Cardiovascular Revascularization Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Systemic corticosteroid exposure and atrioventricular conductance delays after transcatheter aortic valve implantation

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ARTICLE INFO

Article history:
Received 31 May 2021
Accepted 28 June 2021
Available online xxxx

Keywords:
Transcatheter aortic valve implantation
Atrioventricular conduction delay
Permanent pacemaker implantation
Left bundle branch block
Systemic corticosteroids

ABSTRACT

Background: Atrioventricular conduction delays (AVCD) are common after transcatheter aortic valve implantation (TAVI) and frequently require implantation of a permanent pacemaker (PPM). Autopsy studies demonstrated the role of ischemia, inflammation, and oedema in the pathogenesis of AVCD. Corticosteroids (CS) reduce inflammation and oedema and hence might lead to a lower rate of AVCD.

Methods: Based on a prospective single-center registry, we performed a propensity score (PS) matched analysis of subjects treated with or without systemic CS (>2.5 mg prednisolone-equivalent per day) at the time of TAVI. The primary endpoint was a composite of PPM-implantation and new-onset left bundle branch block (LBBB) within 30 days after TAVI.

Results: Among 2213 consecutive patients undergoing TAVI (51.5% female, mean age 82.1 ± 6.1 years) 89 patients were treated with systemic CS, of which 87 were included in the PS matched analysis. At 30 days, rates of the composite of PPM and LBBB were comparable between patients with versus without CS both in the overall cohort (33.7% versus 33.0%, $p = 0.89$) and the PS matched cohort (34.5% versus 40.2%, $p = 0.443$). There were no differences in a composite of major or minor vascular complications and major or life-threatening bleeding events between patients with versus without CS in the overall cohort (34.8% versus 26.6%, $p = 0.088$) or the PS matched cohort (33.3% versus 33.3%, $p \geq 0.999$).

Conclusion: In this exploratory study, intake of systemic CS among patients undergoing TAVI was not associated with differences in rates of AVCD, vascular complications, or bleeding events after TAVI.

1. Introduction

Advances in transcatheter treatment strategies, refinement of valve systems, and increasing experience of the heart teams have led to a reduction of procedural complications [1] and expedited the expansion of transcatheter aortic valve implantation (TAVI) to younger and surgical low-risk patients [2–5]. Nevertheless, atrioventricular conduction delays (AVCD), including new-onset left bundle branch block (LBBB) remain the most frequent adverse event [6–8]. AVCD that require permanent pacemaker (PPM) implantation, including complete heart block (CHB) or high-grade atrioventricular block (HAVB) occur in approximately 12–17% of patients after TAVI [9,10], and are associated with heart failure and mortality, extended hospitalization duration and increase in readmissions and health-care costs [11–13].

The underlying mechanisms of AVCD after TAVI include direct mechanical injury to the conduction system, local tissue inflammation, and oedema caused by the implanted TAVI prosthesis [7,14–16]. AVCD is often transient, with two studies showing that more than half of the patients receiving a PPM after TAVI do not require pacing at 30 days and one year, respectively [17,18]. Thus, it can be hypothesized that the use of anti-inflammatory drugs like systemic corticosteroids (CS) modifies the risk of new PPM implantation and LBBB after TAVI by mitigating inflammation-related AVCD [19]. Conversely, it has been suggested that vascular fragility induced by systemic CS intake may increase the risk of vascular complications and bleeding in patients undergoing TAVI [20–23].

Previous retrospective studies conducted in small unmatched cohorts yielded conflicting evidence on the effect of CS on the incidence of AVCD or vascular complications after TAVI [19,24]. Hence, the present analysis aimed to determine the association between systemic CS intake and short-term outcomes including AVCD and vascular complications after TAVI.

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https://doi.org/10.1016/j.carrev.2021.06.127

2. Methods

2.1. Study design and patient population

All patients undergoing TAVI at Bern University Hospital/Switzerland between August 2007 and July 2019 were enrolled into an institutional registry, which is part of the SwissTAVI registry (NCT01368250), and were screened for the present study. The registry complied with the Declaration of Helsinki and was approved by the local ethics committee. Patients provided written informed consent for participation. Patients with previously implanted PPM or transvenous Implantable Cardioverter Defibrillator were excluded. TAVI was performed via transfemoral access by default. Alternative access including the transapical, carotid, subclavian, axillary and transcaval route, was used in patients with unfavourable femoral vascular anatomy. The decision for prosthesis type and size was made by consensus in a dedicated Heart Team. Post-procedural care included continuous rhythm monitoring until discharge and daily 12-lead electrocardiograms (ECG).

2.2. Data collection and definitions

Key baseline clinical, procedural, and follow-up data were prospectively entered into a dedicated web-based database, held at the Clinical Trials Unit (CTU) of the University of Bern, Switzerland. Systemic CS intake was retrospectively retrieved from chart review and defined as a dosage of at least 2.5 mg prednisolone equivalent once daily for a minimum duration of one week before the intervention. Clinical follow-up data were prospectively scheduled and obtained by standardized interviews, documentation from referring physicians, and hospital discharge summaries at 30 days. All adverse events were systematically collected and adjudicated by a clinical event committee according to the Valve Academic Research Consortium criteria (VARC-2) [25]. The primary endpoint was defined as a composite of PPM-implantation and new LBBB within 30 days after TAVI. Secondary endpoints were PPM-implantation, new LBBB, major and minor vascular complications, major and life-threatening bleeding events, and death.

2.3. Statistical analysis

All analyses were performed using IBM SPSS Statistics 25 for Windows and an integration plug-in for *R* 3.3 for Windows (R Foundation for Statistical Computing). Descriptive data are reported as means and standard deviation (±SD) for metric variables and frequencies and percentage for categorical variables. Unpaired *t*-tests were used to compare means of continuous variables between groups. If Levene's-test revealed a violation of homoscedasticity the Welch t-test was used. Skewed metric variables without normal distribution at baseline were processed by Mann-Whitney *U* tests. Categorical variables were analysed using Chi-Square- or Fishers exact test. To assemble well-balanced groups (CS intake vs. no CS-intake), patients were matched using propensity score (PS) analysis. PS was calculated using a multivariable logistic regression model including the following variables: age, gender, body-surface-area (BSA), predicted risk of mortality according to the Society of Thoracic Surgeons (STS-PROM)-Score, symptoms corresponding to New York Heart association classes (NYHA) III and IV, left ventricular ejection fraction (LVEF), history of arterial hypertension, dyslipidaemia, atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease (COPD) and coronary artery disease (CAD), native aortic valve mean gradient, size of the implanted valve, pre-existing increase of the pR-interval >200 ms, LBBB and RBBB and valve type (balloon-expandable (BEV), self-expanding (SEV), mechanically expanding (MEV)). These variables were selected based on their presumed association with the short-term outcomes under investigation. A caliper width of 0.2 standard deviations was applied to match patients in a 1:1 ratio using the nearest neighbour matching algorithm. Event curves were generated using the Kaplan Meier method. Hazard ratios (HR) were determined using cox regression models. The two-tailed significance level was set at $\alpha < 0.05$.

3. Results

A total of 2439 patients underwent TAVI between August 2007 and July 2019. After exclusion of 226 patients due to previous PPM implantation, 2213 patients remained for the purpose of the present analysis

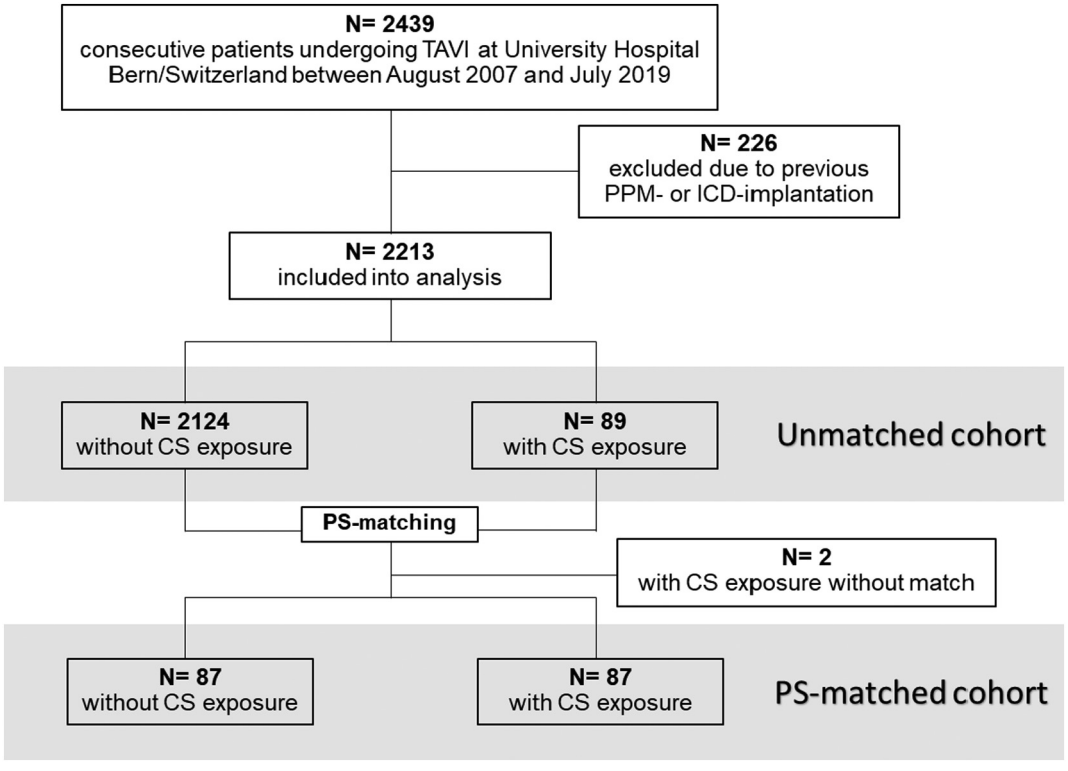

Fig. 1. Study flow-chart.

Table 1
Baseline- and procedural characteristics.

	Unmatched cohort			PS matched cohort		
	No corticosteroids $n = 2124$	Corticosteroids $n = 89$	p value	No corticosteroids $n = 87$	Corticosteroids $n = 87$	p value
Age [years] (mean ± SD)	82.1 ± 6.0	80.4 ± 6.8	0.008	81.5 ± 6.6	80.5 ± 6.7	0.353
Sex (female)	1101 (51.8%)	39 (43.8%)	0.138	38 (43.7%)	39 (44.8%)	0.879
STS PROM (mean ± SD)	5.41 ± 3.97	6.23 ± 6.58	0.086	6.04 ± 4.21	5.80 ± 3.35	0.666
NYHA III or IV	1440 (67.9%)	62 (70.5%)	0.614	55 (64.0%)	61 (70.1%)	0.389
History of arterial hypertension	1818 (85.6%)	77 (86.5%)	0.808	75 (86.2%)	75 (86.2%)	>0.999
Dyslipidemia	1384 (65.2%)	66 (74.2%)	0.081	67 (77.0%)	64 (73.6%)	0.598
Diabetes mellitus	551 (25.9%)	28 (31.5%)	0.246	27 (31.0%)	28 (32.2)	0.870
COPD	263 (12.4%)	15 (16.9%)	0.214	15 (17.2%)	14 (16.1%)	0.839
History of coronary artery disease	1312 (61.8%)	51 (57.3%)	0.396	50 (57.5%)	49 (56.3%)	0.878
Previous myocardial infarction	310 (14.6%)	13 (14.6%)	0.998	15 (17.2%)	11 (12.6%)	0.395
History of atrial fibrillation	679 (32.0%)	35 (39.3%)	0.146	29 (33.3%)	35 (40.2%)	0.346
AV block I	344 (19.7%)	11 (13.1%)	0.132	16 (19.0%)	11 (13.4%)	0.326
Intraventricular conduction delay			0.860			0.959
LBBB	214 (10.8%)	8 (9.1%)		6 (7.0%)	7 (8.1%)	
RBBB	185 (9.3%)	9 (10.2%)		9 (10.5%)	9 (10.5%)	
LVEF [%] (mean ± SD)	54.6 ± 14.6	55.7 ± 14.1	0.510	56.8 ± 15.0	56.3 ± 13.7	0.809
AVA [cm^2] (mean ± SD)	0.66 ± 0.25	0.73 ± 0.23	0.012	0.69 ± 0.25	0.73 ± 0.23	0.287
Mean gradient [mmHg] (M ± SD)	40.72 ± 17.45	38.64 ± 15.6	0.283	39.38 ± 19.55	39.0 ± 15.6	0.905
Implanted device			0.429			0.678
Balloon-expandable	1026 (48.6%)	49 (55.1%)		50 (57.5%)	48 (55.2%)	
Self-expanding	976 (46.2%)	37 (41.6%)		32 (36.8%)	36 (41.4%)	
Mechanically-expanding	110 (5.2%)	3 (3.4%)		5 (5.7%)	3 (3.4%)	

Abbreviations: AVA – aortic valve area, BSA – body surface area, COPD – chronic obstructive pulmonary disease, L/RBBB – left/right bundle branch block, LVEF – left ventricular ejection fraction, M – mean, NYHA – New York Heart Association, PCI – percutaneous coronary intervention, PS – propensity score, SD – standard deviation, STS PROM – predicted risk of mortality according to the society of the Society of Thoracic Surgeons.

(Fig. 1). Systemic CS intake (median 5 (IQR 5–10) mg prednisone-equivalent daily) was recorded in 89 patients (4.0%), resulting in 87 PS matched pairs. Indication for CS were polymyalgia rheumatica ($n = 20$), rheumatoid arthritis ($n = 18$), vasculitis ($n = 9$), COPD ($n = 8$), gout ($n = 4$), sarcoidosis ($n = 3$), systemic lupus erythematosus ($n = 2$), adrenal insufficiency ($n = 2$), co-medication in chemotherapy due to prostate cancer ($n = 2$), psoriasis arthritis ($n = 2$), prior organ transplantation ($n = 2$), allergic asthma ($n = 2$), others ($n = 13$) or unknown ($n = 2$). Baseline characteristics of patients before and after PS matching are provided in Table 1. In the unmatched cohort, patients taking CS were significantly younger (80.4 vs. 82.1 years, $p = 0.008$) than those not taking CS. After PS matching, differences were controlled and all reported baseline characteristics were well-balanced in patients with and without exposure to CS.

Peri-procedural adverse events and 30-day clinical outcomes are presented in Table 2. In the unmatched cohort, the primary composite endpoint of PPM and LBBB occurred in 33.7% of patients in the CS group and in 33.0% of patients in the CS naïve group ($p = 0.890$). Rates of major vascular complications were higher in the CS group (22.5 versus 9.7%, $p < 0.001$). However, rates of the secondary composite endpoint of major or minor vascular complications and major or life-threatening bleeding events were comparable between patients with

Table 2
Outcomes after transcatheter aortic valve implantation.

	Unmatched cohort			PS matched cohort		
	No corticosteroids $n = 2124$	Corticosteroids $n = 89$	p value	No corticosteroids $n = 81$	Corticosteroids $n = 81$	p value
Peri-procedural complications						
Valve dislocation/embolization	37 (1.7%)	3 (3.4%)	0.216	3 (3.4%)	3 (3.4%)	>0.999
Conversion to SAVR	11 (0.5%)	1 (1.1%)	0.390	3 (3.4%)	1 (1.1%)	0.621
Cardiac tamponade	12 (0.6%)	1 (1.1%)	0.414	0	1 (1.1%)	>0.999
Cerebrovascular events	88 (4.1%)	3 (3.4%)	0.719	5 (5.7%)	3 (3.4%)	0.720
Coronary artery occlusion	10 (0.5%)	0	>0.999	1 (1.1%)	0	>0.999
Echocardiographic measures						
Aortic valve area	1.73 ± 0.5	1.75 ± 0.44	0.65	1.72 ± 0.38	1.7 ± 0.47	0.392
Mean gradient	9.8 ± 4.6	9 ± 3.5	0.096	10.25 ± 4.4	10.25 ± 4.35	0.964
Severe aortic regurgitation	5	0	>0.999	0	0	–
Outcomes within 30d after TAVI						
Death	70 (3.3%)	3 (3.4%)	>0.999	5 (5.7%)	2 (2.3%)	0.443
PPM-implantation	434 (20.4%)	19 (21.3%)	0.834	22 (25.3%)	19 (21.8%)	0.592
New LBBB	388 (24.3%[a])	14 (18.7%[a])	0.268	24 (31.6%[a])	14 (18.9%[a])	0.075
Combination of PPM and LBBB	701 (33.0%)	30 (33.7%)	0.890	35 (40.2%)	30 (34.5%)	0.443
Minor vascular complication	200 (9.4%)	8 (9.0%)	0.892	10 (11.5%)	8 (9.2%)	0.619
Major vascular complication	205 (9.7%)	20 (22.5%)	<0.001	14 (16.1%)	19 (21.8%)	0.334
Major and life-threatening bleeding	399 (18.8%)	23 (25.8%)	0.097	19 (21.8%)	21 (24.1%)	0.719
Combination of minor and major VC and major and life-threatening bleeding	566 (26.6%)	31 (34.8%)	0.088	29 (33.3%)	29 (33.3%)	>0.999

Abbreviations: AF – atrial fibrillation, LBBB – left/right bundle branch block, PPM – permanent pacemaker, PS – propensity score, SAVR – surgical aortic valve replacement, TAVI – transcatheter aortic valve implantation, VC – vascular complication.
[a] Patients with pre-existing LBBB excluded.

versus without CS (34.8% versus 26.6%, $p = 0.088$). In addition, there were no between-group differences in all-cause death or any other components of the primary or secondary endpoint.

The main results of the PS matched cohort were consistent with the unmatched analysis and showed no differences in the primary composite (34.5% versus 40.2%, $p = 0.443$), or the secondary composite endpoint (33.3% versus 33.3%, $p > 0.999$) between patients with versus without CS intake, nor in the individual components of these endpoints (major vascular complications rate: 21.8% versus 16.1%, $p = 0.334$). Kaplan-Meier curves and hazard-ratios for the endpoints in the PS matched cohort are provided in Fig. 2. A stratified analysis for the primary endpoint by the implanted valve type (BEV, SEV, and MEV) showed no significant differences in any of the groups (Fig. 3). Dichotomizing patients on CS by the daily dose of prednisolone equivalent showed no differences between patients taking ≥10 mg ($n = 19$) versus patients taking <10 mg prednisolone equivalent ($n = 62$) once daily with regard to primary or secondary endpoints.

4. Discussion

In the present PS matched analysis conducted in a large prospective TAVI cohort, systemic CS intake was neither associated with a reduced risk of AVCD nor with an increased risk of vascular complications or bleeding events after TAVI. In our study, PPM-implantation was required in about 20% of patients, while previous meta-analyses reported rates between 12 and 17% with a large range from 2% to 51% in individual studies [9,10]. This could be related to the number of patients receiving SEV, which was higher in our analysis (46.0%) compared with other studies (31.2% in the meta-analysis of Xi et al. [9]). Recent studies investigating the association of AVCD with CS-exposure were conducted in smaller cohorts (CS-exposure in $n = 39$ (Havakuk et al. [24]) and $n = 16$ (Oestreich et al. [19]), respectively), without PS matching. While Havakuk et al. did not report any association of CS-exposure with AVCD, Oestreich et al. found a significant reduction of AVCD in patients with CS-exposure. Differences in baseline characteristics and in

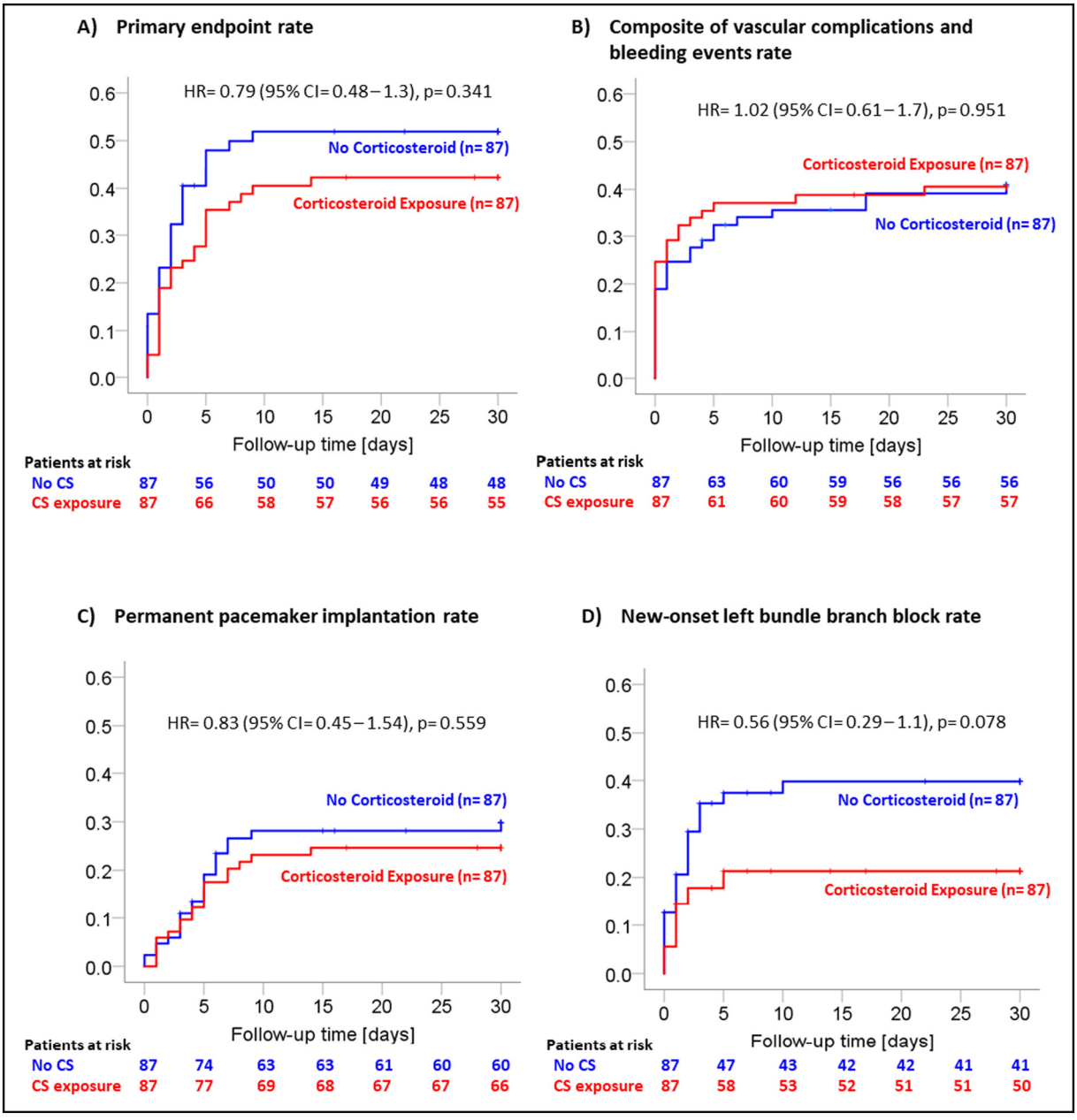

Fig. 2. Cumulative event curves and hazard ratios for primary- and secondary endpoints in PS matched patients with and without exposure to systemic corticosteroids up to 30 days after TAVI.

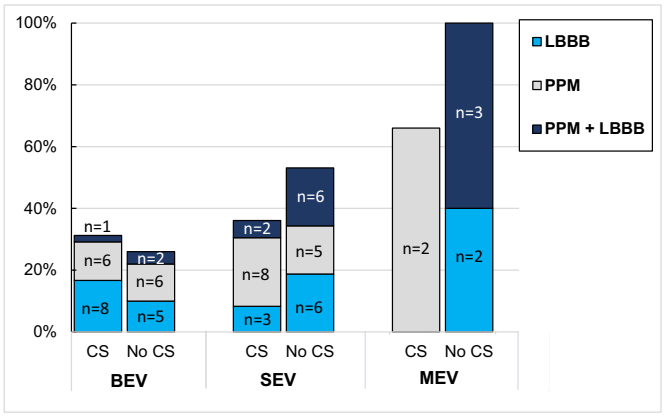

Fig. 3. Frequencies of atrioventricular conduction delays with and without exposure to corticosteroids stratified by transcatheter aortic valve type in the propensity matched cohort.

particular the fact that patients with CS-exposure more often received smaller valve prostheses (23 mm) might have contributed to the findings of the latter study [19]. In our study, no association between CS intake and the risk of AVCD was found, neither in the unmatched cohort nor after PS matching. AVCD mostly arise from the pressure on the AV-node or the Infra-Hisian conduction system exerted by radial forces of the valve prosthesis in the left ventricular outflow tract [14,26]. The absence of an impact of CS intake on the risk of AVCD suggests that the occurrence of AVCD is primarily related to direct mechanical injury to the conduction system rather than local inflammation or oedema. Consequently, the potential to influence AVCD by medical therapy may be limited. Many patient-specific factors that determine the susceptibility for AVCD cannot be influenced by medical therapy, e.g. inter-individual heterogeneity in the anatomical location of the AV-node or the bundle of His [27], the presence of calcium in the left ventricular outflow tract (LVOT) [28], and preexisting AVCD [10]. Further adjustment of modifiable risk factors like design of the prostheses [10], implantation depth in relation to the length of membranous septum and extension into the LVOT [29], and number of post dilatations [30] are more promising in reducing the rate of PPM-implantations after TAVI than anti-inflammatory treatment.

Although CS-exposure was previously linked to vascular complications after TAVI [20–22], the present analysis showed similar rates of minor and major vascular complications and major and life-threating bleeding events in patients with and without CS-intake in the PS-matched cohort.

5. Limitations

The findings of our study need to be interpreted in light of several limitations. First, the findings of our retrospective analysis are at risk of residual and unmeasured confounding. Patients with CS-intake generally suffer from underlying comorbidities, which may not have been adequately reflected in our PS matched analysis. Differences in baseline-characteristics that might have been neglected in PS matching may have led to an underestimation of the association of CS to the endpoints. Second, indications for PPM-implantations after TAVI are not standardized and are subject to interpretation of the treating physician and also comprise bradyarrhythmias other than AVCD. This heterogeneity in clinical indications complicates the identification of factors associated with PPM-implantation due to AVCD after TAVI. Nevertheless, also observer-independent indicators of a diseased conduction system like the rate of new LBBB were not associated to CS-use in our analysis. Third, patients did not receive long-term rhythm monitoring prior to TAVI. It consequently remains unclear whether the rate of AVCD after the intervention was primarily driven by TAVI. Recent evidence indicates that about one third of newly diagnosed AVCD after TAVI had already existed before valve implantation [31]. Fourth, treating physicians were not blinded in terms of CS-use and precautionary procedural measures with regards to vascular access may have introduced selection bias for the secondary endpoint. And finally, CS-dosages were rather low in our study. It remains to be determined, whether there is a dose-response effect on the occurrence of AVCD or vascular complications.

6. Conclusion

In this exploratory analysis, intake of systemic CS was not associated with a difference in PPM-implantations, new-onset LBBB and vascular complications or bleeding events after TAVI.

Funding

None.

Declaration of competing interest

Dr. Windecker reports research and educational grants to the institution from Abbott, Amgen, BMS, Bayer, Boston Scientific, Biotronik, Cardinal Health, CardioValve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Johnson&Johnson, Medtronic, Querbet, Polares, Sanofi, Terumo, Sinomed. Dr. Pilgrim reports having received research grants to the institution from Symetis/Boston Scientific, and Biotronik, and speaker fees from Boston Scientific and Biotronik, and consultancy from HighLife SAS and Edwards Lifesciences. Dr. Stortecky reports having received research grants to the institution by Edwards Lifesciences, Medtronic, Abbott, and Boston Scientific, and speaker fees from Boston Scientific, Teleflex, and BTG. Dr. Praz has received travel expenses from Edwards Lifesciences, Abbott Medical, and Polares Medical. All other authors have no relationships relevant to the contents of this article to disclose.

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