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EDITORIAL COMMENT

Cardiovascular Mortality in Takotsubo Syndrome

A Mystery Awaiting Solving*

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Although more than 30 years have passed since its first description, the natural history of takotsubo syndrome (TTS) is still not fully elucidated. The recovery of transient myocardial stunning with an appreciable increase in ventricular function within days or weeks induced to think that the outcome of these patients might be quite benign.

Despite early observations suggesting that the long-term outcome of TTS patients was similar to that of the general population, Parodi et al reported higher long-term mortality in TTS, probably as a consequence of the coexisting comorbidities.[1,2] More recently, the International Takotsubo Registry showed that TTS patients had long-term outcomes comparable to those of age- and sex-matched patients with acute coronary syndromes.[3,4] Additionally, these studies found that TTS recurrence was not infrequent, as it can occur even many years after the index event.[5]

In this regard, researchers have attempted to understand the determinants of mortality and the characteristics predisposing to TTS recurrence.

Rudd et al,[6] in a case-control study, implemented national electronic healthcare records (EHRs) to investigate the clinical outcome, the causes of mortality, and drug prescribing of patients with TTS included in the Scottish Takotsubo Registry. A total of 620 TTS patients were matched for age, sex, and geographic distribution with patients with myocardial infarction (MI) diagnosis (1:1 ratio) and with individuals from the Scottish general population (1:4 ratio).

The study reported that all-cause mortality was higher in patients with TTS compared to the general population and only slightly lower than patients with MI at a median 5.5-year follow-up. Patients with TTS had a higher risk of cardiovascular death compared to the general population but lower compared to patients with MI; in contrast, noncardiovascular mortality was similar in both groups.

In the analysis of prescribing recorded at any time during follow-up, the authors reported that renin-angiotensin-aldosterone system inhibitor (RAASi) was the only cardiovascular therapy associated with lower mortality. Conversely, diuretic and psychotropic therapies were associated with higher mortality. In the analysis of prescribing recorded for at least 50% of the time during follow-up, no cardiovascular therapy was associated with improved survival in patients with TTS.

The most remarkable piece of evidence in this study concerns the assessment of specific causes of mortality, which confirmed the higher risk profile of patients with TTS than the general population but was comparable to patients with MI. Interestingly, the leading cause of mortality in TTS was cardiovascular disease, particularly heart failure, confirming previous results from multicenter registries.[3] Thus, as in post-MI patients, preventing major adverse cardiac events through the implementation of effective secondary prevention strategies is of major importance in TTS.

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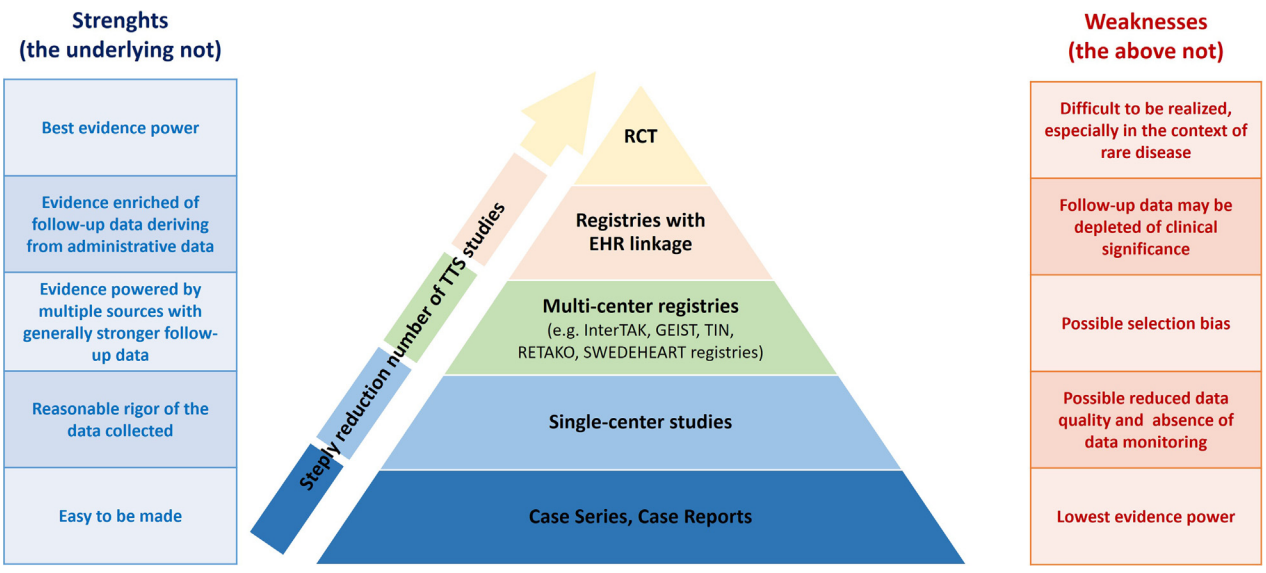
FIGURE 1 Evidence Pyramid in TTS With Strengths and Weaknesses of Each Step



EHR = electronic health records; RCT = randomized clinical trial; TTS = Takotsubo syndrome.

Previous cohort studies investigated the association between cardiovascular medications and the risk of mortality, but with nonuniform results.[3,7-9] Several registries, including the Takotsubo Italian Network registry, described an association of beta-blocker therapy with longer survival in TTS.[7-9] Conversely, the International Takotsubo Registry reported a survival benefit from the use of RAASi.[3]

Compared to the previous studies, which used prescribing at discharge as exposure, the strength of the study by Rudd et al was the retrieval of claims from the entire follow-up to evaluate prescribing at any moment after discharge and the duration of medication dispensing. Although this approach evaluates patients who have really taken the drug for at least half of the follow-up time, there remains the issue of exposure misclassification due to the absence of information about treatment starting and/or interruption.[10,11] The criteria used to define the exposure may be poorly restricted to perform inferences on mortality outcomes,[12] as suggested by the discordant results about RAASi at the analysis of prescribing at any time compared to the analysis of prescribing recorded for at least 50% of the time.

Another issue concerns the balance between treatment groups, which is critical for observational studies dealing with the association of medication with outcomes among nonrandomized subjects.[13] Interestingly, this study reported that patients taking psychotropic drugs have higher mortality. However, as previously described, TTS patients with psychiatric disorders have an unfavorable outcome.[4] Thus, it remains undetermined whether the mortality rate is related to exposure to psychotropic drugs or to individual patient characteristics. The balance of the Cox regression analysis for a few covariates, in fact, was probably not sufficient to manage the risk of selection bias.

In this study, diuretics were not associated with improved outcomes as in other heart failure patient settings. This finding suggests the potential use of new drugs that have demonstrated beneficial prognostic effects in patients with heart failure with preserved ejection fraction (eg, glifozins), even in TTS population.

Whether medication works or not remains difficult to determine in observational studies. However, the authors should be commended for:

- Linking data from the Scottish Takotsubo Registry with EHR through the unique Community Health Index number of every Scottish citizen.
- Providing data on cardiovascular mortality during one of the longest available follow-ups in TTS.

In the future, the development of artificial intelligence with the implementation of 'neural engine

techniques' for the analysis of the national EHR will enable us to achieve a more comprehensive interpretation of big data.[14]

Current evidence about the treatment of TTS comes from case series, small single-center studies, and a few multicenter registries. Due to the absence of data from randomized clinical trials (RCTs), this study ranks at the highest level of evidence available to date in the TTS 'pyramid of evidence' (**Figure 1**).

Planning and conducting RCTs on TTS is difficult to realize due to the relatively low incidence of TTS and its clinical heterogeneity secondary to differences in multiple coexisting comorbidities, etiology (primary and secondary forms), pattern of left ventricular dysfunction (apical or atypical forms), and clinical course (arrhythmias and mechanical complications). Moreover, financial support for the identification of new uses of existing drugs (eg, beta-blockers or RAASi) may be difficult to obtain.

This study suggests the importance of further research for more appropriate management of patients with acute and long-term TTS. A more comprehensive understanding of the pathophysiological mechanisms of TTS and long-term morphological and functional impairment might contribute to the development of new targeted therapies for preventing major cardiovascular events and improving survival.

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