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# 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 $\beta_2$-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 $\beta_2$-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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**ABBREVIATIONS AND ACRONYMS**

**ATC** = Anatomical Therapeutic Chemical

**CAD** = coronary artery disease

**CI** = confidence interval

**COPD** = chronic obstructive pulmonary disease

**HR** = hazard ratio

**ICD** = International Classification of Diseases

**MI** = myocardial infarction

**TSC** = Takotsubo stress cardiomyopathy

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.

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## 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 (nonobstructive 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.

Previous diagnosis of MI and angina pectoris was less common in patients with TSC than in CAD control subjects but there were no differences in heart failure or atrial fibrillation (Table 2). COPD and migraine were more common in patients with TSC than in CAD control subjects. There were no differences in previous diagnoses of cancer between the 2 groups. Affective and anxiety disorders were more common in patients with TSC than in CAD control subjects. Beta-blocker use was less common but use of $\beta_2$-adrenergic agonist agents was more common in patients with TSC than CAD control subjects. There were no differences between the 2 groups regarding the use of anxiolytics or antidepressants the year before index admission.

**COMPARISON BETWEEN PATIENTS WITH TSC AND CONTROL SUBJECTS WITHOUT CAD.** Compared with control subjects without CAD (n = 1,007), patients with TSC were more likely to be active smokers, but had less treatment for hypertension and hyperlipidemia (Table 1). There were no differences regarding diabetes mellitus type 1 and 2. Yearly disposable income was higher for patients with TSC than for control subjects without CAD but there was no difference in education. A previous diagnosis of MI was more common in patients with TSC than in control subjects without CAD (Table 2). Previous diagnoses of angina pectoris and atrial fibrillation were less common in patients with TSC than in CAD control subjects but there were no differences in heart failure. COPD was more common in patients with TSC than in control subjects without CAD. Hyperthyroidism tended to be more common in patients with TSC than in control subjects without CAD, but there were no differences in previous diagnoses of cancer between the 2 groups. Affective disorders and a diagnosis of alcohol abuse were more common in patients with TSC than in control subjects without CAD. The use of beta-blockers and diuretics was less common, whereas the use of $\beta_2$-adrenergic agonist agents was more common in patients with TSC compared with control subjects without CAD. There were no differences between the 2 groups regarding the use of anxiolytics or antidepressants the year before index admission.

**MORTALITY DURING FOLLOW-UP.** The mortality rates in patients with TSC and control subjects with CAD were similar (log-rank p = 0.46) and higher than control subjects (log-rank p < 0.01) without CAD (Central Illustration). Being a patient with TSC was associated with an HR of 2.1 for death compared with control subjects without CAD (95% CI: 1.4 to 3.2), which was similar to the rate seen for CAD control subjects when compared with control subjects without CAD (HR: 2.5; 95% CI: 1.8 to 3.3). These associations remained significant after adjusting for cardiovascular disease risk factors and risk markers for TSC found in the present study (adjusted HR: 2.3 and 1.9, respectively) (Online Table 2). Death from cardiovascular causes (I code ICD-10) was most common in control subjects with CAD (90 of 151; 60%) followed by patients with TSC (15 of 35; 43%) and control subjects without CAD (20 of 59; 34%). The second most common cause of death was cancer (C code ICD-10) for all groups: 29% in patients with TSC, 21% in control subjects with CAD, and 30% in control subjects without CAD.

**TABLE 1 Patient Characteristics**

| | Patients With TSC I (n = 505) | CAD Control Subjects II (n = 1,010) | Control Subjects Without CAD III (n = 1,007) | p Value I Versus II | p Value I Versus III |
|---|---|---|---|---|---|
| Female | 442 (87.5) | 884 (87.5) | 881 (87.5) | NA | NA |
| Age groups, yrs | | | | NA | NA |
| <60 | 98 (19.4) | 196 (19.4) | 196 (19.5) | | |
| 60–69 | 183 (36.2) | 366 (36.2) | 366 (36.3) | | |
| 70–79 | 172 (34.1) | 344 (34.1) | 344 (34.2) | | |
| >80 | 52 (10.3) | 104 (10.3) | 101 (10.0) | | |
| Smoking | | | | **<0.01** | **<0.01** |
| Never smoked | 259 (51.3) | 442 (43.8) | 609 (60.5) | | |
| Former smoker | 138 (27.3) | 250 (24.8) | 287 (28.5) | | |
| Present smoker | 73 (14.5) | 262 (25.9) | 79 (7.8) | | |
| Missing | 35 (6.9) | 56 (5.5) | 32 (3.2) | | |
| Treated hypertension | 229 (45.3) | 547 (54.2) | 538 (53.4) | **<0.01** | **<0.01** |
| Missing | 16 (3.2) | 16 (1.6) | 13 (1.3) | | |
| Treated hyperlipidemia | 132 (26.1) | 412 (40.8) | 439 (43.6) | **<0.01** | **<0.01** |
| Missing | 20 (4.0) | 31 (3.1) | 13 (1.3) | | |
| Diabetes mellitus type 1 | 5 (1.0) | 61 (6.0) | 25 (2.5) | **<0.01** | 0.05 |
| Diabetes mellitus type 2 | 28 (5.5) | 139 (13.8) | 70 (7.0) | **<0.01** | 0.32 |
| Income groups, kr | | | | **<0.01** | **<0.01** |
| ≤100,000 | 71 (14.1) | 218 (21.6) | 172 (17.1) | | |
| 100,001–200,000 | 246 (48.8) | 575 (57.0) | 585 (58.2) | | |
| 200,001–300,000 | 109 (21.6) | 162 (16.1) | 171 (17.0) | | |
| >300,001 | 78 (15.5) | 53 (5.3) | 78 (7.8) | | |
| Higher education (>12 yrs) | 133 (26.9) | 141 (15.8) | 226 (23.7) | **<0.01** | 0.29 |

Values are n (%). **Bold** p values are significant differences.

CAD = coronary artery disease; kr = Swedish krona (crowns); NA = not applicable; TSC = Takotsubo stress cardiomyopathy.

## DISCUSSION

The results of the present registry-based study showed that patients with TSC are characterized by a low cardiovascular risk factor profile but with increased COPD, migraine, and affective disorders. The use of beta-blockers was less common, whereas $\beta_2$-adrenergic agonist agents were used more frequently in patients with TSC compared with either control group. Mortality was similar in patients with TSC and CAD control subjects, which were both higher than seen in control subjects without CAD.

**TABLE 2 Previous Diagnoses and Treatments**

| | Patients With TSC I | CAD Control Subjects II | Control Subjects Without CAD III | p Value I Versus II | p Value I Versus III |
|---|---|---|---|---|---|
| Diagnosis | | | | | |
| Myocardial infarction | 33 (6.5) | 157 (15.5) | 8 (0.8) | **<0.01** | **<0.01** |
| Angina pectoris | 51 (10.1) | 216 (21.4) | 234 (23.2) | **<0.01** | **<0.01** |
| Heart failure | 20 (4.0) | 59 (5.8) | 56 (5.6) | 0.14 | 0.21 |
| Atrial fibrillation | 30 (5.9) | 66 (6.5) | 119 (11.8) | 0.74 | **<0.01** |
| Stroke/TIA | 27 (5.3) | 69 (6.8) | 73 (7.2) | 0.31 | 0.19 |
| Asthma | 31 (6.1) | 41 (4.1) | 65 (6.5) | 0.10 | 0.82 |
| COPD | 51 (10.1) | 46 (4.6) | 38 (3.8) | **<0.01** | **<0.01** |
| Migraine | 13 (2.6) | 10 (1.0) | 19 (1.9) | **0.02** | 0.45 |
| Fibromyalgia | 6 (1.2) | 9 (0.9) | 5 (0.5) | 0.78 | 0.20 |
| Rheumatoid arthritis | 11 (2.2) | 27 (2.7) | 34 (3.4) | 0.61 | 0.20 |
| Hyperthyroidism | 13 (2.6) | 17 (1.7) | 11 (1.1) | 0.33 | 0.05 |
| Solid malignancies | 69 (13.7) | 108 (10.7) | 106 (10.5) | 0.11 | 0.07 |
| Blood malignancies | 3 (0.6) | 7 (0.7) | 5 (0.5) | 1.00 | 1.00 |
| Breast cancer | 21 (4.2) | 39 (3.9) | 31 (3.1) | 0.88 | 0.30 |
| Affective disorders | 44 (8.7) | 54 (5.3) | 44 (4.4) | **0.02** | **<0.01** |
| Anxiety disorders | 40 (7.9) | 48 (4.8) | 59 (5.9) | **0.02** | 0.15 |
| Alcohol abuse | 14 (2.8) | 15 (1.5) | 9 (0.9) | 0.11 | **<0.01** |
| Treatment | | | | | |
| Beta-blockers | 50 (9.9) | 154 (15.2) | 163 (16.2) | **<0.01** | **<0.01** |
| ACEIs/$A_2$ blockers | 68 (13.5) | 142 (14.1) | 105 (10.4) | 0.81 | 0.09 |
| Calcium-channel blockers | 27 (5.3) | 69 (6.8) | 54 (5.4) | 0.31 | 1.00 |
| Diuretics | 32 (6.3) | 88 (8.7) | 101 (10.0) | 0.13 | **0.02** |
| Statins | 41 (8.1) | 100 (9.9) | 106 (10.5) | 0.30 | 0.14 |
| $\beta_2$-adrenergic agonist agents | 45 (8.9) | 44 (4.4) | 55 (5.1) | **<0.01** | **<0.01** |
| Levothyroxine | 24 (4.8) | 38 (3.8) | 62 (6.2) | 0.41 | 0.29 |
| Estrogen | 40 (7.9) | 61 (6.0) | 94 (9.3) | 0.19 | 0.39 |
| Antimigraine medication | 10 (2.0) | 4 (0.4) | 13 (1.3) | **<0.01** | 0.37 |
| Benzodiazepines | 14 (2.8) | 36 (3.6) | 32 (32) | 0.45 | 0.75 |
| Antidepressants | 33 (6.5) | 69 (6.8) | 69 (6.9) | 0.91 | 0.83 |

Values are n (%). **Bold** p values are significant differences.

ACEI = angiotensin-converting enzyme inhibitor; $A_2$ = angiotensin 2 receptor; COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack; other abbreviations as in Table 1.

The results of the present study showed that 15% of patients with TSC had psychiatric disorders. The prevalence of both affective and anxiety disorders was higher than in CAD control subjects, which supports findings from previous studies (2–4). Prevalence of psychiatric disorders in patients with TSC was lower than in previous studies, which might be caused by background population and/or the definition of the diagnosis. The finding that COPD was more common in patients with TSC than in control subjects with and without CAD has been suggested by a meta-analysis (7) and is supported by the increased use of $\beta_2$-adrenergic agonist agents in this group of patients. Taking into consideration the hypothesis that sympathetic stimulation plays a role in the pathogenesis of TSC, the use of $\beta_2$-adrenergic agonist agents should be minimized in patients with COPD. Interestingly, the use of beta-blockers was lower in patients with TSC than in control subjects with or without CAD. No firm conclusions can be drawn from this difference in use of beta-blockers regarding a prophylactic effect against TSC, but there is an urgent need for randomized trials of beta-blockers to prevent recurrence of TSC.

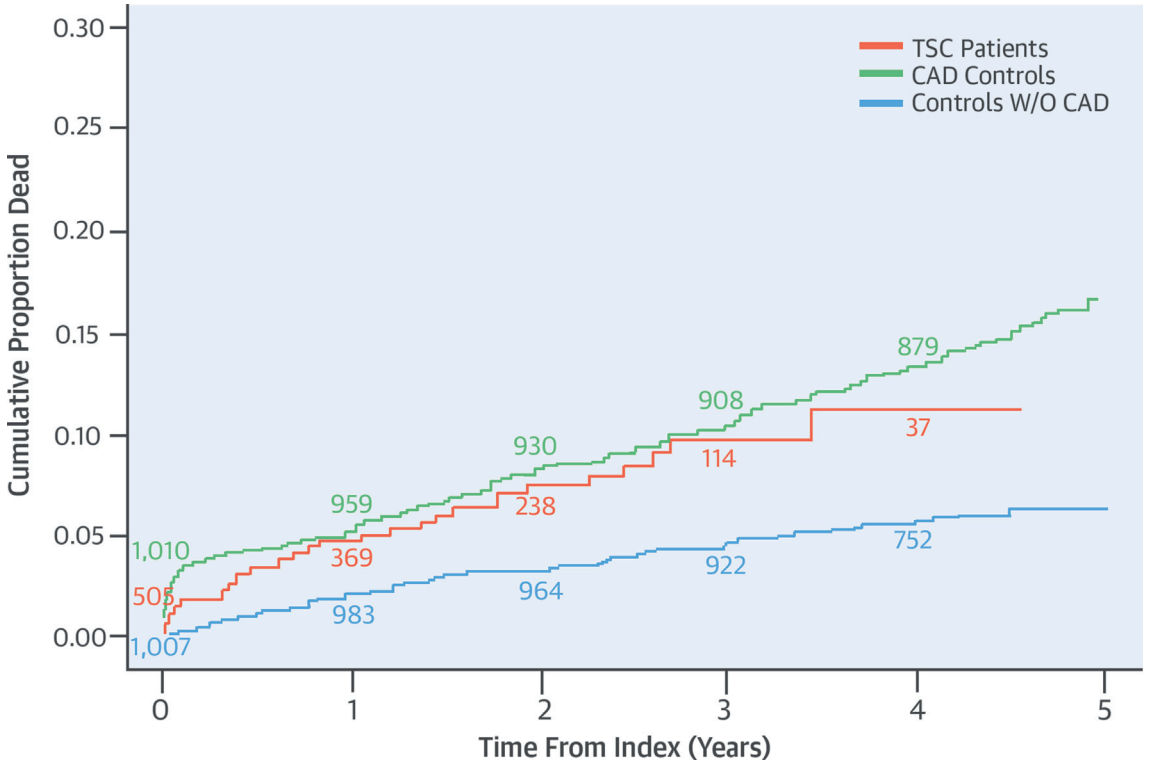
El-Sayed et al. (2) reported an increased prevalence of cancer in patients with TSC. The present study could not confirm these findings despite studying different types of malignancies including breast cancer. The reason for this is not clear but might be caused by differences in the design of the studies; we included all cancer diagnoses up to the year of TSC diagnosis. It is possible that a more recent cancer diagnosis might be a trigger of TSC due to the anxiety caused by the cancer diagnosis or the treatment for cancer rather than by the cancer per se.

An interesting but quantitative small finding was the association with migraine in patients with TSC when compared with CAD control subjects. One previous study of 25 patients with TSC showed similar results but in a much larger proportion of patients (44%) (8). Our finding was supported by the increased use of antimigraine agents, suggesting a role for vasospasm in the pathogenesis of TSC. Another finding of general importance is the use of estrogen (5% to 10%) that was similar in patients with TSC and control subjects with or without CAD. It has been speculated that estrogen might play a role in the pathogenesis of TSC, because most cases are postmenopausal women, and animal studies have shown that estrogen decreases sympathetic activity (9). The results of this study do not support a major role for estrogen as prophylaxis against TSC.

Previous large case series have shown mixed results regarding the prognosis of TSC when compared with healthy control subjects (10,11). However, 2 recent studies have shown that the prognosis is similar to patients with acute coronary syndrome (3,5). Our study extends the results of the previous studies by including only patients with TSC without CAD and matched control subjects including patients without CAD. It can thus be concluded that TSC is not a benign syndrome.

**STUDY LIMITATIONS.** The strength of the present study was its comprehensive approach that includes several population-based registries. Being a registry-based study, however, there were limitations, such as its retrospective nature using information and diagnoses made by many different physicians. However, much of the information was taken from SCAAR, a registry that is monitored regularly (12). Another limitation was that the drug prescription data contain information regarding sold drugs but tell nothing

**CENTRAL ILLUSTRATION** **Mortality in Takotsubo Stress Cardiomyopathy**




Tornvall, P. et al. J Am Coll Cardiol. 2016;67(16):1931–6.

Mortality curves for patients with Takotsubo stress cardiomyopathy (TSC) were similar to those for control subjects with coronary artery disease (CAD) and higher than for control subjects without CAD. The present registry-based case-control study shows that patients with TSC are characterized by a low cardiovascular risk profile but with increased chronic obstructive pulmonary disease, migraine, and affective disorders.

about de facto intake of drugs. A third limitation was that the registries contain no information regarding outpatient care at general practitioner offices, thus possibly underestimating the cardiovascular risk factor profile. A fourth limitation is that the inclusion of patients with TSC and control subjects without CAD might have introduced a selection bias toward healthier patients, influencing analysis of mortality. Another bias, caused by temporal changes in treatments of control subjects with and without CAD, might have been introduced by the selection of control subjects resulting in more control subjects than patients with TSC from 2009. Finally, the study sample was small and it cannot be certain that all patients with TSC have been included during the time period.

## CONCLUSIONS

The results of the present population-based registry study showed that patients with TSC are characterized by a low cardiovascular risk factor profile but with increased COPD, migraine, and affective disorders. The findings of an increased risk associated with $\beta_2$-adrenergic agonist agents together with stress related to affective disorders emphasized the pathogenic role of sympathetic stimulation. Furthermore, the association to migraine and antimigraine agents suggests that vasospasm might have a role in TSC syndrome. Finally, the prognosis regarding mortality was worse than in control subjects without CAD and similar to patients with acute coronary syndrome, emphasizing an urgent need for studies on optimal treatment of TSC.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Patients predisposed to takatsubo stress cardiomyopathy typically have a low cardiovascular risk factor profile but reactive airways disease and affective psychiatric disorders. Risk is increased in those using $\beta_2$-adrenergic agonist agents and medications for migraine. The mortality rate is similar to that in patients with acute coronary syndromes.

**TRANSLATIONAL OUTLOOK:** Further studies should explore the interactions of sympathetic nervous system stimulation and vasospasm in the pathogenesis of this increasingly recognized clinical syndrome.

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**KEY WORDS** control group, mortality, myocardial infarction, prognosis, registry

**APPENDIX** For supplemental tables, please see the online version of this article.