Age-Related Variations in Takotsubo Syndrome in the United States

Takotsubo syndrome (TTS) is characterized by profound and often rapidly reversible systolic dysfunction, usually precipitated by sudden emotional or physical stress resulting in excess release of catecholamine.[1,2] The disorder has traditionally been described mainly in postmenopausal women.[3] Advance age has been shown to be associated with adverse clinical outcomes in patients with variety of cardiovascular disorders. Several small studies have described age-related variation in clinical outcomes of TTS patients with conflicting results.[4,5] Cammann et al recently reported poor outcomes in younger TTS patients from the Inter-Tak registry.[6] The registry comprises data predominantly from European Centers. Previous studies have reported geographic variations in treatment and outcomes of patients with cardiovascular diseases.[7,8] Therefore, we conducted this study from a large national database to evaluate if similar intriguing differences are present in the United States population.

The National Inpatient Sample was used to identify patients with primary admitting diagnosis of TTS using International Classification of Diseases-9th (429.93) procedure code from 2009 to 2015.[9] All patients were stratified according to age at index hospitalization and categorized into 3 groups (younger: ≤50 years, middle age: 51 to 74 years, and older: ≥75 years). Data on patient demographics, co-morbidities, hospital characteristics (teaching status and bed size), and in-hospital complications were extracted. In-hospital outcomes were compared among the 3 age groups. Primary outcome of interest was in-hospital mortality. Secondary outcomes included cardiogenic shock, cardiac arrest, vasopressor use, ventricular arrhythmias (ventricular tachycardia/fibrillation), and use of invasive ventilation. For categorical variables results were presented as percentages, and compared using Pearson chi-square or Fisher's exact test where ever appropriate. For continuous variables, results were presented as mean ± Standard Deviation and compared using Student *t* test, or Mann-Whitney test. Multivariable logistic regression model adjusted for baseline co-morbidities was used to assess adjusted risk of younger and older age using middle age group as reference. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to report the results of logistic regression analysis. All p-values were 2-sided, and statistical significance was set at <0.05. Statistical analysis was performed using SPSS software version 25.0 (IBM Corp., Armonk, New York). This study was exempted from local IRB/ethical approval as National Inpatient Sample contains deidentified data.

Of 40,326 patients with TTS, 11.2% of the patients were ≤50 years of age, 59.95% were 51 to 74 years of age, and 29.0% were ≥75 years of age (Figure 1). Young patients were more likely to be male, and less likely to have hypertension, diabetes mellitus, atrial fibrillation, heart failure, peripheral vascular disease, previous stroke, valvular heart disease, anemia, cancer, chronic kidney disease, and chronic lung disease compared with older age group (p for all <0.05). Our analysis showed that in-hospital mortality was higher in the older age group compared with middle and younger age group (1.9% vs 1.0% vs 1.1%. p <0.001). Younger patients were more likely to have cardiogenic shock (11.9 % vs 4.8% vs 3.4%, p <0.001), cardiac arrest (3.3% vs 1.1% vs 0.8%, p < 0.001), invasive ventilation (14.7% vs 5.4% vs 3.7%, p <0.001), circulatory support (3.0% vs 2.6% vs 1.6%, p <0.001) and ventricular arrhythmias (6.8% vs 3.2% vs 3.5%, p <0.001). There was no significant difference noted for vasopressor use (1% vs 1% vs 1.2%, p = 0.20) among the 3 age groups (Figure 1). On multivariate analysis, using middle age as a reference group, older age was independently associated with in-hospital mortality (OR 1.68; 95% CI 1.37 to 2.07), whereas young age was independently associated with cardiac arrest (OR 2.92; 95% CI 2.33 to 3.63), and ventricular arrhythmias (OR 2.09; 95% CI 1.81 to 2.43).

In this observational analysis of patients with primary admitting diagnosis of TTS in the United States, we examined the comparative outcomes in 3 different age groups similar to Inter-Tak registry. Our findings indicate that young patients have worse in-hospital outcomes. However, mortality remains higher in older patients with TTS.

Our analysis included 40,326 patients with TTS, whereas Inter-TAK registry had 2098 patients. Age group distribution percentage was found to be almost identical in our study population when compared to Inter-Tak registry. Similarly, higher percentage of male patients was noted in the younger age group compared with middle and older age group. When compared with Inter-TAK registry study, our analysis has shown similar results in terms of higher rates of cardiogenic shock, cardiac arrest and respiratory support in younger patients compared with middle and older age population. However, our analysis revealed slightly higher mortality in older age group compared with younger and middle age group. Previous research has shown that male TTS patients have poor in-hospital outcomes compared with their female counterparts.[10] In our study, a significantly higher percentage of patients in the younger age group were males, which may partly explain the poor in-hospital outcomes. In addition, the pathophysiological to such untoward outcome is possibly mediated by an inherent higher or more prolonged catecholamine unbridled surge in younger TTS patients.

There are several limitations of our study. Our analysis is based on an administrative database, and hence lacks information on TTS triggers, laboratory variables, medications used, and echocardiographic parameters. Also, being an inpatient database, it lacks mid- and long-term follow up. Despite these limitations, our analysis included a large

Ethical/IRB approval: Since Nationwide Readmission Database contains deidentified data, our study was exempted from local IRB/ethical approval.

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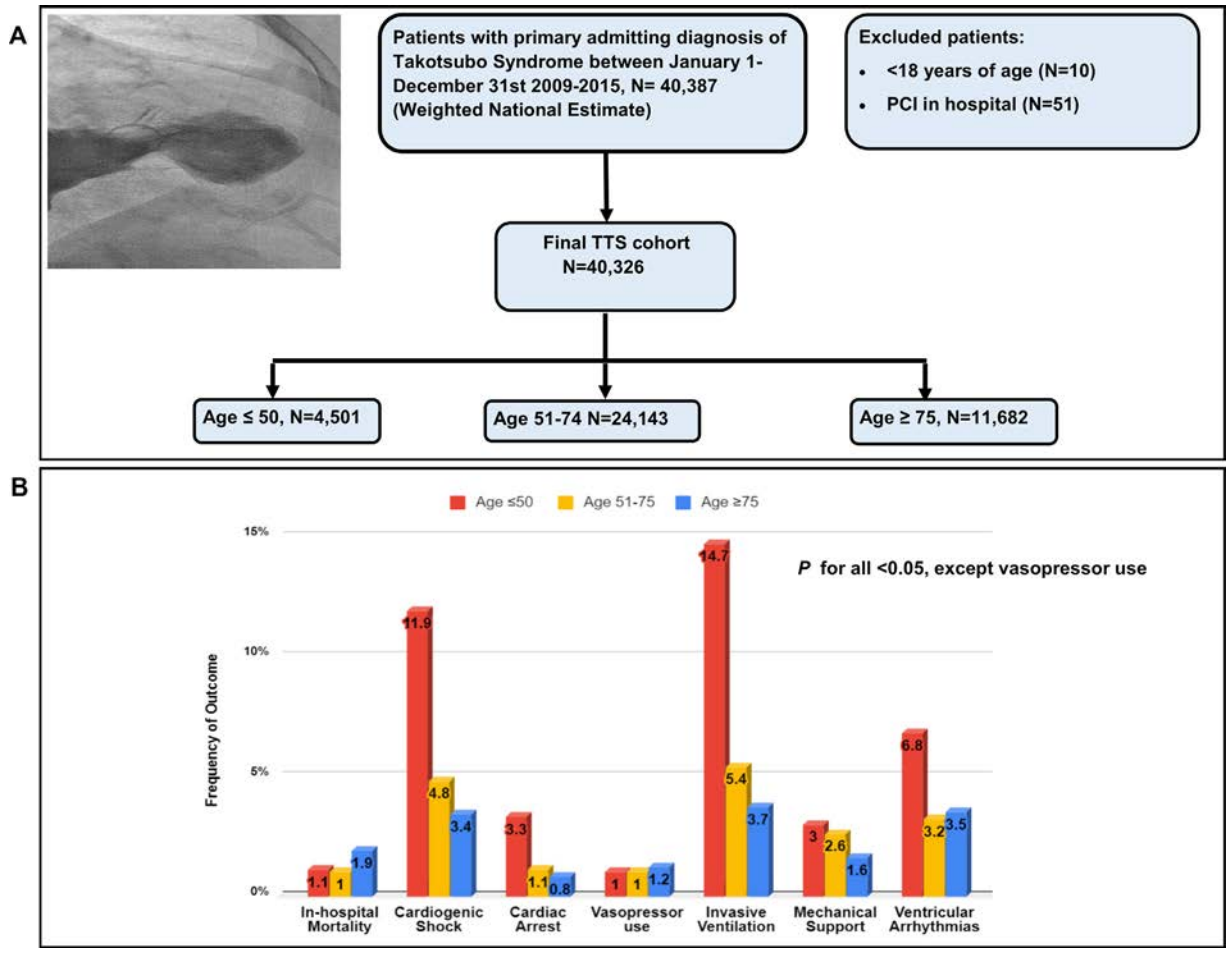

Figure 1. (*A*) Study population selection flowchart; (*B*) In-hospital complications in patients with primary admitting diagnosis of Takotsubo syndrome according to age groups.

number of TTS patients across the United States which yields a significant strength to our study.

To conclude, in accordance with Inter-TAK registry analysis, our study reveals that a substantial number of TTS patients are younger. Also, this group of patients are critically ill with higher rates of cardiogenic shock, cardiac arrest, circulatory support, and ventricular arrhythmias. In addition, they require intensive care stay with invasive ventilation. However, in-hospital mortality was still higher in the older age group. Further studies are needed to better understand the pathophysiological mechanism of poor outcomes in younger TTS patients.

Disclosure

The authors declare no conflict of interest.

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Meta-analysis of Usefulness of Drug Coated Balloon Versus Standard Balloon in the Treatment of Femoropopliteal In-Stent-Restenosis

The current guidelines for the treatment of femoropopliteal disease recommend percutaneous transluminal angioplasty either alone or in combination with atherectomy, drug-coated balloon angioplasty or angioplasty integrated with stent implantation as feasible alternatives. Although the use of stents has improved the patency rates following percutaneous transluminal angioplasty in femoropopliteal disease, the rates of in-stent stenosis (ISR) still ranges from 15% to 32%. The evidence and guidelines for the management of ISR after femoropopliteal stent implantation are not conclusive. Studies have compared drug-coated balloon (DCB) versus standard balloon for the treatment of femoropopliteal ISR in the past. We performed an updated meta-analysis of randomized controlled trials (RCTs) and observation studies comparing DCB versus standard balloon for the treatment of femoropopliteal ISR.

We performed a systematic search of the PubMed and Cochrane databases from the inception of the databases to March 2020. The inclusion criteria were RCTs and observation studies comparing DCB versus standard balloon as a treatment option for femoropopliteal stent ISR. The outcomes of interest were all-cause mortality and target vessel revascularization. We used the inverse variance method with the Paule-Mandel (PM) estimator of tau with Hartung-Knapp-Sidik-Jonkman adjustment to analyze risk ratio (RR) with 95% confidence interval (CI) and 95% prediction interval. All analysis were carried out using R version 3.6.2.

Five studies, 4 RCTs and 1 observational studies were included in the final analysis.[1−5] There was no difference in the risk of all-cause mortality between DCB versus standard balloon as a treatment modality for the treatment of femoropopliteal stent ISR (RR 0.87, 95% CI 0.37 to 2.04, $I^2 = 0\%$, 95% PI 0.28 to 2.76) (Figure 1). Likewise, there was no difference in the risk of target vessel revascularization between the treatment strategies for femoral ISR (RR 0.87, 95% CI 0.37 to 2.04, I2 = 0%, 95% PI 0.28 to 2.76) (Figure 1). The pooled estimate had considerable heterogeneity, however, individual studies were heterogeneous based on treatment effect and were not heterogeneous based on the conclusion.

The present meta-analysis studied DCB versus standard balloon angioplasty as a treatment modality for femoropopliteal stent ISR and found no difference in the risk of all-cause mortality or target vessel revascularization between two treatment modality. The European society of cardiology guidelines provides a

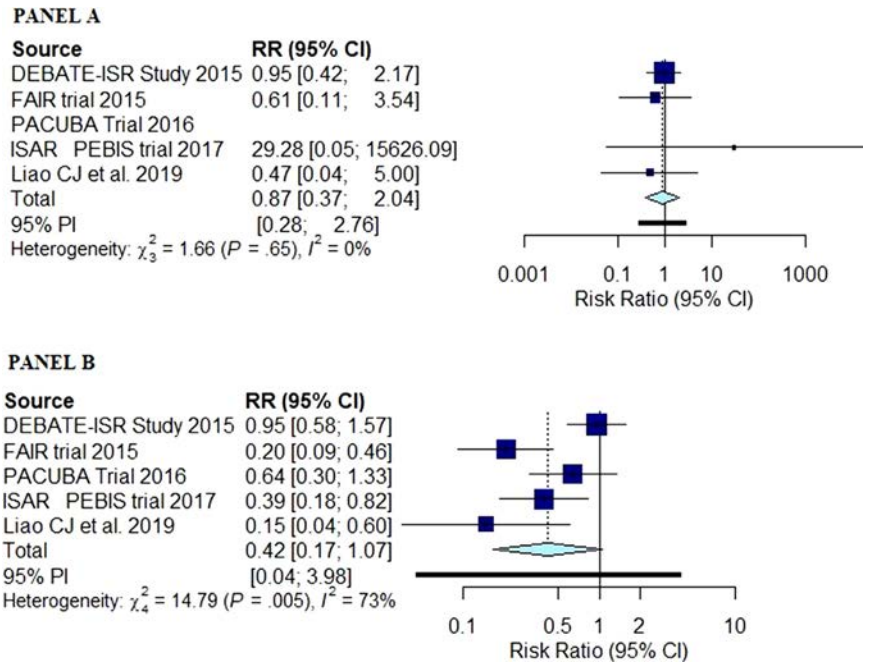

Figure 1. Forest plot for *(PANEL A)* All-cause mortality, *(PANEL B)* target vessel revascularization. CI = confidence interval; PI = prediction interval; RR = Risk Ratio. Risk Ratio for individual study is indicated by square and 99% confidence interval by horizontal line. Overall risk ratio and their confidence interval are represented by diamond.