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ORIGINAL RESEARCH

Repolarization Injury and Occurrence of Torsades de Pointes During Acute Takotsubo Syndrome

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ABSTRACT

BACKGROUND During takotsubo syndrome (TS), QTc prolongation is common, reflecting repolarization injury and providing the substrate for torsades de pointes (TdP). TdP has been reported sporadically in TS, yet QTc prolongation and TdP risk are often overlooked during management.

OBJECTIVES In TS patients, we sought to document TdP incidence, characteristics of patients with TdP, and association of QTc with postdischarge survival.

METHODS Among consecutive TS patients at a single institution, we documented admission and discharge QTc, TdP incidence, and postdischarge 1-year mortality from 2006 to 2019. For perspective regarding TdP-TS risk, we characterized all published TdP cases from 2003 to 2022.

RESULTS Of 259 patients, median age was 68 (range: 59-77) years; 92% were female. The QTc interval was prolonged (≥460 ms) on admission in 129 (49.8%) patients and at discharge in 140 (54%) patients. QTc was ≥500 ms either on admission or at discharge in 98 (37.8%) patients. In-hospital TdP incidence was 0.8%. Postdischarge mortality was associated with admission but not discharge, QTc: <460 ms (1.6%); 460-499 ms (12.6%); ≥500 ms (8.8%); $P = 0.0056$. Among 38 published TdP-TS cases, 80% of TdP events were within 48 hours of hospitalization, 90% of events occurred with QTc ≥500 ms, and 47.5% of events occurred with QTc ≥600 ms. Conditions associated with TdP risk were present in fewer than one-third of patients.

CONCLUSIONS During TS, QTc ≥500 ms was frequent. TdP incidence was low, with unpredictable occurrence and observed almost entirely with QTc ≥500 ms. A normal admission QTc was associated with >98% survival at 1-year postdischarge. (JACC Adv. 2024;3:101263) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

QTc = QT interval corrected for heart rate

TdP = torsades de pointes

TS = takotsubo syndrome

The takotsubo syndrome (TS) has received considerable research interest since its first description in 1990. As a result, the characteristics of this unique acute cardiac condition have evolved beyond their initial reports. There is now substantial diversity observed including a notable incidence in men, a spectrum of regional wall motion abnormalities that extend beyond the classic apical ballooning, and the understanding that TS triggers are not exclusively negative events and may even be absent.[1-4] Furthermore, it is now acknowledged that TS is not a benign condition and carries a considerable risk of cardiogenic shock, major ventricular arrhythmias, and death.[2,5]

Repolarization injury, characterized by QTc interval prolongation and T-wave inversion, is a hallmark of TS yet has received limited research attention.[6-13] The QTc interval typically lengthens progressively during acute TS, followed by gradual resolution over several weeks.[6-13] Given the well-established connection between prolonged QTc interval and occurrence of torsades de pointes (TdP), it is not surprising that this unique arrhythmia has been reported sporadically in patients with TS.[2,5,14-16] The characteristics and incidence of TdP events during TS hospitalization are largely unknown. Furthermore, the length of hospital stay for TS patients in the United States is often short (3-4 days); consequently, the QTc interval may be significantly prolonged at discharge, posing a risk for TdP postdischarge, which could lead to sudden death.[17] To address these uncertainties, we documented admission and discharge QTc intervals, TdP incidence, and 1-year mortality stratified by admission and discharge QTc interval using data from a single institution U.S. registry. For additional perspective, we reviewed and characterized all English language case reports of TdP-TS published through 2022.

METHODS

CONSECUTIVE PATIENT COHORT POPULATION. This study was approved by the Allina Health Institutional Review Board, Minneapolis, Minnesota. The study population included 270 consecutive patients with a first TS event admitted to the Minneapolis Heart Institute at Abbott Northwestern Hospital, Minneapolis, Minnesota, from 2006 to 2019. TS diagnosis was based on criteria published in the International Expert Consensus Document on Takotsubo Syndrome [8] and included the following elements: 1) an acute cardiac event generally presenting with chest pain or dyspnea, ischemic electrocardiographic (ECG) changes, and troponin elevation; 2) a distinctive regional left ventricular contraction abnormality (assessed by left ventricular angiogram, cardiovascular magnetic resonance imaging, or 2-dimensional echocardiography), typically with an apical, midventricular, focal, or basal pattern; 3) exclusion of acute coronary artery obstruction as the cause of the regional wall motion abnormality; 4) complete reversibility of the regional wall motion abnormality; and 5) no evidence for acute myocarditis. Baseline clinical characteristics and demographic information were recorded on admission. For each patient, the presence or absence of a takotsubo trigger was investigated by direct questioning of the patient or the patient's family during the hospital stay. Emotional triggers were categorized as negative ("broken heart") or positive ("happy heart").[3,4]

MEASUREMENTS AND OUTCOMES. The QTc interval was documented on admission and at hospital discharge. The admission QTc interval was obtained from the automated measurement on the first 12-lead ECG (GE Healthcare) in all patients. The GE Healthcare algorithm measures 10 beats across all 12 leads, overlays them, and calculates the median in each sample time.[18] The discharge QTc interval was obtained within 24 hours of discharge from the 12-lead ECG in 126 (49%) patients. In the remaining 133 (51%) patients without a discharge 12-lead ECG, the QTc interval was obtained by manual measurement (threshold method) from the final telemetry strip (typically lead II) at paper speed 25 mm/second using Bazett's formula (CNS-6201 2nd Generation Central Monitor, Nihon Kohden America). We chose the Bazett formula to be consistent with measurements made in previous TS-TdP reports.[16] For atrial fibrillation, the QTc was measured as the average of 10 consecutive beats. A QTc interval above 460 ms is generally considered prolonged in females.[19] Since the patients in this study were overwhelmingly female, we defined prolonged QTc as ≥460 ms, acknowledging the diverse opinions regarding the definition of prolonged QTc. All patients underwent telemetry monitoring during the entire hospitalization. Patients were categorized into three groups: QTc <460 ms, QTc 460 to 499 ms, and QTc ≥500 ms.

Life-threatening ventricular arrhythmias (ventricular fibrillation, sustained monomorphic ventricular tachycardia, and TdP) occurring during hospitalization were documented and characterized by review of the electronic medical record. Discharge medications that might influence heart rate or QTc interval and

discharge potassium, magnesium, and calcium levels were recorded. For each patient, all-cause mortality and TS recurrence were assessed at 1-year post-hospital discharge by examination of the electronic medical record.

TdP CASE REPORT SERIES POPULATION. Case reports describing TdP associated with TS were identified from the National Library of Medicine's PubMed database from 2003 to 2022 using the advanced search criteria "(Takotsubo Cardiomyopathy AND QT) OR (Takotsubo Cardiomyopathy AND Torsade)." The search term "takotsubo cardiomyopathy" includes 16 discrete nomenclature variations for this condition. Publications were included if the following criteria were met: 1) credible evidence of a TS event; 2) credible evidence of TdP; and 3) documented QTc interval or ECG tracing allowing manual measurement of QTc interval at the time of TdP event. For each TdP event, we documented patient age, sex, timing of TdP event, QTc at TdP event, presence of QTc prolonging drugs, electrolyte deficiency, heart rate and rhythm, and presence of T-wave inversion.

STATISTICAL ANALYSES. Categorical variables are expressed as numbers (percent) and were compared using Pearson's chi-square test. Continuous variables are presented as median (IQR) and were compared using the t-test or Wilcoxon rank-sum test, as appropriate. A 2-sided P value of 0.05 was considered statistically significant. All-cause mortality from hospital discharge to 1-year postdischarge was analyzed utilizing an unadjusted Kaplan-Meier estimate. For the mortality assessment, patients were stratified into 3 groups: QTc <460 ms, QTc 460-499 ms, and QTc ≥500 ms. Comparisons among the three groups were performed using the log-rank test. Separate mortality analyses were performed based on the admission QTc and the discharge QTc. All statistical analyses except for the survival analysis were performed with JMP 14.0 (SAS Institute). The survival analysis was performed with the survival, survminer, and finalfit R packages using the Jamovi software (Version 1.2).

RESULTS

CONSECUTIVE PATIENT COHORT. From 2006 to 2019, we evaluated and treated 270 consecutive TS patients, of whom 259 (95.9%) survived to hospital discharge. The 259 surviving patients were the focus of this study; median age was 68 (range: 59-77) years, and 92% were female, with apical ballooning pattern in 56% and ST-segment elevation in 29% (**Table 1**). All emotional triggers were negative (ie, "broken heart"). Admission and discharge QTc intervals are compared in **Figure 1**, **Central Illustration**. Marked QTc prolongation (≥500 ms) was present either on admission or at discharge in 98 (37.8%) patients.

ADMISSION QTc. On admission, the QTc was prolonged in 129 (49.8%) patients (**Table 1**, **Central Illustration**). The median admission QTc was 459 ms (range 382-749 ms) and was ≥500 ms in 46 (17.8%) patients. Ejection fraction, peak troponin, frequency of ST-segment elevation, and ballooning pattern did not differ significantly between those with and without QTc prolongation at admission. Among the 73 patients receiving beta blockers before admission, 56 (77%) were receiving a selective beta blocker and 17 (23%) a nonselective beta blocker. The admission QTc was 474.9 ± 41.3 ms for patients receiving a selective beta blocker vs 479.4 ± 38.3 ms for patients receiving a nonselective beta blocker; $P = 0.70$.

DISCHARGE QTc. At discharge, the QTc interval was prolonged in 140 (54.1%) patients (**Table 2**, **Central Illustration**). The median discharge QTc was 464 ms (range 308-641 ms) and was ≥500 ms in 65 (25.1%) patients. Patients with discharge QTc ≥500 ms had a significantly shorter hospital stay compared to those with QTc <500 ms. Patients with prolonged discharge QTc were more likely to have concomitant T-wave inversion (95.4% in those with QTc ≥500 ms, 80.9% in those with QTc 460-499 ms, and 51.4% in those with QTc <460 ms; $P < 0.001$). Among the 65 patients with discharge QTc ≥500 ms, 33 (51%) were receiving a drug with the potential to cause or aggravate QTc interval prolongation (Supplemental Table 1). Median potassium, magnesium, and calcium levels at discharge were normal and did not differ significantly among the three QTc interval groups.

TdP AND LIFE-THREATENING VENTRICULAR ARRHYTHMIAS. Among the 259 patients who survived to hospital discharge, 8 (3.1%) suffered life-threatening ventricular arrhythmias during hospitalization, including 2 patients (0.8%) with TdP (**Table 3**). The TdP events occurred at 1-hour post-admission (QTc 549 ms) (**Figure 2**) and at 48 hours postadmission (QTc 625 ms) (**Table 3**). Life-threatening ventricular arrhythmias other than TdP included ventricular fibrillation (n = 5) and monomorphic ventricular tachycardia (n = 1). Among the 5 patients with ventricular fibrillation, 3 were monitored at arrhythmia onset, none of whom had

TABLE 1 Patient Characteristics Stratified by Admission QTc Interval

	QTc <460 ms (n = 130, 50.2%)	QTc 460-499 ms (n = 83 32%)	QTc ≥500 ms (n = 46 17.8%)	*P* Value
Age, y	68 (58-78)	68 (61-77)	66 (58-76)	0.40
Sex				
Female	123 (95%)	76 (92%)	40 (87%)	0.20
Male	7 (5.4%)	7 (5.4%)	6 (13%)	
Presentation				
Chest pain	94 (72%)	51 (61%)	32 (70%)	0.20
Syncope	7 (5.4%)	6 (7.2%)	3 (6.5%)	0.80
Dyspnea	57 (44%)	43 (52%)	29 (63%)	0.074
Trigger				
Physical	50 (38%)	40 (48%)	21 (46%)	0.30
Emotional	61 (47%)	37 (45%)	20 (43%)	>0.90
None	19 (15%)	7 (8.4%)	5 (11%)	0.40
Beta-blocker before admission	25 (19%)	29 (35%)	19 (41%)	0.004
Ballooning pattern				
Apical	66 (51%)	49 (59%)	29 (63%)	0.50
Mid	59 (45%)	32 (39%)	16 (35%)	
Focal	2 (1.5%)	1 (1.2%)	1 (2.2%)	
Basal	3 (2.3%)	0	0	
Unknown	0	1 (1.2%)	0	
ST-segment elevation	44 (34%)	25 (30%)	7 (15%)	0.057
Initial heart rate, beats/min	85 (71-108)	94 (79-105)	88 (71-96)	0.11
Atrial fibrillation	5 (3.8%)	5 (6.0%)	4 (8.7%)	0.40
Left bundle branch block	2 (1.5%)	5 (6.0%)	3 (0.6%)	0.15
Ventricular paced rhythm	1 (0.8%)	0	3 (0.6%)	0.002
Ejection fraction %	30 (25-40)	30 (28-40)	30 (20-35)	0.049
Troponin peak, ng/mL	0.71 (0.32-1.95)	0.79 (0.26-2.47)	0.58 (0.16-1.54)	0.20
Mechanical ventilation	13 (10%)	9 (11%)	11 (24%)	0.043
Intra-aortic balloon pump	3 (2.3%)	1 (1.2%)	2 (4.3%)	0.50
Inotropic drug	19 (15%)	11 (13%)	10 (22%)	0.40

Values are median (IQR) or n (%).

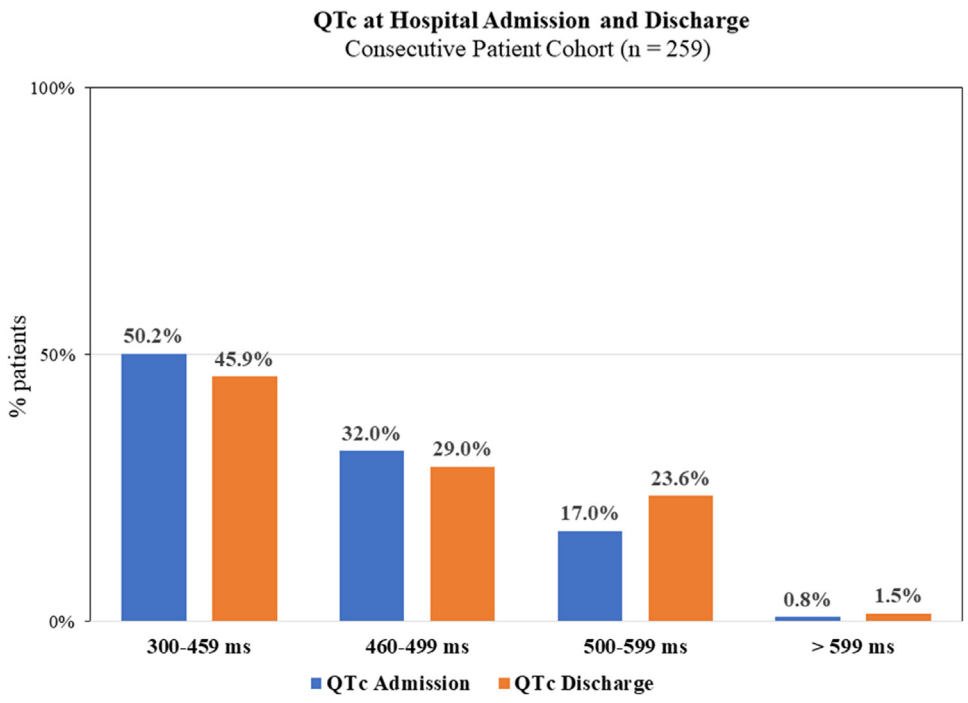
preceding TdP. The majority (n = 6, 75%) of arrhythmic events occurred prehospital or in the emergency department; QTc was prolonged at the time of ventricular arrhythmia in 5 (62.5%) patients. An electrolyte deficiency was present in 4 (50%) patients.

HOSPITAL DEATHS. Eleven patients (4.1%) died during hospitalization; average age was 69.1 ± 9.4 years (range: 51-87 years); all were female; median admission QTc was 469 ms (range: 399-559 ms). At the time of death, median QTc was 414 ms (range: 374-528 ms, unavailable in 1 patient). Cause of death was: acute/chronic respiratory failure (n = 6), subarachnoid hemorrhage (n = 1), acute stroke (n = 1), fungemia (n = 1), anoxic brain injury after out-of-hospital cardiac arrest (n = 1), and small cell lung cancer (n = 1). None of the hospital nonsurvivors had TdP, monomorphic ventricular tachycardia, or ventricular fibrillation during hospitalization.

POSTHOSPITAL OUTCOMES. At 1-year postdischarge, TS recurred in 2 (0.8%) patients; discharge QTc was 487 ms, and 511 ms, respectively. Estimated 1-year mortality postdischarge was significantly associated with admission but not discharge QTc (Figure 3). Among patients with admission QTc <460 ms (50.2% of the population), survival at 1-year postdischarge was 98.4%. The QTc interval was documented at postdischarge follow-up in 163 (62.9%) patients and was ≥460 ms in 61 of 163 (37.4%) patients. QTc decreased significantly between hospital discharge (median 464 ms, IQR: 430-499 ms) and follow-up (median 447 ms, IQR: 425-468 ms); $P < 0.01$.

TdP CASE REPORT SERIES. From 2003 to 2022, we identified 38 unique cases of TdP-TS from 31 published reports (Table 4, Central Illustration). From 2003 to 2012, there were 17 (55%) publications vs 14 (45%) from 2013 to 2022. At the time of TdP-TS event, median age was 68.5 years (range 22-89 years) and 26

FIGURE 1 Distribution of QTc Intervals on Admission and at Discharge in 259 Consecutive Takotsubo Syndrome Patients



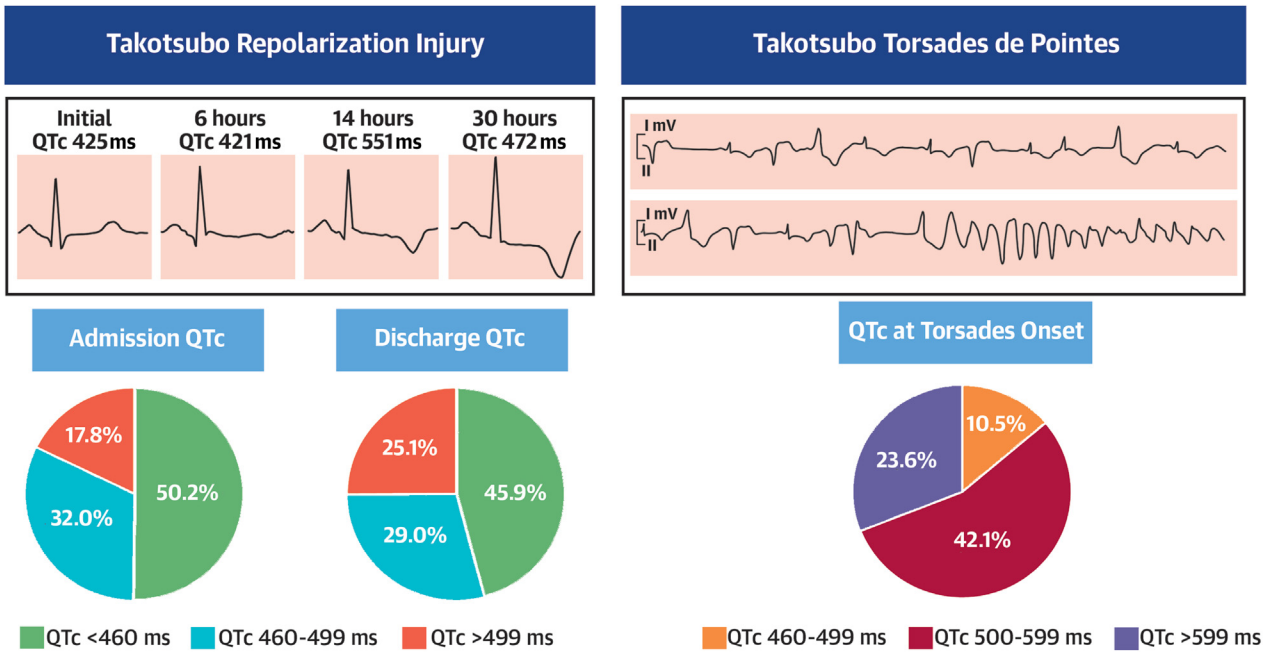
(68%) were female. The range of QTc intervals observed at TdP onset are summarized in Figure 4, Central Illustration. At TdP onset, the median QTc was 580 ms (range 480-920 ms); QTc was ≥500 ms in 34 of 38 (89.5%) patients. Only 4 (11%) TdP events occurred in patients with mild (480-499 ms) QTc prolongation. The TdP event occurred on the first hospital day in 21 (55%) patients, on the second hospital day in 10 (26%) patients, on or beyond the fourth hospital day in 2 (5.2%) patients, and was not reported in 5 (13%) patients. All patients had T-wave inversion associated with QTc prolongation; a bradyarrhythmia was present in 12 (33%) patients, an electrolyte deficiency in 11 (29%) patients, and QTc prolonging drug in 9 (25%) patients. The TdP event was shown in the published manuscript figure in 21 cases and was preceded by a short-long-short R-R interval in 20 (95%). In-hospital outcome was reported in 32 of 38 patients, of whom 4 (12.5%) patients did not survive.

Combining the 2 TdP events in the consecutive patient series with those in the TdP case reports yielded 40 patients with TdP-TS; 90% of TdP events occurred in those with QTc ≥500 ms. Marked QTc prolongation (≥600 ms) was present in 47.5% of the TdP events.

DISCUSSION

The key findings in this report include: 1) QTc interval prolongation ≥500 ms was present either on admission or at discharge in nearly 40% of TS patients; 2) TdP-TS was infrequent; the incidence over a 14-year interval at a single institution was approximately 1%; 3) QTc interval prolongation was generally accompanied by T-wave inversion, a unique TS electrocardiographic phenotype, distinct from that typically observed in drug induced and congenital long QT syndromes; 4) nearly one-half of patients with prolonged QTc interval at hospital discharge were receiving drugs known to prolong the QT interval; 5) the vast majority (90%) of TdP events occurred in patients with QTc ≥500 ms and nearly one-half occurred in individuals with QTc ≥600 ms. Most (80%) TdP-TS events occurred within the first 48 hours of hospitalization; 6) conditions known to increase TdP risk (bradyarrhythmia, electrolyte deficiency, and QTc-prolonging drugs) were present in fewer than one-third of patients, highlighting the idiosyncratic nature of TdP-TS; 7) in TdP-TS patients, hospital mortality (11%) was greater than has been reported in large TS series;[1,8,13,17] and 8) prolonged

CENTRAL ILLUSTRATION **Repolarization Injury and Torsades de Pointes in Takotsubo Syndrome**



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Left: Repolarization injury in takotsubo syndrome includes QTc interval prolongation and T-wave inversion. QTc was ≥500 ms either on admission or at discharge in 98 (37.8%) patients. Right: Torsades de pointes in takotsubo syndrome. Ninety percent of TdP events occurred in those with QTc ≥500 ms, and marked QTc prolongation (≥600 ms) was present in 47.5% of the TdP events. TdP, torsades de pointes.

admission QTc interval was associated with increased postdischarge mortality.

The clinical implications of our report can be summarized as follows: 1) it is advisable to conduct an assessment of repolarization injury in TS patients, which should include periodic monitoring of the QTc interval; 2) given the unpredictability of TdP, all patients with significantly prolonged QTc intervals should be considered at TdP risk. It is advisable to maintain continuous rhythm monitoring in these individuals; 3) factors that promote TdP, such as bradyarrhythmias, QTc-prolonging medications, and electrolyte deficiencies should be considered and mitigated during TS management; and 4) 1 in four patients have QTc ≥500 ms at hospital discharge, a subset that requires careful follow-up and consideration for additional outpatient rhythm monitoring.

Our findings strengthen earlier reports with fewer TdP-TS events. The 2009 review by Samuelov-Kinori et al (15 TdP-TS cases) noted longer QTc intervals in TdP-TS patients compared to non-TdP patients: 679.9 ± 230.6 ms vs 555.9 ± 63.8 ms; $P = 0.06$.[15] Behr et al[14] (11 TdP-TS cases) found that the QTc interval was ≥600 ms in 82% of TdP-TS events.

TdP-TS INCIDENCE. The incidence of TdP-TS is uncertain. Madias et al[16] reported a 5.3% TdP-TS incidence in a 2-institution registry of 95 patients. Streitner et al[20] included summary information from five patients with TdP-TS, gathered from several international institutions. In patients with TdP, the mean QTc on days 1 and 3 was 461 ± 36 ms and 522 ± 74 ms, respectively, vs 448 ± 31 ms and 485 ± 32 ms, respectively, in those without TdP. A single center German study reported polymorphic ventricular tachycardia (presumably TdP) in 2.8% of acute TS cases, although the arrhythmia timing was not documented.[21] A substudy of the RETAKO takotsubo registry noted significantly longer repolarization parameters (QTc, QTc dispersion, and T-wave peak to T-wave end) in 13 patients with ventricular arrhythmias (including 2 with polymorphic ventricular

TABLE 2 Patient Characteristics Stratified by Discharge QTc Interval

	QTc <460 ms (n = 119, 45.9%)	QTc 460-499 ms (n = 75, 29.0%)	QTc ≥500 ms (n = 65, 25.1%)	*P* Value
Age, y	69 (59-77)	67 (58-78)	68 (61-77)	0.70
Female	108 (91%)	71 (95%)	60 (92%)	0.60
Length of stay, d	4 (3-7)	3 (2-6)	3 (2-4)	0.003
Trigger				
Physical	56 (47%)	32 (43%)	23 (35%)	0.30
Emotional	51 (43%)	31 (41%)	36 (55%)	0.20
None	12 (10%)	13 (17%)	9.2%	0.20
Ballooning pattern				
Apical	57 (48%)	44 (59%)	43 (66%)	0.30
Mid	58 (49%)	29 (39%)	20 (31%)	
Focal	2 (1.7%)	1 (1.3%)	1 (1.5%)	
Basal	1 (0.8%)	1 (1.3%)	1 (1.5%)	
ST-segment elevation	35 (29%)	24 (32%)	17 (26%)	0.80
Ejection fraction % (initial)	30 (25-40)	30 (25-40)	30 (25-35)	0.90
Troponin peak, ng/ml	0.61 (0.22-1.50)	0.79 (0.30-2.64)	1.06 (0.33-2.42)	0.130
Discharge heart rate, beats/min	73 (62-83)	72 (62-82)	72 (62-81)	0.80
Discharge rhythm				0.50
Sinus	112 (94%)	70 (93%)	59 (91%)	
Atrial fibrillation	1 (0.8%)	2 (2.7%)	3 (4.6%)	
Pacemaker	3 (2.5%)	2 (2.7%)	1 (1.5%)	
Other/unknown	3 (2.5%)	1 (1.3%)	2 (3.1%)	
Discharge electrolyte level				
Potassium	4 (3.8-4.2)	4 (3.8-4.3)	4 (3.8-4.2)	0.50
Magnesium	1.9 (1.8-2.2)	1.9 (1.8-2.1)	1.9 (1.7-2.1)	0.70
Calcium	8.8 (8.4-9.2)	8.8 (8.5-9.2)	8.8 (8.6-9.3)	0.50
Discharge medications				
Beta-blocker	102 (86%)	68 (91%)	59 (91%)	0.50
QT-prolonging drug	64 (55%)	35 (47%)	33 (51%)	0.70
Antiarrhythmic drug	4 (3.4%)	4 (5.3%)	4 (6.2%)	0.60

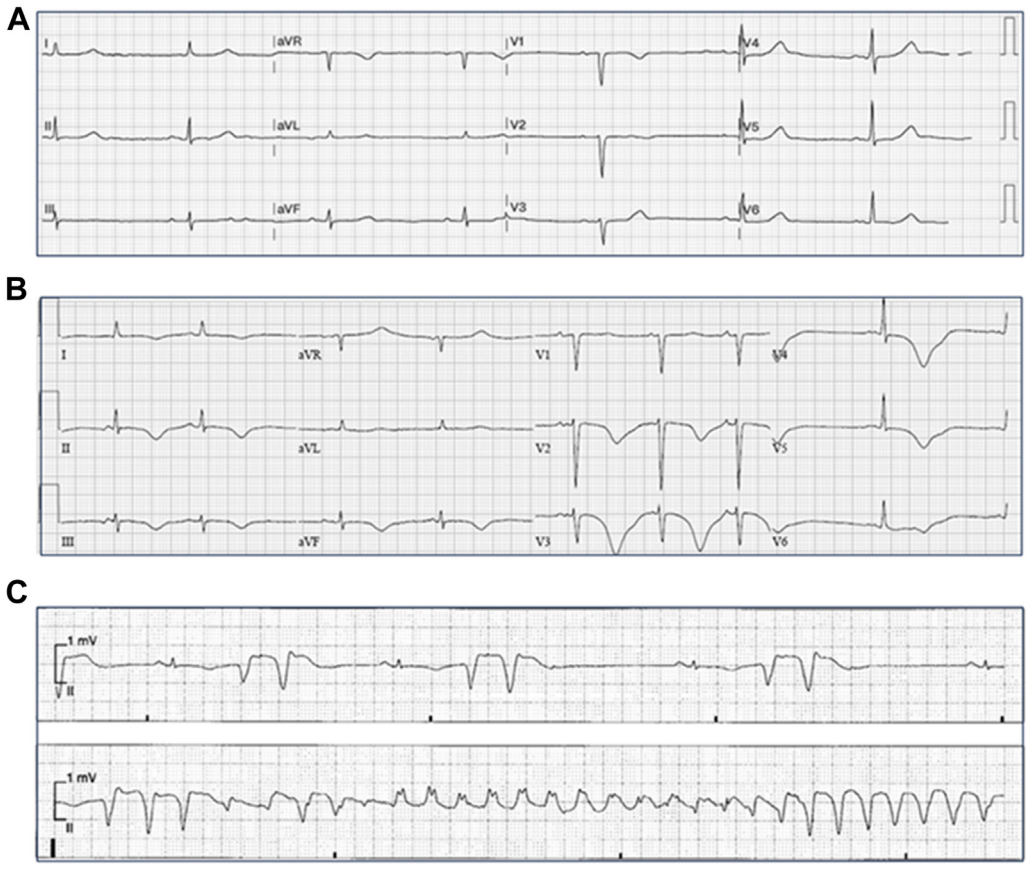
Values are median (IQR) or n (%).

TABLE 3 Characteristics of Life-Threatening Ventricular Arrhythmias During Acute Takotsubo Event

Patient #	Sex/Age, y	Arrhythmia	Timing	Underlying Rhythm	QTc, ms	Electrolyte Abnormality	QT-Prolonging Drug	Outcome
1	F/48	VF	Prehospital	Junctional bradycardia 59 beats/min	441	No	No	Survived ICD
2	M/59	VF	ED	Sinus rhythm 90 beats/min	528	No	oxycodone citalopram	Survived ICD
3	F/84	TdP	ED	Sinus bradycardia 51 beats/min	549	Magnesium 1.4 mg/dL	sotalol	Survived Pacemaker
4	F/85	TdP	Hospital day 2	Ventricular paced 73 beats/min	625	Magnesium 1.8 mg/dL	haloperidol	Defibrillation survived
5	M/83	VT	Hospital day 4	Sinus rhythm + LBBB 85 beats/min	518	Sodium 118 mEq/L	no	Survived
6	F/56	VF	Prehospital	Sinus rhythm 86 beats/min	516	Potassium 1.3 mEq/L	no	Survived
7	F/66	VF	ED	Sinus bradycardia 52 beats/min	434	No	dofetilide	Survived ICD
8	F/32	VF	Prehospital	Sinus tachycardia 113 beats/min	518	Potassium 2.4 mEq/L	no	Survived ICD

ED = emergency department; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; TdP = torsades de pointes; VF = ventricular fibrillation; VT = monomorphic ventricular tachycardia, 163 beats/min.

FIGURE 2 Repolarization Injury and Torsades de Pointes in an Elderly Female During a Takotsubo Event

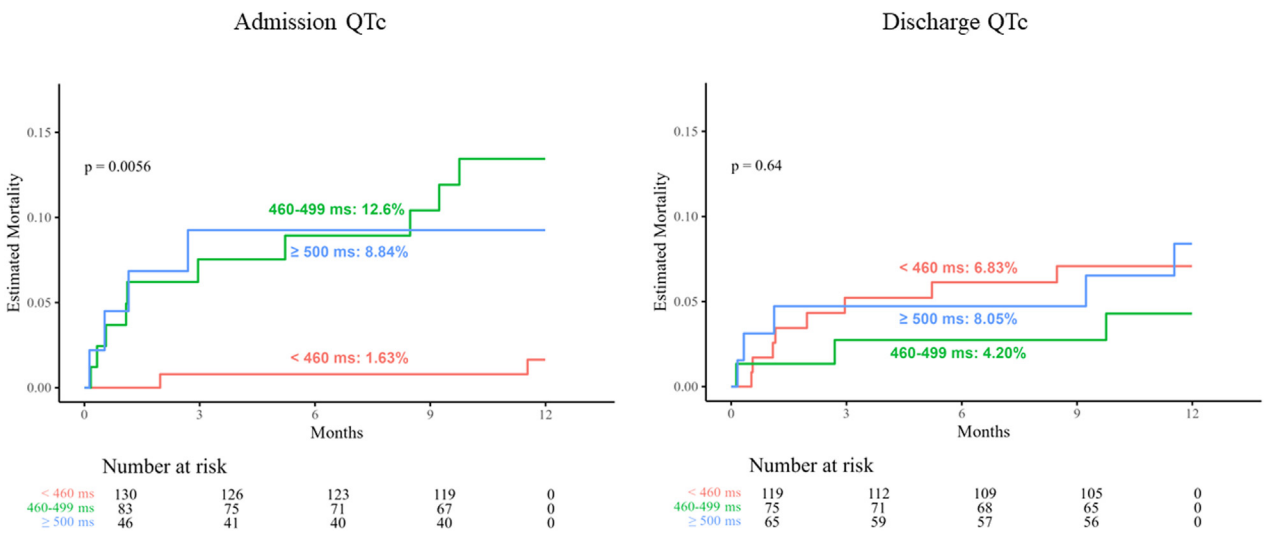


(A) Baseline 12-lead recorded 1-week before takotsubo event demonstrates sinus bradycardia, 40 beats/min, QTc 459 ms. Patient was receiving sotalol and metoprolol for atrial fibrillation. Metoprolol was discontinued because of bradycardia. (B) At takotsubo admission, 12-lead electrocardiographic (ECG) demonstrates irregular sinus bradycardia, 51 beats/min, QTc 549 ms, and new T-wave inversion. Echocardiogram findings included apical ballooning and an ejection fraction of 35%. (C) Lead II rhythm strip demonstrates torsades de pointes at 1-hour postadmission. The arrhythmia resolved with dual chamber pacemaker implantation. Sotalol was discontinued. The ECG in A was enhanced (PMcardio Digitize) from a scanned version courtesy of Dr Robert Herman.

tachycardia).[22] Considering the above publications in aggregate, together with the consecutive patient experience included in our report, the incidence of TdP-TS is likely low. The variability in TdP incidence among studies likely reflects the idiosyncratic nature of this arrhythmia.

QTc AND VENTRICULAR ARRHYTHMIA. Prolonged QTc in TS has been linked to life-threatening ventricular arrhythmias other than TdP. An InterTAK study (n = 2,098) reported that 4.9% of TS patients experienced cardiac arrest, and those with cardiac arrest had significantly longer admission QTc (476.6 ± 46.8 ms) compared to those without (457.7 ± 47.3 ms).[23] While this difference was statistically significant, the absolute difference was small, 17 ms. No TdP events were reported by the authors. A recent U.S. report (n = 105) documented in-hospital ventricular fibrillation or sustained ventricular tachycardia in 9.5% of TS patients.[24] In patients with ventricular arrhythmia, the median admission QTc was 470 ms vs 417 ms for those without arrhythmia. No TdP episodes were reported. In both of the above studies, patients with malignant ventricular arrhythmias were hemodynamically unstable with frequent

FIGURE 3 Estimated 1-Year Mortality of 259 Consecutive Patients With Takotsubo Syndrome Stratified by QTc Interval at Hospital Admission and at Discharge



cardiogenic shock and inotropic drug support. It appears that hemodynamic instability itself plays a crucial role in triggering some TS-associated life-threatening ventricular arrhythmias, with prolonged QTc representing a "bystander" phenomenon.[25] In this regard, Viskin et al recently introduced the concept of "pseudo-TdP," emphasizing the importance of distinguishing serious ventricular arrhythmias that occur "because" of a long QTc interval from those that occur "despite" a long QTc interval.[26,27]

QTc AND POSTHOSPITAL SURVIVAL. The arrhythmic risk of prolonged QTc after hospital discharge is unknown. In the current study, admission but not discharge QTc was associated with posthospital survival, a finding that seems counterintuitive. Presumably, a prolonged QTc interval negatively impacts survival through an arrhythmogenic mechanism. There is no obvious physiologic reason for the admission rather than discharge QTc to impact post-discharge 1-year survival. Previous studies regarding the association of QTc interval with postdischarge outcomes have yielded inconsistent results. For example, in a 2015 study of 56 TS patients from the United States, a shorter QTc at presentation was associated with greater risk of death.[28] In contrast, a 2021 study of 246 TS patients from Spain noted that a prolonged admission QTc was independently associated with all-cause death at 4-month follow-up.[29] Given the conflicting findings and relatively small number of patients, further study is necessary to understand the association of QTc with long-term TS survival. Advances in wearable electrocardiographic device technology will improve posthospital QTc interval surveillance in TS patients after hospital discharge.

TdP IN OTHER CONDITIONS. Our analysis reveals TdP-TS shares several common elements with TdP associated with drug-induced and congenital long QT syndromes, including an onset preceded by short-long-short R-R interval and the presence of aggravating factors such as bradycardia, electrolyte deficiencies, presence of QTc interval prolonging drug, and QTc interval ≥500 ms.[30-32] Drug-induced and congenital long QT syndromes may be present in patients with TS, thereby amplifying the TS-related repolarization abnormalities and potentially promoting TdP occurrence.[14,15]

REPOLARIZATION INJURY MECHANISM. The mechanism underlying the repolarization injury observed in TS is unknown. Some have postulated that myocardial edema in acutely injured myocardium creates a geographic left ventricular repolarization gradient, resulting in the distinctive ECG changes.[33] Others have suggested the repolarization abnormalities represent the expression of the electrophysiologic properties of the mid-myocardial M cell in

TABLE 4 Torsades de Pointes and Takotsubo Cardiomyopathy Case Reports 2003-2022 (N = 38)

	Clinical Characteristics			TdP Event Characteristics					QTc Interval (ms)		
First Author[a]	Age, y/Sex	QTc-Prolonging Medications	Electrolyte Abnormality	Day of Event	T-Wave Inversion	Rhythm	Rate	Long-Short RR[b]	Initial	TdP	Recovery
Ahmed (Suppl Ref 1)	48 F	No	No	1	Yes	Brady	51	NA	554	554	NA
Ahn (Suppl Ref 2)	78 F	No	No	2	Yes	Brady	20	Yes	580	720	552
Banavalikar (Suppl Ref 3)	31 F	No	No	1	Yes	V-paced	60	NA	630	630	428
Furushima (Suppl Ref 4)	61 F	No	No	2	Yes	SR	60	Yes	740	560[c]	470
Ghosh (Suppl Ref 5)	59 F	No	↓ K^+	NA	Yes	Tachy	108	NA	534[c]	669	NA
Gotyo (Suppl Ref 6)	70 M	No	No	20	Yes	A-tachy	132	NA	NA	624[c]	NA
Grilo (Suppl Ref 7)	37 F	Ketoconazole	No	1	Yes	Brady	51	Yes	534	721	473
Gysel (Suppl Ref 8)	71 F	citalopram, sotalol, pantoprazole	↓ K^+	1	Yes	SR	90	NA	554	554	NA
Hirose (Suppl Ref 9)	63 F	No	↓ K^+	1	Yes	SR	75	Yes	549	549	439
Inoue (Suppl Ref 10)	82 F	No	No	1	Yes	CHB	38	NA	630	630	424
Kawano (Suppl Ref 11)	80 M	No	↓ K^+, Mg^{2+}, Ca^{2+}	1	Yes	SR	95	NA	800	580[c]	490
Kawano (Suppl Ref 12)	30 F	No	↓ K^+	1	Yes	Tachy	100	NA	497	613	499
Kurisu (Suppl Ref 13)	87 F	No	No	1	Yes	RBBB 2° AVB	42	Yes	880	880	440
Kurisu (Suppl Ref 13)	78 M	No	No	1	Yes	RBBB 3° AVB	40	Yes	920	920	480
Madias (Suppl Ref 14)	78 M	No	No	1	Yes	SR	NA	Yes	480	725	NA
Madias (Suppl Ref 14)	81 M	No	No	NA	Yes	PVCs	NA	Yes	NA	547	NA
Madias (Suppl Ref 14)	74 F	No	No	NA	Yes	NA	NA	Yes	NA	529	NA
Madias (Suppl Ref 14)	73 F	No	No	NA	Yes	NA	NA	Yes	NA	480	NA
Madias (Suppl Ref 14)	61 F	No	No	NA	Yes	NA	NA	Yes	NA	688	NA
Mahida (Suppl Ref 15)	55 F	No	No	2	Yes	PVCs	60	No	510	510	490
Nakagawa (Suppl Ref 16)	85 M	No	No	2	Yes	PVCs	65	Yes	NA	555	NA
Nault (Suppl Ref 17)	76 M	No	↓ K^+	2	Yes	SR	75	Yes	630	786	NA
Oshima (Suppl Ref 18)	77 F	No	No	2	Yes	CHB	35	NA	590	493[c]	NA
Pacha (Suppl Ref 19)	64 M	No	No	2	Yes	SR	74	NA	517	763[c]	NA
Patel (Suppl Ref 20)	51 M	No	No	1	Yes	Tachy	100	NA	446	491	NA
Perez-Castellanos (Suppl Ref 21)	43 M	No	↓ K^+	1	Yes	Tachy	115	Yes	691	691	NA
Perez-Castellanos (Suppl Ref 21)	52 M	No	No	4	Yes	SR	75	Yes	596	539[c]	460
Peter (Suppl Ref 22)	62 F	Antipsychotics	No	1	Yes	Brady	20	Yes	410	480[c]	420
Purvis (Suppl Ref 23)	67 F	Fluoxetine, ondansetron	↓ Mg^{2+}	1	Yes	SR	70	Yes	524	524	454
Roach (Suppl Ref 24)	89 M	Amiodarone	No	1	Yes	SR	63	NA	569[c]	570	NA
Rotondi (Suppl Ref 25)	57 F	No	↓ K^+, Mg^{2+}, Ca^{2+}	1	Yes	SR	75	Yes	650	570	550
Sacha (Suppl Ref 26)	42 F	No	No	2	Yes	CHB PVCs	50	NA	650	685[c]	440
Sasaki (Suppl Ref 27)	22 F	No	↓ K^+	1	Yes	PVCs	50	NA	730	730	460
Shimizu (Suppl Ref 28)	66 F	No	No	2	Yes	Brady	59	Yes	490[c]	716[c]	NA
Valbusa (Suppl Ref 29)	75 F	Escitalopram	No	2	Yes	SR	87	Yes	NA	640	NA
Yoshida (Suppl Ref 30)	84 F	No	↓ K^+, Mg^{2+}	1	Yes	Tachy	126	NA	464	580	620
Yamada (Suppl Ref 31)	89 F	No	No	1	Yes	CHB	48	NA	550	550	580
Yamada (Suppl Ref 31)	81 F	Clarithromycin	No	1	Yes	AF	75	NA	550	550	620

[a]References are included in the Supplemental Appendix. [b]Long-short R-R interval preceding onset of torsades de pointes. [c]QTc measured manually from figure provided in publication.

AVB = atrioventricular block; AF = atrial fibrillation; A-tachy = atrial tachycardia; Brady = bradycardia; Ca^{2+} = calcium; CHB = complete heart block; K^+ = potassium; Mg^{2+} = magnesium; NA = not available; PAC = premature atrial contraction; PVC = premature ventricular contraction; RBBB = right bundle branch block; SR = sinus rhythm; Tachy = tachycardia; TdP = torsades de pointes; UNK = unknown; V-Paced = ventricular pace.

response to acute injury [34] or injury to the myocardial autonomic nervous system.[35] Kurisu et al[7] compared repolarization abnormalities in TS with those of reperfusion treated acute anterior myocardial infarction; both groups experienced resolution of regional left ventricular dysfunction, and both demonstrated the same temporal pattern of QTc interval lengthening and T-wave inversion. In addition,

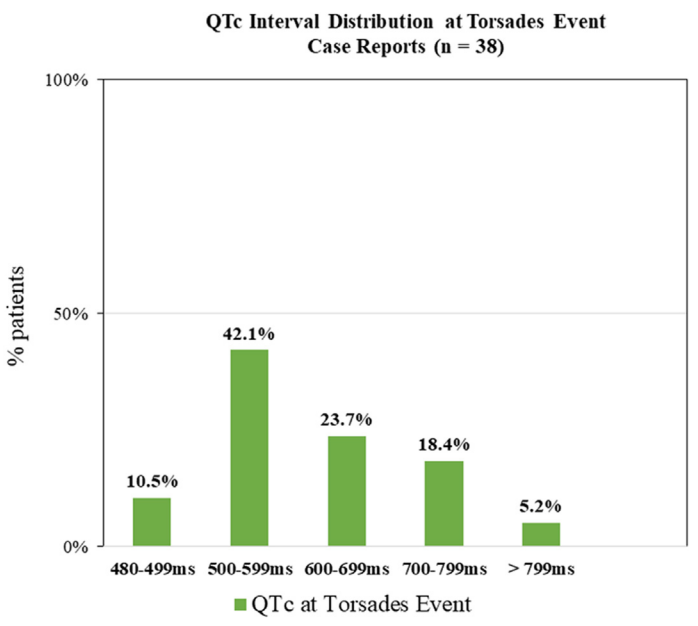
radionuclide imaging studies have demonstrated that QTc prolongation with deep T-wave inversion in acute anterior myocardial infarction is associated with myocardial salvage.[36] Therefore, QTc interval prolongation and T-wave inversion may be an electrophysiologic marker of stunned myocardium following either ischemic injury or TS injury, suggesting a common link between the two conditions.[37-40]

STUDY LIMITATIONS. This study was retrospective, with a relatively small number of patients, potentially introducing biases and confounding variables. Performance of 12-lead ECGs during hospitalization was not standardized; therefore, this study did not examine QTc intervals other than at hospital admission and discharge. By necessity, the discharge QTc was measured from the discharge telemetry strip in one-half of patients, which could introduce inaccuracies. To date, TdP-TS has likely been underreported, as the opportunities for publishing case reports in peer-reviewed journals are limited. Idiosyncratic events, such as TdP-TS, require study of larger populations to determine incidence, risk factors, and long-term consequences. In 2023, the Centers for Medicare and Medicaid Services published an International Classification of Diseases code for TdP (an International Classification of Diseases code for TS was published in 2006). Going forward, it will be possible to query administrative databases to better understand the characteristics of TdP-TS in a larger population. The patients included in the consecutive patient series were North American and predominantly white; therefore, the findings cannot necessarily be extrapolated to the global TS population.

CONCLUSIONS

Repolarization injury, although often overlooked, is frequent in TS and carries an associated risk of TdP. It is important to document the QTc interval and consider TdP risk in the management of TS patients. Many intriguing aspects of repolarization injury and occurrence of TdP in TS remain unexplained, offering avenues for further study. For instance, it would be valuable to investigate why some TS patients are susceptible to TdP while others, despite similar or even greater QTc prolongation, are not. The association of admission QTc with posthospital survival requires validation in a larger number of patients and may prove a useful prognostic marker.

FIGURE 4 Distribution of QTc Intervals at Onset of Torsades de Pointes Gathered From 38 Case Reports



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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Repolarization injury is common in TS, a process characterized by QTc interval lengthening and T-wave inversion. More than half of patients have QTc prolongation during hospitalization, and one-quarter have QTc >500 ms, providing the substrate for TdP. This arrhythmia is uncommon in TS, usually occurring in those with QTc >500 ms and within 48 hours of hospital admission. Most patients do not have conditions known to increase the risk of TdP; therefore, this arrhythmia is unpredictable in this setting. In most patients, QTc prolongation and T-wave inversion resolve at follow-up. Prolonged QTc at admission may be associated with worse long-term survival.

TRANSLATIONAL OUTLOOK: TS represents a unique form of reversible acquired long QT syndrome in which both mechanical and electrophysiologic stunning coexist. TS is no longer uncommon; therefore, this condition provides an opportunity for further research into acquired long QT syndrome and for further understanding of the factors that promote the occurrence of TdP.

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KEY WORDS QTc prolongation, repolarization injury, takotsubo cardiomyopathy, takotsubo syndrome, torsades de pointes

APPENDIX For a supplemental table, please see the online version of this paper.