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STRUCTURAL

Optimal Implantation Depth and Adherence to Guidelines on Permanent Pacing to Improve the Results of Transcatheter Aortic Valve Replacement With the Medtronic CoreValve System

The CoreValve Prospective, International, Post-Market ADVANCE-II Study

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ABSTRACT

OBJECTIVES The aim of the CoreValve prospective, international, post-market ADVANCE-II study was to define the rates of conduction disturbances and permanent pacemaker implantation (PPI) after transcatheter aortic valve replacement with the Medtronic CoreValve System (Minneapolis, Minnesota) using optimized implantation techniques and application of international guidelines on cardiac pacing.

BACKGROUND Conduction disturbances are a frequent complication of transcatheter aortic valve replacement. The rates of PPI in the published reports vary according to bioprosthesis type and the indications for PPI.

METHODS The primary endpoint was the 30-day incidence of PPI with Class I/II indications when the Medtronic CoreValve System was implanted at an optimal depth (≤6 mm below the aortic annulus). The timing and resolution of all new-onset conduction disturbances were analyzed.

RESULTS A total of 194 patients were treated. The overall rate of PPI for Class I/II indications was 18.2%. An optimal depth was reached in 43.2% of patients, with a nonsignificantly lower incidence of PPI in patients with depths ≤6 mm, compared with those with deeper implants (13.3% vs. 21.1%; $p = 0.14$). In a paired analysis, new-onset left bundle branch block and first-degree atrioventricular block occurred in 45.4% and 39.0% of patients, respectively, and resolved spontaneously within 30 days in 43.2% and 73.9%, respectively. In patients with new PPI, the rate of intrinsic sinus rhythm increased from 25.9% at 7 days to 59.3% at 30 days ($p = 0.004$).

CONCLUSIONS Optimal Medtronic CoreValve System deployment and adherence to international guidelines on cardiac pacing are associated with a lower rate of new PPI after transcatheter aortic valve replacement, compared with results reported in previous studies. (CoreValve Advance-II Study: Prospective International Post-Market Study [ADVANCE II]; NCT01624870) (J Am Coll Cardiol Intv 2015;8:837–46) © 2015 by the American College of Cardiology Foundation.

ABBREVIATIONS AND ACRONYMS

AV = atrioventricular

CD = conduction disturbances

CI = confidence interval

ECG = electrocardiogram

ESC = European Society of Cardiology

IV = interventricular

LBBB = left bundle branch block

MCS = Medtronic CoreValve System

MSCT = multislice computed tomography

MVP = managed ventricular pacing

PPI = permanent pacemaker implantation

TAVR = transcatheter aortic valve replacement

TTE = transthoracic echocardiography

Transcatheter aortic valve replacement (TAVR) is now an established and safe therapy for patients with aortic stenosis who are at high risk for surgical aortic valve replacement (1,2). Conduction disturbances (CD) requiring permanent pacemaker implantation (PPI) frequently occur following implantation of the self-expanding Medtronic CoreValve System (MCS) (Medtronic Inc., Minneapolis, Minnesota). However, the reported rate of PPI varies widely, ranging from 10% to 47% (3–7). Although improvement in operator skill has led to a consistent reduction in the occurrence of such complications, the variability in PPI rates persists. This is most likely due to varying criteria underlying pacemaker implantation decisions and lack of consensus on the treatment strategy for CD after TAVR.

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The purpose of ADVANCE II (the CoreValve Prospective International Post-Market Advance II Study) was to evaluate the rate of new PPI according to Class I or II indications as recommended by the European Society of Cardiology (ESC) (8) when the MCS was optimally deployed at a depth of ≤6 mm below the aortic annulus. In addition, we assessed the rate of new-onset CD and the time course of their resolution, as well as the safety and efficacy outcomes associated with the TAVR procedure.

METHODS

POPULATION. Patients undergoing TAVR for symptomatic aortic stenosis and treated with the MCS were prospectively enrolled after heart team evaluation. Inclusion and anatomic exclusion criteria were consistent with manufacturer recommendations. Patients with a pre-existing device that regulated heart rhythm, as well as patients with pre-existing class I or II indications for a new PPI according to the 2007 ESC guidelines were not eligible. Persistent and permanent atrial fibrillation were also exclusion criteria as these conditions preclude accurate assessment of new-onset conduction disturbances.

PROCEDURAL DETAILS. All patients underwent TAVR with CoreValve and the 18-F delivery system with the AccuTrak Stability Layer as previously described (1). Valve size was selected based on annular perimeter measurements that were obtained from multislice computed tomography (MSCT) prior to the TAVR procedure. Device oversizing was calculated as follows: [(perimeter of the prosthesis - MSCT derived perimeter of the annulus) / MSCT derived perimeter of the annulus) × 100].

All centers were asked to comply with the following recommendations: 1) balloon valvuloplasty using an undersized straight balloon; 2) temporary high-frequency pacing during balloon valvuloplasty; 3) a waiting period ≥3 days prior to PPI if clinically justified; 4) PPI based on Class I or II 2007 ESC guidelines as determined by 12-lead surface electrocardiogram (ECG); and 5) use of pacemakers with the managed ventricular pacing (MVP) feature (or similar) and the ability to provide rhythm analysis reports. MVP was intended to promote intrinsic conduction, thereby allowing the pacemaker to be programmed to minimize unnecessary ventricular pacing.

IMPLANT DEPTH. Implant depth was defined as the maximal distance (millimeters) between the intraventricular end of the bioprosthesis and the aortic annulus at the level of the noncoronary cusp, as measured by angiography in the projection chosen

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for deployment. Implant depth was measured during the procedure by the operator and off-line by an independent core laboratory (Cardialysis, Rotterdam, the Netherlands). "Correct implantation" was defined as a depth ≤6 mm below the annulus plane, and a depth >6 mm was considered to be a low implantation.

ECG DATA COLLECTION. Twelve-lead ECG recordings were obtained before and immediately after TAVR and at 7 and 30 days of follow-up. Traces were examined by a core laboratory (Cardialysis) for rate and rhythm using the criteria of the World Health Organization and International Society and Federation for Cardiology Task Force (9).

ECHO DATA COLLECTION. Transthoracic echocardiography (TTE) was performed prior to TAVR and at days 7 and 30 post-TAVR. Images were examined by the core laboratory (Cardialysis). Paravalvular leak was determined according to VARC-1 (Valvular Academic Research Consortium-1) criteria (10).

STUDY DESIGN AND ENDPOINTS. The ADVANCE II study was a prospective, multicenter, observational study performed in 9 high-volume European centers. The primary endpoint was the incidence of new-onset Class I or Class II indications for PPI (including sinus node disease, acquired atrioventricular (AV) block, and bifascicular/trifascicular block) according to ESC guidelines at 30 days post-procedure in patients with a MCS implanted at a depth of ≤6 mm below the aortic annulus. An independent advisory committee consisting of 3 electrophysiologists adjudicated the indication for all PPI.

Secondary endpoints included: 1) evaluation of safety outcomes according to VARC-2 (11) definitions adjudicated by an independent clinical events committee; 2) characterization of CD by 12-lead ECG before TAVR, post-procedure, and at 7 and 30 days post-TAVR; 3) exploration of the determinants of AV and interventricular (IV) conduction abnormalities; and 4) determining the frequency of pacing and pacemaker dependency in patients with a new PPI, assessed at 30 days using pacemaker interrogation.

The ethics committee at each center approved the study protocol, and written informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki. The study was designed and funded by Medtronic Inc.

STATISTICAL METHODS. Continuous variables are reported as mean ± SD, mean ± SE, and median and interquartile range, where appropriate. Categorical variables are reported as frequencies and percentages. PPI rates and other outcome rates were calculated using Kaplan-Meier analysis. For patients without an event, the date of censoring was the latest date of all follow-up visits (including study exit) and events (including death). Corresponding 2-sided 95% confidence intervals (CIs) were constructed using the Peto standard error. Thirty-day PPI Kaplan-Meier rates were compared between implant depth groups (≤6 mm vs. >6 mm) using a z test. Implant depth and percentage of oversizing comparisons were based on pooled Student *t* tests, and post-dilation percentages were compared using Fisher exact tests. McNemar test was used to compare paired data of new-onset left bundle branch block (LBBB) and first-degree AV block between baseline versus 7 days post-implantation, and 7-days versus 30-days post-implantation. Cox regression models were used to determine significant predictors of PPI. Univariable predictors of PPI with a p value <0.20 were entered in the multivariable model. Receiver operating curves were derived to assess the predictive value of implant depth on PPI. The trend of implant depth groups by valve size was tested using a Cochran-Armitage trend test. Changes in intrinsic rate percentages from 7 to 30 days were based on generalized estimating equations accounting for repeated measures for patients with paired data, and the changes in percentage of ventricular pacing were tested using a signed rank test to account for the non-normality of the values. All analyses were performed using SAS software (version 9.3, Cary, North Carolina).

TABLE 1 Baseline Patient Characteristics (N = 200)

Age, yrs	80.2 ± 6.7
STS predictive risk of mortality score, %	7.2 ± 6.8
Logistic EuroSCORE II, %	9.0 ± 8.9
New York Heart Association class III or IV	148/199 (74.4)
Diabetes mellitus	62/200 (31.0)
Coronary artery disease	120/199 (60.3)
Previous myocardial infarction	30/199 (15.1)
Previous coronary artery bypass graft	31/199 (15.6)
Cerebrovascular disease	30/198 (15.2)
Aortic aneurysm	4/199 (2.0)
Peripheral vascular disease	55/199 (27.6)
Chronic obstructive pulmonary disease	42/199 (21.1)
Renal failure	3/200 (1.5)
Atrial fibrillation	21/200 (10.5)
Hypertension	154/199 (77.3)
Previous porcelain aorta	4/191 (2.1)
Hyperlipidemia	92/194 (47.4)

Values are mean ± SD or n/N (%).
EuroSCORE = European System for Cardiac Operative Risk Evaluation; STS = Society of Thoracic Surgeons.

RESULTS

DEMOGRAPHIC AND BASELINE CHARACTERISTICS. Between October 13, 2011 and April 16, 2013, 200 patients were enrolled, which represented approximately 65% of the total number of patients treated with the MCS in the participating centers. The demographic and clinical characteristics are described in Table 1. The mean age of the population was 80.2 ± 6.7 years and the mean Society of Thoracic Surgeons score was 7.2 ± 6.8. Most of the patients were in New York Heart Association class III or IV (74.4%).

AV conduction was normal in 75.8% of patients, whereas IV conduction was normal in 76.8%. TTE showed the mean aortic valve area to be 0.8 ± 0.2 cm^2 and the mean gradient 42.4 ± 14.4 mm Hg, with a preserved left ventricular ejection fraction in 53.7% of the population. Imaging and ECG parameters are summarized in Table 2.

PROCEDURAL CHARACTERISTICS. Of 200 patients enrolled, 6 did not receive a MCS bioprosthesis (1 patient refused implantation, 3 were reassigned to AVR, 1 received a new PPI after enrollment but before treatment, and 1 was treated with a different TAVR prosthesis). Between implantation and day 30, 5 patients had died, 1 patient withdrew consent, and 5 patients missed their 30-day follow-up visit. Therefore, 183 of the 194 implanted patients were available for 30-day follow-up.

Valve sizing was based on MSCT measurements in 89.7% of the patients and on TTE in the remaining 10.3%. The following MCS sizes were implanted: 23 mm in 2.6%, 26 mm in 29.9%, 29 mm in 55.2%, and 31 mm in 12.4% of patients. Transfemoral access was used in 89.7% of the procedures, whereas 6.2% and 4.1% of the procedures were from the subclavian and direct aortic approach, respectively. Aortic valve predilation was performed in 96.4% of patients, using a straight balloon in 73.3%, whereas post-dilation was performed in 22.2%. Two valves were implanted in 7.7% of patients (valve-in-valve in 2.1% and embolization of the first valve into the aorta in 5.7%).

Core lab-assessed implant depth measurements were available in 192 of the treated patients. The mean depth of implantation in the overall population was 6.9 ± 4.3 mm. The target depth of ≤6 mm was reached in 83 patients (43.2%), and the mean implantation depth in this group was 3.0 ± 2.2 mm. The target was not reached in 109 patients (56.8%), and the mean implant depth was 9.9 ± 2.8 mm.

PRIMARY ENDPOINT AND NEW CONDUCTION DISTURBANCES. The overall 30-day Kaplan-Meier

TABLE 2 Baseline Imaging and ECG Characteristics (N = 200)

Electrocardiogram	
PQ interval, ms	186.6 ± 39.3 (190)
Normal AV conduction	144/190 (75.8)
First-degree AV block	46/190 (24.2)
Normal IV conduction	152/198 (76.8)
LBBB	11/198 (5.6)
RBBB	12/198 (6.1)
LAFB	21/198 (10.6)
LPFB	1/198 (0.5)
Transthoracic echocardiography	
Effective orifice area, cm^2	0.8 ± 0.2 (171)
Mean gradient, mm Hg	42.4 ± 14.4 (180)
Aortic annulus diameter, mm	24.5 ± 2.0 (179)
Aortic regurgitation, moderate or severe	32/184 (17.4)
Mitral regurgitation, moderate or severe	20/184 (10.9)
LVEF >55%	94/175 (53.7)
Multislice computer tomography	
Aortic annulus perimeter, mm	76.8 ± 6.4 (179)
Patients implanted with the 23-mm valve	68.3 ± 2.5 (5)
Patients implanted with the 26-mm valve	72.3 ± 4.5 (53)
Patients implanted with the 29-mm valve	78.4 ± 5.1 (94)
Patients implanted with the 31-mm valve	83.3 ± 6.6 (22)
Perimeter-derived aortic annulus diameter, mm	24.5 ± 2.0 (179)
Aortic annulus area, mm^2	452.2 ± 77.3 (179)
Aortic leaflet calcium, mm^3	611.2 ± 479.1 (163)
Aortic root angulation, degrees	33.4 ± 8.4 (174)

Values are mean ± SD (n) or n/N (%).

AV = atrioventricular; ECG = electrocardiogram; IV = interventricular; LBBB = left bundle branch block; LAFB = left anterior fascicular block; LPFB = left posterior fascicular block; LVEF = left ventricular ejection fraction; RBBB = right bundle branch block.

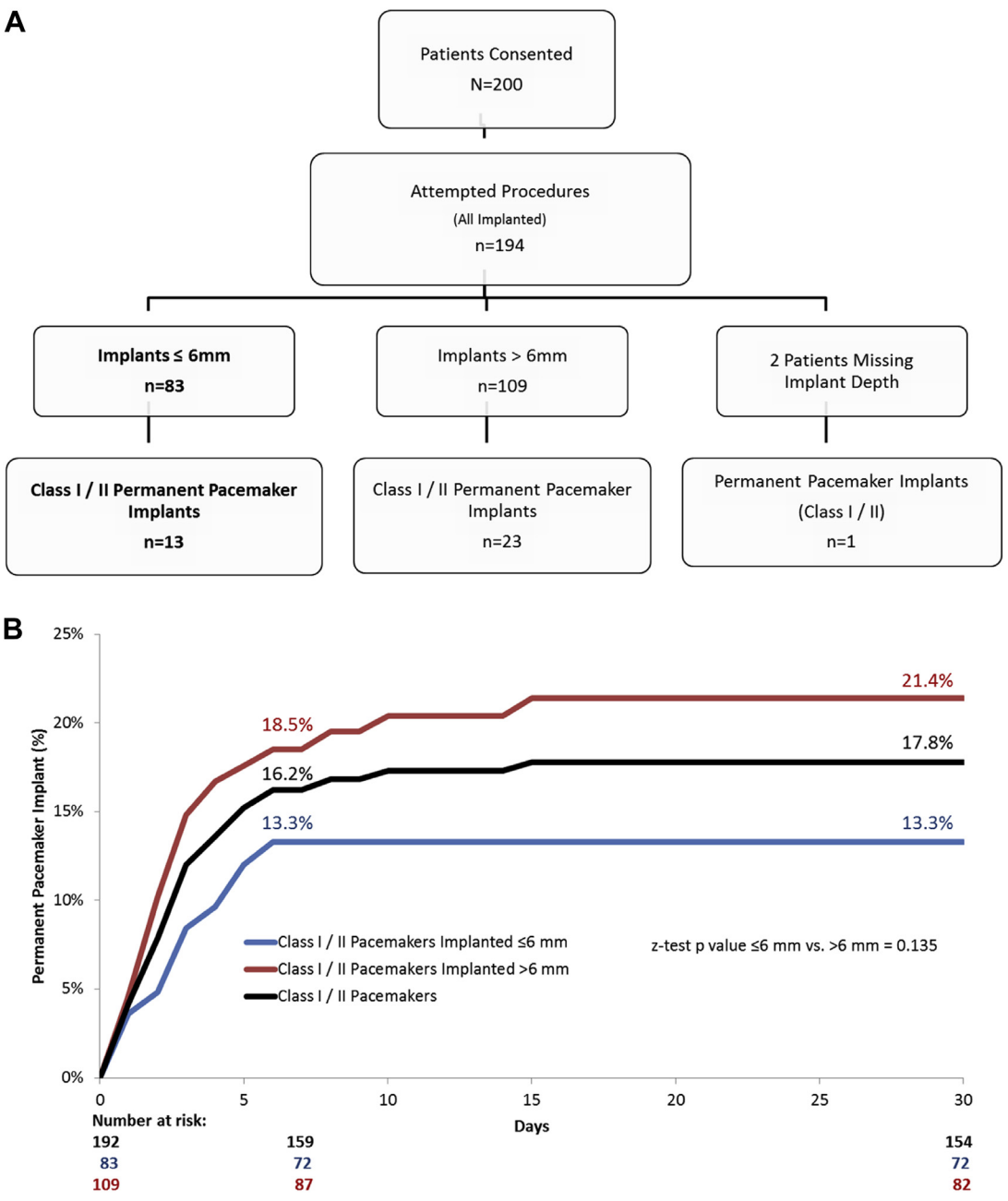
TABLE 3 Safety Outcomes at 30 Days

All-cause mortality*	1.6 (3) (0.4–4.2)
Myocardial infarction*†	0.5 (1) (0.0–2.7)
Stroke*†	2.1 (4) (0.7–4.9)
Cardiovascular mortality*†	1.6 (3) (0.4–4.2)
Life-threatening or disabling bleeding*†	4.1 (8) (1.9–7.7)
Vascular complications*†	23.2 (45) (17.5–29.5)
Major	11.9 (23) (7.8–16.9)
Minor	12.4 (24) (8.2–17.5)
Acute kidney injury (stage III)*†	0.5 (1) (0.0–2.7)
Pacemaker implantation*†	24.4 (47) (18.6–30.7)
Paravalvular leak, moderate or severe*‡	8.5 (10) (3.5–13.6)
VARC-2 device success§	73.6 (114/155)
Absence of procedural mortality	100 (194/194)
Correct position of 1 valve in the proper location	92.3 (179/194)
Mean gradient <20 mm Hg or peak velocity <3 m/s	99.4 (173/174)
Absence of moderate or severe regurgitation	90.2 (156/173)
Absence of patient prosthesis mismatch	89.2 (141/158)

Implanted patients, n = 194. *Kaplan-Meier rates are reported with n (95% confidence intervals). †Kaplan-Meier rates defined according to the VARC-2 (Valve Academic Research Consortium-2) definitions. ‡Calculated as a percentage of 117 patients with echocardiograms available at 30 days. §Rate presented as a percentage and n/n patients available for each component.

rate of new PPI with Class I/II indications according to the guidelines was 18.2% (n = 35). An acquired AV block was the main indication for PPI (34 of 35; 97.1%). Twelve patients received a permanent pacemaker without a Class I/II indication as adjudicated by the independent advisory committee, bringing the total PPI rate to 24.4% (Table 3). Within the subgroup of patients with available implant depth (n = 192), the rate of PPI with class I/II indications was 17.8% (n = 34, 1 patient with a Class I/II indication was

FIGURE 1 Categorization of PPI



(A) Flow chart describing how patients with permanent pacemaker implantations (PPI) were categorized within the study. **(B)** Kaplan-Meier curves for 30-day permanent pacemaker rates in patients with known implant depths (n = 192).

TABLE 4 Incidence and Timing of CD

Visit*	LBBB	RBBB	LAFB	LPFB	First-Degree AV Block	Third-Degree AV Block
Baseline	11/192 (5.7)	12/192 (6.3)	21/192 (10.9)	1/192 (0.5)	45/185 (24.3)	0/185 (0.0)
Post-TAVR	85/169 (50.3)	13/169 (7.7)	18/169 (10.7)	1/169 (0.6)	57/156 (36.5)	2/156 (1.3)
24 h	83/169 (49.1)	7/169 (4.1)	12/169 (7.1)	0/169 (0.0)	53/155 (34.2)	2/155 (1.3)
48 h	70/147 (47.6)	8/147 (5.4)	8/147 (5.4)	0/147 (0.0)	56/128 (43.8)	4/128 (3.1)
7 days	74/149 (49.7)	6/149 (4.0)	12/149 (8.1)	0/149 (0.0)	67/135 (49.6)	0/135 (0.0)
30 days	43/135 (31.9)	8/135 (5.9)	14/135 (10.4)	0/135 (0.0)	43/127 (33.9)	0/127 (0.0)

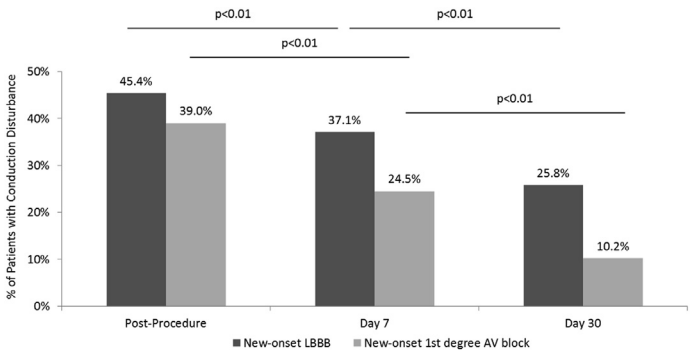
Values are n events of n interpretable ECG at the given time point, followed by percentages. *Available 12-lead ECG data at each visit.
CD = conduction disturbance; TAVR = transcatheter aortic valve replacement; other abbreviations as in Table 2.

missing implant depth). The rate of PPI for Class I/II indications in patients with implantation of the MCS at a depth ≤6 mm was 13.3% (n = 11). In patients with low implantation >6 mm, the PPI rate with Class I/II indications was 21.4% (n = 23) (Figure 1).

Of the 35 patients with a Class I/II indication for PPI regardless of implant depth, 34 were implanted during the index hospital stay. Importantly, no episodes of third-degree AV block or sudden death occurred between discharge and 30 days post-TAVR.

The timing of new-onset CD is described in Table 4. The most frequent CD were new LBBB and first-degree AV block. According to a paired analysis in patients with normal conduction at baseline and an available ECG at post-procedure (within 48 h), day 7, and day 30 (n = 97 for LBBB, n = 59 for first-degree AV block), LBBB and first-degree AV block resolved by 30 days in 43.2% and 73.9%, respectively, as shown in Figure 2.

FIGURE 2 CD Resolution With Time



Percentages of patients with new-onset left bundle branch block (LBBB) or new-onset first-degree atrioventricular (AV) block at post-procedure, day 7, and day 30 are shown. There was a statistically significant decrease in both types of conduction disturbance (CD) between post-procedure and day 7, and between day 7 and day 30. Patients with normal baseline AV conduction were considered for new-onset AV block. Patients with normal baseline IV conduction were considered for new-onset LBBB. New-onset is defined as a new conduction disturbance which initiates within 48 h of TAVR. Patients receiving new permanent pacemakers were excluded. Paired data for each type of conduction disturbance. LBB n = 97, 1st degree n = 59. TAVR = transcatheter aortic valve replacement.

New Class I/II PPI at 30 days and all new CD were significantly associated with low MCS implantation (Figure 3). No relation was observed between new CD and oversizing, which was observed in 10.9% (n = 19) of patients with available MSCT data. Similarly, post-dilation was not related to any CD.

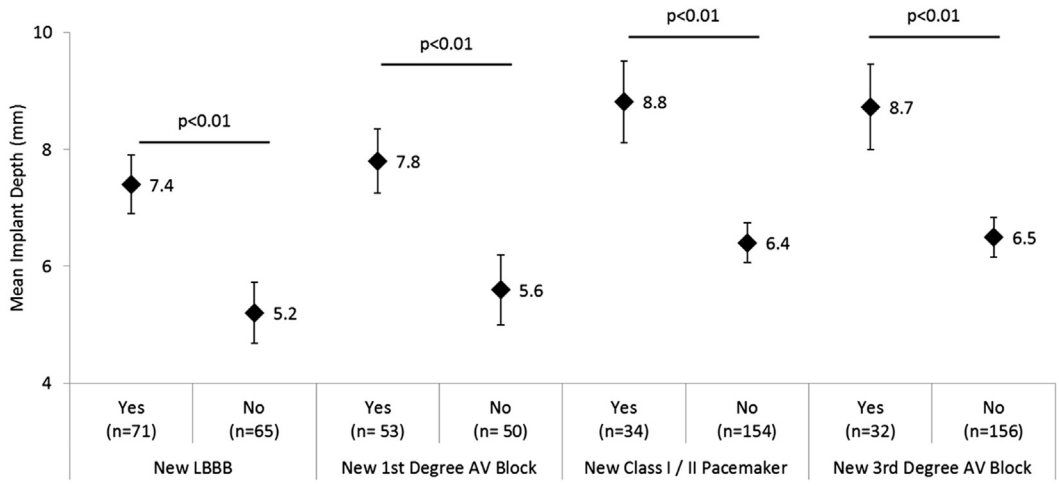
The only independent predictor of new PPI for Class I/II indications at 30 days by multivariable analysis was implantation depth (hazard ratio: 1.12 per 1 mm depth increase; 95% CI: 1.04 to 1.22; p = 0.005).

By receiver operating curve analysis, an implantation depth of <4 mm, which was achieved in 25.5% of the patients, was found to have the best negative predictive value (93.9%) for new PPI, although the positive predictive value was only 21.7% (sensitivity 91.2%, specificity 29.1%).

Finally, smaller MCS bioprosthesis size was associated with a higher rate of optimal implantation depth, which decreased from 80% to 51.7%, 41.0%, and 25.0% for the 23-, 26-, 29-, and 31-mm valve sizes, respectively (p = 0.008) (Figure 4).

Interrogation of pacemakers implanted for Class I/II indications regardless of implant depth showed that the rate of available intrinsic rhythm, evaluated via transient VVI programming at 30 beats/min, significantly increased from 25.9% at 7 days to 59.3% at 30 days (p = 0.004). We also observed a trend of reduced ventricular pacing time from 7 to 30 days (from 90.7 ± 24.1% to 80.8 ± 32.8%, p = 0.135). An MVP algorithm was available at the 7-day interrogation in 64.3% of patients and activated in 66.7% of them, whereas at 30-day follow-up, it was available in 56.3% of patients and activated in 50.0% of them. A trend toward a reduction in the activation of MVP was observed between 7- and 30-day follow-up, whereas no significant change was observed in other parameters.

FIGURE 3 Relationship Between Depth of Implantation and New CD



Patients with new LBBB, first-degree AV block, PPI, and third-degree AV block had significantly deeper valve implants than those patients without new CD or PPI. Pooled *t* test p values, standard error is shown as error bars. New pacemaker at 30 days, new conduction disturbance is defined as a conduction disturbance not present at baseline which developed within 30 days of TAVR. 3rd degree AV block data from CEC adjudication, LBBB and 1st degree AV block from core lab adjudication. Implant depth defined as the distance from the lower edge of the non-coronary leaflet to the ventricular edge of the frame. CEC = clinical events committee; other abbreviations as in **Figures 1 and 2**.

ACUTE AND 30-DAY OUTCOMES

The 30-day Kaplan-Meier rates of adverse events were as follows: all-cause mortality and cardiovascular mortality 1.6%; stroke 2.1%; life-threatening or disabling bleeding 4.1%; major vascular complications 11.9%; myocardial infarction 0.5%; and acute kidney injury (stage III) 0.5%. Paravalvular leak was moderate or severe in 8.5% of patients and mild or less in 91.5%. These data are summarized in **Table 3**.

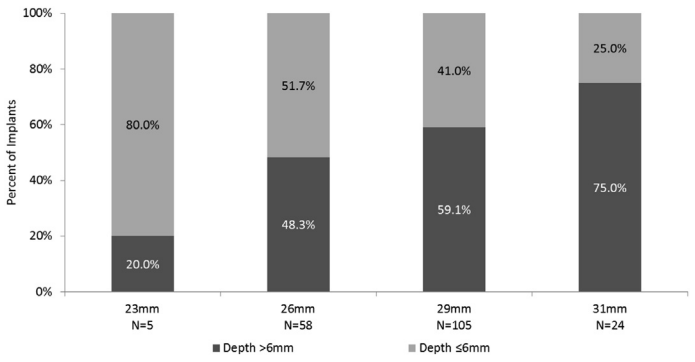
DISCUSSION

This is the first observational TAVR study with prospectively applied best implantation practices, rigorous data collection, and independent core laboratory analysis of all imaging and electrocardiographic data. Moreover, the acute and 30-day results showed a very low rate of major adverse cardiac and cerebrovascular events, in agreement with the most recent randomized TAVR trial with the MCS (1).

The close anatomic relationship between the aortic valve and some of the components of the cardiac conduction system explains the frequent occurrence of CD after interventions on the aortic valve. The MCS bioprosthesis contains of a self-expanding Nitinol frame with a high radial force that interacts with tissue a few millimeters below the aortic annulus, where the left bundle branch emerges from the left side of the ventricular septum (12). Mechanical compression leading to temporary inflammation or permanent damage in the conduction pathways is probably the main determinant of CD. This mechanism may be affected further by anatomic characteristics such as the presence of extensive calcium deposits (3) or by procedural steps such as crossing of the aortic valve with a wire and valvuloplasty (13).

FACTORS ASSOCIATED WITH PERMANENT PACEMAKER IMPLANTATION RATE. In addition to the pre-operative electrocardiographic and anatomic features that can influence the occurrence of CD, it is important to consider the impact of implantation technique. Among several studies focused on the search for the predictors of PPI, most identified implantation depth as an independent predictor (14–17), whereas a few did not confirm this association (5,18). However, these studies were mostly retrospective, were not homogeneous in procedural technique, and included small cohorts of patients. The importance of the correct implantation depth of the MCS was originally highlighted by Piazza et al. (12), and recently Tchetche et al. (6) demonstrated that a high implantation using the AccuTrak delivery system allowed for a reduction in new PPI. The importance of implantation

FIGURE 4 Relationship Between Valve Size and Implant Depth



Larger valve sizes were associated with deeper implants (Cochran-Armitage trend test, p = 0.008).

depth to prevent LBBB was also described for the balloon-expandable prosthesis by Urena (19). The ADVANCE II study is a prospective observational study designed to examine the best possible results by ensuring homogenous patient selection and procedural technique. Although the mean implantation depth in the overall population was close to 6 mm (6.9 ± 4.3 mm), in those patients in whom a correct implantation was achieved, the mean depth was 3.0 ± 2.2 mm. This is comparable to that obtained in the experience described by Tchetche et al. (6). The importance of a shallow implantation depth in limiting the need for PPI after TAVR was confirmed by the 4-mm cutoff value obtained in our study. In particular, a depth shallower than 4 mm was associated with a Kaplan-Meier rate of Class I/II PPI of 6.1%.

The importance of implantation depth is also highlighted by the tight association with CD at 30 days (**Figure 3**), both for AV and IV disturbances. No significant association was observed between CD and either oversizing or post-dilation. This is at variance with Schroeter et al. (20), who described a relationship between CD onset and both oversizing and use of larger diameter prostheses. In our experience, oversizing was calculated based on the nominal perimeter of the MCS and not on a direct measure after implantation and was observed in only 10.9% of patients. Importantly, prosthesis size was decided according to pre-operative MSCT measurements in 89.7% of patients and not on TTE measurements as in previous studies (21). In addition, in the ADVANCE II study, all 4 valve sizes were used, in contrast to the majority of previous studies in which the 23-mm and 31-mm prostheses were seldom used. Interestingly, as valve size increased, the probability of a low implant depth increased (p = 0.008), possibly related to the wider frame design. This last observation could in part explain the fact that optimal MCS implantation was reached in only one-half of the population. The depth of implantation with larger valves can be partially controlled by careful manipulation of the stiff wire in combination with controlled pacing (100 to 120 beats/min) during the first third of deployment; however, these maneuvers do not guarantee exact positioning. The attempt to obtain optimal implantation may explain the incidence of valve-in-valve (2.1%) and embolization (5.7%) (**Table 3**).

In our experience post-dilation was not associated with the occurrence of new CD; however, the limited number of patients undergoing post-dilation in the study (possibly because of the frequent use of pre-dilation) does not allow generalization of this finding.

Some of the baseline ECG parameters that were previously described to predict new CD after TAVR, including right bundle branch block, left anterior hemiblock, and atrial fibrillation were not associated with PPI on multivariable analysis. This may be a result of patient selection bias, as normal baseline ECG was preferred to facilitate the interpretation of new-onset CD.

INDICATIONS FOR NEW PERMANENT PACEMAKERS. In the design of the ADVANCE II study, adherence to the 2007 ESC guidelines on pacing was recommended, which is in contrast to previous studies that either did not specify the indications (17) or used prophylactic pacing in patients with new LBBB and prolonged PR interval (3,22). In our study, all new PPI but 1 were implanted during the index hospital stay, and no adverse events related to CD were observed at 30 days. In addition, no total AV block or sudden death occurred between discharge and 30 days. A reason for very early or prophylactic PPI may be the push for early discharge for economic reasons, favored by the decrease in procedural complications in recent years. However, the expansion of TAVR to lower risk and younger patients in the future will require a careful approach to PPI. Thygesen et al. (23) recently demonstrated in a retrospective analysis a reduction in PPI from 27.4% to 19.7% simply by reassessing indications to PPI. Accordingly, our rigorous pacing policy resulted in a PPI rate of 18.2%, which is similar to the rate reported in the most recent randomized TAVR trial (1) and reached 13.3% in patients with correct implantation. Absence of rigorous criteria explain the different incidence of new PPI in the CHOICE (A Comparison of Transcatheter Heart Valves

in High Risk Patients With Severe Aortic Stenosis) trial (24) that may have led to a high rate not only for MCS prosthesis (37.6%) but also for Sapien XT device, where it reached 17.3%.

TIMING AND RESOLUTION OF CONDUCTION DISTURBANCES. A high rate of new AV and IV CD was observed within the first 48 h of TAVR, with a significant resolution by 30 days (**Table 4**). Specifically, the rate of new LBBB and first-degree AV block had decreased by 43.2% and 73.9%, respectively (**Figure 2**), in agreement with previous observations (14,19,25) and similar to the recent data from the PARTNER (The PARTNER trial: Placement of Aortic Transcatheter Valve Trial) (26) on LBBB where 57.9% of the new-onset LBBB resolved at 30 days after balloon-expandable valve implantation. The transient nature of these CD can be explained in part by the temporary inflammation caused by the mechanical trauma occurring during the various steps of the TAVR procedure (13). This finding supports the importance of avoiding a liberal use of early PPI after TAVR. In particular, the occurrence of a new LBBB in a patient with a normal baseline ECG should not be an indication for pacing. Investigation of the sub-Hisian conduction with an electrophysiologic study in patients with new LBBB and very long PR interval (>300 ms), especially when these CD persist for over 72 h, may be advocated.

Finally, we observed a significant increase in the rate of available intrinsic rhythm at 30 days, together with a trend of reduced ventricular pacing time. Therefore, even with a conservative pacing policy as in our study, some implants prove unnecessary in the short term, in agreement with recent findings (23).

STUDY LIMITATIONS. This study describes conduction disturbances and new PPI after MCS implantation with pre-defined indications in a relatively small population. The low baseline prevalence of atrial fibrillation (10.5%) and pre-operative AV (24.2%) and IV (23.2%) CD should be considered a potential selection bias that could have reduced the incidence of PPI and prevented generalization of the results. Patients with persistent and permanent atrial fibrillation were excluded to reduce ambiguous or unfeasible interpretation of CD following TAVR. The lack of ambulatory ECG monitoring in the follow-up analysis should be taken in account in the evaluation of CD resolution at 7 and 30 days.

Although the study included 9 sites very experienced in MCS implantation, optimal implant depth was only achieved in 43.2% of the patients. At the moment, the new PPI rate of 13.3% may be the best result achievable with the present device and delivery system.

CONCLUSIONS

CD are multifactorial events occurring after both surgical valve replacement and TAVR that should be monitored and properly treated. The tendency toward CD resolution after TAVR and the rarity of late-onset complete AV block support a conservative approach to PPI that is driven by international guidelines. For this reason, it appears mandatory to avoid the practice of unnecessary or prophylactic pacemaker implantation. The best results can be obtained with a careful, high implantation of the MCS prosthesis; however, in this study, the optimal implant depth was achieved in less than 50% of patients. It is likely that newer generation devices that are repositionable and recapturable will improve the ability to properly position the device. This may lead to reduced rates of PPI, which is of key importance as the use of TAVR in lower-risk and younger patients is under consideration.

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PERSPECTIVES

WHAT IS KNOWN? The rates of new PPI and their indications in TAVR, especially with self-expanding devices, vary widely.

WHAT IS NEW? In this study, optimal deployment with high implant depth as well as strict adherence to international guidelines on the management of conduction disturbances resulted in a lower rate of PPI. In this set-up, there is a negligible risk of adverse events after hospital discharge.

WHAT IS NEXT? New device designs, including repositionable systems, will allow for better control of device positioning within the landing zone and might further improve the rate of PPI.

REFERENCES

1. Adams DH, Popma JJ, Reardon MJ, et al., for the U.S. CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790–8.

2. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol 2014;63:1972–81.

3. Latsios G, Gerckens U, Buellesfeld L, et al. "Device landing zone" calcification, assessed by MSCT, as a predictive factor for pacemaker implantation after TAVI. Catheter Cardiovasc Interv 2010;76:431–9.

4. Erkapic D, Kim WK, Weber M, et al. Electrocardiographic and further predictors for permanent pacemaker requirement after transcatheter aortic valve implantation. Europace 2010;12:1188–90.

5. Bleiziffer S, Ruge H, Horer J, et al. Predictors for new-onset complete heart block after transcatheter aortic valve implantation. J Am Coll Cardiol Intv 2010;3:524–30.

6. Tchetche D, Modine T, Farah B, et al. Update on the need for a permanent pacemaker after transcatheter aortic valve implantation using the CoreValve AccuTrak system. EuroIntervention 2012;8:556–62.

7. van der Boon RM, Van Mieghem NM, Theuns DA, et al. Pacemaker dependency after transcatheter aortic valve implantation with the self-expanding Medtronic CoreValve System. Int J Cardiol 2013;168:1269–73.

8. Vardas PE, Auricchio A, Blanc JJ, et al. Guidelines for cardiac pacing and cardiac resynchronization therapy: The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Eur Heart J 2007;28:2256–95.

9. Willems JL, Robles de Medina EO, Bernard R, et al., for the World Health Organizational/International Society and Federation for Cardiology Task Force Ad Hoc. Criteria for intraventricular conduction disturbances and pre-excitation. J Am Coll Cardiol 1985;5:1261–75.

10. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol 2011;57:253–69.

11. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438–54.

12. Piazza N, Onuma Y, Jesserun E, et al. Early and persistent intraventricular conduction abnormalities and requirements for pacemaking after percutaneous replacement of the aortic valve. J Am Coll Cardiol Intv 2008;1:310–6.

13. Nuis RJ, Van Mieghem NM, Schultz CJ, et al. Timing and potential mechanisms of new conduction abnormalities during the implantation of the Medtronic CoreValve System in patients with aortic stenosis. Eur Heart J 2011;32:2067–74.

14. De Carlo M, Giannini C, Bedogni F, et al. Safety of a conservative strategy of permanent pacemaker implantation after transcatheter aortic CoreValve implantation. Am Heart J 2012;163:492–9.

15. Baan J Jr., Yong ZY, Koch KT, et al. Factors associated with cardiac conduction disorders and permanent pacemaker implantation after percutaneous aortic valve implantation with the CoreValve prosthesis. Am Heart J 2010;159:497–503.

16. Franzoni I, Latib A, Maisano F, et al. Comparison of incidence and predictors of left bundle branch block after transcatheter aortic valve implantation using the CoreValve versus the Edwards valve. Am J Cardiol 2013;112:554–9.

17. Guetta V, Goldenberg G, Segev A, et al. Predictors and course of high-degree atrioventricular block after transcatheter aortic valve implantation using the CoreValve Revalving System. Am J Cardiol 2011;108:1600–5.

18. Khawaja MZ, Rajani R, Cook A, et al. Permanent pacemaker insertion after CoreValve transcatheter aortic valve implantation: incidence and contributing factors (the UK CoreValve Collaborative). Circulation 2011;123:951–60.

19. Urena M, Mok M, Serra V, et al. Predictive factors and long-term clinical consequences of persistent left bundle branch block following transcatheter aortic valve implantation with a balloon-expandable valve. J Am Coll Cardiol 2012;60:1743–52.

20. Schroeter T, Linke A, Haensig M, et al. Predictors of permanent pacemaker implantation after Medtronic CoreValve bioprosthesis implantation. Europace 2012;14:1759–63.

21. Moat NE, Ludman P, de Belder MA, et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. J Am Coll Cardiol 2011;58:2130–8.

22. Buellesfeld L, Stortecky S, Heg D, et al. Impact of permanent pacemaker implantation on clinical outcome among patients undergoing transcatheter aortic valve implantation. J Am Coll Cardiol 2012;60:493–501.

23. Bjerre Thygesen J, Loh PH, Cholteesupachai J, Franzen O, Søndergaard L. Reevaluation of the indications for permanent pacemaker implantation after transcatheter aortic valve implantation. J Invasive Cardiol 2014;26:94–9.

24. Abdel-Wahab M, Mehilli J, Frerker C, et al., for the CHOICE Investigators. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. JAMA 2014;311:1503–14.

25. Jilaihawi H, Chin D, Vasa-Nicotera M, et al. Predictors for permanent pacemaker requirement after transcatheter aortic valve implantation with the CoreValve bioprosthesis. Am Heart J 2009;157:860–6.

26. Nazif TM, Williams MR, Hahn RT, et al. Clinical implications of new-onset left bundle branch block after transcatheter aortic valve replacement: analysis of the PARTNER experience. Eur Heart J 2014;35:1599–607.

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