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Short- and Long-Term Incidence of Thromboembolic Events in Takotsubo Syndrome as Compared With Acute Coronary Syndrome

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Abstract

Thromboembolic events are a common complication in Takotsubo syndrome (TTS). However, their long-term incidence compared with acute coronary syndrome (ACS) is lacking. In-hospital and long-term incidence of thromboembolic events of 138 consecutive patients with TTS were compared with 138 sex- and age-matched patients with ACS. Predictors of events were analyzed. The incidence of thromboembolic events in TTS was 2-fold higher than ACS (21% vs 9%; $P < .01$) over a mean follow-up of 5 years. Although the left ventricular ejection fraction (LVEF) at event was significantly lower in TTS compared with ACS (38% [9%] vs 54% [11%]; $P < .01$), the follow-up LVEF was comparable. Patients with TTS suffering from thromboembolic events were more often treated with anticoagulation compared with ACS (44.8% vs 8.3%, $P = .03$). However, more patients presenting with ACS (100% vs 48.3%; $P < .01$) were discharged on aspirin. Only elevated C-reactive protein was a predictor of thromboembolic events using multivariate analysis (hazard ratio 1.1, 95% confidence interval, 1.0-1.2; $P < .01$). In conclusion, the risk of thromboembolic events in TTS was significantly higher than the risk of thromboembolic events in ACS over a mean follow-up of 5 years.

Keywords

Takotsubo, thromboembolic events, acute coronary syndrome, left ventricular heart failure, thrombus

Introduction

Takotsubo syndrome (TTS) has been associated with a favorable prognosis.[1-4] However, different complications have been reported in TTS, including sudden cardiac arrest, atrial fibrillation, thromboembolic events, cardiogenic shock, and mitral valve regurgitation.[5-9] Although the detailed pathophysiology of TTS is lacking, a role of catecholamine excess and estradiol protective effect have been debated.[10-12] Recently published data showed a protective effect of estradiol using human cardiomyocytes from induced pluripotent stem cells.[2,11]

The incidence and clinical significance of thromboembolic events in TTS has not yet been clearly established. Data documenting these events are scarce; the recent literature highlights an incidence of 2% to 11%.[13-18] Moreover, the long-term incidence of thromboembolic events compared with acute coronary syndrome (ACS) is lacking.

In the present study, we determined the incidence of thromboembolic events in TTS compared with ACS in-hospital and over a 5-year follow-up. Additionally, predictors of thromboembolic events were evaluated.

Methods

Data of consecutive patients presenting with TTS from 2003 to 2017 were included in the study retrospectively and prospectively (TTS group). Takotsubo syndrome was defined by the Mayo clinic criteria.[19] To assess the diagnosis of TTS, the angiograms, echocardiograms, and electrocardiograms were reviewed by 2 independent experienced cardiologists. Data of patients who presented from 2007 to 2010 with ACS (non-ST-segment-elevation myocardial infarction or ST-segment elevation myocardial infarction) in the Clinic for Cardiology,

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University Hospital Mannheim and who were subsequently treated with percutaneous coronary intervention and stent implantation were assessed from the department's database. Of the >500 patients, a group of patients with ACS was matched to the patients with TTS by age and sex, resulting in 138 patients with either disease. Baseline characteristics of demographic and clinical data were assessed by chart review, as were in-hospital events (arrhythmias, cardiac rupture, thromboembolic events, pulmonary congestion with use of noninvasive positive pressure ventilation, intubation, use of a temporary pacemaker, use of inotropic agents, and death). Patients with ACS were followed up retrospectively.

This study was conducted in compliance with the Declaration of Helsinki. The study protocol was approved by the ethics committee of University Medical Centre Mannheim.

Study End Point

The endpoint of the study was the occurrence of thromboembolic events in patients with TTS compared with patients with ACS. Additionally, outcomes including all-cause mortality, life-threatening arrhythmia, heart failure, respiratory failure, and use of respiratory support were assessed by chart review and/or telephone review. If information concerning the circumstances of death could not be retrieved by medical records or the treating physicians, it was defined as death due to unknown cause.

Statistics

Data are shown as means (standard deviation) for continuous variables with a normal distribution, median (interquartile range) for continuous variables with a non-normal distribution, and as frequency (%) for categorical variables. The Kolmogorov-Smirnov test was used to assess normal distribution. Normally or non-normally distributed continuous variables were compared with Student t test and Mann-Whitney U test, respectively. Categorical variables were compared by χ^2 test or Fisher exact test. Two-tailed Fisher exact test was applied in tests with sample size of n = 5 or below. Fisher exact ratio test was used for calculation of the relative risk for the occurrence of events. Results are shown with 95% confidence intervals (CIs). The Kaplan-Meier procedure was performed to evaluate group differences by log-rank test. Independent predictors for thromboembolic events were determined by univariate analysis. Predictors with $P<.10$ were subsequently entered into the Cox multivariate regression analysis. Results are described as hazard ratios with 95% CI. Statistical analysis was performed with SPSS 23.0; a $P<.05$ (2 tailed) was considered significant.

Results

Patients with ACS suffered more often from chest pain compared with those with TTS (83% vs 38%; Table 1). Systolic blood pressure was significantly lower in patients with TTS compared with patients with ACS (134 [62-220] mm Hg vs 159 [120-205] mm Hg); heart rate was significantly higher in patients with TTS (100 [25] beats/min vs 73 [13] beats/min). ST-segment elevation and inverted T waves were significantly more common in patients TTS compared with patients with ACS. The left ventricular ejection fraction (LVEF) was significantly lower in TTS compared with ACS (38% [9%] vs 54% [11%]). However, follow-up LVEF was comparable in both groups. Additionally, mitral regurgitation and tricuspid regurgitation were more common in patients with TTS compared with patients with ACS.

Although drugs on admission were similar in TTS and ACS, patients with TTS were significantly more treated with therapeutic anticoagulation at discharge, but with less aspirin.

In-Hospital Complications

Life-threatening arrhythmia, inotropic agents, resuscitation, in-hospital death, and cardiogenic shock were similar in both patients with TTS and ACS. However, respiratory failure and need of respiratory support were significantly higher in patients with TTS compared with patients with ACS (51.7% vs 8.3%; Table 2).

Short- and Long-Term Incidence of Thromboembolic Events

Table 3 and Figure 1 illustrate thromboembolic events and their distribution with a predominance of stroke events (TTS: n = 9 vs ACS: n = 7) over follow-up. Patients with TTS suffered more often from thromboembolic events.

Predictors of Thromboembolic Events

Using multivariate analysis, only C-reactive protein (CRP) was an independent predictor of thromboembolic events (Table 4).

Discussion

We have described the short- and long-term incidence of thromboembolic events in TTS from our hospital in comparison with a sex- and age-matched ACS population.

(i) Patients with TTS suffered more often from thromboembolic events compared with patients with ACS; (ii) more patients with TTS are at high risk of thromboembolic events over long-term outcome with a predominance of stroke; and (iii) CRP is an independent predictor of thromboembolic events.

Thromboembolism is a relevant complication of TTS. Defined by events such as a stroke, the formation of ventricular thrombi, and peripheral embolization, these can present at any time in the disease course. In the present study, we sought to determine the epidemiological as well as the clinical aspects of thromboembolic events in TTS compared with ACS.

Predominantly, postmenopausal women are affected by TTS, which is usually provoked by emotional or physical stress.[3,10] An enhanced sympathetic activity with an elevation in catecholamine levels has been documented in these patients

Table 1. (A) Characteristics of 29 Patients With TTS and 12 Matched Patients With ACS and Thromboembolic Events. (B) Baseline Characteristics of 29 Patients With TTS and 12 Matched Patients With ACS and Thromboembolic Events.

Variables	TTS All, n = 138	ACS All, n = 138	TTS With Thromboembolic Events, n = 29	ACS With Thromboembolic Events, n = 12	P[a]
(A)					
Demographics					
Age, years, mean (SD)	67 (11)	68 (14)	71 (11)	75 (10)	.42
Female, n (%)	117 (84.8)	117 (84.8)	25 (86.2)	11 (91.7)	.63
Symptoms, n (%)					
Dyspnea	54 (39.1)	42 (30.4)	11 (37.9)	3 (25.0)	.43
Chest pain	69 (50.4)	103 (74.6)	11 (37.9)	10 (83.3)	<.01
Clinic parameter					
Systolic BP, mm Hg	141 (62-240)	140 (50-240)	134 (62-220)	159 (120-205)	.03
Diastolic BP, mm Hg	79 (40-151)	76 (7-120)	76 (40-100)	83 (63-105)	.22
Heart rate, bpm	99 (26)	82 (21)	100 (25)	73 (13)	<.01
ECG data, n (%)					
ST-segment elevation	41 (29.9)	19 (13.8)	15 (51.7)	11 (8.3)	.01
Inversed T waves	123 (93.2)	80 (58.0)	28 (96.5)	8 (66.7)	<.01
PQ interval	159 (28)	166 (32)	161 (31)	176 (31)	.17
QTc (milliseconds)	475 (62)	456 (358-614)	475 (355-554)	454 (405-496)	.46
Laboratory values, mean (SD)					
Troponin I, U/L, median (IQR)	63.15 (0.01-2738.00)	11.71 (0.03-228.09)	4.10 (0.03-24)	4.14 (0.64-15.85)	.98
Creatine kinase (CK), U/L, median (IQR)	587 (39-26600)	751 (35-10250)	413 (43-4478)	532 (35-2959)	.67
CK-MB, U/L, median (IQR)	35 (1-415)	55 (2-741)	39 (4-167)	40 (7-186)	.96
C-reactive protein, mg/L, median (IQR)	48.2 (0.4-467.1)	44.1 (0.6-594.0)	75.9 (1.5-467.1)	37.1 (1.9-147.9)	.24
Hemoglobin, g/dL, median (IQR)	12.2 (2.0)	12.6 (1.7)	11.9 (2.3)	12.5 (2.0)	.42
Creatinine, mg/dL, median (IQR)	1.12 (0.40-5.56)	1.30 (0.43-8.33)	1.37 (0.52-5.56)	1.16 (0.60-1.68)	.55
Echocardiography data, n (%)					
LVEF%	39 (10)	50 (13)	38 (9)	54 (11)	<.01
LVEF% follow-up	52 (11)	50 (13)	52 (12)	54 (11)	.56
Mitral regurgitation	66 (47.8)	43 (31.2)	21 (72.4)	2 (16.7)	<.01
Tricuspid regurgitation	54 (39.1)	22 (15.9)	15 (51.7)	1 (8.3)	.01
Medical history, n (%)					
Smoking	41 (29.7)	44 (31.9)	5 (17.2)	4 (33.3)	.26
Diabetes mellitus	31 (22.5)	57 (41.3)	9 (37.5)	7 (58.3)	.02
BMI >25, kg/m^2	36 (31.3)	73 (52.9)	9 (37.5)	8 (66.7)	.10
Hypertension	82 (59.4)	107 (77.5)	18 (62.1)	11 (91.7)	.06
COPD	28 (20.3)	15 (10.9)	3 (10.3)	1 (8.3)	.84
Atrial fibrillation	26 (18.8)	21 (15.2)	7 (24.1)	2 (16.7)	.60
History of malignancy	28 (20.3)	11 (8.0)	4 (13.8)	1 (8.3)	.63
(B)					
Drugs on admission, n (%)					
β-Blocker	46 (35.4)	47 (34.6)	6 (23.1)	6 (50.0)	.10
ACE inhibitor	51 (39.2)	41 (29.9)	12 (46.2)	7 (58.3)	.49
Aldosterone inhibitor	1 (0.8)	2 (1.5)	0 (0.0)	0 (0.0)	
Aspirin	36 (27.7)	39 (28.5)	16 (61.5)	7 (58.3)	.25
Therapeutic anticoagulation	12 (9.3)	11 (8.0)	2 (7.7)	1 (8.3)	.95
Drugs on discharge, n (%)					
β-Blocker	103 (74.6)	110 (79.7)	22 (75.9)	11 (91.7)	.25
ACE inhibitor	82 (59.4)	90 (65.2)	23 (79.3)	7 (58.3)	.17
Aldosterone inhibitor	2 (1.4)	1 (0.7)	0 (0.0)	0 (0.0)	
Aspirin	53 (38.4)	117 (84.8)	14 (48.3)	12 (100.0)	<.01
Therapeutic anticoagulation	33 (23.9)	10 (7.2)	13 (44.8)	1 (8.3)	.03

Abbreviations: ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; BMI, body mass index; BP, blood pressure; CK-MB, creatine kinase–muscle/brain; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; IQR, interquartile range; LVEF, left ventricular ejection fraction; SD, standard deviation; TTS, Takotsubo syndrome.

[a]*P* values for the comparison between TTS with thromboembolic events and ACS with thromboembolic events.

Table 2. In-Hospital Events and Treatment Strategy in Patients With Takotsubo Syndrome and Acute Coronary Syndrome With Thromboembolic Events.

Variables	TTS All, n = 138	ACS All, n = 138	TTS With Thromboembolic Events, n = 29	ACS With Thromboembolic Events, n = 12	P[a]
Life-threatening arrhythmia	12 (8.8)	16 (11.6)	4 (13.8)	0 (0.0)	.30
NPPV and or intubation	80 (58.0)	13 (9.4)	15 (51.7)	1 (8.3)	.01
Inotropic agents	23 (16.7)	15 (10.9)	5 (17.2)	0 (0.0)	.30
Resuscitation	4 (12.5)	16 (11.6)	3 (10.3)	0 (0.0)	.54
Device implantation	4 (2.9)	9 (6.5)	3 (10.3)	0 (0.0)	.54
Admission to ICU, length of stay, days, median (IQR)	5 (0-52)	3 (0-14)	3 (0-8)	3 (2-5)	.89
Thromboembolic events	18 (13.0)	3 (2.2)	18 (62.1)	3 (25.0)	.03
In-hospital death	10 (7.2)	12 (8.7)	2 (6.9)	0 (0.0)	1.00
Cardiogenic shock	25 (18.5)	15 (10.9)	6 (21.4)	0 (0.0)	.15

Abbreviations: ACS, acute coronary syndrome; ICU, intensive care unit; IQR, interquartile range; NPPV, noninvasive positive pressure ventilation; TTS, Takotsubo syndrome.
[a]*P* values for the comparison between TTS with thromboembolic events and ACS with thromboembolic events.

Table 3. Distribution of Thromboembolic Events in Patients With TTS and ACS.

Variables	TTS, n = 29	ACS, n = 12
Acute artery occlusion	3	0
Lung artery embolism	3	1
Stroke	9	7
Ventricular thrombus formation	8	3
Left atrial thrombus formation	3	1
Spleen infraction	1	0
Coronary embolism	1	0
Kidney infarction	1	0

Abbreviations: ACS, acute coronary syndrome; TTS, Takotsubo syndrome.

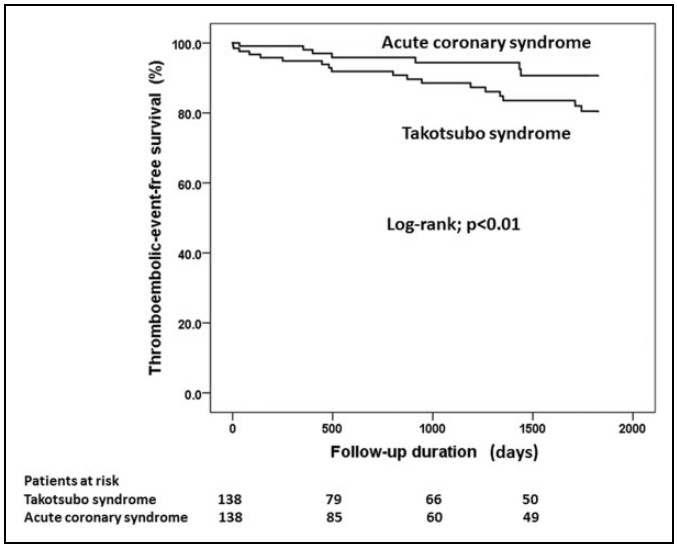

Figure 1. Rate of thromboembolic events in Takotsubo syndrome as compared with acute coronary syndrome over long-term follow-up.

and debated as a possible mechanism for the pathophysiology of TTS.[12,20] Nevertheless, a defining explanation of the underlying pathogenesis remains unresolved. In general, a

Table 4. Predictors of Thromboembolic Events.

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P	HR	95% CI	P
Male	1.49	0.5-4.3	.46			
Age	1.03	1.0-1.06	.08	1.03	0.9-1.0	.07
Apical ballooning	2.0	0.7-5.2	.15			
Right ventricular involvement	1.61	0.7-3.4	.21			
QTc prolongation	0.68	0.3-1.5	.34			
Life-threatening arrhythmia	1.75	0.6-5.0	.29			
Malignancy	1.61	0.5-4.6	.37			
LVEF	0.98	0.9-1.0	.40			
Diabetes mellitus	0.72	0.3-1.7	.48			
Arterial hypertension	0.86	0.4-1.8	.70			
Pulmonary disease	0.33	0.1-1.1	.07	0.38	0.1-1.2	.12
Atrial fibrillation	1.63	0.7-3.8	.25			
Cardiogenic shock	2.01	0.8-4.9	.12			
Emotional stress	1.07	0.5-2.3	.85			
CRP	1.04	1.0-1.2	<.01	1.1	1.0-0.1.2	<.01

Abbreviations: ACS, acute coronary syndrome; CRP, C-reactive protein; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; TTS, Takotsubo syndrome.

ventricular thrombus can occur in the setting of ventricular dysfunction, especially in the acute stage after ACS, or different cardiomyopathies/dilated cardiomyopathy. Additionally, the risk of thromboembolic event is increased in patients with noncompaction cardiomyopathy (characterized anatomically by prominent left ventricular (LV) trabeculae and deep intratrabecular recesses), and therefore, an effective anticoagulation therapy is required.[21-26]

The low blood flow in heart chambers may explain the development of thromboembolic events in patients with TTS. It is known that recovery of LV function might be achieved within 2 weeks after TTS events. The improvement in wall motion abnormality in TTS might promote discharge of an intraventricular thrombus into the peripheral bloodstream, thus

initiating an embolic event and stroke. However, recently published data showing an altered coagulation system in patients with TTS contribute to its role in the development of thromboembolic events in patients with TTS.[27] Several endothelial markers, clotting activation biomarkers (von Willebrand factor and plasminogen), and lipoprotein a levels were higher in patients with TTS as compared with the healthy population, suggesting a role of endothelial dysfunction and similar pathologies contributing to the hyperviscosity of blood flow in TTS.[28] One potential explanation for the high rate of thromboembolic events in TTS compared with ACS might be due to the fact that the recovery from impaired LV function is much earlier than in the setting of an ACS. However, in the long term, the risk of thromboembolism is higher in TTS compared with ACS. At the same time, our data showed a higher rate of cancer in patients with TTS compared with patients with ACS over follow-up.[27] This might suggest the mechanism of thromboembolic events in TTS over years of follow-up.

Remarkably, in the present study, only 30% of patients with TTS suffering from thromboembolic events have shown a ventricular thrombus formation. Two-dimensional echocardiogram and transesophageal echocardiogram remain the gold standard to diagnose thrombus formation. However, operator skills and use of contrast agents may all influence the sensitivity and specificity of this tool in thrombus detection. Although intraventricular thrombus formation might usually be in the LV apex, other possible sites including papillary muscles should be looked for.[16] Even more, it has been reported that thrombus formation is a common finding in the right ventricle, especially in TTS cases with right ventricular involvement.[28] Additionally, in rare cases, tumor or thrombus formation may challenge physicians, leading to overlooking thrombus formation.[29,30] In rare cases, the use of computed tomography and cardiac magnetic resonance imaging might be required to rule out intraventricular thrombus.

In the present study, patients suffering from TTS were less often treated with aspirin at discharge. A review of the current literature reveals that most patients with TTS suffering from thrombus formation have been treated with anticoagulants such as warfarin and/or heparin. However, the type of anticoagulant drug prescribed was variable and details as to the dosage and therapy duration were often not reported. Although in the present study patients with TTS were more discharged with a temporary anticoagulation, this might not prevent long-term thromboembolic events. Although anticoagulation therapy in the presence of LV thrombus is recommended, a retrospective study has recommended antiplatelet therapy during index hospitalization to prevent this complication.[31] Due to the retrospective character of current data and sparse reports of the long-term use of antiplatelet therapy in patients with TTS, this topic needs future prospective multicenter studies.

Conclusions

The risk of thromboembolic events in TTS is significantly higher at TTS presentation and even more after 5-year follow-up when compared with patients with ACS. An elevated CRP level might be a predictor of thromboembolic events. Prospective studies are warranted to define the real risk of thromboembolic events in TTS and to develop an algorithm for the treatment of these events.

Study Limitations

The present study is a retrospective, single-center study. It is possible that the thromboembolic event rate was underestimated. A further point is the therapeutic approach at discharge. It is possible that some patients with TTS discontinued their treatment.

Declaration of Conflicting Interests

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