Takotsubo syndrome (TTS) is an acute heart failure syndrome that predominantly affects post-menopausal women. It is characterized by substantial morbidity and mortality, which equal those of acute coronary syndromes (ACS) and are still underappreciated (1). TTS and ACS share many clinical features on admission, and an estimated 1% to 2% of all patients with suspected ACS are finally diagnosed with TTS (2). However, knowledge of diagnostic criteria is often incomplete (e.g., regarding the possible coexistence of coronary artery disease [CAD]) and atypical forms are frequently not recognized, both of which contribute to the low reported incidence of TTS. In early years, the disease was considered to be typically preceded by an emotional trigger; however, recent studies demonstrate that physical triggers are equally important and that TTS may frequently occur without an evident trigger (1,3). A hallmark of TTS patients is the predominant prevalence of neuropsychiatric comorbidities (1,4,5). However, despite many efforts, the exact pathophysiological mechanism behind TTS remains elusive and primarily relies on assumptions (6).

In this issue of the Journal, Tornvall et al. (7) report data from 505 TTS patients identified from the SCAAR (Swedish Angiography and Angioplasty Register) from 2009 to 2013. SCAAR data was combined with records from the Swedish national patient registry, the prescribed drug register, and the cause of death registry. The authors conducted a case-control study of TTS patients without coexisting CAD and compared it with 2 control groups. As stated by the authors, 1 had “unstable CAD or STEMI treated with percutaneous coronary intervention” and the other had “chest pain of unknown cause and nonobstructive coronaries,” as documented by coronary angiography (7). The main finding was that adjusted long-term mortality of TTS is comparable to that of ACS but is worse than that of control subjects with chest pain but without CAD. The authors conclude that TTS is a serious condition and affects long-term prognosis. Their findings are important, as it is still widely but erroneously assumed that prognosis of TTS is universally benign. However, previous studies have shown that in-hospital outcome of TTS and ACS is comparable (1), and 2 studies on long-term prognosis compared with a reference cohort showed conflicting results (3,8). The study of Tornvall et al. (7) is the first that investigates long-term outcome of TTS compared with ACS.

The present study follows an important and potentially insightful aim: to make use of national (governmental) registries for assessing mortality and risk factors of an understudied and rather rare disease. Scandinavian countries host high-quality databases on morbidity and mortality, which have already provided valuable information on other entities (9). However, data quality of registries generally depends on accurate entries and maintenance. In the present study, many parameters were assessed on the basis of International Classification of Diseases-10th Revision codes, and verification of source data integrity was probably not possible. As such, conclusions need to be drawn with great caution.

Numerous differences in baseline characteristics between groups were noted, which corroborates data from others (1,10,11). In general, TTS can be detected as a “primary” or as a “bystander” disease in patients
hospitalized for other reasons. Therefore, it is conceivable that “primary” TTS patients have a favorable outcome but that “bystander” TTS patients have a worse prognosis, possibly associated with coexisting disease. Thus, independent predictors of adverse outcome are urgently needed to identify those TTS patients who need closer surveillance during follow-up than others. The higher mortality of TTS patients compared with control subjects is in line with a recent study (3) and emphasizes a new recognition of the disease, which carries a higher risk than previously assumed. Further prospective studies are needed to find measures for risk assessment.

A methodological issue of the study is the definition of study groups. First, diagnoses were captured from registry entries on the basis of International Classification of Diseases, 10th Revision, codes and could probably not be verified afterwards. Second, the authors precluded TTS patients with coexisting CAD from the study, which is a major limitation. We have recently demonstrated coexistence of CAD in 15% of TTS patients (1), which corroborates findings from previous smaller studies (12–15). Therefore, excluding CAD patients from the TTS cohort leads to a certain bias in outcome data. It is very likely that coexisting CAD affects the prognosis of these patients. This may have prompted the authors to investigate a “TTS only” cohort, but unfortunately supports the widespread “CAD neglect” in the recognition of TTS. On the basis of the modified Mayo Criteria from 2008, obstructive CAD is not an exclusion criterion to diagnose TTS (2), but the paper from 2008 gave this information in a footnote only, which may explain why it is widely unknown. With this in mind, it is further problematic that the CAD control group was defined as “unstable CAD or STEMI.” This leaves room for interpretation, as the Third Universal Definition of Myocardial Infarction (16) does not use the term “unstable CAD,” as it is mainly defined by symptoms and therefore prone to errors. Keeping in mind that TTS patients have elevated cardiac biomarkers and electrocardiogram changes in nearly all cases, a group of non-ST-segment elevation and ST-segment elevation ACS (consistent with the Third Universal Definition) would be the correct counterpart for TTS. As such, the definition of patients in the present study remains somewhat uncertain. Notwithstanding, the choice of the second control group was remarkable, as this group contained patients with chest pain but without coronary lesions confirmed by angiography—a superior TTS control group compared with other studies.

Despite 25 years of research, the etiology and pathogenesis of TTS largely remain elusive (Figure 1). Initially vasospasm was suspected (17); however this is unlikely, as the wall motion abnormalities in TTS are mostly not congruent with a coronary territory. The present study concludes that the presence of migraine as well as the use of antimigraine drugs suggests that vasospasm is indeed involved in the mechanism of TTS. However, according to their data, 95.4% of patients did not have migraine, and 98% of patients did not take antimigraine drugs. This obviously tells us that migraine and antimigraine drugs are not involved in the onset of TTS in at least 95.4% of patients. Hence, it remains highly speculative to build an association to vasospasm on the basis of these data. Of note, this is even more symptomatic of TTS research: a piece of the unsolved puzzle, in this case vasospasm, is often forced into place again and again (18,19). We should not refuse to accept things we do not want to believe. The same holds true for other prominent hypotheses, for example, spontaneously resolved coronary thrombi or spontaneous dissection. As outlined, wall motion abnormalities usually do not follow coronary territories in TTS, a feature that is most impressive in the midventricular form.

A hallmark of TTS is the proposed association with catecholamines, stress, and the autonomic nervous system. From early years on, the disease was believed to be induced by a spillover of catecholamines and to be precipitated by a trigger. Indeed, there are several arguments for a role of the catecholaminergic system in the onset of TTS (20). However, following the famous work of Robert Koch (21), unequivocal evidence is required to prove the relation between cause and effect. We should not be satisfied with associations. For instance, it is true that many patients develop TTS with a stressful trigger. However, about 30% of patients spontaneously develop TTS without any identifiable trigger. Do these patients have a different “TTS-like” syndrome? Probably not. If we also include histories of ACS patients, we would discover lots of “triggers”; thus, there is obviously a relevant awareness bias. On the other hand, TTS research underlines the need for reversion to the classical medical skill of history taking. In a previous study, we could demonstrate a high prevalence of neurological and psychiatric disease in TTS patients, which outnumbered that of ACS patients (1). The present study found a much lower prevalence (about one-third of our numbers). As also stated by the authors, the value of registries critically depends on careful maintenance, and thus, data obtained from registries may significantly differ between studies.

Another ongoing debate relates to beta-blockers and beta-agonists. Although beta-blockers are often essential in the acute phase and might be life-saving
in patients with left ventricular outflow tract obstruction during apical TTS, there are no data reported yet supporting a role of beta-blockers for long-term secondary prevention after TTS. In contrast, 30% of all patients in the InterTAK (International Takotsubo) Registry and 50% of all patients with recurrent TTS were on beta-blockers on admission, strongly suggesting that beta-blockers are not effective in preventing TTS (1). This was also the case in other cohorts (3). In turn, it is unclear if
beta-agonists given during exacerbated chronic obstructive pulmonary disease or asthma are sufficient to induce TTS. It is not surprising that beta-agonists are most prevalent in patients with acute obstruction, and it is equally possible that acute lung disease itself contributes to the onset of TTS, for example, by hypoxemia- or hypercapnia-associated alteration of cerebral metabolism (22). Thus, the role of beta-blockers and beta-agonists remains unclear. The conclusion of the authors to generally avoid beta-agonists to prevent potential TTS events is not advisable, considering the prevalence of chronic obstructive pulmonary disease and asthma versus the incidence of TTS. In the present study, data on medication was retrieved from the prescribed drug registry, which counts drugs prescribed to patients the year before the event. It is unclear whether patients actually used the prescription and took the drug the year after. Regarding this and the fact that outcome related to medication cannot finally be estimated from retrospective trials, all analysis of medication in the present study should be interpreted with caution. For instance, the authors state that 40.8% of CAD patients had treated hyperlipidemia, but only 9.9% of the same group were on statins. How were the remaining 30.9% treated? Notwithstanding the great potential of registry-based studies, this discrepancy reflects their problems and pitfalls, especially when connecting data from different registries.

In summary, pathogenesis of TTS appears to be multifactorial. Catecholamine levels, beta-agonist use, triggers, hormone status, and microvascular dysfunction are all true, but probably not sufficient per se to induce TTS. The present study adds to previous data, emphasizing that TTS carries a substantial risk of morbidity and mortality. However, prospective studies are now needed to elucidate pathogenesis and management of this peculiar disease.

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