ORIGINAL ARTICLE

Sex-dependent differences in clinical characteristics and in-hospital outcomes in patients with takotsubo syndrome

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ABSTRACT

INTRODUCTION   Takotsubo syndrome (TTS) is an acute reversible left ventricular dysfunction, which occurs mainly in postmenopausal women.

OBJECTIVES   The goal of this study was to compare the course of the disease and prognoses in men and women with TTS in 2 large Polish university hospitals.

PATIENTS AND METHODS   The analysis included 232 patients (211 women and 21 men) hospitalized at the 1st Chair and Department of Cardiology at the Medical University of Warsaw and at the 1st Department of Cardiology at the Medical University of Gdańsk.

RESULTS   Men who developed TTS were more likely to live alone than women. Physical stress triggered TTS more often in men than in women. There were no differences in the prevalence of risk factors and comorbidities, except for a higher prevalence of smoking in men. With regard to the cardiac biomarkers, both admission and peak levels of N-terminal prohormone of brain natriuretic peptide were higher in women. ST-segment depression was found more frequently in men than in women (25% vs 6.2%). Despite the same length of hospitalization, ejection fraction at discharge was lower in men than in women (50% vs 60%). In-hospital outcomes (arrhythmias, mechanical complications, cardiogenic shock, mortality rate) were similar in both groups. β-Adrenolytics and statins were more often prescribed to women than to men (74.5% vs 52.4% and 68.3% vs 38.1%). Moreover, there was a tendency toward more frequent use of P2Y12 inhibitors in men than in women (23.8% vs 10.4%).

CONCLUSIONS   Differences occurred in the clinical course of TTS between men and women. However, in-hospital outcomes were similar in both groups.

INTRODUCTION   Takotsubo syndrome (TTS) is a transient left and/or right ventricular dysfunction, which is often preceded by emotional or physical stress. It occurs mainly in postmenopausal women.[1] Multiple diagnostic criteria have been proposed for TTS, with the most current International Takotsubo Diagnostic Criteria.[2]

One of the criteria for diagnosing TTS suggests that it occurs predominantly in postmenopausal women. Although most patients with TTS are postmenopausal women and the possible pathomechanism is related to female hormones, including estrogens, men can also suffer from TTS.[3] Therefore, we chose the potential difference in clinical characteristics and the course of the disease between men and women as the topic of this study. The goal of the study was to compare the prevalence, course of the disease, and prognosis in men and women with TTS in 2 large Polish university hospitals, which are experienced in the diagnosis and treatment of TTS and participate in the International Takotsubo Registry.

WHAT'S NEW?

We present the most comprehensive data on sex differences in patients with takotsubo syndrome in the Polish population. It is of importance mainly because only about 10% of patients with takotsubo syndrome are men. The prevalence of risk factors and comorbidities as well as in-hospital complications (arrhythmias, mechanical complications, cardiogenic shock, and mortality) were similar in men and women. However, in men, we reported lower level of N-terminal prohormone of brain natriuretic peptide at admission, and lower ejection fraction at discharge. Furthermore, ST-segment depression was more frequent in men than in women.

However, this study was designed in Warsaw and Gdańsk, independently of the above-mentioned registry.

PATIENTS AND METHODS Our analysis included 232 patients with TTS hospitalized at the 1st Chair and Department of Cardiology at the Medical University of Warsaw and the 1st Department of Cardiology at the Medical University of Gdańsk from 2009 to 2018. In all patients, the diagnosis was based on echocardiography showing a typical transient left ventricular dysfunction and characteristic levels of cardiac biomarkers. Angiography was performed in all but 2 patients in whom it was contraindicated. In case of doubt, magnetic resonance imaging was performed. In all patients, follow-up echocardiography showed the typical full resolution of the ventricular systolic dysfunction.

Data on the diagnosis, comorbidity, course of TTS, and the results of electrocardiography, echocardiography, and angiography were collected and analyzed.

Statistical analysis The normality of the distribution of continuous variables was assessed using the Shapiro–Wilk test. All continuous variables were nonnormally distributed and presented as median and interquartile range. For categorical variables, absolute and relative frequencies were presented. The difference in the categorical variables between men and women was tested using the Fisher exact test, while the difference in the continuous variables between both groups was assessed by the Mann–Whitney test. Risk factors of the composite endpoint (atrial fibrillation, ventricular tachycardia, ventricular fibrillation, cardiogenic shock, death) were evaluated with a logistic regression analysis. Because of the low number of events per variable, multivariate logistic regression analysis was not performed. A P value of less than 0.05 was considered significant for all tests. Statistical analysis was performed using the SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina, United States).

The study was approved by an ethics committee (decision no., 25/2011) and all patients provided written informed consent to participate in the study.

RESULTS The analysis included 232 patients, 211 (91.4%) of whom were women. The patient characteristics are shown in **TABLE 1**. Laboratory parameters and the results of electrocardiography and echocardiography are presented in **TABLE 2**. All data come from 2 centers, except for the levels of the N-terminal prohormone of brain natriuretic peptide (NT-proBNP), which were reported only for the patients from the Warsaw registry.

Men tended to be younger than women (median [interquartile range] age, 63 [54–72] vs 71 [61–79] years; $P = 0.055$). Emotional stress was the most frequent cause of TTS in both men and women, but physical stress triggered TTS more often in men than in women (35% vs 14.2%; $P = 0.02$). Interestingly, men who developed TTS were more likely to live alone than women.

Comorbidity Risk factors like obesity, hypertension, hypercholesterolemia, diabetes, and family history of cardiovascular disease were equally frequent in men and women. The only difference was observed in smoking habits: 24.4% of women and 57.1% of men were smokers. The prevalence of TTS as a comorbidity of chronic obstructive pulmonary disease, cancer, or hyperthyroidism did not differ between men and women.

Biomarkers The elevated levels of biomarkers with high levels of NT-proBNP and relatively low elevation of troponin levels in both men and women were suggestive of TTS.[4] In both groups, similarly elevated levels of markers of myocardial necrosis were found: troponin, creatine kinase, and creatine kinase isoenzyme MB mass. Both the peak NT-proBNP levels and the NT-proBNP levels measured on admission to hospital were higher in women.

Electrocardiography The most frequent abnormality detected by electrocardiography on admission was ST-segment elevation. Isolated ST-segment depression was found more frequently in men than in women (25% vs 6.2%). The QT interval corrected for heart rate (QTc) was the same for men and women, both on admission and on days 3 and 5 after admission. The QTc prolongation of more than 450 ms was found in 53% of men on day 1, in 60% on day 3, and in 30% on day 5 after admission. The QTc prolongation of more than 460 ms was found in 44% of women on day 1, in 60% on day 3, and in 49% on day 5 after admission.

Echocardiography Most frequently, TTS occurred in both men and women in its apical form, which was found in 85.7% of men and 84.4% of women. The reverse and midventricular types were less frequent. There were no differences in the prevalence of particular types of TTS (apical, midventricular, reverse) between women and men. Regional wall motion abnormalities in the right ventricular function were found in 16.8% of women and 6.3% of men, but this difference between

TABLE 1 Clinical characteristics of patients

Variable	Women (n = 211)	Men (n = 21)	P value
Age, y, median (IQR)	71 (61–79)	63 (54–72)	0.06
BMI, kg/m², median (IQR)	24.5 (21.1–27.5)	24 (22–25.8)	0.73
Living alone	13 (11.4); 114	5 (31.3); 16	0.047
Stress factors			
Emotional stress	119 (56.4); 211	8 (40); 20	0.17
Physical stress	30 (14.2); 211	7 (35); 20	0.02
Exacerbation of a chronic disease	28 (13.3); 211	2 (9.5); 21	>0.99
Signs and symptoms on admission			
Chest pain	177 (84.3); 210	17 (81); 21	0.75
Dyspnea	103 (49.3); 209	8 (38.1); 21	0.37
Symptom duration, h, median (IQR)	2 (1–9)	3.5 (1–12)	0.58
HR, bpm, median (IQR)	85 (73–98)	80 (67–100)	0.78
SBP, mm Hg, median (IQR)	130 (120–145)	140 (130–145)	0.3
DBP, mm Hg, median (IQR)	80 (70–83)	80 (70–80)	0.5
Risk factors			
Smoking	51 (24.4); 209	12 (57.1); 21	0.01
Hypercholesterolemia	94 (44.8); 210	8 (40); 20	0.82
Family history of CVD	40 (19.6); 204	3 (14.3); 21	0.77
Hypertension	144 (68.6); 210	12 (57.1); 21	0.33
Diabetes	36 (17.2); 209	2 (9.5); 21	0.54
Comorbidities			
COPD	27 (12.8); 211	4 (19.1); 21	0.50
Hyperthyroidism	22 (10.6); 208	2 (10); 20	>0.99
Malignancy	25 (12); 209	3 (14.3); 21	0.73

Data are presented as number (percentage); total number of patients in whom a variable was analyzed unless otherwise indicated.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease, DBP, diastolic blood pressure; HR, heart rate; IQR, interquartile range; SBP, systolic blood pressure

the groups was not significant. There were also no differences between the 2 groups in the prevalence of pericardial effusion or thrombus formation. Acute functional mitral valve regurgitation tended to be more frequent in women than in men (38.7% vs 12.5%; *P* = 0.05). Left ventricular ejection fraction (LVEF) was similar for men and women on admission and on days 3 and 5 after admission, but appeared to be lower in men at discharge despite the same length of hospitalization in both groups.

Course of the disease   Clinical symptoms were similar in men and women. The most frequent symptom on admission was chest pain, which was present in 84.3% of women and in 81% of men. The median time from symptom onset to hospitalization did not differ between the groups. Heart rate and systolic and diastolic pressure were similar in both groups. Furthermore, a similar percentage of men and women needed catecholamines, an intra-aortic balloon pump, and mechanical ventilation.

The prevalence and types of complications during hospitalization are presented in **TABLE 3**. There were no differences between men and women in

the prevalence of arrhythmias: atrial fibrillation, ventricular fibrillation, and ventricular tachycardia. The prevalence of ventricular septal rupture and cardiogenic shock was similar in both patient groups, and so was the length of hospitalization. Six women and no men died, but this did not show a significant difference.

We performed the logistic regression analysis of predictors of in-hospital complications including atrial fibrillation, ventricular tachycardia, ventricular fibrillation, cardiogenic shock, and death. The predictors of composite endpoint were: chest pain on admission (odds ratio [OR], 0.44; 95% CI, 0.20–0.97), dyspnea on admission (OR, 2.50; 95% CI, 1.70–6.98), heart rate on admission (OR, 1.03; 95% CI, 1.01–1.04), and LVEF on admission (OR, 0.90; 95% CI, 0.86–0.95). Sex was not considered a predictor of in-hospital complications (**TABLE 4**).

Treatment   Angiotensin-converting enzyme inhibitors were the most frequently prescribed drugs at discharge. β-Adrenolytics and statins were more often prescribed to women than to men, and acetylsalicylic acid was recommended in about 70% of patients, regardless of sex. There was a tendency toward more frequent use of P2Y12 inhibitors in men than in women (23.8% vs 10.4%; *P* = 0.08). No difference was observed in medications and mechanical circulatory assist devices utilized in both centers.

DISCUSSION   The available literature suggests that TTS in men is more frequent in Asian populations.[5] In Western Europe, about 10% of patients with TTS are men.[6,7] Our analysis shows a similar prevalence of TTS in men in the Polish population (9%). Some authors perceive the prevalence of TTS as still underestimated,[8] especially in men, who are more frequently admitted to hospital after either successful or unsuccessful cardiopulmonary resuscitation, which precludes the diagnosis of TTS.[6] In the Japanese population, autopsy in patients who had suffered sudden cardiac death, 85% of whom were men, revealed that a sudden, stress-induced cardiac dysfunction was the most likely cause of death in 19.8% of these patients.[9]

In most cases, the onset of TTS is preceded by an identifiable trigger.[10] In our patient sample, emotional stress was the prevailing trigger of TTS. Physical stress triggered TTS more frequently in men than in women, and this confirms previous research findings.[6,10-12] It is significant that men who developed TTS were more likely to be alone (defined as "living alone") than women, and this might confirm the role of emotional triggers in TTS and suggest that lack of emotional support might increase predisposition to TTS.

We did not find any differences in the prevalence of most cardiovascular risk factors between men and women in our sample. The only difference we found concerned smoking habits: men

TABLE 2 Laboratory parameters and results of electrocardiography and echocardiography

Variable		Women (n = 211)	Men (n = 21)	*P* value
Biomarkers				
TnI on admission	N	206	20	0.11
	Median (IQR), ng/ml	2.04 (0.53–5.59)	0.61 (0.25–3.82)	
Peak TnI	N	205	21	0.6
	Median (IQR), ng/ml	3.16 (1.3–6.55)	1.76 (0.77–10.43)	
CK on admission	N	94	9	0.49
	Median (IQR), ng/ml	129.5 (67–235)	123 (101–208)	
CK-MB mass on admission	N	153	15	0.83
	Median (IQR), ng/ml	5 (1.9–13.9)	4.6 (1.8–14.4)	
Peak CK-MB mass	N	152	16	0.41
	Median (IQR), ng/ml	7.1 (2.6–17.6)	12.1 (2.6–15.9)	
NT-proBNP on admission[a]	N	94	11	<0.001
	Median (IQR)	2.2 (0.04–20.5)	1.3 (0.2–10.2)	
Peak NT-proBNP[a]	N	127	11	<0.001
	Median (IQR)	4.8 (0.1–38.4)	4.7 (0.3–30)	
Electrocardiography				
ST-segment elevation on admission		129 (61.4); 210	12 (60); 20	>0.99
ST-segment depression on admission		13 (6.2); 209	5 (25); 20	0.01
LBBB on admission		6 (2.9); 209	0	>0.99
QTc on admission, ms, median (IQR)		456 (422–486)	452 (417–480)	0.69
QTc on day 3, ms, median (IQR)		477 (441–506)	453 (432–488)	0.12
QTc on day 5, ms, median (IQR)		455 (435–477)	431 (399–478)	0.33
Echocardiography				
Apical TTS		178 (84.4); 211	18 (85.7); 21	>0.99
Reverse TTS		8 (3.8); 211	1 (4.8); 21	0.58
Midventricular TTS		24 (11.4); 211	2 (9.5); 21	>0.99
LVEF, %, median (IQR)	Day 1	40 (35–45)	40 (35–49)	0.35
	Day 3	48 (41–55)	57.5 (46–61)	0.18
	Day 5	53.5 (43–60)	53.5 (44–59)	0.96
	At discharge	60 (54.5–65)	50 (45–50)	0.002
RV dysfunction		17 (16.8); 101	1 (6.3); 16	0.46
Thrombus		5 (2.4); 210	1 (4.8); 21	0.44
Acute functional MR		41 (38.7); 106	2 (12.5); 16	0.05
Pericardial fluid		10 (9.6); 104	1 (6.3); 16	>0.99

Data are presented as number (percentage); total number of patients in whom a variable was analyzed (N) unless otherwise indicated.

a   Upper limits of the normal range for N-terminal prohormone of brain natriuretic peptide

Abbreviations: CK, creatine kinase; CK-MB mass, creatine kinase isoenzyme MB mass; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RV, right ventricle; TnI, troponin I; QTc, QT interval corrected for heart rate; others, see TABLE 1

with TTS were more likely to smoke than women, which is consistent with the literature.[13]

The majority of patients admitted to hospital with TTS show abnormalities on electrocardiogram.[14] In our patient group, ST-segment elevation was the most common abnormality, and ST-segment depression, rarely found in the population with TTS, was detected more often in men than in women. No differences were found between men and women with regard to the QTc interval neither on admission nor on days 3 and 5 after admission. It should be noted, however, that men have a shorter QTc than women, which

is why it is especially important to detect ventricular arrhythmias in that population. The meta-analysis of research data suggests that the risk of torsade de pointes is higher among men.[15] In our study population, LVEF at discharge was lower in men, even though the length of hospital stay was similar in men and women. Despite no differences in LVEF on admission and similar prevalence of right ventricular dysfunction, pericardial effusion, and ventricular thrombus formation, the time required for the complete recovery of left ventricular systolic function was longer in men than in women. This might cause

TABLE 3 In-hospital complications, mortality rate, and treatment

Variable	Women (n = 211)	Men (n = 21)	P value
Unstable on admission	26 (12.3); 211	3 (14.3); 21	0.73
Mechanical ventilation	13 (6.2); 211	1 (4.8); 21	>0.99
IABP	0 (0); 210	1 (4.8); 21	0.09
AF	11 (5.2); 210	2 (9.5); 21	0.33
VT	9 (4.3); 210	0 (0); 21	>0.99
VF	14 (6.7); 210	1 (4.8); 21	>0.99
Ventricular septal rupture	1 (0.48); 210	0 (0); 21	>0.99
Left ventricular free wall rupture	0 (0); 210	0 (0); 210	>0.99
Cardiogenic shock	20 (9.5); 211	1 (4.8); 21	0.70
Death	6 (2.9); 210	0 (0); 21	>0.99
Length of hospitalization, d, median (IQR)	7 (5–12)	6 (5–6)	0.17
Beta adrenolytics	152 (74.5); 204	11 (52.4); 21	0.04
ACEI	150 (73.5); 204	17 (81); 21	0.60
CCB	9 (4.5); 202	2 (9.5); 21	0.28
ASA	146 (72.6); 201	14 (66.7); 21	0.61
VKA/NOAC	11 (5.5); 201	1 (4.8); 21	>0.99
P2Y$_{12}$ inhibitors	21 (10.4); 202	5 (23.8); 21	0.08
Statins	138 (68.3); 202	8 (38.1); 21	0.008

Data are presented as number (percentage); total number of patients in whom a variable was analyzed unless otherwise indicated.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ASA, acetylsalicylic acid; CCB, calcium channel blocker; IABP, intra-aortic balloon pump; NOAC, novel oral anticoagulants; VF, ventricular fibrillation; VKA, vitamin K antagonists; VT, ventricular tachycardia

TABLE 4 Logistic regression analyses of predictors of in-hospital complications (atrial fibrillation, ventricular tachycardia, ventricular fibrillation, cardiogenic shock, death)

Variable	Univariate analysis		
	OR	95% CI	P value
Female sex	2.5	0.56–11.15	0.23
Age	1.02	0.99–1.05	0.17
Unstable[a]	54.17	17.18–170.74	<0.001
Chest pain[a]	0.44	0.20–0.97	0.04
Dyspnea[a]	3.45	1.70–6.98	<0.001
Symptom duration	0.97	0.94–1.01	0.14
HR[a]	1.03	1.01–1.04	<0.001
SBP[a]	0.99	0.98–1.01	0.20
DBP[a]	0.99	0.96–1.01	0.23
Peak TnI	1.02	0.99–1.05	0.27
Peak NT-proBNP	1.00	1.00–1.00	0.14
LVEF	0.90	0.86–0.95	<0.001

a Assessed or measured on admission.

Abbreviations: OR, odds ratio; others, see **TABLES 1** and **2**

delays in the final diagnosis of TTS and suggest the need for longer hospitalization in men. However, lower LVEF at discharge is not correlated with the frequency of complications during hospitalization, including death. In the Polish population, we did not confirm observations made on a large patient sample from the United States in which a higher mortality rate was observed in men.[13] Angiotensin-converting enzyme inhibitors were the medications most frequently prescribed at discharge, which probably reflected 2 phenomena: 1) that patients with TTS were often hypertensive and 2) that these medications have been proved to be beneficial in preventing recurrence of the disease.[16] β-Adrenolytics were more frequently prescribed to women than to men. This was likely to be caused by doctors' belief that these medications can be effective in patients with overactive sympathetic nervous system, persistent anxiety, or palpitations, which are more frequently experienced by women. While the prevalence of hypercholesterolemia was similar in both groups, statins were prescribed more frequently to women and it is something we cannot explain. Despite lack of evidence as to the benefits of antiplatelet therapies, acetylsalicylic acid was prescribed to approximately 70% of patients. We should emphasize that this analysis included patients hospitalized since 2009 and little was known about therapies for TTS at that time. Currently, the use of acetylsalicylic acid is not recommended in patients with TTS.[17]

It should also be noted that dual antiplatelet therapy was conducted in almost one-fourth of men and in about every tenth woman, which shows that over the years, TTS has been treated similarly to myocardial infarction. This is particularly apparent in men and associated with doctors' limited experience that results from the low prevalence of TTS in the general population. Of note, the average hospitalization period for patients in our sample, drawn from 2 large Polish hospitals, was twice as long as that in the American study, which affects the cost-effectiveness of hospitalization. This might suggest that the extended length of hospitalization in Poland is unwarranted.[13]

Excessive catecholamine release in response to a stressor is the most widely accepted cause of TTS.[18] The reason for the higher prevalence of TTS in women is not known. Some researchers suggest that lower estrogen production might be the culprit.[19] Estrogens have a cardioprotective effect that works through a variety of mechanisms, such as inhibition of the renin-angiotensin system, modulation of the release of natriuretic peptide,[20] weakening of the catecholamine and glucocorticoid response to stress, and improvement of noradrenaline-induced vascular contraction.[21,23] Estrogen levels in postmenopausal women are lower than in premenopausal women and lower than in men of the same age,[22] which could be the reason for the higher prevalence of TTS in postmenopausal women.[24-26] Factors that predispose men to TTS are not known. Risk factors and the course of the disease in men and women differ in terms of several of the above-mentioned factors. Therefore, there is a need for further multicenter studies, which would include hormone analysis and psychological evaluation of patients.

Limitations The main limitation of the study is lack of hormone analysis as well as investigation of psychological factors and patient's personality. We are aware that the number of male patients is small but it results from the rare occurrence of TTS in men in the general population. This may be the reason for underestimating the incidence of complications. In addition, the difference between primary and secondary TTS in men and women cannot be reliably assessed. Moreover, a long-term follow-up is needed, which is the subject of our further analyses.

Conclusions The prevalence of TTS in men is lower than in women. Clinical characteristics and the course of the disease were similar in both groups. However, some differences were noted. Physical stress was a more common cause of TTS in men. Men who developed TTS lived alone more often than women. The only difference with regard to risk factors and comorbidities was observed in smoking habits: men smoked more frequently than women. The NT-proBNP levels, both peak and measured on admission, were higher in women. The isolated ST-segment depression was detected more often in men. Moreover, men had lower LVEF at discharge.

Despite these differences, in-hospital outcomes (atrial fibrillation, ventricular tachycardia, ventricular fibrillation, cardiogenic shock) and mortality rate were similar in both groups.

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