

## Risk Stratification for In-Hospital and Long-Term Outcomes in Takotsubo Cardiomyopathy

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### Abstract

Takotsubo cardiomyopathy (TC) or Takotsubo syndrome is a clinical presentation comprising of left ventricular dysfunction which mimics acute coronary syndrome but without any evidence of obstructive coronary artery disease. TC development often has an intense preceding emotional or physical trigger. Pathophysiology is incompletely understood but believed to have a multifactorial etiological pathway circling around a heart-brain-endocrine axis. TC often is mostly associated with apical hypokinesis, but recently other phenotypic variants have also been recognized. Once known to be a benign reversible ventricular dysfunction, recent studies have suggested that it may neither be completely benign nor completely reversible phenomenon as TC may have significant short- and long-term complications which impact its overall prognosis. Still, several gaps in the knowledge about TC exist and there remains a tremendous potential for future research opportunities.

**Keywords:** Takotsubo Syndrome; Clinical Outcomes; Predictive Risk Factors

### Introduction

Initially described in Japan three decades ago, the term Takotsubo cardiomyopathy (TC) first referred to reversible left ventricular (LV) dysfunction in the absence of coronary artery disease in the setting of increased ventricular wall movement in the basal segments while a reduced or minimal movement in the apical segments [1-5]. This motion resembled a Japanese fishing pot used to trap octopuses from which the syndrome's name originates. It has since been described by many other terms including 'broken heart syndrome', 'Takotsubo syndrome' and 'stress induced cardiomyopathy' [6-8]. Patients present with clinical signs and symptoms nearly identical to those of acute coronary syndrome including chest pain, shortness of breath, syncope, elevated troponin and electrocardiographic (ECG) changes in the setting of a likely predisposing emotional or physical trigger [6-11]. The Revised Mayo Clinic Criteria was one of the first standards used to diagnose the disease, however in more recent years numerous other benchmarks including the Heart Failure Association European Society of Cardiology Criteria and International Takotsubo Diagnostic Criteria have also been used [9-12].

Despite being labeled as reversible LV dysfunction, Takotsubo syndrome is associated with significant in-hospital and long-term cardiovascular morbidity and mortality. Takotsubo syndrome is seen predominantly in post-menopausal women with four unique subtypes

identified based on the area of ventricular ballooning known as apical, biventricular, mid-cavitary and basal [14-17]. The apical subtype is the most common and is known as typical Takotsubo pattern, whereas all other subtypes have been thought to be variant morphological presentations. In direct comparison, patients with atypical presentations are usually diagnosed at a relatively younger age, have higher chance of pre-existing neurological disease and are more frequently noticed to have ECG changes such as ST depression [16-20]. However, despite these differences, both typical and atypical presentations have similar outcomes [10]. Patients with Takotsubo syndrome present with an array of ECG changes which may include ST elevation or depression, QT prolongation, Q-wave formation (usually transient) and T-wave inversions [12-13]. On analysis of ECG changes as a prognosticator for in-hospital major adverse cardiovascular events (MACE), T-wave inversions were found to significantly reduce such events which have been hypothesized to be due to the presence of lower secondary risk of ventricular arrhythmias. In addition, patients with sinus rhythm were found to have better clinical outcomes related to MACE when compared to patients in atrial arrhythmias [14]. However, some studies have found no significant association with atrial fibrillation and MACE event risk based on their independent analysis [15].

Despite a lower prevalence of disease in men, data on gender disparities on clinical outcomes is mixed, some studies have shown male gender to have no clinical significance on in-hospital outcomes when compared to women whereas others have revealed a significantly increased risk of cardiogenic shock, ventricular arrhythmias and acute kidney injury along with a four-fold increase in mortality [16,17,21-25]. Other studies have also established peak troponin I as a predictor of in hospital mortality, whereas basal natriuretic peptide and cardiogenic shock on admission were predictors for long term overall mortality [26-30]. Cardiac magnetic resonance imaging has established a significant relationship between right ventricle in patients presenting with Takotsubo syndrome and worsening of left ventricular function [31-34]. Left ventricular ejection fraction (LVEF) at presentation of less than or equal to 35% is associated with a significantly higher risk of development of cardiogenic shock, requirement for a temporary mechanical circulatory support and acute heart failure in the early stages of the disease whereas on long-term follow up major adverse cardiovascular events and hospital readmissions were significantly increased [26-30].

Some of the plausible pathophysiologic mechanisms for development of Takotsubo syndrome include catecholamine surplus with hyperactive sympathetic nervous system, transient coronary artery spasm, microcirculatory dysfunction (as depicted by abnormal Thrombolysis In Myocardial Infarction Frame Count), myocardial stunning due to microvascular dysfunction [34-40], estrogen deficiency, association with inflammatory and autoimmune conditions and associated oxidative stress due to catecholamine excess, however, the true mechanism still remains elusive [41-45]. Recently, a novel prognostic score for in-hospital complications has been proposed by the German and Italian Stress Cardiomyopathy (GEIST) registry after analysis of multiple variables which helped validate some earlier studies in revealing LVEF, male gender, involvement of right ventricle and history of neurological disorder as independent prognosticators for in-hospital complications for patients with Takotsubo syndrome [28]. Long-term outcomes were not assessed in the study however were thought to be related to in-hospital outcomes [28-29].

The data from the recent studies has suggested that TC may not be a benign reversible phenomenon, as once previously thought and was popularized described as reversible LV dysfunction [27-30]. This is due to the fact that there remains a risk for higher recurrence of adverse events, diastolic dysfunction and associated mortality rates. There is usually a higher risk for future adverse event rates in those patients who present with severely reduced LVEF. The prognosis and mortality is also dictated by the underlying trigger for TC. TC is primarily divided in two forms: Primary and secondary TC. Primary TC occurs in the setting of either psychic or emotional stimuli or without clear identifiable triggers (idiopathic), whereas secondary TC is triggered by physical stressors such as intracranial hemorrhage or cerebrovascular accident, trauma, sepsis, surgery, or other critical illnesses. Secondary forms of TC are usually associated with much worse short- and long-term prognoses [29]. Primary TC, in comparison to secondary TC, generally has a relatively benign spectrum and a good overall prognosis, unless complicated by cardiogenic shock. Analysis of the previous large registries such as RETAKO (Spanish National Registry for TAKOtsubo cardiomyopathy) have demonstrated a significantly higher rate of morbidity and mortality in patients with

secondary TC compared to primary forms, who otherwise had a comparable demographic, functional and cardiovascular risk profiles. Similarly, secondary forms of TC have higher rates of cardiogenic shock, peak cardiac enzymes, increased use of inotropes, mechanical ventilator requirement, increased future recurrence and also higher readmission rates due to cardiovascular events.

In some studies, diabetes mellitus has been proposed to be somewhat protective to the development of TC due to associated autonomic dysfunction in diabetic patients; however this needs further confirmation in larger future studies and registries [45-48].

### Conclusion

Risk factors for both in-hospital and long-term outcomes in patients with Takotsubo syndrome have although been described but need further exploration in randomized controlled investigations and large registries in the future [1,48-50]. Multiple studies have demonstrated several risk factors which may be helpful to stratify risk for in-hospital events with recent development of the first risk stratification score for in-hospital complications. Despite the apparent initial myocardial functional recovery in TC, these patients deserve a closer clinical monitoring and appropriate preventive therapies to improve their future outcomes. Risk factors for long-term MACE and rehospitalization need to be further investigated to help prognosticate disease and determine need for closer out-patient follow up. A risk stratification score could then be hypothesized once underlying risk factors for long-term complications are determined.

### Conflict of Interest Statement

The authors have no conflict of interest to declare.

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