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Comparing the consistency of electrocardiogram interval measurements by resting ECG versus 12-lead Holter

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Abstract

In clinical trials, traditionally only a limited number of 12-lead resting electrocardiograms (ECGs) can be recorded and, thus, long intervals may elapse between assessment timepoints and valuable information may be missed during times when patients' cardiac electrical activity is not being monitored. These limitations have led to the increasing use of Holter recorders which provide continuous data registrations while reducing the burden on patients and freeing up time for clinical trial staff to perform other tasks. However, there is a shortage of data comparing the two approaches. In this study, data from a randomized, double-blind, four-period, crossover thorough QT study in 40 healthy subjects were used to compare continuous 12-lead Holter recordings to standard 12-lead resting ECGs which were recorded in parallel. Heart rate and QT interval data were estimated by averaging three consecutive heartbeats. Values exceeding the sample average by more than 5% were tagged as outliers and excluded from the analysis. Visual comparisons of the ECG waveforms of the Holter signal showed a good correlation with resting ECGs at matching timepoints. Resting ECG data revealed sex differences that Holter data did not show. Specifically, women were found to have a longer QTcF of 20 ms, while men had a lower heart rate. We found that continuous recordings provided a more accurate reflection of changes in cardiac electrical activity over 24 hr. However, manual adjudication is still required to ensure the quality and accuracy of ECG data, and that only artifacts are removed thereby avoiding loss of true signals.

KEYWORDS

AMPS/BRAVO, GE Getemed, Holter, QT/cQT, resting ECG

1 | INTRODUCTION

Twelve-lead electrocardiogram (ECG) recordings are a standard and readily available method used to assess patient cardiac health and detect cardiac abnormalities. Their use is ubiquitous in clinical practice and in most clinical trials, where a standard 10-s 12-lead ECG is considered an essential component to determine the

physiological effect of an investigational medicinal product (IMP) (ICH E14, 2005).

To accurately assess the effect of a drug on the QT/QTc interval and determine whether an IMP causes QT prolongation, and by extension increased risk for cardiac arrhythmia and sudden death (Roden, 2004), the QT/QTc interval changes are closely monitored at predetermined predose and postdose timepoints during clinical

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trials. A standard resting ECG provides 10 s of data and logistics dictate that only a limited number of these procedures can be performed during a trial. In some cases, the intervals between time points may be lengthy and, thus, information obtained from discrete resting ECGs may not ameliorate the risk of missing vital data pertaining to QT/QTc changes that may only occur between ECG samples (Sarapa, 2005). In order to address this limitation, the use of 12-lead Holter recordings during clinical trials is now more common (Sarapa, 2005). Compared with previous three-lead recordings, modern Holter devices provide continuous 12-lead data for a clearer and more complete picture of an IMP's effects (Su et al., 2013). This makes twelve-lead Holter recordings a particularly suitable method to measure QT interval changes during phase I clinical trials (Badilini et al., 2009; Sarapa, 2005; Hingorani et al., 2016; Su et al., 2013) and thorough QT (TQT) studies.

Some medications have a characteristic feature of lengthening cardiac repolarization which in turn prolongs the ECG QT interval. A longer QT interval is associated with an increased risk of cardiac arrhythmias such as Torsade de Pointes (TdP), a polymorphic ventricular tachyarrhythmia that can deteriorate into ventricular fibrillation with sudden fatal consequences. As the QT interval is dependent upon heart rate (HR), it is typically presented as the QTc interval—a measurement that is corrected for HR (Postema & Wilde, 2014). Certain medications that are known to be associated with an increased risk of developing life-threatening arrhythmias, such as TdP, have been restricted or withdrawn from the market in recent years on account of their QT-prolonging effect (Täubel et al., 2019; Salvi et al., 2010; Roden, 2004). The risk of arrhythmia due to QT prolongation has also prompted the development of guidelines for *in vitro* and *in vivo* assessment of a drug's effect on the QT interval (Shah et al., 2015). To assess the safety and tolerability of a new IMP, guidelines published by the International Conference on Harmonisation (E14) recommend that all new drugs with systemic bioavailability undergo a TQT study to determine their impact upon cardiac repolarization and the QT interval, and thus assess its potential to cause potentially fatal cardiac arrhythmia (ICH E14, 2005).

However, there is a lack of data comparing concordance between resting ECGs and 12-lead Holter recordings in the measurement of the QT interval and other ECG parameters. Similarly, concerns have been raised about the quality of data obtained from ECGs extracted from a Holter versus multiple resting ECGs (Badilini et al., 2009) and that noise and artifacts associated with portable devices may lead to misinterpretation of Holter data (Shah, 2005). At the same time, it has been noted that 12-lead ECG recordings extracted from continuous Holter may produce good quality recordings and robust QTc data (Badilini et al., 2009).

Furthermore, there appears to be insufficient literature comparing QT/QTc interval changes measured by resting ECG versus data obtained from continuous Holter monitoring, although some studies report no significant discrepancy in estimated mean values with regard to QT and several other ECG parameters when both methods were compared (Strnadova, 2005; Wang et al., 2016). This article seeks to address this gap in the available literature by comparing concordance between both methods to uncover whether one is more effective than

the other in accurately determining HR, QT/QTc, and other QT subinterval changes obtained predose during a phase I clinical trial. We also compared two different Holter algorithms (GE Getemed and BRAVO) to ascertain whether there may be discrepancies in automated measurement of QTcF and HR between the two algorithms.

2 | METHODS

2.1 | Study design

The data analyzed in this study were obtained from a randomized, double-blind, placebo, and positive controlled, four-period, crossover TQT study designed to investigate the effect of an intravenous IMP upon the QT/QTc interval. This phase I trial (NCT02661594) took place between 2013 and 2014 and involved 40 healthy volunteers of both sexes (male: $N = 23$; female: $N = 17$) aged 21 and 45 years of Caucasian ($N = 23$) and Japanese ($N = 17$) ethnicity. All subjects provided written informed consent for the trial which was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) and a Research Ethics Committee. The trial was performed in accordance with guidelines established by the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.

Data were obtained from all volunteers on Day -1 via continuous 12-lead Holter recording and resting ECGs were performed at specific timepoints (at dosing, and at 2, 8, and 30 min, and 1, 1.5, 2, 3, 4, 6, and 12 hr predosing).

2.2 | Cardiac assessments and statistical analysis

Resting ECGs were obtained using the MAC-1200 devices with interval measurements performed by the Muse 12SL algorithm, while data obtained from the Holter devices (Getemed Holter ECG recorders) were analyzed using the Getemed algorithm (all equipment by GE Healthcare). When Holter data were extracted in 2016 and compared with automated measurements from the resting ECG recordings, it emerged that there were some discrepancies between data generated from the 12-lead Holter and resting ECGs. This was believed to be due to each device using a different algorithm to calculate the HR and QTcF interval. Accordingly, it was determined that both the resting ECGs and the Holter ECGs ought to use the same QT measurement algorithm to determine whether any discrepancy found in the QTcF values was related to the ECG device or the algorithm used. Thus, in 2019, both the ECG and Holter data were reanalyzed using the BRAVO algorithm (Kligfield et al., 2018) by Analyzing Medical Parameters for Solutions (AMPS) LLC. A description of how the BRAVO algorithm performs automated measurements of ECG intervals has been described previously (Kligfield et al., 2018).

We compared individual HR and QTcF data (GE Getemed—2016 and BRAVO—2019), alongside mean QTcF and HR values calculated by both algorithms at 10-min intervals. We also compared differences in mean HR and QTcF measurements when both resting ECGs

and Holter data were analyzed using the BRAVO algorithm in order to identify differences between the recording devices. The JT_{peak} and T_pT_e peak durations were both extracted from the QT data by AMPS. JT_{peak} was corrected for HR using the Johannesen proposed correction ($JT_{pc} = JT_p/RR^{0.58}$) (Johannesen et al., 2014). T_pT_e was not corrected for HR.

3 | RESULTS

3.1 | Volunteer disposition

Out of the 40 volunteers enrolled, two withdrew during the trial after Day -1. One volunteer chose not to continue with the study while the other was excluded because of nonadherence to protocol restrictions. All available ECG data pertaining to these two volunteers, up to the point of withdrawal, were included in the analysis.

With regard to Holter data, one volunteer had no Holter data available on Day -1 while four volunteers generated untrustworthy

Holter data. Thus, final predosing Holter data came from 35 volunteers (21 males and 14 females) only.

3.2 | Differences in resting ECG versus Holter measurements

With respect to Holter-generated QTcF data, the GE Getemed algorithm (Figure 1a) provided values approximately 10 ms greater than those calculated using the BRAVO algorithm. However, this variation was consistent across all timepoints. Very little difference was seen in the measurement of HR by the two separate Holter algorithms (Figure 1b).

Holter and ECG measurements of the QTcF interval were concordant for all timepoints until the 6 hr timepoint when analyzed using the BRAVO algorithm (Figure 2a). Thereafter, the degree of concordance could not be determined because resting ECGs were not performed until 12 hr postdose. Little concordance was seen between resting ECG and Holter measurements of HR, with Holter

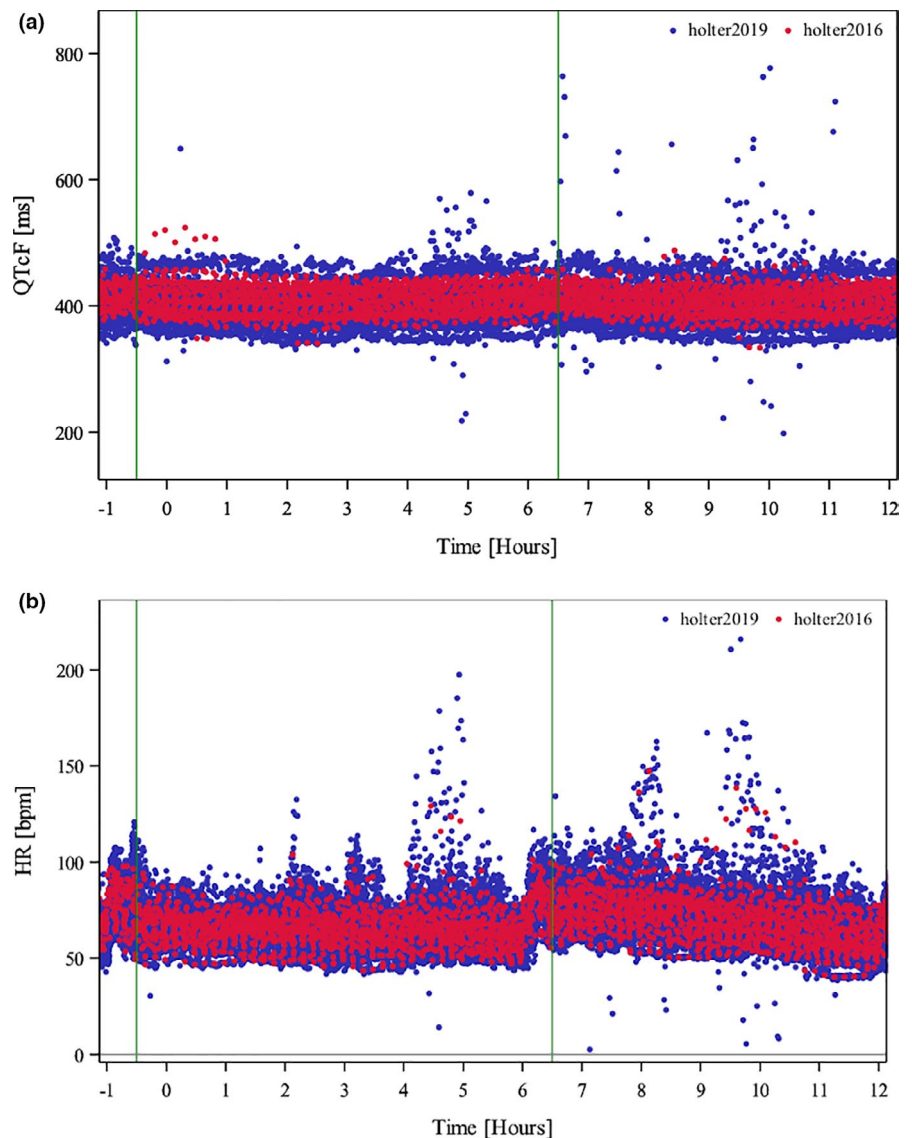


FIGURE 1 (a) Differences in QTcF values and (b) HR values as calculated by two separate Holter algorithms. Red—Getemed; Blue—BRAVO

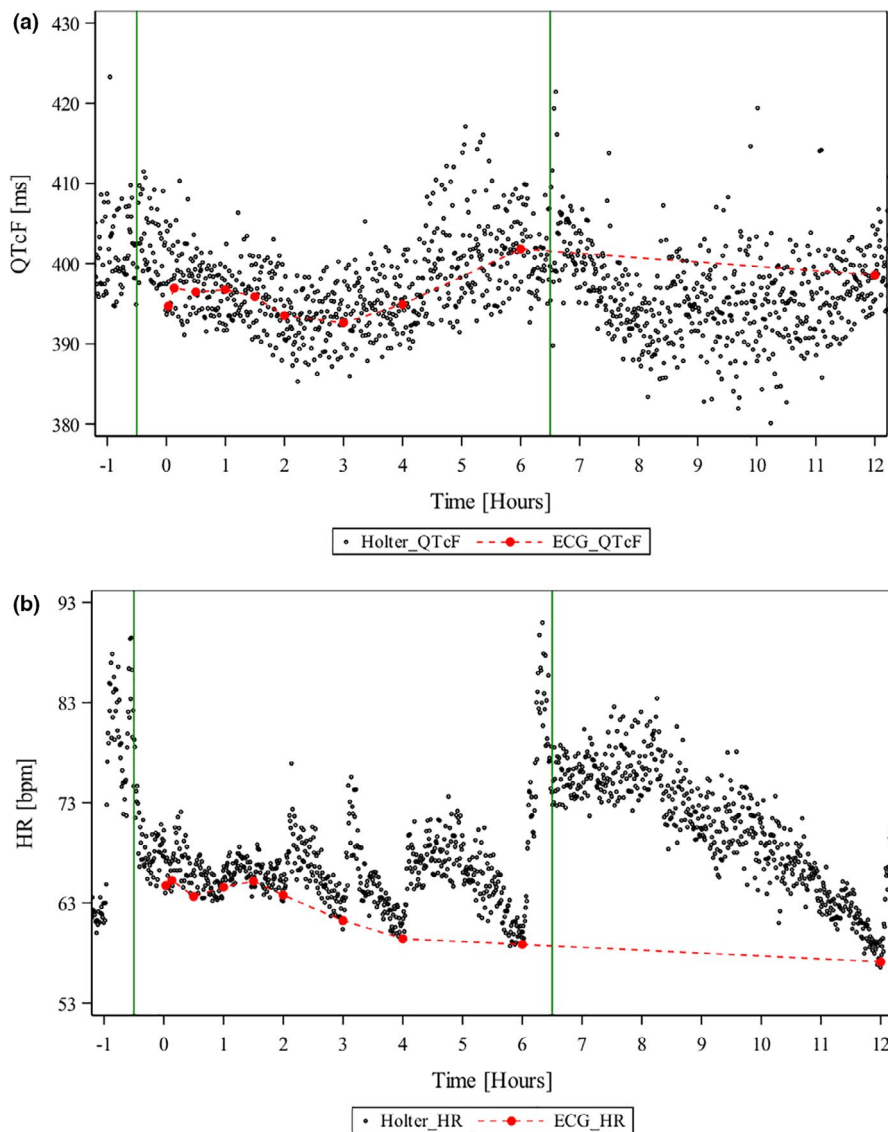


FIGURE 2 (a) Mean QTcF values and (b) mean HR values as calculated by the BRAVO algorithm for Holter and resting ECG. Black—Holter; Red—resting ECG

measurements generally being higher than those of resting ECGs (Figure 2b).

Data obtained from both 12-lead Holter readings and resting ECGs were analyzed using the AMPS BRAVO algorithm. Resting ECGs revealed that, on average, female QTcF readings were approximately 20 ms longer than those seen in males (Figure 3a). Although Holter data showed little difference between male and female volunteers in terms of HR, resting ECG data revealed that men had lower HRs compared with women (Figure 3b). The JTpC subintervals in female volunteers were observed to be approximately 20 ms longer than those in males using resting ECG readings, accounting for most of the difference in the QTcF (Figure 3c). No significant sex differences were observed in TpTe subinterval duration (Figure 3d).

ECG triplicate data were averaged and the best matching corresponding Holter recording was obtained for each parameter to see whether there were any differences in QT subinterval measurements between continuous Holter recordings and resting ECG readings. The graphs below show minimal differences between resting ECG and Holter measurements for HR, QTcF, and JTpC concerning both

sex and overall data, none of which were significant (Figure 4a–c). Small differences up to 2 ms were observed for the TpTe interval between resting ECG and Holter readings which were less pronounced in male than female volunteers (Figure 4d).

4 | DISCUSSION

This study assessed the differences between standard 12-lead resting ECG and Holter recording devices and between two different Holter processing algorithms (GE Getemed and BRAVO). We found a small but consistent disparity of approximately 10 ms between the GE Getemed and BRAVO algorithms with respect to Holter measurements of the QTcF interval. It is important to note that even a small difference in QTcF interval measurement could have significant implications on both patient safety and the validity of clinical trial data because conflicting conclusions may be drawn depending on the algorithm used. This divergence may be even more pronounced among volunteers who received an IMP. Using different algorithms to calculate changes in QTcF

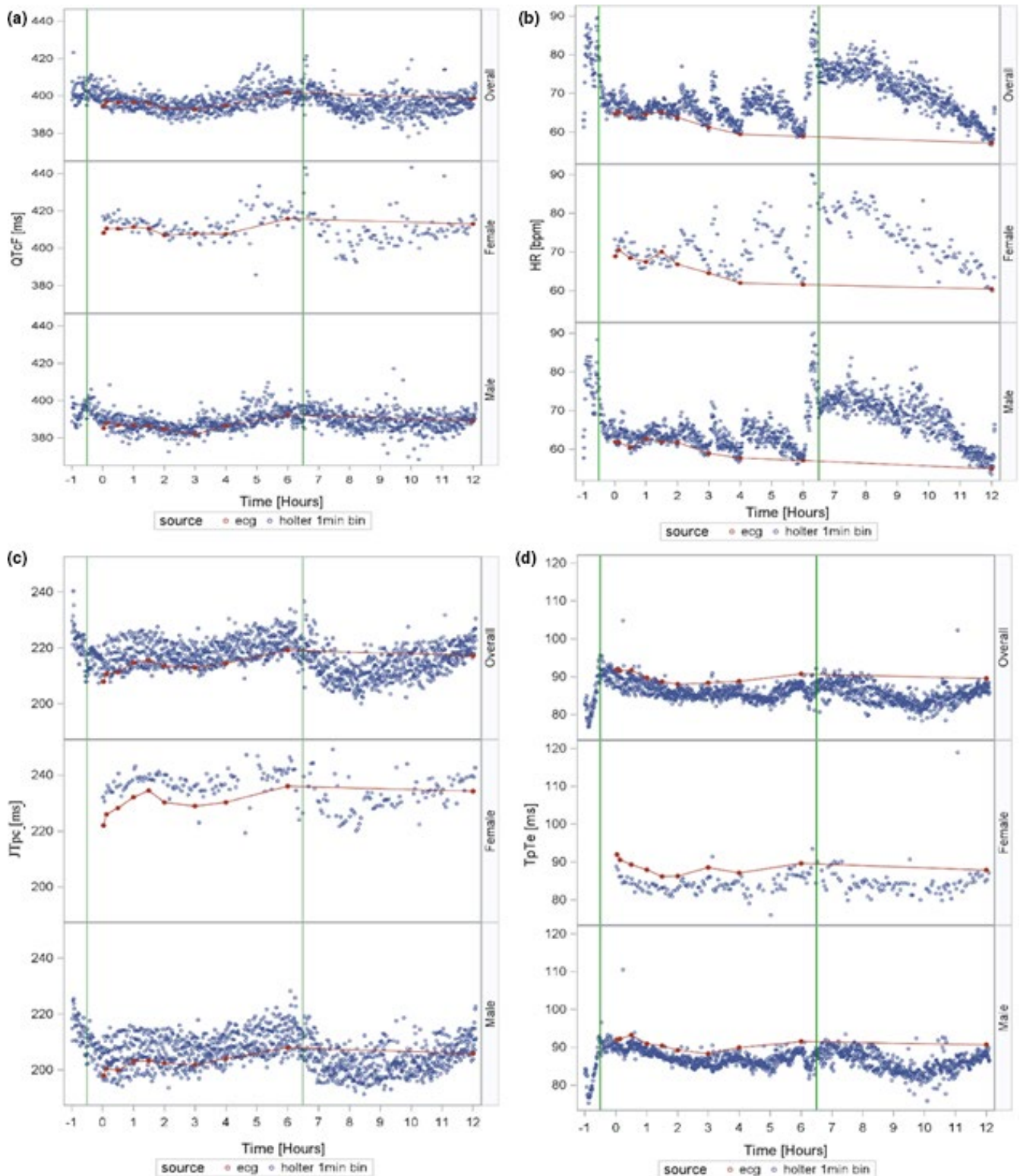


FIGURE 3 (a) Average QTcF, (b) average HR, (c) average JTpc, and (d) average TpTe according to sex, as calculated using the BRAVO algorithm. Red—resting ECG; Blue—Holter

predosing and postdosing could either result in an underestimate of QTcF interval changes—potentially placing volunteers at risk—or an overestimate, which could lead to the unjustified dose reduction or even withdrawal of a drug from clinical trials.

Our findings are also consistent with previously published data comparing performance of different ECG algorithms (Kligfield et al., 2018). Kligfield et al. found small but significant differences between algorithm measurements in normal subjects and even

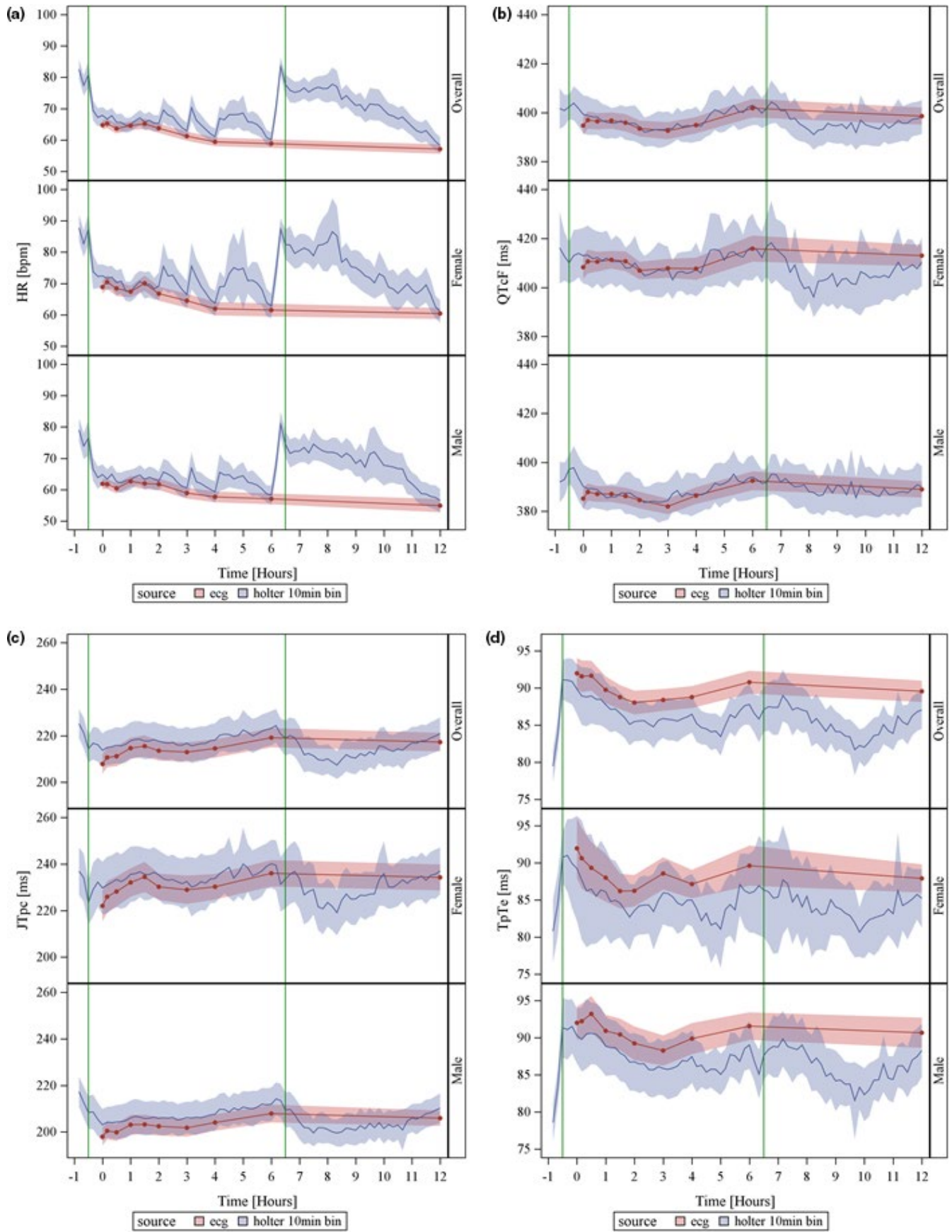


FIGURE 4 Mean and 2-sided 95% confidence intervals of the mean for (a) HR, (b) QTcF, (c) JTpc, and (d) TpTe as calculated using BRAVO algorithm. Red—resting ECG, blue—Holter

larger differences in long QT syndrome (LQTS) patients, ranging from 2.0 to 14.0 ms for QRS duration and from 0.8 to 18.1 ms for the QT interval.

Therefore, it is vital to ensure that the same algorithm is used to measure ECG intervals, especially when the data are used to conclude an IMP's effects. Alternatively, if multiple ECG devices and different algorithms have been used and the ECG waveforms are available digitally, it would be advisable to run the entire ECG dataset through a single algorithm for a consistent measurement output and a unified statistical analysis, as demonstrated in the current study.

We found a concordance between ECG and Holter measurements for the QTcF interval for all timepoints between 0 hr and 6 hr when both devices used the same algorithm. However, we were unable to determine concordance thereafter because of the absence of resting ECG measurements between the 6 hr and 12 hr timepoints. For HR, resting ECG measurements correlated with the lowest Holter HR readings, affirming that HR is at its lowest when volunteers are at rest (hence, "resting ECG") and higher when volunteers can move freely during Holter recordings. When ECG triplicate data were averaged and compared with the corresponding (same time) Holter recordings, little difference was found in ECG interval measurements.

Using a 12-lead Holter to provide continuous feedback about changes in HR, QTcF, and other ECG intervals would appear to be a preferable and more convenient approach to obtain discrete data at fixed timepoints from standard resting ECGs. Our study was limited in that no resting ECG measurements were taken between 6 hr and 12 hr postdose. Additionally, our datasets only captured the predose ECG values. Therefore, further studies are necessary to examine how each method would perform during the administration of an IMP, especially those with marked HR and QT prolongation effects.

The difference between the methods in the duration of the cardiac subintervals JT_{pc} and TpTe was not statistically significant. Understanding that the JT_{pc} subinterval is comparable between testing methods is useful when comparing reports from diverse studies. A potential limitation of this analysis is the use of Johannesen's correction coefficient, as this may not be the most optimal method for JT_{peak} correction (Hnatkova et al., 2017), and thus not universally representative of various populations. However, it should be noted that one study found no significant differences between the application of Fridericia's and Johannesen's correction coefficients (Zareba et al., 2017). The duration of TpTe is closely related to that of the QTcF interval and has been shown to increase proportionately with QTcF when looking at drug-induced abnormal repolarization (Bhuiyan et al., 2015). It has also previously been shown that TpTe itself is not necessarily predictive of mortality (Smetana et al., 2011). Nonetheless, it remains encouraging that the TpTe subinterval is comparable between Holter and bedside testing methods.

Continuous Holter measurements arguably provide a better indication of changes in cardiac electrical activity that may occur between protocol time points following dosing. However, volunteers wearing Holter ECG devices tend to be free to mobilize throughout a study which can lead to higher HR values. Therefore, special care

needs to be taken when interpreting such data as these HR values may be misinterpreted as an IMP effect. Arguably, dynamic Holter data provide a better reflection of how a drug affects an individual as patients taking medication are not bound by the restrictions inherent to clinical trials. Hence, Holter data are more representative of in vivo ECG changes. Yet, cardiac changes while patients are mobile are more difficult to control for and may introduce confounding effects. Thus, performing resting ECGs at predefined postdose time points could prove useful in complementing Holter measurements and helping to verify postdose changes and concentration effects observed.

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CONFLICT OF INTEREST

JT, TP, and DC are employees of Richmond Pharmacology Ltd. CS and AF are employees of the Richmond Research Institute. BM is an employee of Cardiac Safety Consultants Ltd. CG is an employee of the University of Aalborg.

AUTHOR CONTRIBUTIONS

JT and DC conceived the study. DC, BM, and CG analyzed the data. TP, CS, AF, and BM oversaw the preparation of the manuscript. All authors approved the final submitted version and agreed to the publication.

ETHICAL APPROVAL

Following Good Clinical Practice guidelines, the study was approved by the NHS Health Research Authority and registered with clinicaltrials.gov (NCT02661594). Informed, written consent for data to be published was obtained from all volunteers. No identifying details of any volunteers has been published.

DATA AVAILABILITY STATEMENT

Requests for access to data should be addressed to the corresponding authors.

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