OBSERVATIONS: BRIEF RESEARCH REPORTS

Morbidity After Takotsubo Syndrome: A Report From the Scottish Takotsubo Registry

Background: Takotsubo syndrome is characterized by transient left ventricular dysfunction, often precipitated by intense emotional or physical stress. Although its clinical presentation is like that of acute myocardial infarction, there is no culprit or obstructive coronary artery disease on coronary angiography. After the acute phase, the left ventricular ejection fraction fully recovers (1). Despite this, several registries have reported reduced long-term survival after an episode of acute takotsubo syndrome (2–4). The Scottish Takotsubo Registry showed this reduced long-term survival to be specifically attributable to cardiovascular mortality (4). However, the extent and causes of subsequent illness after recovery from an episode of takotsubo syndrome are unknown.

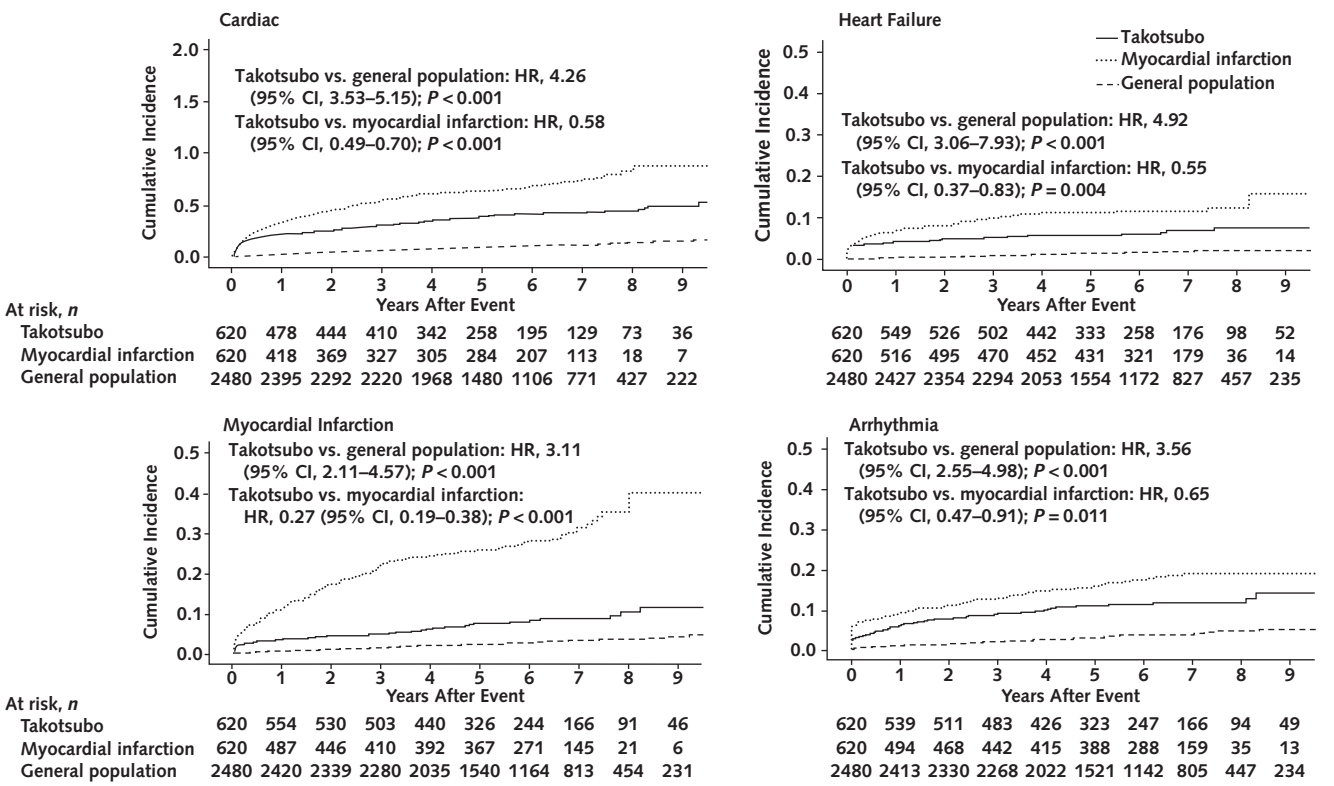
Objective: To explore the incidence and causes of all subsequent hospital readmissions affecting patients with takotsubo syndrome.

Methods: The Scottish Takotsubo Registry records all (unselected) cases of patients with takotsubo syndrome diagnosed in Scotland from 1 January 2010 (ClinicalTrials.gov: NCT03299569). This cohort study reports on patients diagnosed until 31 December 2017 and followed until death or 31 May 2021, whichever was earliest. Nearest-neighbor matching was used to select control participants matched on age, sex, and geographic location (1:4; $n = 2480$) from the Scottish general population and patients with acute myocardial infarction (1:1; $n = 620$) from the population of the High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome) trial (ClinicalTrials.gov: NCT01852123) (4, 5).

Demographic and clinical characteristics of the current cohort were previously published (4, 5). Electronic data linkage connected the unique Community Health Index number of each participant with the Public Health Scotland national database using International Classification of Diseases, 10th Revision, diagnosis codes and included all hospital admission episodes.

Hazard ratios with 95% CIs were estimated from Cox proportional hazards regression models, with deaths from unrelated causes considered competing events. Groups were compared using Kaplan–Meier cumulative event curves. Analyses were done for the total follow-up period and time scaled as years after the index event. Patterns were similar when Fine–Gray models were used as a sensitivity analysis.

Figure. Cardiac causes of hospital readmission in patients with takotsubo syndrome compared with control participants from the general population and patients with myocardial infarction.



Cumulative incidence curves of the main cardiovascular causes leading to hospital readmission in patients with takotsubo syndrome (*solid lines*) compared with patients with myocardial infarction (*dotted lines*) and the general Scottish population (*dashed lines*). Relative excess was calculated, and data are displayed as HRs with 95% CIs. HR = hazard ratio.

Table. Noncardiac Hospitalizations in Patients With Takotsubo Syndrome Relative to General Population Control Participants and Patients With Myocardial Infarction*

Cause of Hospitalization	Incidence Rate per 1000 Person-Years			Hazard Ratio (95% CI)	
	Takotsubo Syndrome ($n = 620$)	General Population ($n = 2480$)	Myocardial Infarction ($n = 620$)	Takotsubo Syndrome ($n = 620$) vs. General Population ($n = 2480$)	Takotsubo Syndrome ($n = 620$) vs. Myocardial Infarction ($n = 620$)
Attempted suicide and mental health	15.89	2.97	13.50	3.74 (2.35–5.94)	1.56 (0.90–2.70)
Pulmonary	59.44	12.84	36.91	3.49 (2.61–4.66)	1.32 (0.95–1.84)
Neurovascular	9.42	5.00	12.30	1.97 (1.32–2.93)	0.87 (0.55–1.37)
Stroke†	8.24†	3.92†	11.40†	1.88 (1.16–3.03)	0.70 (0.41–1.18)
Neurologic	34.72	4.32	21.60	1.92 (1.21–3.05)	1.04 (0.60–1.80)
Infective	49.14	21.35	57.61	1.77 (1.41–2.22)	0.75 (0.58–0.97)
Diabetes and endocrine	5.89	1.69	5.10	1.77 (0.73–4.27)	0.30 (0.13–0.70)
Peripheral vascular diseases	5.59	2.84	12.30	1.74 (1.01–3.01)	0.64 (0.35–1.16)
Natural causes/accidents	30.02	20.20	20.00	1.49 (1.16–1.91)	1.28 (0.92–1.77)
Gastrointestinal	58.56	40.13	54.61	1.46 (1.19–1.80)	1.34 (1.02–1.77)
Renal	26.19	16.21	40.51	1.39 (1.03–1.89)	0.58 (0.41–0.81)
Cancer	63.56	68.91	41.71	1.24 (0.95–1.62)	1.09 (0.77–1.54)
Inflammatory	15.30	11.21	11.10	1.21 (0.82–1.76)	0.92 (0.58–1.47)
Dementia and Alzheimer disease	1.47	1.28	1.50	0.86 (0.45–1.64)	0.91 (0.40–2.06)

* Data are presented for relative excess.
† Incidence rates represent first subsequent admission due to stroke.

Results: Of the total 12 873 hospitalizations, the incidence rate of hospital readmissions was 743 per 1000 person-years for patients with takotsubo syndrome, 365 per 1000 person-years for control participants from the general Scottish population, and 750 per 1000 person-years for patients with myocardial infarction.

Compared with the general population, patients with takotsubo syndrome were twice as likely to be hospitalized for any cause (hazard ratio, 1.96 [95% CI, 1.78 to 2.17]; $P < 0.001$) and especially for cardiovascular causes, such as myocardial infarction, heart failure, or arrhythmia (**Figure**). Patients with takotsubo syndrome and incident coronary artery disease (11%) were at similar risk for being admitted for cardiovascular causes compared with those with normal coronary arteries (hazard ratio, 1.32 [CI, 0.88 to 1.98]; $P = 0.180$). There were also excess admissions for mental health, stroke, pulmonary, neurologic, infectious, gastrointestinal, and peripheral vascular disease causes (**Table**).

Compared with patients with myocardial infarction, patients with takotsubo syndrome had lower admissions for myocardial infarction, heart failure, and arrhythmia (**Figure**) but similar admissions for stroke and mental health (**Table**).

Discussion: We show that patients with takotsubo syndrome have double the risk for rehospitalization after their index presentation compared with the general population, a risk similar to that observed in patients with acute myocardial infarction. Patients with takotsubo syndrome are particularly susceptible to hospitalization from cardiac, mental health, pulmonary, stroke, neurologic, and infective conditions. Compared with patients with myocardial infarction, patients with takotsubo syndrome are less likely to present with myocardial infarction, heart failure, or arrythmia but equally likely to be admitted with stroke or noncardiovascular causes, including mental health, pulmonary, cancer, and neurologic conditions. The stroke risk in patients with takotsubo syndrome has been assigned to the development of left ventricular thrombus during the acute phase, but in the longer term, atrial arrythmias are likely to contribute.

We previously reported similar rates of medication prescribing (both cardiovascular and noncardiovascular therapies) in this cohort of patients with takotsubo syndrome or myocardial infarction (4). However, despite a similar risk profile and receipt of similar medication, we have shown here that substantial subsequent morbidity remains after takotsubo syndrome. This highlights these patients' increased vulnerability and a need for better discharge advice, clinical follow-up, and a focused search for therapeutic strategies directed to the specific pathophysiology of this condition. Further studies are required to understand the overlap and differences between takotsubo syndrome and other cardiac conditions and cardiomyopathies.

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Reproducible Research Statement: *Study protocol:* Available from Ms. Rudd (e-mail, a.e.rudd@abdn.ac.uk). *Statistical code:* Available from Dr. Horgan (e-mail, g.horgan@abdn.ac.uk). *Data set:* Available from Public Health Scotland (e-mail, phs.edris@phs.scot).

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