










Manual vs. automatic assessment of the QT-interval and corrected QT

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Aims

Sudden cardiac death (SCD) is challenging to predict. Electrocardiogram (ECG)-derived heart rate-corrected QT-interval (QTc) is used for SCD-risk assessment. QTc is preferably determined manually, but vendor-provided automatic results from ECG recorders are convenient. Agreement between manual and automatic assessments is unclear for populations with aberrant QTc. We aimed to systematically assess pairwise agreement of automatic and manual QT-intervals and QTc.

Methods and results

A multi-centre cohort enriching aberrant QTc comprised ECGs of healthy controls and long-QT syndrome (LQTS) patients. Manual QT-intervals and QTc were determined by the tangent and threshold methods and compared to automatically generated, vendor-provided values. We assessed agreement globally by intra-class correlation coefficients and pairwise by Bland–Altman analyses and 95% limits of agreement (LoA). Further, manual results were compared to a novel automatic QT-interval algorithm. ECGs of 1263 participants (720 LQTS patients; 543 controls) were available [median age 34 (interquartile range 35) years, 55% women]. Comparing cohort means, automatic and manual QT-intervals and QTc were similar. However, pairwise Bland–Altman-based agreement was highly discrepant. For QT-interval, LoAs spanned 95 (tangent) and 92 ms (threshold), respectively. For QTc, the spread was 108 and 105 ms, respectively. LQTS patients exhibited more pronounced differences. For automatic QTc results from 440–540 ms (tangent) and 430–530 ms (threshold), misassessment risk was highest. Novel automatic QT-interval algorithms may narrow this range.

Conclusion

Pairwise vendor-provided automatic and manual QT-interval and QTc results can be highly discrepant. Novel automatic algorithms may improve agreement. Within the above ranges, automatic QT-interval and QTc results require manual confirmation, particularly if T-wave morphology is challenging.

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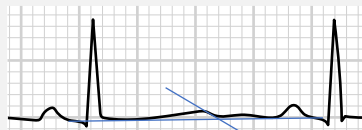
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Graphical Abstract

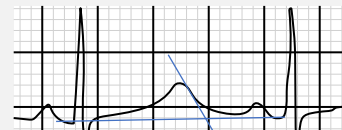
ECG examples

Automatic QT-interval / QTc too short



Automatic: QT-interval 388ms, QTc 403ms
Manual: QT-interval 471ms, QTc 514ms

Automatic QT-interval / QTc too long

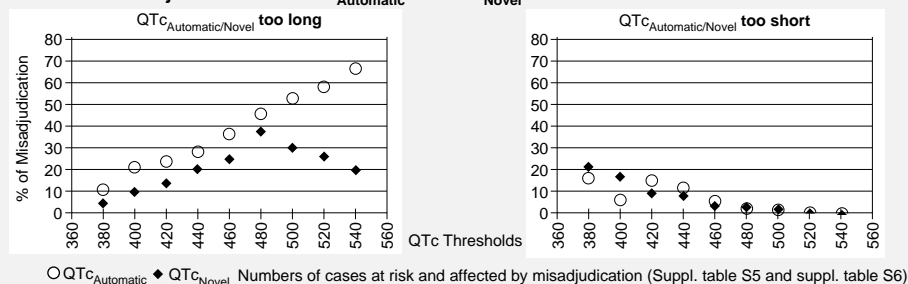


Automatic: QT-interval 578ms, QTc 591ms
Manual: QT-interval 471ms, QTc 505ms

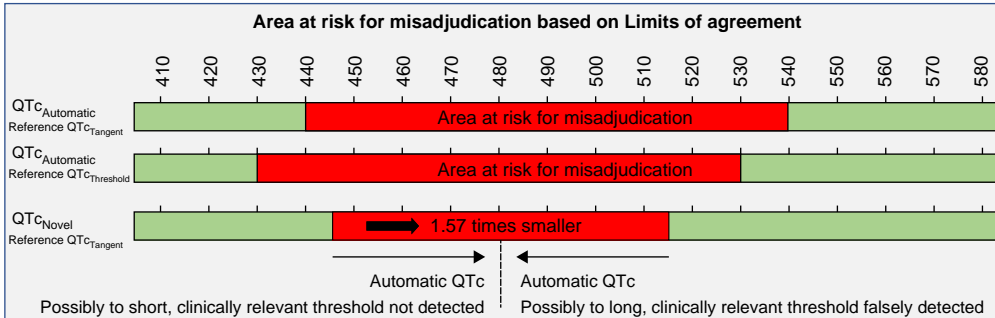
➔ Manual and automatic results are discrepant.

Effective misadjudication

Misadjudication with QTc_{Automatic} and QTc_{Novel} in various QTc-interval thresholds



Area at risk for misadjudication



Keywords

QT-interval • QTc • Electrocardiogram • Misassessment • Long QT syndrome • Sudden cardiac death

What's new?

- One of the largest and diverse cohorts enriched for aberrant QT-intervals to assess pairwise agreement between vendor-provided automatic and manual QT-interval and heart-rate corrected QT (QTc).
- Automatic and manual QT-intervals and QTc values are highly discrepant.
- A wide range of automatic QT-interval and QTc results is prone to misinterpretation.
- We recommend a range for reviewing automatic QT-interval and QTc results manually, particularly when the T-wave morphology is challenging.

Introduction

Sudden cardiac death (SCD) results in the loss of life-years in often young and previously healthy individuals,^{1–3} and most SCD events occur in the general population.^{4–7} A prolonged ventricular

repolarization, reflected by a prolonged QT-interval and heart rate (HR)-corrected QT (QTc) on the electrocardiogram (ECG), predisposes to SCD.^{8–13} QT-interval and QTc prolongation are observed in the context of structural heart disease, cardiac ischaemia, and congestive heart failure but may also be induced by several drugs both for cardiac and non-cardiac morbidities.¹⁴

Since ECGs are non-invasive and easily accessible, the QT-interval and QTc are widely used across medical specialties to guide risk adjudication and decision-making.^{15–17} The QT-interval is also an important aspect for diagnosing the long-QT syndrome (LQTS), a cardiac arrhythmia disorder associated with malignant arrhythmias and SCD.^{16–19} Despite the importance of QT-interval and QTc prolongation for SCD risk, no commonly accepted standard exists for their assessment.^{16,17} QT-interval experts advocate manual and serial measurements by the tangent or threshold methods.²⁰ Although measurements by both experts and non-experts are reliable, many physicians, including cardiologists, appear to misadjudicate a normal vs. abnormal QT-interval.^{21,22} In fact, for convenience, many healthcare professionals routinely use QT-interval and QTc values that are automatically provided by ECG recorders. The agreement between

automatic QT-interval and QTc results and those assessed manually is not sufficiently clear.

Here, we systematically quantified the agreement between vendor-provided automatic and manual QT-interval and QTc assessments. QT-interval and QTc assessments are particularly challenging in case of complex T-wave morphologies as often present in LQTS patients.²³ To evaluate a cohort enriched for aberrant QTc values and T-wave morphologies, we therefore investigated a large cohort of both controls and LQTS patients with various degrees of LQTS expressivity and hypothesized that a discrepancy between automatic and manual QT-interval and QTc findings was more pronounced among the latter. Secondly, we accessed measurement agreement using a recently reported, academia-developed QT algorithm.²⁴

Methods

Study cohort

Patients with confirmed pathogenic mutations in the LQTS Type-1 (*KCNQ1*), Type-2 (*KCNH2*), and Type-3 (*SCN5A*) genes were included as cases and healthy genotype-negative family members as controls. Participants were recruited at two large academic cardiology departments, the Amsterdam UMC, in Amsterdam, the Netherlands, and the University Hospital of the Ludwig-Maximilians-Universität Munich, Germany, as described previously.²⁵

Data collection and management

We used the first available 12 lead resting ECG (index-ECG) of all participants. When the index-ECG was unavailable, a subsequent ECG was used. We excluded ECGs with missing automatic QT-interval and QTc values or in case of ventricular pacing, arrhythmias hindering QT-interval and QTc analysis (e.g. atrial fibrillation), higher degree conduction disorders, complete bundle branch blocks, or poor ECG quality (see [Supplementary material online, Table S1](#)). For our secondary analysis involving the novel automatic algorithm for automatic QT-interval and QTc assessment, we additionally excluded individuals lacking digital raw signal ECG (see [Supplementary material online, Figure S1](#)). The AMC Review Board approved the study waiving individual informed consent as only retrospective routine care data were used. All ECGs were pseudonymized. Enrolment ended in December 2016.

Manual ECG measurements

Specific methods of how ECGs were manually measured have been reported before.²⁵ The leads preferred for measurement were lead II, followed by lead V5, followed by any lead if lead II or lead V5 was unsuitable. On all ECGs, three pre-selected, consecutive P-QRS-T complexes including their respective preceding RR-intervals were measured independently by three readers.²⁵ Subsequently, measurements were averaged across complexes and readers. Of note, both the inter- and intra-reader validity of our standard manual QT-interval assessment were systematically examined before.²⁵ More specifically, across manual measurement methods, the inter-reader intra-class correlation coefficient (ICC) was >0.96 with a small systematic error of maximally 15 ms. Similarly, the intra-reader validity was 0.99 with a systematic error of 4 ms. Measurements included manual HR (HR_{Manual}), manual PR interval (PR_{Manual}), manual QRS duration (QRS_{Manual}), and the QT-interval determined by both the tangent (QT_{Tangent}) and threshold methods ($QT_{\text{Threshold}}$). For the tangent method, the end of the T-wave was defined as the point where the tangent on the steepest point of the terminal limb of the T-wave intersects with the isoelectric baseline. For the threshold method, the end of the T-wave was defined as the intersection of the terminal limb of the T-wave with the isoelectric baseline (see [Supplementary material online, Figure S2](#)).²⁵ Specific instructions on how to deal with complicated T-wave morphology including U waves have been described in the previous publication and are additionally visualized (see [Supplementary material online, Figure S2](#)).²⁵ Considering the clinically most widespread use and its shown applicability also at higher HRs,^{26,27} QT-intervals were corrected for HR using Bazett's formula (QTc_{Tangent} ; $QTc_{\text{Threshold}}$).

Alternative QTc correction formulas (Fridericia; Framingham; Hodges; Rautaharju) were calculated for comprehensiveness.

Automatic ECG measurements

From the vendor-provided automatic output of the ECG recorders, we obtained HR ($HR_{\text{Automatic}}$), PR-interval ($PR_{\text{Automatic}}$), QRS duration ($QRS_{\text{Automatic}}$), QT-interval ($QT_{\text{Automatic}}$), and QTc ($QTc_{\text{Automatic}}$). For ECGs recorded with GE Healthcare ECG recorders (General Electric Company, MUSE software, Chicago, IL, USA) applying the company's proprietary 12SL algorithm;²⁸ $QTc_{\text{Automatic}}$ was determined by Bazett's formula. The formula remained undisclosed for other manufacturers.

Novel automatic QT-interval algorithm

A novel, automatic QT-interval algorithm was developed and validated previously by our group.²⁹ In short, a QRS-T-complex was defined after excluding measurements from leads that deviated more than 2 standard deviations from the median. On this QRS-T-complex, the QT-interval (QT_{Novel}) was determined using the tangent method, which was HR corrected using Bazett's formula (QTc_{Novel}).

ECG-based diagnosis of LQTS

Importantly, diagnosing LQTS requires a comprehensive clinical and genetic evaluation. Clinical practice guidelines recommend applying the so called Schwartz score to support a LQTS diagnosis.^{16,17,30} However, the same clinical practice guidelines suggest to at least consider a significant QTc prolongation indicative of a LQTS diagnosis if, in the absence of QTc-prolonging drugs or other correctable factors, a $QTc \geq 480$ ms is determined on repeated ECGs.^{16,17} Correct determination of QT-interval and QTc is thus critically important. If $QTc_{\text{Automatic}}$ values deviate markedly from the standard of manual QTc assessment, such a clinically relevant QTc cut-off may be misassessed.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics 27 (IBM, Armonk, NY, USA). Categorical data are presented as frequencies (percentages, %) and compared using χ^2 or Fisher's exact tests as appropriate. Continuous data are presented as mean \pm standard deviation (SD) compared by Student's *t*-tests or as median and inter-quartile range compared by the Wilcoxon test. Two-sided *P*-values <0.05 were considered statistically significant.

We assessed agreement between automatic and manual ECG measurements. For **global agreement**, we calculated the intra-class correlation coefficient (ICC) and 95% confidence intervals (CIs) for multiple measurements based on a two-way consistency model according to Cicchetti and Sparrow.³¹ For **pairwise evaluations**, we quantified and visualized Bland–Altman limits of agreement (LoA).³² Analyses are presented for the overall cohort and separately for controls and LQTS patients.

Using manual ECG measurements as the standard, we calculated the **absolute difference of QT-interval and QTc values** between (i) QT-interval/ $QTc_{\text{Automatic}}$ and QT-interval/ QTc_{Tangent} ; (ii) QT-interval/ $QTc_{\text{Automatic}}$ and QT-interval/ $QTc_{\text{Threshold}}$; and (iii) QT-interval/ QTc_{Novel} and QT-interval/ QTc_{Tangent} . To focus on clinically relevant discrepancies between automatic and manual measurements, we considered the previously described intra- and inter-observer variability of manual measurements²⁵ and determined the percentage of individuals with an absolute pairwise measurement difference $\geq \pm 15$ ms.

For the ECG-based diagnosis of LQTS, based on our Bland–Altman LoAs, we defined and visualized $QTc_{\text{Automatic}}$ ranges at risk for possible misassessment. For both the tangent and threshold methods, from the guideline-suggested cut-off of QTc 480 ms, we deducted the lower LoA and added the upper LoA observed in our overall cohort.

We also examined cut-off-based discrepancies between automatic and manual QTc assessments from 380 to 540 ms. We determined the frequency of $QTc_{\text{Automatic}}$ and QTc_{Novel} ECGs exceeding these cut-offs, whereas the manual QTc_{Tangent} and $QTc_{\text{Threshold}}$ assessments remained below the cut-off value. Conversely, we determined the frequency of $QTc_{\text{Automatic}}$ and QTc_{Novel} ECGs undercutting the cut-offs, whereas the

Table 1 Cohort characteristics

| | Overall cohort <i>n</i> = 1263 | Controls <i>n</i> = 543 | LQTS <i>n</i> = 720 | <i>P</i> -value |
|--------------------------------|-----------------------------------|----------------------------|------------------------|-----------------|
| Females, <i>n</i> (%) | 692 (55) | 283 (52) | 409 (57) | 0.10 |
| Age at ECG (years) | 34 (35) | 42 (34) | 27 (34) | <0.001 |
| HR _{Manual} (bpm) | 74 ± 20 | 74 ± 19 | 75 ± 22 | 0.19 |
| HR _{Automatic} (bpm) | 74 ± 20 | 73 ± 19 | 74 ± 22 | 0.32 |
| PR _{Manual} (ms) | 146 ± 26 | 148 ± 24 | 144 ± 28 | 0.027 |
| PR _{Automatic} (ms) | 145 ± 25 | 145 ± 22 | 145 ± 27 | 0.82 |
| QRS _{Manual} (ms) | 82 ± 14 | 85 ± 13 | 80 ± 14 | <0.001 |
| QRS _{Automatic} (ms) | 88 ± 14 | 90 ± 13 | 86 ± 14 | <0.001 |
| QT _{Tangent} (ms) | 392 ± 56 | 366 ± 36 | 411 ± 60 | <0.001 |
| QT _{C-Tangent} (ms) | 427 ± 43 | 399 ± 26 | 448 ± 40 | <0.001 |
| QT _{Threshold} (ms) | 402 ± 56 | 379 ± 38 | 419 ± 60 | <0.001 |
| QT _{C-Threshold} (ms) | 438 ± 41 | 412 ± 25 | 458 ± 39 | <0.001 |
| QT _{Automatic} (ms) | 405 ± 56 | 383 ± 40 | 422 ± 61 | <0.001 |
| QT _{C-Automatic} (ms) | 438 ± 41 | 413 ± 21 | 456 ± 42 | <0.001 |
| Novel automatic analyses | <i>n</i> = 996 | <i>n</i> = 470 | <i>n</i> = 526 | |
| HR _{Novel} (bpm) | 74 ± 20 | 74 ± 19 | 75 ± 22 | 0.51 |
| QT _{Novel} (ms) | 390 ± 51 | 367 ± 33 | 411 ± 55 | <0.001 |
| QT _{C-Novel} (ms) | 425 ± 41 | 400 ± 28 | 447 ± 40 | <0.001 |

Formal comparison for controls vs. LQTS patients. Results for QT-interval/QT_{C-Novel} analyses restricted to individuals with available digital ECG data.

ECG, electrocardiogram; HR, heart rate; LQTS, long QT syndrome; HR_{Manual}, manual HR; HR_{Automatic}, automatic HR; PR_{Manual}, manual PR-interval; PR_{Automatic}, automatic PR-interval; QRS_{Manual}, manual QRS; QRS_{Automatic}, automatic QRS; QT_{Automatic}, automatic QT-interval; QT_{C-Automatic}, automatic corrected QT-interval; QT_{Threshold}, threshold QT-interval; QT_{C-Threshold}, threshold corrected QT-interval; QT_{Tangent}, tangent QT-interval; QT_{C-Tangent}, tangent corrected QT-interval.

manual QT_{C-Tangent} and QT_{C-Threshold} assessments remained above the cut-off value.

Results

Cohort characteristics

Of 1577 individuals overall, 1263 were eligible for the comparison between automatic and manual ECG measurements after exclusions (see [Supplementary material online, Figure S1](#)). The median age was 34 (interquartile range 35) years, and 55% were females ([Table 1](#)). The majority (90.3%) of ECGs was recorded with GE-Healthcare devices applying Bazett's correction formula. The remaining ECGs were recorded with devices from Welch Allyn (1.3%), AMEDTEC (1.2%), or other manufacturers (7.3%) (see [Supplementary material online, Table S2](#)). LQTS patients tended to be younger than controls and had longer mean QT-intervals and QT_C both applying the tangent and threshold methods ([Table 1](#)).

Automatic vs. manual QT-interval and QT_C assessments

In our overall cohort, mean QT_{Tangent}, QT_{Threshold}, and QT_{C-Tangent} were shorter than mean QT_{Automatic} and QT_{C-Automatic} ($P < 0.001$ for all), respectively. Mean QT_{C-Threshold} was similar to QT_{C-Automatic} ($P = 0.56$) ([Table 1](#)). By **overall agreement** analysis, QT-intervals determined by the tangent and threshold methods showed excellent agreement with QT_{Automatic} (ICC 0.94, 95% CI 0.87–0.96 and ICC 0.95, 95% CI 0.95–0.96, respectively; [Table 2](#)). Overall agreement with

QT_{C-Automatic} was weaker, both for QT_C values derived by the tangent (ICC 0.86, 95% CI 0.80–0.90) and the threshold methods (ICC 0.88, 95% CI 0.87–0.89; [Table 2](#)). Overall agreement analyses for QT_C correction formulas other than Bazett's formula are reported in [Supplementary material online, Table S3](#).

Pairwise agreement analysis

Pairwise agreement by Bland–Altman analyses revealed discrepancies between vendor-provided automatic and manual measurements. For QT_{Automatic} compared to QT_{Tangent}, the LoAs ranged from –34 to 61 ms (spread 95 ms). For QT_{Automatic} compared to QT_{Threshold}, the spread was marginally narrower (92 ms; –43 to 49 ms). For all comparisons, LQTS patients exhibited wider 95% LoAs than controls ([Figure 1; Table 2](#)). For QT_C in the overall cohort, QT_{C-Automatic} and QT_{C-Tangent} LoAs ranged from –43 to 65 ms (spread 108 ms), whereas QT_{C-Automatic} and QT_{C-Threshold} LoAs ranged from –53 to 52 ms (spread 105 ms). LQTS patients showed a larger variation in QT_C than controls ([Figure 1; Table 2](#)). The frequencies of individuals with absolute pairwise measurement differences ≤15 ms are presented in [Supplementary material online, Table S4](#). Pairwise agreement with different QT_C correction formulas is presented in [Supplementary material online, Table S3](#).

Cut-off-based discrepancy analysis

By cut-off-based discrepancy analysis, we identified ECGs where QT_{C-Automatic} either exceeded or undercut the respective cut-off compared to the manual results. For 480 ms as the clinically most relevant QT_C cut-off, 45.8% (82/179) of QT_{C-Automatic} results exceeded QT_{C-Tangent} findings. Of these, 90.2% (74/82) had a pairwise difference

Table 2 Pairwise ECG measurement agreement analysis

| | Overall cohort | | Controls | | LQTS | |
|-------------------------|------------------------------------|-----------------------------------|------------------------------------|-----------------------------------|------------------------------------|------------------------------------|
| | Automatic vs. manual | Novel vs. manual | Automatic vs. manual | Novel vs. manual | Automatic vs. manual | Novel vs. manual |
| | <i>n</i> = 1263 | <i>n</i> = 996 | <i>n</i> = 543 | <i>n</i> = 470 | <i>n</i> = 720 | <i>n</i> = 526 |
| | Mean diff. (lLoA to uLoA) | Mean diff. (lLoA to uLoA) | Mean diff. (lLoA to uLoA) | Mean diff. (lLoA to uLoA) | Mean diff. (lLoA to uLoA) | Mean diff. (lLoA to uLoA) |
| | ICC (95% CI) | ICC (95% CI) | ICC (95% CI) | ICC (95% CI) | ICC (95% CI) | ICC (95% CI) |
| HR (bpm) | 0 (−7 to 7) 0.99 (0.99–0.99) | 0 (−10 to 9) 0.99 (0.98–0.99) | 0 (−7 to 7) 0.99 (0.99–0.99) | 0 (−6 to 5) 0.99 (0.99–1.0) | −1 (−8 to 7) 0.99 (0.99–0.99) | 0 (−12 to 12) 0.98 (0.98–0.98) |
| PR (ms) | −1 (−25 to 23) 0.94 (0.93–0.95) | NA | −3 (−22 to 16) 0.95 (0.93–0.96) | NA | 0 (−27 to 27) 0.93 (0.92–0.94) | NA |
| QRS (ms) | 6 (−14 to 25) 0.81 (0.65–0.88) | NA | 5 (−15 to 25) 0.77 (0.614–0.85) | NA | 6 (−13 to 25) 0.83 (0.65–0.90) | NA |
| QT-interval (ms) | | | | | | |
| Tangent | 13 (−34 to 61) 0.94 (0.87–0.96) | 0 (−31 to 32) 0.98 (0.97–0.98) | 17 (−14 to 48) 0.91 (0.40–0.97) | 1 (−22 to 24) 0.97 (0.97–0.98) | 11 (−45 to 67) 0.93 (0.90–0.95) | −1 (−38 to 37) 0.97 (0.97–0.98) |
| Threshold | 3 (−43 to 49) 0.95 (0.95–0.96) | NA | 4 (−27 to 36) 0.95 (0.94–0.96) | NA | 2 (−52 to 57) 0.95 (0.94–0.95) | NA |
| QTc (ms) | | | | | | |
| Tangent (ms) | 11 (−43 to 65) 0.86 (0.80–0.90) | 0 (−36 to 36) 0.95 (0.94–0.95) | 15 (−24 to 53) 0.72 (0.34–0.85) | 2 (−29 to 32) 0.91 (0.90–0.93) | 8 (−55 to 70) 0.82 (0.78–0.85) | −1 (−41 to 39) 0.92 (0.91–0.94) |
| Threshold (ms) | 0 (−53 to 52) 0.88 (0.87–0.89) | NA | 1 (−37 to 39) 0.79 (0.75–0.82) | NA | −2 (−62 to 59) 0.83 (0.80–0.85) | NA |

In each table cell, upper line indicates mean difference and lower and upper limits of agreement based on Bland–Altman analyses [mean diff. (lLoA–uLoA)]; lower line indicates ICC and 95% CI. HR, heart rate; LQTS, long QT syndrome; LoA, limits of agreement; HR, heart rate; ICC, inter-class correlation coefficient; CI, confidence interval; NA, not available.

of $\geq \pm 15$ ms. QT_{CAutomatic} results less frequently [2.8% (30/1084)] undercut the 480 ms cut-off value, but 90.0% (27/30) exceeded ± 15 ms (see [Supplementary material online, Table S5](#); [Figure 2](#)).

Agreement analysis based on the automatic measurements from the novel algorithm

As a secondary analysis, we compared the automatic analysis using a novel algorithm with the manual QT-interval and QTc assessments. Mean QT-interval and QT_{CNovel} values were similar ($P = 0.54$ and $P = 0.59$, respectively). Also, overall agreement was very high. Bland–Altman pairwise agreement LoAs ranged from −31 to 32 ms (spread 63 ms) for QT-intervals and from −36 to 36 ms (spread 72 ms) for QTc ([Figure 3](#); [Table 2](#)). LoAs were narrower for controls than for LQTS patients. Absolute pairwise measurement differences for QT-interval/QT_{CNovel} are presented in [Supplementary material online, Table S4](#). Cut-off-based discrepancy results for QT_{CNovel} are shown in [Supplementary material online, Table S6](#); [Figure 2](#).

Area at risk for mis-adjudication

To visualize ranges prone to automatic vs. manual QTc misassessment in clinical application, we present [Figure 2](#). For QT_{C^{Tangent}}, from the practice guideline recommended 480 ms QTc cut-off, we deducted the lower (480 ms − 43 ms = 437 ms) and added the upper LoA (480 ms + 65 ms = 545 ms) in the overall cohort, resulting in a clinically intuitive QT_{CAutomatic}

range from approximately 440–540 ms at risk for mis-assessment. Within this range, 4.8% of QT_{CAutomatic} ECGs were ≤ 480 ms, whereas the pairwise QT_{C^{Tangent}} was > 480 ms. Conversely, 53.3% of QT_{CAutomatic} results exceeded 480 ms, whereas the pairwise QT_{C^{Tangent}} result was ≤ 480 ms. QT_{C^{Threshold}} resulted in a similar, clinically intuitive range of 430–530 ms. Using QT_{C^{Novel}}, the range prone to mis-assessment was 1.57 times narrower (445–515 ms) ([Figure 2](#); see [Supplementary material online, Table S7](#)).

Automatic vs. manual HR, PR, and QRS measurements

We also analysed HR, PR, and QRS. The mean HR, PR-interval, and QRS-duration were similar between automatic and manual measurements ([Table 1](#)), and the overall agreement analysis revealed a good to excellent agreement (ICC > 0.80 ; [Table 2](#)). Bland–Altman analyses indicated only a minimal pairwise variation for HR (LoAs from −8 to 7 ms) and small pairwise variations for PR-interval (LoAs from −25 to 23 ms) and for QRS-duration (LoAs from −14 to 25 ms) ([Figure 4A–C](#)).

Discussion

QT-interval and QTc are established markers of ventricular arrhythmia risk in clinical practice, but accurate determination is critical. Besides the standard of manual QT-interval assessment, for convenience,

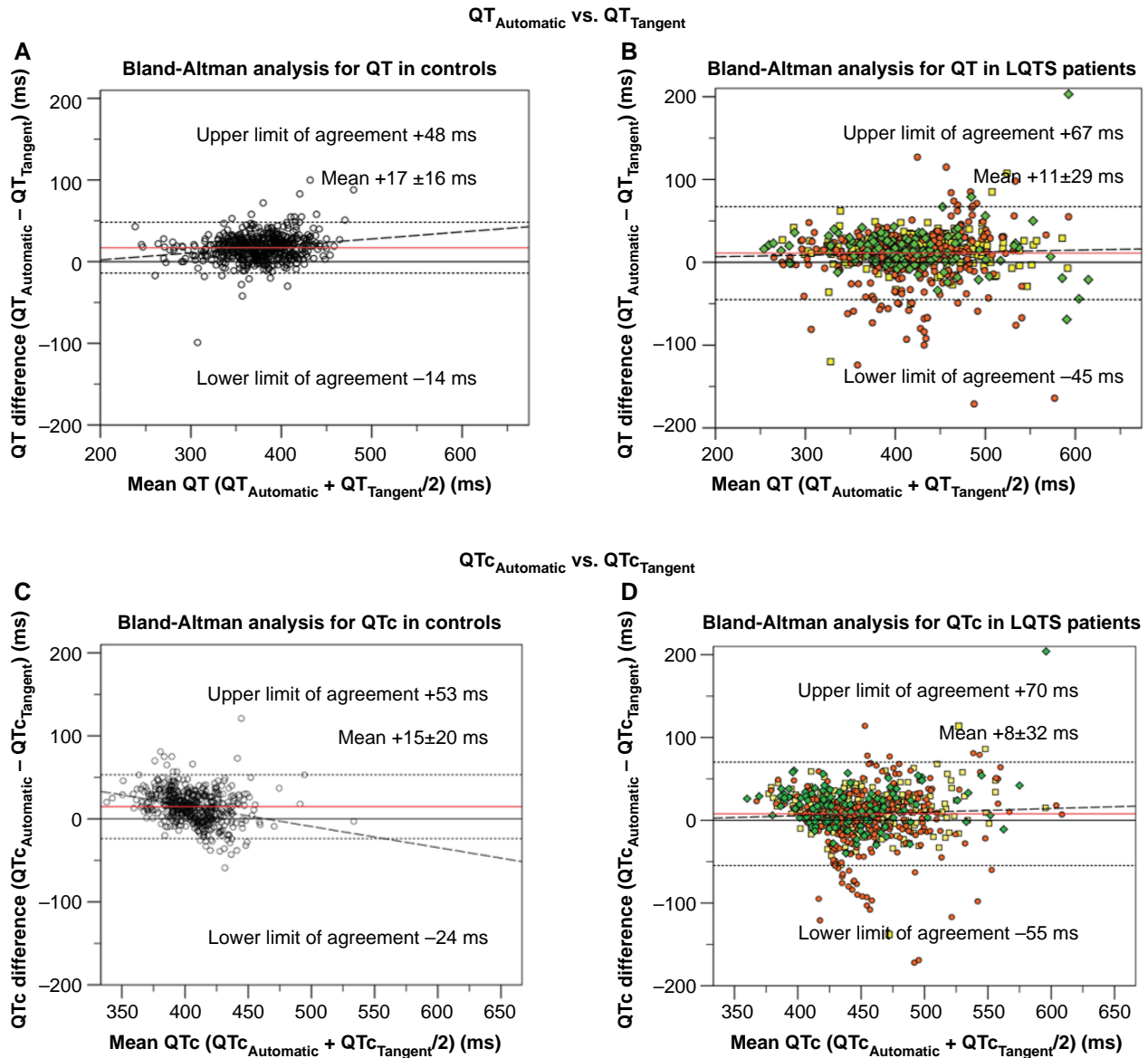


Figure 1 Bland–Altman analysis for pairwise automatic vs. manual QT-interval and heart-rate corrected QT (QTc) agreement. All panels display Bland–Altman analyses. Horizontal (red) lines indicate the mean difference between assessment methods. Horizontal dotted lines indicate the upper and lower limits of agreement. Dashed lines indicate the regression line of pairwise differences. (A) Pairwise agreement between automatic QT-interval (QT_{Automatic}) and tangent QT-interval (QT_{Tangent}) among controls. (B) Pairwise agreement between QT_{Automatic} and QT_{Tangent} among LQTS patients. (C) Pairwise agreement between automatic corrected QT-interval (QTc_{Automatic}) and tangent corrected QT-interval (QTc_{Tangent}) among controls. (D) Pairwise agreement between QTc_{Automatic} and QTc_{Tangent} among long QT syndrome (LQTS) patients. (E) Pairwise agreement between QT_{Automatic} and threshold method QT-interval (QT_{Threshold}) among controls. (F) Pairwise agreement between QT_{Automatic} and QT_{Threshold} among LQTS patients. (G) Pairwise agreement between QTc_{Automatic} and threshold method corrected QT-interval (QTc_{Threshold}) among controls. (H) Pairwise agreement between QTc_{Automatic} and QTc_{Threshold} among LQTS patients.

physicians frequently use automatic, vendor-provided measurements. In our cohort, enriched for aberrant QT-interval and QTc values, we systematically investigated the agreement of automatic and manual QT-interval and QTc assessments. We demonstrate that their pairwise agreement is highly discrepant, especially in the presence of aberrant QTc values and T-wave morphologies. The extent of discrepancy limits using automatic QT-interval/QTc values in clinical practice. Hence, we clearly suggest manual review of automatic QTc results, but most importantly for automatic QTc results between 440 and 540 ms.

Optimized automatic algorithms to determine QT-interval/QTc may improve pairwise agreement. Also, manufacturers may facilitate recapitulating their automatic QT-interval and QTc measurements by visualizing their measurement landmarks.

Automatic vs. manual measurements

The mean difference between automatic and manual measurement results considers the average of the entire cohort rather than the pairwise

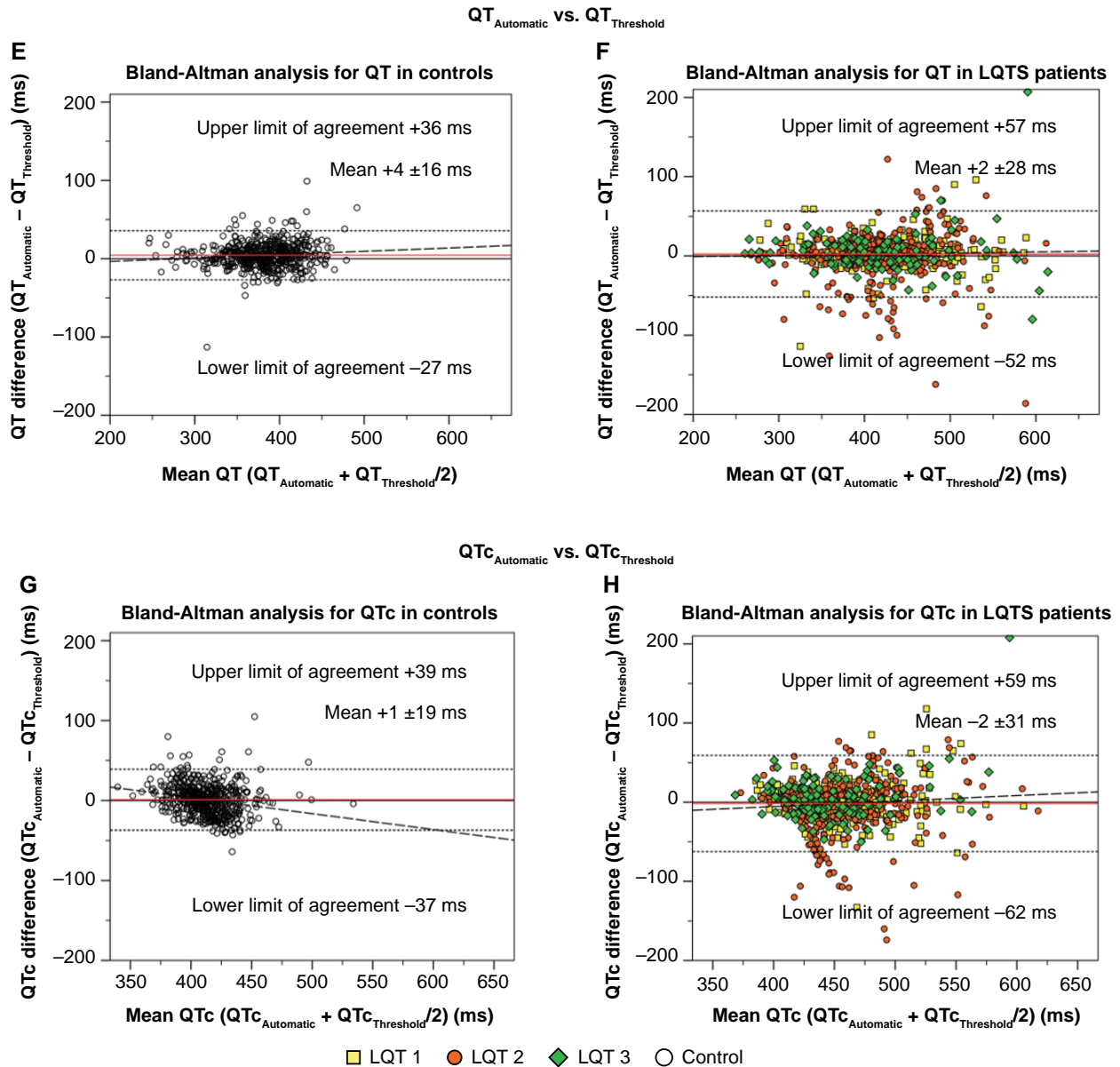


Figure 1 Continued

difference of individuals. Considering such cohort means, agreement between vendor-provided automatic and manual QT-interval assessment appears good. Yet importantly, by pairwise Bland-Altman analyses, we found a great variability between QT-interval and QTc assessments. The range covering 95% of the pairwise QT-interval measurements spans a wide 95 ms for QT_{Tangent} and 92 ms for QT_{Threshold}. For QTc_{Tangent} (108 ms) and for QTc_{Threshold} (105 ms), this spread is even wider. All pairwise comparisons thus exceed a degree of variation that is clinically acceptable.

Pairwise agreement between automatic and manual QT-interval assessments has been investigated before. A modestly sized study by Savelieva *et al.*³³ analysed 54 patients with hypertrophic cardiomyopathy and 70 controls. ECGs were interpreted by a single reader averaging ECG complexes in an individually chosen lead. A relevant

pairwise disagreement was identified with a 95% LoA spread of 70 ms in controls and of 55 ms in in cardiomyopathy patients. The smaller LoA spread in hypertrophic cardiomyopathy patients might be due to the less complex T-wave morphologies in these patients. In contrast, Hnatkova *et al.*³⁴ examined a large cohort of healthy individuals. Here, the 95% LoA spread was 10–30 ms, and 94–99% of ECGs exhibited absolute measurement differences ≤15 ms. These findings appear contradictory to our results. However, the authors studied ECGs recorded under highly standardized experimental conditions to compare versions of the same analysis algorithm.³⁴ Instead, we interpreted ECGs obtained in clinical care and thus submit that our study setting better reflects ECG analysis in everyday practice. Also, a ‘Thorough QT study’ reported pairwise Bland-Altman results,³⁵ yet in few healthy individuals without any overt ECG pathologies and

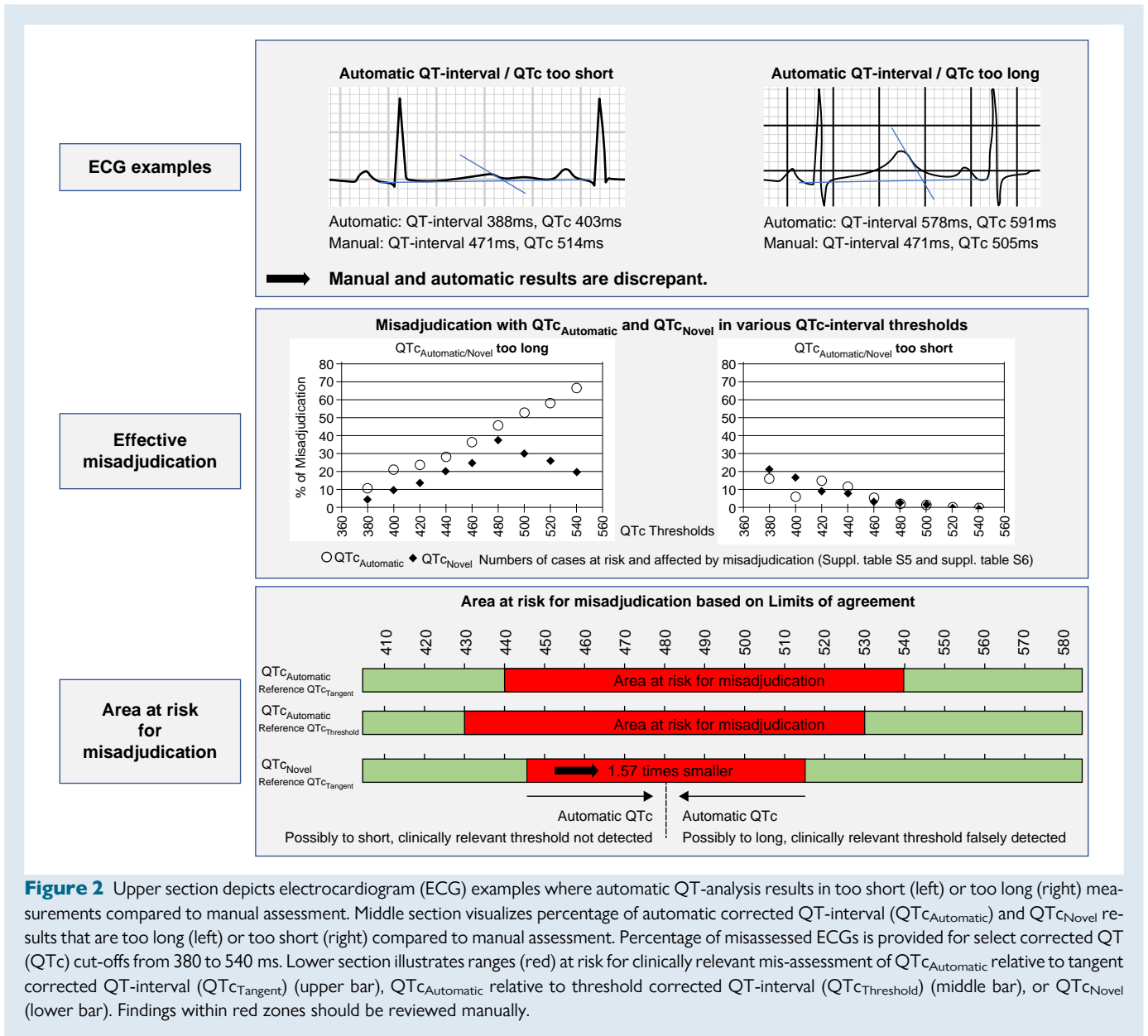


Figure 2 Upper section depicts electrocardiogram (ECG) examples where automatic QT-analysis results in too short (left) or too long (right) measurements compared to manual assessment. Middle section visualizes percentage of automatic corrected QT-interval (QTc_{Automatic}) and QTc_{Novel} results that are too long (left) or too short (right) compared to manual assessment. Percentage of misassessed ECGs is provided for select corrected QT (QTc) cut-offs from 380 to 540 ms. Lower section illustrates ranges (red) at risk for clinically relevant mis-assessment of QTc_{Automatic} relative to tangent corrected QT-interval (QTc_{Tangent}) (upper bar), QTc_{Automatic} relative to threshold corrected QT-interval (QTc_{Threshold}) (middle bar), or QTc_{Novel} (lower bar). Findings within red zones should be reviewed manually.

limited to an automatic QTc of ≤ 450 ms. Even in this very homogenous cohort, the LoAs were wide (± 32.3 ms). Also, the variability across different vendor provided QTc algorithms has been provided before. In a report by Kligfield et al.,³⁶ the pairwise differences of means of the QT interval were markedly smaller than in our study comparing automatic vs. manual ECG analyses.³⁶ Yet, also in the analysis by Kligfield et al.,³⁶ LQTS patients exhibited larger QT variability compared to normal individuals.

Clinical relevance

Regarding the clinical relevance of our findings, several aspects are important. First, we compared manual QT-interval and QTc results to vendor-provided automatic ones. Such automatic results are frequently used in clinical practice. We counter these easily accessible automatic results with two standardized manual methods, the tangent and threshold methods.²⁰ We further apply the most commonly used Bazett QTc

formula in our main analyses. For comprehensiveness, we also report our findings for other QT-interval correction formulas including the one by Fridericia. Importantly, we describe highly discrepant pairwise comparison findings for both QT-interval assessment methods. We thus believe that our discrepant findings are not solely explained by nuances of differing methodology.

Second, interpreting automatic QT-interval and QTc results without manual review may lead to incorrect and possibly consequential conclusions, whenever the length of QT-interval and QTc is of importance. An example is the QT-interval and QTc in the context of drug therapy given the knowledge that numerous drugs interfere with cardiac repolarization.¹⁴ Such drugs include antiarrhythmics like amiodarone, antibiotics like moxifloxacin, antidepressants like citalopram, and anti psychotics like quetiapine.¹⁴ We cannot comment on the performance of automatic QT-interval and QTc assessments on serial ECG recordings. Yet, a single incorrect QT-interval and QTc could lead to erroneous decisions in drug prescription. Similarly, an incorrect QT-interval

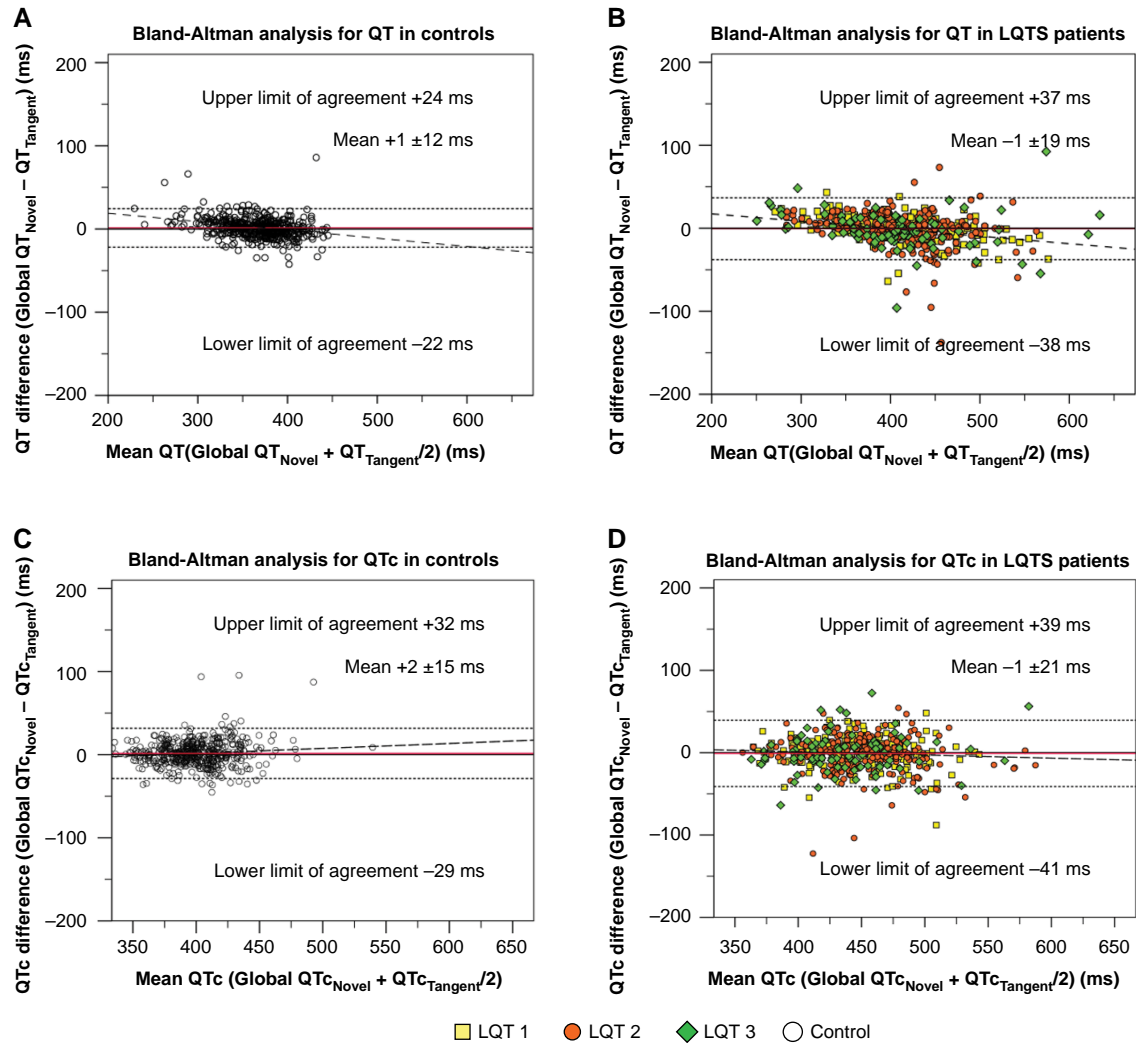


Figure 3 Bland–Altman analysis for pairwise automatic vs. manual QT-interval and corrected QT (QTc) agreement using a novel automatic algorithm. All panels display Bland–Altman analyses. Horizontal (red) lines indicate the mean difference between assessment methods. Horizontal dotted lines indicate the upper and lower limits of agreement. Dashed lines indicate the regression line of pairwise differences. (A) Pairwise agreement between QT_{Novel} and tangent QT-interval (QT_{Tangent}) among controls. (B) Pairwise agreement between QT_{Novel} and QT_{Tangent} among long QT syndrome (LQTS) patients. (C) Pairwise agreement between QTc_{Novel} and tangent corrected QT-interval (QTc_{Tangent}) among controls. (D) Pairwise agreement between QTc_{Novel} and QTc_{Tangent} among LQTS patients.

and QTc may incorrectly raise the suspicion of LQTS.³⁷ Diagnosing LQTS requires a comprehensive assessment.³⁸ Nevertheless, clinical practice guidelines suggest to at least consider a LQTS diagnosis when QTc is repeatedly ≥ 480 ms.^{16,17} Incorrect QTc assessment may hence result in misinterpreting such a clinically relevant cut-off. Considering the wide LoA range of discrepant QT-interval and QTc findings, we submit that both over- and underestimating QT-interval and QTc are serious challenges in clinical practice. We visualize this issue in Figure 2 and suggest a range where automatic QT-interval and QTc results warrant manual review.

Third, our cohort combines LQTS patients and controls. The variability between automatic and manual QT-interval and QTc assessments was larger among the former. An explanation may be challenging T-wave morphologies, including biphasic, notched, and low-amplitude T-waves, which are commonly present in LQTS

patients.^{39–43} Importantly, T-wave morphology is not typically assessed by automated algorithms, while T-wave morphology is an important denominator of repolarization pathology.³⁰ We thus strongly encourage a manual review of automatic QT-interval and QTc assessments in known or suspected LQTS patients or when a challenging T-wave morphology is present.

We encourage manual review of automatic QT-interval and QTc assessments. However, the advantages of confidently using automatic assessments in clinical routine are evident. Yet, this disposal of physicians' responsibility of manual assessment for the gain of convenience bears a risk of accepting incorrect automatic results. Aiming to minimize such negative effects, we have hence tested a recently developed, novel ECG analysis algorithm.²⁹ Applying this algorithm to our cohort, the discrepancy between automatic and manual QT-interval and QTc assessments was markedly smaller, narrowing the range recommended for

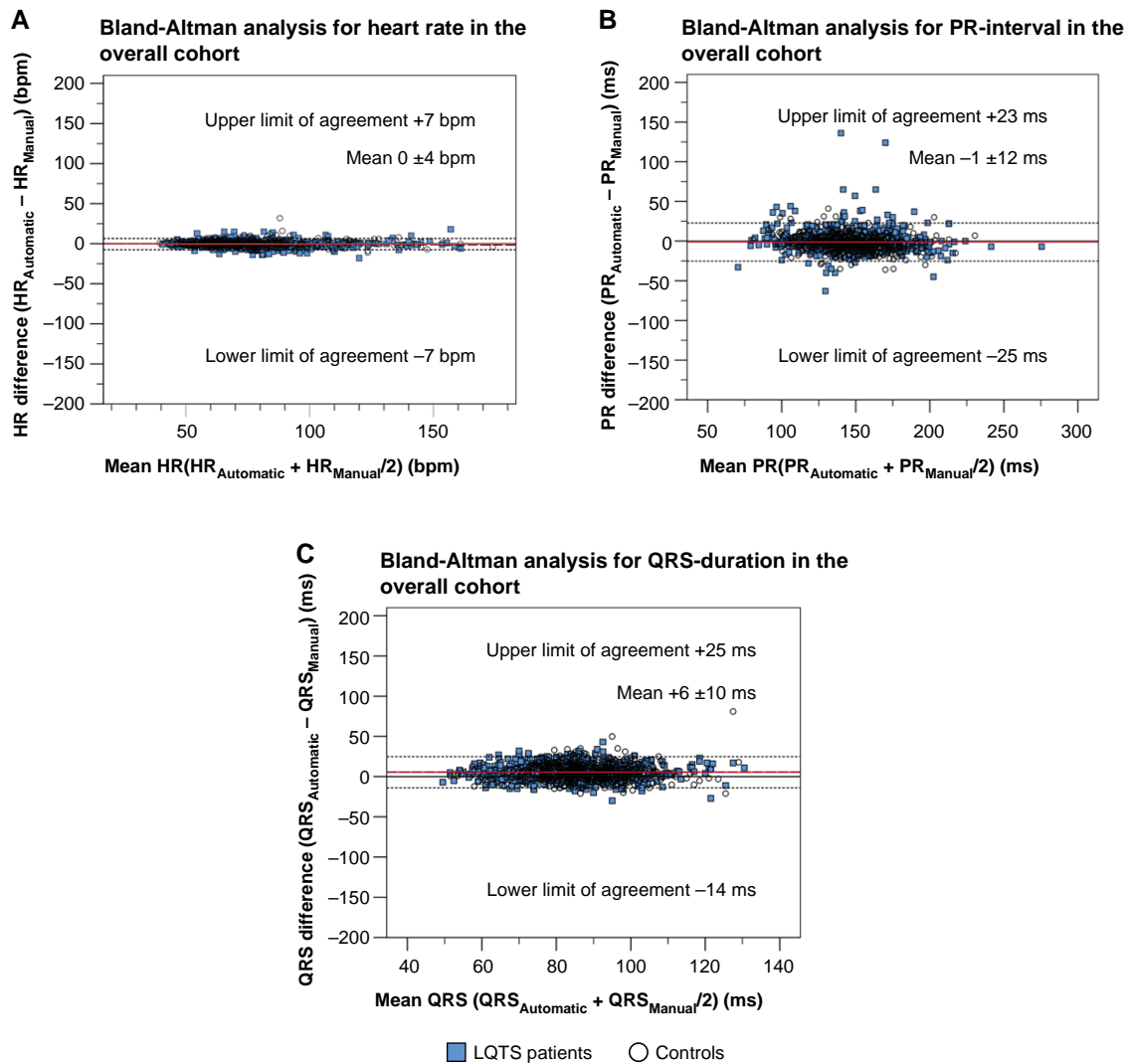


Figure 4 Bland–Altman analysis for pairwise automatic vs. manual heart rate, PR-interval, and QRS-duration agreement. All panels display Bland–Altman analyses. Horizontal (red) lines indicate the mean difference between assessment methods. Horizontal dotted lines indicate the upper and lower limits of agreement. Dashed lines indicate the regression line of pairwise differences. (A) Pairwise agreement for heart rate (HR) between automatic ($HR_{Automatic}$) and manual (HR_{Manual}). (B) Pairwise agreement for PR-interval between automatic ($PR_{Automatic}$) and manual (PR_{Manual}). (C) Pairwise agreement for QRS duration between automatic ($QRS_{Automatic}$) and manual (QRS_{Manual}).

manual review 1.57-fold compared with vendor-provided automatic measurements (Figure 2). Pending independent validation, we envision future improvements in automatic QT-interval measurements including the application of artificial intelligence will further narrow and eventually close the range for manual QTc reassessment. In the meantime, clinicians may additionally be supported by visualizations where commercial ECG recorders defined their measurements. We thus encourage manufacturers to routinely display such measurement landmarks.

Limitations

Several aspects require consideration. Most ECGs were recorded using the GE 12SL algorithm limiting transferability to other manufacturers. Importantly, QT-interval measurement methods and QTc correction formulas were not documented for all automatic ECGs. To reduce

bias, we have assessed several QT-interval correction formulas, while focusing on the clinically most relevant Bazett formula. Our cohort composition of LQTS patients and their genotype-negative relatives may not fully reflect the general population. However, most ECGs in clinical practice are not recorded in healthy general population individuals but recording is triggered by clinical need. Such need may arise from symptoms or from known pathologies. In both instances, pathologic ECG findings are prevalent. Hence, we intentionally chose our study composition to include a sufficient spectrum of abnormal QT-intervals. Moreover, with this selection we were able—as opposed to other studies with general population or healthy control ECGs—to establish cases vs. controls. Importantly, a yet unpublished comparison of our control ECGs with the population-based Maastricht Study indicated very good comparability. We thus consider our cohort composition a clear strength as it is enriched for challenging T-wave

morphologies encountered in clinical practice but not routinely encountered in the general population. Despite our large cohort size and the systematic assessment by three trained readers, independent validation may further increase their relevance.

Conclusion

In conclusion, pairwise agreement of vendor-provided automatic vs. manual assessments of QT-interval and of QTc is highly discrepant, independent of the QT-interval measurement method. Interestingly, we observed no large discrepancies for HR, PR-interval, and QRS-duration, indicating that QT-interval and QTc are more vulnerable to misassessment. Our data support that novel, transparent, automatic QT-interval algorithms may reduce discrepancies. Hence, manual review of vendor-provided automatic QT-interval and QTc assessments is critical and clearly recommended. As this may not always be feasible, a manual review should at least be considered for QTc between 440 and 540 ms, especially when T-wave morphologies are challenging.

Authors' contribution

The design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication were the sole responsibility of the authors.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: None declared.

Data availability

Data supporting the findings of this study are available upon reasonable request. Access to the data is subject to approval from the corresponding author and compliance with privacy regulations. Interested researchers can contact the corresponding author at msinner@med.lmu.de to request access to the de-identified dataset and [supplementary materials](#).

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