ORIGINAL RESEARCH

Risk Stratification Using the CHA_2DS_2-VASc Score in Takotsubo Syndrome: Data From the Takotsubo Italian Network

Guido Parodi, MD, PhD; Fernando Scudiero, MD; Rodolfo Citro, MD, PhD; Angelo Silverio, MD; Benedetta Bellandi, MD; Concetta Zito, MD, PhD; Francesco Antonini-Canterin, MD; Fausto Rigo, MD; Chiara Zocchi, MD; Eduardo Bossone, MD, PhD; Jorge Salerno-Uriarte, MD, PhD; Federico Piscione, MD, PhD; Carlo Di Mario, MD, PhD; on the behalf of Takotsubo Italian Network (TIN)*

***Background*—**The CHA_2DS_2-VASc score predicts stroke in patients with atrial fibrillation and has been reported to have a prognostic role even in acute coronary syndrome patients. The Takotsubo syndrome is a condition that mimics acute coronary syndrome and may present several complications including stroke. We sought to assess the ability of CHA_2DS_2-VASc score to predict adverse events in Takotsubo syndrome patients.

***Methods and Results*—**Overall, 371 Takotsubo syndrome patients were enrolled in a prospective registry. Patients were divided into 3 groups according to the CHA_2DS_2-VASc score: Group A (≤1), B (2–3), and C (≥4). The median CHA_2DS_2-VASc score was 3 (interquartile range: 2–4). Overall, 9%, 42%, and 49% were included in Group A, B, and C, respectively. Follow-up length was 26±20 months. The mortality rate was 6%, 7%, and 17% in Group A, B, and C, respectively (P=0.011). The stroke rate was 3% and not different among the 3 groups. Estimated major adverse cardiac and cerebrovascular events (the composite of death, myocardial infarction, and stroke) rates in the 3 groups were 6%, 9%, and 17% in Group A, B, and C, respectively (P=0.033). The CHA_2DS_2-VASc score resulted as a predictor of major adverse cardiac and cerebrovascular events (odds ratio 2.1, 95% confidence interval, 1.2–3.6; P=0.01) and all-cause mortality (odds ratio 1.5, 95% confidence interval, 1.2–1.9; P=0.001).

***Conclusions*—**In Takotsubo syndrome, the CHA_2DS_2-VASc score allows prediction of cardiovascular events and mortality at long-term follow-up. **(*J Am Heart Assoc*. 2017;6:e006065. DOI: 10.1161/JAHA.117.006065.)**

Key Words: anticoagulant • cardiovascular events • CHA_2DS_2-VASc score • stroke • Takotsubo • Takotsubo cardiomyopathy • Takotsubo syndrome

The validity of CHA_2DS_2-VASc score on stroke-risk stratification in patients with atrial fibrillation (AF) has been well documented [1,2] and, although initially developed only for patients with AF, it has proved to be a helpful scoring system for evaluating the complexity of comorbidities in different clinical settings. The application of CHA_2DS_2-VASc score in patients without AF is relatively new and only a few non-AF studies have explored this simple method of risk assessment.[3–5]

Goto et al[6] demonstrated the potential of $CHADS_2$ score in predicting not only stroke but also cardiovascular death in stable outpatients at risk of atherothrombosis. Moreover, the $CHADS_2$ score has been reported to have a prognostic role in acute coronary syndrome patients without AF.[4]

The Takotsubo syndrome (TTS) is an increasingly recognized cardiac condition that mimics an acute coronary syndrome and predominantly affects postmenopausal women. Several major cardiovascular and cerebrovascular events can complicate TTS, which should be considered as an acute heart failure syndrome with substantial morbidity and mortality.[7–10] In particular, a stroke or transient ischemic attack rate of 1.7% per patient-year in a recent multicenter Registry was reported.[10]

Oral anticoagulation is recommended in patients with TTS, if intraventricular thrombus is detected, but the role of prophylactic anticoagulation remains to be determined. A

From the Cardiovascular and Thoracic Department, Careggi University Hospital, Florence, Italy (G.P., F.S., B.B., C. Zocchi, C.D.M.); Clinical and Interventional Cardiology, Sassari University Hospital, Sassari, Italy (G.P.); University Hospital 'San Giovanni di Dio e Ruggi d'Aragona', Salerno, Italy (R.C., A.S., E.B., F.P.); Department of Clinical and Experimental Medicine, University of Messina, Italy (C. Zito); Division of Cardiology, S. Maria degli Angeli Hospital, Pordenone, Italy (F.A.-C.); Department of Cardiology, Dell'Angelo Hospital, Mestre, Italy (F.R.); Department of Cardiology, University of Insubria, Ospedale di Circolo and Fond. Macchi, Varese, Italy (J.S.-U.).

*A complete list of the Takotsubo Italian Network investigators can be found in the Appendix at the end of the article.

Correspondence to: Guido Parodi, MD, PhD, Cardiovascular and Thoracic Department, Careggi University Hospital, Largo Brambilla 3, Florence, Italy. E-mail: parodiguido@gmail.com

Received March 31, 2017; accepted July 28, 2017.

Clinical Perspective

What Is New?

- This study demonstrated the ability of CHA_2DS_2-VASc score to predict a long-term composite end point of death, myocardial infarction, and stroke in Takotsubo patients.

What Are the Clinical Implications?

- CHA_2DS_2-VASc score could be considered an acceptable method for long-term risk stratification in Takotsubo patients, and likely in other patient populations without atrial fibrillation.

clinic score that is able to predict short- and long-term complications and that is useful to guide the management of TTS patients is still lacking.

The aim of this study is to assess the ability of CHA_2DS_2-VASc scores to predict adverse events in TTS patients.

Methods

The design of this study was a multicenter, observational registry. Patients admitted to 20 centers participating in the Takotsubo Italian Network were included in the Registry according to the Takotsubo Italian Network diagnostic criteria[11]: (1) Typical transient left ventricular wall motion abnormalities extending beyond a single epicardial vascular distribution with complete functional normalization within 6 weeks; (2) Absence of potentially culprit coronary stenosis, or angiographic evidence of acute plaque rupture, dissection, thrombosis, or spasm; (3) New and dynamic ST-segment abnormalities or T-wave inversion or new-onset transient or permanent left bundle branch block; (4) Mild increase in myocardial injury markers (creatine kinase-MB value >50 U/L); (5) Clinical and/or instrumental exclusion of myocarditis; (6) Postmenopausal woman (optional); (7) Antecedent stressful event (optional). Antecedent stressful trigger event was defined as an occurrence that produced short-term physiological change that may lead directly to the onset of acute cardiovascular disease. They could be either emotional or physical (including acute medical or surgical emergencies).[12] Coronary angiography was performed as soon as possible (ideally within 48 hours from admission).

The study was approved by the local Ethics Committees. All patients provided informed consent. The CHA_2DS_2-VASc score was calculated for each patient. Patients were divided into 3 groups according to the CHA_2DS_2-VASc score: Group A (≤1), B (2–3), and C (≥4).Patients were asked to return to our outpatient clinic for follow-up evaluation at 1 and 6 months, and annually thereafter. The primary end point was the composite of all-cause death, myocardial infarction, and stroke. Individual components of the primary end point as well as rehospitalization and AF were secondary end points.

Discrete data are expressed as frequencies, and continuous data as mean±SD or median and interquartile range as appropriate. The χ^2 test was used to compare categorical variables, and ANOVA with the Tukey post hoc test was used to assess differences in the baseline characteristics between the 3 study groups. Survival curves were generated with the use of the Kaplan–Meier method, and the difference between groups was assessed by log-rank test. To address concerns over the potential confounding variables to affect the prognostic performance of the CHA_2DS_2-VASc score, we constructed a multivariate Cox proportional hazards model. We used a parsimonious model including variables with $P<0.10$ by univariate test as a candidate for the multivariate analysis, such as CHA_2DS_2-VASc score as a continuous variable, age, female sex, diabetes mellitus, left ventricular ejection fraction, and apical ballooning. Multicollinearity was assessed using collinearity diagnostics. The variance inflation factors showed no significant collinearity (<2.5) among the covariates. A $P<0.05$ was considered significant. All tests were 2-sided. Analyses were performed with SPSS 19 statistical package (IBM Corporation, Somers, NY).

Results

A total of 371 TTS patients were included in this observational registry (Table 1 summarizes baseline characteristics). The median CHA_2DS_2-VASc score was 3 (interquartile range: 2–4), ranging from 1 to 8. No patient showed a score of 0. Overall, 9%, 42%, and 49% subjects were included in Group A, B and C, respectively.

Patients with lower CHA_2DS_2-VASc score were more likely to have a trigger stressful event (91%, 79%, and 68% in Group A, B, C; $P=0.007$). They also had a lower rate of AF history (0%, 12%, 22%, $P=0.002$) and anticoagulant therapy at admission (0%, 8%, 14%, $P=0.049$). Of note, left ventricular ejection fraction at admission was significantly lower in Group C (0.37±0.10) compared with patients of Group A and B (0.41±0.10 and 0.40±0.10, $P=0.007$). During hospital stay, echographic evidence of left ventricular thrombosis was detected in 7 patients and none of them developed a clinical evidence of a cerebrovascular event. No significant difference in echographic evidence of left ventricular thrombosis was observed between the 3 study groups, at least in part influenced by the previous and in-hospital therapies and by the generally transitory and short-lived nature of the intraventricular thrombosis. The mean follow-up length was 26±20 months and the follow-up rate was 95%. The incidence of the primary end point as well as of all-cause

Table 1. Baseline Characteristics of Study Patients

Variables	All (n=371)	Group A (n=33)	Group B (n=155)	Group C (n=183)
Age, y	73±10	55±10*†	70±8‡†	78±6‡*
Female sex	339 (91)	30 (91)	135 (87)†	174 (95)*
Family history of CAD	58 (16)	0 (0)†	12 (8)†	46 (25)‡*
Smoker	86 (23)	13 (39)†	37 (24)	36 (20)‡
Hypertension	236 (64)	1 (3)*†	72 (46)‡†	163 (89)‡*
Dyslipidemia	123 (33)	8 (24)	50 (32)	65 (35)
Diabetes mellitus	52 (14)	1 (3)†	7 (4)†	44 (24)‡*
Congestive heart failure	3 (1)	0 (0)	0 (0)	3 (2)
Peripheral vascular disease	38 (10)	0 (0)†	3 (2)†	35 (19)‡*
Previous stroke/TIA	37 (10)	0 (0)†	1 (1)†	36 (20)‡*
Trigger stressful event	275 (74)	30 (91)†	120 (79)	125 (68)‡
Variant type				
Apical	245 (66)	28 (85)*	94 (61)‡	123 (67)
Midventricular	127 (34)	13 (39)	55 (36)	59 (32)
Basal	16 (4)	1 (3)	7 (4)	8 (4)
LVEF at admission	38±10	41±10†	40±10†	37±10‡*
LVEF≤40%	235 (63)	14 (45)†	94 (61)	127 (69)‡
LV thrombosis	7 (2)	0 (0)	4 (3)	3 (2)
Previous AF	59 (16)	0 (0)†	19 (12)†	40 (22)‡*
Oral anticoagulant at admission	37 (10)	0 (0)†	12 (8)	25 (14)‡
Discharge therapy				
Aspirin	278 (75)	26 (81)	112 (73)	139 (76)
P2Y12 inhibitor	129 (35)	12 (38)	48 (31)	68 (37)
Dual antiplatelet agents	83 (22)	8 (24)	32 (21)	43 (23)
Oral anticoagulant	46 (12)	0 (0)‡	14 (9)	33 (18)‡

AF indicates atrial fibrillation; CAD, coronary artery disease; LV, left ventricle; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.
*P<0.05 Group B; †P<0.05 Group C; ‡P<0.05 vs Group A.

death was significantly higher in patients with high CHA_2DS_2-VASc scores than in patients with low CHA_2DS_2-VASc scores. All the other secondary end points did not significantly differ between groups (Table 2 summarizes the outcomes). During follow-up, 7 strokes occurred in this cohort of patients: 4 strokes were ischemic and attributed to AF-related embolism, 2 strokes were fatal events without additional diagnostic procedures, and 1 ischemic stroke occurred soon after surgical mitral valve repair. Estimated cumulative incidences of major adverse cardiac and cerebrovascular events in Group A, B, C are reported in Figure.

The CHA_2DS_2-VASc score was found to be a strong predictor of cardiovascular events (odds ratio 2.1, 95% confidence interval, 1.2–3.6; P=0.01) and mortality (odds ratio 1.5, 95% confidence interval, 1.2–1.9; P=0.001, Table 3).

Discussion

TTS patients, being postmenopausal women with high hypertension and other comorbidity rates, are usually characterized by high CHA_2DS_2-VASc scores. This study demonstrated the ability of the CHA_2DS_2-VASc score to predict a composite end point of death, myocardial infarction, and stroke in TTS patients, suggesting its use as an acceptable method for long-term risk stratification in these patients. The CHA_2DS_2-VASc score has several desirable characteristics to be applied in TTS patients because it is easy to calculate and utilizes clinical data that are available at admission. Patients with CHA_2DS_2-VASc ≥4 showed a higher major adverse cardiac and cerebrovascular events rate, mainly driven by increased fatal events. Older age and a higher prevalence of comorbidities certainly contributed to the higher mortality rate in Group C

Table 2. Long-Term Outcome in the 3 Study Groups

	All (n=371)	Group A (n=33)	Group B (n=155)	Group C (n=183)	*P* Value*
MACCE	48 (13)	2 (6)	14 (9)	32 (17)	0.033
All-cause death	44 (12)	2 (6)	11 (7)	31 (17)	0.011
MI	4 (1)	0 (0)	2 (1)	2 (1)	0.808
Stroke	7 (2)	0 (0)	4 (3)	3 (2)	0.577
Rehospitalization	53 (14)	3 (9)	20 (13)	30 (16)	0.473
Atrial fibrillation	13 (3)	0 (0)	6 (4)	7 (4)	0.498

MACCE indicates major adverse cardiac and cerebrovascular events (all-cause death, myocardial infarction, stroke); MI, myocardial infarction.
*By log-rank test.

Table 3. Predictors of MACCE and All-Cause Death

MACCE	HR	95% CI	*P* Value
CHA_2DS_2-VASc score	2.10	1.21 to 3.62	0.01
Age, y	1.13	1.04 to 1.23	0.003
All-cause death			
CHA_2DS_2-VASc score	1.51	1.20 to 1.93	0.01
Age, y	1.11	1.06 to 1.16	<0.001
Diabetes mellitus	2.86	1.29 to 6.35	0.01

CI indicates confidence interval; HR, hazard ratio; MACCE, major cardio-cerebrovascular events, the composite of death, infarction, and stroke.

patients as compared with Group A and B patients. On the contrary, nonfatal event rates (ie, myocardial infarction and ischemic stroke) were not significantly different between groups. It is unknown whether the more frequent use of anticoagulants in Group C has influenced this result.

Since myocardial dysfunction fully recovers in almost all of the patients within a few weeks, a substantial impact of Takotsubo-related left ventricular dysfunction on long-term outcomes seems unlikely. However, patients who had a TTS episode remain at risk for TTS recurrences and associated complications. On the other hand, it has been speculated that associated comorbidities could be relevant determinants of long-term prognosis of TTS.[13]

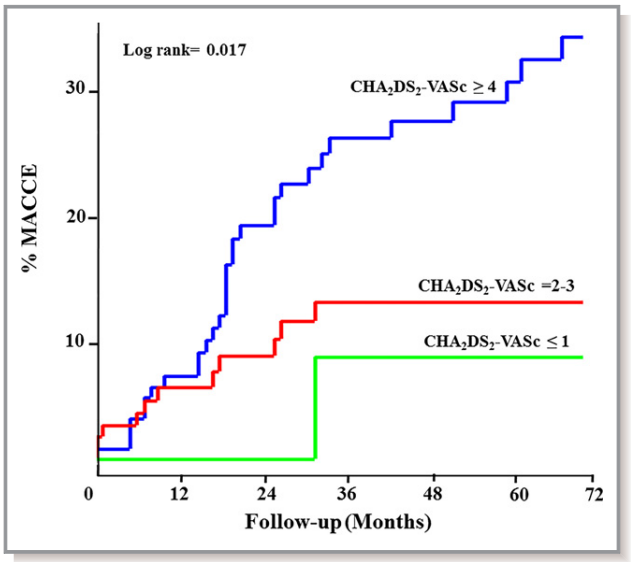

Figure. Cumulative incidence curves depicting adverse event (MACCE; primary end point: the composite of death, infarction, and stroke) rates according to the CHA_2DS_2-VASc score: Group A, (≤1); Group B, (2–3); Group C, (≥4). MACCE indicates major adverse cardiac and cerebrovascular events.

In our cohort of TTS subjects, with a low AF prevalence before and after the index event, the stroke rate at follow-up was lower than predicted by the CHA_2DS_2-VASc score, and not significantly different between groups, at least in part because of the low study power for this end point. However, no stroke occurred in TTS patients with CHA_2DS_2-VASc score ≤1.

TTS patients have a 10-fold higher risk of being affected by cerebrovascular accidents[7] but the mechanisms underlying this association remain unclear. Probably, in the early phase, cardioembolism, because of the formation of intraventricular thrombus caused by transient but severe left ventricular systolic dysfunction, has a pivotal role. During hospitalization, daily monitoring of the left ventricular wall motion recovery by echocardiography is recommended to rule out apical thrombus in patients with persistent myocardial contraction abnormalities.[14] However, the timing of thrombus formation and subsequent development of cardiogenic embolism has not been well documented. After the resolution of wall motion abnormalities and the recovery of systolic function, the formation of intraventricular thrombi is less likely. Indeed additional factors may play a role in the onset of cerebrovascular events. We should acknowledge that the variables included in the CHA_2DS_2-VASc score represent well-known cardiovascular risk factors (ie, age, hypertension, and diabetes mellitus) or manifestations of cardiovascular diseases (ie, heart failure, vascular disease, previous stroke/transient ischemic attack) able by themselves to impact patient long-term outcome. Therefore, TTS patients with high CHA_2DS_2-VASc score should not be considered at low risk for subsequent cardiovascular events. These patients should be carefully evaluated and a strict follow-up should be planned. Given the relevant event rates observed in patients with high CHA_2DS_2-VASc score, the intensification of secondary prevention strategies, including the selective use of antithrombotic agents (after careful bleeding risk assessment) seem justified in this subgroup of TTS patients.

Our results must be evaluated in light of some study limitations. First, this is a multicenter observational study and

the impact of clinical decision making based on risk stratification by CHA_2DS_2-VASc score in TTS patients is currently unknown. We also need to consider that no previous study evaluated the potential impact of pharmacological and preventive strategies on TTS long-term outcome, and the current management is largely empirical and variable among centers and attending physicians. Second, because of limited sample size, our study was probably not properly powered for rarely occurring events such as stroke. Finally, we cannot exclude the contribution of atherosclerotic coronary artery disease development to the higher long-term mortality rate of TTS with high CHA_2DS_2-VASc score as compared with the other groups. In fact, endothelial dysfunction, which constitutes the first step of atherosclerosis, has been suggested to be present in TTC,[7–9] and several components of the score represent well-known coronary artery disease risk factors. However, coronary artery disease was demonstrated by baseline angiography in only a few patients and nonfatal myocardial infarction occurred in only 2 patients during follow-up.

Conclusions

The CHA_2DS_2-VASc score demonstrated significant discriminatory ability in predicting the incidence of major adverse cardiac and cerebrovascular events and the all-cause mortality at follow-up in our cohort of TTS patients. Further data are needed to identify the features of TTS patients with high risk of cardiovascular events, and to accurately select the most convenient antithrombotic treatment.

Appendix

Takotsubo Italian Network (TIN) Investigators

Corinna Armentano, MD, Ospedale Guglielmo da Saliceto, Piacenza, Italy; Costantino Astarita, MD, and Antonino Coppola, MD, Ospedale S. Maria della Misericordia, Sorrento, Naples, Italy; Amelia Ravera MD, Costantina Prota MD, and Pompea Bottiglieri, MD, Azienda Ospedaliera Universitaria "San Giovanni di Dio e Ruggi d'Aragona," Salerno, Italy; Daniella Bovelli, MD, and Marco Mariano Patella, MD, Ospedale S. Maria, Terni, Italy; Marco Fabio Costantino, MD, Ospedale San Carlo, Potenza, Italy; Giovanni Gregorio, MD, and Michele Santoro, MD, Ospedale San Luca, Vallo della Lucania, Salerno, Italy; Fiore Manganelli, MD, and Francesco Rotondi, MD, Azienda Ospedaliera San Giuseppe Moscati, Avellino, Italy; Stefano Del Pace, MD, Careggi Hospital, Florence, Italy; Marco Pascotto, MD, Ospedale Fatebenefratelli, Naples, Italy; Elisabetta Grolla, MD, Ospedale Umberto I, Mestre, Venice, Italy; Ercole Tagliamonte, MD, Ospedale Umberto I, Nocera Inferiore, Salerno, Italy; Alfredo Bianchi, MD, Giovanni Marinosci, MD, Michele Pappalettera, MD, and Andrea Pozzi MD, Ospedale di Circolo and Fondazione Macchi, Università dell'Insubria, Varese, Italy; Federico Nardi, MD, Ospedale Castelli, Verbania, Italy; Giuseppina Novo, MD, University of Palermo, Palermo, Italy; Francesco Antonini-Canterin, MD, S. Maria degli Angeli Hospital, Pordenone, Italy; Francesco Bovenzi, MD, U.O. di Cardiologia, Ospedale Campo di Marte, Lucca.

Sources of Funding

This study was supported by A.R. CARD Foundation, Florence, Italy.

Disclosures

Dr Parodi reported receiving consulting or lecture fees from AstraZeneca, Bayer, Chiesi, Daiichi Sankyo/Eli Lilly, and Merck. Di Mario received research grants from Abbott and Medtronic. The remaining authors have no disclosures to report.

References

1. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870.
2. Boriani G, Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, Ricci R, Biffi M, De Santo T, Corbucci G, Lip GY. Improving stroke risk stratification using the $CHADS_2$ and CHA_2DS_2-VASc risk scores in patients with paroxysmal atrial fibrillation by continuous arrhythmia burden monitoring. *Stroke*. 2011;42:1768–1770.
3. Mitchell LB, Southern DA, Galbraith D, Ghali WA, Knudtson M, Wilton SB. Prediction of stroke or TIA in patients without atrial fibrillation using $CHADS_2$ and CHA_2DS_2-VASc scores. *Heart*. 2014;100:1524–1530.
4. Poci D, Hartford M, Karlsson T, Herlitz J, Edvardsson N, Caidahl K. Role of the CHADS2 score in acute coronary syndromes: risk of subsequent death or stroke in patients with and without atrial fibrillation. *Chest*. 2012;141:1431–1440.
5. Morillas P, Pallares V, Facila L, Llisterri JL, Sebastian ME, Gomez M, Castilla E, Camarasa R, Sandin M, Garcia-Honrubia A. The $CHADS_2$ score to predict stroke risk in the absence of atrial fibrillation in hypertensive patients aged 65 years or older. *Rev Esp Cardiol*. 2015;68:485–491.
6. Goto S, Bhatt DL, Rother J, Alberts M, Hill MD, Ikeda Y, Uchiyama S, D'Agostino R, Ohman EM, Liau CS, Hirsch AT, Mas JL, Wilson PW, Corbalan R, Aichner F, Steg PG. Prevalence, clinical profile, and cardiovascular outcomes of atrial fibrillation patients with atherothrombosis. *Am Heart J*. 2008;156:855–863.
7. Pelliccia F, Parodi G, Greco C, Antoniucci D, Brenner R, Bossone E, Cacciotti L, Capucci A, Citro R, Delmas C, Guerra F, Ionescu CN, Lairez O, Larrauri-Reyes M, Lee PH, Mansencal N, Marazzi G, Mihos CG, Morel O, Nef HM, Nunez Gil IJ, Passaseo I, Pineda AM, Rosano G, Santana O, Schneck F, Song BG, Song JK, Teh AW, Ungprasert P, Valbusa A, Wahl A, Yoshida T, Gaudio C, Kaski JC. Comorbidities frequency in Takotsubo syndrome: an international collaborative systematic review including 1109 patients. *Am J Med* 2015;128:654.e11–654.e19.
8. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, Figtree GA, Parodi G, Akashi YJ, Ruschitzka F, Filippatos G, Mebazaa A, Omerovic E. 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.
9. Parodi G, Del S, Carrabba N, Salvadori C, Memisha G, Simonetti I, Antoniucci D, Gensini GF. Incidence, clinical findings and outcome of

women with left ventricular apical ballooning syndrome. *Am J Cardiol*. 2007; 99:182–185.

10. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, Seifert B, Hellermann J, Schwyzer M, Eisenhardt K, Jenewein J, Franke J, Katus HA, Burgdorf C, Schunkert H, Moeller C, Thiele H, Bauersachs J, Tschope C, Schultheiss HP, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Bohm M, Erbel R, Cuneo A, Kuck KH, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Cuculi F, Banning A, Fischer TA, Vasankari T, Airaksinen KE, Fijalkowski M, Rynkiewicz A, Pawlak M, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Franz WM, Empen K, Felix SB, Delmas C, Lairez O, Erne P, Bax JJ, Ford I, Ruschitzka F, Prasad A, Luscher TF. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. *N Engl J Med*. 2015;373:929–938.

11. Parodi G, Citro R, Bellandi B, Provenza G, Marrani M, Bossone E. Revised clinical diagnostic criteria for Tako-tsubo syndrome: the Tako-tsubo Italian Network proposal. *Int J Cardiol*. 2014;172:282–283.

12. Del Pace S, Parodi G, Bellandi B, Zampini L, Venditti F, Ardito M, Antoniucci D, Gensini GF. Anxiety trait in patients with stress-induced cardiomyopathy: a case-control study. *Clin Res Cardiol*. 2011;100:523–529.

13. Parodi G, Bellandi B, Del Pace S, Barchielli A, Zampini L, Velluzzi S, Carrabba N, Gensini GF, Antoniucci D. Natural history of tako-tsubo cardiomyopathy. *Chest*. 2011;139:887–892.

14. Citro R, Lyon AR, Meimoun P, Omerovic E, Redfors B, Buck T, Lerakis S, Parodi G, Silverio A, Eitel I, Schneider B, Prasad A, Bossone E. Standard and advanced echocardiography in Takotsubo (stress) cardiomyopathy: clinical and prognostic implications. *J Am Soc Echocardiogr*. 2015;28:57–74.