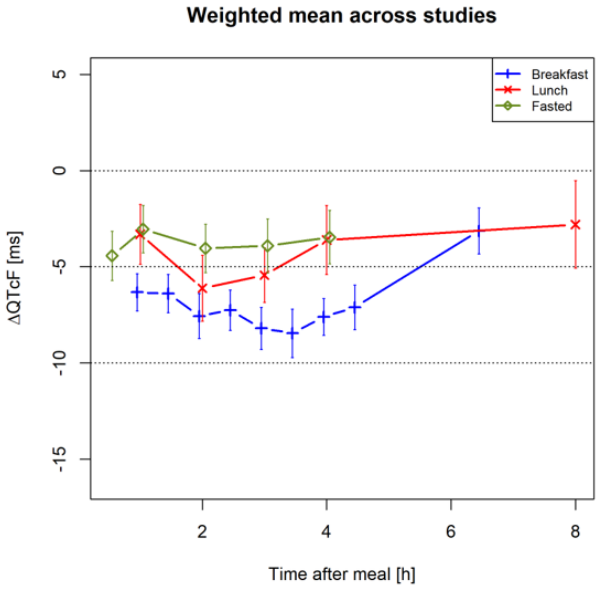

Figure 1

COMPARISON ACROSS MEAL TYPES - JOINT ANALYSIS

The joint analysis of three meal types does not take into account that there may be between study variability but attributes this variability to the between subject one. This approach is conservative, as it results in wider confidence intervals. Only timepoints common to all meal types were used. This analysis suggests that the effect seen after breakfast is composed of an effect that is specific for the study conditions ("study effect") and, therefore, also seen under fasted conditions and one that is due to the meal. The size of the three effects – the two meal related ones and the study effect is about similar, but the time course differs. However, the effect of lunch is larger at 2 h.

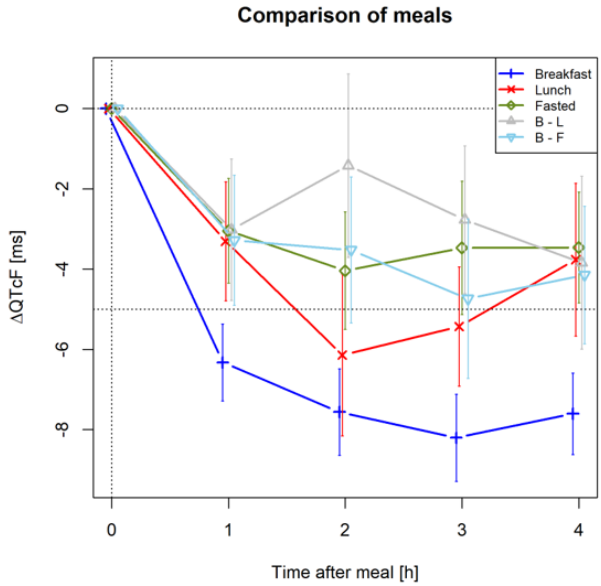

Figure 2

ANALYSIS BY GENDER

Figure 3 shows the mean effects across studies by gender. Consistently, women show a smaller effect than men. However, this effect is only significant for breakfast and the fasted condition, suggesting that the study effect is the one that contributes most to the difference.

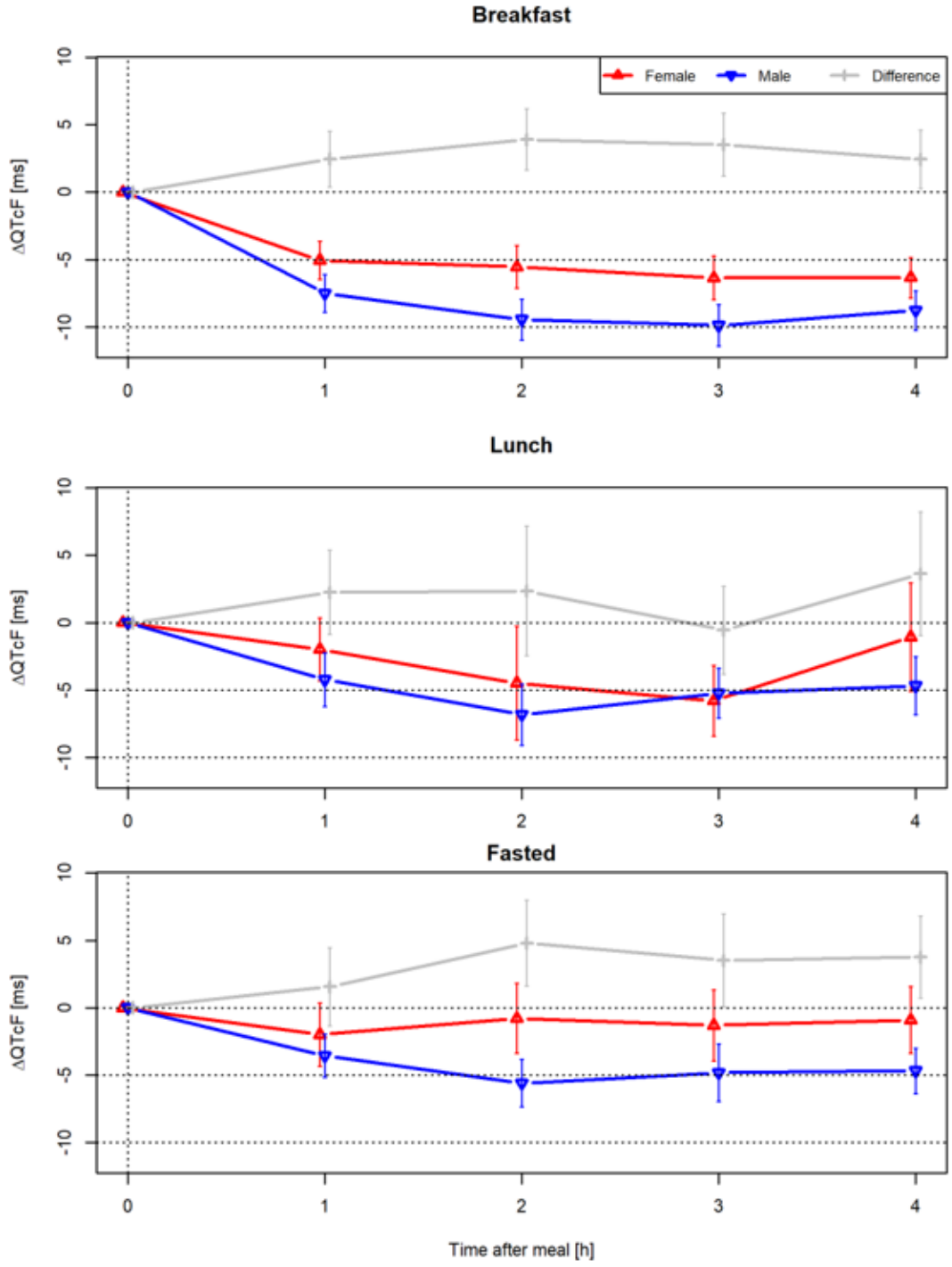

Figure 3

Discussion

One focus of our investigation is to remove the necessity of conducting a dedicated TQT study (waiver) by leveraging ECG data from other studies, aligning with the principle of assay sensitivity to demonstrate the absence of an effect. Unlike moxifloxacin, which predominantly induces ion channel blockade, the QTc changes induced by food are primarily attributed to physiological heart effects. Our objective aligns with the ICH E14 guidelines, which stipulate that a study should be capable of identifying a QTcF shift in the range of 5 to 10 milliseconds to qualify as a positive control.

In our analysis encompassing data from nine distinct studies (not primarily designed to show this effect), both descriptive and model-based methods unequivocally reveal a significant shortening of QTcF following a meal, while smaller changes are also observed during sustained fasting in the first four hours after start of the study. Nonetheless, it is noteworthy that the temporal dynamics and the extent of this effect exhibit disparities between different meal types. After breakfast, we observe a QTcF reduction ranging from 5 to 10 milliseconds, whereas after lunch, the reduction is consistently less than 5 milliseconds across various timepoints and studies. Figure 2 above suggests that the effect seen after breakfast is a superimposition of an effect due to the meal and the shortening that was also observed under fasting conditions at the same timepoints, while after lunch, this additional shortening is no longer present. It is important to highlight that substantial variability is prevalent among these studies.

Our comprehensive, model-based analysis incorporates a joint approach, accounting for individual baseline differences and, as a result, mitigating some of the observed variability. This approach consistently demonstrates that the QTcF shortening following breakfast significantly exceeds 5 milliseconds at all four postprandial timepoints. However, the same cannot be said for the post-lunch period.

The achievement of this consistent 5-millisecond threshold post-breakfast aligns with the positive control requirement defined by ICH E14, further supporting the reliability and validity of our approach. These results suggest that the observed QTcF effect post-breakfast cannot be solely attributed to the meal itself; rather, it appears to encompass a component that reflects the unique circumstances of the first day of a study or study period. This may include accommodation to the study environment and initial adjustments by both the study personnel and participants in the initial hours of the study.

Our study endeavours to avoid the necessity of a dedicated TQT study by leveraging existing ECG data to exhibit assay sensitivity in confirming the absence of a QTc effect. The modest changes observed after a meal, especially in comparison to the pronounced effects of moxifloxacin, present inherent challenges within studies not explicitly designed for QT effect assessment. However, our findings demonstrate the reproducibility of the observed effect across various studies, further bolstering the reliability of our approach and diminishing the likelihood of type I errors, even in cases of limited statistical power.

Conclusion

This meta-analysis provides further evidence of the effect of meals on QTcF intervals in clinical trials. By analysing data from various studies, we have demonstrated reproducible differences in meal induced QTcF changes, particularly between breakfast and lunch that achieve the assay validation requirement of ICH E14. These findings have significant implications for the design and interpretation of cardiac safety studies, especially in Phase I investigations. Further research may be needed to explore gender-related differences and refine our understanding of the meal effect on QTcF, but this meta-analysis represents a valuable step towards improving cardiac safety assessment in drug development.

TQT studies may be replaced or incorporated into phase I/II studies. Understanding meal related QTcF changes is crucial the correct measurement and assessment of changes to QTcF. Further enhancing the safety assessment of new drugs and ensuring the well-being of patients. This meta-analysis also provides for the opportunity to explore the removal of a positive control, i.e., Moxifloxacin, to confirm assay sensitivity reducing unnecessary exposure to harmful challenge agents and supports a reduction of antibiotic consumption a key element in reducing AMR globally.

In conclusion, this meta-analysis not only advances our understanding of meal-induced QTcF changes and their significance in cardiac safety assessment but also opens the door to more efficient and patient-focused drug development practices, contributing to enhanced safety and a brighter future in the fight against antimicrobial resistance on a global scale.

Declaration of conflicting interests:

Jorg Taubel, Dilshat Djumanov, Ulrike Lorch, Edward Jackson, and Joao Almeida Melo are employees of Richmond Pharmacology Ltd. James Rickard is an employee of the Richmond Research Institute, an independent research organization funded by Richmond Pharmacology Ltd. Georg Ferber is an employee of Statistik Georg Ferber GmbH who has received honoraria for consulting from Richmond Pharmacology.

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Appendices:

Table 2 – Food effect across studies

Meal	Time [h]	N	Mean	SD	90 % CI	
Lunch	-1.0	53	0.0	2.11	-0.5	0.5
	0.0	36	0.0	2.58	-0.8	0.7
	1.0	53	-3.6	7.60	-5.3	-1.8
	2.0	36	-5.6	6.77	-7.5	-3.7
	3.0	67	-5.4	7.75	-7.0	-3.9
	4.0	36	-3.3	6.17	-5.1	-1.6
	8.0	35	-2.6	7.64	-4.8	-0.4
Fasted	-2.0	35	-0.4	3.60	-1.4	0.7
	-1.0	36	-0.4	2.71	-1.1	0.4
	-0.5	36	0.7	3.32	-0.2	1.7
	0.0	32	0.0	0.00	0.0	0.0
	0.5	56	-4.4	5.76	-5.7	-3.1
	1.0	68	-3.0	6.24	-4.3	-1.8
	1.5	32	-5.0	5.99	-6.8	-3.2
	2.0	68	-4.0	6.19	-5.3	-2.8
	2.5	32	-5.8	5.60	-7.5	-4.1
	3.0	54	-3.9	6.07	-5.2	-2.5
	3.5	32	-4.5	7.52	-6.7	-2.2
	4.0	68	-3.5	6.82	-4.8	-2.1
	6.0	32	-4.6	6.56	-6.6	-2.6
Breakfast	-1.5	6	0.4	3.36	-2.4	3.2
	-0.5	6	0.0	2.94	-2.4	2.4
	0.0	126	0.0	0.67	-0.1	0.1
	1.0	126	-6.3	7.27	-7.4	-5.3
	1.5	126	-6.4	7.49	-7.5	-5.3
	2.0	126	-7.6	9.05	-8.9	-6.2
	2.5	126	-7.3	8.47	-8.5	-6.0
	3.0	125	-8.2	8.68	-9.5	-6.9
	3.5	88	-8.6	8.44	-10.1	-7.1
	4.0	126	-7.6	7.81	-8.8	-6.5
	4.5	88	-7.2	8.13	-8.6	-5.8
	6.5	88	-3.2	7.57	-4.6	-1.9

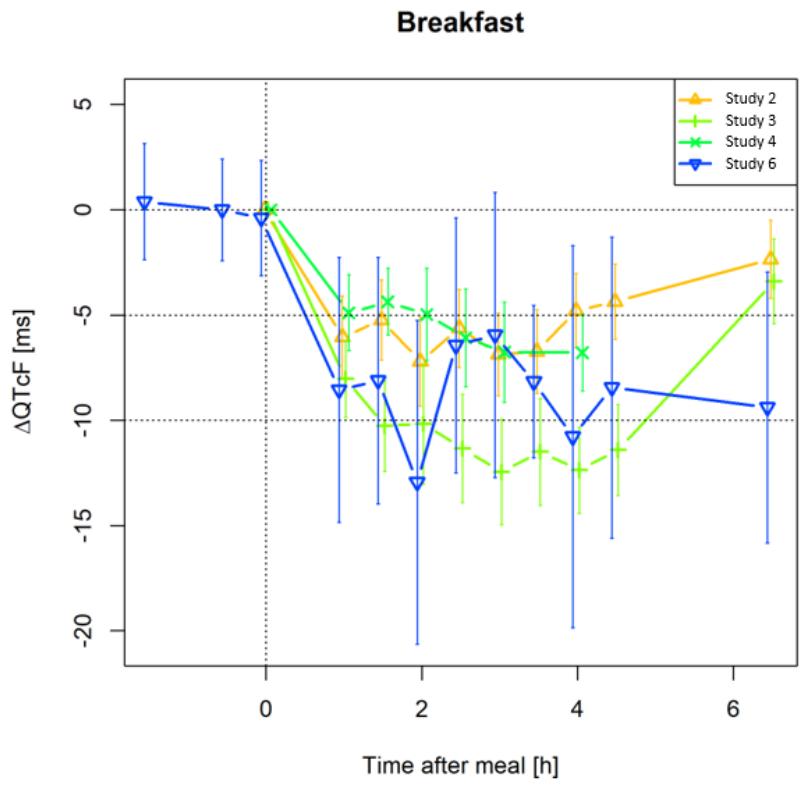

Figure 4 – Effect of breakfast by study

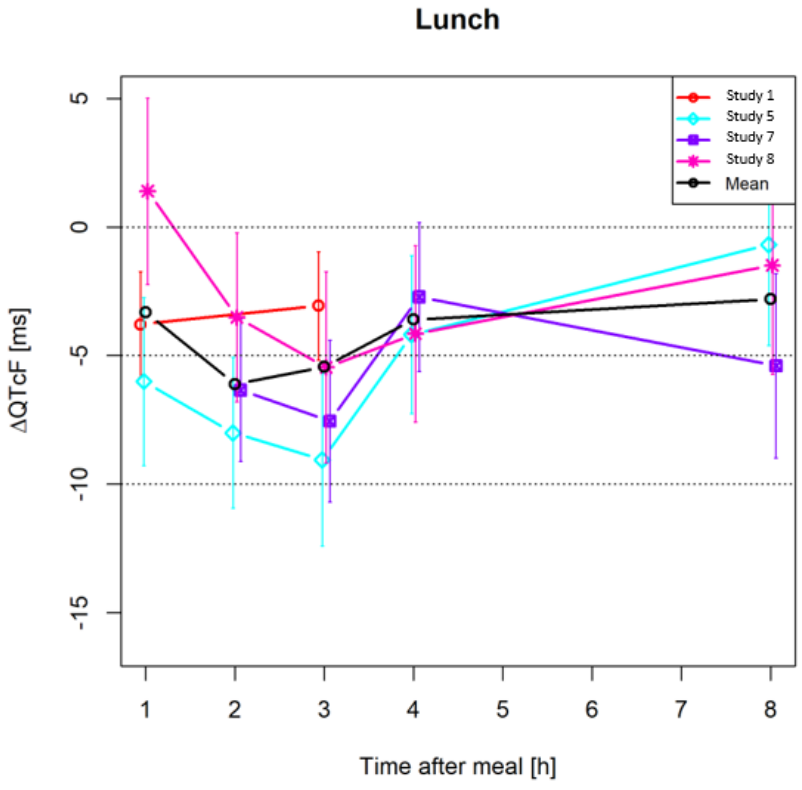

Figure 5 – Effect of lunch by study

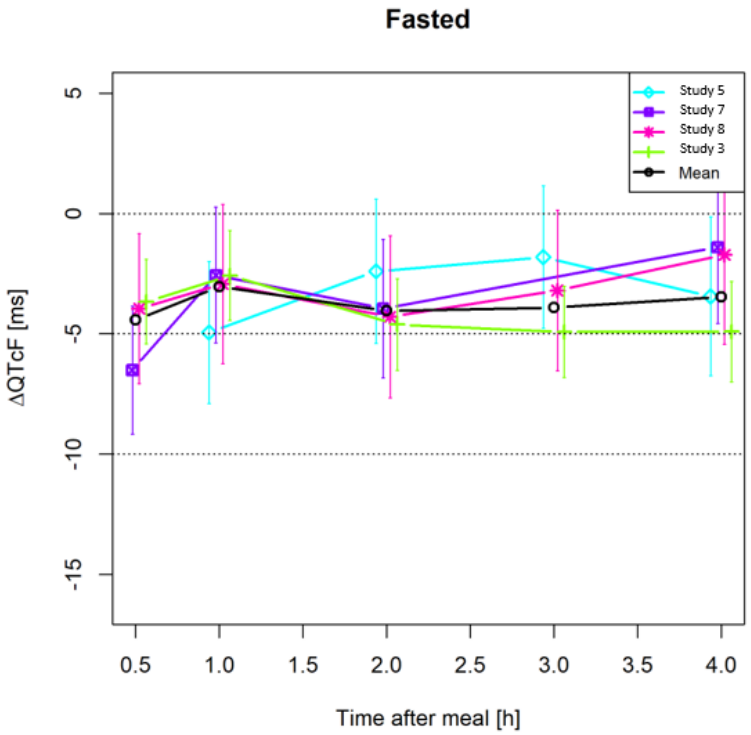

Figure 6 – Control: time after drug administration in fasted state

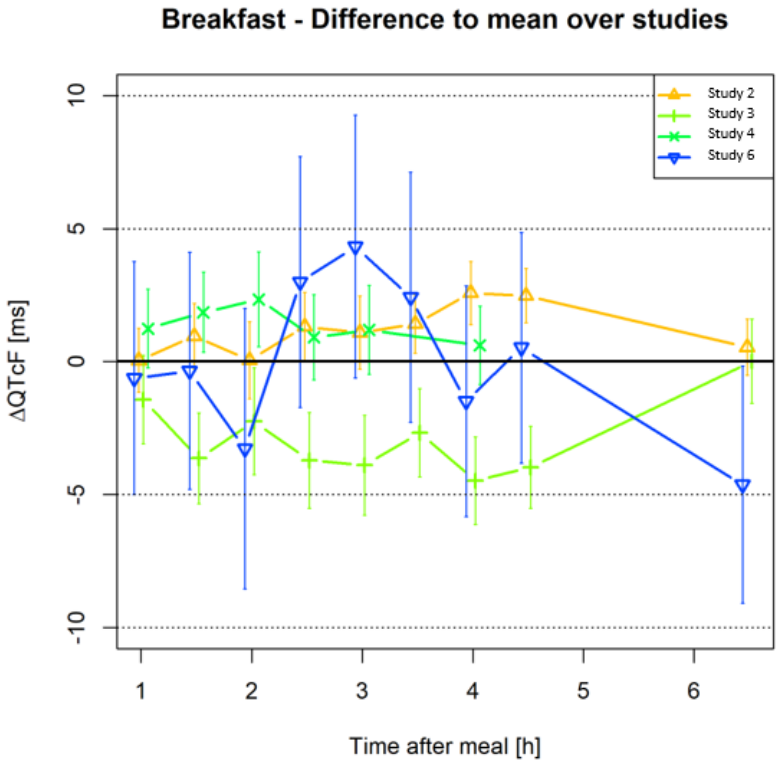

Figure 7 – Breakfast: difference to mean over studies

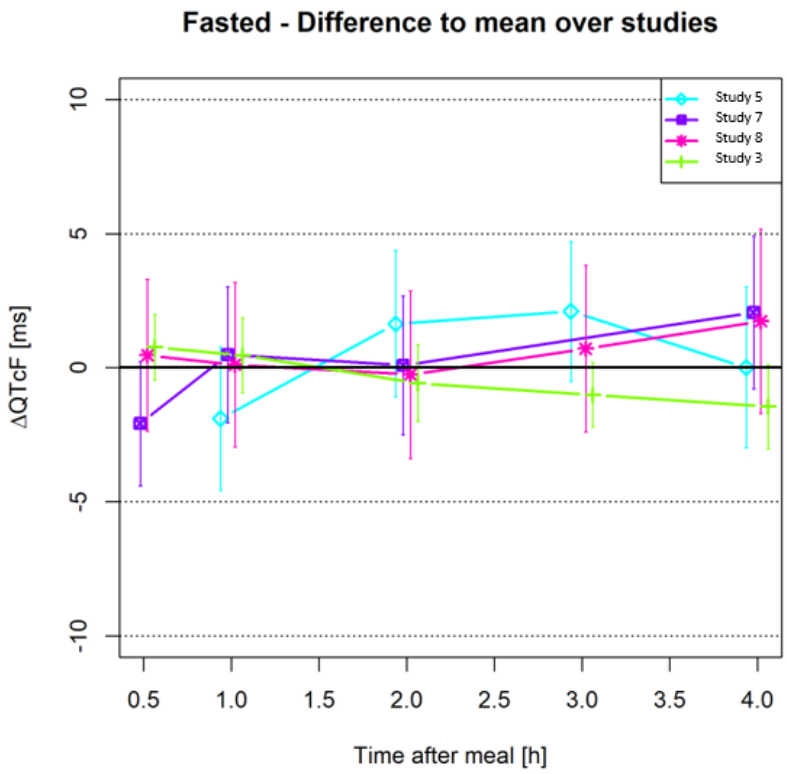

Figure 8 – Fasted: difference to mean over studies

Table 3 - Weighted mean values across studies

Time	Meal	Change in QTcF from reference value					
[h]		Estimate	SE	df	t-Value	90 % CI	
0.5	Fasted	-4.4	0.76	52	-5.79	-5.7	-3.1
1.0	Breakfast	-6.3	0.59	121	-10.79	-7.3	-5.4
	Fasted	-3.0	0.74	63	-4.11	-4.3	-1.8
	Lunch	-3.3	0.92	49	-3.58	-4.9	-1.8
1.5	Breakfast	-6.4	0.60	121	-10.69	-7.4	-5.4
2.0	Breakfast	-7.6	0.71	121	-10.71	-8.7	-6.4
	Fasted	-4.0	0.75	63	-5.35	-5.3	-2.8
	Lunch	-6.1	1.01	32	-6.05	-7.8	-4.4
2.5	Breakfast	-7.3	0.63	121	-11.47	-8.3	-6.2
3.0	Breakfast	-8.2	0.66	120	-12.34	-9.3	-7.1
	Fasted	-3.9	0.84	50	-4.65	-5.3	-2.5
	Lunch	-5.4	0.85	62	-6.42	-6.8	-4.0
3.5	Breakfast	-8.5	0.76	84	-11.17	-9.7	-7.2

Time	Meal	Change in QTcF from reference value					
[h]		Estimate	SE	df	t-Value	90 % CI	
4.0	Breakfast	-7.6	0.58	121	-13.09	-8.6	-6.6
	Fasted	-3.5	0.83	63	-4.17	-4.8	-2.1
	Lunch	-3.6	1.06	32	-3.41	-5.4	-1.8
4.5	Breakfast	-7.1	0.70	84	-10.17	-8.3	-5.9
6.5	Breakfast	-3.1	0.72	84	-4.35	-4.3	-1.9
8.0	Lunch	-2.8	1.34	31	-2.09	-5.1	-0.5

It should be noted that the 90 % confidence intervals are based on the intra-study variability and the between study variability has been removed. As a consequence the confidence intervals may be too narrow.

Table 4 - Comparison of meals

Timepoint [h]	Param	Estimate	SE	df	t-value	90 % CI	
1	Breakfast	-6.3	0.58	243	-10.89	-7.3	-5.4
	Lunch	-3.3	0.90	243	-3.69	-4.8	-1.8
	Fasted	-3.0	0.79	243	-3.85	-4.4	-1.7
	B - L	-3.0	1.07	243	-2.82	-4.8	-1.3
	B - F	-3.3	0.98	243	-3.34	-4.9	-1.7
2	Breakfast	-7.6	0.65	226	-11.60	-8.6	-6.5
	Lunch	-6.1	1.22	226	-5.03	-8.2	-4.1
	Fasted	-4.0	0.89	226	-4.55	-5.5	-2.6
	B - L	-1.4	1.38	226	-1.02	-3.7	0.9
	B - F	-3.5	1.10	226	-3.20	-5.3	-1.7
3	Breakfast	-8.2	0.66	242	-12.44	-9.3	-7.1
	Lunch	-5.4	0.90	242	-6.03	-6.9	-3.9
	Fasted	-3.5	1.01	242	-3.45	-5.1	-1.8
	B - L	-2.8	1.12	242	-2.48	-4.6	-0.9
	B - F	-4.7	1.20	242	-3.94	-6.7	-2.8
4	Breakfast	-7.6	0.61	226	-12.37	-8.6	-6.6
	Lunch	-3.8	1.15	226	-3.27	-5.7	-1.9
	Fasted	-3.5	0.84	226	-4.14	-4.8	-2.1
	B - L	-3.8	1.31	226	-2.94	-6.0	-1.7
	B - F	-4.1	1.04	226	-3.99	-5.9	-2.4

B - L: difference between breakfast and lunch; B - F: breakfast corrected for fasted effect

Table 5 - Analysis by gender

Timepoint [h]	Meal	Gender	Estimate	SE	df	t-value	90 % CI	
1	Breakfast	Female	-5.1	0.87	240	-5.83	-6.5	-3.6
		Male	-7.5	0.84	240	-8.97	-8.9	-6.1
		Difference	2.5	1.25	240	1.96	0.4	4.5
	Lunch	Female	-2.0	1.40	240	-1.41	-4.3	0.3
		Male	-4.2	1.20	240	-3.52	-6.2	-2.2
		Difference	2.3	1.89	240	1.19	-0.9	5.4
	Fasted	Female	-2.0	1.43	240	-1.39	-4.3	0.4
		Male	-3.6	0.97	240	-3.66	-5.2	-1.9
		Difference	1.6	1.76	240	0.89	-1.3	4.5
2	Breakfast	Female	-5.5	0.96	223	-5.81	-7.1	-4.0
		Male	-9.4	0.92	223	-10.23	-11.0	-7.9
		Difference	3.9	1.38	223	2.83	1.6	6.2
	Lunch	Female	-4.5	2.55	223	-1.75	-8.7	-0.3
		Male	-6.8	1.37	223	-4.99	-9.1	-4.6
		Difference	2.4	2.92	223	0.81	-2.5	7.2
	Fasted	Female	-0.8	1.57	223	-0.51	-3.4	1.8
		Male	-5.6	1.07	223	-5.22	-7.4	-3.8
		Difference	4.8	1.94	223	2.48	1.6	8.0
3	Breakfast	Female	-6.4	0.98	239	-6.48	-8.0	-4.7
		Male	-9.9	0.94	239	-10.51	-11.4	-8.3
		Difference	3.5	1.42	239	2.48	1.2	5.9
	Lunch	Female	-5.8	1.58	239	-3.68	-8.4	-3.2
		Male	-5.2	1.12	239	-4.68	-7.1	-3.4
		Difference	-0.6	1.98	239	-0.28	-3.8	2.7
	Fasted	Female	-1.3	1.60	239	-0.81	-3.9	1.3
		Male	-4.8	1.30	239	-3.72	-7.0	-2.7
		Difference	3.5	2.09	239	1.69	0.1	7.0
4	Breakfast	Female	-6.3	0.91	223	-6.96	-7.8	-4.8
		Male	-8.8	0.88	223	-9.98	-10.2	-7.3
		Difference	2.4	1.32	223	1.86	0.3	4.6
	Lunch	Female	-1.1	2.43	223	-0.44	-5.1	3.0
		Male	-4.7	1.30	223	-3.59	-6.8	-2.5
		Difference	3.6	2.78	223	1.30	-1.0	8.2
	Fasted	Female	-0.9	1.50	223	-0.61	-3.4	1.6
		Male	-4.7	1.02	223	-4.59	-6.4	-3.0
		Difference	3.8	1.85	223	2.04	0.7	6.8