

BMJ Open Manual QT interval measurement with a smartphone-operated single-lead ECG versus 12-lead ECG: a within-patient diagnostic validation study in primary care

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ABSTRACT

Objective To determine the accuracy of QT measurement in a smartphone-operated, single-lead ECG (1L-ECG) device (AliveCor KardiaMobile 1L).

Design Cross-sectional, within-patient diagnostic validation study.

Setting/participants Patients underwent a 12-lead ECG (12L-ECG) for any non-acute indication in primary care, April 2017–July 2018.

Intervention Simultaneous recording of 1L-ECGs and 12L-ECGs with blinded manual QT assessment.

Outcomes of interest (1) Difference in QT interval in milliseconds (ms) between the devices; (2) measurement agreement between the devices (excellent agreement <20 ms and clinically acceptable agreement <40 ms absolute difference); (3) sensitivity and specificity for detection of extreme QTc (short (≤340 ms) or long (≥480 ms)), on 1L-ECGs versus 12L-ECGs as reference standard. In case of significant discrepancy between lead I/II of 12L-ECGs and 1L-ECGs, we developed a correction tool by adding the difference between QT measurements of 12L-ECG and 1L-ECGs.

Results 250 ECGs of 125 patients were included. The mean QTc interval, using Bazett's formula (QTcB), was 393±25 ms (mean±SD) in 1L-ECGs and 392±27 ms in lead I of 12L-ECGs, a mean difference of 1±21 ms, which was not statistically different (paired t-test (p=0.51) and Bland Altman method (p=0.23)). In terms of agreement between 1L-ECGs and lead I, QTcB had excellent agreement in 66.9% and clinically acceptable agreement in 93.4% of observations. The sensitivity and specificity of detecting extreme QTc were 0% and 99.2%, respectively. The comparison of 1L-ECG QTcB with lead II of 12L-ECGs showed a significant difference (p<0.01), but when using a correction factor (+9 ms) this difference was cancelled (paired t-test (p=0.43) or Bland Altman test (p=0.57)). Moreover, it led to improved rates of excellent (71.3%) and clinically acceptable (94.3%) agreement.

Conclusion Smartphone-operated 1L-ECGs can be used to accurately measure the QTc interval compared with simultaneously obtained 12L-ECGs in a primary care population. This may provide an opportunity for

Strengths and limitations of this study

- First study on the validity of QT interval measurements obtained with single-lead ECG smartphone recordings in a primary care population.
- The single-lead ECGs and the reference standard (12-lead ECGs) were captured simultaneously.
- Since QT interval measurements can only be conducted under optimal conditions, we included only high-quality ECGs.
- Using the tangent method for the manual measurements makes the measurements easy to perform, but may underestimate the QT interval.
- This study lacks automatic measurements with the 1L-ECG device (AliveCor KardiaMobile), which may be a useful addition for future studies.

monitoring the effects of potential QTc-prolonging medications.

INTRODUCTION

Frequently, physicians who carry out consultations will have to prescribe medications that may prolong the QT interval (QTI).^{1–3} QT prolongation increases the likelihood of the malignant ventricular arrhythmia ‘Torsade de Pointes’ and sudden cardiac death, particularly in the presence of risk factors, such as hypokalaemia, use of diuretics, anti-arrhythmic drugs or congenital long QT syndromes.^{4,5} Obtaining an ECG to measure and monitor QTIs is therefore clinically relevant. Although automated ECG interpretation including QTI measurements are available on most ECG machines, these may not be accurate and specialists prefer manual interpretation.⁶ Importantly, practical guidelines on QTI measurements and interpretation are available.⁷

Preferably, general practitioners (GPs) who make ECGs should be able to sufficiently measure and interpret these QTIs.⁸ However, the compliance of GPs to recommendations for ECG monitoring in patients on QT prolonging drugs is very low.⁹ Logistical challenges may present one hurdle, as not every general practice has the possibility to make a standard 12-lead ECG (12L-ECG) and obtaining 12L-ECGs during home visits can be challenging. As such, the recent introduction of handheld single-lead ECG (1L-ECG) devices may present a welcome solution. They allow immediate ECG recording and require minimal effort by holding a device with two hands for up to 1 min, without the need to undress and attach patches.^{10–12} More recently issued 1L-ECGs provide a smartphone-based technique for rhythm and interval registration. Of all CE certified and FDA approved devices, the AliveCor heart monitor is among those most extensively validated against 12L-ECGs as reference standard.¹³ Generally, the device has been studied for accurate detection of atrial fibrillation (AF).¹⁴ Validation studies in which the usability of QT times was assessed are, however, lacking.¹⁵ Only a handful of studies discussed QTI variations.^{10 16–23} Of those, only one assessed 1L-ECGs and 12L-ECGs simultaneously,²⁰ which may have accounted for interval variations in the studies who did not record simultaneously. Moreover, all of these studies reviewed selected patient populations (paediatric/cardiology/athletes), which made them less suitable for community-based populations.

In this study we therefore set out to validate a smartphone-operated 1L-ECG device for accuracy of QTI measurement with a simultaneously recorded 12L-ECG as reference standard in primary care.

METHODS

We followed the standards for reporting diagnostic accuracy (STARD 2015)²⁴ for uniform methodological reporting of our methods and findings. All participants provided written informed consent.

Study design

We conducted a cross-sectional, diagnostic validation study using ECG data from the 'Validation of a mobile bedside ECG Screening and diagnostic Tool for Arrhythmias in general practice' (VESTA) study, which included 222 patients from 10 participating general practices who underwent a standard 12L-ECG for any indication between April 2017 and July 2018. This was a diagnostic validation study that assessed the validity of 1L-ECGs for the detection of AF and rhythm and conduction abnormalities compared with simultaneously performed 12L-ECGs, assessed by blinded cardiologists, as a reference standard.¹⁴

In short, patients consulting their GP underwent a 12L-ECG based on routine medical care, simultaneously a 1L-ECG was obtained. A small capturing device containing two electrodes was held for 30 s between the fingers of both hands, corresponding with lead I of

Einthoven's triangle. The recordings of 1L-ECGs and 12L-ECGs were deidentified and stored in a electronic data capturing system (CastorEDC). Patients were at least 18 years old and provided informed consent. Haemodynamically unstable patients, patients with clinical suspicion of acute coronary syndrome, or with a pacemaker were excluded. Baseline variables included demographics and cardiovascular history and medication. Two independent cardiologists screened the 1L-ECGs and 12L-ECG recordings in random order for arrhythmias or conduction abnormalities. A detailed description of the study design is published elsewhere.¹⁴

Patient involvement

No patients were asked for input in the creation of this article.

AliveCor single-lead ECG

KardiaMobile (AliveCor, Mountain View, CA, USA) is a smartphone-connected, 1L-ECG device that displays ECG-recordings in real time (30 s) using a smartphone application. The recording of 1L-ECGs coincides with a 10 s recording of lead I of 12L-ECGs. The AliveCor device has a sampling rate of 300 /s resulting in a temporal resolution of 3.3 ms. We used the online PDF version of the 1L-ECGs with 200% magnification and a paper speed of 25 mm/s to measure the QTI (figure 1).

ECG selection

We excluded patients with incomplete or non-overlapping ECG pairs. Since the QTI can only be measured under optimal conditions, we excluded ECGs with poor technical quality as assessed visually. Patients with no measurable interval of five consecutive RR-complexes were excluded, as this would impede a valid heart rate assessment. ECGs with AF, bundle branch-blocks (BBB) or other arrhythmias were also excluded because unforeseen changes in the repolarisation may occur if the depolarisation changes, which makes interpretation difficult. Furthermore, most QTc formulas are not suitable to calculate the QT time in other rhythms than a stable sinus rhythm.²⁵

Reading single-lead ECG, as index test

Two independent readers (LB and LPvA) manually measured heart rate, QRS interval and QTI of the 1L-ECGs without any knowledge of clinical data. All measurements required a motion artefact and ectopic beat-free section of five consecutive RR-complexes, as recommended.^{7 25 26} We measured the heart rate by taking the average of this section. A baseline was drawn between the T-wave and the next P-wave of the five RR-complexes, in case of high variability the PQ segments were used. We measured the first five QRS and QT complexes to calculate the mean QRS interval and QTI. The QRS interval was computed from QRS onset to the J-point, the point where the sharp deflections of the QRS complex merge into the ST-segment. Finally, we determined the QTI using the tangent method.^{7 27} We drew a tangent to the steepest slope of the last limb of the T-wave until it crosses the baseline

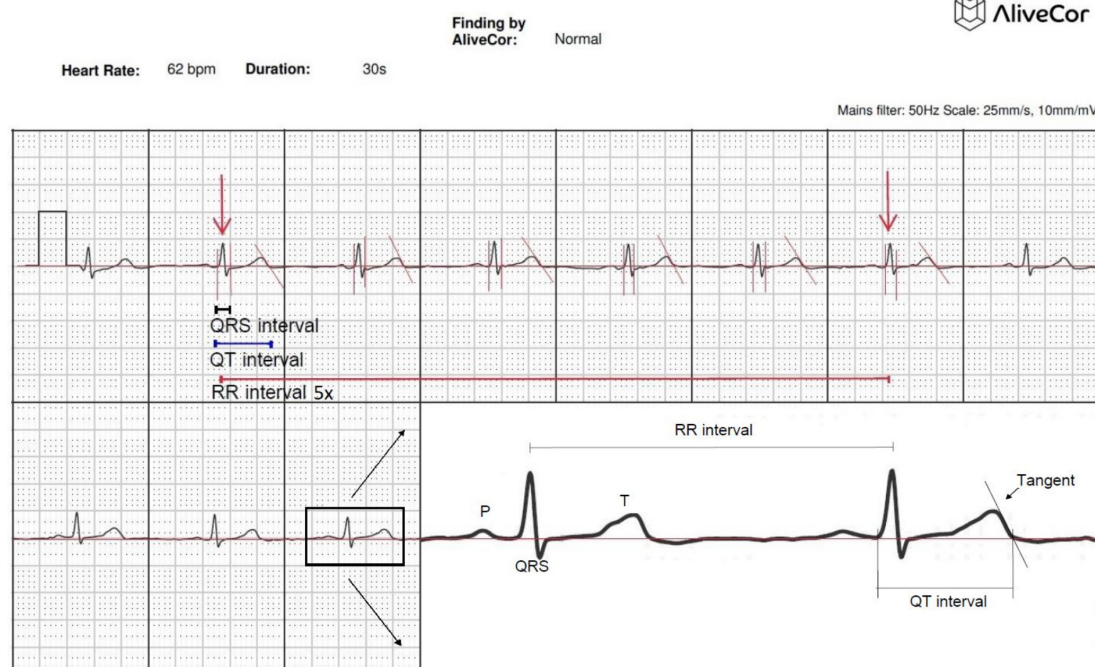


Figure 1 A single-lead ECG with RR, QRS and QT measurements using a tangent.

(see figure 1). When the T-wave consisted of two positive segments or was biphasic, the readers chose the end of the highest wave. U-waves that occurred after the T-wave were not incorporated in QT measurement.⁷ In cases where disagreement about the end of the T-wave could not be solved through consensus, a third ECG reader (REH) was consulted.

Reading 12-lead ECGs, as reference standard

The same two independent readers manually measured heart rate, QRS and QT of randomly ordered 12L-ECGs with a paper speed of 25 mm/s. Blinded for clinical data, they followed the same procedure as described with the 1L-ECGs for setting the baseline, QRS and QT measurements (lead I and II) and frequency (lead II). We chose lead I and II, although QTIs are preferably measured in lead II, a 1L-ECG most closely resembles lead I of the 12L-ECG, and lead I has been proposed as an alternative to lead II in case lead II is uninterpretable.⁷ Prior work showed that when manually assessing QTc intervals, 1L-ECG measurements more closely resemble the 12L-ECG's lead I than lead II.¹⁷

The QRS and QT measurements were performed in the first five P-QRS-T complexes of lead II and in the number of P-QRS-T complexes present in lead I.⁷ If one of the leads I or II was not measurable due to poor baseline, poor T-top quality or premature ventricular or atrial contraction (PVC/PAC), the remaining leads were used for further analysis. A third reader was consulted when disagreement between the two readers about the end of the T-wave could not be solved through consensus.

QT correction

We corrected the QTI for heart rate.^{7 25} The primary correction method for heart rate was Bazett's formula ($QTcB: QT/RR^{1/2}$). We also presented Framingham's formula ($QTcFra: QT+0.154 (1-RR)$) as secondary correction method.^{28 29}

Outcomes of interest

The primary outcome of interest was the absolute mean difference in QTI in milliseconds (ms) between pooled 1L-ECG and 12L-ECG measurements. The secondary outcome was the within-patient interdevice agreement, defined as excellent agreement (<20 ms difference) and clinically acceptable agreement (<40 ms difference) between 1L- and 12L-ECG QTc measurements. Cut-offs for this outcome were based on prior work which showed a 20 ms median QTc difference between 1L- and 12L-ECG, with 20% of all measurements resulting in 40 ms QTc dispersion.³⁰ The same cut-off for excellent agreement was also used in a prior comparison of manual QTc measurements between AliveCor 1L-ECGs and 12L-ECGs.¹⁷ The tertiary outcome of interest was agreement in detecting a clinically relevant short and long QTc interval ('extreme QTc'), defined as ≤ 340 ms or ≥ 480 ms, respectively, in both men and women.³¹

Statistical analysis

We reported continuous data as mean \pm SD and categorical variables as numbers and percentages. Statistical significance in all analyses was assessed at the 0.05 level. The statistical analysis was performed using IBM SPSS software.

We used three different methods to assess the diagnostic accuracy of QT measurements of 1L-ECGs compared with 12L-ECGs:

1. Primary outcome: we assessed statistical difference using the paired t-test and Bland Altman methods. We calculated the absolute mean difference, SD and 95% CI for heart frequency, QRS, QT and QTc intervals. We plotted the difference with 95% CI of the two measurement techniques against the mean. All of these tests were conducted for QTcB and QTcFra. We expected that a minimum of 63 patients would have to be included to be sufficiently (80%) powered with 5% chance of type I errors, assuming that QTis (as continuous variable, in ms) on 1L-ECGs would deviate up to 20 ms from 12L-ECGs with a SD of 40 ms. We based these assumptions conservatively on a prior study on manually assessed QTc difference between AliveCor 1L-ECG and 12L-ECG.¹⁷
2. Secondary outcome: we presented the percentage of QTc comparisons resulting in excellent and clinically acceptable agreement between 1L-ECG and 12L-ECG leads I and II.
3. Tertiary outcome: We presented 2×2 contingency tables for the presence or absence of extreme QTc intervals on 1L- versus 12L-ECG leads I and II, and determined the sensitivity and specificity of detecting an extreme QTc value on 1L-ECGs with 12L-ECGs as reference standard.

Finally, in case of a significant discrepancy between 12L-ECG measurements (lead I or II) and 1L-ECGs, we explored whether such a difference may have been due to systematic differences in assessment between lead I and II. We developed a correction tool by adding the difference between the QT measurements of 12L-ECGs to the 1L-ECGs, and then reassessed agreement between 1L-ECG and 12L-ECG using the newly acquired correction factor.

RESULTS

Between April 2017 and July 2018, 222 eligible patients were included. We excluded 13 patients (5.9%) for incomplete or non-overlapping ECG-pairs. After visual inspection of the 1L-ECGs and 12L-ECGs, 84 patients (37.8%) were excluded due to poor technical quality (n=25), no measurable heart rate (n=23), no sinus rhythm (n=25) or BBB (n=11). The ECG related exclusion criteria separated for 1L- and 12L-ECGs are listed in online supplemental table 1. The final study population consisted of 125 patients, with 250 simultaneously obtained ECGs, as shown in figure 2. In 7 of the 125 included ECG pairs, one of the leads I or II was excluded due to poor baseline or T-top quality, or due to PVCs/PACs causing arrhythmia. The remaining leads were used for further analysis (see figure 2 for participant flowchart).

Mean age of included patients was 61±14 years, half of patients (n=62, 49.6%) were female. One ECG was obtained because new medication (verapamil) was started, the other ECGs were made because of symptoms (n=61) or were

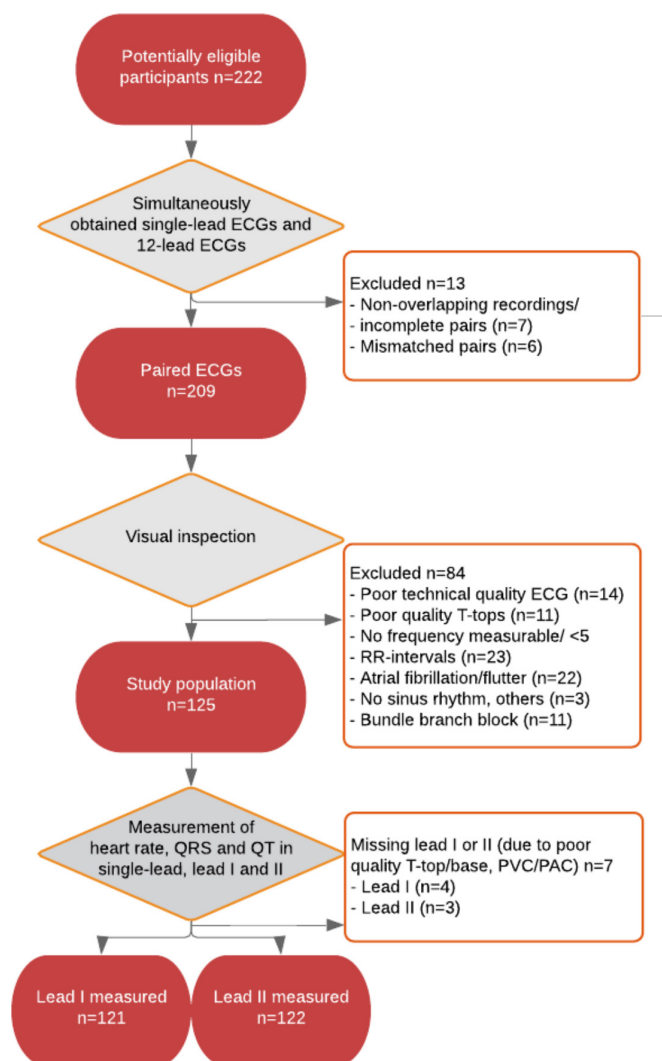


Figure 2 Flow of participants and exclusion criteria. PAC, premature atrial contraction; PVC, premature ventricular contraction.

protocol driven (n=63). Regarding cardiovascular medication, 12.0% of the patients used calcium channel blockers (n=15) and 15.2% used beta-blockers (n=19). Baseline characteristics of the study population are shown in table 1.

QTc differences in milliseconds

As shown in table 2, the mean QTcB interval was 393±25 ms in 1L-ECGs and 392±27 ms in lead I of the 12L-ECGs, with a mean difference of 1±21 ms. Comparing QTcB of 1L-ECGs with those of lead II of 12L-ECGs showed a mean difference of 8±22 ms. Table 2 additionally lists the mean and SD of heart rate, QRS and QT of all leads. Comparisons using Framingham's formula resulted in similar differences between 1L-ECG and lead I and II of 12L-ECGs (online supplemental tables 2 and 3).

Mean QT and QTcB comparison showed no significant difference (p=0.94 and p=0.51, respectively) between 1L-ECG and lead I. However, QT and QTcB measurements in 1L-ECGs differed significantly compared with lead II (p<0.01). There were no statistically significant differences in the comparisons of mean heart rate and

Table 1 Baseline characteristics of the VESTA QTc study population (n=125)

Variable	Subcategory	Mean, SD	Number (n=)	Percentage (%)
Age (years)		61±14		
Gender (female)			62	49.6
Obesity (BMI >30 kg/m ²)			29	23.2
Smoking (current)			25	20.0
Alcohol abuse			6	4.8
Hypertension			44	35.2
Diabetes			42	33.6
Hypercholesterolaemia			33	26.4
Atrial fibrillation			3	2.4
Other arrhythmias			5	4.0
Bradycardia			26	11.7
Coronary heart disease			9	7.2
TIA or ischaemic stroke			7	5.6
Valvular heart disease			2	1.6
Heart failure			1	0.8
Chronic obstructive pulmonary disease			15	12.0
Peripheral vascular disease			12	9.6
Chronic renal failure			11	8.8
eGFR of patients with chronic renal failure (mL/min/1.73 m ²)		51±5		
Medication	Sodium channel blocker		0	0.0
	Beta blockers		19	15.2
	Potassium channel blocker		0	0.0
	Calcium channel blocker		15	12.0
	Digoxin		0	0.0

BMI, body mass index; eGFR, estimated glomerular filtration rate; TIA, transient ischaemic attack; VESTA, Validation of a mobile bedside ECG Screening and diagnostic Tool for Arrhythmias in general practice.

QRS difference between the three analysed leads (see table 3). The Bland Altman analysis detected no significant proportional bias ($p=0.23$) of QTcB on 1L-ECG versus lead I (see online supplemental figure 1).

There were no significant differences between 1L-ECGs when looking at genders separately. The males and females within our population showed similar outcome measurements between 1L-ECGs (385 ± 26 ms and 401 ± 20 ms, respectively) and lead I (383 ± 28 ms and 400 ± 24 ms, respectively). In online supplemental table 4, heart rate, mean QT, QRS and QTc are listed for males and females.

Within-patient agreement between 1L-ECG and 12L-ECG

There was excellent agreement of QTcB in 66.9% of 1L-ECGs compared with lead I, as illustrated by cases within the green lines in figure 3. Of the measurements, 93.4% were within the limits of clinically acceptable agreement, as illustrated by cases within the red lines in figure 3. Comparing uncorrected QT resulted in a higher degree of excellent agreement (71.9%) as well as acceptable agreement (95.9%) than with QTcB.

Agreement in detecting clinically relevant extreme QTc values

In comparing 1L-ECG with 12L-ECGs as reference for detecting extreme QTcB values, the sensitivity and specificity for extreme QTcB in 1L-ECGs with lead I as reference were 0% and 99.2%, respectively (see online supplemental table 5 for 2×2 contingency tables for QTcB as well as QTcFra analyses). As shown in figure 3, the majority of cases where 1L-ECG and lead I measurements disagreed on assessing a case as extreme (indicated as blue dots outside of the limits for short and long QTcB, in orange) was within the clinically acceptable agreement between the two devices. Assessing QTcB for 1L-ECGs compared with lead II gave similar specificity (99.2%), with inability to calculate the sensitivity due to the absence of extreme cases on lead II.

Correction of single-lead QTc

As shown above, the QTc-interval of 1L-ECGs differed significantly from the QTc-interval of lead II of 12L-ECGs. The mean QTcB of lead I of the 12L-ECGs was 9 ± 17 ms (median=9 ms) shorter than in lead II. We performed a new analysis comparing 1L-ECGs with lead II while adding

Table 2 Comparison of the mean heart rate, QTcB, QT and QRS in single-lead ECGs versus leads I and II of 12-lead ECGs

	Single-lead	12-lead ECG	
		Lead I	Lead II
Heart rate (/min)			
n	125		125
Mean	73		72
SD	13		13
QRS (ms)			
n	125	121	122
Mean	85	83	84
SD	8	10	10
QT (ms)			
Mean	360	360	369
SD	29	33	32
QTcB (ms)			
Mean	393	392	401
SD	25	27	26

QTcB, corrected QT interval by Bazett's formula.;

9 ms to the QTc of 1L-ECGs. Comparing the QTc +9 ms of 1L-ECGs with lead II showed a non-significant difference of both the t-test ($p=0.43$) and Bland Altman ($p=0.57$). There were now 71.3% of cases with excellent agreement, and 94.3% with clinically acceptable agreement between 1L-ECG and lead II. The specificity using the cut-off values for detection of short or long QTc was now 100%, with inability to calculate the sensitivity due to absence of extreme cases on lead II.

DISCUSSION

Smartphone-operated 1L-ECGs showed good diagnostic accuracy for QTI measurement versus concomitantly obtained 12L-ECGs in a primary care population, as assessed by a low absolute mean QTc difference and high rate of cases with excellent and clinically acceptable

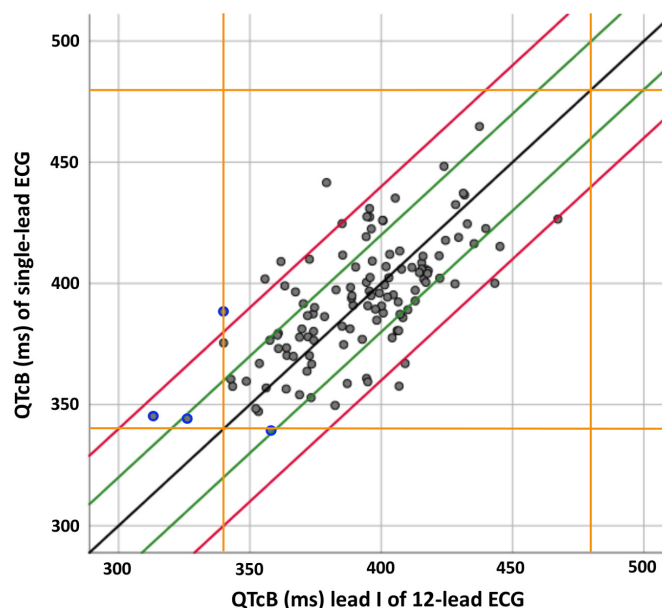


Figure 3 Scatter plot of measurement agreement of single-lead ECGs and lead I of 12L-ECGs, using QTcB ($n=119$). QTcB, corrected QT interval by Bazett's formula.

interdevice agreement. In detecting clinically significant extreme QTc intervals, however, 1L-ECG showed poor sensitivity in this low-prevalent population. The degree of agreement between the QTc of 1L-ECGs was higher when compared with lead I than compared with lead II of 12L-ECGs, with QTc intervals of 1L-ECGs being significantly shorter compared with lead II. The use of a correction factor obtained by adding the QTc difference between leads I and II of the 12L-ECG to 1L-ECG QTc values led to improvement of the comparison between 1L-ECG and lead II. Overall, these results suggest that smartphone-obtained ECGs can be used for QTI assessment in primary care, however caution is warranted in cases where an extreme QTI is suspected.

Strengths and limitations

This study represented primary care patients who underwent ECG for any clinical indication as assessed by local

Table 3 Comparing single-lead ECGs with leads I and II of 12-lead ECGs in paired samples

		Paired differences							
			Mean diff.	SD mean	SE mean	95% CI of diff.		T	Sig. (2-tailed)
						Lower	Upper		
Heart rate (/min)	Single-lead vs	Lead II	0.79	5.36	0.48	-0.16	1.74	1.65	0.10
QRS (ms)	Single-lead vs	Lead I	1.55	11.35	1.03	-0.50	3.59	1.50	0.14
		Lead II	1.13	11.36	1.03	-0.91	3.17	1.10	0.27
QT (ms)	Single-lead vs	Lead I	0.13	19.13	1.74	-3.57	3.31	0.07	0.94
		Lead II	9.39	20.99	1.90	-13.16	-5.63	4.94	<0.001
QTcB (ms)	Single-lead vs	Lead I	1.29	21.32	1.94	-2.55	5.12	0.66	0.51
		Lead II	7.78	21.89	1.98	-11.70	-3.85	3.92	<0.001

diff., difference; QTcB, corrected QT time by Bazett's formula; Sig. (2-tailed), two-tailed significance of t-value; T, t-value.;

GPs. The study was sufficiently powered, with almost double the number of participants ($n=125$) needed according to the power analysis ($n=63$). To the best of our knowledge, this is the first study with simultaneously obtained 1L-ECGs and 12L-ECGs in a general population, comparing manual QT measurements. Through simultaneous registration and subsequently excluding non-overlapping ECGs, we limited the risk of interval variation. This differentiated the current study from earlier studies.^{10 16 17 19} Finally, the results were obtained by blinded assessment and standardised interpretation of the randomised 1L-ECGs and 12L-ECGs.

There were multiple limitations. First, we had to exclude a substantial number of patients. The main reason for exclusion was GPs using 12L-ECG devices without a 10 s lead II strip or with poor quality. In 1L-ECGs, exclusion was mostly due to poorly measurable T-waves. This indicates the challenges of QT measurements in 1L-ECG as there is no alternative lead to measure in the absence of a steady baseline or evident T-waves. Second, the 12L-ECGs were performed using different devices. Since sampling rates of the recorders were not recorded in VESTA, it is not sure how this may have affected our conclusions. Third, automatic QT measurements for the 1L-ECGs were absent from the data set. At time of 1L-ECG recordings in the VESTA study, the KardiaMobile did not provide automatic interval measurements. Since the raw data are stored on AliveCor servers, our group was unable to analyse raw data using external software or methods proposed elsewhere.³² This prevented a comparison of automatic measurements against manual measurements in 1L-ECGs as used in other studies, and as is common clinical practice.^{10 17} We do note that manual QT measurement has been recommended over automatic assessment.⁶ Fourth, we were only able to assess the 1L-ECG derived through handheld recording—comparable to lead I of the 12L-ECG—while QT measurement is historically recommend to be performed based on lead II.⁷ Authors have proposed a lead II-like measurement with the AliveCor by placing its left-sided sensor on the knee rather than the left hand.¹⁶ Such measurements were however absent from the VESTA study data.¹⁴ Since we were aware of this limitation, we added the analysis on a correction factor for lead II comparison, which showed improved innerobserver agreement. Further research is required, however, to externally validate the clinical use of this correction factor. Fifth, the VESTA baseline data did not specifically include QT prolonging medication and medical history as the study was mainly aimed at AF detection. Finally, the sample included a low number of extreme QTc cases. This resulted in a major limitation in interpreting the sensitivity and predictive value of QTc assessment on 1L-ECG, as well as in generalising the results of our analyses to more high-risk populations for whom the use of a mobile 1L-ECG may be especially relevant. We have tried to cope with this limitation by providing the Bland Altman plot and p-value where we saw no indication for more severe disagreement between

1L-ECG and 12L-ECG towards the clinical extremes of QTc range. Further research is however needed to assess the validity of 1L-ECG for diagnosing extreme QTIs in primary care patients at higher risk of clinically relevant extreme QTc values.

Comparison with prior studies

Only a limited number of studies have previously evaluated the accuracy of QTc interval assessment using 1L-ECGs with 12L-ECGs as reference standard. Earlier validation studies used different smartphone-operated 1L-ECG devices, AliveCor^{10 17 20} and ECG Check.¹⁹ In line with prior studies, our work showed that the QT and QTc intervals in 1L-ECGs more closely resembled those in lead I of the 12L-ECGs. The mean QTcB of our population (393 ± 25 ms) was comparable to the healthy volunteers (398 ± 3 ms) of Garabelli *et al.*¹⁷ The difference in QTcB measurements between lead I of 12L-ECGs and 1L-ECGs (1 ± 21 ms) in our work also corroborates with Garabelli *et al.* (4 ± 11 ms),¹⁷ but had been much higher in another previous study on the AliveCor versus 12-lead ECG.¹⁰

Our comparison of lead II with 1L-ECGs showed a significant difference. Haverkamp *et al.*¹⁹ also demonstrated a significant difference in QTc, although it was not clear whether this involved lead I or II. In contrast, Garabelli *et al.*¹⁷ observed no significant differences between 1L-ECGs and any of the leads of a 12L-ECG. Only the QTI and corresponding QTcB in lead II showed a significant difference from 1L-ECGs. This implies that heart rate and QRS interval had no significant influence. Similar to Haberman *et al.*¹⁰ our study revealed smaller differences between 1L-ECGs and 12L-ECGs in heart rate and QRS, than in QT and QTc.

Garabelli *et al.* reported 72% of their QTc times to be in excellent agreement.¹⁷ Our percentages were similar for QTI (71.9%). After QTI correction, our percentages were slightly lower for QTcB (66.9%). We chose to add the category of clinically acceptable agreement as well based on previous work where QTc difference between devices remained <40 ms in 80% of cases.³⁰ We were aware that a difference of 40 ms between 1L-ECG and 12L-ECG may have a consequence for clinical assessment when occurring near the limits of long or short QT, for example, on whether or not dofetilide can be started. We therefore reported on the cases where interdevice disagreement resulted in different clinical conclusions, and what proportion of such cases had <40 or even <20 ms difference between the devices.

Consistent with Viskin *et al.*³³ our results on detecting clinically relevant extreme QTc values (≤ 340 or ≥ 480 ms) showed longer QTc intervals measured in women than in men. However, the number of cases with abnormal QTI in our sample was limited, and this has likely limited the ability to validly compare these results to previous work.

QT interval correction

We used Bazett's formula for QTc calculation since it is the most commonly used formula. In addition, we

presented the results of Framingham's formula in the supplemental material since this method was reported to be superior for rate correction.^{34 35} QTcB showed lower rates of excellent and clinically acceptable agreement than QTcFra in our analyses, which could indicate that the correction of heart rate by Bazett had a negative effect on the agreement. VanderBerk *et al* also concluded that Framingham's linear formula showed better results in QT-correction. A second difference between the QTc formulas concerned the Bland Altman method. Despite corresponding paired t-tests, this method presented a significant difference using QTcFra and no significant difference using QTcB. This should indicate correct measurement of the QTcB of 1L-ECGs compared with lead I and minor measurement differences between the two when using QTcFra. We were not able to identify any other explanation for this difference than the formula itself.

Implications for clinical practice and future directions

QT measurement is an essential part of medicine, given the risk of ventricular arrhythmias in short or prolonged QTc time. Unfortunately, QT measurements are challenging as automatic measurements can overestimate the QTc interval^{35 36} and manual measurements are difficult to perform and to interpret for physicians.³⁷ Considering that conventional QT measurements are cumbersome, the use of a 1L-ECG could lower the threshold to perform QT measurements in daily practice. This simplicity is supported by Garabelli *et al*¹⁷ who stated that using the two-handed technique in 1L-ECGs is perhaps the easiest method to obtain an ECG. Likewise, young subjects preferred 1L-ECGs over 12L-ECGs,¹⁰ with an increasing need for assistance in elderly.¹⁹ Therefore, similarity between the QTc of 1L-ECGs and 12L-ECGs shown by our results is relevant for the potential use of easy-to-perform measurement equipment in clinical practice. Here, the use of an automatic algorithm for QTc measurements in 1L-ECGs would make the use even more practical. Further research could focus on the validity and use of automatic interval assessment in 1L-ECGs. An important point to mention here is that the 1L-ECG can be considered an easy method to use, but the ECG must be of a good quality to measure the QT time. The user will have to look at this critically, because it is not possible to resort to another lead, as is the case with a 12L-ECG.

The use of QT time influencing medication poses a risk, just as patients with underlying congenital long QT syndrome are exposed to this risk as well.⁴⁵ QT measurements with 1L-ECGs could contribute to the implementation of a standard baseline measurement and a second measurement after the start of medication. This could improve timely notification of a potentially fatal condition. In addition, the 1L-ECG could potentially assist in the initiation of various antiarrhythmic drugs, such as dofetilide or sotalol, which currently requires extensive clinical monitoring. Prior work has already showed the

potential of using AliveCor for this purpose in newly treated dofetilide patients.¹⁶

Future work could focus on examining cost-effectiveness and the best way to implement 1L-ECGs in primary care. Such studies may concentrate on the measurement and interpretation of QTc times in 1L-ECGs by GPs. Based on Postema *et al*,⁸ we expect that even inexperienced ECG readers will be able to accurately distinguish normal and extended QTc times when using the tangent technique. However, this will require further research on the best formulas for QT correction and suitable cut-off values for QTc time in 1L-ECGs.

CONCLUSION

Rhythm strips obtained from AliveCor's 1L-ECGs can be used to accurately measure the QTc compared with simultaneously obtained 12L-ECGs in a cohort of primary care patients. However, before 1L-ECGs can be implemented for QT measurement in primary care, further work is needed on the measurement and interpretation of the QT(c) interval by GPs, and to extend validation to primary care populations at higher risk of clinically relevant QTc extremes.

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REFERENCES

- Aström-Lilja C, Odeberg JM, Ekman E, *et al*. Drug-Induced torsades de pointes: a review of the Swedish pharmacovigilance database. *Pharmacoepidemiol Drug Saf* 2008;17:587–92.
- Poluzzi E, Raschi E, Moretti U, *et al*. Drug-Induced torsades de pointes: data mining of the public version of the FDA adverse event reporting system (AERS). *Pharmacoepidemiol Drug Saf* 2009;18:512–8.
- Roden DM. Drug-Induced prolongation of the QT interval. *N Engl J Med* 2004;350:1013–22.
- Schwartz PJ, Stramba-Badiale M, Crotti L, *et al*. Prevalence of the congenital long-QT syndrome. *Circulation* 2009;120:1761–7.
- Benoit SR, Mendelsohn AB, Nourjah P, *et al*. Risk factors for prolonged QTc among US adults: third National health and nutrition examination survey. *Eur J Cardiovasc Prev Rehabil* 2005;12:363–8.
- Al-Khatib SM, LaPointe NMA, Kramer JM, *et al*. What clinicians should know about the QT interval. *JAMA* 2003;289:2120–7.
- Postema PG, Wilde AAM. The measurement of the QT interval. *Curr Cardiol Rev* 2014;10:287–94.
- Postema PG, De Jong JSSG, Van der Bilt IAC, *et al*. Accurate electrocardiographic assessment of the QT interval: teach the tangent. *Heart Rhythm* 2008;5:1015–8.
- Warnier MJ, Rutten FH, Souverein PC, *et al*. Are ECG monitoring recommendations before prescription of QT-prolonging drugs applied in daily practice? the example of haloperidol. *Pharmacoepidemiol Drug Saf* 2015;24:701–8.
- Haberman ZC, Jahn RT, Bose R, *et al*. Wireless smartphone ECG enables large-scale screening in diverse populations. *J Cardiovasc Electrophysiol* 2015;26:520–6.
- Friberg L, Engdahl J, Frykman V, *et al*. Population screening of 75- and 76-year-old men and women for silent atrial fibrillation (STROKESTOP). *Europace* 2013;15:135–40.
- Tieleman RG, Plantinga Y, Rinkes D, *et al*. Validation and clinical use of a novel diagnostic device for screening of atrial fibrillation. *Europace* 2014;16:1291–5.
- Witvliet MP, Karregat EPM, Himmelreich JCL, *et al*. Usefulness, pitfalls and interpretation of handheld single-lead electrocardiograms. *J Electrocardiol* 2021;66:33–7.
- Himmelreich JCL, Karregat EPM, Lucassen WAM, *et al*. Diagnostic accuracy of a Smartphone-Operated, Single-Lead electrocardiography device for detection of rhythm and conduction abnormalities in primary care. *Ann Fam Med* 2019;17:403–11.
- Bansal A, Joshi R. Portable out-of-hospital electrocardiography: a review of current technologies. *J Arrhythm* 2018;34:129–38.
- Chung EH, Guise KD. Qtc intervals can be assessed with the AliveCor heart monitor in patients on dofetilide for atrial fibrillation. *J Electrocardiol* 2015;48:8–9.
- Garabelli P, Stavrakis S, Albert M, *et al*. Comparison of QT interval readings in normal sinus rhythm between a smartphone heart monitor and a 12-lead ECG for healthy volunteers and inpatients receiving sotalol or dofetilide. *J Cardiovasc Electrophysiol* 2016;27:827–32.
- Gropler MRF, Dalal AS, Van Hare GF, *et al*. Can smartphone wireless ECGs be used to accurately assess ECG intervals in pediatrics? A comparison of mobile health monitoring to standard 12-lead ECG. *PLoS One* 2018;13:e0204403.
- Haverkamp HT, Fosse SO, Schuster P. Accuracy and usability of single-lead ECG from smartphones - A clinical study. *Indian Pacing Electrophysiol J* 2019;19:145–9.
- Karacan M, Celik N, Gul EE, *et al*. Validation of a smartphone-based electrocardiography in the screening of QT intervals in children. *North Clin Istanb* 2019;6:48–52.
- Koltowski L, Balsam P, Glowczynska R, *et al*. Kardia mobile applicability in clinical practice: a comparison of Kardia mobile and standard 12-lead electrocardiogram records in 100 consecutive patients of a tertiary cardiovascular care center. *Cardiol J* 2021;28:543–548.
- Strik M, Caillol T, Ramirez FD, *et al*. Validating QT-interval measurement using the apple Watch ECG to enable remote monitoring during the COVID-19 pandemic. *Circulation* 2020;142:416–8.
- Bekker CL, Noordergraaf F, Teerenstra S, *et al*. Diagnostic accuracy of a single-lead portable ECG device for measuring QTc prolongation. *Ann Noninvasive Electrocardiol* 2020;25:e12683.
- Bossuyt PM, Reitsma JB, Bruns DE, *et al*. Stard 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ* 2015;351:h5527.
- Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is "normal". *J Cardiovasc Electrophysiol* 2006;17:333–6.
- Panicker GK, Karnad DR, Natekar M, *et al*. Intra- and interreader variability in QT interval measurement by tangent and threshold methods in a central electrocardiogram laboratory. *J Electrocardiol* 2009;42:348–52.
- Lepeschkin E, Surawicz B. The measurement of the Q-T interval of the electrocardiogram. *Circulation* 1952;6:378–88.
- Sagie A, Larson MG, Goldberg RJ, *et al*. An improved method for adjusting the QT interval for heart rate (the Framingham heart study). *Am J Cardiol* 1992;70:797–801.
- BAZETT HC. An analysis of the TIME-RELATIONS of electrocardiograms. *Annals of Noninvasive Electrocardiology* 1997;2:177–94.
- Malik M, Bradford A. Human precision of operating a digitizing board: implications for electrocardiogram measurements. *Pacing Clin Electrophysiol* 1998;21:1656–62.
- Priori SG, Blomström-Lundqvist C, Mazzanti A, *et al*. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of cardiology (ESC). endorsed by: association for European paediatric and congenital cardiology (AEPC). *Eur Heart J* 2015;36:2793–867.
- Baumert M, Starc V, Porta A. Conventional QT variability measurement vs. template matching techniques: comparison of performance using simulated and real ECG. *PLoS One* 2012;7:e41920.
- Viskin S. The QT interval: too long, too short or just right. *Heart Rhythm* 2009;6:711–5.
- VanderBerk BV, Robyns E, Vandenbergh T, *et al*. Which QT correction formulae to use for QT monitoring? *J Am Heart Assoc* 2018;7:e004252.
- Rautaharju PM, Surawicz B, Gettes LS, *et al*. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: Part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American heart association electrocardiography and arrhythmias Committee, Council on clinical cardiology; the American College of cardiology Foundation; and the heart rhythm Society. endorsed by the International Society for computerized Electrocardiology. *J Am Coll Cardiol* 2009;53:982–91.
- Kautzner J. Qt interval measurements. *Card Electrophysiol Rev* 2002;6:273–7.
- Viskin S, Rosovski U, Sands AJ, *et al*. Inaccurate electrocardiographic interpretation of long QT: the majority of physicians cannot recognize a long QT when they see one. *Heart Rhythm* 2005;2:569–74.