Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work

eAppendix 1. Study Centers

Leading Study Center
University Heart Center, Department of Cardiology, University Hospital Zurich

Participating Study Centers
Austria
Internal Medicine III (Cardiology), Medical University Innsbruck, Innsbruck

Finland
Heart Center, Turku University Hospital and University of Turku, Turku

France
Department of Cardiology, University Hospital of Rangueil, Toulouse

Germany
Department of Cardiology and Angiology, Hannover Medical School, Hannover
Department of Cardiology, Heidelberg University Hospital, Heidelberg
University Heart Center Luebeck, Department of Cardiology, Luebeck
Department of Cardiology, Charité, Campus Rudolf Virchow, Berlin
Department of Internal Medicine III, Heart Center University of Cologne, Cologne
Department of Internal Medicine III, Cardiology, Saarland University, Homburg
Department of Cardiology, University Hospital Essen, Essen
Division of Cardiology, Asklepios Clinics St. Georg Hospital, Hamburg
Clinic for Cardiology, Georg August University Goettingen, Goettingen
Department of Internal Medicine II – Cardiology, University of Ulm, Ulm
Internal Medicine/Cardiology, Magdeburg University, Magdeburg
University Medicine Greifswald, Department of Internal Medicine B, Greifswald

Italy
Department of Cardiovascular Sciences, Catholic University Rome, Rome

Poland
First Department of Cardiology, Medical University of Gdansk, Gdansk
Department of Cardiology, Medical University of Warsaw, Warsaw

Switzerland
Department of Cardiology, Kantonsspital Lucerne, Lucerne
Department of Cardiology, Kantonsspital Winterthur, Winterthur
Department of Cardiology, University Hospital Basel, Basel

United Kingdom
Department of Cardiology, John Radcliffe Hospital, Oxford
Department of Cardiology, Kings College Hospital, Kings Health Partners, London

United States
Division of Cardiovascular Medicine, University of Kentucky, Lexington KY
Division of Cardiovascular Diseases Mayo Clinic, Rochester MN

eAppendix 2. Online Methods

Patients

Diagnosis of takotsubo syndrome (TTS) at local study centers was based on modified Mayo Clinic Diagnostic Criteria including transient left ventricular wall motion abnormality beyond a single epicardial coronary artery perfusion territory. Lack of an obstructive coronary artery disease or angiographic evidence of acute plaque rupture, new electrocardiographic abnormalities or elevation in cardiac troponin values, and absence of pheochromocytoma and myocarditis. Exceptions to these criteria were the presence of coexisting coronary artery disease, wall-motion abnormality that was congruent with a single coronary artery territory matching all other criteria, and death during the acute phase before wall motion recovery.[1,2]

Definition of TTS forms

Based on left ventricular angiography and/or transthoracic echocardiography, different TTS types were defined and previously described as:[1] The apical type as hypo-, dys- or akinesia of the midventricular and apical segments of the anterior, septal, inferior and lateral wall of the left ventricle and compensatory hyperkinesia of the basal segments. The midventricular type was defined as hypo-, dys- or akinesia of midventricular segments associated with normo- or hyperkinesia of the basal and apical segments. The basal TTS type was classified as hypo-, dys- or akinesia of basal segments and normo- or hyperkinesia of midventricular and apical segments of the left ventricle. Finally, the focal type was defined as localized hypo-, dys- or akinesia of any segment of the left ventricle, which in majority of the cases included the anterolateral segment. The location of the wall motion abnormalities was beyond a single coronary territory except for the focal type, which could be localized to a single perfusion territory. Patients with an apical ballooning pattern were categorized as typical and patients with a midventricular, basal or focal type as atypical TTS.

Data collection

Data collection included: clinical presentation, precipitating factors, cardiovascular risk factors, comorbidities, electrocardiograms on admission, laboratory values, medications on admission and discharge, demographics as well as in-hospital complications. Left ventricular ejection fraction (LVEF) and left ventricular end-diastolic pressure were included if available. Similarly, echocardiography data were collected if performed. Follow-up data were collected from medical records, clinical visits or telephone interviews.

Statistics

Multiple Cox-regression was performed to adjust for variables, which differed significantly between groups and could have an impact on outcomes (age over 70 years, atrial fibrillation, ST-segment elevation, LVEF less than 45%, hypertension, positive family history, neurologic disorders, acute psychiatric disorders).

eTable 1. Full Characteristics of Patients, Comparison of Apical, Midventricular, Basal, and Focal TTS.

Characteristic	Characteristics of Patients				P Value
	Apical (n=1430)	Midventricular (n=255)	Basal (n=39)	Focal (n=26)	
Demographics					
Female sex - no./total no. (%)	1284 / 1430 (89.8)	232 / 255 (91.0)	31 / 39 (79.5)	24 / 26 (92.3)	.17
Age - yr - mean±SD	67.3 ± 12.9 (n=1430)	62.9 ± 13.0 (n=255)	57.8 ± 11.5 (n=39)	65.9 ± 17.2 (n=26)	<.001
Body mass index - kg/m² - mean±SD	25.1 ± 5.3 (n=1092)	25.0 ± 5.5 (n=201)	24.9 ± 5.6 (n=24)	24.4 ± 3.8 (n=23)	.91
Triggers - no./total no. (%)					
Physical	509 / 1430 (35.6)	102 / 255 (40.0)	10 / 39 (25.6)	9 / 26 (34.6)	.29
Emotional	384 / 1430 (26.9)	83 / 255 (32.5)	9 / 39 (23.1)	9 / 26 (34.6)	.21
Both emotional and physical	111 / 1430 (7.8)	22 / 255 (8.6)	3 / 39 (7.7)	1 / 26 (3.8)	.85
No evident	426 / 1430 (29.8)	48 / 255 (18.8)	17 / 39 (43.6)	7 / 26 (26.9)	.001
Symptoms on admission - no./total no. (%)					
Chest pain	1014 / 1325 (76.5)	173 / 236 (73.3)	24 / 33 (72.7)	18 / 25 (72.0)	.67
Dyspnea	623 / 1320 (47.2)	110 / 241 (45.6)	20 / 34 (58.8)	7 / 25 (28.0)	.13
Syncope	104 / 1317 (7.9)	16 / 240 (6.7)	3 / 35 (8.6)	1 / 25 (4.0)	.81
Cardiac biomarkers - median (IQR)					
Troponin on admission - factor increase in ULN [a]	8.00 (2.21 - 24.93) n=1151	6.70 (2.35 - 21.02) n=209	11.63 (3.20 - 27.49) n=34	5.80 (0.24 - 8.81) n=17	.13
Troponin maximum - factor increase in ULN[a]	14.00 (4.60 - 42.54) n=1160	11.48 (4.36 - 33.43) n=211	12.70 (7.82 - 36.20) n=34	8.81 (4.80 - 38.16) n=18	.47
Creatine kinase on admission - factor increase in ULN	0.86 (0.51 - 1.52) n=990	0.86 (0.57 - 1.27) n=160	0.67 (0.43 - 1.19) n=26	0.92 (0.49 - 1.51) n=17	.55
Creatine kinase maximum - factor increase in ULN	1.11 (0.61 - 2.08) n=1008	1.06 (0.70 - 1.62) n=165	0.87 (0.44 - 2.86) n=27	0.98 (0.44 - 1.75) n=19	.79
BNP on admission - factor increase in ULN [b]	6.59 (2.25 - 16.63) n=363	4.11 (1.07 - 11.87) n=74	10.54 (2.40 - 26.12) n=9	2.98 (0.50 - 8.56) n=4	.03
BNP maximum - factor increase in ULN [b]	9.34 (3.72 - 22.54) n=464	9.84 (2.58 - 20.11) n=97	24.17 (6.98 - 29.14) n=12	4.93 (4.08 - 7.49) n=5	.08
Inflammatory markers - median (IQR)					
CRP on admission - mg/l	4.20 (1.46 - 13.55) n=916	3.00 (1.00 - 9.00) n=167	5.00 (1.50 - 20.20) n=23	3.85 (0.60 - 5.60) n=22	.07
CRP maximum - mg/l	9.10 (2.98 - 40.00) n=966	7.05 (2.68 - 25.10) n=174	17.55 (2.65 - 89.00) n=24	4.80 (1.35 - 9.78) n=22	.04
WBC on admission - 10^3/µl	9.72 (7.40 - 12.70) n=1197	9.60 (7.49 - 13.18) n=213	10.45 (7.47 - 14.70) n=34	9.41 (8.20 - 11.17) n=21	.89
WBC maximum - 10^3/µl	10.60 (8.11 - 13.80) n=1214	10.40 (8.00 - 14.76) n=219	10.48 (7.50 - 17.40) n=34	9.90 (8.20 - 11.51) n=21	.98
Electrolytes - median (IQR)					
Sodium on admission - mmol/l	138.00 (136.00 - 141.00) n=1219	139.00 (136.00 - 141.00) n=216	138.20 (136.80 - 140.00) n=35	139.00 (135.75 - 141.00) n=22	.87
Sodium maximum - mmol/l	140.00 (138.00 - 142.00) n=1227	140.50 (138.00 - 143.00) n=220	140.00 (138.20 - 144.00) n=35	141.00 (138.75 - 141.00) n=22	.38
Potassium on admission - mmol/l	3.90 (3.60 - 4.30) n=1217	4.00 (3.60 - 4.30) n=217	3.85 (3.50 - 4.30) n=35	3.70 (3.50 - 4.20) n=22	.30
Potassium maximum - mmol/l	4.20 (3.89 - 4.50) n=1229	4.20 (3.98 - 4.50) n=220	3.93 (3.70 - 4.60) n=35	3.99 (3.75 - 4.40) n=22	.15
Lipid status - median (IQR)					
Triglyceride - mmol/l	1.15 (0.83 - 1.66) n=684	1.03 (0.76 - 1.46) n=122	1.07 (0.78 - 1.94) n=14	1.00 (0.47 - 1.36) n=11	.12
Cholesterol - mmol/l	4.87 (4.00 - 5.59) n=679	5.05 (4.22 - 5.79) n=121	5.03 (3.90 - 5.45) n=14	4.43 (3.94 - 5.13) n=11	.35
HDL cholesterol - mmol/l	1.42 (1.11 - 1.80) n=590	1.56 (1.24 - 2.01) n=106	1.47 (1.09 - 1.74) n=11	1.56 (1.78 - 2.47) n=10	.02
LDL cholesterol - mmol/l	2.80 (2.05 - 3.44) n=563	2.90 (2.12 - 3.74) n=101	2.86 (2.25 - 4.31) n=10	2.61 (1.69 - 3.34) n=10	.52
ECG on admission - no./total no. (%)					
Sinus rhythm	1186 / 1298 (91.4)	214 / 224 (95.5)	36 / 38 (94.7)	23 / 24 (95.8)	.14
Atrial fibrillation	100 / 1298 (7.7)	9 / 224 (4.0)	2 / 38 (5.3)	1 / 24 (4.2)	.22
Pacemaker rhythm	15 / 1242 (1.2)	1 / 210 (0.5)	0 / 32 (0.0)	0 / 24 (0.0)	.67
AV block (I, II or III)	75 / 1298 (5.8)	9 / 224 (4.0)	0 / 38 (0.0)	1 / 24 (4.2)	.84
ST-segment elevation	593 / 1292 (45.9)	77 / 224 (34.4)	14 / 38 (36.8)	6 / 24 (25.0)	.002
ST-segment depression	90 / 1292 (7.0)	22 / 224 (9.8)	7 / 38 (18.4)	2 / 24 (8.3)	.04
T-wave inversion	548 / 1292 (42.4)	77 / 224 (34.4)	10 / 38 (26.3)	13 / 24 (54.2)	.02
Left bundle branch block	67 / 1292 (5.2)	8 / 224 (3.6)	2 / 38 (5.3)	2 / 24 (8.3)	.66
QTc prolongation	454 / 929 (48.9)	74 / 180 (41.1)	17 / 29 (58.6)	5 / 15 (33.3)	.10
QTc - ms - mean±SD	458.7 ± 50.6 (n=929)	448.9 ± 41.1 (n=180)	477.3 ± 56.9 (n=29)	450.2 ± 50.6 (n=15)	.01
Hemodynamic findings - mean±SD					
Heart rate - beats/min	87.9 ± 21.5 (n=1173)	85.8 ± 22.4 (n=215)	85.1 ± 23.7 (n=36)	86.2 ± 30.6 (n=23)	.54
Systolic blood pressure - mm Hg	130.3 ± 29.1 (n=1168)	131.5 ± 27.4 (n=220)	128.4 ± 25.6 (n=36)	143.5 ± 30.9 (n=24)	.14
Diastolic blood pressure - mm Hg	76.1 ± 17.0 (n=1154)	78.3 ± 17.4 (n=214)	79.3 ± 15.1 (n=35)	82.6 ± 14.5 (n=23)	.07
Left ventricular ejection fraction - %[c]	40.6 ± 12.0 (n=1312)	42.9 ± 10.2 (n=231)	41.9 ± 10.2 (n=32)	50.8 ± 13.6 (n=24)	<.001
Left ventricular end-diastolic pressure - mm Hg	21.5 ± 8.2 (n=841)	20.6 ± 7.2 (n=168)	24.3 ± 8.6 (n=16)	18.5 ± 5.8 (n=16)	.12
Cardiovascular risk factors / history - no./total no. (%)					
Hypertension	924 / 1385 (66.7)	145 / 250 (58.0)	19 / 37 (51.4)	18 / 25 (72.0)	.01
Diabetes mellitus	194 / 1387 (14.0)	36 / 250 (14.4)	7 / 37 (18.9)	5 / 25 (20.0)	.70
Current smoking	260 / 1353 (19.2)	62 / 242 (25.6)	5 / 36 (13.9)	6 / 25 (24.0)	.14
Hypercholesterolemia	435 / 1381 (31.5)	74 / 249 (29.7)	14 / 37 (37.8)	7 / 25 (28.0)	.76
Positive family history	240 / 1233 (19.5)	66 / 228 (28.9)	11 / 35 (31.4)	5 / 25 (20.0)	.005
Coexisting medical condition - no./total no. (%)					
Coronary artery disease [d]	206 / 1307 (15.8)	34 / 232 (14.7)	2 / 35 (5.7)	3 / 23 (13.0)	.42
Cancer (total)	222 / 1301 (17.1)	34 / 243 (14.0)	6 / 35 (17.1)	5 / 25 (20.0)	.66
COPD or asthma	212 / 1359 (15.6)	48 / 249 (19.3)	7 / 37 (18.9)	4 / 25 (16.0)	.51
Hyperthyroidism	84 / 1374 (6.1)	13 / 249 (5.2)	1 / 36 (2.8)	2 / 25 (8.0)	.77
Hypothyroidism	156 / 1374 (11.4)	36 / 249 (14.5)	4 / 36 (11.1)	2 / 25 (8.0)	.51

(Continued)

Neurologic or psychiatric disorders - no./total no. (%) [e]	580 / 1251 (46.4)	114 / 230 (49.6)	10 / 20 (50.0)	10 / 24 (41.7)	.77
Neurologic disorders (total) [e]	286 / 1251 (22.9)	71 / 230 (30.9)	6 / 20 (30.0)	4 / 24 (16.7)	.05
Acute neurologic disorders	110 / 1255 (8.8)	29 / 229 (12.7)	3 / 20 (15.0)	1 / 24 (4.2)	.17
Past or chronic neurologic disorders	229 / 1238 (18.5)	56 / 230 (24.3)	5 / 20 (25.0)	3 / 24 (12.5)	.15
Psychiatric disorders (total) [e]	404 / 1251 (32.3)	71 / 230 (30.9)	8 / 20 (40.0)	9 / 24 (37.5)	.79
Acute psychiatric disorders	132 / 1254 (10.5)	14 / 227 (6.2)	1 / 20 (5.0)	2 / 24 (8.3)	.19
Past or chronic psychiatric disorders	360 / 1238 (29.1)	67 / 230 (29.1)	8 / 20 (40.0)	9 / 24 (37.5)	.59
Medication on admission - no./total no. (%)					
Cardiovascular medication					
ACE inhibitor or ARB	442 / 1141 (38.7)	65 / 211 (30.8)	15 / 32 (46.9)	10 / 21 (47.6)	.08
Beta-blocker	385 / 1141 (33.7)	49 / 211 (23.2)	14 / 32 (43.8)	8 / 21 (38.1)	.01
Calcium-channel antagonist	88 / 1110 (7.9)	11 / 210 (5.2)	0 / 31 (0.0)	3 / 21 (14.3)	.12
Statin	202 / 1110 (18.2)	34 / 210 (16.2)	4 / 31 (12.9)	6 / 21 (28.6)	.45
Aspirin	376 / 1110 (33.9)	57 / 210 (27.1)	17 / 31 (54.8)	9 / 21 (42.9)	.01
ADP receptor inhibitor	102 / 1110 (9.2)	6 / 210 (2.9)	7 / 31 (22.6)	0 / 21 (0.0)	<.001
Coumarin	50 / 1110 (4.5)	10 / 210 (4.8)	0 / 31 (0.0)	1 / 21 (4.8)	.68
Psychiatric medication					
Antidepressant	143 / 1110 (12.9)	26 / 210 (12.4)	3 / 31 (9.7)	3 / 21 (14.3)	.95
Selective serotonine-reuptake inhibitor	84 / 1110 (7.6)	13 / 210 (6.2)	2 / 31 (6.5)	2 / 21 (9.5)	.88
Benzodiazepine	91 / 1110 (8.2)	13 / 210 (6.2)	4 / 31 (12.9)	1 / 21 (4.8)	.51
Neuroleptic	32 / 1110 (2.9)	6 / 210 (2.9)	1 / 31 (3.2)	0 / 21 (0.0)	.88
Medication at discharge - no./total no. (%)					
Cardiovascular medication					
ACE inhibitor or ARB	995 / 1252 (79.5)	178 / 222 (80.2)	22 / 35 (62.9)	20 / 24 (83.3)	.11
Beta-blocker	996 / 1252 (79.6)	154 / 222 (69.4)	30 / 35 (85.7)	17 / 24 (70.8)	.004
Calcium-channel antagonist	109 / 1252 (8.7)	14 / 222 (6.3)	4 / 35 (11.4)	4 / 24 (16.7)	.28
Statin	663 / 1252 (53.0)	93 / 222 (41.9)	19 / 35 (54.3)	11 / 24 (45.8)	.02
Aspirin	853 / 1252 (68.1)	135 / 222 (60.8)	26 / 35 (74.3)	17 / 24 (70.8)	.14
ADP receptor inhibitor	145 / 1252 (11.6)	21 / 222 (9.5)	3 / 35 (8.6)	4 / 24 (16.7)	.62
Coumarin	109 / 1252 (8.7)	15 / 222 (6.8)	1 / 35 (2.9)	1 / 24 (4.2)	.41
Psychiatric medication					
Antidepressant	185 / 1252 (14.8)	31 / 222 (14.0)	4 / 35 (11.4)	4 / 24 (16.7)	.93
Selective serotonine-reuptake inhibitor	109 / 1252 (8.7)	14 / 222 (6.3)	3 / 35 (8.6)	3 / 24 (12.5)	.59
Benzodiazepine	132 / 1252 (10.5)	21 / 222 (9.5)	6 / 35 (17.1)	1 / 24 (4.2)	.40
Neuroleptic	45 / 1252 (3.6)	6 / 222 (2.7)	1 / 35 (2.9)	1 / 24 (4.2)	.91
In-hospital complications - no./total no. (%)					
Cardiogenic shock	147 / 1404 (10.5)	19 / 250 (7.6)	4 / 37 (10.8)	0 / 25 (0.0)	.19
Ventricular thrombus	22 / 1404 (1.6)	1 / 250 (0.4)	0 / 37 (0.0)	0 / 25 (0.0)	.38
Ventricular tachycardia	42 / 1404 (3.0)	9 / 250 (3.6)	1 / 37 (2.7)	0 / 25 (0.0)	.78
Ventricle and / or septum rupture	3 / 1404 (0.2)	0 / 250 (0.0)	0 / 37 (0.0)	0 / 25 (0.0)	.88
Death	62 / 1430 (4.3)	8 / 255 (3.1)	2 / 39 (5.1)	0 / 26 (0.0)	.57
Acute cardiac care treatment - no./total no. (%)	285 / 1421 (20.1)	60 / 252 (23.8)	12 / 37 (32.4)	3 / 25 (12.0)	.11
Intra-aortic balloon pump	38 / 1421 (2.7)	6 / 252 (2.4)	1 / 37 (2.7)	0 / 25 (0.0)	.86
Invasive or noninvasive ventilation	241 / 1421 (17.0)	48 / 252 (19.0)	9 / 37 (24.3)	3 / 25 (12.0)	.49
Cardiopulmonary resuscitation	128 / 1421 (9.0)	17 / 252 (6.7)	4 / 37 (10.8)	0 / 25 (0.0)	.26
Catecholamine use	177 / 1421 (12.5)	31 / 252 (12.3)	4 / 37 (10.8)	0 / 25 (0.0)	.31
Long-term outcome - rate per patient-year					
MACCE [f]	10.0%	10.1%	8.0%	2.2%	.46
Death	6.0%	4.5%	3.1%	0	.14

Abbreviations: ACE, angiotensin-converting-enzyme; ADP, adenosine diphosphate; ARB, angiotensin-receptor blocker; AV block, atrioventricular block; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRP, c-reactive protein; ECG, electrocardiogram; HDL, high density lipoprotein; IQR, interquartile range; LDL, low density lipoprotein; MACCE, major adverse cardiac and cerebrovascular events; QTc, QT interval corrected for heart rate; SD, standard deviation; TTS, takotsubo syndrome; ULN, upper limit of the normal; WBC, white blood cell count.
Data are presented as no./total no. (%), mean+SD, or median (interquartile range).

[a] Including upper limits of the normal range for troponin T, high-sensitivity troponin T, and troponin I.

[b] Including upper limits of the normal range for brain natriuretic peptide and the N-terminal of prohormone brain natriuretic peptide.

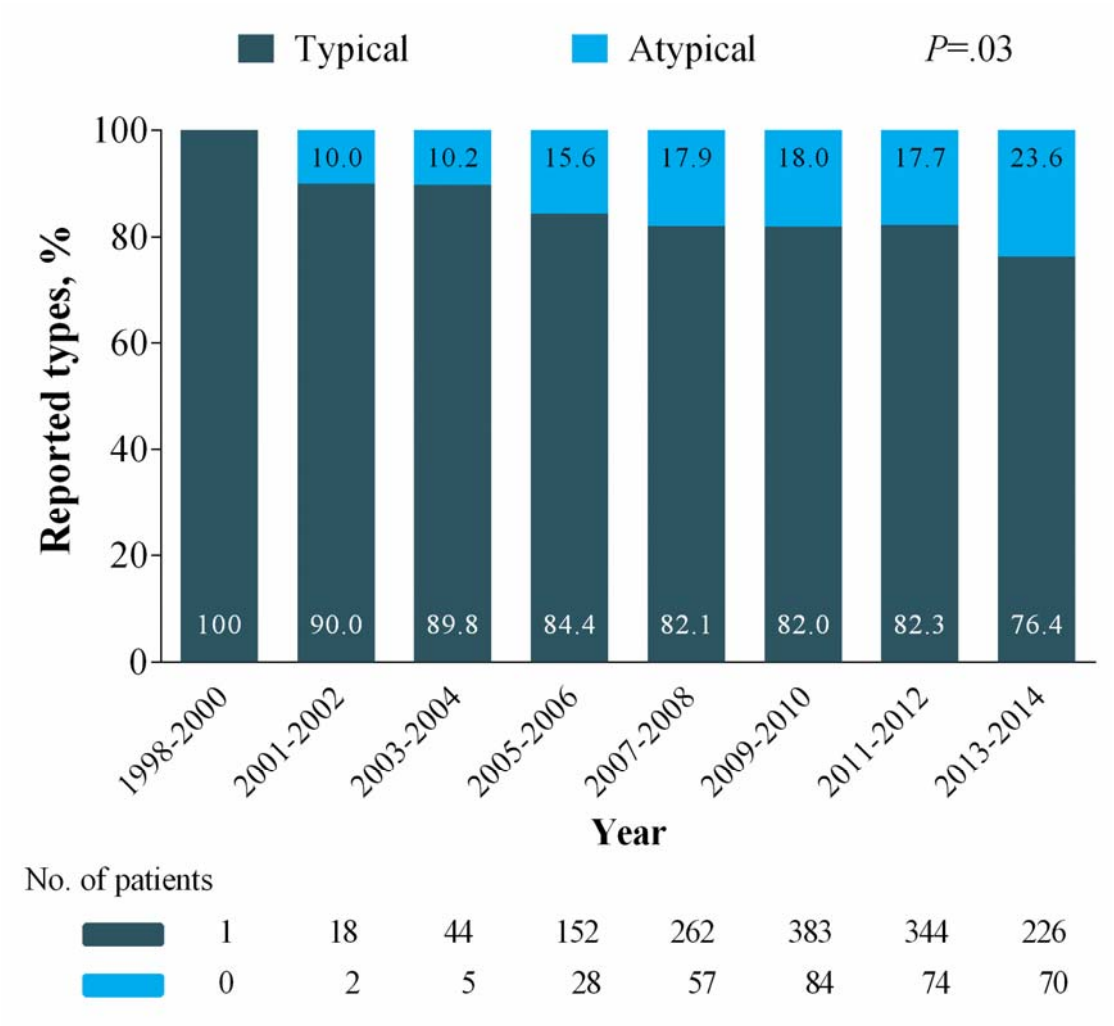
[c] Data obtained during catheterization or echocardiography; if both results were available data from catheterization were used.

[d] Coexisting coronary artery disease during acute hospitalization.

[e] Category includes patients with either an acute as well as past or chronic disorder.

[f] Composite of death from any cause, takotsubo syndrome recurrence, stroke or transient ischemic attack, or myocardial infarction.

eFigure 1. Temporal Trends of Typical and Atypical TTS



Distribution of typical and atypical takotsubo syndrome (TTS) forms during 1998-2014 demonstrating increased reporting of atypical takotsubo types (*P*=.03).

eTable 2. Full Characteristics of Patients, Typical vs Atypical TTS

Characteristic	Characteristics of Patients Typical TTS (n=1430)	Atypical TTS (n=320)	P Value
Demographics			
Female sex - no./total no. (%)	1284 / 1430 (89.8)	287 / 320 (89.7)	.96
Age - yr - mean±SD	67.3 ± 12.9 (n=1430)	62.5 ± 13.3 (n=320)	<.001
Body mass index - kg/m² - mean±SD	25.1 ± 5.3 (n=1092)	24.9 ± 5.4 (n=248)	.57
Triggers - no./total no. (%)			
Physical	509 / 1430 (35.6)	121 / 320 (37.8)	.46
Emotional	384 / 1430 (26.9)	101 / 320 (31.6)	.09
Both emotional and physical	111 / 1430 (7.8)	26 / 320 (8.1)	.83
No evident	426 / 1430 (29.8)	72 / 320 (22.5)	.009
Symptoms on admission - no./total no. (%)			
Chest pain	1014 / 1325 (76.5)	215 / 294 (73.1)	.22
Dyspnea	623 / 1320 (47.2)	137 / 300 (45.7)	.63
Syncope	104 / 1317 (7.9)	20 / 300 (6.7)	.47
Cardiac biomarkers - median (IQR)			
Troponin on admission - factor increase in ULN [a]	8.00 (2.21 - 24.93) n=1151	7.17 (2.28 - 20.98) n=260	.31
Troponin maximum - factor increase in ULN [a]	14.00 (4.60 - 42.54) n=1160	11.48 (5.00 - 34.00) n=263	.18
Creatine kinase on admission - factor increase in ULN	0.86 (0.51 - 1.52) n=990	0.84 (0.54 - 1.27) n=203	.44
Creatine kinase maximum - factor increase in ULN	1.11 (0.61 - 2.08) n=1008	1.03 (0.65 - 1.75) n=211	.70
BNP on admission - factor increase in ULN [b]	6.59 (2.25 - 16.63) n=363	4.18 (1.31 - 12.07) n=87	.02
BNP maximum - factor increase in ULN [b]	9.34 (3.72 - 22.54) n=464	9.86 (4.00 - 23.07) n=114	.90
Inflammatory markers - median (IQR)			
CRP on admission - mg/l	4.20 (1.46 - 13.55) n=916	3.00 (1.03 - 8.98) n=212	.02
CRP maximum - mg/l	9.10 (2.98 - 40.00) n=966	7.00 (2.56 - 26.75) n=220	.10
WBC on admission - 10^3/µl	9.72 (7.40 - 12.70) n=1197	9.84 (7.61 - 13.00) n=268	.75
WBC maximum - 10^3/µl	10.60 (8.11 - 13.80) n=1214	10.40 (8.01 - 13.95) n=274	.82
Electrolytes - median (IQR)			
Sodium on admission - mmol/l	138.00 (136.00 - 141.00) n=1219	139.00 (136.00 - 141.00) n=273	.63
Sodium maximum - mmol/l	140.00 (138.00 - 142.00) n=1227	140.00 (138.00 - 142.75) n=277	.10
Potassium on admission - mmol/l	3.90 (3.60 - 4.30) n=1217	4.00 (3.60 - 4.30) n=274	.66
Potassium maximum - mmol/l	4.20 (3.89 - 4.50) n=1229	4.11 (3.90 - 4.50) n=277	.66
Lipid status - median (IQR)			
Triglyceride - mmol/l	1.15 (0.83 - 1.66) n=684	1.03 (0.75 - 1.47) n=147	.02
Cholesterol - mmol/l	4.87 (4.00 - 5.59) n=679	4.97 (4.18 - 5.71) n=146	.23
HDL cholesterol - mmol/l	1.42 (1.11 - 1.80) n=590	1.55 (1.22 - 2.00) n=127	.003
LDL cholesterol - mmol/l	2.80 (2.05 - 3.44) n=563	2.90 (2.11 - 3.70) n=121	.33
ECG on admission - no./total no. (%)			
Sinus rhythm	1186 / 1298 (91.4)	273 / 286 (95.5)	.02
Atrial fibrillation	100 / 1298 (7.7)	12 / 286 (4.2)	.04
Pacemaker rhythm	15 / 1242 (1.2)	1 / 266 (0.4)	.33 [g]
AV block (I, II or III)	75 / 1298 (5.8)	10 / 286 (3.5)	.12
ST-segment elevation	593 / 1292 (45.9)	97 / 286 (33.9)	<.001
ST-segment depression	90 / 1292 (7.0)	31 / 286 (10.8)	.03
T-wave inversion	548 / 1292 (42.4)	100 / 286 (35.0)	.02
Left bundle branch block	67 / 1292 (5.2)	12 / 286 (4.2)	.49
QTc prolongation	454 / 929 (48.9)	96 / 224 (42.9)	.11
QTc - ms - mean±SD	458.7 ± 50.6 (n=929)	452.7 ± 44.9 (n=224)	.08
Hemodynamic findings - mean±SD			
Heart rate - beats/min	87.9 ± 21.5 (n=1173)	85.8 ± 23.3 (n=274)	.15
Systolic blood pressure - mm Hg	130.3 ± 29.1 (n=1168)	132.1 ± 27.6 (n=280)	.33
Diastolic blood pressure - mm Hg	76.1 ± 17.0 (n=1154)	78.8 ± 16.8 (n=272)	.02
Left ventricular ejection fraction - % [c]	40.6 ± 12.0 (n=1312)	43.4 ± 10.7 (n=287)	<.001
Left ventricular end-diastolic pressure - mm Hg	21.5 ± 8.2 (n=841)	20.8 ± 7.3 (n=200)	.24
Cardiovascular risk factors / history - no./total no. (%)			
Hypertension	924 / 1385 (66.7)	182 / 312 (58.3)	.005
Diabetes mellitus	194 / 1387 (14.0)	48 / 312 (15.4)	.52
Current smoking	260 / 1353 (19.2)	73 / 303 (24.1)	.06
Hypercholesterolemia	435 / 1381 (31.5)	95 / 311 (30.5)	.74
Positive family history	240 / 1233 (19.5)	82 / 288 (28.5)	.001
Coexisting medical condition - no./total no. (%)			
Coronary artery disease [d]	206 / 1307 (15.8)	39 / 290 (13.4)	.32
Cancer (total)	222 / 1301 (17.1)	45 / 303 (14.9)	.35
COPD or asthma	212 / 1359 (15.6)	59 / 311 (19.0)	.15
Hyperthyroidism	84 / 1374 (6.1)	16 / 310 (5.2)	.52
Hypothyroidism	156 / 1374 (11.4)	42 / 310 (13.5)	.28

	(Continued)		
Neurologic or psychiatric disorders - no./total no. (%) [e]	580 / 1251 (46.4)	134 / 274 (48.9)	.45
Neurologic disorders (total) [e]	286 / 1251 (22.9)	81 / 274 (29.6)	.02
Acute neurologic disorders	110 / 1255 (8.8)	33 / 273 (12.1)	.09
Past or chronic neurologic disorders	229 / 1238 (18.5)	64 / 274 (23.4)	.07
Psychiatric disorders (total) [e]	404 / 1251 (32.3)	88 / 274 (32.1)	.96
Acute psychiatric disorders	132 / 1254 (10.5)	17 / 271 (6.3)	.03
Past or chronic psychiatric disorders	360 / 1238 (29.1)	84 / 274 (30.7)	.60
Medication on admission - no./total no. (%)			
Cardiovascular medication			
ACE inhibitor or ARB	442 / 1141 (38.7)	90 / 264 (34.1)	.16
Beta-blocker	385 / 1141 (33.7)	71 / 264 (26.9)	.03
Calcium-channel antagonist	88 / 1110 (7.9)	14 / 262 (5.3)	.15
Statin	202 / 1110 (18.2)	44 / 262 (16.8)	.59
Aspirin	376 / 1110 (33.9)	83 / 262 (31.7)	.50
ADP receptor inhibitor	102 / 1110 (9.2)	13 / 262 (5.0)	.03
Coumarin	50 / 1110 (4.5)	11 / 262 (4.2)	.83
Psychiatric medication			
Antidepressant	143 / 1110 (12.9)	32 / 262 (12.2)	.77
Selective serotonine-reuptake inhibitor	84 / 1110 (7.6)	17 / 262 (6.5)	.55
Benzodiazepine	91 / 1110 (8.2)	18 / 262 (6.9)	.48
Neuroleptic	32 / 1110 (2.9)	7 / 262 (2.7)	.85
Medication at discharge - no./total no. (%)			
Cardiovascular medication			
ACE inhibitor or ARB	995 / 1252 (79.5)	220 / 281 (78.3)	.66
Beta-blocker	996 / 1252 (79.6)	201 / 281 (71.5)	.003
Calcium-channel antagonist	109 / 1252 (8.7)	22 / 281 (7.8)	.64
Statin	663 / 1252 (53.0)	123 / 281 (43.8)	.005
Aspirin	853 / 1252 (68.1)	178 / 281 (63.3)	.12
ADP receptor inhibitor	145 / 1252 (11.6)	28 / 281 (10.0)	.44
Coumarin	109 / 1252 (8.7)	17 / 281 (6.0)	.14
Psychiatric medication			
Antidepressant	185 / 1252 (14.8)	39 / 281 (13.9)	.70
Selective serotonine-reuptake inhibitor	109 / 1252 (8.7)	20 / 281 (7.1)	.39
Benzodiazepine	132 / 1252 (10.5)	28 / 281 (10.0)	.77
Neuroleptic	45 / 1252 (3.6)	8 / 281 (2.8)	.54
In-hospital complications - no./total no. (%)			
Cardiogenic shock	147 / 1404 (10.5)	23 / 312 (7.4)	.10
Ventricular thrombus	22 / 1404 (1.6)	1 / 312 (0.3)	.10 [g]
Ventricular tachycardia	42 / 1404 (3.0)	10 / 312 (3.2)	.84
Ventricle and / or septum rupture	3 / 1404 (0.2)	0 / 312 (0.0)	1.0 [g]
Death	62 / 1430 (4.3)	10 / 320 (3.1)	.32
Acute cardiac care - no./total no. (%)	285 / 1421 (20.1)	75 / 341 (23.9)	.13
Intra-aortic balloon pump	38 / 1421 (2.7)	7 / 314 (2.2)	.65
Cardiopulmonary resuscitation	128 / 1421 (9.0)	21 / 314 (6.7)	.18
Invasive or noninvasive ventilation	241 / 1421 (17.0)	60 / 314 (19.1)	.36
Catecholamine use	177 / 1421 (12.5)	35 / 314 (11.1)	.52
Long-term outcome - rate per patient-year			
MACCE [f]	10.0%	9.2%	.42
Death	6.0%	3.9%	.05

Abbreviations: ACE, angiotensin-converting-enzyme; ADP, adenosine diphosphate; ARB, angiotensin-receptor blocker; AV block, atrioventricular block; BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRP, c-reactive protein; ECG, electrocardiogram; HDL, high density lipoprotein; IQR, interquartile range; LDL, low density lipoprotein; MACCE, major adverse cardiac and cerebrovascular events; QTc, QT interval corrected for heart rate; SD, standard deviation; TTS takotsubo syndrome, ULN, upper limit of the normal; WBC, white blood cell count.

Data are presented as no./total no. (%), mean+SD, or median (interquartile range).

[a] Including upper limits of the normal range for troponin T, high-sensitivity troponin T, and troponin I.

[b] Including upper limits of the normal range for brain natriuretic peptide and the N-terminal of prohormone brain natriuretic peptide.

[c] Data obtained during catheterization or echocardiography; if both results were available data from catheterization were used.

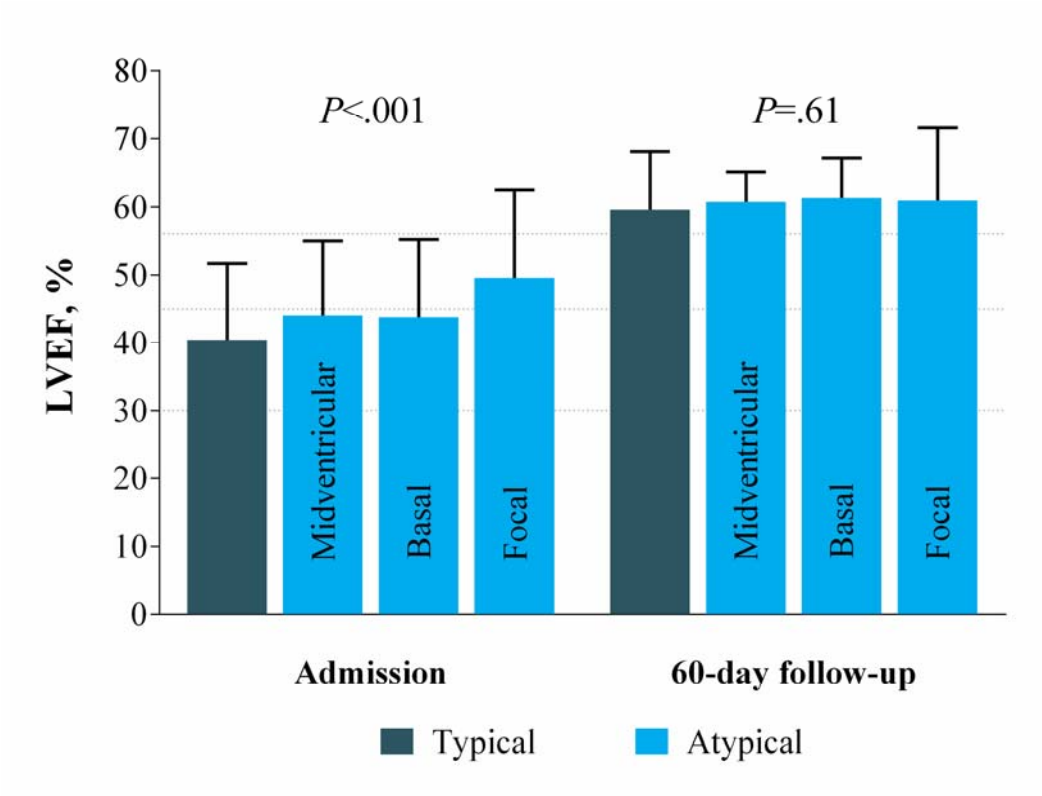
[d] Coexisting coronary artery disease during acute hospitalization.

[e] Category includes patients with either an acute as well as past or chronic disorder.

[f] Composite of death from any cause, takotsubo syndrome recurrence, stroke or transient ischemic attack, or myocardial infarction.

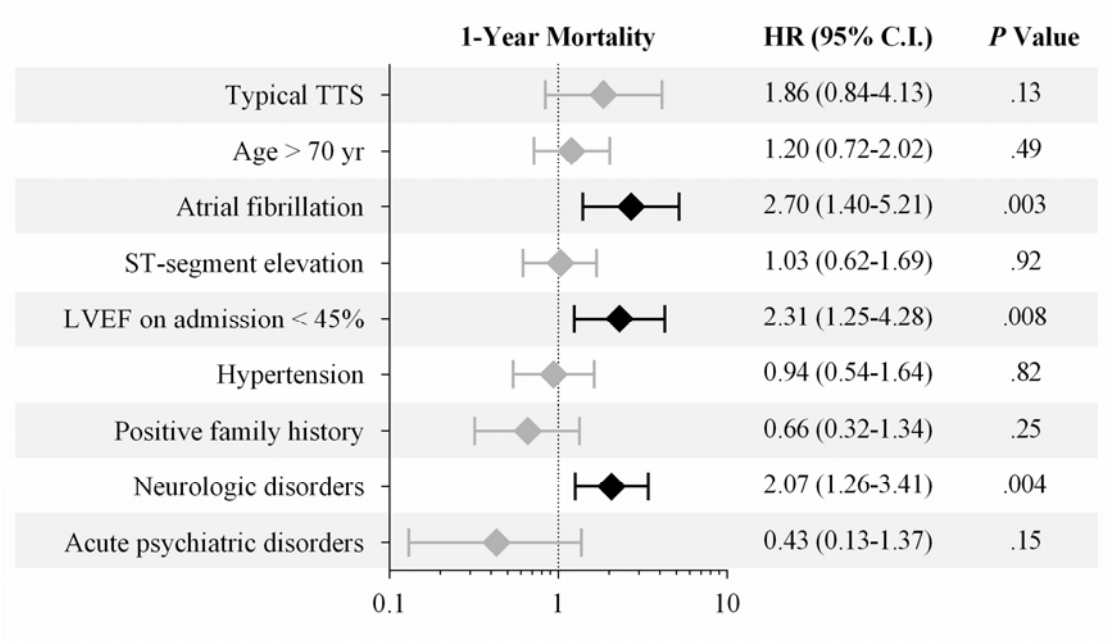
[g] Fisher's exact test.

eFigure 2. Recovery of Left Ventricular Ejection Fraction Over Time



Systolic left ventricular function on admission (n=1179) and after 60-day follow-up (n=290) in the four different takotsubo syndrome (TTS) types measured with echocardiography. Mean left ventricular ejection fraction (LVEF) in typical TTS increased from 40.5% (admission, left) to 59.6% (60-day follow-up, right). Mean LVEF in midventricular TTS increased from 43.8% (admission, left) to 61.3% (60-day follow-up, right). Mean LVEF in basal TTS increased from 44.0% (admission, left) to 60.8% (60-day follow-up, right). Mean LVEF in focal TTS increased from 49.5% (admission, left) to 61.0% (60-day follow-up, right). Error bars indicate standard deviation.

eFigure 3. Predictors of Mortality



Multiple Cox-regression to adjust for potential confounders revealed that not the TTS type but atrial fibrillation, LVEF less than 45% and neurologic disorders were independent predictors of mortality during the first year. Grey: non-significant, black: statistically significant. Error bars indicate 95% confidence interval.
Abbreviations: C.I., confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; TTS, takotsubo syndrome.

References

1. Templin C, Ghadri JR, Diekmann J, et al. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. *N Engl J Med.* Sep 3 2015;373(10):929-938.
2. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J.* Mar 2008;155(3):408-417.