JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 68, NO. 7, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.05.065

ORIGINAL INVESTIGATIONS

# Predictors of Early Cerebrovascular Events in Patients With Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement

Vincent Auffret, MD, MSc,[a,b] Ander Regueiro, MD,[a] María Del Trigo, MD,[a] Omar Abdul-Jawad Altisent, MD,[a] Francisco Campelo-Parada, MD,[a] Olivier Chiche, MD,[a] Rishi Puri, MBBS, PhD,[a] Josep Rodés-Cabau, MD[a]

## ABSTRACT

**BACKGROUND** Identifying transcatheter aortic valve replacement (TAVR) patients at high risk for cerebrovascular events (CVE) is of major clinical relevance. However, predictors have varied across studies.

**OBJECTIVES** The purpose of this study was to analyze the predictors of 30-day CVE post-TAVR.

**METHODS** A systematic review of studies that reported the incidence of CVE post-TAVR while providing raw data for predictors of interest was performed. Data on study, patient, and procedural characteristics were extracted. Crude risk ratios (RRs) and 95% confidence intervals for each predictor were calculated.

**RESULTS** Sixty-four studies involving 72,318 patients (2,385 patients with a CVE within 30 days post-TAVR) were analyzed. Incidence of CVE ranged from 1% to 11% (median 4%) without significant differences between single and multicenter studies, or according to CVE adjudication availability. The summary RRs indicated lower risk for men (RR: 0.82; $p = 0.02$) and higher risk for patients with chronic kidney disease (RR: 1.29; $p = 0.03$) and with new-onset atrial fibrillation post-TAVR (RR: 1.85; $p = 0.005$), and for procedures performed within the first half of center experience (RR: 1.55; $p = 0.003$). The use of balloon post-dilation tended to be associated with a higher risk of CVE (RR: 1.43; $p = 0.07$). Valve type (balloon-expandable vs. self-expandable, $p = 0.26$) and approach (transfemoral vs. nontransfemoral, $p = 0.81$) did not predict CVE.

**CONCLUSIONS** Female sex, chronic kidney disease, enrollment date, and new-onset atrial fibrillation were predictors of CVE post-TAVR. This study provides effect estimates to identify high-risk TAVR patients for early CVE, providing possible guidance for tailored preventive strategies. (J Am Coll Cardiol 2016;68:673–84)


Transcatheter aortic valve replacement (TAVR) has expanded considerably in the past decade and now is standard of care for patients with aortic stenosis (AS) deemed at prohibitive surgical risk, while posing a reasonable alternative in high-operative risk patients (1). The recently published PARTNER-2 (Placement of AoRTic TraNscathetER-2) trial (2) confirmed the results of prior studies (3,4),

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Quebec Heart & Lung Institute, Laval University, Quebec City, Quebec, Canada; and the [b]Rennes 1 University, Signal and Image Processing Laboratory, Rennes, France. Dr. Auffret received fellowship support from the Fédération Française de Cardiologie; and has received research grants from Abbott, Edwards Lifesciences, Medtronic, Biosensors, Terumo, and Boston Scientific. Dr. Rodés-Cabau has received research grants from Edwards Lifesciences, Keystone, Medtronic, and St. Jude Medical. Drs. Regueiro, Del Trigo, and Abdul-Jawad Altisent have received fellowship support from the Fundacion Alfonso Martin Escudero (Spain). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Deepak L. Bhatt, MD, MPH, served as Guest Editor for this paper. Anthony Bavry, MD, served as Assistant Guest Editor for this paper.

Manuscript received April 22, 2016; accepted May 14, 2016.

**ABBREVIATIONS AND ACRONYMS**

**AF** = atrial fibrillation

**AS** = aortic stenosis

**BPD** = balloon post-dilation

**CAD** = coronary artery disease

**CI** = confidence interval

**CKD** = chronic kidney disease

**CVE** = cerebrovascular events

**DAPT** = dual antiplatelet therapy

**ESV** = Edwards-Sapien valve

**MSV** = Medtronic CoreValve

**NOAF** = new-onset atrial fibrillation

**PAD** = peripheral artery disease

**RR** = risk ratio

**SAPT** = single antiplatelet therapy

**TAVR** = transcatheter aortic valve replacement

**TF** = transfemoral

**TIA** = transient ischemic attack

**TV-in-TV** = transcatheter valve within a transcatheter valve

**TVE/M** = transcatheter valve embolization or migration

paving the way for a shift toward treating lower surgical-risk patients. Nonetheless, ongoing concerns about periprocedural complications could still compromise such an expansion.

Compared with earlier TAVR appraisals (5,6), recent studies (2,7–11) suggested a decrease in cerebrovascular events (CVE) over time, down to rates of 2.5% to 3%. However, CVE still represents 1 of the most dreadful complications of TAVR. Numerous potential risk factors for CVE have been highlighted by reviews (12–15), and a few dedicated studies (16–21) identified independent predictors that appear to differ from one study to another. Given that the exact place of embolic protection devices in the TAVR therapeutic armamentarium and the optimal antithrombotic regimen post-TAVR remain debated, it is nonetheless of paramount importance to have reliable predictors of CVE in order to offer the possibility of tailored peri- and post-procedural management to patients undergoing TAVR. Therefore, this study sought to provide effect estimates for clinically relevant predictors of CVE within 30 days post-TAVR.

SEE PAGE 685

## METHODS

**SEARCH STRATEGY.** A systematic review of published data on CVE in patients undergoing TAVR was conducted in accordance to the guidance and reporting items specified in the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (22). A broad computerized search was performed to identify all relevant studies from PubMed and EMBASE databases. The following key word terms were used: *transcatheter aortic valve*, *TAVI*, *TAVR*, *transcutaneous aortic valve*, and *percutaneous aortic valve*. The MeSH term *Transcatheter Aortic Valve Replacement* was also used. The search strategy is outlined in the Online Appendix. We limited our search to studies published after January 1, 2003, and databases were last accessed on December 9, 2015.

**ELIGIBILITY CRITERIA AND STUDY SELECTION.** We included any study of original design including at least 50 patients that assessed the incidence of CVE post-TAVR between 2 groups of patients dichotomized according to the presence/absence of a potential predictor. We included studies in which quantitative raw data were available that enabled the calculation of risk ratios (RRs) for the incidence of CVE for the predictors of interest. When potential overlapping study populations were detected (based on participating institutions and inclusion periods), the most recent publication or the publication with the most information of interest was included in the analysis. This process was conducted for each predictor separately. Case reports or studies published in a non-English language were excluded.

Two investigators (V.A. and A.R.) independently conducted the literature searches, study eligibility assessment, and data extraction in duplicate. Any discrepancies were resolved by consensus by a third investigator (J.R.-C.).

**DATA EXTRACTION.** We extracted data of patients and studies using a standardized data abstraction sheet. The following study-, patient-, and procedure-related data were extracted from the main paper and accompanying supplemental appendix: study design, number of participating centers, region, and period of enrollment, number of patients, length of follow-up, number of CVE post-TAVR, age, sex, baseline procedural risk assessment (by logistic European System for Cardiac Operative Risk Evaluation [EuroSCORE] or Society of Thoracic Surgeons Predicted Risk of Mortality [STS-PROM] score), number of patients with prior stroke and atrial fibrillation (AF) at baseline, access site, valve type, number of patients requiring balloon post-dilation (BPD) or acute valve-in-valve (TV-in-TV), and in-hospital or 30-day all-cause mortality as reported by the authors.

**ENDPOINT.** Given the important heterogeneity in reporting CVE across TAVR studies, we used the following pre-specified hierarchical order to define the single outcome used for each study: 30-day stroke/transient ischemic attack (TIA); 30-day all stroke; 30-day major stroke; in-hospital stroke/TIA; in-hospital all stroke, and in-hospital major stroke. The selected outcomes were then pooled to provide summary RRs of short-term CVE after TAVR.

**PREDICTORS OF INTEREST.** On the basis of recently published studies and review (5,12–21), we focused on 16 previously proposed predictors of CVE that could be separated as patient- and procedural-related. The following patient-related factors were studied: age (≥90 years); sex (male); obesity (i.e., body mass index ≥30 kg/m$^2$); diabetes mellitus; prior AF; known coronary artery disease (CAD); chronic kidney disease (CKD) defined by an estimated glomerular filtration rate <60 ml/min·1.73 m$^2$; and peripheral artery disease (PAD). The procedure-related predictors included in the present study were as follows: nontransfemoral (TF) approach versus TF approach; the self-expandable valve (CoreValve, Medtronic, Dublin, Ireland) (MCV) versus balloon-expandable valve