BMJ Open

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| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2018-027814 |
| Article Type: | Research |
| Date Submitted by the Author: | 08-Nov-2018 |
| Complete List of Authors: | Wallström, Sara; Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg; University of Gothenburg Centre for Person-Centred Care, Sahlgrenska Academy, University of Gothenburg<br>Ekman, Inger; Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg; University of Gothenburg Centre for Person-Centred Care, Sahlgrenska Academy, University of Gothenburg<br>Omerovic, Elmir; Department of Cardiology, Sahlgrenska University Hospital; Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg<br>Ulin, Kerstin; Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg; University of Gothenburg Centre for Person-Centred Care, Sahlgrenska Academy, University of Gothenburg<br>Gyllensten, Hanna ; Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg; University of Gothenburg Centre for Person-Centred Care , Sahlgrenska Academy, University of Gothenburg |
| Keywords: | CARDIOLOGY, HEALTH ECONOMICS, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adult cardiology < CARDIOLOGY, Heart failure < CARDIOLOGY, Cardiomyopathy < CARDIOLOGY |
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# A cohort study of health care use, costs and diagnoses from onset to 6 months after discharge for takotsubo syndrome in Sweden

Sara Wallström[1,2], Inger Ekman[1,2], Elmir Omerovic[3], Kerstin Ulin[1,2], Hanna Gyllensten[1,2]

[1]Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Box 457, 405 30 Gothenburg, Sweden

[2]University of Gothenburg Centre for Person-Centred Care (GPCC), Sahlgrenska Academy, University of Gothenburg, Box 457, 405 30 Gothenburg, Sweden

[3]Department of Cardiology, Sahlgrenska University Hospital, 413 45 Gothenburg, Sweden
Department of Molecular and Clinical Medicine, The Wallenberg Laboratory, Sahlgrenska Academy, University of Gothenburg, 413 45 Gothenburg, Sweden

Corresponding author: Sara Wallström, Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Box 457, 405 30 Gothenburg, Sweden
Telephone: +46(0)31-786 60 79. Fax: +46(0)31-786 60 50
E-mail: sara.wallstrom@gu.se

**Word count:** 3684

# ABSTRACT

**Objective:** Little is known about the economic impact of takotsubo syndrome (TS) in patients after their initial discharge from hospital. Therefore, this study aimed to describe the use of health care resources and calculate direct health care costs for TS from hospitalisation to 6 months after discharge. We also explored the distribution of costs between TS and other diagnoses in patients with TS.

**Method, participants and setting:** Cohort study investigating direct health care costs from hospitalisation, specialised outpatient care and primary care. Information on use of care resources during 6 months after diagnosis of TS was collected for 58 consecutive patients from the Regional Patient Register. Incidence-based direct health care costs, in 2015 values, were calculated using diagnosis-related group weights and unit costs from national statistics on health care costs.

**Results:** The mean length of hospital stay was 10.2 days, index 6.4 days and readmissions 3.8 days. The mean number of follow-up encounters per patient was 15.6, of which two thirds were specialised outpatient care and one third primary care, resulting in an average cost of EUR 10,360. Of this cost, costs of EUR 8,026 (77.5%) occurred during encounters for which at least one of the registered conditions was cardiovascular. Costs differed little according to background characteristics.

**Conclusion:** This study shows that patients use hospital care, specialised outpatient care and primary care after discharge for TS. Most direct health care costs relate to cardiac diagnoses. Patients with TS would likely benefit from a supportive follow-up programme after discharge from hospital.



# KEY WORDS

- CARDIOLOGY
- HEALTH ECONOMICS
- Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT
- Adult cardiology < CARDIOLOGY
- Heart failure < CARDIOLOGY

## STRENGTHS AND LIMITATIONS

- This study explores an under-investigated area, namely cost of illness and health economics in patients with takotsubo syndrome.
- Register offered the opportunity to investigate direct health care costs from inpatient, specialised outpatient care and primary care.
- This study provides insight on the distribution of costs in patients with takotsubo syndrome.
- Limitations include a small sample size and that the data were limited to direct health care costs.

# INTRODUCTION

Takotsubo syndrome (TS) is an acute reversible heart failure that usually recovers spontaneously in 12 weeks from time of onset. Its clinical presentation at onset has similar features to those of an acute myocardial infarction (AMI) with chest pain, dyspnoea, ECG changes and raised markers of myocardial necrosis.[1 2] TS is characterised by regional wall motion abnormalities affecting one or both ventricles of the heart and absence of flow-limiting lesions in coronary arteries. The pathophysiological mechanisms underlying TS are not fully understood, but a surge of the hormone catecholamines is believed to play a vital role. Onset is often preceded by a stressful event, either psychological or physical.[2]

TS is most common in postmenopausal women: 84–91% of cases are female and the mean age varies between 63 and 76 years.[3-5] Knowledge about potential risk factors is scarce, but smoking, hyperlipidemia, alcohol abuse and anxiety have been acknowledged.[6] Because of a lack of diagnosis uniformity, it has been difficult to determine the exact number of TS cases per annum; however, estimates suggest that there are 50–100,000 cases per year in the USA and a similar number in Europe.[2] There are no reliable figures for Sweden, but an estimation based on the population would be 1,500–3,000 cases per annum in Sweden. This figure is in accordance with the estimation of 2,000 cases per annum in Sweden from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR).[7]

TS was previously assumed to be relatively benign and have little impact on long-term survival. However, recent studies have shown that TS affects both short- and long-term survival, which is comparable to, or worse than, survival in patients affected by AMI.[4 8] Mortality from cardiovascular causes is comparable between these groups, but the excess mortality in patients with TS is related to noncardiovascular or unknown causes. Male sex, Killip class III or IV at admission according to classification for heart failure and diabetes mellitus increase the likelihood of mortality in patients with TS.[8]

There are currently few guidelines for care or follow-up for patients with TS. At hospital, investigations often include coronary angiography, ultra-cardiogram and cardiac biomarkers. Treatment is primarily aimed at supportive care to sustain life and minimise complications during the recovery of normal cardiac function. At least one follow-up visit is arranged with a specialist after discharge from hospital to review medication and confirm recovery of cardiac function.[2] Little is known of health care resources used for this follow-up. To our knowledge, there are only two published studies examining costs after TS, both conducted in the same American setting. These studies calculated the average cost of hospital stay for patients with TS to USD 16,723 in 2007–2011[9] and the total average charges to USD 61,034 in 2006–2010 for TS patients without arrhythmias[10] (concurrent arrhythmias may increase the average inpatient charge by USD 11,334[10]).

Apparently, there are no studies on the use of health care resources for TS from Europe, a healthcare system that, in many aspects, is different from that in the US. In addition, little is known about the economic impact of TS for patients and for the healthcare system after initial discharge from hospital. Such studies, often called cost of illness (COI) studies, describe the economic burden of disease on society. They are useful to compare the burden of a disease on the healthcare system, compare TS to other diseases and to identify important costs and variation in costs in the treatment of a specific disease (such as TS).[11] Therefore, the primary aim of this study was to describe the use of health care resources and calculate direct health care costs for TS from hospitalisation to 6 months after discharge. A secondary aim was to explore the distribution of costs between TS and other diagnoses in patients with TS.

# METHODS

## Study population and settings

Patients from two hospitals in a city in western Sweden were included consecutively from January 2012 to October 2015. There is no specific code in the Swedish version of the ICD International

Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10). Consequently, all coronary angiography records from the participating hospitals were screened to identify patients with TS. Patients were included after identification with coronary angiography and confirmation of the diagnosis by a cardiologist. The inclusion criteria were (1) having a diagnosis of TS, (2) speaking and reading Swedish, (3) having a predicted survival of more than 6 months and (4) living in the Västra Götaland region. In total, 110 patients with TS were identified during the study period; of those, 29 declined participation, 10 had a predicted survival of <6 months, 5 did not speak Swedish or were otherwise unable to fill out the questionnaires, 2 participated in another incompatible research study, 2 died and 4 accepted participation but were excluded because they did not live in the region of Västra Götaland and were thus not included in the Regional Patient Register (VEGA). The remaining 58 (53%) patients with TS were included in the study.

## Data collection

Clinical information about the disease and potential risk factors (e.g., history of cardiovascular disease, nicotine use, Killip class and hypertension) were retrieved from medical records during the initial hospital stay. Data on socioeconomic factors were collected from each participant using a questionnaire. Register data about the consumption of health care resources and its cost were obtained from the Regional Patient Register (VEGA), which contains information about all inpatient care, specialised outpatient care and primary care in the Västra Götaland region. The VEGA database has near full coverage of care used by the residents of the region.[12 13] Costs for medications and health care services provided by the municipalities were not included. Patient information retrieved covered the period from the day patients were admitted to hospital for TS and the following 6 months. Health care encounters were classified based on the main diagnosis registered (according to the ICD-10 guidelines) as chapters A-Z and using a more detailed level for categorising disorders within chapter I (Circulatory system disorders).

Incidence-based direct health care costs were calculated for consecutive patients, including costs for use of health care resources during a 6-month period starting at diagnosis of TS for each patient. Both all-cause costs and costs for resource use, for which cardiovascular causes were the main diagnosis, were calculated. Calculations were made based on the economic perspective of the healthcare sector (in 2015 values). Costs for specialised health care were calculated using diagnosis-related group (DRG) weights retrieved from VEGA.[14] Costs calculated from DRG weights were updated to 2015 values using the Swedish healthcare inflation index, which is a price index for the counties.[15] Primary care encounters were assigned unit costs based on national statistics for health care use and costs.[16] As per national statistics, the cost for primary care physician visits was SEK 1,397 (EUR 149) in 2014; this cost was updated to the 2015 values using the Swedish healthcare inflation index. A visit to other health care personnel was weighted as 40% of the cost of a physician visit; phone calls were weighted as one-third of the cost of a visit; and home health care as twice the cost of a visit.[16] Length of stay in hospital is recorded for each hospital in the registry and therefore transfers between hospitals are registered as readmissions. Indirect costs resulting from lost productivity and intangible costs related to harm and suffering were not included in the analyses.

For two participants, information about index hospitalisation was not obtained from VEGA. Data for these participants were requested a second time to eliminate errors in the database extraction process but no data could be obtained. Instead, length of hospital stay and diagnosis were identified through electronic medical records. The cost was calculated based on the median cost per day for the other participants' index hospitalisation multiplied by the number of days in hospital identified from the medical records. Correct register data for follow-up visits were obtained for both patients. Costs in EUR and USD were calculated using the average exchange rate in 2015 (EUR 1 = SEK 9.3562, USD 1 = SEK 8.435).[17]

## Analyses

Descriptive statistics were used to explore the clinical information and background characteristics of the study population. Quantities and direct health care costs were calculated by type of resource used and diagnoses. Because of the expected skewed distribution of costs, confidence intervals for costs were calculated with the bootstrap method (using 1000 iterations, seed 1234).[18] For the baseline clinical data, SPSS v. 22 (IBM Corp., Armonk, NY, USA) was used. For the register data, statistical analyses were performed using Stata SE 14.2 (Stata Corp, College Station, TX, USA).

## Patient and Public Involvement

The public or the patients were not directly involved in this study.

# ETHICS

The study was approved by the Regional Ethical Review Board in Gothenburg (approval reference numbers: Dnr 275-11, T693-11 and T392-15) and complies with the declaration of Helsinki. Written informed consent was obtained from all participants.

# RESULTS

Of the 58 patients included, 53 (91.4%) were women and 5 (8.6%) men (Table 1). In total, the 58 patients with TS were hospitalised for 593 days during the study period, which equals a mean of 10.2 days per person. The length of stay of the baseline hospitalisations was, on average, 6.4 days (interquartile range: 2–8). In addition, 20 of the 58 patients were readmitted 40 times during the 6-month study period (median 2 readmissions per readmitted patient, range 1-5). Eleven of these patients were readmitted during the first 30 days. There was a total of 18 readmissions during the first 30 days and 10 of these had registered conditions belonging to Circulatory system diseases (chapter I) in the ICD-10. The hospitalisations of eight people (13 readmissions within 30 days) had a

main diagnosis in the ICD subchapters I42-I429 (Cardiomyopathy), where TS is usually registered. An additional three readmissions were for Circulatory system disorders (main diagnosis). During the 6-month study period, 19 readmissions were for Circulatory system disorders (main diagnosis) and 13 for the ICD subchapters I42-I429 (Cardiomyopathy). A further two readmissions were for unexplained chest pain (R074).

For the 58 patients with TS, the mean number of follow-up encounters per patient was 15.6 during the 6 months following discharge for TS. This figure includes all categories of health care professionals, both direct and indirect (e.g., telephone contact, writing letters, etc.) encounters and visits at specialist outpatient clinics and primary care. The most common form of outpatient care used was physician visits, followed by physiotherapist or occupational therapist visits, which include cardiac rehabilitation groups, and registered nurse (RN) visits. Other visits in outpatient care included visits to a social counsellor, biomedical analyst, audiologist, assistant nurse and psychologist. In primary care visits with physicians were also most common but RN visits were next most common in this care setting. Other visits in primary care included visits to a social counsellor, assistant nurse, podiatrist and psychologist.

When dividing costs by care level (Table 2), most costs were associated with index hospitalisation (EUR 260,623), followed by hospital readmissions (EUR 169,739), outpatient care (EUR 143,911) and primary care (EUR 26,602). The average cost per index hospitalisation and readmissions were almost the same: EUR 4,494 and 4,243, respectively. The total cost for outpatient and primary care for the 58 patients during the 6-month follow-up post-discharge for TS was EUR 170,514.

For this sample, there was no clear pattern of costs based on socioeconomic factors, previous disease or risk factors, although there is a higher, though statistically nonsignificant, mean cost in certain age groups and among men (Table 3). Because only five men participated in the study, further division based on sex was deemed unreliable.

The mean direct health care costs during the 6-month study period was EUR 10,360 (95% confidence interval (CI): EUR 8,310–12,409) in the 58 patients with TS. Of these direct health care costs, costs of EUR 8,026 (77.5%) occurred during health care encounters for which at least one of the registered conditions was in ICD chapter IX (I00–I99 Circulatory system diseases). Costs of EUR 7,135 (68.9% of all costs) were for health care encounters in which the main condition was in ICD chapter IX.

During the study period, TS was found in ICD I42-I429, which was also the subchapter with the highest costs of all ICD chapters analysed based on the main diagnosis of health care encounters (Table 4). Analysing costs by main diagnosis, other ICD chapters with high costs were I209, I200, I21-I219 and I5-I599. In addition to Circulatory system diseases, the highest costs among TS patients were in the ICD chapter Mental and behavioural disorders, Respiratory system disorders and in the ICD chapter Factors influencing health status and contacts with health services.

**Table 1 Sociodemographic and disease characteristics among 58 patients diagnosed with TS.**

| | **Patients with TS** n=58 |
|---|---|
| Women (%) | 53 (91.4) |
| Age, median (range) | 67.6 (39-86) |
| Marital status[a] | |
| Married/co-habitant (%) | 31 (54.4) |
| Single (%) | 5 (8.8) |
| Divorced (%) | 12 (21.1) |
| Widow/widower (%) | 9 (15.8) |
| Education[a] | |
| Primary and secondary (%) | 33 (57.9) |
| High (%) | 24 (41.4) |
| Country of birth, Sweden[a] (%) | 49 (86.0) |
| Nicotine use[b] | |
| Current (%) | 11 (21,2) |
| Previous (%) | 19 (34,6) |
| Cardiovascular disease history | |
| Previous AMI (%)[c] | 6 (11.1) |
| Previous stroke (%)[d] | 3 (5,4) |
| Previous angina (%)[a] | 2 (3,6) |
| Diabetes mellitus (%)[d] | 3 (5,4) |
| Hypertension (%)[a] | 31 (54,4) |
| Killip class[a] | |
| I | 40 (70,2) |
| II | 13 (22,8) |
| III | 4 (7,0) |
| IV | 0(0) |

[a] 1 missing

[b] 6 missing

[c] 4 missing

[d] 2 missing

AMI = acute myocardial infarction, TS = Takotsubo syndrome.

Table 2 Distribution of health care encounters and costs after diagnosis of TS by type of health care provider.

| Type of health care provider | Inpatient care | | | Outpatient care | | | Primary care | | | All care | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | Unit cost EUR (95%CI) | Total cost EUR (% of all) | No. | Unit cost EUR (95%CI) | Total cost EUR (% of all) | No. | Unit cost EUR | Total cost EUR (% of all) | No. | Average cost per patient | Total cost EUR (% of all) |
| Physician, visit | | | | 214 | 282 (243-320) | 60,295 (10.0) | 109 | 149 | 16,275 (2.7) | 323 | 1,320 | 76,570 (12.7) |
| Physician, indirect encounter | | | | 5 | 0[b] | 0 | 16 | 50 | 796 (0.1) | 21 | 14 | 796 (0,1) |
| Registered nurse, visit | | | | 119 | 255 (225-285) | 30,389 (5.1) | 93 | 58 | 5,368 (0.9) | 212 | 616 | 35,757 (6.0) |
| Physiotherapist and occupational therapist, visit | | | | 191 | 87 (82-93) | 16,707 (2.8) | 19 | 46 | 875 (0.1) | 210 | 303 | 17,582 (2.9) |
| Physiotherapist and occupational therapist, indirect encounter | | | | | | | 26 | 46 | 1,198 (0.2) | 26 | 21 | 1,198 (0.2) |
| Other visit | | | | 67 | 123 (99-147) | 8,244 (1.4) | 35 | 60 | 2,090 (0.3) | 112 | 178 | 10,334 (1.7) |
| Hospitalisation | 98 | 4,391 (3,743-5,040) | 430,362 (71.6) | | | | | | | 98 | 7,420 | 418,840 (71.6) |
| Index admission[a] | 58 | 4,494 (4,134-4,853) | 260,623 (43.4) | | | | | | | 58 | 4,494 | 249,101 (43.4) |
| Readmission | 40 | 4,243 (2,724-5,763) | 169,739 (28.2) | 8 | 3,535 (2,893-4,176) | 28,276 (4.7) | | | | 48 | 3,418 | 198,015 (33.0) |
| **Total cost** | 98 | | **430,362 (71.6)** | 604 | | **143,911 (24.0)** | 298 | | **26,602 (4.4)** | **904[c] 98[d]** | **10,360** | **600,876 (100)** |

Number of encounters and mean unit costs by cost components among 58 patients during the 6 months after diagnosis of TS.

[a]Data missing for two patients. Cost was calculated based on length of stay and median cost per day for the other participants' index hospitalisation

[b]Zero cost assigned because of lack of both registered diagnosis and diagnosis-related group.

[c]Outpatient and primary care contacts

[d]Hospitalisations

TS = Takotsubo syndrome

Table 3: Mean direct health care costs after diagnosis of TS by patient characteristics.

| **Patient characteristic** | **No.** N = 58 | **Mean cost** EUR (95% CI) |
|---|---|---|
| Sex | | |
| Women | 53 | 9,907 (7,815-11,999) |
| Men | 5 | 15,161 (6,268-24,054) |
| Age | | |
| <65 years | 20 | 9,711 (6,446-12,976) |
| 65-75 years | 24 | 11,724 (8,167-15,282) |
| ≥75 years | 14 | 8,948 (6,142-11,754) |
| Country of birth[a] | | |
| Sweden | 49 | 10,426 (8,336-12,517) |
| Other | 8 | 10,071 (3,381-16,762) |
| Education[a] | | |
| Upper secondary school | 33 | 11,296 (8,301-14,291) |
| Post-secondary school | 24 | 9,112 (6,262-11,962) |
| Nicotine use[b] | | |
| No current or previous use | 22 | 9,256 (6,153-12,359) |
| Current or previous use | 30 | 10,611 (8,015-13,206) |
| Disease history[a] | | |
| Previous heart attack, angina or stroke | 10 | 9,480 (6,134-12,825) |
| No previous heart attack, angina or stroke | 47 | 10,651 (8,298-13,005) |
| Comorbidity[a] | | |
| Hypertension | 31 | 9,860 (7,388-12,331) |
| No hypertension | 26 | 10,969 (7,556-14,383) |
| **Total** | **58** | **10,360 (8,310–12,409)** |

[a]1 missing

[b]6 missing

TS = Takotsubo syndrome

Table 4 Total costs for health care encounters in 58 patients categorised by main conditions for each encounter during 6 months after diagnosis of TS.

| **ICD chapter and subchapter**[a] | **Costs by chapters** | | **Costs by subchapters**[b] | |
|---|---|---|---|---|
| | Total cost | Mean cost per encounter | Total cost | Mean cost per encounter |
| | EUR | EUR (95% CI) | EUR | EUR (95% CI) |
| I Certain infectious and parasitic diseases (A00-B99) | 448 | 149 (-) | | |
| II Neoplasms (C00-D48) | 25,557 | 1,065 (4-2,126) | | |
| III Blood and blood-forming organ diseases and certain disorders involving the immune mechanism (D50-D89) | 207 | 104 (38-169) | | |
| IV Endocrine, nutritional and metabolic diseases (E00-E90) | 6,599 | 347 (11-684) | | |
| V Mental and behavioural disorders (F00-F99) | 36,206 | 647 (-197-1,490) | | |
| VI Nervous system diseases (G00-G99) | 5,980 | 460 (216-704) | | |
| VII Eye and adnexa diseases (H00-H59) | 1,088 | 109 (44-174) | | |
| VIII Ear and mastoid process diseases (H60-H95) | 739 | 246 (169-324) | | |
| IX Circulatory system diseases (I00-I99) | 413,841 | 1,019 (823-1,215) | | |
| IX 3 (I1-I159) | | | 6,811 | 184 (77-291) |
| IX 5 (I21-I219, I200, and I209) | | | 32,876 | 2,055 (1,090-3,020) |
| IX 9 (I25-I259) | | | 7,722 | 106 (55-156) |
| IX 11 (I3-I399) | | | 381 | 381 (-) |
| IX 12 (I40-I419 and I43-I499) | | | 18,914 | 822 (201-1,443) |
| IX 13 (I42-I429) | | | 268,632 | 1,272 (1,011-1,533) |
| IX 14 (I5-I599) | | | 52,138 | 1,448 (728-2,169) |
| IX 15 (I60-I999) | | | 25,368 | 3,171 (-1,973-8,315) |
| X Respiratory system diseases (J00-J99) | 29,002 | 806 (374-1,237) | | |
| XI Digestive system diseases (K00-K93) | 5,173 | 1,293 (208-2,378) | | |
| XII Skin and subcutaneous tissue diseases (L00-L99) | 1,121 | 224 (171-277) | | |
| XIII Musculoskeletal system and connective tissue diseases (M00-M99) | 14,166 | 354 (137-571) | | |
| XIV Genitourinary system diseases (N00-N99) | 579 | 97 (47-146) | | |
| XVIII Symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified (R00-R99) | 15,106 | 321 (210-433) | | |
| XIX Injury, poisoning and certain other consequences of external causes (S00-T98) | 4,359 | 363 (-182-908) | | |
| XXI Factors influencing health status and contact with health services (Z00-Z99) | 30,060 | 423 (264-583) | | |
| XXII Codes for special purposes (U00-U99) | 3,915 | 186 (170-202) | | |
| Not registered | 6,731 | 30 (26-34) | | |
| **Total cost** | **600,876** | | | |
| Of which at least one condition was in chapter IX[c] (% of total cost) | 465,493 (77.5) | | | |

| | |
|---|---|
| Of which the main condition was in chapter IX (% of total cost) | 413,841 (68.9) |

[a]No costs were associated with the omitted chapters and subchapters.

[b]Only specified for ICD chapter IX Circulatory system diseases.

[c]At least one condition in chapter IX 3: EUR 176,829; IX 5: EUR 62,397; IX 9: EUR 41,120; IX 11: EUR 4,678; IX 12: EUR 51,190; IX 13: EUR 304,623; IX 14: EUR 117,898; IX 15: EUR 42,600. Costs for a specific visit may be included in the sum for more than one subchapter.

TS = Takotsubo syndrome, CI = confidence interval

# DISCUSSION

The present findings indicate that the initial hospitalisation represents only 2/5 of the direct health care costs during the 6 months after diagnosis of TS. Additional costs were incurred by readmissions, often for Circulatory system disorders (including TS), and an average of more than 15 additional health care visits per patient during the period. Overall, Circulatory system disorders were the main condition in health care encounters, corresponding to almost 70% of all costs in this patient population.

We found little difference in cost of care related to age, country of birth and present or previous smoking behaviour. Patients with previous diagnoses of AMI, angina, stroke or hypertension had lower costs of care than those without but the differences were small and these results may not be generalisable to the population. Men had higher costs of care than women; however, because only five men participated, this result should be viewed with caution and may not represent the general population of men. Still, previous reports suggest that men suffer from more complications,[9] which is reflected in the higher cost of care in our study. Despite the small number of men in the sample, the proportion and age are similar to that of larger cohorts.[2 19] The proportion of patients with diabetes mellitus was lower than in previous studies,[6 20] but similar to that of a larger Swedish cohort.[4] This circumstance may have affected the total cost of care.

The total average length of hospital stay during the study period was 10.2 days, with index hospitalisation constituting 6.4 days of this period. Previous studies have reported average hospital stays of 3.6 to 8 days for index hospitalisation.[9 10 21] Average length of stay in hospital decreased from 4.3 to 3.8 days between 2007 and 2012.[21] In Sweden, the median hospital stay for patients <80 years who were discharged alive after an AMI was 4 days in 2015. This figure has not changed since 2008.[22] Common procedures during hospitalisation were coronary angiography, Doppler echocardiogram, conventional ECG and oesophageal ECG.

In this study we found that the total average health care cost per patient from hospitalisation to 6 months after discharge for TS was EUR 10,360, the equivalent of USD 11,491, of which less than half of the costs (43.4 %) were incurred during index hospitalisation. This was not in agreement with the calculated average cost of USD 16,723 for only hospitalisation found by Khera et al.[9] The large discrepancy in cost may be due to organisational differences between the healthcare systems in Europe and the US. The divergence between reported costs for TS hospitalisations in the two previous studies[9 10] may be due to the difference between costs and charges in those two studies, given that cost-to-charge ratios can vary between 0.12 and 0.96.[23]

There were 40 readmissions during the 6 months after initial discharge, 11 of which occurred during the first 30 days. This figure equals a 30-day readmission rate of 19%, which is higher than the 11.6% that has previously been reported in patients with TS.[21] No data on the 6-month or 1-year (all-cause) readmission rate of patients with TS could be found but the readmission rate in Sweden 1 year after an AMI was 35% for females 65–75 years old and 28% for females 0–64 years old. Approximately half of these readmissions were for non-cardiovascular causes.[22] The readmission rate for patients with TS in this study is comparable (34.5%) but in half the time. The proportion of noncardiovascular causes for readmission was also similar in the current study, where 21 of 40 readmissions had a noncardiovascular main diagnosis. This finding indicates that health is affected after TS, which is in line with previous studies.[24 25] There is a large potential for cost savings if the readmission rate can be reduced, even if this means increasing the number of outpatient and primary care visits. In our study the cost for readmission (EUR 169,739) was equivalent to the total cost of all outpatient and primary care encounters combined (EUR 170,514).

Most costs in our study originated from ICD chapter IX (I00–I99 Circulatory system diseases) and most of these costs related to subchapter I42–I49, which is where TS is usually diagnosed. There is no specific ICD code for TS in the Swedish version of the ICD-10 (in some countries TS has the ICD code I51.81, according to ICD-10-CM coding practices). Thus, much of the care that these patients use

relates to TS or other cardiovascular diseases. Other main conditions that rendered substantial costs originated from ICD chapters II (C00–D48 Neoplasms), V (F00–F99 Mental and behavioural disorders), and X (J00–J99 Respiratory system diseases). These costs are expected considering previously reported comorbidities for TS. Other TS comorbidities are neurologic, renal and endocrine diseases, although there were small concurrent costs for these conditions in this sample.[6 20]

Studies mapping resource use and costs related to a disease are commonly called COI studies. COI studies are often criticised for the lack of comparison between different healthcare programmes and therefore are of less use in decision making. Although insufficient to provide guidance on treatment choices, descriptive COI estimates can be applied to understand the magnitude of the disease in relation to other diagnoses and to identify patient groups for prioritising research and the development of intervention programmes.[11 26 27] In a disease such as TS in which the preconception has been that the disease is relatively benign[4 8] and where follow-up guidelines are lacking,[2] COI can be a useful tool to help place the disease in perspective to other diagnoses.[11] Furthermore, studies on the use of health care resources after initial discharge from hospital are needed given that the healthcare system and availability of, for example, specialised outpatient care will greatly affect the length of initial hospitalisation.

It appears from the results in this and previous studies that patients with TS have comparable readmission and mortality rates as patients with AMI.[4 8] Together, these results indicate that the health care of TS patients' needs to be further developed, including implementing a supportive follow-up programme of individualised care. Recent studies evaluating a person-centred intervention from hospital to primary care for patients with acute coronary syndrome found a significant increase in self-efficacy in the intervention-group that was sustainable up to 2 years.[28 29] Follow-up programmes recognising the patient as a person with a unique life history and needs have proven efficient by reducing readmissions to hospital in patients with severe chronic heart failure.[30 31] Previous studies have also shown that patients with TS often have persisting symptoms, such as pain,

fatigue and shortness of breath for up to 4 years after discharge[24 25 32] and would thus probably benefit from this kind of supportive follow-up programme.

## Methodological discussion

The main strengths of this study were the comprehensive data on resource use available in the VEGA database and medical records, which makes follow-up feasible after initial hospitalisation. The study, however, was limited by the small sample size, which was related to the regional demarcation of the VEGA database (thus making inclusion of patients from other regions impossible) and by the set inclusion and exclusion criteria, i.e. only patients that had undergone coronary angiography were included (because the lack of a specific ICD-code for TS in the Swedish version of ICD-10 makes identification of TS more difficult) and patients with a predicted survival of <6 months were excluded from the study. The issue of selection bias also must be considered. Patients with TS that did not undergo coronary angiography were not included in the study. The study concerns patients hospitalised for TS in Sweden and the results may therefore not be generalized to other settings. Moreover, the study do not include information on if the participants had primary or secondary TS. All of these factors may also influence use of care and its accompanying costs. Costs were calculated based on template costs, i.e. the DRG weights and an average cost per DRG and weighted costs from national statistics for primary care visits. These results are proxies for the actual health care costs and calculations and are used nationally to compare costs, for example, between counties. The estimated costs should thus include the burden to the healthcare system of standard treatments and examinations during health care encounters but may fail to cover unusual health care interventions. Finally, the study was limited to 6 months after diagnosis of TS, which increases the follow-up compared with previous studies in this field but still neglecting costs occurring during later stages of the TS disease. Yet, the 6-month study period is expected to cover most resource use related to TS in that the cardiac function usually recovers within that period.[2] The study should be viewed as a first step towards a more comprehensive understanding of the economic burden of TS to the healthcare

system. Future studies are warranted to address the long-term economic outcomes after TS. The introduction of a specific ICD code for TS in the Swedish version of the ICD is also needed and would make research easier and more reliable.

# CONCLUSION

The current study shows that health care costs from hospitalisation to 6 months after discharge for TS primarily relate to a cardiac condition. Although there are frequent encounters with outpatient clinics and primary care, most costs stem from hospitalisations, of which readmissions contributed substantially to the total cost. Patients with TS would probably benefit from a supportive follow-up programme after discharge from hospital.

# AUTHORS' CONTRIBUTIONS

SW and HG contributed to designing and planning of the study, conducting and analysing the data, and writing and reviewing the manuscript. IE, KU and EO contributed to designing and planning the study and writing and reviewing the manuscript.

# DATA SHARING STATEMENT

No additional data are available.

# FUNDING

This work was supported by the Centre for Person-Centred Care (GPCC), University of Gothenburg, Sweden. GPCC is funded by the Swedish Government´s grant for Strategic Research Areas, Care Sciences (Application to Swedish Research Council no. 2009-1088) and co-funded by the University of Gothenburg, Sweden. It was also supported in accordance to the Swedish agreement between the government and the county councils concerning economic support for providing an infrastructure for

research and education of doctors (ALF). Swedish Heart and Lung Association (E093/13, E088/14 and E127/15), the Emelle Fund (161/14) and the Royal and Hvitfeldtska Foundation also contributed to the funding of the study.

# DECLARATION OF CONFLICTING INTRESTS

Elmir Omerovic reports grants and personal fees from AstraZeneca and grants from Abbott outside the submitted work. Sara Wallström, Inger Ekman, Kerstin Ulin and Hanna Gyllensten have no conflicts of interest to report.

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**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4+5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4+5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5-7 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5-7 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5-7 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | n/a |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5-7 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *5-7* |
| Bias | 9 | Describe any efforts to address potential sources of bias | 19+20 |
| Study size | 10 | Explain how the study size was arrived at | 5-7 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 5-7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6+7 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | n/a |
| | | (*c*) Explain how missing data were addressed | 5-7 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | 5-7 |
| | | (*e*) Describe any sensitivity analyses | n/a |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 5-7 |
| | | (b) Give reasons for non-participation at each stage | 5-7 |
| | | (c) Consider use of a flow diagram | - |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 8-11 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 5-7 |
| | | (c) Summarise follow-up time (eg, average and total amount) | n/a |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 8-15 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 8-15 |
| | | (*b*) Report category boundaries when continuous variables were categorized | n/a |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | n/a |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | n/a |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 16-20 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 16-20 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 16-20 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 20+21 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

# A cohort study of health care use, costs and diagnoses from onset to 6 months after discharge for takotsubo syndrome in Sweden

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|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2018-027814.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 17-Jan-2019 |
| Complete List of Authors: | Wallström, Sara; Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg; University of Gothenburg Centre for Person-Centred Care, Sahlgrenska Academy, University of Gothenburg<br>Ekman, Inger; Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg; University of Gothenburg Centre for Person-Centred Care, Sahlgrenska Academy, University of Gothenburg<br>Omerovic, Elmir; Department of Cardiology, Sahlgrenska University Hospital; Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg<br>Ulin, Kerstin; Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg; University of Gothenburg Centre for Person-Centred Care, Sahlgrenska Academy, University of Gothenburg<br>Gyllensten, Hanna ; Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg; University of Gothenburg Centre for Person-Centred Care , Sahlgrenska Academy, University of Gothenburg |
| Primary Subject Heading: | Cardiovascular medicine |
| Secondary Subject Heading: | Health economics |
| Keywords: | CARDIOLOGY, HEALTH ECONOMICS, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adult cardiology < CARDIOLOGY, Heart failure < CARDIOLOGY, Cardiomyopathy < CARDIOLOGY |
| | |

# A cohort study of health care use, costs and diagnoses from onset to 6 months after discharge for takotsubo syndrome in Sweden

Sara Wallström[1,2], Inger Ekman[1,2], Elmir Omerovic[3], Kerstin Ulin[1,2], Hanna Gyllensten[1,2,4]

[1]Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Box 457, 405 30 Gothenburg, Sweden

[2]University of Gothenburg Centre for Person-Centred Care (GPCC), Sahlgrenska Academy, University of Gothenburg, Box 457, 405 30 Gothenburg, Sweden

[3]Department of Cardiology, Sahlgrenska University Hospital, 413 45 Gothenburg, Sweden
Department of Molecular and Clinical Medicine, The Wallenberg Laboratory, Sahlgrenska Academy, University of Gothenburg, 413 45 Gothenburg, Sweden

[4]Department of Clinical Neuroscience, Karolinska Institutet, 171 77 Stockholm, Sweden
This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Corresponding author: Sara Wallström, Institute of Health and Care Sciences, Sahlgrenska Academy, University of Gothenburg, Box 457, 405 30 Gothenburg, Sweden
Telephone: +46(0)31-786 60 79. Fax: +46(0)31-786 60 50
E-mail: sara.wallstrom@gu.se

**Word count:** 3550

# ABSTRACT

**Objective:** Little is known about the economic impact of takotsubo syndrome (TS) for patients and for the health system after initial discharge from hospital. Therefore, the aim of this study was to describe the healthcare resource use and calculate direct healthcare costs for TS, from hospitalization to six months after discharge, and explore the distribution of costs between TS and other diagnoses among patients with TS.

**Method, participants and setting:** Cohort study investigating direct healthcare costs from hospitalization, open specialized outpatient and primary care. Healthcare resource use during six months after diagnosis with TS, were collected for 58 consecutive patients from the Regional Patient Register. Incidence-based direct healthcare costs, in 2015 values, were calculated using diagnosis-related group weights and unit costs from national statistics on healthcare costs.

**Results:** The mean length of hospital stay was 10.2 days, index 6.4 and readmissions 3.8 days. The mean number of follow-up encounters per patient was 15.6, of which 2/3 was specialized outpatient and 1/3 was primary care. This resulted in an average cost of EUR 10,360. Of this, costs of EUR 8,026 (77.5%) occurred during encounters for which at least one of the registered conditions was cardiovascular. Costs differed little according to background characteristics.

**Conclusion:** This study shows that patients utilize hospital, specialized outpatient and primary care after discharge for TS. Most direct healthcare costs relate to cardiac diagnoses. Patients with TS would probably benefit from a supportive follow-up program after discharge from hospital.



# KEY WORDS

- CARDIOLOGY
- HEALTH ECONOMICS
- Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT
- Adult cardiology < CARDIOLOGY
- Heart failure < CARDIOLOGY


# STRENGTHS AND LIMITATIONS

- This study explores an under- investigated area: cost of illness and health economics in patients with takotsubo syndrome.
- Register offered the opportunity to investigate direct health care costs from inpatient, specialized outpatient and primary care.
- This study provides insight on the distribution of cost among patients with takotsubo syndrome.
- Limitations include a small sample size, that the data was limited to direct health care costs, which are based on proxy and the limited study period.

# INTRODUCTION

Takotsubo syndrome (TS) is a form of acute reversible heart failure, which usually recovers spontaneously in 12 weeks. Its clinical presentation at onset has similar features to those of an acute myocardial infarction (AMI) with chest pain, dyspnoea, ECG changes, and raised markers of myocardial necrosis.[1 2] TS is characterized by regional wall motion abnormalities affecting one or both ventricles of the heart and absence of flow-limiting lesion in coronary arteries. The pathophysiological mechanisms underlying TS are not fully understood, but a surge of the hormone catecholamines is believed to play a vital part. Onset is often preceded by a stressful event, either psychological or physical.[2]

TS is most common among postmenopausal women; 84%–91% of cases are female and the mean age varies between 63 and 76 years.[3-5] Knowledge regarding potential risk factors is scarce, but smoking, hyperlipidemia, alcohol abuse, and anxiety have been recorded.[6] Due to a lack of diagnosis uniformity, it has been difficult to determine the exact number of TS cases per annum; but estimates suggest that there are 50–100,000 cases per year in the United States and a similar number in Europe.[2] There are no reliable figures for Sweden, but an estimation based on population would be 1,500–3,000 cases per annum in Sweden. This is in line with the estimation of 2,000 cases per annum in Sweden from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR).[7]

TS was previously assumed to be relatively benign and to have little impact on long-term survival. However, recent studies have shown that TS affects both short- and long-term survival, which are comparable to, or worse than, those in patients affected by AMI.[4 8] Mortality from cardiovascular causes is comparable between these groups; but the excess mortality among patients with TS is related to non-cardiovascular or unknown causes. Male sex, Killip class III or IV at admission according to classification for heart failure, and diabetes mellitus increases the likelihood of mortality among TS patients.[8]

There are currently few guidelines for care or follow-up for patients with TS. At hospital investigations often include coronary angiography, ultra-cardiogram and cardiac biomarkers. Treatment is aimed at supportive care to sustain life and minimize complications during the recovery of normal cardiac function. At least one follow-up visit with a specialist after discharge from hospital to review medication and confirm recovery of cardiac function.[2] Little is known of healthcare resources used for this follow-up. To our knowledge there are only two published studies examining costs after TS, both conducted in one American setting. These studies calculated the average cost of hospital stay for patients with TS to USD 16,723 in 2007–2011[9] and the total average charges to USD 61,034 in 2006–2010 for TS patients without arrhythmias[10] (concurrent arrhythmias may increase the average inpatient charge by USD 11,334[10]).

To our knowledge, there are no studies on the utilization of healthcare resources for TS from Europe, which health system in many aspects are different from that in the US. In addition, little is known about the economic impact of TS for patients and for the health system after initial discharge from hospital. Such studies, often called cost of illness (COI) studies, are useful both for comparing the burden on the healthcare system, of TS to other diseases, and to identify important costs and variation in costs in the treatment of a specific disease, like TS.[11] Therefore, the aim of this study was to describe the healthcare resource use and calculate direct healthcare costs for TS, from

hospitalization to six months after discharge, and to explore the distribution of costs between TS and other diagnoses among patients with TS.

# METHODS

## Study population and settings

Patients from two hospitals in a city in western Sweden were included consecutively from January 2012 to October 2015. There is no specific code in the Swedish version of ICD International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10), so all coronary angiography records from the participating hospitals were screened to identify patients with TS. Patients were included after identification with coronary angiography and confirmation of diagnosis with cardiologist. The inclusion criteria were (1) having a diagnosis of TS, (2) speaking Swedish, (3) having a predicted survival of more than 6 months, and (4) living in Region Västra Götaland. In total, 110 patients with TS were identified during the study period: of those, 29 declined participation, ten had a predicted survival of less than six months, five did not speak Swedish or were otherwise unable to fill out the questionnaires, two participated in another incompatible research study, two died and four accepted participation but were excluded because they did not live in Region Västra Götaland and were thus not possible to follow through register data. The remaining 58 patients with TS were included in the study.

## Data collection

Clinical information about the disease and potential risk factors, for example cardiovascular disease history, nicotine use, Killip class and hypertension, were retrieved from medical records during the initial hospital stay. Data on socioeconomic characteristics was collected from each participant using a questionnaire. Register data about use of healthcare resources and its cost were obtained from the Regional Patient Register (VEGA), which contains information about all inpatient care, specialized outpatient care, and primary care in the Region Västra Götaland. The VEGA-database has a near full coverage of care utilized by the residents of the region.[12 13] Costs for medications and healthcare provided by the municipalities were not included. Patient information retrieved covered the period from the day patients were admitted to hospital for TS and the following six months. Healthcare encounters were classified based on the main diagnosis registered, according to the ICD-10, as chapters A-Z and using a more detailed level for categorizing disorders within chapter I (Circulatory system disorders).

Incidence-based direct healthcare costs were calculated for consecutive patients, including costs for healthcare resource use during the six months starting at diagnosis with TS for each patient. Both all-cause costs and costs for resource use for which cardiovascular causes was the main diagnosis were calculated. Calculations were made based on the economic perspective of the healthcare sector and in 2015 values. Costs for specialized health care were calculated using diagnosis-related group (DRG) weights, retrieved from VEGA.[14] Costs calculated from diagnosis-related group weights were updated to 2015 values using the Swedish healthcare inflation index, which is a price index for the counties.[15] Primary care encounters were assigned unit costs based on national statistics for healthcare use and costs.[16] According to national statistics, the cost for primary care physician visits was SEK 1,397 (EUR 149) in primary care in 2014; this was updated to 2015 values using the Swedish healthcare inflation index. A visit to other healthcare personnel was weighted as 40% of the cost of a physician visit,

phone calls were weighted as one-third of the cost of a visit, and home health care as twice the cost of a visit.[16] Length of stay in hospital is recorded for each hospital in the registry, thus transfers between hospitals is registered as re-admissions. Indirect costs resulting from lost productivity and intangible costs for harm and suffering were not included in the analyses.

For two participants, information about the index hospitalization was not obtained from VEGA. Data for these participants was requested a second time to eliminate errors in the database extraction but no data could be obtained. Instead, length of hospital stay and diagnosis were identified from the electronic medical records and the cost was calculated based on the median cost per day for the other participants' index hospitalization multiplied by the number of days in hospital identified from the medical records. Using the median provides a conservative estimate of the cost. Register data for follow-up visits was obtained correctly for both patients. Costs in EUR and USD were calculated using the average exchange rate in 2015 (EUR 1 = SEK 9.3562, USD 1= SEK 8.435).[17]

## Analyses

Descriptive statistics were used to explore the clinical information and background characteristics of the study population. Quantities and direct healthcare costs were calculated, by type of resource use and by diagnoses. Due to the expected skewed distribution of costs, confidence intervals for costs were calculated using bootstrap (using 1000 iterations, seed 1234).[18] For the baseline clinical data SPSS v. 22 (IBM Corp., Armonk, NY, USA) was used. For the register data, statistical analyses were performed using Stata SE 14.2 (Stata Corp, College Station, TX, USA).

## Patient and Public Involvement

Patients and or public were not involved in this study.

# ETHICS

The study was approved by the Regional Ethical Review Board in Gothenburg (approval reference numbers: Dnr 275-11, T693-11, and T392-15) and complies with the declaration of Helsinki. Written informed consent were obtained from all participants.

# RESULTS

Of the 58 patients included, 53 (91,4%) were women and five (8,6%) men (Table 1). In total, the 58 patients with TS were hospitalized for 593 days during the study period, which equals a mean of 10.2 days per person. The baseline hospitalizations length of stay was on average 6.4 days (interquartile range: 2–8). In addition, 20 of the 58 patients were readmitted a total of 40 times during the six months study-period (median 2 readmissions per readmitted patient, range 1-5). Eleven of these patients were readmitted during the first 30 days. There were a total of 18 readmissions during the first 30 days and 10 of these had registered conditions belonging to in Circulatory system diseases (chapter I) in ICD-10. The hospitalizations of eight people (13 readmissions within 30 days) had a main diagnosis in the ICD sub-chapters I42-I429 (Cardiomyopathy), were TS is usually registered. An additional 3 readmissions were for Circulatory system disorders (main diagnosis). During the six months, 19 readmissions were for Circulatory system disorders (main diagnosis), and 13 were for the ICD sub-chapters I42-I429 (Cardiomyopathy). A further two were for unexplained chest pain (R074).

The 58 patients with TS had on average 15.6 follow-up encounters per patient during the six months following discharge for TS. This includes all categories of healthcare professionals, both direct and indirect (e.g. telephone contact, writing letter etc.) encounters and visits with both specialist outpatient clinics and primary care. The most common form of outpatient care utilized was physician visits, followed by physiotherapist or occupational therapist, which include cardiac rehabilitation groups, and Registered Nurse (RN) visits. Other visits in outpatient care include consular, biomedical analyst, audiologist, assistant nurse and psychologist. In primary care, visits with physicians was also most common but here followed by RN visits. Other visits in primary care included consular, assistant nurse, podiatrist and psychologist.

When dividing costs by care level (Table 2), the most costs were associated with the index hospitalisation (EUR 260,623), followed by re-admissions (EUR 169,739), outpatient care (EUR 143,911) and primary care (EUR 26,602). The average cost per index hospitalization and re-admission were almost the same: EUR 4,494 and 4,243, respectively. The total cost for outpatient and primary care for the 58 patients during the six months following discharge for TS was EUR 170,514.

For this sample, there was no clear pattern regarding costs according to socioeconomic factors, previous disease, or risk factors, although there is a higher (statistically non-significant) mean cost in particular age groups and among men (Table 3). As only five men participated in the study, further division based on sex was deemed unreliable.

The mean direct healthcare costs during the six months study period was EUR 10,360 (95% confidence interval (CI): EUR 8,310–12,409) among the 58 patients with TS. Of this, costs of EUR 8,026 (77.5%) occurred during healthcare encounters for which at least one of the registered conditions was in the ICD chapter IX (I00–I99 Circulatory system diseases). Costs of EUR 7,135 (68.9% of all costs) were for healthcare encounters in which the main condition was in ICD chapter IX.

During the study period, TS was found in ICD I42-I429, which was also the category with the highest costs of all ICD categories analysed based on main diagnosis of healthcare encounters (Table 4). Other ICD categories with high costs, when analysing costs by main diagnosis, were I209, I200, I21-I219 and I5-I599. In addition to Circulatory system diseases, the highest costs among TS patients were in the ICD categories Mental and behavioural disorders, Respiratory system disorders, and in the category Factors influencing health status and contacts with health services.

**Table 1 Sociodemographic and disease characteristics among 58 patient diagnosed with TS.**

| | **Patients with TS** n=58 |
|---|---|
| Women (%) | 53 (91.4) |
| Age median (range) | 67.6 (39-86) |
| Marital status[a] | |
| Married/ co-habitant (%) | 31 (54.4) |
| Single (%) | 5 (8.8) |
| Divorced (%) | 12 (21.1) |
| Widow/ widower (%) | 9 (15.8) |
| Education[a] | |
| Primary and secondary (%) | 33 (57.9) |
| High (%) | 24 (41.4) |
| Country of birth, Sweden[a] (%) | 49 (86.0) |
| Nicotine use[b] | |
| Current (%) | 11 (21,2) |
| Previous (%) | 19 (34,6) |
| Cardiovascular disease history | |
| Previous AMI (%)[c] | 6 (11.1) |
| Previous stroke (%)[d] | 3 (5,4) |
| Previous angina (%)[a] | 2 (3,6) |
| Diabetes mellitus (%)[d] | 3 (5,4) |
| Hypertension (%)[a] | 31 (54,4) |
| Killip class[a] | |
| I | 40 (70,2) |
| II | 13 (22,8) |
| III | 4 (7,0) |
| IV | 0(0) |

[a] 1 missing

[b] 6 missing

[c] 4 missing

[d] 2 missing

AMI = acute myocardial infarction, TS = Takotsubo syndrome.

Table 2 Distribution of healthcare encounters and costs after TS, by type of healthcare providers.

| Type of healthcare provider | Inpatient care | | | Outpatient care | | | Primary care | | | All care | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | Unit cost EUR (95%CI) | Total cost EUR (% of all) | No. | Unit cost EUR (95%CI) | Total cost EUR (% of all) | No. | Unit cost EUR | Total cost EUR (% of all) | No. | Average cost per patient | Total cost EUR (% of all) |
| Physician, visit | | | | 214 | 282 (243-320) | 60,295 (10.0) | 109 | 149 | 16,275 (2.7) | 323 | 1,320 | 76,570 (12.7) |
| Physician, indirect encounter | | | | 5 | 0[b] | 0 | 16 | 50 | 796 (0.1) | 21 | 14 | 796 (0,1) |
| Nurse, visit | | | | 119 | 255 (225-285) | 30,389 (5.1) | 93 | 58 | 5,368 (0.9) | 212 | 616 | 35,757 (6.0) |
| Physiotherapist and occupational therapist, visit | | | | 191 | 87 (82-93) | 16,707 (2.8) | 19 | 46 | 875 (0.1) | 210 | 303 | 17,582 (2.9) |
| Physiotherapist and occupational therapist, indirect encounter | | | | | | | 26 | 46 | 1,198 (0.2) | 26 | 21 | 1,198 (0.2) |
| Other visit | | | | 67 | 123 (99-147) | 8,244 (1.4) | 35 | 60 | 2,090 (0.3) | 112 | 178 | 10,334 (1.7) |
| Hospitalization | 98 | 4,391 (3,743-5,040) | 430,362 (71.6) | | | | | | | 98 | 7,420 | 430,362 (71.6) |
| Index admission[a] | 58 | 4,494 (4,134-4,853) | 260,623 (43.4) | | | | | | | 58 | 4,494 | 260,623 (43.4) |
| Re-admissions | 40 | 4,243 (2,724-5,763) | 169,739 (28.2) | 8 | 3,535 (2,893-4,176) | 28,276 (4.7) | | | | 48 | 3,418 | 198,015 (33.0) |
| **Total cost** | 98 | | **430,362 (71.6)** | 604 | | **143,911 (24.0)** | 298 | | **26,602 (4.4)** | **902[c] 98[d]** | **10,360** | **600,876 (100)** |

Number of encounters and mean unit costs by cost components among 58 patients during the six months after diagnosis of TS.

[a]Data missing for two patients. Cost was calculated based on length of stay and median cost per day for the other participants' index hospitalization

[b]Zero cost assigned due to lack of both registered diagnosis and diagnosis related group.

[c] Outpatient and primary care contacts

[d] Hospitalisations

TS = Takotsubo syndrome

Table 3: Mean direct healthcare costs after TS, by person characteristics.

| **Patient characteristics** | **No.** N = 58 | **Mean cost** EUR (95% CI) |
|---|---|---|
| Sex | | |
| Women | 53 | 9,907 (7,815-11,999) |
| Men | 5 | 15,161 (6,268-24,054) |
| Age | | |
| Below 65 years | 20 | 9,711 (6,446-12,976) |
| 65-75 years | 24 | 11,724 (8,167-15,282) |
| 75 years or older | 14 | 8,948 (6,142-11,754) |
| Country of birth | | |
| Sweden | 49 | 10,426 (8,336-12,517) |
| Other | 8 | 10,071 (3,381-16,762) |
| Education[a] | | |
| Upper secondary school | 33 | 11,296 (8,301-14,291) |
| Post-secondary school | 24 | 9,112 (6,262-11,962) |
| Nicotine use[b] | | |
| No current or previous use | 28 | 10,091 (7,040-13,142) |
| Current or previous use | 30 | 10,611 (8,015-13,206) |
| Disease history[a] | | |
| Previous heart attack, angina or stroke | 10 | 9,480 (6,134-12,825) |
| No previous heart attack, angina or stroke | 48 | 10,543 (8,157-12,930) |
| Comorbidity[a] | | |
| Hypertension | 31 | 9,860 (7,388-12,331) |
| No hypertension | 26 | 10,969 (7,556-14,383) |
| **Total** | **58** | **10,360 (8,310–12,409)** |

[a] 1 missing

[b] 6 missing

TS = Takotsubo syndrome

Table 4 Total costs for healthcare encounters among 58 patients, categorised by main conditions for each encounter, during six months after diagnosis with TS.

| **ICD chapter and sub-chapter**[a] | **Costs by chapters** | | **Costs by sub-chapters**[b] | |
|---|---|---|---|---|
| | Total cost | Mean cost per encounter | Total cost | Mean cost per encounter |
| | EUR | EUR (95% CI) | EUR | EUR (95% CI) |
| I Certain infectious and parasitic diseases (A00-B99) | 448 | 149 (-) | | |
| II Neoplasms (C00-D48) | 25,557 | 1,065 (4-2,126) | | |
| III Blood and blood-forming organs diseases and certain disorders involving the immune mechanism (D50-D89) | 207 | 104 (38-169) | | |
| IV Endocrine, nutritional and metabolic diseases (E00-E90) | 6,599 | 347 (11-684) | | |
| V Mental and behavioural disorders (F00-F99) | 36,206 | 647 (-197-1,490) | | |
| VI Nervous system diseases (G00-G99) | 5,980 | 460 (216-704) | | |
| VII Eye and adnexa diseases (H00-H59) | 1,088 | 109 (44-174) | | |
| VIII Ear and mastoid process diseases (H60-H95) | 739 | 246 (169-324) | | |
| IX Circulatory system diseases (I00-I99) | 413,841 | 1,019 (823-1,215) | | |
| IX 3 (I1-I159) | | | 6,811 | 184 (77-291) |
| IX 5 (I21-I219, I200, and I209) | | | 32,876 | 2,055 (1,090-3,020) |
| IX 9 (I25-I259) | | | 7,722 | 106 (55-156) |
| IX 11 (I3-I399) | | | 381 | 381 (-) |
| IX 12 (I40-I419 and I43-I499) | | | 18,914 | 822 (201-1,443) |
| IX 13 (I42-I429) | | | 268,632 | 1,272 (1,011-1,533) |
| IX 14 (I5-I599) | | | 52,138 | 1,448 (728-2,169) |
| IX 15 (I60-I999) | | | 25,368 | 3,171 (-1,973-8,315) |
| X Respiratory system diseases (J00-J99) | 29,002 | 806 (374-1,237) | | |
| XI Digestive system diseases (K00-K93) | 5,173 | 1,293 (208-2,378) | | |
| XII Skin and subcutaneous tissue diseases (L00-L99) | 1,121 | 224 (171-277) | | |
| XIII Musculoskeletal system and connective tissue diseases (M00-M99) | 14,166 | 354 (137-571) | | |
| XIV Genitourinary system diseases (N00-N99) | 579 | 97 (47-146) | | |
| XVIII Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99) | 15,106 | 321 (210-433) | | |
| XIX Injury, poisoning and certain other consequences of external causes (S00-T98) | 4,359 | 363 (-182-908) | | |
| XXI Factors influencing health status and contact with health services (Z00-Z99) | 30,060 | 423 (264-583) | | |
| XXII Codes for special purposes (U00-U99) | 3,915 | 186 (170-202) | | |
| Not registered | 6,731 | 30 (26-34) | | |
| **Total cost** | **600,876** | | | |
| Of which at least one condition was in chapter IX[c] (% of total cost) | 465,493 (77.5) | | | |
| Of which the main condition was in chapter IX (% of total cost) | 413,841 (68.9) | | | |

[a]No costs were associated with the omitted chapters and subchapters.

[b]Only specified for ICD chapter IX Circulatory system diseases.

[c]At least one condition in chapter IX 3: EUR 176,829; IX 5: EUR 62,397; IX 9: EUR 41,120; IX 11: EUR 4,678; IX 12: EUR 51,190; IX 13: EUR 304,623; IX 14: EUR 117,898; IX 15: EUR 42,600. Costs for a specific visit may be included in the sum for more than one subchapter.

TS = Takotsubo syndrome

# DISCUSSION

These findings indicate that the initial hospitalization represents only 2/5 of the direct healthcare costs during the six months following diagnosis with TS. Additional costs were incurred by readmissions, often for circulatory system disorders (including TS), and an average of more than 15 additional healthcare visits per patient during the period. Overall, circulatory system disorders were the main condition in healthcare encounters corresponding to almost 70% of all costs in this patient population.

We found little difference in cost of care related to age, country of birth, and present or previous smoking behaviour. Patients with previous diagnoses of AMI, angina, stroke, or hypertension had lower costs of care than those without but the differences were small and these results may not be generalizable to the population. Men had higher costs of care than women, but as only five men participated, this result should be viewed with caution and may not be reflected in a larger cohort. However, previous reports suggest that men suffer from more complications,[9] and this may be reflected in the higher cost of care in our study. Despite the small number of men in the sample, the proportion and age are similar to that of larger cohorts.[2 19] The proportion of patients with diabetes mellitus was lower than in previous studies,[6 20] but similar to that of a larger Swedish cohort,[4] and this may have affected the total cost of care.

The total average length of hospital stay during study period was 10.2 days, the index hospitalization constituted 6.4 days of this. Previous studies have reported average hospital stays of 3.6–8 days for the index hospitalization.[9 10 21] Average length of stay in hospital decreased from 4.3 to 3.8 days between 2007 and 2012.[21] In Sweden, the median hospital stay for patients <80 years old, who were discharged alive after an AMI, was 4 days in 2015. This had not changed since 2008.[22] Common procedures during the hospitalisation were coronary angiography, Doppler echocardiogram, conventional ECG and oesophageal ECG.

In the current study, we found that the total average healthcare cost per patient from hospitalization to six months after discharge for TS was EUR 10,360, the equivalent of USD 11,491, of which less than half the costs (43.4 %) were incurred during the index hospitalisation. This was not in line with the calculated average cost of USD 16,723 for only hospitalization found by Khera et al.[9] The large discrepancy in cost may be due to organizational differences between the health systems in Europe and the US. The divergence between reported costs for TS hospitalizations in the previous two studies[9 10] may be because of the difference between costs and charges in those two studies, as cost-to-charge ratios can vary between 0.12 and 0.96.[23]

There were 40 readmissions during the 6 months after initial discharge, 11 of which were during the first 30 days. This equals a 30-day readmission rate of 19%, which is higher than the 11.6% that has previously been reported for patients with TS.[21] No data on the six month or one year (all-cause) re-admission rate of patients with TS could be found but the readmission rate in Sweden one year after an AMI was 35% for females 65–75 years old and 28% for females 0–64 years old. Approximately half of these were for non-cardiovascular causes.[22] The readmission rate for patients with TS in this study is comparable (34,5%) but in half the time. The proportion of non-cardiovascular causes for readmission was also similar in the current study, 21 of 40 readmissions had a non-cardiovascular main diagnosis. This indicates that health is affected after TS, which is in line with previous studies.[24]

[25] There is a large potential for cost savings if the re-admission rate can be reduced, even if this means increasing the number of outpatient and primary care visits. In the current study, the cost for the re-admissions (EUR 169,739) was equivalent to the total cost of all outpatient and primary care encounters combined (EUR 170,514).

In our study, most costs originated from ICD chapter IX (I00–I99 Circulatory system diseases) and most of these costs related to subchapter I42–I49, which is where TS is usually diagnosed. There is no specific ICD-code for TS is in the Swedish version of ICD 10 (in some countries it is categories as I51.81, according to ICD-10-CM coding practices). This indicates that much of the care that these patients utilize relates to TS or other cardiovascular diseases. Other main conditions that rendered substantial costs originated from ICD chapters II (C00–D48 Neoplasms), V (F00–F99 Mental and behavioural disorders), and X (J00–J99 Respiratory system diseases). These costs are expected if one considers previously reported comorbidities for TS. Other TS comorbidities are neurologic, renal, and endocrine diseases, but there were small concurrent costs for these conditions in this sample.[6 20]

Studies mapping resource use and costs related to a disease are commonly called COI studies. COI studies are often criticised for the lack of comparison between different healthcare programmes, thus of less use in decision making. Although insufficient to provide guidance on treatment choices, descriptive COI estimates can be used to understand the magnitude of the disease in relation to other diagnoses, and to identify patient groups for prioritizing research and the development of intervention programmes.[11 26 27] In a disease like TS, where the preconception has been that the disease is relatively benign,[4 8] and where follow up guidelines are lacking,[2] COI can be a useful tool for putting the disease in perspective to other diagnoses.[11] Furthermore, studies on the utilization of healthcare resources after initial discharge from hospital are needed, as the health system and availability of, for example, specialized outpatient care will greatly affect the length of initial hospitalization.

It appears from the results in this and previous studies that patients with TS have comparable readmission rates as well as mortality rates as patients with AMI. [4 8] Together, these results indicate that the healthcare of TS patients need to be further developed, including a follow up programme. Recent studies evaluating a person-centred intervention from hospital to primary care for patients with acute coronary syndrome found a significant increase in self-efficacy in the intervention-group that was sustainable up to two years.[28 29] Follow-up programs focusing the patient as a person with needs and abilities have proved efficient by for example reducing readmissions to hospital also in patients with severe chronic heart failure.[30 31] Previous studies have also shown that patients with TS often have persisting symptoms, such as pain, fatigue and shortness of breath, for as long as four years after discharge[24 25 32] and would therefore probably benefit from this kind of supportive follow-up program.

## Methodological discussion

The main strengths of this study was the comprehensive data on resource use available in the VEGA database and medical records, thus making follow-up feasible also after the initial hospitalization. The study was however limited by the small sample of patients, which was related both to the regional demarcation of the VEGA database (thus making inclusion of patients from other regions impossible) and by the set inclusion and exclusion criteria; only patients that had undergone coronary angiography were included (as the lack of a specific ICD-code for TS in the Swedish version

of ICD 10, makes identification of TS more difficult), and patients with a predicted survival of less than 6 months were excluded from the study. Both factors may also influence utilization of care, and its accompanying costs. Costs were calculated based on template costs i.e., the DRG weights and an average cost per DRG, and weighted costs from national statistics for primary care visits. These results are proxies for the actual healthcare costs, and calculations like these are used nationally to compare costs between e.g., counties. The estimated costs should thus include the burden to the healthcare system of standard treatments and examinations during healthcare encounters, but may to some extent fail to cover unusual healthcare interventions. Finally, the study was limited to six months after diagnosis, thus increasing the follow-up compared to previous studies in this field but still neglecting costs occurring during later stages of the TS disease. This study period is, however, expected to cover most resource use related to TS, as the cardiac function usually recovers within that period.[2] The study should be viewed as a first step towards a more comprehensive understanding of the economic burden of TS to the health system. Future studies are thus warranted of the long-term economic outcomes after TS. The introduction of a specific ICD-code for TS in the Swedish version of ICD is also needed and would make research easier and more reliable.

# CONCLUSION

The current study shows that healthcare costs from hospitalization to six months after discharge for TS primarily relate to a cardiac condition. Although there is frequent encounter with outpatient clinics and primary care, most costs stem from hospitalizations, of which readmissions contributed substantially to the total cost. Patients with TS would probably benefit from a supportive follow-up program after discharge from hospital.

# AUTHORS' CONTRIBUTIONS

SW and HG contributed to design and planning of the study, conducting and analyzing the data, and writing and reviewing the manuscript. IE, KU and EO contributed to designing and planning the study, and writing and reviewing the manuscript.

# DATA SHARING STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information

# FUNDING

This work was supported by the Centre for Person-Centred Care (GPCC), University of Gothenburg, Sweden. GPCC is funded by the Swedish Government´s grant for Strategic Research Areas, Care Sciences (Application to Swedish Research Council no. 2009-1088) and co-funded by the University of Gothenburg, Sweden. It was also supported in accordance to the Swedish agreement between the government and the county councils concerning economic support for providing an infrastructure for research and education of doctors (ALF). Swedish Heart and Lung Association (E093/13, E088/14 and E127/15), the Emelle Fund (161/14) and, the Royal and Hvitfeldtska Foundation also contributed to the funding of the study.

# DECLARATION OF CONFLICTING INTRESTS

Elmir Omerovic reports grants and personal fees from AstraZeneca, grants from Abbott, outside the submitted work. Sara Wallström, Inger Ekman, Kerstin Ulin and Hanna Gyllensten have no conflicts of interest to report.

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**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4+5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4+5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 5-7 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5-7 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 5-7 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | n/a |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5-7 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *5-7* |
| Bias | 9 | Describe any efforts to address potential sources of bias | 19+20 |
| Study size | 10 | Explain how the study size was arrived at | 5-7 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 5-7 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6+7 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | n/a |
| | | (*c*) Explain how missing data were addressed | 5-7 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | 5-7 |
| | | (*e*) Describe any sensitivity analyses | n/a |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 5-7 |
| | | (b) Give reasons for non-participation at each stage | 5-7 |
| | | (c) Consider use of a flow diagram | - |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 8-11 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 5-7 |
| | | (c) Summarise follow-up time (eg, average and total amount) | n/a |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 8-15 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 8-15 |
| | | (*b*) Report category boundaries when continuous variables were categorized | n/a |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | n/a |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | n/a |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 16-20 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 16-20 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 16-20 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 20+21 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.