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# Extracranial carotid artery stenosis and outcomes of patients undergoing transcatheter aortic valve replacement☆

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ABSTRACT

*Background:* Transcatheter aortic valve replacement (TAVR) is an alternative to open cardiac surgery in selected patients with severe aortic stenosis (AS). Carotid artery stenosis (CAS) has been associated with an increased risk of stroke following cardiac surgery, although the association between CAS and outcomes following TAVR is unclear. We therefore sought to study the prognostic impact of CAS on outcomes of patients undergoing TAVR.
*Methods:* Consecutive patients (n = 312) with severe symptomatic AS who underwent a carotid Doppler study immediately prior to TAVR were followed prospectively. Major adverse cardiovascular event (MACE) rates were stratified by the presence of CAS, defined in accordance with current practice guidelines.
*Results:* Carotid atherosclerosis (CA, defined as any carotid plaque) was present in 301 (96.5%) of patients and CAS (peak systolic velocity [PSV] ≥ 125 cm/s; ≥50% diameter stenosis) in 97 (31.1%) patients. Severe CAS (PSV ≥ 230 cm/s; ≥70% stenosis, or near occlusion) was found in 20 (6.4%) patients. At long-term follow-up (248 ± 205 days), composite (20.9% vs. 19.6%, p = 0.50) and individual (all-cause mortality, stroke, myocardial infarction, readmission for heart failure [19.5%% vs. 14.4%%, p = 0.24; 3.3% vs. 2.1%, p = 0.47; 1.4% vs. 0%, p = 0.22; and 7.9% vs. 8.2%, p = 0.84 respectively]) MACE rates did not differ significantly between patients without versus those with CAS. By multivariate analysis, CAS was not independently predictive of late MACE rates (HR = 0.85, [95%CI 0.50–1.78], p = 0.85).
*Conclusions:* CAS was not associated with worse outcomes following TAVR. The relative prognostic significance of CAS in patients considered for either surgical or transcatheter valve replacement merits further research.


## 1. Introduction

In appropriately selected patients with severe symptomatic aortic stenosis (AS), transcatheter aortic valve replacement (TAVR) is a safe and efficacious alternative to surgical valve replacement [1–3]. Notwithstanding, ischemic stroke, which complicates TAVR in 1.5–6% [4] remains an important safety concern. Mechanisms responsible for stroke in the setting of TAVR include atheroembolism from the implantation site and aortic arch [4,5], though hemodynamic compromise during rapid ventricular pacing and valve deployment may also be of importance [6], particularly in patients with obstructive carotid artery disease.

Extracranial carotid artery stenosis (CAS) is associated with an enhanced risk of periprocedural stroke in patients undergoing isolated coronary artery bypass surgery [7] and possibly isolated aortic valve replacement [8,9]. These associations notwithstanding, a direct causal role for CAS in the pathogenesis of adverse neurological outcomes following cardiac surgery is questionable [10] and recent practice guidelines do not provide specific recommendations concerning systematic screening for CAS or its management in patients undergoing valve surgery [7,11,12]. Data on the prognostic implications of CAS in patients undergoing TAVR are even more limited so the role of screening and carotid revascularization in this setting is unknown.

In a previous study, we reported a high prevalence of CAS in TAVR candidates [13]. The present study represents an extension of our previous report, examining the long-term prognostic impact of carotid artery disease in a single-center, prospective TAVR registry.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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## 2. Methods

### 2.1. Study population

Consecutive patients (n = 312) undergoing non-emergent TAVR between 08/2012 and 05/2015 for whom an interpretable preprocedural carotid Doppler ultrasonic study was available constitute the present study cohort. Following informed consent, participants were enrolled in the Tel-Aviv Prospective Angiography Study, approved by the institutional ethical committee as previously described [13]. Enrolment in the registry involved a routine carotid Doppler ultrasound study during hospitalization for TAVR, prior to the procedure itself. Diagnosis of severe AS was made on the basis of clinical, echocardiographic and hemodynamic criteria. Suitability and eligibility for TAVR was determined by a Heart Team, consisting of an interventional cardiologist, an echocardiographer and a cardiac surgeon [13].

### 2.2. TAVR procedure

Procedural stages have been described previously [13]. One of the aortic valve prostheses commercially available throughout the study period were used as follows: The CoreValve or Evolut-R prostheses (Medtronic, MN, USA) in 189 patients, the Sapien XT or S3 prostheses (Edwards Lifesciences, California, USA) in 116, the Lotus prosthesis (Boston Scientific, Natick, Massachusetts) in 1 and the Portico Transcatheter Aortic Heart Valve (St. Jude medical, MN, USA) in 4. Two individuals did not receive a prosthetic valve due to intraprocedural complication/mortality prior to device implantation. Given the small number of Portico and Lotus implants, these patients were grouped with the CoreValve recipients (in the self-expandable prosthesis category) for all analyses. Sapien XT and S3 recipients were grouped as the balloon-expandable prosthesis category.

### 2.3. Definition of CAS

The Carotid Doppler ultrasound protocol has been previously described [14]. Briefly, the internal carotid arteries were scanned using carotid duplex equipment (HD11 XE, Philips healthcare, Andover, MA) with a 3–12 MHz linear-array transducer. Internal CAS was evaluated by the maximum percentage of diameter reduction recorded by B-mode ultrasound, and by the peak systolic and diastolic velocities (PSV and PDV, respectively) per Doppler. Lesion severity was defined as the greatest stenosis observed either on the right or left internal carotid artery. Ultrasound and Doppler findings were classified according to consensus imaging guidelines [15]: normal study (PSV < 125 cm/s with no signs of atherosclerotic lesions); mild CAS (PSV < 125 cm/s in the presence of an atherosclerotic lesion); moderate CAS (PSV 125–230 cm/s, corresponding to 50–70% diameter stenosis); severe CAS (PSV > 230 cm/s, >70% diameter stenosis); total or near occlusion (defined as zero PSV and no visible flow). For the purposes of the present study, CAS was defined as any carotid lesion exceeding 50% diameter stenosis, whereas evidence of any atherosclerotic plaque, regardless of lesion severity, was considered as carotid atherosclerosis (designated as CA). The study definition for the symptomatic status of identified carotid lesions was in keeping with the definitions used in contemporary randomized trials of carotid revascularization (i.e., no history of an ipsilateral stroke or transient ischemic attack within the 6-months preceding TAVR [16].

#### 2.3.1. Study endpoints

The primary endpoint was the composite rate of major adverse cardiovascular events (MACE), including all-cause mortality, stroke, myocardial infarction, and readmission for heart failure (defined as any admission for signs and symptoms of heart failure following discharge from the index TAVR hospitalization). Additional endpoints were periprocedural and 30-day safety events including new pacemaker requirement, vascular complications, bleeding events and acute kidney injury. All endpoints were defined according to the VARC-2 criteria [17].

### 2.4. Statistical analysis

All data are displayed as mean (±standard deviation) for continuous variables and as the number (percentage) of patients in each group for categorical variables. Continuous variables were compared with the student's *t*-test following Levene's test for homogeneity. Categorical variables were compared with the $\chi^2$ and Fischer exact tests. Cox proportional hazards models in which MACE and all-cause mortality were the outcomes evaluated were adjusted for CAS, baseline variables and periprocedural complications found to be significant in the univariate models. All analyses were considered significant at a 2-tailed *P* value of less than 0.05. The SPSS statistical package was used to perform all statistical evaluation (SSPS, Chicago, IL).

## 3. Results

### 3.1. Baseline features

Of 312 patients included in the study, CA was evident in the majority (301 [96.5%]), CAS of any degree was present in 97 (31.1%), and severe CAS found in 20 (6.4%). In all patients with identified CAS, the carotid disease was considered asymptomatic (i.e., no history of an ipsilateral stroke or transient ischemic attack within the 6-months preceding TAVR). Bilateral CAS of any degree was present 32 (10.2%) patients, with severe bilateral CAS present in only one patient (0.3%). Baseline demographic, clinical, and procedural characteristics for the study population stratified by the presence of CAS are presented in Table 1. Manifest vascular disease and the presence of co-morbidities (also reflected in the Euro II and STS scores) were more frequent in patients with versus those without CAS, whereas baseline echocardiographic features such as valve area and left ventricular ejection fraction were similar in both patient groups.

#### 3.1.1. Clinical outcomes by CAS status

Complete (i.e., all study endpoints) follow-up was available for 312 patients (248 ± 205 days, median 204 days). All-cause mortality data were available at 688 ± 331 days. MACE occurred with similar rates in patients with versus those without CAS (Fig.1). As with the composite MACE endpoint, the rates of its individual components (stroke, myocardial infarction and readmission due to heart failure) did not differ significantly among patients without CAS compared to those with either CAS of any degree, severe or bilateral CAS (Table 2).

With regards to the other study endpoints and periprocedural safety, acute kidney injury (stage ≥ 2) occurred more commonly in patients with severe CAS compared with those without CAS or those with only moderate CAS. Otherwise, procedural safety measures did not differ according to CAS status (Table 2).

#### 3.1.2. Correlates of MACE

Univariate and multivariate predictors of late MACE by Cox proportional hazard analysis are shown in Tables 3 and 4, respectively. CAS (any degree or severe) was not independently associated with either the primary composite endpoint (HR = 0.85, 95%CI 0.50–1.78, p = 0.85; HR = 0.34, 95% CI 0.13–2.00, p = 0.34, respectively) or all-cause mortality (HR = 0.94, 95%CI 0.45–1.96, p = 0.87; HR = 0.37, 95%CI 0.08–1.77, p = 0.21, respectively).

## 4. Discussion

The principal finding of the present study is that although it is common in TAVR candidates, the presence of CAS does not adversely impact patient outcomes following this procedure.

### 4.1. CAS and outcomes following surgical valve replacement

Clinical data prior to the TAVR era pertaining specifically to the impact of CAS on the outcomes of patients undergoing surgical aortic valve replacement are scarce. In a study by Anselmi et al. in patients undergoing isolated aortic valve surgery (n = 498) [9], moderate (≥50 − ≤69%) or severe (≥70%) CAS was found in 35% and 6%, respectively. The risk of perioperative adverse neurological events in patients with severe CAS was roughly double that observed in those with wither moderate or no CAS. During long-term follow-up (≈7-years), adverse cerebrovascular events were more common in patients with moderate CAS compared to those without CAS. In a separate study from Germany (n = 1014) [8], severe CAS (>70%) was identified in 9% of patients undergoing surgical aortic valve replacement with a stentless valve and was found to be an independent predictor of stroke at late follow-up (≈7-years). In-hospital stroke rates were not reported. Conversely, Zayed et al. analyzed Doppler data from 177 patients undergoing isolated valve surgery, of whom 98 patients had severe AS [18]. Overall, only 5 (2.8%) patients in this study had severe (≥70%) CAS. However, the prevalence of CAS specifically in AS patients was not reported. Even under the assumption that all carotid stenoses identified in this study occurred in patients with AS, the prevalence of clinically-significant CAS could not have exceeded 5% so the very low prevalence of CAS in this study did not permit meaningful outcome analyses.

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