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CASE STUDY

Takotsubo Syndrome – Case Review

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INTRODUCTION

Takotsubo syndrome (TTS) is an acute and usually reversible heart failure syndrome. Although rare, TTS is diagnosed more frequently than in the past. Recent medical publications have presented increasing evidence that the condition is not as benign and straightforward as it was once thought. This review will discuss the current understanding of the syndrome in the context of a case study and offer a framework for risk stratification.

CASE PRESENTATION

A 58-year-old female applied for life coverage of $1 million. Four years ago, she was treated for Takotsubo syndrome (TTS) following the death of her child. Her angiogram showed no coronary artery disease at the time of diagnosis. The ventriculogram showed an apical variant of TTS. Her left ventricular ejection fraction (LVEF) was estimated at 35%-40% at the time of diagnosis. It improved within hours and was 53% at the time of discharge. At her 3-month assessment post hospitalization, her LVEF was 67%, and her echocardiogram was normal. Her age and amount electrocardiogram (ECG) was normal. Her recent exercise stress test was normal, and she demonstrated an exercise capacity of 9 Mets. She is on an ACE inhibitor. Her blood pressure is well controlled at 120/75, and age and amount bloodwork show normal lipids. Her NT-proBNP is 100 pg/mL, which is considered normal for age and gender. Her BMI is 25. She has no significant family history. Her only other known medical condition is depression, diagnosed 10 years ago, for which she is on a selective serotonin uptake inhibitor.

BACKGROUND

Takotsubo syndrome (TTS) is an acute and usually reversible heart failure syndrome. The initial presentation of the syndrome has similar features to ST-segment elevation myocardial infarction (STEMI) or non-ST-segment myocardial infarction (NSTEMI). However, TTS is different from acute coronary syndrome (ACS) because patients generally have a normal coronary angiogram and left ventricular dysfunction exceeds the territory supplied by a single coronary artery. The prognosis of the condition, based on a limited number of cases, was thought to be benign, but more recent studies have demonstrated that in-hospital complications, and both short-term and long-term mortality is higher than previously recognized

TTS was first described by Japanese authors in 1990, as Takotsubo Cardiomyopathy.[1] The original name reflects the left ventricular angiogram appearance of the left ventricle at end-systole, resembling the appearance of the octopus pots used by Japanese fisherman in Hiroshima fish markets. Other names that have been used for the condition are stress or stress induced cardiomyopathy, apical ballooning syndrome, broken heart syndrome (related to bereavement), and ampullary shaped cardiomyopathy.[2-14]

The majority (90%) of patients diagnosed with TTS are postmenopausal females.[2-5] In many cases, the initial presentation is preceded by an acute physical or emotional stress.[2,5-8] Two suggested clinical subtypes are primary and secondary TTS.[2] In primary TTS, cardiac symptoms resembling ACS are the reasons for seeking medical care. If there is a stressful trigger present it is often emotional and there is no primary condition that is responsible for elevated levels of catecholamines. Secondary TTS develops in patients that are already hospitalized for another medical, surgical, obstetric, psychiatric, or anesthetic condition and TTS is a complication of the condition due to sudden activation of the sympathetic nervous system or a rise in catecholamines.[2] Some authors have suggested that the term TTS be only used to refer to a classical phenotype and differentiate it from a TTS-like syndrome that develops in post physical stress which would be referred to as a TTS phenocopy.[5] In some articles, primary TTS is referred to as principal TTS,[8,9] and secondary TTS is referred to as a bystander.[9]

ANATOMICAL VARIANTS

Anatomical variants of TTS include an apical type with or without involvement of the mid ventricular wall. This type occurs in 75% – 90% of cases.[2,3] Other variants include isolated mid ventricular, basal, and focal TTS types.[2,3] In the majority of cases, TTS affects only the left ventricle but right ventricular involvement is possible and estimated to be present in 30% of the cases.[2,10] Echocardiographic hallmarks during the acute phase of the condition are large areas of dysfunctional myocardium that extend beyond the territory that is supplied by a single coronary artery[2,3,5,6,10-12] and a circumferential pattern of regional wall motion abnormalities.[2,10,11]

PATHOPHYSIOLOGY

The pathophysiology of TTS is incompletely understood. There are multiple hypotheses attempting to explain the myocardial changes and heart appearance during the TTS acute phase. There are two main parts that play leading roles. The first one is related to an elevated level of epinephrine and norepinephrine release with involvement of cognitive centers of the brain and hypothalamic-pituitary-adrenal axis[2,5,11] while the second part involves an exaggerated or disrupted response of the sympathetic nervous system and cardiovascular system to the catecholamine surge.[2,5] There are many pathophysiological mechanisms suggested, that likely overlap, and cause left ventricular dysfunction. Microvascular disease, myocardial

stunning, endothelial dysfunction associated with loss of protective function of estrogen, and microvascular spasm are some of the suggested explanations.[2-5, 10-12] Recently, enhanced beta adrenergic signaling and increased sensitivity to catecholamines identified in TTS phenotypes were reproduced in an in-vitro induced pluripotent stem cell model of TTS suggesting possible genetic predisposition to catecholamine toxicity.[13] Some prior studies that demonstrated occurrence of TTS in families, also support the idea of genetic vulnerability of some TTS patients.[2,10]

CLINICAL FEATURES

The most frequent symptom during the initial presentation of TTS is chest pain (54%-80%),[2-7] followed by dyspnea,[3-7,10] palpitations,[3,7] and general fatigue.[3,7] It may also present as pulmonary edema,[5] or syncope.[5]

Lab findings during the acute phase include elevation of natriuretic peptides, BNP and NT-proBNP. The degree of elevation of BNP and NT-proBNP levels correlate with the area of LV involvement.[2,11] In 87% of cases, cardiac troponin is elevated,[6,14] but the elevation is modest and less than would be expected as a result of STEMI.[2,5,6,10,15] The combination of highly elevated natriuretic peptide and small elevation of cardiac troponin can be helpful in differentiating TTS from ACS.[7]

In the acute phase, the ECG may show ST elevation in multiple leads, ST depression, T wave inversions, QTc prolongation, and new LBBB.[2,5] Some ECG findings may be helpful in differentiating TTS from anterior STEMI. For example, often there is an absence of reciprocal ST depression in inferior leads during the TTS acute phase, when there is ST elevation in anterior chest leads.[4,5] Nevertheless, generally it is accepted that TTS cannot be reliably distinguished from STEMI based on the ECG alone.[2,4,5]

Echocardiography plays a key role in the diagnosis of TTS providing information on systolic function of the heart, the ballooning pattern, extent of wall motion abnormality and identifying acute complications like left ventricular outflow tract (LVOT) obstruction, or apical thrombosis[2,3] as well as guiding treatment and follow up assessment.[2,4]

The acute presentation requires coronary angiography to rule out STEMI or NSTEMI. If CAD is present, it should be determined if the severity of CAD is sufficient to cause LV dysfunction since the presence of CAD does not exclude the diagnosis of TTS.[2] Based on the angiography, occlusive coronary artery and/or plaque rupture are not expected in patients with primary TTS.[2] In many cases, coronary arteries are clear, but in 10%-15% of cases there is evidence of coronary artery disease.[2,5,14,16] Although CAD is not the causative condition, the concomitant presence of it is a risk factor for a more severe form of heart failure during the acute episode.[2]

In primary TTS patients, intravascular ultrasound (IVUS) and optical coherence tomography (OCT) may be done as a part of angiography during the acute phase to confirm that there is no significant coronary obstruction, dissection, plaque rupture, or intravascular thrombosis.[2] OCT done during an angiogram in combination with cardiac magnetic resonance imaging (CMR) findings are helpful in determining the diagnosis in borderline cases when concomitant CAD is present.[16]

Ventriculography is useful in the diagnosis of TTS and defines the pattern of it.[4] It is especially important in the acute phase since wall motion abnormalities may be short lived and no longer be present later in recovery.[2]

CMR, if available, can provide useful information by demonstrating a typical pattern of regional wall motion abnormalities. CMR is superior to echocardiography in the assessment of RV involvement. It is also a better choice for detection of an apical thrombus. CMR differentiates TTS from MI by demonstrating an absence of late gadolinium

enhancement (LGE).[2,4,7] There have been cases when mild patchy LGEs were reported during the acute phase but were absent in the follow up.[2]

COMPLICATIONS

Patients with TTS may develop complications about 52% of the time.[2] Acute heart failure has been reported in 12% – 45% of the patients with TTS. Hypercontractility of the basal area and systolic anterior motion of mitral valve may cause dynamic LVOT obstruction in 10%-25% of cases, often with accompanying mitral regurgitation (14%-25%). Cardiogenic shock occurs in 10%-20% of the TTS patients[6] and three times more frequently than NSTEMI patients.[7] Due to apical hypokinesia, patients with TTS may develop apical thrombus in 2%-8% of cases.[2] Atrial fibrillation develops in 5%-15% of patients for the first time and ventricular arrhythmias develop in 4%-9% of cases but are the cause of cardiac arrest in up to 6% of the cases.[2] Right ventricular involvement has been associated with more complications and worse long term outcome.[2,7]

Some patients continue to experience cardiac symptoms after recovery from an acute episode ranging from chest pain, dyspnea with exercise, palpitations, and anxiety.[2,7] In some patients, subtle abnormalities noticeable on CMR and advanced echocardiography remain present 3 or 6 months after the acute episode. After recovery, NT-proBNP may remain elevated for a long term in comparison with the baseline level.[7]

DIAGNOSIS

There has been no single, universally accepted diagnostic definition for TTS. The Mayo Clinic diagnostic criteria (Table 1) were originally proposed in 2004 [17] and subsequently modified in 2008,[18] and have been the most widely used in clinical practice and research.

Table 1. 2008 Mayo Clinic Modified Diagnostic Criteria for Takotsubo Syndrome Criteria

- Transient akinesis or dyskinesis of LV wall-motion abnormalities (ballooning) with chest pain
- Electrocardiographic changes (ST-segment elevation or T-wave inversion)
- No substantial obstructive epicardial coronary artery disease
- Absence of pheochromocytoma or myocarditis

As understanding of TTS has evolved, several additional diagnostic criteria have been proposed by various institutions and working groups, including those by the Japanese Takotsubo Cardiomyopathy Group,[19] the Gothenburg Group[20] and the Takotsubo Italian Network.[21] In 2015, the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) adapted and revised previous models to formulate new TTS diagnostic criteria, which compromise several previously defined factors but also include a series of footnotes capable of making these criteria more encompassing.[2] It includes seven points:

1. Transient regional wall motion abnormalities of left ventricle or right ventricle, which are frequently, but not always, preceded by a stressful trigger (emotional or physical).
2. The regional wall motion abnormalities usually extend beyond a single epicardial vascular distribution and often result in circumferential dysfunction of the ventricular segments involved.
3. The absence of culprit atherosclerotic coronary artery disease, including acute plaque rupture, thrombus formation, and coronary dissection or other pathologic conditions to explain the pattern of temporary left ventricle dysfunction observed (eg, hypertrophic cardiomyopathy and viral myocarditis)
4. New and reversible ECG abnormalities (ST-segment elevation, ST depression, left bundle branch block, T-wave inversion, and/or

QTc prolongation) during the acute phase (3 months)
5. Significantly elevated serum natriuretic peptide (brain natriuretic peptide or N-terminal prohormone of brain natriuretic peptide) during the acute phase
6. Positive but small elevation in cardiac troponin measured with a conventional assay (ie, disparity between the troponin level and the amount of dysfunctional myocardium present)
7. Recovery of ventricular systolic function on cardiac imaging at follow-up (3-6 months)[2]

PROGNOSIS

Early studies, containing a limited number of patients, suggested that TTS had a benign prognosis. However, more recent studies have presented increasing evidence of significant short and long-term mortality, suggesting that the condition is not as benign and straightforward as was once thought.

In 2015, Templin et al published a report based on data from the International Takotsubo Registry, 26 centers in Europe and US. The research included 1750 patients with TTS. The diagnosis of TTS was based on the Mayo Clinic modified criteria. A subgroup of 455 patients with TTS were compared with age and sex matched patients with ACS (including diagnosis of STEMI, NSTEMI, and unstable angina). In-hospital complications that were recorded included cardiogenic shock, use of catecholamines or ventilation, cardiopulmonary resuscitation, and death by any cause. The follow-up analysis looked at major adverse cardiac and cerebrovascular events (MACE) that included MI, stroke, TIA, recurrence of TTS, or death from any cause. Of those of patients, 21.8% had serious in-hospital complications, equal or higher than patients with ACS. The 30-day mortality was 5.9%. It is notable that the study used Mayo criteria, which includes both primary and secondary TTS by the definition proposed by HFA. Of patients with TTS included in the study, 36% had a physical trigger, 27.7% had an emotional trigger, and 7.8% had both. The study found that emotional triggers were more common in female patients, while physical triggers were more prevalent in male patients. Presence of only an emotional trigger independently predicted lower incidence of in-hospital complication.[6]

Long-term follow up of TTS patients showed a MACE rate of 9.9% per patient-year and rate of death 5.6% per patient-year. Recurrence of TTS was 1.8% per patient-year. The incidence of stroke or TIA was 1.7% per patient-year. Males had a higher risk of death from any cause per patient year than females (12.9% vs 5.0%) and increased risk of MACE (16% vs 8.7%).[6] Of note, the study results also indicated that a higher number of TTS patients were diagnosed with an acute or chronic neurologic disorder and a past or chronic psychiatric disorder than patients with ACS. The study also demonstrated that ACE Inhibitors prescribed at discharge provided survival benefit to TTS patients.[6]

In 2015, Redfors et al compared the short and long-term mortality of 302 patients with TTS from Swedish Coronary Angiography and Angioplasty Registry (SCAAR) patients with STEMI and NSTEMI. The research demonstrated that the 30-day mortality in TTS patients was 4.1% and comparable with STEMI and NSTEMI.[22]

In 2016, Murugiah et al reported on short term outcomes for TTS among Medicare fee-for-serve beneficiaries from 2007 to 2012. All patients included in the study had coronary angiography and did not require coronary revascularization. The authors studied and compared patients with primary and secondary TTS. Hospitalization rates, in-hospital, 30-day and 1-year mortality, and all cause 30-day readmission rates were analyzed. The study found that diagnosis of TTS more than doubled from 2007 to 2012 (from 5.7 per 100 000 person-years in 2007 to 17.4 in 2012). Patients were predominantly women both with primary and secondary TTS (94.3% and 92.6%, respectively) but

patients with secondary TTS were more likely to be male. Thirty-day mortality was 2.5% in patients with primary TTS and 4.7% with secondary TTS. One-year mortality rate for primary TTS was 6.9% and secondary TTS 11.4%.[8]

Another study published in 2015 by Núñez-Gil et al compared short- and long-term mortality in patients with primary TTS with secondary TTS patients. The study included 238 subjects with TTS between 2003 and 2013 from a local database, fulfilling Mayo diagnostic criteria. Primary TTS patients were considered ones with no or an emotional trigger and secondary with a physical trigger. The patients with secondary TTS were associated with longer in-hospital stay, death (HR 3.41 95% CI: 1.01 – 2.6, P = 0.04), and recurrences (HR 1.85, 95% CI 1.06 – 3.22, P = 0.02).[23]

Tornvall et al published a case control study with 505 subjects in 2016 that compared TTS patients with patients with or without CAD. All TTS subjects were from SCAAR and diagnosed between 2009 and 2013. TTS was defined by Mayo Clinic diagnostic criteria. For every TTS patient, there were 2 age- and sex-matched controls selected. Mortality rates in TTS patients were close to patients with CAD and higher than controls without CAD (TTS HR: 2.1 95% CI: 1.4 to 3.2 and CAD HR: 2.5 95% CI: 1.8 to 3.3).[24]

Stiermyer et al published a study in 2016 that compared 286 patients with TTS with the same number of age and gender matched patients with STEMI. The follow up was available for 3.8 ± 2.5 years. The study compared 28-day mortality, 1-year and long-term mortality. While there was no statistically significant difference in 28-day or 1-year mortality, TTS patients demonstrated higher long-term mortality than STEMI (24.7% vs 15.1%, HR: 1.58, 95% CI 1.07–2.33; P = 0.02). The authors also identified predictors of long-term mortality. They were male sex (HR 1.97, 95% CI 1.03 – 3.78 P = 0.04), diabetes mellitus (HR 2.11 95% CI 1.23 – 3.65 P<0.01), and severity of presentation (Killip class 3/4) on admission (HR 6.03, 95% CI 3.26 – 11.17; P <0.01).[15]

In 2017, Giannakopoulos et al reported on 84 patients diagnosed with TTS from 2003 to 2015. The TTS patients were divided in 2 groups based on the trigger event. For 24.21% of the patients, the trigger was emotional and for 60.52% of patients it was physical. The endpoints were in-hospital thromboembolic complications and life-threatening arrhythmias, MI, death from any cause, stroke, heart failure, or recurrence of TTS. Mean follow up was for 5 years. The Kaplan-Meier analysis demonstrated that over this time the group with a physical trigger had a significantly lower event-free rate in comparison with the group that developed TTS following an emotional trigger. It was noted that there were a significantly higher number of women in the group of TTS patients with emotional trigger. The male gender (HR 2.5 95% CI 1.1 – 5.4; p = 0.04), EF equal or less 35% (HR 1.79, 95% CI 0.9 – 3.3 p = 0.07), atrial fibrillation (HR 2.08, 95% CI 1.0 – 4.2 p = 0.04) were independent positive predictors of endpoint while emotional trigger only was a negative independent predictor (HR 0.43, 95% CI: 0.2 – 0.9).[12]

CASE DISCUSSION

The above research data provides us with a risk selection framework for assessing the long-term mortality risk of our applicant. There are some favorable factors that we may take into consideration including: female gender, primary TTS (emotional trigger), no history or evidence of diabetes, no history or evidence of atrial fibrillation and being treated with ACE inhibitors. The low systolic function at the time of presentation could be associated with a high Killip score and considered to be an unfavorable factor. However, we do know that it recovered and there were no structural abnormalities during follow up. Although we do not have an up to date echocardiogram, her favorable NT-proBNP levels and good exercise tolerance for her age suggest her cardiac function is within normal limits. While her long-term mortality is not consistent with a standard risk, based on current

research results and the above described favorable factors, we might place her in a mild to moderate substandard risk category.

CONCLUSION

Takotsubo syndrome is an enigmatic disease with multifactorial pathophysiology which is incompletely understood. The condition is diagnosed more frequently than in the past. The diagnostic criteria are not universally agreed upon. There is a paucity of data related to long term outcome. Based on current research, TTS can no longer be considered as a condition having benign outcome. The long-term prognosis varies based on gender and trigger of the disease as well as severity of the initial presentation. The presence of diabetes increases the long-term mortality of TTS. Primary TTS carries more favorable long-term prognosis than secondary TTS. Treatment with ACE Inhibitors after the acute condition appears to provide survival benefit in patients with a history of TTS. Underwriting of cases with TTS may benefit from looking at these variables for risk stratification.

REFERENCES

1. Sato H, Tateishi H, Uchida T. Takotsubo-type cardiomyopathy due to multivessel spasm. In: Kodama K, Haze K, Hon M, eds. *Clinical Aspect of Myocardial Injury: From Ischemia to Heart Failure*. Tokyo: Kagakuhyoronsha Publ Co; 1990:56-64.
2. 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. doi:10.1002/ejhf.424.
3. Yoshikawa T. Takotsubo cardiomyopathy, a new concept of cardiomyopathy: Clinical features and pathophysiology. *Int J Cardiol*. 2015;182(C):297-303. doi:10.1016/j.ijcard.2014.12.116.
4. Mejía-Rentería HD, Núñez-Gil IJ. Takotsubo syndrome: Advances in the understanding and management of an enigmatic stress cardiomyopathy. *World J Cardiol*. 2016;8(7):413. doi:10.4330/wjc.v8.i7.413.
5. Pelliccia F, Kaski JC, Crea F, Camici PG. Pathophysiology of Takotsubo Syndrome. *Circulation*. 2017;135(24):2426-2441. doi:10.1161/CIRCULATIONAHA.116.027121.
6. Templin C, Ghadri JR, Diekmann J, et al. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. *N Engl J Med*. 2015;373:929-938. doi:10.1056/NEJMoa1406761.
7. Morley-smith AC, Bchir MB. Challenge of Chronic Cardiac Problems in Survivors of Takosubo Syndrome. *Heart Fail Clin*. 2016;12:551-557. doi:10.1016/j.hfc.2016.06.006.
8. Murugiah K, Wang Y, Desai NR, et al. Trends in Short- and Long-Term Outcomes for Takotsubo Cardiomyopathy Among Medicare Fee-for-Service Beneficiaries, 2007 to 2012. *JACC Hear Fail*. 2016;4:197-205. doi:10.1016/j.jchf.2015.09.013.
9. Stiermaier T, Thiele H, Eitel I. Prognosis in Patients with Takotsubo Cardiomyopathy. *JACC Hear Fail*. 2016;4(6):519-520.
10. Limongelli G, Masarone D, Maddaloni V, et al. Genetics of Takotsubo Syndrome. *Heart Fail Clin*. 2016;12(4):499-506. doi:10.1016/j.hfc.2016.06.007.
11. Akashi YJ, Nef HM, Lyon AR. Epidemiology and pathophysiology of Takotsubo syndrome. *Nat Rev Cardiol*. 2015;12(7):387-397. doi:10.1038/nrcardio.2015.39.
12. Konstantinos G, El-Battrawy I, Schramm K, et al. Comparison and outcome analysis of patients with takotsubo cardiomyopathy triggered by emotional stress or physical stress. *Front Psychol*. 2017;8(APR):1-6. doi:10.3389/fpsyg.2017.00527.
13. Borchert T, Hübscher D, Guessoum CI, et al. Catecholamine-Dependent β-Adrenergic Signaling in a Pluripotent Stem Cell Model of Takotsubo Cardiomyopathy. 2017. doi:10.1016/j.jacc.2017.06.061.
14. Templin C, Napp LC, Ghadri JR. Takotsubo Syndrome Underdiagnosed, Underestimated, but Understood? *J Am Coll Cardiol*. 2016;67(16):1937-1940. doi:10.1016/j.jacc.2016.03.006.
15. 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(6):650-656. doi:10.1002/ejhf.494.
16. Alfonso CE. Takotsubo Cardiomyopathy and Coronary Artery Disease: A Meaningful Coincidence? *J Am Heart Assoc*. 2016;5(12):e005131. doi:10.1161/JAHA.116.005131.
17. Bybee KA, Kara T, Prasad A, et al. Systematic Review: Transient Left Ventricular Apical Ballooning: A Syndrome That Mimics ST-Segment Elevation Myocardial Infarction. *Ann Intern Med*. 2004;141(11):858. doi:10.7326/0003-4819-141-11-200412070-00010.

18. 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(3):408-417. doi:10.1016/J.AHJ.2007.11.008.
19. Kawai S, Kitabatake A, Tomoike H, Takotsubo Cardiomyopathy Study Grou TCS. Guidelines for Diagnosis of Takotsubo (Ampulla) Cardiomyopathy. *Circ J*. 2007;71(6):990-992. doi:10.1253/circj.71.990.
20. Omerovic E. How to think about stress-induced cardiomyopathy? – Think "out of the box"! *Scand Cardiovasc J.* 2011;45(2):67-71. doi:10.3109/14017431.2011.565794.
21. Parodi G, Citro R, Bellandi B, et al. Revised clinical diagnostic criteria for Tako-tsubo syndrome: the Tako-tsubo Italian Network proposal. *Int J Cardiol*. 2014;172(1):282-283. doi:10.1016/j.ijcard.2013.12.239.
22. Redfors B, Vedad R, Angerås O, et al. Mortality in takotsubo syndrome is similar to mortality in myocardial infarction — A report from the SWEDEHEART11Swedish web system for enhancement of evidence-based care in heart disease evaluated according to recommended therapies. registry. *Int J Cardiol*. 2015;185:282-289. doi:10.1016/j.ijcard.2015.03.162.
23. Núñez Gil IJ, Andrés M, Almendro Delia M, et al. Characterization of Tako-tsubo Cardiomyopathy in Spain: Results from the RETAKO National Registry. *Rev Española Cardiol (English Ed)*. 2015;68(6):505-512. doi:10.1016/j.rec.2014.07.026.
24. Tornvall P, Collste O, Ehrenborg E, Järnbert-Petterson H. A Case-Control Study of Risk Markers and Mortality in Takotsubo Stress Cardiomyopathy. *J Am Coll Cardiol*. 2016;67(16):1931-1936. doi:10.1016/j.jacc.2016.02.029.