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Effects of coronary artery disease in patients undergoing transcatheter aortic valve implantation: A study of age- and gender-matched cohorts

Anna Franzone [a,1,2], Stefan Stortecky [a,1,2], Lorenz Räber [a,2], Dik Heg [b,2], Kyohei Yamaji [a,2], Raffaele Piccolo [a,2], Masahiko Asami [a,2], Jonas Lanz [a,2], Fabien Praz [a,2], Kostantinos Koskinas [a,2], Thomas Zanchin [a,2], Peter Wenaweser [a,2], Marco Valgimigli [a,2], Peter Jüni [c,d,2], Thomas Pilgrim [a,2], Stephan Windecker [a,*,2]

[a] Department of Cardiology, Swiss Cardiovascular Center, University Hospital, Bern, Switzerland
[b] Institute of Social and Preventive Medicine and Clinical Trials Unit, Bern University Hospital, Bern, Switzerland
[c] Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute of St. Michael's Hospital, Canada
[d] Department of Medicine, University of Toronto, Canada

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ABSTRACT

Background: The prognostic role of concomitant coronary artery disease (CAD) among patients undergoing transcatheter aortic valve implantation (TAVI) is still uncertain.
Methods: Data from the Bern TAVI Registry and the Bern PCI Registry were analyzed. Patients with concomitant CAD undergoing TAVI (TAVI + CAD) were age- and gender-matched to the following two cohorts: patients without CAD undergoing TAVI (TAVI-noCAD) and patients with stable CAD undergoing percutaneous coronary intervention (CAD-noAS). Major adverse cardiovascular and cerebrovascular events (MACCE), defined as the composite of cardiovascular death, myocardial infarction, or cerebrovascular events, represented the primary endpoint at 1-year.
Results: Out of 9478 procedures performed between 2007 and 2013 (807 TAVI; 8671 PCI), three cohorts, each including 248 subjects, were derived. At 1-year, MACCE were significantly increased among TAVI + CAD compared with TAVI-noCAD (16.8% vs. 9.8%, hazard ratio, HR, 1.75, 95% confidence intervals, CI, 1.06–2.89, p = 0.030) and CAD-noAS patients (16.8% vs. 9.5%, HR 1.85, 95%CI 1.11–3.09, p = 0.018) whereas no difference was found between TAVI-noCAD and CAD-noAS patients. The higher rate of MACCE among TAVI + CAD patients was mainly driven by an increased risk of cardiovascular mortality compared with the TAVI-noCAD (HR 1.86, 95%CI 1.03–3.36, p = 0.040) and CAD-noAS cohorts (HR 2.29, 95%CI 1.22–4.30, p = 0.010). The 1-year rate of MACCE was similar between TAVI-noCAD and CAD-noAS patients (9.8% vs. 9.5%, HR 1.05, 95%CI 0.59–1.87, p = 0.86).
Conclusions: Concomitant CAD in the setting of TAVI conveyed an increased risk of ischemic events and cardiovascular mortality at 1-year follow-up.

1. Introduction

Aortic stenosis (AS) and coronary artery disease (CAD) frequently coexist owing to several common pathobiological factors [1,2]. Obstructive CAD has been associated with impaired clinical outcomes among patients undergoing surgical aortic valve replacement [3,4]. Yet, its prognostic role in the setting of transcatheter aortic valve implantation (TAVI) remains controversial [5–7]. Indeed, while some studies showed an increased risk of mortality and cardiovascular events after TAVI in the presence of concomitant CAD [8–10], other studies provided neutral findings [11–14]. A lack of uniformity in the definition of CAD and a limited power are important limitations inherent to these studies [15,16]. In this context, the evaluation of the prognostic effect of concomitant CAD is also challenged by the risk profile of TAVI patients. Advanced age is likely to be a significant confounding factor with the potential to camouflage or rather heighten the risk of CAD-related outcomes after TAVI. Furthermore, the need for myocardial revascularization was a key exclusion criterion among pivotal trials that have established the role of TAVI in the management of severe AS [15,16].

Therefore, the aim of the present study was to define the prognostic role of CAD among TAVI patients by comparing the 1-year clinical outcomes of patients with concomitant CAD undergoing TAVI with age- and gender- matched cohorts of TAVI patients without CAD and patients with stable CAD in absence of AS who underwent percutaneous coronary intervention (PCI).

* Corresponding author at: Department of Cardiology, Bern University Hospital, University of Bern, 3010 Bern, Switzerland.
E-mail address: stephan.windecker@insel.ch (S. Windecker).
[1] Drs. Franzone and Stortecky contributed equally to this work.
[2] This author takes 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. Patient population and study cohort definitions

The present study presents a three-arm, age- and gender-matched cohort design. All patients undergoing TAVI were included in the Bern TAVI registry (which is part of the Swiss TAVI Registry, NCT01368250) and all patients undergoing PCI were included in the Bern PCI registry (NCT02241291). All TAVI patients were evaluated for the presence of significant CAD, defined as history of surgical and/or percutaneous coronary revascularization, previous myocardial infarction (MI) and/or at least one significant lesion (diameter stenosis ≥50%) at the site of a major native coronary vessel or bypass graft by visual assessment in the coronary angiography performed within four weeks prior to TAVI. From the Bern PCI registry, only patients with stable CAD were deemed eligible for matching.

The study complied with the declaration of Helsinki. Both registries were approved by the local ethics committee and all patients gave written informed consent to participate.

2.2. Procedures

The eligibility for TAVI was discussed within the local Heart Team and based on an extensive clinical and anatomical pre-operative assessment. Patients eligible for TAVI with concomitant CAD received PCI prior TAVI or during the same procedure on the basis of a consensus decision taking into account the myocardium at risk, the lesion complexity and symptom status. At this regard, internal guidelines, recommending preventive revascularization of significant proximal stenosis of major coronary arteries were followed. Functional ischemia testing was not routinely performed in view of the low diagnostic yield of stress testing in patients with aortic stenosis.

Patients in the TAVI cohort received either the Medtronic CoreValve bioprosthesis (Medtronic, Minneapolis, MN, USA), the Edwards Sapien transcatheter heart valve (Edwards LifeSciences, Irvine, CA, USA), or the Symetis Acurate TA aortic bioprosthesis (Symetis, Ecublens, Switzerland) through the femoral, transapical, or subclavian access, as previously described [17].

Current practice guidelines were followed in all patients in case of PCI [18]. Unfractionated heparin at a dose of at least 5000 IU or 70–100 IU/kg was administered during the procedure. Management of antithrombotic medication consisted of dual antiplatelet therapy (DAPT) with acetylsalicylic acid and clopidogrel initiated before, at the time, or immediately after the procedure and recommended typically for 6 months after TAVI and for 12 months after PCI (with or without TAVI). Acetylsalicylic acid was continued indefinitely after single or combined procedures.

2.3. Clinical follow-up

Patients included in the Bern TAVI registry were prospectively evaluated for the occurrence of adverse cardiac and cerebrovascular events in-hospital, at discharge and were contacted after 30 days and 12 months by means of clinic visit or standardized telephone interview. Patients in the Bern PCI registry were prospectively followed after the index PCI and were contacted after hospital discharge, during any unscheduled hospital visit or planned hospital visits (e.g. staged procedures), and at 1 year after the index procedure.

2.4. Study endpoints and definitions

The primary study endpoint was a composite of major adverse cardiovascular and cerebrovascular events (MACCE), including cardiovascular death, myocardial infarction (MI), or cerebrovascular events, at 1 year. Secondary endpoints were the individual components of the primary endpoint as well as all-cause mortality.

Events occurring in patients undergoing TAVI were adjudicated by a clinical event committee consisting of interventional cardiologists and cardiac surgeons, according to the updated recommendations of the Valve Academic Research Consortium (VARC-2).

For patients in the Bern PCI Registry, a clinical event committee adjudicated all adverse events. Cardiac death was defined as any death due to an immediate cardiac cause, procedure-related mortality, and death of unknown cause; MI was defined as peri-procedural (<48 h after PCI) in presence of electrocardiographic signs of ischemia and elevation of biomarkers of cardiac damage (increase in CK to more than twice the normal value with increased values of CK-MB fraction or troponin higher than usual) or spontaneous (>48 h after PCI) if recurrent thoracic chest pain or ischemic equivalent symptoms occurred together with new ischemic electrocardiographic signs and biomarker elevation with rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile upper reference limit. Stroke was defined as rapid development of clinical signs of focal or global disturbance of cerebral function lasting >24 h with imaging evidence of acute, clinically relevant brain lesion.

2.5. Statistical analysis

Triple matching (1:1:1) of patients with TAVI and concomitant CAD (TAVI + CAD) vs. TAVI without CAD (TAVI-noCAD) vs. patients with stable CAD undergoing PCI (CAD-noAS) was performed. Triplets were matched according to gender and age (using a caliper of 0.02), randomly selected from a cohort of 795 TAVI patients from the Bern TAVI Registry and 3528 patients with stable CAD from the Bern PCI Registry (see Fig. 1 for patient flow). Discrete data were summarized as numbers and frequencies (%) whereas continuous data were presented as means ± standard deviations (SD). P-values for characteristics recorded at the patient level were calculated with un-paired *t*-tests, chi-square tests, or Fisher's exact tests, except when specified. Statistical significance was considered at $p < 0.05$.

Clinical outcomes at 30 days and 1 year were expressed as counts and incidence rates computed according to the Kaplan–Meier method (censored at 30 days or 1 year, respectively). Hazard ratios were computed using Cox's regressions for death, cardiovascular death, CVE, MI, and the composites of these endpoints. A landmark analysis at 30 days was performed to evaluate clinical events through the different study cohorts during the early (0–30 days) and late (31–365 days) follow-up period. Statistical analyses were performed using Stata 13.1 (College Station, TX: StataCorp LP).

3. Results

Out of 9478 procedures performed between 2007 and 2013 (807 TAVI; 8671 PCI), three cohorts were derived as follows (Supplemental Fig. 1): among 795 patients included in the Bern TAVI registry, CAD at baseline was identified in 514 (65%) patients (TAVI + CAD), leaving 281 (35%) patients without CAD (TAVI-noCAD). A total of 3528 patients with stable CAD and without AS (CAD-noAS) underwent PCI and were included in the Bern PCI registry. After matching for age and gender (TAVI + CAD: TAVI-noCAD: CAD-noAS, 1: 1: 1), three cohorts including 248 patients each (62% male) were obtained.

3.1. Baseline characteristics

Table 1 shows baseline clinical characteristics of the three study cohorts (baseline features of the population prior to matching are detailed in Supplemental Table 1). TAVI + CAD and CAD-noAS patients had a similar risk profile, except for diabetes mellitus (33.5% vs. 18.5%, $p < 0.001$), chronic renal failure (76.1% vs. 63.0%, $p = 0.002$), and peripheral artery disease (19.8% vs. 11.3%, $p = 0.01$) occurring at higher rate in the TAVI + CAD cohort. Hypercholesterolemia and arterial hypertension were more common among patients with CAD (TAVI + CAD and CAD-noAS) as compared with the TAVI-noCAD cohort. Regarding medication at discharge, CAD-noAS patients were more likely to receive DAPT, whereas TAVI patients more frequently had oral anticoagulants related to a higher prevalence of atrial fibrillation.

Procedural details among patients undergoing TAVI with or without CAD are summarized in Supplemental Table 2.

3.2. Clinical events throughout 1-year follow-up

Rates of clinical outcomes across the study cohorts are reported in Table 2. At 30-day follow-up, there was no significant difference for the primary endpoint of MACCE between the TAVI + CAD and TAVI-noCAD (7.3% vs. 5.6%, HR 1.30, 95% CI 0.64–2.61, $p = 0.47$). Similarly, the risk of MACCE was not significantly different between the TAVI + CAD and the CAD-noAS groups (7.3% vs. 3.6%, HR 2.02, 95% CI 0.91–4.50, $p = 0.085$). Cerebrovascular events occurred more frequently among TAVI patients, irrespective of CAD status (TAVI + CAD: 3.2%; TAVI-noCAD: 4.4%, CAD-noAS: 0%; $p = 0.007$ for both TAVI + CAD and TAVI-noCAD vs. CAD-noAS).

At 1-year follow-up, MACCE were significantly increased among TAVI + CAD patients compared with TAVI-noCAD (16.8% vs. 9.8%, HR 1.75, 95% CI 1.06–2.89, $p = 0.030$) and CAD-noAS patients (16.8% vs. 9.5%, HR 1.85, 95% CI 1.11–3.09, $p = 0.018$) (Fig. 1). This difference was mainly driven by a higher rate of cardiovascular mortality in the TAVI + CAD cohort relative to the TAVI-noCAD (12.7% vs. 7.0%, HR 1.86, 95% CI 1.03–3.36, $p = 0.040$) and CAD-noAS groups (12.7% vs. 5.8%, HR 2.29, 95% CI 1.22–4.30, $p = 0.010$). In TAVI patients without CAD, the rate of MACCE was similar to CAD patients undergoing PCI (9.8% vs. 9.5%, HR 1.05, 95% CI 0.59–1.87, $p = 0.86$).

The landmark analysis at 30-day follow-up showed that during the peri-procedural period, the MACCE rate was consistently higher among patients undergoing TAVI (irrespective of CAD) when compared with the CAD-noAS patient population. However, beyond 30 days, event curves were similar for TAVI-noCAD and CAD-noAS patients, whereas

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