



## ORIGINAL ARTICLE

# Multicenter retrospective database evaluation of Takotsubo syndrome in subjects undergoing catheter ablation for atrial fibrillation

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## Abstract

**Background:** Intracardiac catheter ablation for atrial fibrillation with pulmonary vein isolation may result in Takotsubo syndrome (TS), but the frequency, predisposing factors (age, sex, mental health disorders), and outcomes are currently unknown. This study sought to assess the frequency, predisposing factors, and outcomes of subjects who underwent intracardiac catheter ablation for atrial fibrillation with pulmonary vein isolation and were diagnosed with TS.

**Methods:** This was a retrospective observational cohort study utilizing TriNetX® electronic health record (EHR) data. We included subjects aged older than 18 years who underwent intracardiac catheter ablation for atrial fibrillation with pulmonary vein isolation. The study population was divided into two groups (no TS diagnostic code presence and TS diagnostic code presence). We analyzed the distributions of age, sex, race, diagnostic codes, common terminology procedures (CPT), and vasoactive medication codes and examined mortality rate within 30 days.

**Results:** We included 69,116 subjects. Of these, 27 (0.04%) had a TS diagnostic code, the cohort was comprised mostly of females [17 (63.0%)], and 1 (3.7%) death within 30 days was reported. There were no significant differences in age and frequency of mental health disorders between those patients in TS and non-TS cohorts. Adjusting for age, sex, race, ethnicity, patient regionality, and mental health disorder diagnostic code, those patients who developed TS had a significantly higher odds of dying in 30 days after catheter ablation compared to those without TS (OR=15.97, 95% CI: 2.10–121.55,  $p=.007$ ).

**Conclusions:** Approximately 0.04% of subjects who underwent intracardiac catheter ablation of atrial fibrillation by pulmonary vein isolation had a subsequent diagnostic code of TS. Further study is needed to determine whether there are predisposing factors associated with the development of TS in subjects who undergo catheter ablation of atrial fibrillation by pulmonary vein isolation.

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## KEYWORDS

atrial fibrillation, stress-induced cardiomyopathy, Takotsubo syndrome

## 1 | INTRODUCTION

Takotsubo syndrome or stress cardiomyopathy is a transient left ventricular dysfunction in the absence of coronary artery occlusion.<sup>1</sup> It was first described in 1990 and is associated with emotional or physical stress that potentially triggers a catecholamine release.<sup>2,3</sup> This results in dysfunction of the coronary microcirculation, myocardial stunning, and myocardial toxicity.<sup>4-6</sup> While not completely understood, it is associated primarily with postmenopausal women, older adults, patients with mental health disorders, with a prevalence of approximately 2% in patients suspected to have acute coronary syndrome.<sup>7-9</sup>

Patients with recurrent atrial fibrillation are triggered by an electrical discharge most commonly from one of the pulmonary veins.<sup>10,11</sup> Through the use of catheter ablation, atrial fibrillation burden may be decreased if the pulmonary veins are electrically isolated. Despite a success rate of over 70%, it is a technically difficult procedure and is associated with complications including embolism, cardiac tamponade, coronary stenosis, and death.<sup>12,13</sup> One complication that was recently reported was Takotsubo syndrome.<sup>14,15</sup>

In various case series and single-center studies, Takotsubo syndrome has been associated with recent ablation for atrial fibrillation.<sup>14-16</sup> The mechanism is thought to be sympathetic dominance due to vagal denervation during the procedure.<sup>15</sup> Due to the rare occurrence of this condition, it is not known how frequent Takotsubo syndrome occurs after ablation for atrial fibrillation. An understanding of the frequency, patient characteristics, and outcomes of this potential complication may better inform the approach to ablation for atrial fibrillation.

The objective of this present study is to describe the frequency, patient characteristics, and outcomes of subjects who underwent ablation for atrial fibrillation and developed Takotsubo syndrome.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

This is a retrospective observational cohort study utilizing the TriNetX® electronic health record (EHR) database of subjects aged above 18 years of age who underwent catheter ablation for atrial fibrillation [common procedural terminology (CPT) 93,656: "Comprehensive electrophysiologic evaluation including transeptal catheterizations, insertion and repositioning of multiple electrode catheters with induction or attempted induction of an arrhythmia including left or right atrial pacing/recording when necessary, right ventricular pacing/recording when necessary, and His bundle recording when necessary with intracardiac catheter ablation of atrial

fibrillation by pulmonary vein isolation"] for the first time in their EHR database history and did not have diagnostic codes prior to this procedure indicating a history of Takotsubo syndrome [International Classification of Diseases, 9th (ICD-9) 429.83 and 10th edition diagnostic codes (ICD-10) I51.81]. TriNetX is a United States-based global federated research network that collects aggregated EHR data elements (including diagnoses, medications, procedures, laboratory values) of approximately 68 million patients in 56 large health care organizations (HCOs). These data elements are made available after deidentification within a user-friendly browser-based software in real-time. TriNetX, LLC is compliant with the Health Insurance Portability and Accountability Act (HIPAA), a United States federal law protecting healthcare information privacy and security, and any additional data privacy regulations applicable to the contributing HCO. TriNetX is certified to the ISO 27001:2013 standard and maintains an Information Security Management System (ISMS). This ensures the protection of the healthcare data it is provided access to and to meet HIPAA Security Rule requirements. Any data set generated by the TriNetX Platform that contains patient-level data is deidentified as per the deidentification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. Data deidentification processes are attested to through a formal determination by a qualified expert as defined in Section §164.514(b)<sup>1</sup> of the HIPAA Privacy Rule. No protected health information is provided; thus, the Penn State Health Institutional Review Board (IRB) predetermined this study to be nonhuman research.

### 2.2 | Data collection

The data used in this study were collected on November 3, 2022 from the TriNetX Research Network. After the data set was received, we analyzed the following EHR data: age, sex, race, ethnicity, CPT procedure codes associated with atrial fibrillation catheter ablation, associated predisposing factors (Mental, Behavioral, and Neurodevelopmental disorder diagnostic code categories), and ICD-9 and ICD-10 associated with Takotsubo syndrome within 30 days after procedure code entry for catheter ablation. Between 0 and 2 days after Takotsubo diagnostic code entry, we evaluated mechanical ventilation, medication codes of critical care agents utilized to support the cardiovascular system, and the need for cardiac catheterization (Tables S1 and S2).

Because Takotsubo syndrome is thought to occur after a trigger (and is likely immediate), we defined deaths as those occurring within 30 days of catheter ablation.<sup>1,2</sup> Exact death dates were not provided by the TriNetX® database for patient privacy reasons, only the month and year. To meet the definition of death within 30 days, we first added 30 days to the first recording of catheter ablation. If

the month and year of the death date provided matched this calculation, then the patient met the definition of death within 30 days. For example, if the patient had undergone catheter ablation on January 1, 2020 (i.e., day of catheter ablation), the patient would not have been classified as a death within 30 days if the death date was reported as February 2020 but would have been if the death date was reported as January 2020. Because the data provided was deidentified, no date of birth was provided; therefore, ages are approximate. For example, a subject born in 1950 reported to have undergone catheter ablation on January 1, 2020 (i.e., day of catheter ablation), the subject was determined to be 70 years of age.

## 2.3 | Statistical analysis

Summary statistics using mean and standard deviation or proportions were reported by Takotsubo syndrome status for clinical and demographic characteristics of the patients included in the study. Two-sample t-test was applied to compare the age between the groups with and without Takotsubo syndrome; Fisher's exact tests were applied for categorical factors including sex, race, ethnicity, patient regional location, and death within 30 days; and Pearson's chi-square test was used for comparing the mental health disorder status in two groups.

Univariable and multivariable logistic regression analyses were conducted to investigate the association between the death within 30 days and the disease status. In the regression analyses, we removed the small number of missingness in "sex" (16 observations), while the "unknown" category in "race", "ethnicity", and "patient regional location" were kept as a separate level due to their relatively higher proportions in the sample. Also, we combined "Asian", "American Indian or Alaska Native", and "Native Hawaiian or Other Pacific Islander" in "race" to the "Other" category due to their small proportions in the data. We first fit univariable logistic regression models for age, Takotsubo syndrome status, sex, race, ethnicity, regional patient location, and mental health disorder status to estimate the unadjusted odds ratios (ORs) with 95% confidence intervals (CIs). To probe the effects controlling for other factors, we then fit a multivariable model including all covariates. The adjusted ORs with 95% CIs were summarized in Table 3 in parallel to the univariable results.

Statistical software R v.4.2.2 was used to preprocess the data, conduct the statistical tests, and perform the logistic regression analyses. *P*-values of less than or equal to .05 were regarded as statistically significant.

## 3 | RESULTS

### 3.1 | Patient demographics

This study included 69,116 subjects [69,089 (99.9%) without Takotsubo syndrome and 27 (0.04%) with Takotsubo syndrome] who were reported to have undergone catheter ablation for atrial

fibrillation. Among the included patients, 204 (0.3%) died in 30 days and 1 death was reported in the Takotsubo syndrome cohort. Race, ethnicity, sex, and regionality were reported in 64,334 (93.1%), 58,390 (84.5%), 69,100 (100.0%), and 62,799 (90.9%) subjects, respectively. In subjects without Takotsubo syndrome, the average age was  $64.8 \pm 10.4$  years and comprised primarily of males [45,575 (66.0%)], while for subjects who had a diagnostic code entered for Takotsubo syndrome, the average age was similar ( $66.2 \pm 12.0$ ,  $p = .558$ ) and comprised mostly of females [17 (63.0%),  $p = .009$ ]. The frequency of mental health disorders was similar between the two groups ( $p = .275$ ). Moreover, the overall distributions of patient regional location ( $p = .022$ ) were significantly different between those patients in two groups (Table 1).

### 3.2 | Medical therapy provided to subjects with Takotsubo syndrome

In subjects who were diagnosed with Takotsubo Syndrome, 21 subjects had a diagnostic code entered within 7 days of catheter ablation. Six subjects had a diagnostic code entered on an average of  $18.8 \pm 8$  days from catheter ablation. Vasoactive support was required in 7 (25.9%) subjects, mechanical ventilation in 3 (11.11%) subjects, and cardiac catheterization was performed in 1 (3.7%) subject (Table 2).

### 3.3 | Association of death within 30 days, the demographic factors, and disease statuses

There was one death within 30 days reported in those with Takotsubo syndrome. The first death occurred on the same day of catheter ablation for atrial fibrillation. Adjusting for age, sex, race, ethnicity, patient regionality, and mental health disorder diagnostic code, the patient with Takotsubo syndrome had a significantly higher odds of dying in 30 days compared to those without that syndrome (OR = 15.97, 95% CI: 2.10–121.55,  $p = .007$ ). In addition, those patients with the mental health disorder diagnostic code had a higher odds for death in 30 days while controlling for other factors (OR = 2.68, 95% CI: 2.00–3.60,  $p < .001$ ). Furthermore, when controlling for other demographic and disease characteristics, those female patients had a lower odds for death in 30 days than those male patients (OR = 0.73, 95% CI: 0.54–0.99,  $p = .044$ ), those Black or African American had a higher odds for death in 30 days than those white (OR = 1.78, 95% CI: 1.02–3.11,  $p = .042$ ), and those patients in the West had a higher odds for death in 30 days than those in the South (OR = 2.68, 95% CI: 2.00–3.60,  $p < .001$ ) (Table 3).

## 4 | DISCUSSION

We sought to examine the frequency, patient characteristics, and outcomes of subjects who underwent catheter ablation for atrial

**TABLE 1** Demographic and clinical characteristics of subjects who have developed Takotsubo Syndrome after catheter ablation for atrial fibrillation.

	All patients (n = 69,116)	No Takotsubo syndrome (n = 69,089)	Takotsubo syndrome present (n = 27)	p-value
Age (years, mean, standard deviation)	64.8 ± 10.4	64.8 ± 10.4	66.2 ± 12.0	.558
Sex (n, %)				
Female	23,515 (34.0%)	23,498 (34.0%)	17 (63.0%)	.009
Male	45,585 (66.0%)	45,575 (66.0%)	10 (37.0%)	
Unknown	16 (0.0%)	16 (0.0%)	0 (0.0%)	
Race (n, %)				
American Indian or Alaska Native	100 (0.1%)	100 (0.1%)	0 (0.0%)	.330
Asian	610 (0.9%)	610 (0.9%)	0 (0.0%)	
Black or African American	3511 (5.1%)	3509 (5.1%)	2 (7.4%)	
Native Hawaiian or Other Pacific Islander	51 (0.1%)	51 (0.1%)	0 (0.0%)	
White	60,062 (86.9%)	60,041 (86.9%)	21 (77.8%)	
Unknown	4782 (6.9%)	4778 (6.9%)	4 (14.8%)	
Ethnicity (n, %)				
Hispanic or Latino	1594 (2.3%)	1593 (2.3%)	1 (3.7%)	.426
Not Hispanic or Latino	56,796 (82.2%)	56,775 (82.2%)	21 (77.8%)	
Unknown	10,726 (15.5%)	10,721 (15.5%)	5 (18.5%)	
Patient Regional Location (n, %)				
Midwest	7877 (11.4%)	7871 (11.4%)	6 (22.2%)	.022
Northeast	21,465 (31.1%)	21,451 (31.0%)	14 (51.9%)	
South	27,963 (40.5%)	27,958 (40.5%)	5 (18.5%)	
West	5494 (7.9%)	5493 (8.0%)	1 (3.7%)	
Unknown	6317 (9.1%)	6316 (9.1%)	1 (3.7%)	
Deaths within 30Days (n, %)	204 (0.3%)	203 (0.3%)	1 (3.7%)	p = .077
Mental, Behavioral and Neurodevelopmental Disorder Diagnostic Category (n, %)	22,619 (32.7%)	22,607 (32.7%)	12 (44.4%)	p = .275

fibrillation and developed Takotsubo syndrome. Using a multi-center EHR database, our main findings were that the frequency of Takotsubo syndrome after catheter ablation for atrial fibrillation was low and comprised mostly of females. In addition, one death occurred (within the same day) after having a Takotsubo syndrome diagnostic code. This study may inform clinical decision making in subjects who require catheter ablation for atrial fibrillation.

Takotsubo is a clinical syndrome that is associated with emotional and physical triggers.<sup>17</sup> The pathophysiology is likely driven by excess catecholamine release inducing myocardial stunning and/or direct catecholamine myocardial toxicity.<sup>2,4</sup> Most patients with this disease recover (often within 1–4 weeks), but are reported to have a higher rate of complications (including acute heart failure, shock, stroke) when compared with patients who have had an acute myocardial infarction, especially in the older adult population.<sup>18–20</sup> While associated with postmenopausal women and older adults, it is unknown who is predisposed to developing this condition.<sup>8,19,21</sup>

**TABLE 2** Overview of vasoactive medication codes, need for mechanical ventilation, and cardiac catheterization provided at the time of Takotsubo Syndrome diagnostic code entry.

Patient treatment	Takotsubo syndrome (n = 27)
Vasoactive/Inotropes <sup>a</sup>	7 (25.9%)
Dobutamine	1 (3.7%)
Dopamine	1 (3.7%)
Epinephrine	2 (7.4%)
Norepinephrine	2 (7.4%)
Phenylephrine	5 (18.5%)
Vasopressin (USP)	1 (3.7%)
Mechanical Ventilation	3 (11.1%)
Cardiac catheterization	1 (3.7%)

<sup>a</sup>7 subjects were reported to have a vasoactive/inotropic medication code. 3 subjects were reported to have multiple vasoactive/inotropic medication codes.

**TABLE 3** Univariable and multivariable analysis for death within 30 days and association with age, Takotsubo Syndrome presence, sex, race, ethnicity, patient regional location, and mental, behavioral, neurodevelopmental disorder diagnostic category.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age				
1-year increase	1.03 (1.02–1.05)	<.001	1.04 (1.02–1.05)	<.001
Takotsubo syndrome presence (Ref: No takotsubo syndrome)				
Takotsubo syndrome	13.05 (1.76–96.61)	.012	15.97 (2.10–121.55)	.007
Sex (Ref: Male)				
Female	0.89 (0.66–1.19)	.423	0.73 (0.54–0.99)	.044
Race (Ref: White)				
Black or African American	1.39 (0.81–2.41)	.233	1.78 (1.02–3.11)	.042
Other	1.38 (0.44–4.32)	.583	1.55 (0.49–4.91)	.454
Unknown	1.10 (0.65–1.86)	.736	1.31 (0.76–2.28)	.332
Ethnicity (Ref: Not Hispanic or Latino)				
Hispanic or Latino	1.23 (0.54–2.78)	.620	1.10 (0.47–2.56)	.829
Unknown	0.73 (0.48–1.12)	.148	0.29 (0.18–0.48)	<.001
Patient regional location (Ref: South)				
Northeast	0.76 (0.52–1.11)	.157	0.72 (0.49–1.06)	.092
Midwest	1.38 (0.89–2.14)	.147	1.17 (0.75–1.82)	.499
West	3.63 (2.53–5.20)	<.001	5.78 (3.84–8.69)	<.001
Unknown	0.68 (0.36–1.28)	.229	1.12 (0.58–2.13)	.737
Mental, Behavioral Neurodevelopmental Disorder Diagnostic Category (Ref: Absence)				
Presence	2.89 (2.18–3.82)	<.001	2.68 (2.00–3.60)	<.001

Therefore, when it occurs, especially after the patient has undergone a medical procedure such as catheter ablation, it is important to understand the clinical circumstances of the event.

Atrial fibrillation often requires a trigger within or near the atrium (particularly the pulmonary veins).<sup>22</sup> These foci are often targeted during catheter ablation.<sup>23</sup> Because the heart is innervated by the autonomic nervous system (ANS) through its sympathetic and parasympathetic nerves, with cardiac ganglionated plexi (GP) located mainly around the pulmonary vein ostia, it is possible to stimulate the GP during ablation or cause vagal denervation causing sympathetic dominance.<sup>15,24,25</sup> Therefore, it is possible that the procedure for catheter ablation itself may cause Takotsubo syndrome.<sup>15</sup> Recent case reports and case series have reported the occurrence of Takotsubo syndrome in association with recent catheter ablation for atrial fibrillation, but to our knowledge, a multicenter retrospective study of subjects has not been performed to date.<sup>14,15</sup>

On the basis of our findings, Takotsubo syndrome appears to be a rare occurrence after catheter ablation for atrial fibrillation. It is possible that the condition was underrecognized and not reported. Takotsubo syndrome presents with signs and symptoms similar to acute myocardial infarction and may not have been considered.<sup>26,27</sup> Future studies evaluating the indications and outcomes of cardiac catheterizations may be required to determine whether this is the case. Subjects who have undergone

catheter ablation at a particular institution may not have returned to the same institution to be diagnosed and receive treatment for Takotsubo syndrome thereby leaving us unable to evaluate these subjects. Takotsubo syndrome may not be related at all to the ablation procedure. Finally, diagnostic codes identifying Takotsubo syndrome may have been underutilized.

The catheter ablation procedure itself may not be the only factor that places the subject at risk for developing Takotsubo syndrome. In our study, the only predisposing factor that we were able to identify was that the cohort was predominantly made up of females. Older age and a higher frequency of mental health disorder were unable to be identified in patients who developed Takotsubo syndrome. These findings suggest that when a patient undergoes catheter ablation for atrial fibrillation and develops signs and symptoms that are consistent with acute coronary syndrome or acute heart failure, Takotsubo syndrome should also be considered if the subject is female. Further study may be needed to determine whether older age and a history of mental health issues is a predisposing factor for the development of Takotsubo syndrome in subjects who undergo catheter ablation for atrial fibrillation.

Our study found one death within 30 days. This death occurred on the same day of catheter ablation for atrial fibrillation. There are several reasons why this death may have occurred. First, Takotsubo syndrome may have been unrecognized and clinically indistinguishable from other conditions potentially resulting in a delay of care.

Physical triggers, such as surgical procedures, may have placed the patient at a higher risk category.<sup>28</sup> Finally, the patient was reported to be 82 years old, and because the patient was older, possibly was at higher risk of complication.

#### 4.1 | Study limitations

This study had several limitations. First, due to database limitations, no clinical documentation, electrocardiographic, or echocardiogram reports were available to review. Thus, we relied on diagnostic code entry to identify subjects with Takotsubo syndrome, in which the accuracy may be potentially subject to clinician bias. It is unknown if there were other diagnoses and/or procedures present that were not coded. Because the TriNetX® database does not currently extract text or data from procedures, including catheter ablations, we were unable to note the ablation strategy, procedure time, or any hemodynamic information from the procedure itself. Subjects may have received care at one institution which was continued in another institution not part of the TriNetX research network. Admission dates and discharge dates were not provided; thus, the length of hospitalization was unable to be evaluated. Because of database limitations, only the month and year of the death date were provided. Thus, it is possible that the calculation we applied counted some deaths outside the window of 30 days. Finally, limitations of this database prevented us from performing a closer examination of this patient population (including whether atrial fibrillation recurred postprocedure).

## 5 | CONCLUSION

In our study, approximately 0.04% of subjects who underwent intracardiac catheter ablation of atrial fibrillation by pulmonary vein isolation developed Takotsubo syndrome. Further study is needed to determine whether there are predisposing factors associated with the development of Takotsubo syndrome in subjects who undergo catheter ablation of atrial fibrillation by pulmonary vein isolation.

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#### CONFLICT OF INTEREST STATEMENT

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Conrad Krawiec receives funding from the New England Journal of Medicine for educational materials and content.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from TriNetX®. Restrictions apply to the availability of these data, which were used under license for this study.

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#### ETHICS STATEMENT

The Penn State Health Institutional Review Board (IRB) predetermined this study to be nonhuman research (STUDY00020794).

#### PATIENT CONSENT STATEMENT

As only deidentified data were obtained and no protected health information was shared, patient consent was not obtained.

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#### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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