Comparison of QT Interval Measurement Methods and Correction Formulas in Atrial Fibrillation

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Antiarrhythmic drugs used in atrial fibrillation (AF) cause QT prolongation and are associated with torsades de pointes, a deadly ventricular arrhythmia. No consensus exists on the optimal method of QT measurement or correction in AF. Therefore, we compared common methods to measure and correct QT in AF to identify the most accurate approach. We identified patients who had electrocardiograms done at Stanford Hospital (Stanford, California) between January 2014 and October 2016 with conversion from AF to sinus rhythm (SR) within a 24-hour period. QT intervals were determined using different measurement methods and corrected using the Bazett's, Framingham, Fridericia, or Hodges formulas for heart rate (HR). Comparisons were made between QT in a patient's last instance of AF to SR. Computerized measurements were taken from 715 patients. Manual measurements were taken from a 50-patient subset. Bazett's formula produced the longest corrected QT in AF compared with other formulas (p <0.005). Measuring QT as an average over multiple beats resulted in a smaller difference between AF and SR than choosing a single beat. Determining QT from a 5-beat average resulted in a QTc that was 19.0 ms higher (interquartile range 0.30 to 43.7) in AF than SR. After correcting for residual effect of HR on QTc, there was not a significant difference between QTc in AF to SR. In conclusion, measuring QT over multiple beats produces a more accurate measurement of QT in AF. Differences between QTc in AF and SR exist because of imperfect HR correction formula and not due to an independent effect of AF. **(Am J Cardiol 2019;123:1822−1827)**

Atrial fibrillation (AF) is associated with elevated heart rate (HR) and beat-to-beat variation in the length of the QT and RR interval making correction of the QT interval challenging. Antiarrhythmic drugs (AAD) for AF, such as class III antiarrhythmics, have QT prolonging effects creating risk for torsades de pointes. Additionally, it has been suggested that AF alone can independently lengthen QT interval.[1] Therefore, a reliable measurement of corrected QT (QTc) in AF is necessary. However, there is an official recommendation against correcting QT for HR in AF given the beat-to-beat variability in RR interval.[2] In practice, clinicians are correcting QT in these patients and there is significant variation in techniques. Previous studies investigating the QT interval in AF are limited by small sample size and have focused on comparing QT correction formulas and not methods for measuring the QT interval in AF.[1,3] In this study, we use a large electronic medical record database of ECGs to conduct a real-world analysis comparing QT in AF and SR in the same patients to determine the optimal QT measurement method and correction technique in AF, the risk of developing dangerous QT prolongation after conversion to SR from AF, and the effect of the AF rhythm on QT interval duration independent of HR.

Methods

We performed a retrospective single-center study of all patients who underwent 12-lead ECG recording (Philips Healthcare, Andover, Massachusetts) for standard clinical indications at Stanford Hospital and Clinic − a 613 bed, community and tertiary care facility in Stanford, CA − from January 2014 to October 2016. Patients who had an ECG in AF and a subsequent ECG in SR within 24 hours were included. Only a patient's last ECG in AF and first ECG in SR were included in the analysis. Patients with atrial or ventricular paced rhythms were excluded. A clinical cardiologist made rhythm interpretation.

Patient demographic, medication administration, and ECG data were obtained from the Stanford Translational Research Integrated Database Environment clinical data warehouse.[4] Demographic data extracted from the medical record included age at time of ECG, gender, and race. Data elements extracted from each ECG included time of study, HR, RR interval, uncorrected QT interval, and cardiologist rhythm interpretation.

The average HR, RR interval, and uncorrected QT interval for each ECG were determined over a 10-second window using the Philips DXL algorithm (Philips Healthcare, Andover, Massachusetts). This algorithm has been described, validated, and shown to be precise.[5] QT measurements were corrected using Bazett's ($QTc = QT/(RR^{1/2})$), Fridericia ($QTc = QT/(RR^{1/3})$), Framingham

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(QTc = QT + 0.154 (1 − RR)), and Hodges (QTc = QT + 1.75 (HR − 60)) formulas.

Using a random number generator, 50 patients were chosen randomly for manual QT measurements. For these patients, the QT and RR intervals were manually measured on 10 consecutive beats in lead II. QT was measured using the tangent method.[6] If the end of the T wave was difficult to determine in lead II, another lead with clearly defined T waves − most commonly V2 or V3 − was chosen and compared between ECGs from the same patient. If T waves were difficult to discern due to low voltage, poor quality tracing, or biphasic T waves in all leads another patient was chosen at random. "Global QT and RR intervals" for these manually measured ECGs were then determined using the following 7 methods: a 10-beat average, 5-beat average, 3-beat average, the QT that followed the longest RR interval, the QT that followed the RR interval closest to 60 beats/min, the QT following a randomly selected RR interval, and the average of the QT associated with the longest and shortest RR interval. These measured global QT and RR interval values were then used for correction of QT using the same correction formulas listed above. Random RR intervals were determined using a computer program to select an interval at random for each ECG.

The distribution of manually measured QT and QTc intervals determined from 10-beat averages in AF and SR were visualized using box plots. Pairwise comparisons were made between QT corrected with different formulas in AF or SR using the ANOVA and Tukey honest significance tests. ΔQT was calculated for each patient as (QTc in last instance of AF) − (QTc in first instance of SR). For calculation of ΔQT: (1) Bazett's formula was used for HR correction, (2) QTc in first instance of SR was measured as the 10-beat average for each patient, (3) QTc in last instance of AF was measured using the 7 methods described above. Box plots were created to compare ΔQT calculated using the different measurement methods. Manually measured QT and computer-measured QT in SR were compared using pairwise *t* test. A hexbin scatter plot was created of the computer-measured QTc in a patient's last instance of AF and first instance of SR. Chi-square test was used to compare patients with QTc >500 ms before and after conversion from AF to SR. Using computer-measured QT and RR intervals, univariate and multivariate mixed linear models were used to determine the independent effect of AF and HR on QTc. In the mixed-linear model, HR and AF were treated as fixed effects, QT corrected by Bazett's, Framingham, Fridericia, and Hodges formulas as dependent variables, and subject as a random effect.

Statistical analyses were conducted using Stata version 13.1 (StataCorp, College Station, Texas). The level of significance was set at p <0.05 and all tests were 2-tailed. This study received IRB approval by the Stanford University review board.

Results

A total of 31,028 patients received 103,618 ECGs at Stanford Hospital and Clinics during the study period. A total of 7,932 ECGs from 3,550 different patients were found to be in AF. A total of 715 patients were identified who had conversion from AF to SR within 24 hours. Table 1 includes demographic data on the entire 715 patient cohort, which was used for analysis with computer-generated measurements, and a subset of 50 randomly selected patient, which was used for analysis of manually measured intervals. In the 715 patient cohort, the average HR (standard deviation) in AF was 114.2 (31.6) beats/min and in SR was 77.8 (17.5) beats/min.

Table 1
Demographics

	Manual (n = 50)	Automatic (n = 715)	p
Gender			<0.001
Female	17 (34.0%)	288 (40.3%)	
Male	33 (66.0%)	427 (59.7%)	
Age (years)			0.072
<40	3 (6.0%)	21 (2.9%)	
40-50	2 (4.0%)	32 (4.5%)	
50-60	8 (16.0%)	103 (14.3%)	
60-70	13 (26.0%)	208 (29.1%)	
70-80	13 (26.0%)	216 (30.2%)	
>80	11 (22.0%)	135 (18.8%)	
Race			0.255
Asian	7 (14.0%)	82 (11.5%)	
Black	0 (0.0%)	15 (2.1%)	
Native American	0 (0.0%)	1 (0.1%)	
Pacific Islander	0 (0.0%)	11 (1.5%)	
White	28 (56.0%)	472 (66%)	
Hispanic	8 (16.0%)	66 (9.2%)	
Other	7 (14.0%)	68 (9.5%)	
Medications			
Amiodarone	4 (8.7%)	132 (20.5%)	0.354
Sotalol	1 (2.2%)	15 (2.3%)	0.07
Dofetilide	4 (8.7%)	32 (5.0%)	<0.001
Flecainide	0 (0.0%)	3 (0.5%)	0.422
Propafenone	0 (0.0%)	1 (0.2%)	0.378
Procainamide	0 (0.0%)	1 (0.2%)	0.256
Metoprolol	12 (26.1%)	138 (21.4%)	0.898
Digoxin	1 (2.2%)	19 (3.0%)	0.083
Diltiazem	7 (15.2%)	54 (8.4%)	0.455

For 50 patients in AF and SR, QT was manually measured as the 10-beat average and corrected using Bazett's, Framingham, Fridericia, and Hodges formulas (Figure 1). In SR, there were no significant differences between QTc corrected using the different formulas. However in AF, QTc corrected using Bazett's formula was significantly longer compared with QTc corrected with all other techniques (p <0.005). In AF, QT corrected with Hodges formula was longer than QT corrected with Framingham's formula (p <0.005).

ΔQT, the differences between QT in the last instance in AF and first instance in SR, was calculated using the 7 different techniques (Figure 2) for manually measuring QT in AF. Using Bazett's correction formula to correct for rate, box plots were created of ΔQTc (Figure 2). QTc calculated in AF by techniques that average intervals over multiple beats, in general, produced a longer QTc in AF compared with SR, and produced a smaller variability in ΔQT than other methods (Figure 2). The median (interquartile range) ΔQTc calculated using the 10-beat average method was 20.

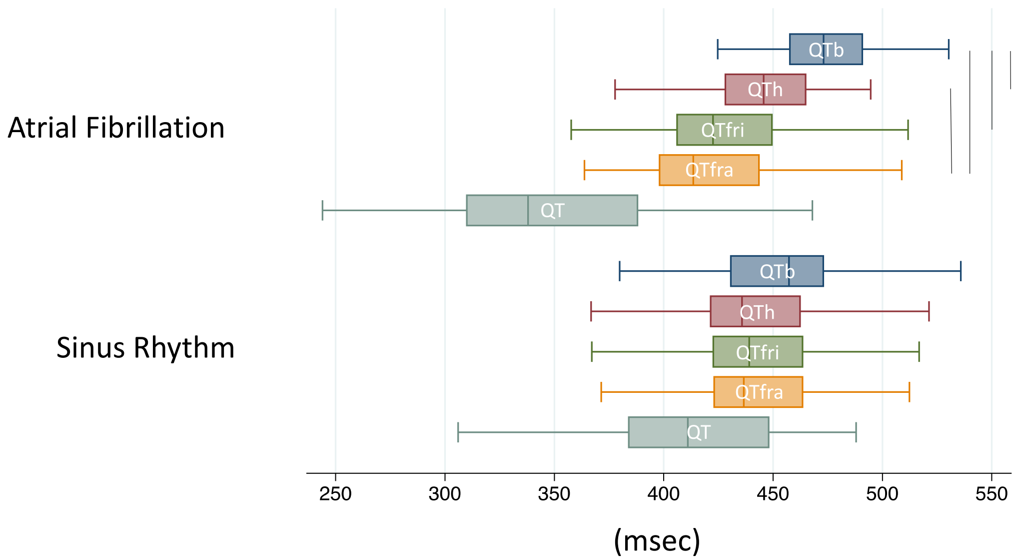

Figure 1. QTc in atrial fibrillation differs significantly depending on correction formula used − Bazett's is the longest. Box plot of QT manually measured on 50 patients in atrial fibrillation and in sinus rhythm were corrected using different correction formulas. QTb = Bazett's; QTh = Hodges; QTfri = Fridericia; and QTfra = Framingham. Each plot represents the median, interquartile range, and adjacent values. QT and RR were determined from a 10-beat average. Black bars indicate a significant difference (p <0.005). Pairwise comparisons were made using Tukey Honest Significant Difference test. In atrial fibrillation, QTc corrected by Bazett's formula was longer than any other correction methods and Hodges correction was significantly longer than using the Framingham correction. There were no significant difference between QTc calculated using different techniques in sinus rhythm.

9 (−7.5 to 36.4) ms and for the long + short method was 22.1 (−17.0 to 39.2) ms. The median (interquartile range) ΔQTc calculated using the longest RR interval method −32.2 (−62.4 to −1.0) ms or the RR interval closest to 60 beats/min method −27.2 (−54.4 to−1.0) ms resulted in a lower QTc during AF compared with SR. Randomly selecting a beat to calculate QTc produced the measurement closest to SR (ΔQT = 12.3 ms), but the largest variability in ΔQT (−26.2 to 57.6) ms. We also compared the ΔQTc calculated using the 5-beat average method using the manually measured 5-beat QT average and either the manually measured 5-beat RR average or the computer-calculated RR interval. The median (interquartile range) with the manually measure 5-beat RR average was 19.0 (0.30 to 43.7) ms and with the computer-calculated RR interval 29.2 (1.3 to 45.3) ms.

To validate computerized measurements of QT intervals in the broader cohort of 715 patients, the 10-beat manual average QT interval in SR from 50 randomly selected patients was compared with the computerized measurement of the QT interval. The average difference between computer-determined and manually measured QT was −0.63 ± 9.14 ms (p = 0.629).

We created a hexbin scatter plot to visualize the distribution of computerized measurement of QTc using Bazett's correction in 715 patients during AF plotted against their QTc in SR (Figure 3).

We used univariate and multivariate linear regression analyses of AF and HR on QTc to understand if AF had an effect on QTc independent of HR. In univariate analysis both AF and HR were associated with significant differences in QTc during AF versus SR, regardless of correction technique (Table 2). In multivariate analysis, AF was not significantly associated with a change in QTc; however, HR remained significantly associated with QTc in all correction models.

Differences in QT between AF and SR were compared between patients with HR > 110 beats/min and those with HR ≤ 110 beats/min in AF. The differences in QTc between AF and SR were more pronounced at higher HR using all 4 correction formulas (Bazett's 6.95 vs 20.66, p <0.001; Fridericia −5.19 vs −19.4, p <0.001; Framingham −6.75 vs −30.66, p <0.001, and Hodges −4.46 vs 17.90, p <0.001).

Discussion

In the present study we aimed to determine which QT correction formula and method for interval measurement was best for determining QTc in AF. We also assessed if AF had an independent effect on QT interval duration. We used a large electronic medical record database to compare QTc between a patient's last instance in AF and their first instance of SR. Currently, there is not a consensus on how best to measure or correct QT for HR in AF.

One of the challenges in correcting the QT interval properly during AF is that the HR tends to be higher. We found that differences between the QT correction formulas (Bazett's, Framingham, Fridericia, or Hodges) were more pronounced during AF, compared with SR. This is likely a reflection of the higher HR observed during AF, as these formulas tend to perform poorly at the extremes of HR.[7,8] We found that ΔQTc between AF and SR was greatest in patients with HR > 110 beats/min in AF compared with those with HR ≤ 110 beats/min. In addition, the significant difference between QTc in AF and SR resolved after

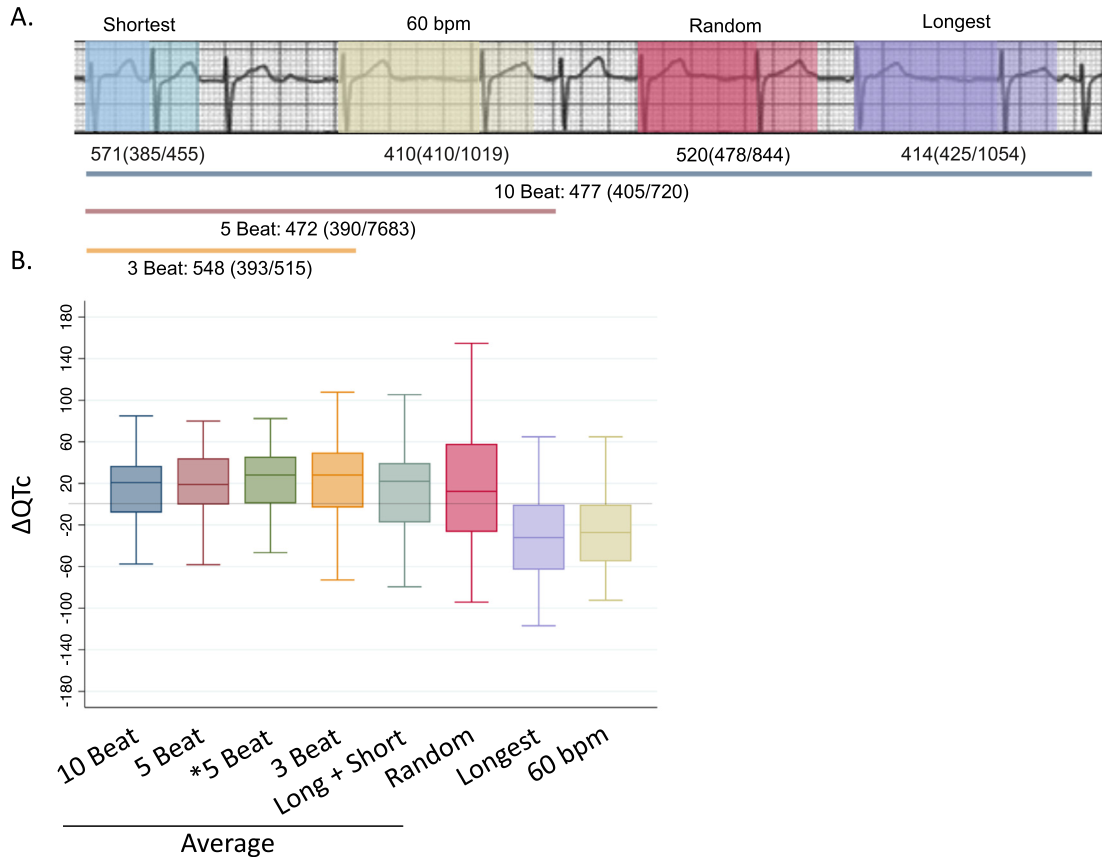

Figure 2. Techniques for measuring QT in atrial fibrillation. *(A)* Example ECG strip showing different QT and RR intervals used for QT correction. QT and RR interval were measured as a 10-beat, 5-beat, or 3-beat average, average of the longest + shortest interval, or from a random RR interval, the longest RR interval, or the RR interval closest to 60 beats/min. Dark and light shading corresponds to RR and QT intervals, respectively. Shown in the figure are QTc (QT interval/RR interval) in milliseconds. *(B)* Box plots of the difference in QTc between atrial fibrillation and sinus rhythm. QT manually measured using different techniques for 50 patients in atrial fibrillation and subtracted from the 10-beat average in sinus rhythm. *5 beats corresponds to QTc calculated from the 5-beat manually measured average QT interval and the computer-calculated RR interval. Techniques that measured QT from average of multiple beats in general had longer QTc in atrial fibrillation and smaller interquartile range than other techniques. Randomly selecting a beat to measure QT produced the greatest variability. Selecting the longest RR interval or the one closest to 60 beats/min resulted in a lower QT in atrial fibrillation compared with sinus rhythm. Correction made using Bazett's formula.

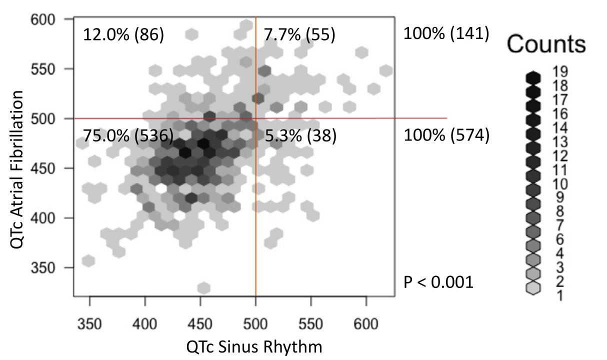

Figure 3. Hexbin scatterplot of QTc in atrial fibrillation and in sinus rhythm. QTc from a patient's last instance of atrial fibrillation and first instance of sinus rhythm were plotted using a hexbin scatter plot. Individual data points were grouped within hexagonal bins which are colored to represent density of points within. Red lines denote QTc of 500 ms. A total of 5.3% of patients had QTc < 500 ms while in atrial fibrillation, but QTc > 500 ms upon conversion to sinus rhythm. A total of 12.0% of patients had QTc > 500 ms while in atrial fibrillation, but QTc < 500 ms upon conversion to sinus rhythm. Comparison made using chi-square test. QTc was corrected using Bazett's formula. Computer-generated QT and RR intervals for 715 patients were used.

adjusting for the remaining effect of HR on QTc for each correction method. Therefore, while the different formulas performed comparably at the lower HR, care should be taken in relying on QTc, regardless of the correction formula, at high HR during AF. In these conditions, Bazett's and Hodges correction formula tended to produce elevated QTc measurements compared with SR, while Framingham and Fridericia produced lower estimates.

The ideal formula for correction of QT in AF is only part of the question. There is no consensus on how to manually measure the QT during AF given the beat-to-beat variability in the RR interval. We found that the different methods also produced a wide variation in results. Measuring QT over 10- or 5-beat averages resulted in only a slightly higher QTc in AF compared with SR and the smallest variation in difference in QTc. While multibeat averaging methods may be the most reliable, clinicians may find them too laborious to adopt routinely. However, simply selecting a single beat for calculating QTc resulted in higher variability, particularly when a beat is chosen randomly. While the popular method of averaging the longest and the shortest beat is better than choosing a random

Table 2
Univariate and multivariate linear regression analysis of atrial fibrillation and heart rate on QT interval

		Univariate			Multivariate		
		β	95 % CI	p	β	95 % CI	p
QT	Atrial fibrillation	−55.93	−59.95 to −51.91	<0.001	−0.65	−4.18 to 2.87	0.717
	Heart rate	−1.53	−1.58 to −1.48	<0.001	−1.52	−1.59 to −1.46	<0.001
QTb	Atrial fibrillation	14.28	11.25 to 17.31	<0.001	1.50	−2.43 to 5.42	0.456
	Heart rate	0.37	0.32 to 0.43	<0.001	0.35	0.28 to 0.43	<0.001
QTfra	Atrial fibrillation	−19.65	−22.15 to −17.14	<0.001	−0.014	−3.22 to 3.19	0.993
	Heart rate	−0.54	−0.59 to −0.50	<0.001	−0.54	−0.60 to 0.48	<0.001
QTfri	Atrial fibrillation	−12.87	−15.52 to −10.23	<0.001	0.50	−3.10 to 4.10	0.785
	Heart rate	−0.36	−0.41 to −0.31	<0.001	−0.37	−0.44 to −0.30	<0.001
QTh	Atrial fibrillation	7.52	4.83 to 10.21	<0.001	−0.65	−4.18 to 2.87	0.717
	Heart rate	0.22	0.17 to 0.27	<0.001	0.23	0.16 to 0.29	<0.001

QTb = Bazett's correction; QTfra = Framingham; QTfri = Fridericia; QTh = Hodges.

beat, it still results in more variability than multibeat averaging methods.

Given the results of this study, we recommend against measuring QT in AF from a randomly selected beat, longest beat, or the beat closest to 60 beats/min and instead measuring it from an average of beats. We recognize that averaging methods are the most time intensive for measuring QT and RR interval in AF; however, we showed that using the manually measured QT averaged over 5 beats with the computer-generated RR is a reasonable and time saving alternative.

Choice of QT correction formula and measurement method during AF becomes clinically significant when deciding on whether or not to start a QT-prolonging AAD. For example, dofetilide has a black box warning which limits its use in patients with a baseline QTc > 440 ms; however, the warning does not specify which QT correction formula to use. Using a correction formula like Bazett's which overestimates QTc in AF may result in fewer patients qualifying for this medication compared with patients with QTc in AF calculated with Framingham correction which underestimates QTc − something that has been suggested by a previous study.[3] However, even by conservatively choosing to correct with Bazett's formula, there were still a handful of patients (5.3%) who had QTc < 500 ms in AF followed by QTc > 500 ms after conversion to SR.

Strengths of this study include its large sample size, diverse patient population, the direct comparison of QT in SR to AF for each patient, and to our knowledge, it is the first study to look at different manual methods for measuring QT interval in AF. A limitation of our study was that it was retrospective in nature, and was therefore biased toward patients who successfully converted to SR. However, comparisons of AF versus SR were made within patients, which we believe limits selection biases. We did not control for factors that could prolong the QT interval, such as use of AADs. However, by having a 24-hour window within which the comparator ECG was selected, we minimized any intervening effect these medications may have had. Part of our analysis used computer-automated ECG measurements. We recognize that, although the computerized QT measurements were over read by a cardiologist, there may be some degree of intraprovider variability.

Table 3
Key points

In atrial fibrillation, QTc corrected by Bazett's is significantly longer compared with other correction formula
Averaging intervals produced QTc longer in atrial fibrillation compared with sinus rhythm, but with smallest variability
Randomly selecting a single beat in atrial fibrillation to calculate QTc produced the measurement closest to sinus rhythm, but with greatest variability
Care should be taken in relying on QTc no matter how it is calculated at high heart rates in atrial fibrillation
Atrial fibrillation did not have an effect on QTc independent of heart rate

However, using a 50-patient validation, we saw minimal differences between manually measured QT and computerized measurements.

In conclusion, as in SR, there is not a perfect formula for the correction of QT for HR in AF. Clinicians should be aware of inherent biases when selecting the correction formula they use for HR correction, particularly at higher HR, and how this may influence the decisions of starting an AAD. In AF, averaging QT interval over at least 5 consecutive beats is the method that results in the least variability in QTc. Finally, AF itself is not independently associated with QT prolongation (Table 3).

Disclosures

The authors have no conflicts of interest to report.

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