A Case-Control Study of Risk Markers and Mortality in Takotsubo Stress Cardiomyopathy

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ABSTRACT

BACKGROUND Takotsubo stress cardiomyopathy (TSC) is a syndrome characterized by transient myocardial dysfunction with unknown etiology. Although recent studies have suggested that the syndrome is associated with comorbidity and has a dismal prognosis, there is a lack of comprehensive data describing the epidemiology and prognosis of TSC.

OBJECTIVES This study compared risk markers and mortality in patients with TSC with that of individuals with or without coronary artery disease (CAD).

METHODS Patients with TSC and control subjects were identified from the Swedish Coronary Angiography and Angioplasty Register between 2009 and 2013 and linked with the Swedish national patient registry, cause of death registry, prescription drug registry, and education and income registries.

RESULTS Patients with TSC were characterized by a low cardiovascular risk factor profile but with increased chronic obstructive pulmonary disease, migraine, and affective disorders. The use of beta-blockers was less common but use of β_2-adrenergic agonist agents was more common in patients with TSC compared with either of the control groups. Being a patient with TSC was associated with a hazard ratio of 2.1 for death compared with the control subjects without CAD (95% confidence interval: 1.4 to 3.2). This was similar to the excess mortality risk seen among the CAD control subjects compared with control subjects without CAD (hazard ratio: 2.5; 95% confidence interval: 1.8 to 3.3). These associations remained significant after adjusting for CAD risk factors and risk markers for TSC.

CONCLUSIONS The findings of increased risk associated with β_2-adrenergic agonist agents together with stress related to affective disorders emphasize the pathogenic role of sympathetic stimulation. The prognosis regarding mortality is worse than in control subjects without CAD and similar to patients with CAD emphasizing the urgent need for studies on optimal treatment of TSC. (J Am Coll Cardiol 2016;67:1931–6) © 2016 by the American College of Cardiology Foundation.

Takotsubo stress cardiomyopathy (TSC) is a clinical syndrome characterized by transient myocardial dysfunction with several typical patterns (1). The mechanisms behind this syndrome are not clear but likely related to sympathetic activation because most TSC events are triggered by physical or psychological stress (1). Most publications regarding TSC have been case series or registry studies; hence, there is a lack of controlled epidemiological studies regarding risk factors or markers for risk and prognosis. Previous studies evaluating risk markers for TSC have suggested that the syndrome

is associated with cancer, neurological disease, and psychiatric disorders (2–4). In contrast, patients with TSC have been shown to have a low cardiovascular risk profile (2,3). Two recent publications have suggested that the mortality of patients with TSC is similar to patients with acute coronary syndrome, but this conclusion is limited by the fact that patients with TSC included in the analyses also, to some degree, had coronary artery disease (CAD), meaning no inclusion of control groups without CAD (3,5).

The present comprehensive population-based registry study aims to expand the knowledge about the

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epidemiology of TSC by including not only previous morbidity but also previous medications. Furthermore, the present study included a CAD control group and control subjects and patients with TSC without CAD for comparison of mortality.

METHODS

We designed this as a case-control study and identified all study participants using individuals from the Swedish Angiography and Angioplasty Register (SCAAR).

PATIENTS WITH TSC AND CONTROL SUBJECTS. In the fall of 2008, the variable of TSC was introduced into SCAAR. The definition was based on the Mayo Clinic diagnostic criteria (6). Because only a small number of patients were registered the first year, cases for the present study included the years 2009 to 2013. We defined the index date as the first time the individual appeared in SCAAR because of an acute event. Only patients with TSC with a normal coronary angiography or who had atheromatosis (non-obstructive coronaries) were included. In total, 505 patients with TSC and nonobstructive coronary arteries were included. The indication for coronary angiography, unstable CAD, or ST-segment elevation myocardial infarction (MI) occurred in 79% of the population; specifically, 27% of patients presented with ST-segment elevation on electrocardiogram.

For every patient with TSC, 2 control subjects were included, matched for age and sex. The indication for angiography in these control subjects was unstable CAD or ST-segment elevation MI (38% of all patients) who were treated with percutaneous coronary intervention, thus becoming the CAD control subjects. Similarly, for every patient with TSC, another 2 control subjects were matched for age and sex but without a previous MI according to SCAAR. These patients had undergone coronary angiography for chest pain of unknown cause but were determined to have nonobstructive coronaries. This group became the control group without CAD. Matched control subjects were selected from among all individuals fulfilling the inclusion criteria from 2009 to 2013 using sex, date of birth, and age ±5 years of the TSC index case. It was not possible to find 3 matched control subjects without CAD.

REGISTRIES. The individuals selected from SCAAR were linked and matched with the Swedish national patient registry and the prescription drug registry, and education and income registries. Date of death was collected from the cause of death registry. The variables, including Anatomical Therapeutic Chemical (ATC) and International Classification of Diseases-10 (ICD-10) codes, used from the respective registry, are shown in Online Table 1. ICD-10 codes were analyzed as risk markers if they occurred any time before the acute event. Prescribed drugs, according to ATC, bought the year before the acute event also were considered. The highest degree of education was determined and the total disposable income the year before the acute event was calculated.

STATISTICAL METHODS. Descriptive data are shown in numbers (percentages) or mean ± SD. All analyses treated the 3 groups as independent, whereas the matching for each case was individual. Differences in previous diagnoses and risk markers between the groups were tested using chi-square tests. To study survival time between the groups, we used the Kaplan-Meier method and corresponding log-rank test. In addition, to study the association between mortality and TSC after adjustments for known risk factors for cardiovascular disease and risk markers for TSC noted in the present study, we used Cox regression. Adjustment was made for previous MI, angina pectoris, heart failure, atrial fibrillation, stroke/transient ischemic attack, hyperlipidemia, diabetes mellitus type 1 and 2, smoking, chronic obstructive pulmonary disease (COPD), migraine, and affective and anxiety disorders. We present hazard ratio (HR) with corresponding 95% confidence interval (CI). The proportional hazard assumption was verified by studying the log-minus-log plot. We defined time from index date to death or to December 31, 2013, whichever occurred first. All tests were 2-sided. The results were considered significant at $p < 0.05$. Analyses were done with the use of SPSS versions 22 and 23 (IBM, Armonk, New York) and R version 3.1.1.

RESULTS

Of the 505 patients with TSC, 442 (87.5%) were women with a mean age of 67 ± 10 years. The largest age group was between 60 and 69 years old with one-fifth of the patients <60 years of age (Table 1).

COMPARISON BETWEEN PATIENTS WITH TSC AND CAD CONTROL SUBJECTS. In comparison with CAD control subjects (n = 1,010), patients with TSC were less likely to be active smokers, and received less treatment for hypertension and hyperlipidemia (Table 1). Diabetes mellitus, type 1 or 2, was also less common in patients with TSC compared with CAD control subjects. Yearly disposable income and education were higher for patients with TSC than for CAD control subjects.