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Systematic review and meta-analysis of incidence and correlates of recurrence of takotsubo cardiomyopathy ☆

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ABSTRACT

Aim: Takotsubo cardiomyopathy (TTC) is a disorder of myocardial inflammation induced by high catecholamine levels and is associated with acute complications. In the long-term TTC is associated with a risk of single or multiple recurrences, but risk of such occurrences is not clear. We performed a systematic review and meta-analysis to identify and consolidate the evidence on the incidence and clinical correlates of cases of TTC recurrence.

Methods: A comprehensive search of four major databases (EMBASE, OVID Medline, PubMed and Google Scholar) was performed from their inception to first week of Jan 2014. We included original research studies, recruiting ≥5 participants, with ≥3 months follow-up, published in English language that reported data on recurrence in patients with TTC.

Results: Out of 298 studies searched, 31 cohorts (1664 TTC patients) were included in the analyses. Out of 74 cases of recurrence, with a mean follow-up of 24.5 months (95% CI, 19.3 to 33 months), extensive recurrence data were available for 23 cases. Cumulative incidence of recurrence was approximately 5% at 6 years. Annual rate of recurrence was approximately 1.5%. Furthermore, 14% of cases had recurrent chest pain and 11% reported dyspnea without definite evidence of recurrent TTC. Discharge medications at index admission included β-adrenoceptor antagonists (BB) in 66.8% and ACE inhibitors (ACEi) and ARB in 67.4%. Recurrence rate was independent of clinic utilization of BB prescription, but inversely correlated ($r = -0.45$, $p = 0.016$) with ACEi/ARB prescription. Patients with severe TTC at index admission were noted to have more recurrences.

Conclusions: (1) TTC is associated with only 1–2% annual recurrence rate but substantially greater frequency of ongoing symptoms. (2) ACEi/ARB rather than BB may reduce risk of recurrence.

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1. Introduction

Takotsubo cardiomyopathy (TTC) is now a well-known cardiac condition that predominantly affects women and can be associated with acute and chronic complications. Interestingly, TTC was first reported only 25 years ago in Japan and one of the earliest descriptions in humans was even more recent [1]. The acute stage of the disease can be complicated by hypotension, shock, arrhythmias, heart failure and death [2]. While our understanding of acute complication is clear, the knowledge of the natural history and long term TTC complications is limited because of relatively small number and limited follow-up of the patients. Recurrence of TTC is common and is a well reported long term issue in TTC cohort [3]. However, the exact incidence and correlates of recurrence are not known. We therefore performed a meta-analysis and systematic review to determine the global incidence of recurrence of TTC and to consolidate the evidence.

In the current study, we sought to determine utilizing a systematic review/meta-analysis approach the incidence of recurrence of TTC episodes and cause of its variability. We also prospectively evaluated the impact of discharge medications, left ventricular ejection fraction (LVEF) and type of stressor during initial episode on recurrence.

2. Methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. We included comparative studies of any design (randomized control trials, cohort, case control and cross sectional). Eligible studies needed to have ≥5 patients and a minimum follow-up of 3 months with confirmed documentation of recurrence of TTC. Inclusion of studies was limited to English language and foreign studies where translation in English was available. When data was reported from interrelating study samples (e.g., publications from the same group), the study with the highest number of

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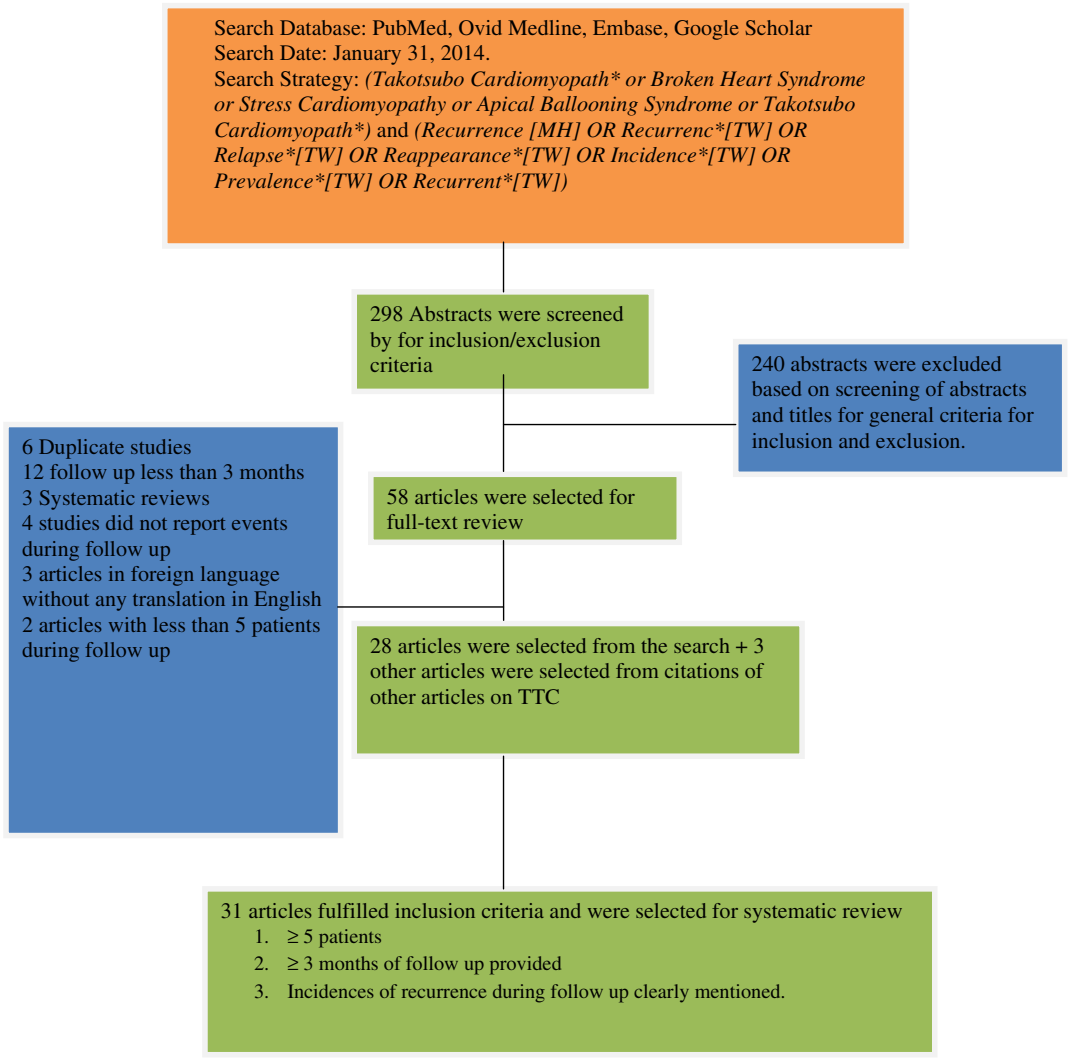

Fig. 1. Schematic of database search and identification of studies.

patients and the longest follow-up was included in the analysis. Single case reports, case series with less than 5 patients or where the follow-up was not conducted were not included. Systematic reviews of TTC were not included in the analysis.

A thorough computer based search was performed using OVID MEDLINE, EMBASE, Google Scholar and PubMed databases. Search terms included (Takotsubo Cardiomyopath* [TW] OR Broken Heart Syndrome [TW] OR Stress Cardiomyopathy [TW] OR Apical Ballooning Syndrome [TW] OR Tako-Tsubo Cardiomyopath* [TW])) and (Recurrence [MH] OR Recurrence*[TW] OR Relapse*[TW] OR Reappearance*[TW] OR Incidence*[TW] OR Prevalence*[TW] OR Recurrent*[TW]). No limit to the start date was applied and the search was conducted up to 31 January 2014. We hand searched the references cited in the previous reviews and important articles on recurrence on TTC. We contacted the corresponding authors of the studies where relevant information was missing [4].

Two reviewers (KS and RS) screened all titles and abstracts individually. This was followed by the full manuscript review of the selected articles by the reviewers. One reviewer (KS) extracted data independently from selected studies using a standardized, pilot tested extraction template. The following data was extracted: study characteristics (author, country where investigation was conducted, study design, number of participants and objective of the study), participant characteristics (age and gender), clinical characteristics (ACS type for TTC, predisposing physical and emotion stressors, left ventricular ejection fraction (LVEF), acute complications, acute mortality, length of stay, discharge medications), recurrences (number and time of recurrence after initial diagnosis) and complications during long term follow up (death, chest pain, dyspnea, fatigue and heart failure).

Two reviewers (RS and KS) assessed quality of included studies using a sub-set of the Tooth et.al, manuscript titled 'Quality of Reporting of Observational Longitudinal Research' [5], including only the 23 quality domains relevant to a meta-analysis of observational studies. We evaluated potential biases using classifications of 'low risk of bias' when data for the criterion were described, 'high risk of bias' when data were not stated and 'unclear risk of bias' when the criterion was not relevant to the study design. Review Manager software version 5.2 was used to make the risk of bias graph. Any classification, which was not straightforward, was solved by discussion with a third reviewer KC.

Continuous variables were reported as means ± standard deviation (SD), while skewed data were described as medians ± interquartile range. Categorical variables were reported using odds ratios (OR) with 95% confidence intervals (CI). If formal meta-analysis was not possible due to a skewed distribution of the number of patients between each study, we overlooked the individual studies and used data as if obtained from a single study. Studies with missing data were excluded from meta-analyses and details extrapolated in the quality and risk of bias assessments. We then used logistic regression to assess the relationship. Significant interaction between variables was considered when $P < 0.05$. All calculations were performed using Review Manager (RevMan, Computer program, Version 5.2, Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2012), SPSS 18.0 software (SPSS, IL, USA) and Microsoft Excel 2010. We divided the studies above and below the median level of percentage of ACE/ARB, BB and recurrence rate and performed Chi square test. The annual incidence of recurrence per hundred patients for each individual study was calculated. Formula for a CI for a population proportion was used to obtain CI for annual recurrence for each individual study.

3. Results

The literature search on TTC and recurrence yielded 298 citations. The abstracts of all the 298 citations were reviewed and 58 articles were chosen for full text review. Of the 58 articles chosen for the full text review, 34 were selected as per the inclusion and exclusion criteria. Six out of 34 studies were noted to be duplicated (from the same group with overlapping patient data sets) and were excluded. Additional 3 articles were found on the hand search leading to a total of 31 [23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53] articles in the systematic review (Fig. 1). Authors

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