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Diurnal QT analysis in patients with sotalol after cardioversion of atrial fibrillation

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Abstract

Background: The risk of ventricular arrhythmias in patients on QT prolonging drugs is indicated to be increased early after cardioversion (CV) of atrial fibrillation (AF) to sinus rhythm (SR). Sotalol, used to prevent AF relapse, prolongs cardiac repolarization and corrected QT interval (QTc). A pronounced QTc prolongation is an established marker of pro-arrhythmias. Our objective was to use novel technique to quantify and evaluate the diurnal variation of the QTc interval after elective CV to SR in patients on sotalol or metoprolol.

Methods: Fifty patients underwent twelve-lead Holter recording for 24 hr after elective CV for persistent AF. All patients had the highest tolerable stable dose of sotalol (n = 27) or metoprolol (n = 23). Measurements of QT and RR intervals were performed on all valid beats.

Results: A clear diurnal variation of both HR and QTc was seen in both groups, more pronounced in patients on sotalol, where a high percentage of heartbeats with QTc >500 ms was observed, especially at night. Six patients (22%) on sotalol but none on metoprolol had >20% of all heart beats within the 24-hour recording with QTc >500 ms.

Conclusion: Twenty-four-hour Holter recordings with QT-measurement immediately after CV demonstrated that one in five patients on sotalol had >20% of all heart beats with prolonged QTc >500 ms, especially during night-time. The QTc diurnal variation was retained in patients on β-blockade or a potent class III anti-arrhythmic drug with β-blocking properties.

KEYWORDS

anti-arrhythmic, atrial fibrillation, cardioversion, QT interval, sotalol

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia, and despite progress with catheter ablation and pulmonary vein isolation, there is a need for pharmacological treatment alternatives. Few new pharmacological options have been added during the last decade and there is a need for improved risk markers to avoid pro-arrhythmias (Lafuente-Lafuente et al., 2012).

Abbreviations: AA, anti-arrhythmic; AF, atrial fibrillation; CV, electrical cardioversion; QTc, QT interval, corrected for heart rate according to Fridericia; SR, sinus rhythm; TdP, Torsades de Pointes.

In symptomatic AF, or when tachycardiomyopathy is suspected, treatment attempts to restore sinus rhythm (SR). Cardioversion (CV) is often needed and treatment with a β-blocker or antiarrhythmic (AA) drugs are used to maintain SR. Recommended drugs have varied over time; contemporary guidelines suggest first-line treatment with a β- or calcium channel blocker and secondary treatment with a class I or class III AA drug (Hindricks et al., 2020a; Kirchhof et al., 2016). The class III AA drug sotalol is also a β-blocker and acts on cardiac repolarization by blocking the rectifier potassium current (IKr), seen as prolongation of the corrected QT interval (QTc) on ECG (Weeke et al., 2013). It has been suggested that the sensitivity to the QTc prolonging effect of sotalol is increased after CV and the risk of Torsades de Pointes (TdP) thereby increases soon after restoration of sinus rhythm (Darbar et al., 2008; Lenhoff et al., 2016; Roden, 1998). We have previously described QTc prolongation on a standard 12-lead ECG in patients on sotalol, as more pronounced immediately after elective CV, compared to one week later. This prolongation of the QTc interval was not found in patients on metoprolol (Lenhoff et al., 2016).

Our ability to identify patients at risk for TdP is limited, due to the low incidence, as well as the unpredictable nature of TdP. Prolongation of the QTc interval is a recognized risk marker for TdP, but the diurnal variation of drug-induced QTc prolongation has not been well studied, although proposed as a pro-arrhythmic risk marker (Niemeijer et al., 2014). In this study, our aim was to monitor the QTc interval for 24 hr immediately after CV and compare the diurnal variation of this interval between patients on sotalol, that is, with drug-induced QTc prolongation, and those on a pure β-blocker, metoprolol.

2 | MATERIAL AND METHODS

This study was a clinical, prospective, nonrandomized, parallel group study comparing 24 hr of 12-lead Holter recordings in patients with sotalol or metoprolol treatment, immediately after elective CV because of symptomatic persistent AF. Patients with persistent AF planned for electrical CV at Södersjukhuset Hospital, Stockholm, Sweden between August 2013 and October 2014 were eligible for the study. Approximately 500 planned CVs are performed each year at the hospital, and thus 10% were included in the study. Main reasons for lack of inclusion were treatment with amiodarone or other β-blockers than metoprolol and periods during which research personnel were not available.

In line with clinical routine at the hospital and national guidelines (Hindricks et al., 2020b; Socialstyrelsen, 2015), patients were titrated to the highest tolerable dose of sotalol (target dose 160 mg twice daily) or metoprolol (target dose 200 mg once daily) at outpatient visits. All patients were on a stable dose for at least one week before CV. Digoxin was added during the titration period if necessary for rate control. In accordance with our clinical practice, all patients had been treated with metoprolol first, and therefore patients introduced to sotalol had undergone at least one prior CV on metoprolol.

To optimize the comparison of the QTc interval between sotalol and metoprolol, and since measurements of the QTc interval during AF is difficult, only patients in whom SR was restored by CV were included (Musat et al., 2013). CV was performed according to clinical practice with sedation on propofol and biphasic synchronized direct current shock. Digoxin treatment was discontinued after a successful CV. All patients received oral anticoagulation prior to CV. In line with standard care of elective CV, a 12-lead ECGs was recorded at one time-point, usually approximately one hour after CV. The Ethic Committee in Stockholm (2010/659-21/2) approved the study and each patient gave informed consent after CV.

2.1 | Electrocardiographic measurements

Twelve-lead Holter ECG recordings were obtained for 24 hr after CV using a Global Instrumentation (GI) M12R ECG continuous 12-lead digital recorder. The recording started one hour after CV, when the patient was fully awake and again was asked to participate and confirmed consent to participation in the study. The recording lasted for 22–24 hr, depending on the patient's return to the outpatient clinic. The continuous 12-lead digital ECG data were stored onto Secure Digital (SD) memory cards.

The data from the SD card was uploaded to the iCOMPAS software (ERT) for analysis. Beat-to-beat QT intervals were automatically measured with iCOMPAS after GI Enterprise Software provided QRS detection, RR and QRS intervals in all ECG leads, with annotations overlooked by a cardiologist. The generated individual beat-to-beat data with measurements of RR, QRS, and QT/QTc from each patient. Measurements of the QT interval started from the onset of the QRS interval to the end of the T wave, without U waves, as previously described (Musat et al., 2013; Socialstyrelsen, 2015). Lead selection was thoroughly evaluated, and a sensitivity analysis was made by testing the results with different lead selection for QTc.

The ectopic and unmeasurable beats were removed from the analysis. We used an automatic filtering method to remove measurements associated with measurements outside the plausible physiological range, RR <300 ms or >2,000 ms, QTc <300 or >700 ms and beats with differences of QTc >80 ms compared to the preceding beat. The preceding RR interval was used for heart rate correction of QT intervals using the Fridericia formula ($QTcF = QT/RR^{1/3}$) (Giudicessi et al., 2019; Page et al., 2016).

2.2 | QT clock

QT clocks were used to visualize QTc. QT clocks are a novel visual tool for QT analysis, where a computer algorithm plots QTc over time (Figure 1) (Page et al., 2016). Lead selection can be automated,

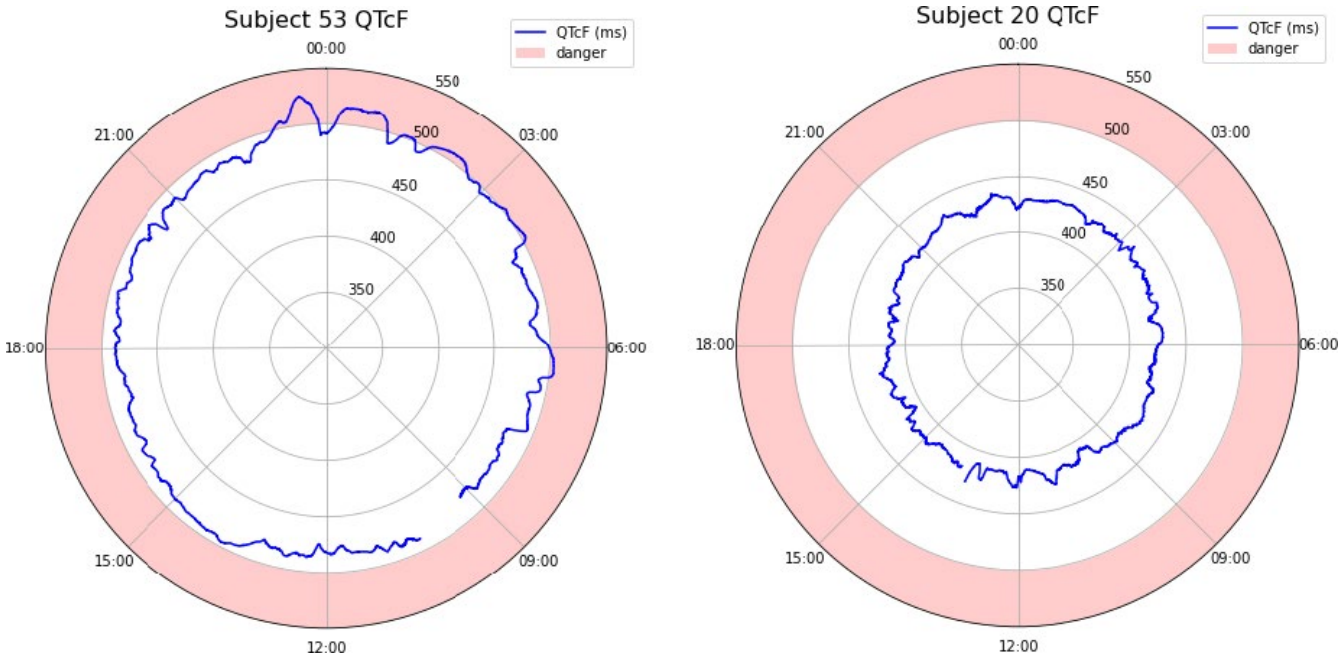

FIGURE 1 Example QT clocks. Median QTc in a patient treated with sotalol (left panel) or metoprolol (right panel) from 24-hour Holter recordings taken immediately after CV. Danger zone is marked as QTc >500 ms in this "24-hour" clock

choosing the lead with the least dispersion in QTc or otherwise prespecified. Both individual clocks and aggregated data for both treatment groups are illustrated, by lead II.

2.3 | Statistics

Categorical data are presented as total number and proportions (%). Continuous variables are presented as mean ± standard deviation (*SD*) or median with interquartile range (IQR) as appropriate. We tested background characteristics with Shapiro–Wilk test to assess normality distribution, and since criteria for normality distribution was met, unpaired Student's *t* test was used to test the difference between treatment groups for continuous variables, except for age and ECG parameters, where Mann–Whitney U tests were used. Categorical variables were compared using the Fishers exact test. The results were regarded as significant if a two-sided test yielded a significance level equal to or less than 0.05. QTc outliers were defined as those patients with >20% of heartbeats with QTc >500 ms within the specified timeframe. For all analysis IBM SPSS Statistics, Version 25.0, IBM Corp. was used.

3 | RESULTS

Fifty-six patients were included in the study and completed the 24-hour recording on the day of CV. Fifty patients (sotalol $n = 27$, metoprolol $n = 23$) remained for baseline analysis after excluding patients with early relapse of AF or noise.

Clinical characteristics of enrolled patients are shown in Table 1. Metoprolol-treated patients were older and congestive heart failure, as well as treatment with ACE inhibitor were more frequent in this group. Ejection fraction measured by echocardiography was 54 ± 3% in sotalol, and 48 ± 10% in metoprolol patients, respectively. Four of the 50 patients had a diagnosis of sleep apnea. It should, however be acknowledged that the condition may be underdiagnosed in this population with a mean BMI close to obesity and with 17 subjects categorized as obese (BMI >30 kg/m^2). Mean dose of sotalol was 270 ± 50 mg and of metoprolol 165 ± 49 mg. The median (IQR) HR before CV was somewhat lower in patients on sotalol (82; 19) bpm as compared to patients on metoprolol (88; 22) bpm, but this difference was not significant ($p = .55$). ECG parameters from a standard 12-lead recording at discharge after CV showed, as expected, a longer QTc interval in patients on sotalol treatment. The QTc value exceeded 480 and 500 ms in four and two patients on sotalol, respectively, as compared to one and no patients on metoprolol.

The mean duration of ECG-recording was 22.7 ± 2.5 hr in sotalol patients and 23.1 ± 1.8 hr in metoprolol patients. In total, 5,583,100 heartbeats were recorded in patients in SR. After filtering, the final analysis of recordings represented 70.4% of total heartbeats; median (IQR) 68,063 (31,239) beats per patient and recording in the sotalol group and 66,919 (72,829) in the metoprolol group. Since results were essentially independent of lead selection, lead II measurements were used in the report.

3.1 | Analyses of HR and QTc

During the 24-hour recording after CV, overall QTcF was generally longer in patients on sotalol as compared to patients on metoprolol, with a median (IQR) of 456 (21) ms and 432 (64) ms ($p = .008$), respectively. Median heart rate was slightly lower in patients on metoprolol

TABLE 1 Baseline descriptives

	Sotalol ($n = 27$)	Metoprolol ($n = 23$)	p value*
Age, years (mean; *SD*)	65 (8)	69 (6)	.05
Age, years (median; IQR)	65 (9)	70 (10)	.49
Women	7 (26)	7 (30)	.72
BMI, kg/m^2 (mean; *SD*)	29 (6)	28 (4)	.71
Duration AF, months (mean; *SD*)	2.8 (2)	2.9 (2)	.77
Smoking (ongoing or previous)	11 (41)	8 (35)	.59
HR prior to CV, bpm (median; IQR)	82 (22)	88 (19)	.55
Hypertension	17 (63)	14 (61)	.88
SBP (mmHg) (mean; *SD*)	128 (13)	131 (19)	.40
IHD	1 (4)	4 (17)	.11
Valvular heart disease**	3 (11)	4 (17)	.48
Diabetes mellitus	3 (11)	2(9)	.78
OSAS	3 (11)	1 (4)	.38
Congestive heart failure	0 (0)	7 (30)	.005
LV ejection fraction, mean (*SD*) %	54 (3)	48 (10)	.002
LA size, mean volume (*SD*) ml/m^2	42 (10)	46 (12)	.12
S-Creatinine (*SD*) mmol/L	83 (16)	85 (18)	.66
S-Potassium, (*SD*) mmol/L	4.2 (0.3)	4.3 (0.2)	.53
ACE inhibitors/ARB (*n*; %)	11 (41)	17 (74)	.02
Digoxin (*n*; %)	1 (4)	7 (30)	.08
Diuretics (*n*; %)	9 (33)	7 (30)	.83
HR, bpm	57 (8)	53 (9)	.16
QRS, ms (mean; *SD*)	95 (15)	102 (23)	.47
QRS ≥120 ms	2 (7)	6 (26)	.12
QTcF, ms (mean; *SD*)	452 (29)	419 (34)	.001
QTcF >500 ms	2 (7)	0 (0)	.49

Note: No. (%) if not otherwise specified. ECG one hour post-CV.

Abbreviations: AF, atrial fibrillation; HR, heart rate; IHD, ischemic heart disease; LA, left atrium; LV, left ventricular; QTcF, QT interval corrected for HR according to Fridericia; SBP, systolic blood pressure; SR, sinus rhythm.

*All p values derived from student's t test or Fishers exact test, except for age and ECG parameters, where we used nonparametric test; $p > .05$ is considered significant.

**Valvular heart disease; valvular stenosis or inufficiency ≥2/3 or prosthetic valve.

compared to patients on sotalol after CV, 56 versus 61 bpm ($p = .04$). No patient suffered any ventricular arrhythmias during the study.

3.1.1 | Heart rate variation over 24 hr

When HR was analyzed across two-hour time windows, diurnal variation was apparent for HR (Figure 2a,b). Mean HR was lowest during early morning hours, with a nadir of 55.9 (90% CI: 52.2–59.5 bpm) in the sotalol group and of 53.0 (90% CI: 49.7–56.2 bpm) in the metoprolol group between 04:00 and 05:59 (Table 2). Mean HR then increased in both groups, an effect that was more pronounced in patients on sotalol. In patients on sotalol, there was a successive increase up to a peak mean HR of 63.9 (90% CI: 60.0–67.7 bpm) in the evening, between 18:00 and 19:59, and then HR declined throughout the night. In patients on metoprolol, this pattern was less pronounced, and mean HR changes were small during the remaining recording, between 55.9 and 57.3 bpm, from the peak value of 58.9 (90% CI: 55.7–62.1 bpm) between 08:00 and 09:59. The difference between the lowest and the peak mean HR over two-hour time windows was therefore smaller in the metoprolol group (58.9 – 53.0; 5.8 bpm) than in the sotalol group (63.9 – 55.9; 8.0 bpm).

3.1.2 | QTcF interval variation over 24 hr

A diurnal variation was seen when mean QTcF was analyzed in two-hour time windows and was more pronounced in patients on sotalol as compared to patients on metoprolol (Figure 2b). In the sotalol group, the longest mean QTcF values were observed during the night, with a peak between 2:00–3.59 (461; 90% CI, 451–472 ms) (Table 2). A successive shortening of QTcF was seen during early morning hours and until 12:00, with the shortest values of the day between 10:00 and 11:59, with a mean QTcF of 440 (90% CI; 432–449 ms). In patients on metoprolol, the variation was less pronounced, with the longest mean QTcF values both early in the morning between 6:00–7:59 (433; 90% CI 419–447 ms) and early evening between 18:00–19:59 (435; 90% CI; 423–447 ms). The shortest mean QTc in patients on metoprolol was seen between 10:00–11:59 (423; 90% CI; 410–436 ms). The difference between the highest and the lowest mean QTc across all two-hour time windows was larger in the sotalol group (461–443; 18 ms) than in the metoprolol group (435–423; 11 ms).

Duration of time with prolonged QTc, more than 480 and 500 ms, respectively, was analyzed in the continuous 24-hour recording over 2-hour time windows (Figure 3a,b). Sotalol patients had a higher proportion of mean heartbeats with QTc prolongation overall. QTc >480 was seen in 16 ± 23% of total heartbeats in patients on sotalol versus. 8 ± 15% in patients on metoprolol ($p = .029$). The proportion of QTc >500 ms in sotalol patients in comparison to metoprolol patients was 6.8 ± 11% versus 1.8 ± 3.3% ($p = .03$).

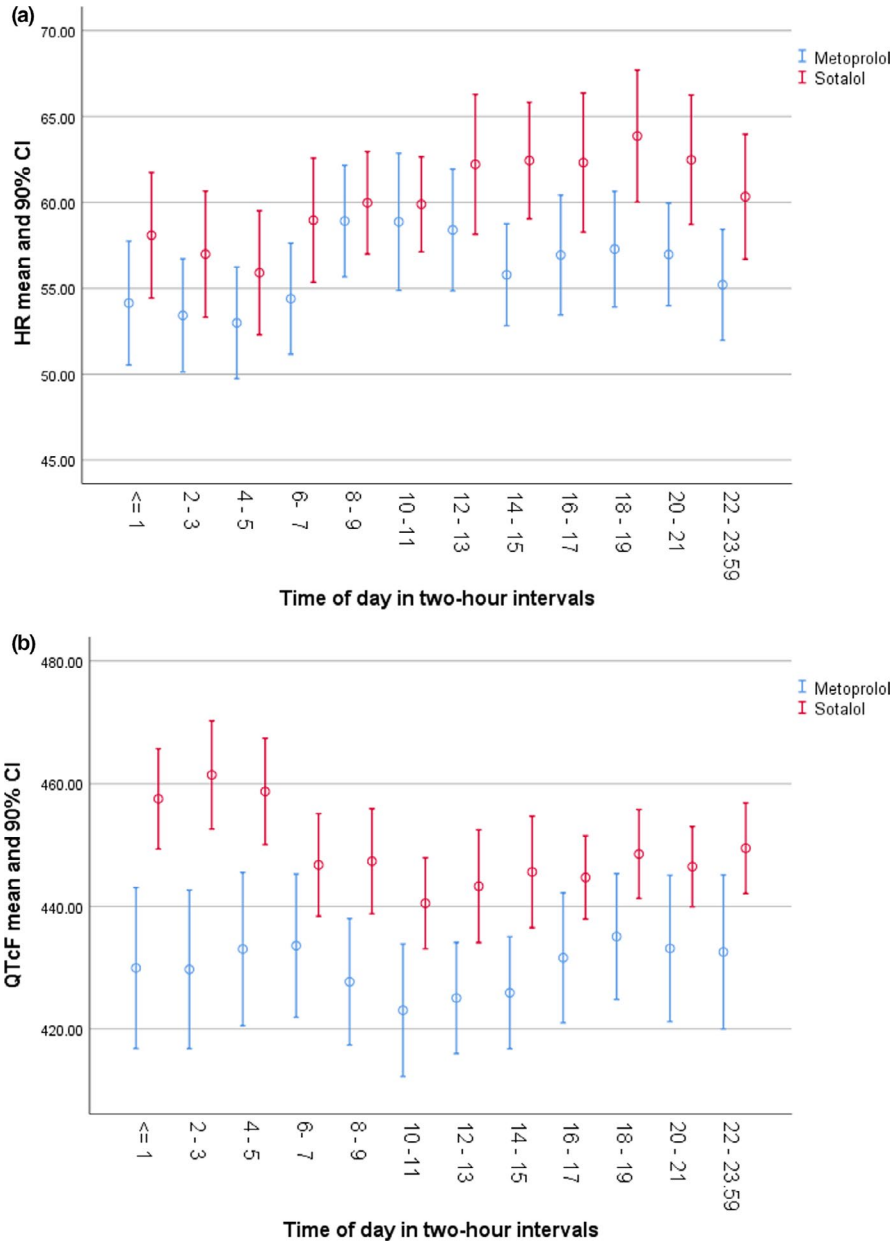

FIGURE 2 *Panel A*: Mean HR and 90% CI in two-hour intervals in patients on sotalol (red) and metoprolol (blue) in 24 hr Holter recordings after CV. *Panel B*: Mean QTc and 90% CI in two-hour intervals in patients on sotalol (red) and metoprolol (blue) in 24 hr Holter recordings after CV

3.1.3 | QTc outliers

In patients on sotalol, the QTc prolongation was pronounced during night-time between 00:00 and 05:59, at which time mean QTcF exceeded 480 ms in four (0:00–1:29), five (2:00–3:59) and seven (4:00–05:59) patients. Corresponding numbers in patients on metoprolol were two, three and three. During the same time windows, mean QTcF exceeded 500 ms in three, four and one patient on sotalol and in no patient on metoprolol.

Eight and six sotalol patients (30% and 22%) were identified as outliers, that is, had >20% of all heartbeats during the 24-hour recording with QTc >480 ms or >500 ms, respectively versus none in the metoprolol group (p = .005 and .018). In total eight patients on sotalol and three on metoprolol exhibited >20% beats with QTcF >500 ms during any of the 2-hour time windows. The frequency of outliers was higher during night, with seven patients on sotalol with >20% of heartbeats with QTc >500 ms between 02:00 and 03:59 and between 04:00 and to 05:59, compared to two and one, respectively in the metoprolol group (Figure 4a,b).

Two patients identified by routine ECG at discharge after CV with QTc >500 ms are visualized as patient E and H in Figure 4a.

QT clocks are shown aggregated for each group in Figure 5 and by patient in Figure 1 and supplement. These confirm the presence of a diurnal variation of QTc.

4 | DISCUSSION

We performed 12-lead ECG Holter monitoring for 24 hr in patients on sotalol and metoprolol immediately after elective CV of AF to SR. As expected, the QTc interval was longer in patients on sotalol than in patients on metoprolol. It was, however unexpected to find

that the diurnal variation was larger on sotalol than on metoprolol and the study revealed that a substantial proportion of patients on sotalol experienced a high percentage of beats with QTc >500 ms; in fact, one in 5 patients on sotalol had QTc >500 ms for more than 20% of time during the entire 24-hour recording and in eight patients this was seen in several 2-hour time windows.

Sotalol is an AA drug with potent blocking of IKr, as well as β-blocking properties, whereas metoprolol is a pure β-blocker. The β-blocking effect was illustrated by the mean HR, with low mean HR in both treatment groups. The potassium-channel blocking effect was visualized as prolongation of the QT interval after correction for HR. Even a modest QT prolongation may act as an early marker for serious cardiovascular events and death and has been proposed to be used as one of the parameters in triage of patients (Beinart et al., 2014; Giudicessi et al., 2019; Zhang et al., 2011). The occurrence of TdP in sotalol treatment was first described in 1979, but has been hard to quantify, recent studies have shown an incidence of TdP of 1.6% in hospital patients and one register-based study in 624 patients with paroxysmal AF, found an incidence of TdP of 10% during a median follow-up time of 20 months, but without fatal arrhythmias (De Vecchis et al., 2019; Vandael et al., 2017). The largest randomized study on patients with AF and sotalol treatment, the PAFAC study, showed a TdP incidence of 2.3% in 384 patients during one year and a total mortality rate of 1.6% (Fetsch et al., 2004). TdP seldom occurs without influence of other risk factors such as hypokalemia, hypomagnesemia, structural heart disease or concomitant medication with other QT prolonging drugs and in conjunction with bradycardia (Roden, 1998). However, even after eliminating risk factors, TdP may appear after a long time of treatment (Ahmad & Dorian, 2007). Restoration of SR in persistent AF has been suggested to increase the risk of TdP (Darbar et al., 2008). There was no difference in HR between patients on sotalol and on metoprolol prior to CV and only a few patients ($n = 6$) had HR >100 bpm, a factor previously judged as a possible contributor to TdP following CV (Vandersickel et al., 2015). We have previously described QTc prolongation after CV that seems reversed one week later (Kirchhof et al., 2016) and Darbar et al showed prolongation of QTc shortly after CV compared to during AF (Bexton et al., 1986). Yamaguchi et al found an attenuated QT/RR slope with a maximum of 4–5 hr after restoration to SR in paroxysmal AF with a diurnal Holter recording in five patients on AA drugs (Darbar et al., 2008; Lenhoff et al., 2016; Yamaguchi et al., 2015). In our study, the diurnal rhythm was more pronounced in patients on sotalol as compared to patients on metoprolol, at night. The difference might, at least partially, be explained by sotalol's reverse use dependence, that is, prolongation of QTc is more pronounced during night-time hours with low heart rates. It is specifically this combination of low heart rates and pronounced prolongation of the QTc interval that may lead to TdP in susceptible patients.

In clinical practice, measurement of QTc after CV is performed on a single discharge ECG, thus only showing a one-point prevalence

TABLE 2 HR and QTc, mean and 90% CI, over 24 hr in two-hour intervals

	Sotalol		Metoprolol	
Clock time	HR (bpm; mean; 90% CI)	QTc (ms; mean; 90% CI)	HR (bpm; mean; 90% CI)	QTc (ms; mean; 90% CI)
0:00 to 01:59	58.1 (54.43–61.74)	457.5 (449.35–465.72)	54.1 (50.53–57.75)	429.9 (416.81–443.04)
02:00 to 03:59	57.0 (53.31–60.66)	461.4 (452.61–470.25)	53.4 (50.13–56.71)	429.7 (416.79–442.65)
04:00 to 05:59	55.9 (52.29–59.51)	458.7 (450.06–467.4)	53.0 (49.73–56.24)	433.0 (420.52–445.55)
06:00 to 07:59	59.0(55.35–62.58)	446.8 (438.40–455.10)	54.4 (51.16–57.62)	433.6 (421.9–445.26)
08:00 to 09:59	60.0(56.99–62.96)	447.4 (438.78–455.93)	58.9 (55.67–62.16)	427.7 (417.37–438.01)
10:00 to 11:59	59.9 (57.13–62.65)	440.1 (433.08–447.92)	58.9 (54.87–62.86)	423.1 (412.27–433.84)
12:00 to 13:59	62.2 (58.14–66.28)	443.3 (434.07–452.47)	58.4 (54.85–61.93)	425.1 (415.99–434.1)
14:00 to 15:59	62.4 (59.04–65.83)	445.6 (436.52–454.71)	55.8 (52.82–58.75)	425.9 (416.77–435.03)
16:00 to 17:59	62.3 (58.26–66.37)	444.7 (437.91–451.49)	58.9(53.45–60.42)	431.6 (421.01–442.20)
18:00 to 19:59	63.9 (60.02–67.71)	448.5 (441.29–455.77)	57.3 (53.92–60.65)	435.1 (424.81–445.33)
20:00 to 21:59	62.5 (58.71–66.25)	446.5 (439.93–453.02)	57.0 (53.99–59.95)	433.1 (421.21–445.06)
22:00 to 23:59	60.33(56.69–63.97)	449.5 (442.08–456.87)	55.2 (51.97–58.44)	432.6 (420.01–445.10)

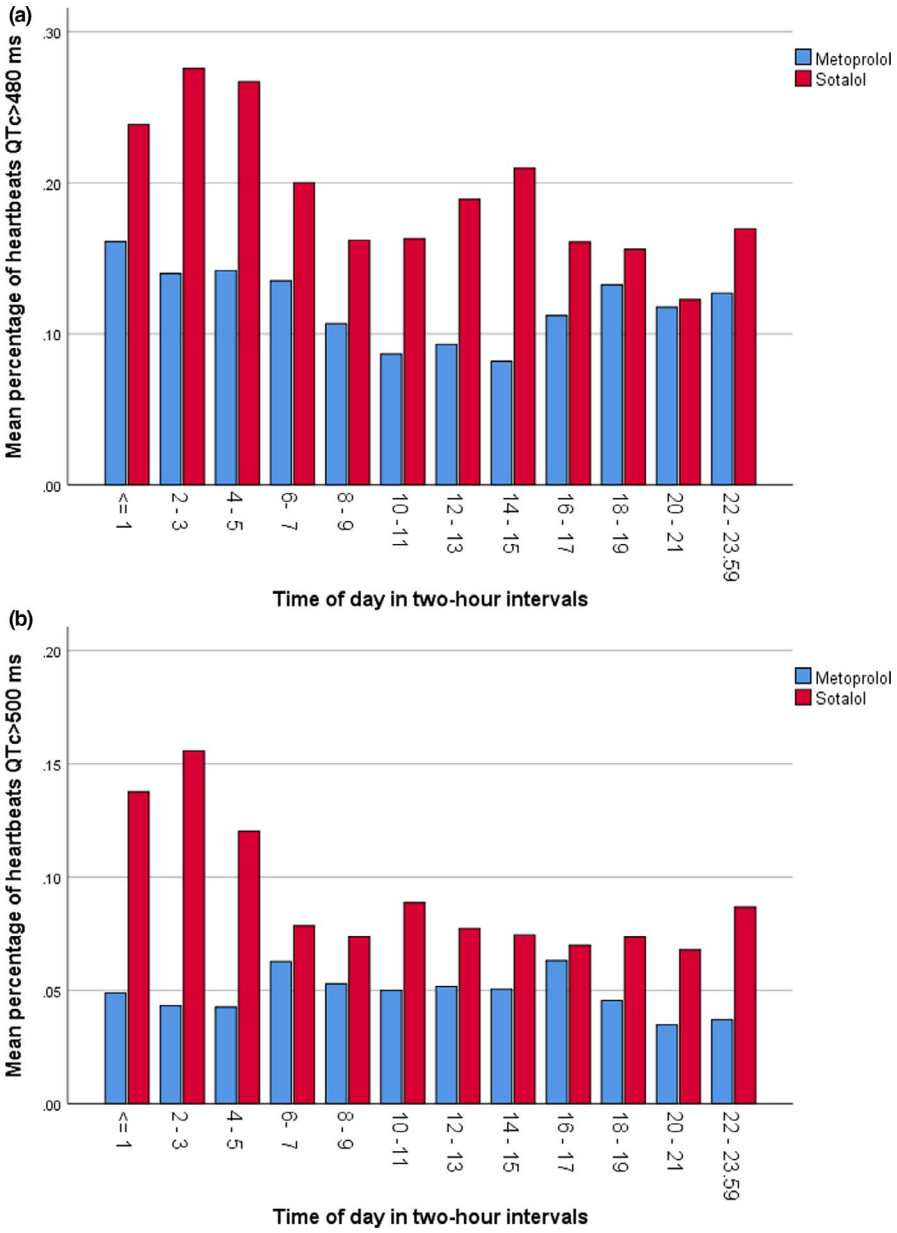

FIGURE 3 Mean fraction of heartbeats with long QTc in 2-hour time windows, in patients on sotalol (red) or metoprolol (blue) the first 24 hr after CV. *Panel A*: QTc >480 ms; *Panel B*: QTc >500 ms

measurement. The standard discharge ECG after CV in our study revealed that two out of 27 patients (7%) had QTc >500 ms, whereas the 24-hour Holter recording after CV revealed six patients (22%) with QTc >500 ms more than 20% of time on sotalol treatment. Holter recordings with QTc monitoring may be a better approach to identify high-risk patients for ventricular arrhythmias than current clinical practice. It seems likely that the aggregated time of prolonged QTc is an important factor in regard to the pro-arrhythmic risk, but a threshold for this parameter is to our knowledge unknown.

To our knowledge the diurnal QTc changes are not well investigated under the influence of AA drugs. The 24-hour rhythm of QTc is well described, with the most prolonged QTc during night and a reduction of the interval during morning hours (Bexton et al., 1986). A Holter-study in patients on antipsychotic drugs showed prolonged QTc and marked variability in HR and QTc over 24 hr as in our study (Tümüklü et al., 2019). We have shown that the diurnal variation of the QTc interval was retained immediately after restoration to sinus rhythm in patients on treatment with a pure β-blocker and on sotalol. Especially at night, a substantial part of patients had long QTc, in fact some patients on sotalol had >40% of heartbeats with QTc >500 ms during several hours. A recent study of 22 Covid-19 patients treated with hydroxychloroquine and azithromycin showed fairly constant QT prolongation on active drugs compared to placebo, while the control group had a more normal variation over 24 hr (Cipriani et al., 2020). In a study in patients with recent myocardial infarction, QTc was prolonged and the diurnal variation diminished. In these patients, treatment with a β-blocker normalized diurnal variation compared to no treatment and to healthy controls. QTc correction was however performed with Bazett formula, known to underestimate the QTc interval as heart rate is reduced, and vice versa (Furukawa et al., 2006). We used QT clocks to illustrate the QTc interval after

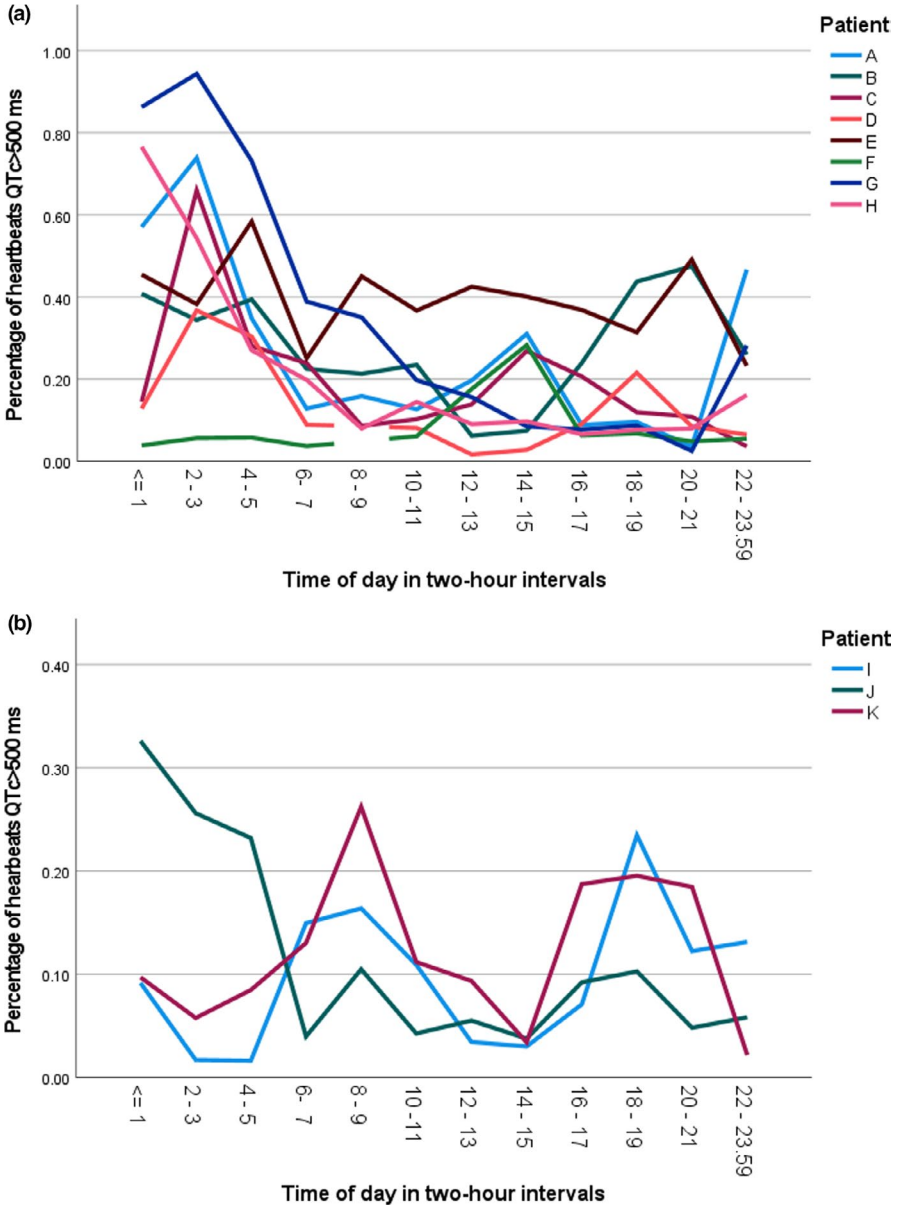

FIGURE 4 Fraction of beats with QTc >500 ms in 2-hour time windows in patients with more than 20% in any window. *Panel A*: Sotalol; *Panel B*: Metoprolol

CV. The QT clock has previously been used to show the diurnal variation of QTc prolongation in patients with inherited LQT 1 and 2 syndrome (Page et al., 2016). To our knowledge, it has never been used with 12-lead Holter, or in patients with AA therapy in conjunction to CV. The QT clock may be a new tool to deliver a level of QTc prolongation burden in patients treated with sotalol.

4.1 | Limitations

This study is limited by the nonrandomized study design, and by the fact that patients on sotalol had previously been treated with metoprolol and relapsed after CV, that is, the groups were therefore not fully comparable. Since we included patients prospectively and simultaneously in the two groups, we could not do a paired comparison in the same patients with two different treatments. It should be noted that patients on sotalol in this study represented a selected population at low risk for pro-arrhythmias, with normal ejection fraction and no history of congestive heart failure. Sleep apnea may cause episodes of bradycardia and may affect QTc variability. The incidence of this condition in the population was not evaluated and an assessment of nighttime oxygen saturation had not been consistently performed. Plasma concentrations of sotalol or metoprolol were not measured. All patients were at steady state, had normal kidney function and no dose changes occurred in the studied population. The heart rate correction of QTc beat-to-beat is suffering from the rigidity of the correction formula. Despite attempts with different population-based formulas, the overall results were however similar. The recordings were performed in an outpatient setting and noise was common, and some data had to be filtered out due to uncertainty of measurements.

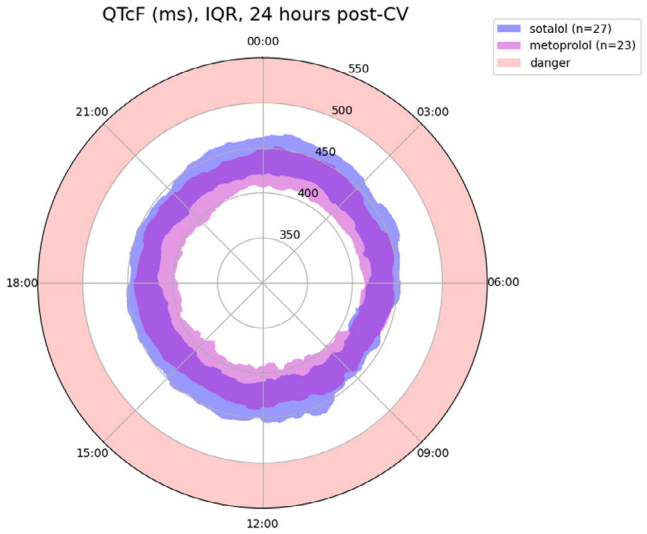

FIGURE 5 Range of QTc in sotalol and metoprolol groups, one day after cardioversion. The plot indicates that lower QTc is achieved in the metoprolol group throughout the day, with an exception around 6–8 a.m. Conversely, QTc is consistently higher in the sotalol cohort, except around the same "wake up" period. The plot also illustrates increased QTc in both cohorts at night, starting around 10 p.m. and peaking from 1–5 a.m.

5 | CONCLUSION

Twenty-four-hour 12-lead Holter revealed that patients on sotalol had a high proportion of QTc >500 ms during the first 24 hr after CV of AF in comparison to patients on metoprolol. The burden of long QTc was highest at night and there was a diurnal rhythm in QT prolongation in patients on sotalol. More patients at risk can be identified with prolonged ECG monitoring.

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CONFLICT OF INTEREST

Dr. Borje Darpo owns shares and is eligible for stock options with ERT, Philadelphia, USA. Dr. Jean-Philippe Couderc is consultant for ERT, Philadelphia, USA. The other authors have no conflicts to disclose.

ETHICS

The Ethic committee in Stockholm (2010/659-21/2) approved this study. Holter recordings were made with the consent of all participants, and the study conforms to the Declaration of Helsinki.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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