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Smartwatch Electrocardiogram and Artificial Intelligence for Assessing Cardiac-Rhythm Safety of Drug Therapy in the COVID-19 Pandemic. The QT-logs study

Baptiste Maille [a,b], Marie Wilkin [a,b], Matthieu Million [c,h], Noémie Rességuier [d], Frédéric Franceschi [a,b], Linda Koutbi-Franceschi [a,b], Jérôme Hourdain [a,b], Elisa Martinez [a,b], Maxime Zabern [a,b], Christophe Gardella [e], Hervé Tissot-Dupont [c,h], Jagmeet P. Singh [f], Jean-Claude Deharo [a,b,*], Laurent Fiorina [g]

[a] Assistance Publique — Hôpitaux de Marseille, Centre Hospitalier Universitaire La Timone, Service de Cardiologie, Marseille, France
[b] Aix Marseille University, C2VN, Marseille, France
[c] IHU-Méditerranée Infection, Marseille, France
[d] Department of Epidemiology and Health Economics, APHM, Marseille, France
[e] Cardiologs Technologies, Paris, France
[f] Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[g] Institut Cardiovasculaire Paris-Sud, Hôpital Privé Jacques Cartier, Ramsay, Massy, France
[h] Aix-Marseille University, IRD, APHM, MEPHI, Marseille, France

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ABSTRACT

Background: QTc interval monitoring, for the prevention of drug-induced arrhythmias is necessary, especially in the context of coronavirus disease 2019 (COVID-19). For the provision of widespread use, surrogates for 12-lead ECG QTc assessment may be useful. This prospective observational study compared QTc duration assessed by artificial intelligence (AI-QTc) (Cardiologs®, Paris, France) on smartwatch single-lead electrocardiograms (SW-ECGs) with those measured on 12-lead ECGs, in patients with early stage COVID-19 treated with a hydroxychloroquine−azithromycin regimen.

Methods: Consecutive patients with COVID-19 who needed hydroxychloroquine−azithromycin therapy, received a smartwatch (Withings Move ECG®, Withings, France). At baseline, day-6 and day-10, a 12-lead ECG was recorded, and a SW-ECG was transmitted thereafter. Throughout the drug regimen, a SW-ECG was transmitted every morning at rest. Agreement between manual QTc measurement on a 12-lead ECG and AI-QTc on the corresponding SW-ECG was assessed by the Bland-Altman method.

Results: 85 patients (30 men, mean age 38.3 ± 12.2 years) were included in the study. Fair agreement between manual and AI-QTc values was observed, particularly at day-10, where the delay between the 12-lead ECG and the SW-ECG was the shortest (−2.6 ± 64.7 min): 407 ± 26 ms on the 12-lead ECG vs 407 ± 22 ms on SW-ECG, bias −1 ms, limits of agreement −46 ms to +45 ms; the difference between the two measures was <50 ms in 98.2% of patients.

Conclusion: In real-world epidemic conditions, AI-QTc duration measured by SW-ECG is in fair agreement with manual measurements on 12-lead ECGs. Following further validation, AI-assisted SW-ECGs may be suitable for QTc interval monitoring.

REGISTRATION: ClinicalTrial.gov NCT04371744.

1. Introduction

The current pandemic due to a new coronavirus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – has so far affected more than 11 million people and caused in excess of half a million deaths. This healthcare emergency made it necessary to explore pharmacologic interventions to treat or prevent the disease. The use of antiviral drugs is one such intervention, but their efficacy remains debated and strategies for their use are evolutive [1]. In the absence of definitive proof of effectiveness, the safety profile of any treatment is a crucial question. Cardiac toxicity is one of the main concerns because many of the proposed treatments, including lopinavir/ritonavir, chloroquine/hydroxychloroquine (HCQ), azithromycin (AZM), moxyfloxacin and remdesivir, have the potential to cause proarrhythmia, particularly in the setting of severe forms of SARS-CoV2 [2,3]. Monitoring the QT

* Corresponding author at: Hôpital La Timone Adultes, 264 Rue Saint.
E-mail address: jean-claude.deharo@ap-hm.fr (J.-C. Deharo).

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interval and cardiac rhythm are essential for safety considerations regarding the use of these drugs. [3]

Some single-lead ECG devices coupled with artificial intelligence (AI) received US Food and Drug Administration clearance for atrial-fibrillation screening [4], but little is known about the feasibility and diagnostic accuracy of their use for QTc assessment [5]. In light of the shortage of resources and widespread use, and in the context of a highly contagious disease, surrogates for 12-lead electrocardiogram (ECG) assessment may be useful, and direct-to-consumer single-lead ECG technology is promising. If previous study had already shown a good agreement between QTc measured on a Smartwatch ECG (SW-ECG) and a 12 leads ECG [6], little is known about the use of AI for QTc measurement. The Cardiologs Platform (Cardiologs Technologies™, Paris, France) is a cloud-based platform for ECG interpretation powered by a deep neural network algorithm. This algorithm has already been validated, especially for 12 lead-ECG interpretation in emergency departments [7], diagnosis of atrial fibrillation [8], and for Holter analysis [9]. An analog watch with an in-built single-lead ECG (Withings Move ECG™, Withings, France), linked to the Cardiologs™ AI platform, can send self-recorded ECGs direct for AI analysis.

We performed a study to compare QTc assessed using this algorithm on smartwatch single-lead ECGs (AI-QTc) with QTc measured using conventional 12-lead ECGs in patients with early stage coronavirus disease 2019 (COVID-19) treated with the HCQ — AZM regimen.

2. Methods

We identified all consecutive adults (≥18 years) who attended the ambulatory care center of the infectious diseases department of our tertiary referral academic hospital from April 16 to April 24, 2020, for polymerase chain reaction (PCR)-positive SARS-CoV-2 infection. Medical history and current medical status were thoroughly assessed for each patient and the decision to treat with HCQ — AZM was taken by the infectious disease specialist. The study is registered at ClinicalTrials.gov, with the unique identifier NCT04371744. The study was reviewed by the medical research committee of our academic hospital (reference number 2020–52) and approved by the ethical committee (reference number: 2020–030). Signed written informed consent was obtained from all participants.

2.1. Cardiac-Rhythm Safety evaluation:

Once the decision to treat was taken, according to local guidelines, Tisdale Score and recent recommendations [3,10] a rhythm safety evaluation was systematically performed to assess QTc prolongation risk. Moreover, treatment with HCQ — AZM was not started if the corrected QT interval (QTc; Bazett's formula) was >500 ms, or if the ECG showed patterns suggesting a channelopathy, or if other significant abnormalities (i.e., pathological Q waves, left ventricular hypertrophy, left bundle branch block) were present. The risk—benefit ratio of HCQ — AZM was estimated by the infectious disease specialist and agreed upon with the cardiologist, for a range between 460 and 500 ms of QTc. In addition, any drug with the potential to prolong the QT interval was discontinued or replaced with another drug for the treatment course. Standard blood chemistry was checked, especially serum creatinine and kalemia in the context of SARS-CoV-2, and the treatment was not started when there was hypokalemia with a serum potassium <3 mEq/l, and was discontinued at day 1 if the serum potassium between 3 and 3.5 mEq/l was not normalized.

2.2. ECG recording:

All patients who were prescribed HCQ — AZM treatment and had no criteria for overnight stay were considered for inclusion in the study if they had a smartphone and were able and willing to perform repeated SW-ECGs. They received a smartwatch (Withings Move ECG™) and were instructed on how to use it. A 12-lead ECG was then recorded at rest (baseline), with a paper speed of 50 mm/s and an amplitude calibration of 10 mm/mV (MAC® 3500 or MAC® 1600 recorder; GE Healthcare Europe, Freiburg, Germany). As soon as technically possible, an ECG recording was taken with the smartwatch. Patients were then allowed to go home. The drug regimen was as follows: hydroxychloroquine (Plaquenil®; Sanofi Aventis, Paris, France), 200 mg three times per day for 10 days, plus azithromycin (Zithromax®; Pfizer Holding, Paris, France), 500 mg once a day on the first day, then 250 mg once a day for 4 days.

The patients were instructed to transmit a SW-ECG every morning at rest and at any time in case of unusual symptoms, including palpitations or dizziness, until the end of the treatment. As per local guidelines, patients were requested to attend a follow-up visit at the ambulatory care center of the infectious disease department for clinical assessment and a 12-lead ECG on the sixth day (day-6, recommended) and on the last day of therapy (day-10, mandatory). They transmitted a SW-ECG as soon as technically possible after the 12-lead ECG recording at day-6 and day-10 (Fig. 1).

2.3. Electrocardiogram Interpretation

2.3.1. Manual Interpretation

On the standard 12-lead ECG recordings obtained at baseline, day-6 and day-10, the QT interval was measured, as recommended [11] in the tangent method, in lead II or V5, and corrected using Bazett's formula. In addition, QTc was assessed on lead I using the same method. Additional measurement included heart rate, and any cases of arrhythmia were recorded. PR interval and QRS duration were measured only at baseline and day-10. The interpretation was blindly performed by two cardiologists, (B.M.) and (M.W.). When there was a < 30 ms discrepancy between the 2 measures, the mean of the 2 values obtained by the 2 operators was used to compare against the AI-based automatic measurement of QTc. When there was a > 30 ms discrepancy between the 2 measures, an additional cardiologist (J-C.D.) performed the measure and this value was used for comparison against the AI-QTc.

The QT interval was manually measured on daily SW-ECGs, using the same method as described above for 12-lead ECGs and compared with the AI-QTc measurements. In addition, manual measurement of the QTc was performed independently by 3 electrophysiologists (B.M., M.W. and L.F.) on the transmitted SW-ECG from day-10. Manual measurements were performed blinded to the AI interpretation, and the mean of the 3 measured values was used for comparison with AI-QTc. In case of SW-ECG transmission due to symptoms, the ECG was interpreted by the same cardiac electrophysiologists. Patients could be contacted in the event of a significant arrhythmia or QTc prolongation >500 ms.

2.4. Artificial intelligence Interpretation

AI-QTc were systematically measured from all received SW-ECG. When the 30-s SW-ECG was performed by a patient, it was automatically transmitted to the Cardiologs platform for assessment of the AI-QTc. The AI-QTc was computed as follows: a deep convolutional neural network identified the onset of QRS complexes and the offset of following T waves of all beats in the SW-ECG. The QTc of each beat was computed with the Bazett formula, using the QT and the preceding RR intervals detected by the neural network. Finally, in order to remove extreme and aberrant values, the AI-QTc of the SW-ECG was computed as the median QTc across all beats.

The convolutional neural network consists of a U-net architecture [12] with 11 convolutional layers and 6 residual blocks. The network takes as input the ECG signal and outputs the onsets and offsets of all detected P, QRS and T waves. The network was trained on 6315 resting ECGs and Holter recordings, with the onsets and offsets of P, QRS and T waves annotated by experts in electrophysiology following standard procedures. No SW-ECG was used during training of the neural

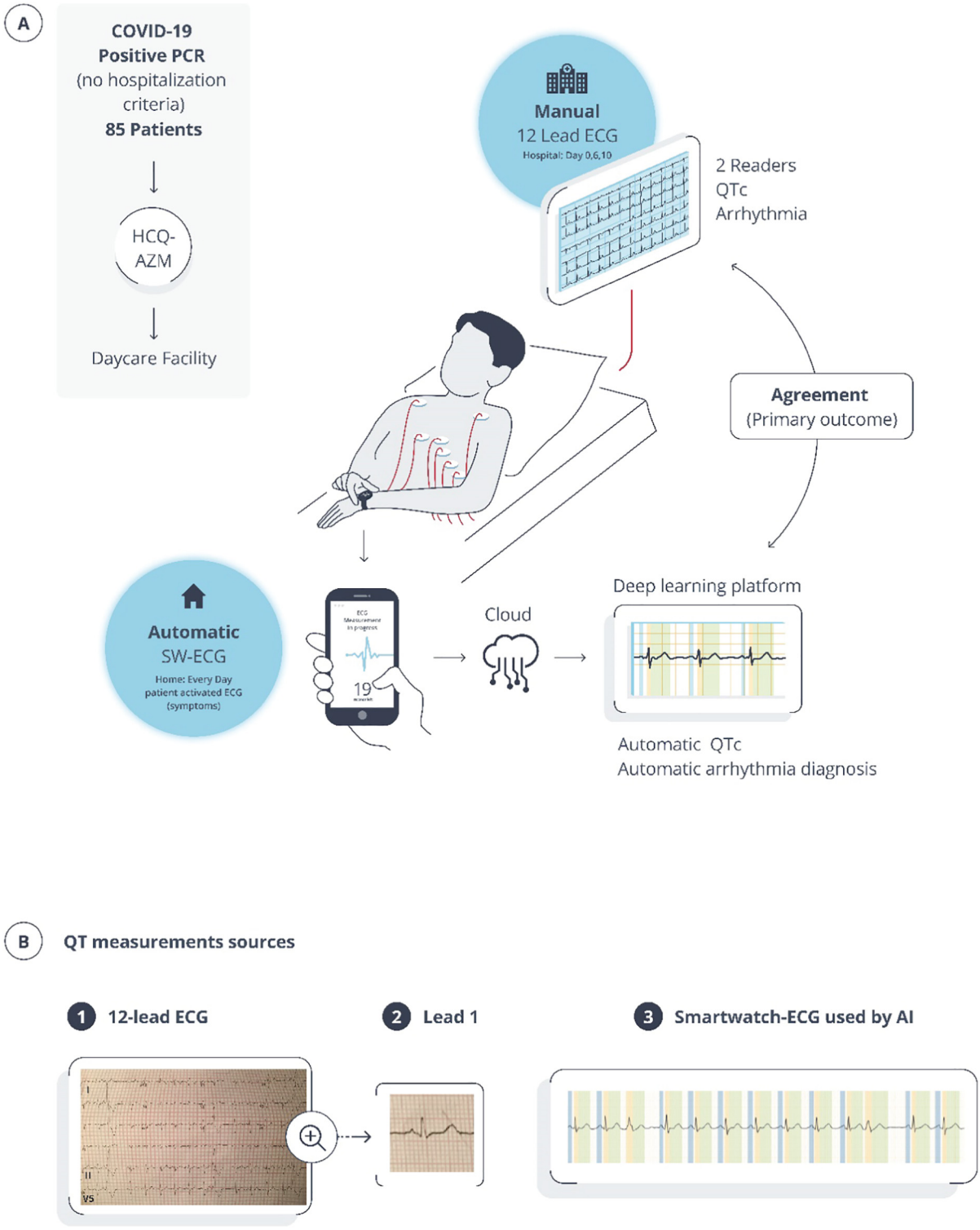

Fig. 1. (Central illustration) Schematic of the Study Protocol and Operation of the Cardiologs® System. AZM denotes azithromycin; ECG, electrocardiogram; HCQ, hydroxychloroquine; PCR, polymerase chain reaction; and SW-ECG, smartwatch electrocardiogram.

network. The SW-ECGs were single lead ECGs lasting 30 s and sampled at 300 Hz, a sampling rate which is similar to the recordings used for training (100 to 500 Hz). The network was implemented in Keras, with a backend in Tensorflow (Google, Mountainview, California), and trained using stochastic gradient descent. Early stopping and dropout regularization were used to avoid overfitting [13]. In order to ensure that the network performs accurately for multiple and single lead ECGs, leads were sometimes randomly subsampled during training. The performance of the AI-QT measurement was evaluated on the Common Standards for Quantitative Electrocardiography database [14]. The bias of the QT measurement was −13.7 ms, with a standard deviation of 7.3 ms.

2.5. Outcome measures

The primary outcome was the agreement between the standard 12-lead QTc interval measured manually in lead II or V5 at baseline and day-10, and the AI-QTc measured on the corresponding SW-ECG.

Secondary outcomes included the agreement between the standard 12-lead QTc measured manually in lead II or V5 at the day-6 visit and the AI-QTc on the corresponding SW-ECG; agreement between the 12-lead QTc measured manually in lead I at baseline, day-6 and day-10 and the AI-QTc on the corresponding SW-ECG; agreement between the QTc measured by the cardiologist on the daily SW-ECG and the AI-QTc on the same SW-ECG, at day-10; and a description of QTc behavior during HCQ-AZM therapy and of arrhythmia occurrence as assessed on daily SW-ECGs or on-demand SW-ECGs (i.e. in case of symptoms).

2.6. Statistical analysis

Quantitative variables are presented as means ± standard deviations (SD) and categorical variables as numbers (percentages). Agreement between QTc measurements (between manual QTc measurement on the 12-lead ECGs and AI-QTc, between QTc measured manually on the same SW-ECG and AI-QTc) was assessed using the Bland-Altman method. The mean of the difference (bias) in QTc interval between the 2 methods was calculated, as well as the lower and upper limits of agreement. Agreement between measures was also numerically assessed by estimating the agreement intraclass correlation coefficient (ICC), with its 95% confidence interval (CI). Daily smartwatch QTc were compared with baseline smartwatch QTc by means of a paired *t*-test. The Benjamini—Hochberg procedure was used for controlling the false positive rate in multiple comparisons.

All analyses were performed using R software, version 3.6.3. All tests were 2-sided, and $P < 0.05$ was considered statistically significant.

3. Results

Between April 16 and April 24, 2020, 108 consecutive adults with a PCR-positive SARS-CoV-2 infection with no criteria for overnight stay were considered for HCQ — AZM combination therapy initiated at our infectious disease ambulatory care department. The patient flow chart is illustrated in Supplemental fig. 1. Of the 85 patients who entered the study, 76 received the drug regimen and were followed with daily SW-ECGs. The epidemiological, clinical, and baseline ECG characteristics of the patient populations are presented in Table 1. In 3 patients (3.9%), serum potassium was between 3 and 3.5 mmol/L at inclusion; they received potassium supplementation, achieving normo-kalemia after 1 day, and could continue the treatment. Ten patients (13.1%) were taking concomitant QT-prolonging drugs (antihistamine drugs) and 2 (2.6%) were taking beta-blockers. These treatments were all discontinued on the decision of the infectious disease specialist as they were not considered essential. No patient had a significant ECG abnormality or underlying severe cardiac disease. Among patients who received the drug regimen and were followed with daily SW-ECGs, median Tisdale score was 7 (6–7). Respectively 26(34.2%), 50(65.8%) and 0(0%) presented a low, moderate and high risk of prolonging QTc.

Mean follow-up was 10.8 ± 1.2 days. One patient had to be admitted to the conventional ward because of a deterioration in his respiratory function at day 5 of treatment and stayed in hospital for 5 days. No more SW-ECGs were recorded after he was admitted to the hospital, but clinical follow-up and a 12-lead ECG at day 10 were still available. By their own decision, 17(22.4%) patients did not attend the optional day-6 visit and 2(2.6%) did not attend day-10 visit. They were contacted at day-10, and it was confirmed that they did not experience palpitations or syncope. One patient declared a minor cutaneous allergic reaction with pruritus related to the watch strap, which did not prevent the patient from sending daily recordings. With this exception, no patient declared any difficulty in the wearing the smartwatch.

Table 1
Patient Characteristics.

Characteristic	Overall Population ($n = 85$)	Patients on HCQ — AZM combination and daily SW-ECG ($n = 76$)
Male sex	30(35.3)	27(35.5)
Mean age, y	38.3 ± 12.2	38.2 ± 12.4
≥65 y	0(0)	0(0)
Body mass index, kg/m^2	26.4 ± 5.4	26.6 ± 5.7
Cardiovascular risk factor		
Hypertension	4(4.7)	4(5.3)
Diabetes mellitus	2(2.4)	2(2.6)
Active smoker	19(22.3)	17(22.4)
Clinical setting		
Oxygen saturation < 94%	1(1.2)	1(1.3)
Systolic blood pressure, mmHg	128 ± 16	129 ± 16
Fever (>38 °C)	7(8.2)	6(7.9)
Cardiovascular treatment		
ACE inhibitor/ARB	2(2.4)	2(2.6)
Beta-blocker	2(2.4)	2(2.6)

For continuous variables, values are mean ± standard deviation; for categorical variables, n(%) is shown.
ACE denotes angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; HCQ — AZM, hydroxychloroquine plus azithromycin combination; and SW-ECG, smartwatch electrocardiogram.

Owing to technical issues in communication between their smartwatch and smartphone, 5/71(6.6%), 5/53(8.6%) and 7/66(9.6%) patients were unable to record a SW-ECG after the 12 lead-ECG during the visit at baseline, day-6, and day-10, respectively. A mean of 9.5 ± 2.1 SW-ECGs were recorded per patient. Fifty (65.8%) patients performed at least 10 SW-ECGs during the 11 days of follow-up, while 6 (7.9%) performed fewer than 6 SW-ECGs. No patient reported palpitations, dizziness, or syncope. The number of patients in whom 12-lead and SW-ECGs could be compared at each visit is detailed in Table 2.

Agreement Between Manual and AI-QTc Intervals.

The delay between completion of the standard 12-lead ECG and the SW-ECG was 55.7 ± 141.3 min at baseline, 38.2 ± 129.1 min at day-6, and — 2.6 ± 64.7 min at day-10. Table 2 shows the agreement between the manually measured QTc on the 12-lead ECG, the manually measured QTc on lead I of the same tracing, and AI-QTc from the corresponding SW-ECG. When the delay between completion of the 12-lead ECG and the SW-ECG was the shortest, at day-10, the Bland-Altmann diagram (Table 2, Fig. 2B) showed the best agreement. Similar results were obtained at day-6 (Table 2, Supplemental Fig. 2). The difference between the two measures was <50 ms in 65(98.2%) patients at day-10 and in 51(96.2%) patients at day-6. At baseline, 69(97.2%) patients presented with a lower than 50 ms difference between the two measures. However, the agreement assessed by the Bland-Altmann was lower (Table 2, Fig. 2A). Consistently across the three visits, the agreement between the QTc measured in lead I and the AI-QTc showed a tendency to overestimate QTc, with a similar limit of agreement to 12 lead ECG (Table 2, Supplemental fig. 3).

Agreement was excellent between the AI-QTc at day 10 and the manual measure of QTc on the same recording (Supplemental fig. 4), showing a bias (limits of agreement) of 0 (−18,+17) ms and an ICC agreement (95% CI) of 0.91 (0.85,0.94).

QTc Behavior During Treatment.

Fig. 3 illustrates daily AI-QTc behavior, during HCQ — AZM therapy. Compared to the baseline value, there was no significant daily prolongation of QTc during treatment (Fig. 3A). Similar results were obtained for QTc interval behavior as manually measured on the 12-lead ECGs (Fig. 3B). At the individual level, as compared to baseline: 18(23.4%), 5

Table 2
Comparison Between 12 Lead-QTc Measured Manually and Automatically Assessed QTc From the Corresponding SW-ECG.

ECG type	Time	QTc, mean ± SD, ms		Bias between measures (95% LoA) (ms)	ICC agreement	
		Manually measured on ECG	AI-determined on SW recording		(95% CI)	*P* Value
12 leads	Baseline (n = 71)	402 ± 27	407 ± 25	−5(−54,+43)	0.54(0.35,0.68)	<0.001
	Day-6 (n = 53)	405 ± 23	406 ± 25	−1(−45,+43)	0.57(0.35,0.72)	<0.001
	Day-10 (n = 66)	407 ± 26	407 ± 22	−1(−46,+45)	0.54(0.34,0.69)	<0.001
Lead I	Baseline (n = 71)	385 ± 27	407 ± 25	−23(−74,+28)	0.38(0.01,0.62)	0.02
	Day-6 (n = 53)	393 ± 26	406 ± 25	−14(−58,+31)	0.53(0.22,0.72)	<0.001
	Day-10 (n = 66)	395 ± 27	407 ± 22	−13(−57,+32)	0.50(0.22,0.69)	<0.001

AI denotes artificial intelligence; CI, confidence interval; ECG, electrocardiogram; ICC, interclass correlation coefficient; LoA, limits of agreement; and SW, smartwatch.

(6.5%) and 7(9.1%) patients had at least one daily SW-QTc prolonged by, respectively, 20–40 ms, 40–60 ms, and > 60 ms. In the meantime, only 29(39.1%), 10(13.6%), and 1(1.4%) were identified by the standard 12-lead ECGs during the follow-up.

One patient had a AI-QTc >500 ms (i.e. 502 ms) on the second day of treatment and was therefore admitted to the day-hospital. The 12-lead ECG showed a prominent U wave in lead I, along with a low T-wave amplitude. In this patient, baseline 12-lead QTc interval was 457 ms and no AI-QTc was available at baseline because of pairing issues between the smartphone and the smartwatch. The 12-lead QTc measured in hospital on day 2 was 471 ms, thus the drug regimen was continued at home. No QTc value >500 ms was observed on either the subsequent daily AI-QTc or 12-lead ECGs during follow-up.

In the general population, a slight but significant PR prolongation was observed at day-10 (154 ± 25 ms at baseline to 161 ± 23 ms at day-10; $P < 0.001$). There was no significant QRS prolongation from baseline (83 ± 19 ms) to day-10 (86 ± 17 ms) ($P = 0.3$).

Four patients (5.2%) presented with asymptomatic premature ventricular contractions (PVC) on their daily SW-ECGs. All of them had also had such PVC's on their 12 lead-ECG at baseline. No other arrhythmia was identified during follow-up.

4. Discussion

We observed a fair agreement between the QTc interval duration measured manually on a standard 12-lead ECG and assessed by AI on single-lead smartwatch recordings. This agreement was observed on different sets of tracings obtained at various points throughout the study, provided they were recorded at similar times. In this young population of patients with early stage COVID-19 and mild-to-moderate symptoms, no significant QTc prolongation was observed on daily AI-QTc and no life-threatening arrhythmias were reported. Whereas one study has already demonstrated the power of a deep learning algorithm for diagnosis of arrhythmia [4], the current is the first to evaluate a deep neural network with SW-ECGs for QT monitoring.

A few studies [15,16] and recent recommendations [17] have highlighted the major interest of using connected devices in the context of the potential use of QT-prolonging drugs in COVID-19 therapy. Previous studies described the utility of various connected ECG recording devices, such as smartphones [15,18], wearable remote monitoring systems [19], smartwatches [6], and mobile cardiac telemetry [16] for QTc monitoring. Some have also described the use of automatic measurement of the QTc using different automatic algorithms, but not neural network-based AI, embedded on recording devices or proprietary. Our study is the first to confirm the feasibility and accuracy of a neural network-based AI-QTc determination, using ECG independently gathered from direct-to-consumer SW-ECG, in real-life conditions of COVID-19 therapy.

Agreement between 12-lead ECG and a SW-ECG QTc measurements have been shown to be dependent on factors such as ECG tracing quality and T-wave amplitude [6]. Different strategies of improving agreement accuracy have been described. Strik et al. used “T-wave mapping” screening to identify the best smartwatch position and withdrew from their study patients in whom the different smartwatch positions did not allow for adequate measurement [6]. Other investigators excluded patients with poor quality of reference ECG tracing. In our real life study, no patient was excluded based on the shape or quality of the SW-ECG, and only standard recording (i.e. with the watch worn on the wrist) was performed. Moreover, no SW-ECG was used during training of our neural network. Due to the COVID 19 pandemic emergency

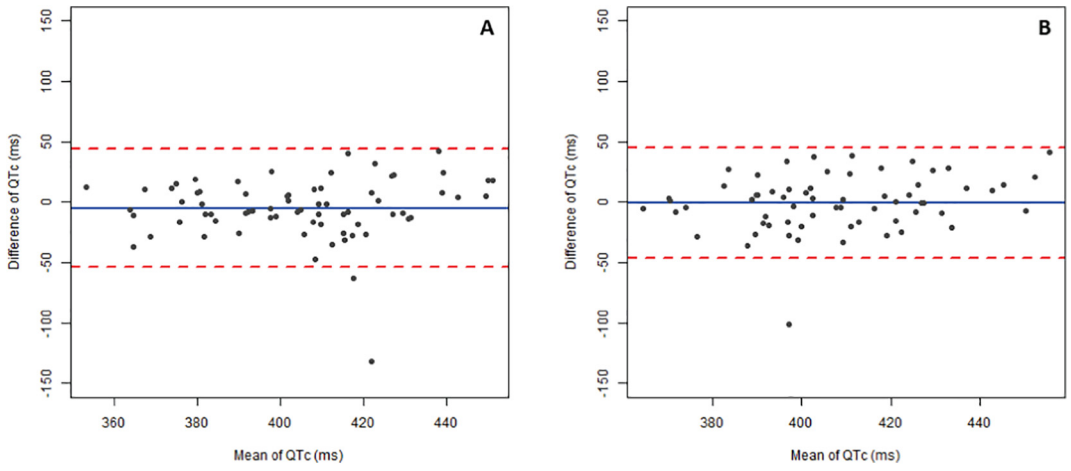

Fig. 2. Comparison of QT-Interval Measurements, using QTc Measured Manually on the 12-Lead ECG and AI-Determined QTc Based on Smartwatch Recordings, at (A) Baseline and (B) Day-10. The Bland–Altman Method was Used for Analysis of Measurement Agreement. Solid blue and dashed red lines represent the bias limit of agreement in the QTc interval between the 2 methods. 12-lead QTc denotes QTc interval measured on a 12-lead ECG; AI artificial intelligence; and ECG, electrocardiogram.

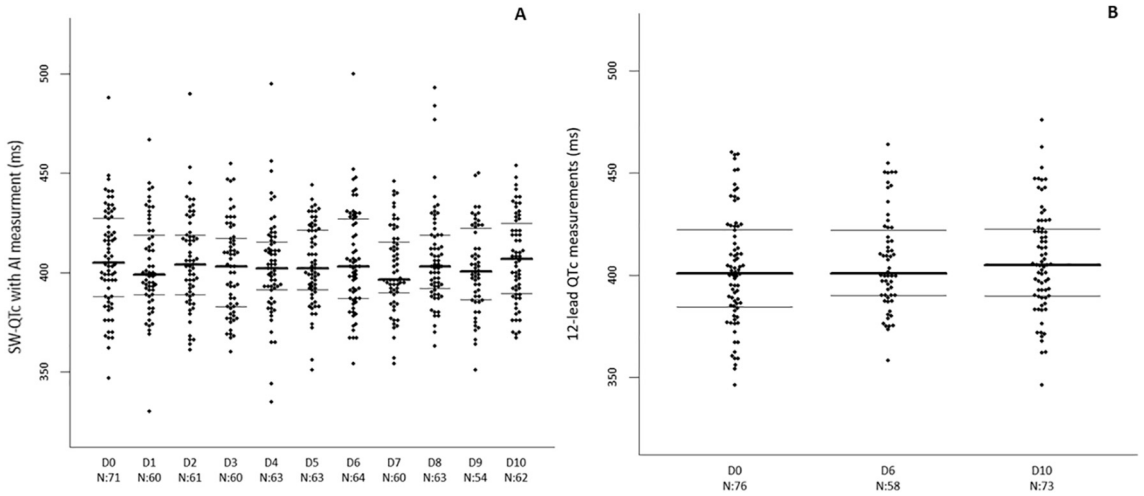

Fig. 3. QTc Behavior With Hydroxychloroquine–Azithromycin Combination Treatment in a Daycare Population with COVID-19. (A) Daily SW-QTc measured by AI. (B) QTc measured manually on a 12-lead ECG. In both cases all changes were non-significant versus baseline. 12-lead QTc denotes QTc interval measured on a 12-lead ECG; AI, artificial intelligence; COVID-19, coronavirus disease 2019; and SW-QTc, QTc interval measured on a Smartwatch ECG.

situation, there was not enough time to apply such a strategy of specific neural network training. Despite this imperfect emergency protocol, we found a fair agreement with manual-QTc, comparable to that reported in the literature [6,15–17,20].. We expect the use of a specific AI trained with SW-ECGs would demonstrate more accurate agreement.

There are numerous sources of potential discrepancy in QTc interval assessment, ranging from interobserver variability and precision of the measurement technology to intrinsic variability of the QTc itself. The discrepancy between manual QTc measurements, even when performed by experts, is wide, ranging from 34 to 80 ms. [20] In addition, QT interval is a highly dynamic parameter, showing well-known circadian variations. Apart from heart rate itself, it is highly sensitive to autonomic nervous system influences [21] and to many pathologic conditions such as ischemia [22]. Even if we did our best to perform smartwatch and 12-lead ECG recordings as close in time as possible, a significant delay was observed in some cases for various reasons that may reflect real life. In spite of a potential multifactorial QTc variability in measurements, we found acceptable agreement.

As the SW-ECG records a lead equivalent to lead I of the ECG, we were expecting stronger agreement between AI and manual QTc when the measure was performed in lead I. AI-QTc was consistently overestimated compared with lead 1 QTc, but a similar limit of agreement with 12-lead QTc was observed. There is no clear explanation, but we assume that it might be due to the fact that lead I is not optimal for QT measurement for various reasons, including the shape or amplitude of the T wave in lead I, and the QT dispersion on a 12-lead ECG [23,24]. We believe that AI may compensate for some of these issues by computing a median over all beats, removing the extreme and aberrant values, whereas manual measurement only relies on a few beats.

While HCQ effectiveness in COVID-19 is criticized [25], its use in connective tissue disease is wide [26] and antiviral strategies in COVID-19 still unresolved. Moreover this study was not designed to test the effectiveness of HCQ — AZM in COVID-19 but rather to examine cardiac safety profile of such medication. The use of HCQ — AZM in patients with early stage COVID-19 with mild-to-moderate symptoms in an ambulatory care center, was not related with significant prolongation of the QTc interval during the drug regimen or significant arrhythmia occurrence. However, HCQ may lead to QT prolongation. HCQ is a derivative of chloroquine and has similarities to quinine, which is a class Ia antiarrhythmic drug that acts as a sodium channel blocker, responsible for prolonging the duration of the action potential, and may therefore prolong the QT interval. However, this effect is expected to be modest [27]. AZM has low affinity for the hERG channel [28], and is therefore considered to have a low risk of QT prolongation. However, combining both drugs, particularly when taking into account the increased risk of electrolyte disorders in patients with severe COVID-19, may result in a proarrhythmic effect. Recent publications [29,30] evaluating HCQ — AZM treatment in hospitalized patients with COVID-19, with a mean age greater than 60 years, and including severe and critically ill patients with COVID-19, have shown important QTc lengthening in some patients. However, other evaluating lower risk patients [31], similarly to our study, showed only modest QTc prolongation. This highlighted the necessity of an initial QTc prolongation risk evaluation and a close QTc monitoring, for patients under prolonging QTc drugs. Thus a home-monitoring ECG is of greatest interest, in the context of the required social distancing, because of the COVID-19 pandemic.

4.1. Limitations

One of the limitations of our study is the very low number of critical QTc prolongations. This is likely due to our cardiac-rhythm safety criteria for HCQ — AZM therapy. Although the accuracy for monitoring pathologic QTc prolongation remains uncertain, the agreement we found makes it a promising strategy.

Our study also highlights some limitations of SW-ECG follow-up, including willingness and capacity to participate, technical skills, and adequate internet coverage. Twelve patients were not included because of an anticipated poor adherence to the study protocol (either related to patient choice or understanding), and 7 additional patients were withdrawn for technical issues after inclusion. A small number of patients occasionally did not transmit daily SW-ECG data. Finally, as previously mentioned, owing to poor internet coverage in the daycare facility, simultaneous 12-lead ECGs and SW-ECGs were unpredictively not feasible. Despite these issues, participation in the study was good, but different study populations, especially older people, may show more technical difficulties.

Since the determination of QTc duration by an ECG recorder is commonly used, we could have compared the values obtained by AI to the values automatically determined by the ECG recorder. However, the latter are specific to each ECG recorder and cannot be taken as reference since their accuracy is debated [32,33]. On the other hand, manual measurement is the gold standard for QT measurement [11], and for this reason we used it for comparison. We see a major benefit of neural network-based QTc determination since it is device-independent and, therefore, generalizable to all ECG recordings having the same characteristics than our SW-ECGs.

5. Conclusions

This first "real-world" study evaluating a neural network-based AI-assessed QTc measurement, gathered from direct-to-consumer smartwatches, shows promising results. Despite variability in the QTc interval, fair agreement was observed between AI and 12-lead ECGs. The use of AI-QTc follow-up could potentially avoid life-threatening arrhythmias by stopping treatments that can cause QT prolongation before occurrence of symptoms. This finding also has the potential to lead to future clinical applications in the evaluation of any drug-induced arrhythmogenicity related with QT prolongation, needing close QT interval monitoring.

Disclosures

Jag Singh is consultant for Medtronic, Boston Scientific, Abbott Laboratories, Microport, EBR, Cardiologs, Nopras Inc., Impulse Dynamics, Biotronik.

Laurent Fiorina is consultant for Cardiologs Technologies®, Paris, France.

Christophe Gardella is employed by Cardiologs Technologies®, Paris, France as a data scientist.

The remaining authors have nothing to disclose.

Author statement

Baptiste Maille: Conceptualization**,** Methodology, Resources**,** Writing - Original Draft **Marie Wilkin:** Conceptualization**,** Methodology, Resources**,** Writing - Original Draft **Matthieu Million:** Resources **Noémie Rességuier:** Methodology, **Frédéric Franceschi:** Resources **Linda Koutbi-Franceschi:** Resources **Jérôme Hourdain:** Resources **Elisa Martinez:** Resources **Maxime Zabern:** Resources **Christophe Gardella:** Conceptualization, Methodology, Software**,** Writing - Original Draft **Hervé Tissot-Dupont:** Resources **Jagmeet P. Singh:** Conceptualization **Jean-Claude Deharo:** Conceptualization**,** Methodology, Writing - Original Draft, Supervision **Laurent Fiorina:** Conceptualization, Methodology, Writing - Original Draft.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.01.002.

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