Electrocardiographic Characteristics and Associated Outcomes in Patients with Takotsubo Syndrome. Insights from the RETAKO Registry

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Abstract: Electrocardiographic disturbances in Takotsubo syndrome have been previously partially described but their consequences remain mostly unknown. Our aim was to describe the prevalence and prognostic significance of different electrocardiographic features in patients with Takotsubo syndrome. Our data come from the Spanish multicenter REgistry of TAKOtsubo syndrome (RETAKO). All patients with an available 12-lead surface electrocardiogram at admission and 48 hours post-admission were included. A total of 246 patients were studied, mean age was 71.3 ± 11.5 and 215 (87.4%) were women. ST-segment elevation was seen in 143 patients (59.1%) and was present in ≥2 wall leads in 97 (39.8%). Exclusive elevation in inferior leads was

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infrequent (5% - 2.0%). After 48 hours, 198 patients (88.0%) developed negative T waves in a median of 8 leads with a mean amplitude of 0.7 ± 0.5 mV and 137 (60.9%) had pathological Q waves. The mean corrected QT interval was 520 ± 72 ms. Corrected QT interval was independently associated with the primary endpoint of all-cause death and nonfatal cardiovascular events ($P = 0.002$) and all-cause death ($P = 0.008$). A higher heart rate at admission was an independent predictor of the primary endpoint ($P = 0.001$) and of acute pulmonary edema ($P = 0.04$). ST-segment elevation with reciprocal depression was an independent predictor of all-cause death ($P = 0.04$). Absence of ST-segment deviation was a protective factor ($P = 0.005$) for the primary endpoint. Tachyarrhythmias were independently associated with cardiogenic shock ($P < 0.001$). Takotsubo syndrome patients present with distinct electrocardiographic features. Prolonged corrected QT interval, tachyarrhythmias, heart rate at admission, and more extensive repolarization alterations are associated with poor outcomes. (Curr Probl Cardiol 2021;46:100841.)

Takotsubo syndrome (TTS) represents 1%−3% of all suspected ST-segment elevation myocardial infarctions (STEMI).[1-3] In some studies, short- and long-term survival of TTS is similar to acute coronary syndromes (ACS).[4-8] Although some TTS electrocardiographic features have been described,[9,10] only few of them have been related to adverse prognostic outcomes,[11-13] and data come mainly from small, mostly retrospective studies. In addition, some electrocardiogram (ECG) changes may be similar to those of ACS,[14] although effort has been made to establish electrocardiographic differences between these entities.[15-17] The most frequent TTS ECG pattern is initial ST-segment elevation and development of diffuse profound T wave inversion and QT interval prolongation during the first 48 hours.[18] ST-segment deviations resolve early after admission, but T wave abnormalities and corrected QT prolongation may last for weeks, the latter predisposing to higher arrhythmic risk.[19] The present study aims to determine the prevalence and prognostic significance of electrocardiographic disturbances in a large real-life cohort of patients with TTS.

Methods

Data come from the Spanish multicenter REgistry of TAKOtsubo syndrome (RETAKO), which includes patients with diagnosed TTS based in the modified Mayo Clinic criteria, ie: 1. transient wall motion abnormalities extending beyond a single epicardial vascular territory, stressful trigger may be present, 2. absence of obstructive coronary disease, 3. new electrocardiographic abnormalities and modest elevation in cardiac troponin and 4. absence of pheochromocytoma and myocarditis.[20] Data from January 1, 2003 until December 31, 2017 from patients with a definitive TTS diagnosis and an available 12-lead surface ECG at admission and 48 hours post-admission were included. Follow-up was performed through review of medical records or telephone contact with the patient, family or the patient's referring physician. Baseline characteristics, ECG measurements, arrhythmia development, in hospital adverse events, pharmacological and device requirement and short- and long-term outcomes were collected through an electronic case report form. The study protocol fulfilled the Declaration of Helsinki, and was approved by the Institutional Ethics Committee of Clinico San Carlos Hospital, Madrid, Spain. All patients provided written informed consent.

Electrocardiographic analysis was performed with a 12-lead surface ECG using 25 mm/sec and 10mm/mV standardization. ECG measurements were carried out by an investigator blinded to patient data. The P wave was measured beginning at the joint of the isoelectric line with the beginning of the P deflection and ending at the joint between the end of the P deflection and the PR segment. The PR interval was measured from the onset of the P deflection to the origin of the QRS complex. The QRS complex was measured from the starting point of the first wave deflection (Q or R) to the last wave of the complex at the joint with the isoelectric ST-segment. Measurement of QT interval extended from the onset of the QRS complex to the end of the T wave. Correction of this interval was calculated with the Bazett formula. The longest P wave, PR interval, QRS complex and QT interval were chosen for the record. ST-segment measurement started from the J Point to the joint with de T wave deflection origin. According to the current definition, ST-segment elevation was established with at least 2 contiguous leads with >2 mm in men or >1.5 mm in women in leads V2−V3 and/or >1 mm in the other leads. ST-segment depression (horizontal or down sloping) was defined as ≥ 0.05 mV in at least 2 contiguous leads. Reciprocal ST-segment depression was assessed if present in at least 2 contiguous leads in a patient with ST-segment elevation. T wave inversion corresponded with

≥0.1 mV negative T waves in at least 2 contiguous leads. Q wave was established as a ≥30 milliseconds (ms) wide and ≥0.1 mV deep wave in at least 2 contiguous leads.[21,22] Patients with repolarization alterations because of bundle branch block, ventricular hypertrophy or pacemaker stimulation were considered non-diagnostic ECGs. Bundle branch block was diagnosed using standard criteria. Arrhythmia development was defined as supraventricular or ventricular tachyarrhythmia present in the 48 hours post-admission ECG or referred to in the case report form.

The primary endpoint of this study was the composite of all-cause mortality and nonfatal cardiovascular events (acute pulmonary edema, cardiogenic shock and new severe mitral regurgitation). Secondary endpoints included all-cause mortality, cardiovascular mortality, acute pulmonary edema, cardiogenic shock, orotracheal intubation, and new severe mitral regurgitation. Consensus of 2 local investigators was necessary for event adjudication and electronic medical records were reviewed if available. Subjects with incomplete data registration, death in the first 48 hours or lack of follow-up were excluded from the statistical analysis.

Continuous variables are displayed as mean ± standard deviation (SD) or median (interquartile range [IQR]) and compared by the Student's t test or the Mann-Whitney U test. Categorical variables are reported as number (percentage) and compared by the chi-square test or Fisher exact test. Electrocardiographic predictors of primary and secondary outcomes are assessed by the multivariate logistic regression method using the stepwise forward model with a p value <0.10 as entry criterion. All *P* values are 2-tailed. All statistical analyses were performed with SPSS software (version 21, SPSS, Chicago, IL).

Results

From the total screened cohort of 946 patients, 246 (26.0%) had complete data record including 12-lead ECG at admission and after 48 hours, and were incorporated for statistical analysis. Median follow-up time was 4 ± 11 months. Baseline characteristics are shown in *Supplementary material online, Table S1*. A total of 7 patients (2.8%) died during hospitalization, 4 (2.0%) had TTS recurrence, and 36 (14.6 %) presented with cardiogenic shock. Electrocardiographic characteristics at admission and after 48 hours are displayed in Table 1. Most patients presented in sinus rhythm (88%), had ST-segment elevation (59%), and positive T waves (52%). Almost 40% had diffuse ST-segment deviation, but only 25% had ST-segment elevation in V1 lead. The mean sum of ST-segment elevation was 9 ± 6 mm and the mean corrected QT interval was 467.4 ± 55 ms.

TABLE 1. Electrocardiographic characteristics at admission and after 48 hours

Variable	At admission	After 48 h
Heart rate at admission (bpm)	74 ± 16	-
Rhythm at admission		
Sinus rhythm	216 (87.8%)	-
Atrial fibrillation	18 (7.3%)	-
Atrial flutter	1 (0.4%)	-
Other supraventricular tachycardia	4 (1.6%)	-
Pacemaker	7 (2.8%)	-
Arrhythmia development	-	56 (23.8%)
Bundle branch block	43 (17.9%)	39 (17.2%)
Advanced interatrial block	13 (5.3%)	-
P wave width (ms)	100 (40)	-
PR interval (ms)	160 (40)	-
QRS width (ms)	100 (30)	-
ST-segment/T wave deviation localization		
Anterior leads	25 (10.2%)	-
Anterolateral leads	62 (25.4%)	-
Anteroinferior leads	5 (2.0%)	-
Lateral leads	23 (9.4%)	-
Inferior leads	5 (2.0%)	-
Inferolateral leads	20 (8.2%)	-
More than two wall leads	97 (39.8%)	-
Non diagnostic electrocardiogram	7 (2.9%)	-
ST-segment deviation		
Normal	31 (12.8%)	153 (68.3%)
Elevation	143 (59.1%)	39 (17.4%)
Depression	30 (12.4%)	19 (8.5%)
Elevation and reciprocal depression	32 (13.2%)	7 (3.1%)
Non diagnostic	6 (2.5%)	6 (2.7%)
Sum of ST-segment elevation (mm)	9 ± 6	-
ST-segment elevation in V1 lead	61 (25.4%)	-
ST-segment elevation in limb leads	146 (60.8%)	-
T wave deviation		
Positive	125 (51.7%)	8 (3.6%)
Negative	70 (28.9%)	198 (88.0%)
Biphasic	41 (16.9%)	18 (8.0%)
Non-diagnostic	6 (2.5%)	1 (0.4%)
Negative T wave in aVR	-	46 (20.4%)
Negative T wave in aVL	-	138 (61.3%)
Positive T wave in V1	-	161 (71.6%)
Number of leads with negative T waves	-	8 (4)
Negative T wave amplitude (mV)	-	0.7 ± 0.5
Pathological Q waves	-	137 (60.9%)
Corrected QT (ms)	467.4 ± 55	520 ± 72

Bpm, beats per minute; mm, millimeters; ms, milliseconds; mV. millivolt.
Values are shown as mean ± SD, median (interquartile range [IQR]) or absolute frequency and percentage (%).

During hospital stay, 24% had tachyarrhythmia. Most patients (68%) had ST-segment normalized and 88% developed negative T waves 48 hours after admission. Negative T waves were observed in a median of 8 (IQR 4) leads per patient, with a mean amplitude of 0.7 ± 0.5 mV. 20% had negative T waves in aVR and 61% in aVL. Corrected QT interval was frequently prolonged with a mean value of 520 ± 72 ms. Figure 1 shows an example of admission and 48 hours post-admission ECGs of a patient with TTS.

The primary endpoint of all-cause death and nonfatal cardiovascular events was significantly higher in patients with longer corrected QT at admission (481.3 ± 63.1 vs 460.3 ± 48.3, $P = 0.004$) and in those who developed any tachyarrhythmia during hospital stay (35.8% vs 17.5%, $P = 0.002$). Significant associations of secondary endpoints with electrocardiographic features such as corrected QT at admission and after 48 hours, ST-segment deviation, and tachyarrhythmia development are shown in Table 2. Table 3 depicts the independent predictors of outcomes. Corrected QT interval at admission was associated with all-cause death risk (hazard ratio [HR] 1.02, 95% confidence interval [CI] 1.01-1.03, $P = 0.008$) and with the primary endpoint (HR 1.01, 95% CI 1.00-1.02, $P = 0.002$). A higher heart rate at admission was also an independent predictor of the primary endpoint (HR 1.1, 95% CI 1.02-1.1, $P = 0.001$) and of the risk of developing acute pulmonary edema (HR 1.0, 95% CI 1.00-1.1, $P = 0.04$). Presence of ST-segment elevation with reciprocal depression was independently associated with all-cause death (HR 11.8, 95% CI 1.2-123.0, $P = 0.04$). Absence of ST-segment deviation was a protective factor for the primary endpoint (HR 0.06, 95% CI 0.01-0.4, $P = 0.005$). Finally, tachyarrhythmias were associated with cardiogenic shock (HR 7.4, 95% CI 2.8-19.5, $P < 0.001$).

Discussion

The results from our study can be summarized as follows: I) Patients with TTS develop characteristic electrocardiographic alterations at presentation and after 48 hours. II) Prolonged corrected QT interval, abnormal ST-segment, higher heart rates and tachyarrhythmia are associated with poor prognosis.

Patients with TTS can mimic ACS both clinically and electrocardiographically. Our cohort presented mostly with ST-segment elevation and only 12% had exclusively ST-segment depression. This is in accordance with previous studies,[23,24] in fact the absence of ST-segment depression has been proposed as a diagnostic criterion supporting TTS.[4,14,19]

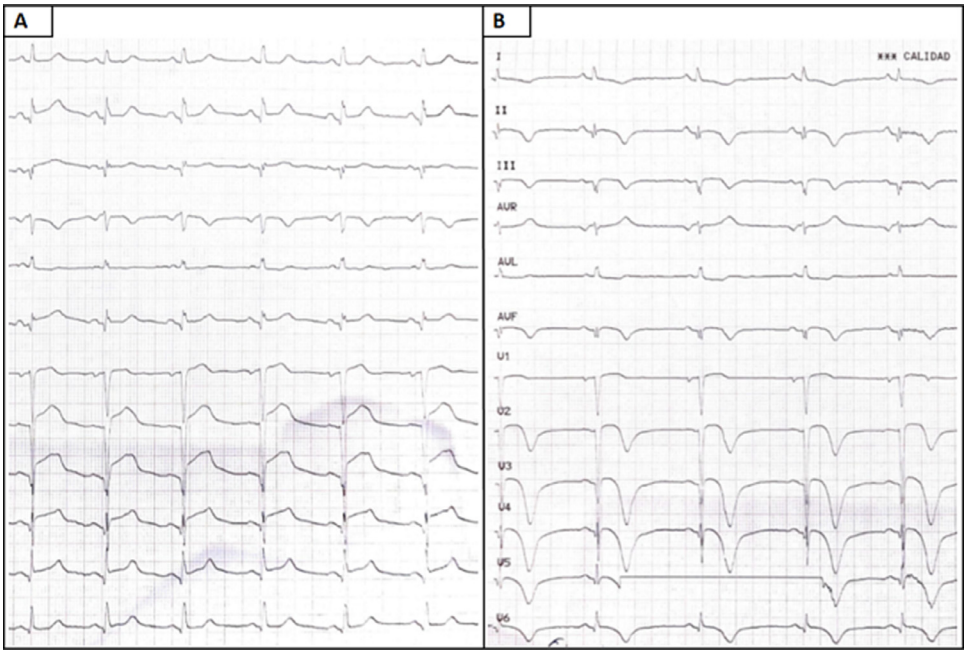

FIG. 1. Characteristic examples of admission (A) and 48 hours post-admission (B) ECGs of a patient with Takotsubo syndrome. (A). Diffuse ST-segment elevation extending beyond 2 leads. ST-segment depression in aVR corresponding with ST-segment elevation in -aVR. Absence of ST-segment elevation in V1. (B). Diffuse profound T wave inversion and QT interval prolongation. Note absence of negative T waves in aVL, aVR and V1.

TABLE 2. Primary and secondary endpoints according to electrocardiographic characteristics

	Arrhythmia[#] development	Sum of ST-segment elevation (mm)	ST-segment deviation localization (>2 leads)	ST-segment deviation	Corrected QT at admission (ms)	Corrected QT after 48 hours (ms)
Primary endpoint (84)						
No	27 (17.5%)	8.2 ± 5.0	56 (35.0%)	91 (57.2%)	460.3 ± 48.3	515.6 ± 62.5
Yes	29 (35.8%)*	9.8 ± 6.3	41 (48.8%)	53 (63.9%)**	481.3 ± 63.1†	529.0 ± 87.5
Cardiogenic shock (36)						
No	38 (19.0%)	8.6 ± 5.4	81 (38.9%)	121 (58.7%)	464.4 ± 50.2	516.8 ± 66.9
Yes	18 (51.4%)‡	9.9 ± 6.4	16 (44.4%)	23 (63.9%)**	485.2 ± 73.6§	540.1 ± 96.4
Cardiovascular death (5)						
No	54 (23.4%)	8.8 ± 5.6	95 (39.7%)	29 (12.2%)	466.0 ± 53.7	518.9 ± 72.1
Yes	2 (50.0%)	6 ± 2.3	2 (40.0%)	3 (25.0%)†,††	551.5 ± 40.5*	594.5 ± 34.0§
All-cause death (7)						
No	54 (23.6%)	8.8 ± 5.6	93 (39.2%)	28 (11.9%)	465.4 ± 52.2	518.5 ± 71.0
Yes	2 (33.3%)	7.1 ± 2.9	4 (57.1%)	4 (66.7%)*,††	549.3 ± 85.1‡	581.8 ± 96.5‖
Orotracheal intubation (16)						
No	46 (20.9%)	8.7 ± 5.6	88 (38.6%)	134 (59.3%)	465.4 ± 50.5	518.6 ± 67.0
Yes	10 (66.7%)‡	10.1 ± 5.7	9 (56.3%)	10 (62.5%)**	495.8 ± 92.6‖	549.8 ± 136
Mitral insufficiency III-IV (26)						
No	49 (23.2%)	8.3 ± 5.6	85 (39.0%)	128 (59.3%)	465.2 ± 54.4	518.0 ± 71.1
Yes	7 (29.2%)	8.9 ± 5.7	12 (46.2%)	16 (61.5%)**	487.1 ± 52.7¶	539.7 ± 80.4

mm, millimeters; ms, milliseconds.

Values shown as absolute frequency and percentage (%) or mean ± SD. Percentages represent the proportion from each primary or secondary endpoint. Primary endpoint: composite of nonfatal cardiovascular events and all-cause death.

*$P = 0.002$.

†$P = 0.004$.

‡$P < 0.001$.

§$P = 0.04$.

‖$P = 0.03$.

¶$P = 0.05$.

#Supraventricular or ventricular tachyarrhythmia.

**ST-segment elevation.

††ST-segment elevation and reciprocal depression.

TABLE 3. Independent predictors of primary and secondary endpoints`

	OR (95% CI)	*P* value
Primary endpoint		
Betablocker	3.4 (1.1 - 10.9)	0.04
ACEI/ARB	0.3 (0.1 – 0.7)	0.007
Heart rate*	1.1 (1.02 – 1.1)	0.001
Negative T wave aVR†	0.2 (0.1 – 0.7)	0.007
Corrected QT interval*	1.0 (1.00 – 1.02)	0.002
Normal ST-segment*	0.06 (0.01 – 0.4)	0.005
Cardiogenic shock		
Arrythmia development‡	7.4 (2.8 – 19.5)	< 0.001
Acute pulmonary oedema		
Smoker	2.9 (1.1 – 7.6)	0.03
Heart rate*	1.0 (1.00 – 1.1)	0.04
Sinus rhythm	0.1 (0.01 – 1.4)	0.09
All-cause death		
Corrected QT interval*	1.02 (1.01 – 1.03)	0.008
ST-segment elevation and reciprocal depression*	11.8 (1.2 – 123.0)	0.04

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; OR, odds ratio.
Primary endpoint: composite of nonfatal cardiovascular events and all-cause death.
*at admission.
†after 48 hours.
‡supraventricular or ventricular tachyarrhythmia.

Previous descriptions of ST-segment elevation patterns in ACS and TTS had conflicting results.[23,25] ST-segment elevation in TTS involves mostly anterior and lateral leads, specially V2-5, II, and -aVR. The lack of V1 elevation has been proposed as a specific criterion for TTS, although its prevalence varies largely among series and this suggestion is mainly derived from studies with small samples.[16,17] Most of our patients had diffuse ST-segment elevation (also an element that helps differentiation from ACS), but only 25% had V1 elevation. The exclusive elevation in inferior leads is very rare in TTS,[14] and was only seen in 2% of our patients. Takashio et al[26] obtained a significative association between the sum in mm and the extent of ST-segment elevation and the risk of cardiovascular complications. In our study, the mean value of ST-segment elevation was 9 mm and there was tendency towards an association with the primary endpoint.

During the 48 hours after TTS onset, generalized profound T wave inversion occurs.[19,27,28] We found an 88% prevalence, although only 20% and 60% developed negative T waves in leads aVR and aVL, respectively. In addition, positive T waves in V1 persisted in 72% of our patients. Kosuge et al[29] studied 34 TTS patients and compared them with anterior STEMI patients and found the highest diagnostic accuracy for

TTS combining positive T wave in aVR and no negative T wave in V1. Positive T waves in aVR (negative T waves in -aVR) correspond to the apical region and positive T waves in V1 are supposed to represent negative T waves in posterior leads, regions that may be affected occasionally in TTS. The number of leads with negative T waves in our study is remarkably high (median 8 leads) and similar to previous works, as it represents myocardial edema in the injured myocardial territory, and their amplitude is usually larger than in STEMI.[29,30] It is suspected that it corresponds with more viable but sympathetically denervated myocardium with delayed repolarization.[31] Data from the Swedish TTS Registry showed a lower risk of the composite endpoint of in-hospital death and arrhythmic complications in patients with T wave inversion at admission. However, other studies point in the opposite direction, as the demonstrated relationship between repolarization inhomogeneity (represented by T wave inversion and QT interval prolongation) and myocardial edema in cardiac magnetic resonance may correspond with the increased arrhythmic risk.[32,33] Moreover, the majority of the patients with TTS develop T-wave inversion during hospital stay, and its presence at admission may be related with delayed presentation, so a better outcome in these patients should not be expected.

Pathological Q waves are not common in TTS, and are often transient, as they also correspond with myocardial stunning.[14] The prevalence in our cohort was 61%, slightly higher than in previous studies, but a large variation among series has been observed.[15,17,34]

Prolongation of corrected QT interval is frequently present in TTS and predisposes to adverse events, characteristically malignant ventricular arrhythmia and sudden cardiac death.[35-38] Previous work regarding prognostic factors of TTS has focused in clinical, echocardiographic, or hemodynamic factors, and less attention has been paid to electrocardiographic features.[4,8,18] Our study shows a significant association between corrected QT interval duration and prognosis. A similar result has been obtained in a recent small observational study.[11] Other significant independent predictors of adverse events in our cohort were heart rate at admission, absence of sinus rhythm at admission or during hospital stay, and ST-segment deviation, the latter probably representing a larger amount of stunned and edematous myocardium. Data from the International Takotsubo Registry reported a significantly higher heart rate than in STEMI patients, which was also an independent predictor of worse outcomes.[4] Patients who present with the above mentioned adverse prognostic factors may benefit from a more aggressive management and closer surveillance during their hospital stay.

The present study has the inherent limitations of observational non-randomized work. Despite the large size of our national registry cohort, the sample size of this sub study was smaller, as several patients did not have a complete ECG at admission and 48 hours afterwards, and patients who died in the first 48 hours post-admission had to be excluded for the analysis. Unfortunately, we had no ECG follow-up after hospital discharge. However, as far as we know, ours is the largest study specifically analyzing electrocardiographic parameters and assessing their prognostic significance in a real-life unselected multicentric cohort of TTS patients.

In conclusion, TTS patients present with distinct electrocardiographic features. Prolonged corrected QT interval, tachyarrhythmias, heart rate at admission, and more extensive repolarization alterations are associated with a poor outcome.

Conflict of Interest

None of the authors have a conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2021.100841.

REFERENCES

1. Ghadri J-R, Wittstein IS, Prasad A, et al. International expert consensus document on takotsubo syndrome (part i): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J* 2018;39:2032–46.
2. Nunez Gil IJ, Andres M, Almendro Delia M, et al. Characterization of tako-tsubo cardiomyopathy in spain: results from the retako national registry. *Rev Esp Cardiol (Engl Ed)* 2015;68:505–12.
3. Lyon AR, Bossone E, Schneider B, et al. Current state of knowledge on takotsubo syndrome: a position statement from the taskforce on takotsubo syndrome of the heart failure association of the european society of cardiology. *Eur J Heart Fail* 2016;18:8–27.
4. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of takotsubo (Stress) cardiomyopathy. *N Engl J Med* 2015;373:929–38.
5. Almendro-Delia M, Nunez-Gil IJ, Lobo M. Short- and long-term prognostic relevance of cardiogenic shock in takotsubo syndrome: results from the RETAKO registry. *JACC Heart Fail* 2018;6:928–36.

6. Perez-Castellanos A, Martinez-Selles M, Mejia-Renteria H, et al. Tako-tsubo syndrome in men: rare, but with poor prognosis. *Rev Esp Cardiol (Engl Ed)* 2018;71:703–8.
7. Madhavan M, Rihal CS, Lerman A, Prasad A. Acute heart failure in apical ballooning syndrome (TakoTsubo/stress cardiomyopathy): clinical correlates and mayo clinic risk score. *J Am Coll Cardiol* 2011;57:1400–1.
8. Stiermaier T, Moeller C, Oehler K, et al. Long-term excess mortality in takotsubo cardiomyopathy: predictors, causes and clinical consequences. *Eur J Heart Fail* 2016;18:650–6.
9. Thakar S, Chandra P, Hollander G, Lichstein E. Electrocardiographic changes in takotsubo cardiomyopathy. *Pacing Clin Electrophysiol* 2011;34:1278–82.
10. Weihs V, Szucs D, Fellner B, et al. Electrocardiogram changes and wall motion abnormalities in the acute phase of tako-tsubo syndrome. *Eur Heart J Acute Cardiovasc Care* 2016;5:481–8.
11. Imran TF, Rahman I, Dikdan S, et al. QT prolongation and clinical outcomes in patients with takotsubo cardiomyopathy. *Pacing Clin Electrophysiol* 2016;39:607–11.
12. Shimizu M, Nishizaki M, Yamawake N, et al. J wave and fragmented QRS formation during the hyperacute phase in Takotsubo cardiomyopathy. *Circ J* 2014;78:943–9.
13. Martin-Demiguel I, Nunez-Gil IJ, Perez-Castellanos A, et al. Prevalence and significance of interatrial block in takotsubo syndrome (from the RETAKO Registry). *Am J Cardiol* 2019;123:2039–43.
14. Ghadri JR, Wittstein IS, Prasad A, et al. International expert consensus document on takotsubo syndrome (Part II): diagnostic workup, outcome, and management. *Eur Heart J* 2018;39:2047–62.
15. Kosuge M, Kimura K. Electrocardiographic findings of takotsubo cardiomyopathy as compared with those of anterior acute myocardial infarction. *J Electrocardiol* 2014;47:684–9.
16. Tamura A, Watanabe T, Ishihara M, et al. A new electrocardiographic criterion to differentiate between Takotsubo cardiomyopathy and anterior wall ST-segment elevation acute myocardial infarction. *Am J Cardiol* 2011;108:630–3.
17. Kosuge M, Ebina T, Hibi K, et al. Simple and accurate electrocardiographic criteria to differentiate takotsubo cardiomyopathy from anterior acute myocardial infarction. *J Am Coll Cardiol* 2010;55:2514–6.
18. Sharkey SW, Windenburg DC, Lesser JR, et al. Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. *J Am Coll Cardiol* 2010;55:333–41.
19. Bennett J, Ferdinande B, Kayaert P, et al. Time course of electrocardiographic changes in transient left ventricular ballooning syndrome. *Int J Cardiol* 2013;169:276–80.
20. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J* 2008;155:408–17.
21. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting

with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2017;39:119–77.
22. Mirvis DM, Goldberger AL. Electrocardiography. In: Mann DL, Zipes DP, Libby P, Bonow RO, Braunwald E, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, Philadelphia: Saunders; 2014:114–54.
23. Frangieh AH, Obeid S, Ghadri JR, et al. ECG Criteria to differentiate between takotsubo (Stress) cardiomyopathy and myocardial infarction. *J Am Heart Assoc* 2016;5.
24. Mitsuma W, Kodama M, Ito M, et al. Serial electrocardiographic findings in women with Takotsubo cardiomyopathy. *Am J Cardiol* 2007;100:106–9.
25. Bybee KA, Motiei A, Syed IS, et al. Electrocardiography cannot reliably differentiate transient left ventricular apical ballooning syndrome from anterior ST-segment elevation myocardial infarction. *J Electrocardiol* 2007;40(38):e31–6.
26. Takashio S, Yamamuro M, Kojima S, et al. Usefulness of SUM of ST-segment elevation on electrocardiograms (limb leads) for predicting in-hospital complications in patients with stress (takotsubo) cardiomyopathy. *Am J Cardiol* 2012;109:1651–6.
27. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J* 2008;155:408–17.
28. Kurisu S, Inoue I, Kawagoe T, et al. Time course of electrocardiographic changes in patients with tako-tsubo syndrome: comparison with acute myocardial infarction with minimal enzymatic release. *Circ J* 2004;68:77–81.
29. Kosuge M, Ebina T, Hibi K, et al. Differences in negative T waves between takotsubo cardiomyopathy and reperfused anterior acute myocardial infarction. *Circ J* 2012;76:462–8.
30. Migliore F, Zorzi A, Marra MP, et al. Myocardial edema underlies dynamic T-wave inversion (Wellens' ECG pattern) in patients with reversible left ventricular dysfunction. *Heart Rhythm* 2011;8:1629–34.
31. Agetsuma H, Hirai M, Hirayama H, et al. Transient giant negative T wave in acute anterior myocardial infarction predicts R wave recovery and preservation of left ventricular function. *Heart* 1996;75:229–34.
32. Jha S, Zeijlon R, Enabtawi I, et al. Electrocardiographic predictors of adverse in-hospital outcomes in the takotsubo syndrome. *Int J Cardiol* 2020;299:43–8.
33. Perazzolo Marra M, Zorzi A, Corbetti F, et al. Apicobasal gradient of left ventricular myocardial edema underlies transient T-wave inversion and QT interval prolongation (Wellens' ECG pattern) in Tako-Tsubo cardiomyopathy. *Heart Rhythm* 2013;10:70–7.
34. Ogura R, Hiasa Y, Takahashi T, et al. Specific findings of the standard 12-lead ECG in patients with 'Takotsubo' cardiomyopathy: comparison with the findings of acute anterior myocardial infarction. *Circ J* 2003;67:687–90.
35. Behr ER, Mahida S. Takotsubo cardiomyopathy and the long-QT syndrome: an insult to repolarization reserve. *Europace* 2009;11:697–700.
36. Migliore F, Zorzi A, Perazzolo Marra M, Iliceto S, Corrado D. Myocardial edema as a substrate of electrocardiographic abnormalities and life-threatening arrhythmias in reversible ventricular dysfunction of takotsubo cardiomyopathy: Imaging evidence, presumed mechanisms, and implications for therapy. *Heart Rhythm* 2015;12:1867–77.

37. Madias C, Fitzgibbons TP, Alsheikh-Ali AA, et al. Acquired long QT syndrome from stress cardiomyopathy is associated with ventricular arrhythmias and torsades de pointes. *Heart Rhythm* 2011;8:555–61.
38. Gopalakrishnan M, Hassan A, Villines D, Nasr S, Chandrasekaran M, Klein LW. Predictors of short- and long-term outcomes of Takotsubo cardiomyopathy. *Am J Cardiol* 2015;116:1586–90.