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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Full Title: Optimal Implantation Depth and Adherence to Guidelines on Permanent Pacing to Improve the Results of TAVI with the Medtronic CoreValve System: The ADVANCE II Study

Brief Title: Thirty Day Outcomes from the ADVANCE II Study

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ABSTRACT

Background: Conduction disturbances (CDs) are frequent in transcatheter aortic valve implantation (TAVI) patients, especially those treated with a self-expanding bioprosthesis. The reported rates of resulting permanent pacemaker implantation (PPI) vary, possibly due to heterogeneous implant conditions and criteria for PPI.

Objectives: The aim of the ADVANCE II study was to define the rate of CDs and new PPI according to international guidelines on cardiac pacing after TAVI.

Methods: This was a multicenter, prospective, observational study with independent evaluation of all clinical, imaging, and electrocardiographic parameters. The primary endpoint was the incidence of new PPI with class I or II indications at 30 days in patients with Medtronic CoreValve System (MCS) implantation at an optimal depth of ≤6 mm below the aortic annulus. The timing and resolution of all new-onset CDs were analyzed.

Results: A total of 194 patients were treated at 9 European centers. At 30 days, the rate of all-cause mortality was 1.6% while the stroke rate was 2.1%. The PPI rate according to the primary endpoint was 13.3% (n=11). New-onset left bundle branch block (LBBB) and 1st degree atrioventricular (AV) block developing within the first 48 hours of TAVI occurred in 52.5% (n=95) and 41.4% (n=58) patients, respectively. A paired analysis showed that 42% of new-onset LBBB and 65% of 1st degree AV block spontaneously resolved by day 30. Pacemaker interrogation showed the rate of available intrinsic rhythm significantly increased from 25.9% at 7 days to 59.3% at 30 days (p=0.004).

Conclusion: A low rate of new PPI after TAVI with the MCS can be achieved through

optimal deployment and adherence to international guidelines on cardiac pacing.

Key Words

Aortic stenosis

Transcatheter aortic valve replacement

Conduction disturbances

Pacemaker implantation

Clinical Trial Registration Information: www.clinicaltrials.gov; unique identifier: NCT01624870

Abbreviations:

TAVI = transcatheter aortic valve implantation

VARC = Valvular Academic Research Consortium

ESC = European Society of Cardiology

MSCT = multislice computed tomography

PPI = permanent pacemaker implantation

CD = conduction disturbances

LBBB = left bundle branch block

AV = atrioventricular

IV = interventricular

MCS= Medtronic CoreValve System

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) 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 (CDs) requiring permanent pacemaker implantation (PPI) frequently occur following implantation of the self-expanding Medtronic CoreValve System (MCS) (Medtronic Inc., Minneapolis, MN). However, the reported rate of PPI varies widely, ranging from 10% to 47% (3-7). Several publications have reported predictors of severe CDs and PPI after TAVI. Although improvement in operator skill has led to a consistent reduction in the occurrence of such complications, the variability in PPI rates persists most likely due to varying criteria underlying PPI decisions and lack of consensus on the treatment strategy for CDs after TAVI.

The purpose of the 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 CDs and the time course of their resolution, as well as the safety and efficacy outcomes associated with the TAVI procedure.

METHODS

Population

Patients undergoing TAVI for symptomatic AS and treated with the MCS were prospectively enrolled. The patients were submitted to TAVI after heart team evaluation. Inclusion and anatomical exclusion criteria were consistent with manufacturer recommendations. Patients with a pre-existing device which regulated heart rhythm, pre-existing class I or II indications for a new PPI according to the 2007 ESC guidelines, and patients presenting with persistent or permanent atrial fibrillation were not eligible.

Procedural Details

All patients underwent TAVI with the MCS valve as previously described (1). Oversizing was calculated as follows: ((perimeter of the prosthesis – MSCT-derived perimeter of the annulus) / MSCT-derived perimeter of the annulus) x 100).

All centers were asked to comply with the following recommendations: 1) balloon valvuloplasty (BAV) using an undersized straight balloon; 2) temporary high-frequency pacing during BAV; 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 ECG; 5) use of pacemakers with the minimum ventricular pacing (MVP) feature 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 (mm) between the intraventricular end of the bioprosthesis and the aortic annulus at the level of the non-coronary cusp, as

measured by angiography in the projection chosen 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 considered a depth ≤6 mm below the annulus plane, while a depth >6mm was considered to be a low implantation.

ECG Data Collection

Twelve-lead ECG recordings were obtained before and immediately after TAVI, and at 7 and 30 days of follow-up. Traces were examined by a core laboratory (Cardialysis, Rotterdam, NL) 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

TTE was performed prior to TAVI, and at day 7 and 30 post-TAVI. Images were examined by the core laboratory (Cardialysis, Rotterdam, The Netherlands). Paravalvular leak was determined according to Valvular Academic Research Consortium-1 (VARC-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 according to ESC guidelines at 30 days post-procedure in patients with a MCS implanted at 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 definitions, adjudicated by an independent clinical events committee; 2) characterization of CDs by 12-lead ECG before TAVI, post-procedure, and at 7 and 30 days post-TAVI; 3) exploration of the determinants of atrioventricular (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. (Minneapolis, MN).

Statistical Methods

Continuous variables are reported as means and standard deviations and medians and interquartile ranges (IQR), 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). Thirty-day PPI Kaplan-Meier rates were compared between implant depth groups (≤6 mm versus >6 mm) using a z-test. Implant depth and percent oversizing comparisons were based on pooled t-tests, and post-dilatation percentages were compared using Fisher's exact tests. 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 (ROC) 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-days to 30-days were based on generalized estimating equations accounting for repeated measures for patients with paired data, and the changes in percent 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, NC, USA).

RESULTS

Demographic and Baseline Characteristics

Between October 2011 and March 2013, 200 patients were enrolled. The demographic and clinical characteristics are described in Table 1. The mean age of the population was 80.2±6.7 years, the mean STS score was 7.2%±6.8%, and 60.3% had coronary artery disease. Most of the patients were in NYHA class III or IV (74.4%).

AV conduction was normal in 75.8% of patients, while 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 42.0±14.4 mmHg, with a preserved left ventricular ejection fraction in 53.7% of the population. Aortic regurgitation was absent or mild in 82.6% while mitral regurgitation was absent or mild in 89.1%. Imaging and ECG parameters are summarized in Table 2.

Procedural Characteristics

Out of 200 patients enrolled, 6 did not receive a MCS bioprosthesis (one patient refused implantation, 3 were re-assigned to AVR, one received a new PPI after enrollment but before treatment, and one was treated with a different TAVI prosthesis). Of the 194 implanted patients, 183 completed a 30-day follow-up visit.

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: 23mm in 2.6%, 26mm in 29.9%, 29mm 55.2% and 31mm in 12.4% of patients. Transfemoral access was used in 89.7% of the procedures, while 6.2% and 4.1% of the procedures were from the subclavian and direct aortic approach, respectively. Aortic valve pre-dilatation was performed in 96.4% of patients, using a straight balloon in 73.3%, whereas post-dilatation 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 ≤ 6mm 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 rate of new PPI with class I or II indications according to the guidelines was 18.2% (n=35). Of the 192 patients with implant depth data available, the rate was 17.8% (n=34). One subject with a missing implant depth was implanted with a pacemaker on the day of the index procedure. The rate of PPI for class I or II indications in patients with correct implantation of the MCS was 13.3% (n=11). In patients with low implantation, the PPI rate with class I or II indications was 21.4% (n=23) (Fig. 1A and 1B).

Out 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 3rd-degree AV block or sudden death occurred between discharge and 30 days post-TAVI.

The timing of new-onset CDs is described in Table 4. The most frequent CDs were new left bundle branch block (LBBB) and 1st-degree AV block. According to a paired analysis in patients with normal conduction at baseline and an available ECG at post-procedure (within 48 hours), day 7, and day 30 (n=114 for LBBB, n=74 for 1st degree AV block), LBBB and 1st-degree AV block resolved by 30 days in 42% and 65%, respectively, as

shown in Figure 2.

New class I and II PPIs at 30 days and all new CDs were significantly associated with low MCS implantation (Fig 3A). On the contrary, no relation was observed between new CDs and oversizing, which was observed in 10.9% (n=19) of patients with available MSCT data (Fig3B). Similarly, post-dilatation was not related to any CDs (Fig. 3C).

The only independent predictor of new PPI for class I or II indications at 30 days by multivariable analysis was implantation depth (HR 1.12 per 1 mm depth increase; 95%CI 1.04-1.22; $p<0.005$).

By ROC analysis, an implantation depth of less than 4 mm 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 ($p=0.008$).

Interrogation of pacemakers implanted for class I or II indications regardless of implant depth showed that the rate of available intrinsic rhythm, evaluated via a transient VVI programming at 30 bpm, 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% and activated in 66.7% of those patients, whereas at 30-day follow-up it was available in 56.3% and activated in 50.0%. 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.

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 and minor vascular complications 11.9% and 12.4%, respectively, myocardial infarction 0.5%, and acute kidney injury (stage III) 0.5%. Paravalvular leak (PVL) 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 TAVI study with prospectively-applied best implantation practices, rigorous data collection, and independent core laboratory analysis of all imaging and electrocardiographic data. The main finding is that TAVI with the MCS is associated with a PPI rate not far from that reported for TAVI with the balloon-expandable bioprosthesis (11,12), provided that the MCS is implanted correctly and that international PPI guidelines are followed. 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 TAVI trial with the MCS bioprosthesis(1).

The close anatomical relationship between the aortic valve and some of the components of the cardiac conduction system explains the frequent occurrence of CDs after interventions on the aortic valve. The MCS bioprosthesis consists of a self-expanding Nitinol frame with a high radial force which interacts with tissue a few millimeters below the aortic annulus, where the left bundle branch emerges from the left side of the ventricular septum (13). Mechanical compression leading to temporary inflammation or permanent damage in the conduction pathways is probably the main determinant of CDs. This mechanism may be impacted further by anatomical 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 (14).

Factors Associated with Permanent Pacemaker Implantation Rate

In addition to the pre-operative electrocardiographic and anatomical features that can influence the occurrence of CDs, 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 (12,15-17), while 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. (13), and recently Tchetche et al. demonstrated that a high implantation using the AccuTrak delivery system allowed for a reduction in new PPI (6). The importance of implantation depth to prevent LBBB was also described for the balloon-expandable prosthesis by Urena (19). The ADVANCE II study is a prospective observational study carefully designed to ensure homogenous high-quality 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, comparable that obtained by Tchetche, et al. (6). The importance of a shallow implantation depth in limiting the need for PPI after TAVI was confirmed by the 4 mm cutoff value obtained in our study. In particular, a depth shallower than 4 mm was associated with a rate of PPI <8%.

The importance of implantation depth is also highlighted by the tight association with CDs at 30 days (Fig. 3A), both for AV and IV disturbances. On the contrary, no significant association was observed between CDs and either oversizing or post-dilatation (Fig. 3B, 3C). This is at variance with Schroeter et al., who described a relationship between CD onset and both oversizing and use of larger diameter prostheses (20). 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. The limited

oversizing observed did not translate into an inadequate coverage of the aortic annular area, as demonstrated by the low rate of more than mild PVL (8.5%). Importantly, prosthesis size was decided according to preoperative 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, at variance with the majority of previous studies where the 23 mm and 31 mm prostheses were seldom used. Interestingly, as valve size increased, the probability of a low implant depth increased (p=0.028), possibly related to the wider frame design. This last observation could in part explain the fact that an optimal MCS implantation was reached in only half of the population.

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

Some of the baseline ECG parameters that were previously described to predict new CDs after TAVI, including RBBB, left anterior hemiblock, and atrial fibrillation, were not associated with PPI on multivariable analysis. This may be because most patients had normal AV and IV conduction at baseline, resulting from a selection bias as normal baseline ECG was preferred in order to facilitate the interpretation of new-onset CDs.

Indications for New Permanent Pacemakers

In the design of the ADVANCE II study, adherence to the 2007 ESC guidelines on pacing was recommended, at variance with 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). This aggressive approach to pacing was motivated by anecdotal reports of sudden death after TAVI described in the very first years of TAVI experience, and not confirmed subsequently. In our study, all new PPIs but one were implanted during the index hospital stay and no adverse events related to CDs were observed at 30 days. In addition, no total AV block or sudden death occurred between discharge and 30 days. Another reason for very early or prophylactic PPI may be the push for early discharge due to economic reasons, favored by the decrease in procedural complications in recent years. However, the expansion of TAVI to lower risk and younger patients in the future will require a very careful approach to PPI. Thygesen, et al. recently demonstrated in a retrospective analysis a reduction in PPI from 27.4% to 19.7% simply by re-assessing indications to PPI (23). Accordingly, our rigorous pacing policy resulted in PPI rate of 18.2%, similar to the rate reported in the most recent randomized TAVI trial (1), and reached 13.3% in patients with correct implantation.

Timing and Resolution of Conduction Disturbances

A high rate of new atrioventricular and interventricular CDs was observed within the first 48 hours of TAVI, with a significant resolution by 30 days (Table 4). Specifically, the rate of new LBBB and 1st-degree AV block had decreased by 42% and 65%, respectively (Fig. 2), in agreement with previous observations (15,19,24). The transient nature of these CDs can be explained in part by the temporary inflammation and edema caused by the mechanical trauma occurring during the various steps of the TAVI procedure (14). This finding supports the importance of avoiding a liberal use of early PPI after TAVI. In particular, the occurrence of a new LBBB in a patient with a normal baseline ECG should not be an

indication for pacing. Yet, investigation of the sub-hisian conduction with an electrophysiologic study in patients with new LBBB and very long PR interval (>300 msec), especially when these CDs persist for over 72 hours 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).

CONCLUSIONS

CDs are multifactorial events occurring after both surgical valve replacement and TAVI that should be monitored and properly treated. The tendency toward CD resolution after TAVI and the absence of late-onset complete AV block point to a conservative approach. An optimal position of the valve was confirmed to be the crucial factor in achieving a low rate of PPI. It appears mandatory to abide by the common recommendations for new PPI without further extension. The AccuTrak Stability Layer (Medtronic Inc., Minneapolis, MN) has improved the ability to properly position the MCS bioprosthesis, but it is likely that newer generations of devices which are repositionable and recapturable will further reduce the gap in PPI rates between balloon-expandable and self-expanding platforms.

PERSPECTIVES

Competency in Medical Knowledge: TAVI with the self-expanding valve is a safe and effective therapy for aortic stenosis patients, and carries with it a low rate of adverse events. The rate of new PPI with the MCS bioprosthesis is similar to that with other devices when good procedural practice is followed.

Competency in Patient Care: Patients treated with the MCS bioprosthesis are at low risk of new PPI if international guidelines are followed. There is a negligible risk of adverse events after hospital discharge, negating the need for prophylactic PPI.

Competency in Procedural Skills: TAVI with the MCS bioprosthesis provides optimal procedural and 30-day outcomes, including a low rate of conduction disturbance events, if high implant depth (<6mm) is achieved.

Translational Outlook: Further reduction in post-TAVI conduction disturbances will be obtained with new generations of valves which are repositionable, allowing for better control to achieve optimal deployment.

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Disclosures:

Anna S. Petronio, Jan Kovac, and Peter de Jaegere are clinical proctors and consultants for Medtronic, Inc. Francesco Bedogni and Marian Branny are proctors for Medtronic, Inc. Giulio Zucchelli is a consultant for Medtronic, Inc. Georg Nickenig has received honorarium as a consultant and presenter from Medtronic, Inc., and has received a research grant from Medtronic, Inc. Nicolas Van Mieghem has received research grants from Claret Medical, Edwards Lifesciences, Boston Scientific, and Medtronic, Inc. Raffi Bekeredjian has nothing to disclose.

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FIGURE LEGEND

Figure 1: Categorization of Permanent Pacemaker Implantations. 1A, flow chart describing how patients with PPI were categorized within the study. 1B, Kaplan-Meier curves for 30-day permanent pacemaker rates in patients with known implant depths (n=192).

Figure 2: Conduction Disturbance Resolution with Time. Percent of patients with new-onset LBBB or new-onset 1st degree AV block at post-procedure, day 7, and day 30 are shown. There was a statistically significant decrease in both types of conduction disturbance between post-procedure and day 7, and between day 7 and day 30.

Figure 3: Impact of Procedural Factors on Conduction Disturbances. 3A, relation between depth of implantation and new CDs. Patients with new LBBB, 1st degree AV block, PPI, and 3rd degree AV block had significantly deeper valve implants than those patients without new CDs or PPI. 3B, valve oversizing had no statistically significant effect on new CDs or PPI. 3C, no statistically significant effect of post-dilatation on new conduction disturbances or PPI was observed.

Figure 1.

Figure 1A.

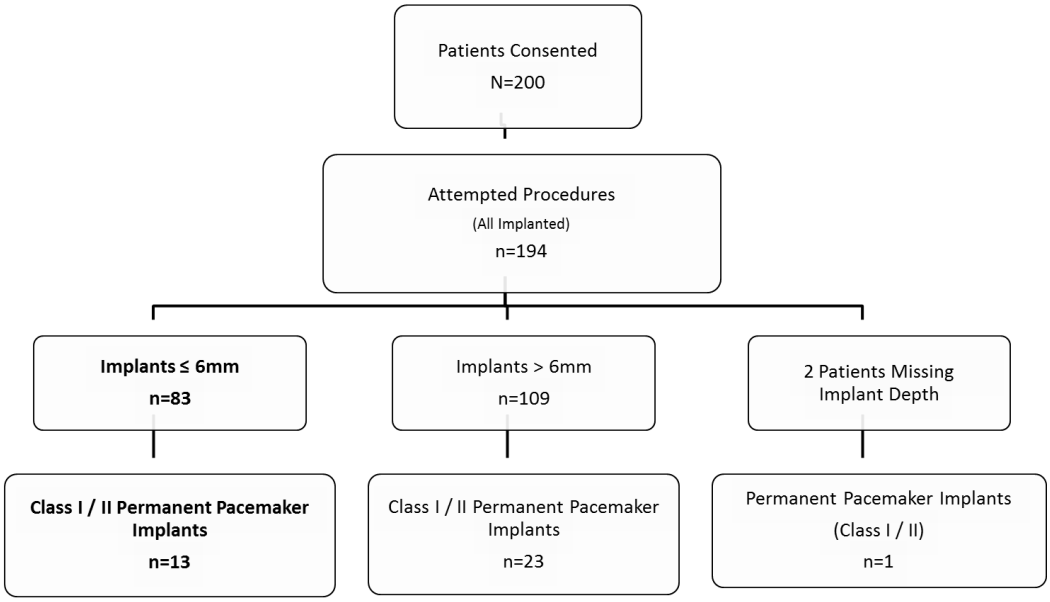


Figure1B.

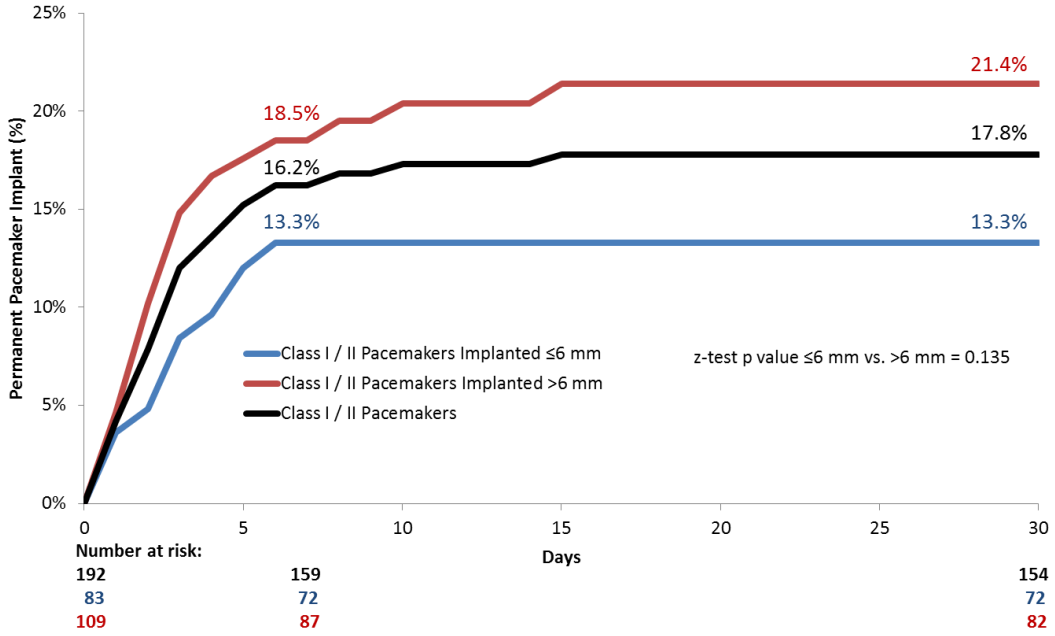
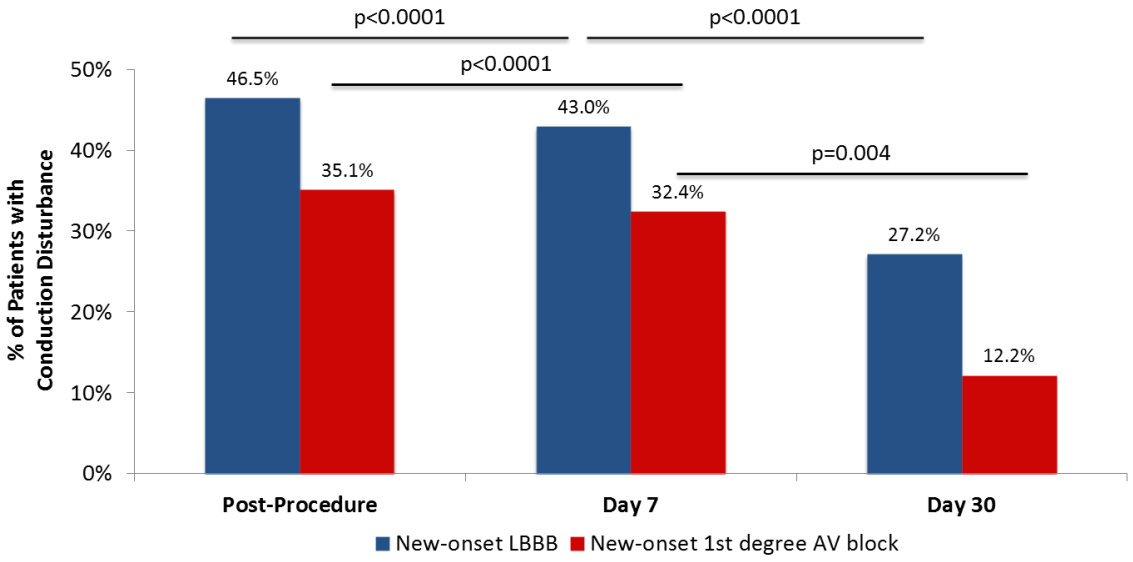


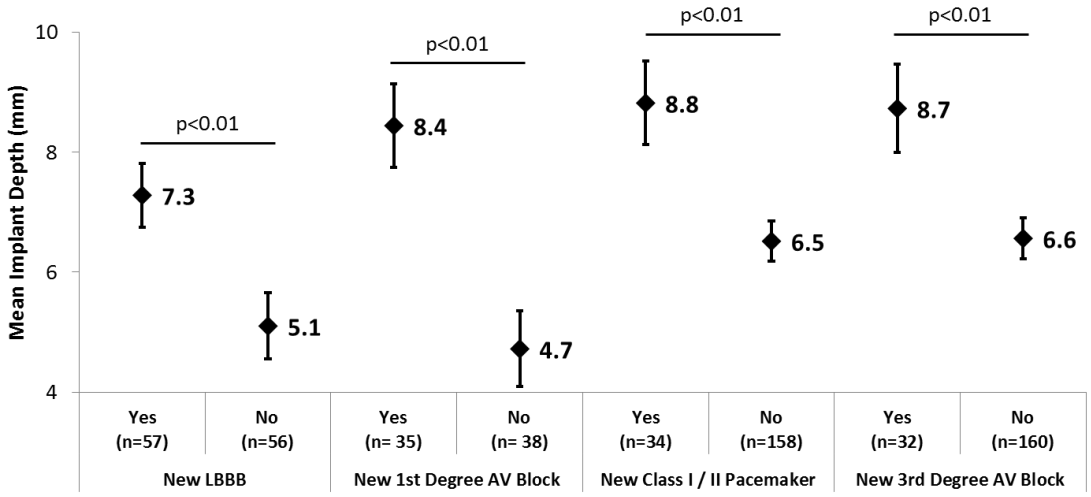
Figure 2.



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 hours of TAVI.
Patients receiving new permanent pacemakers were excluded.
Paired data for each type of conduction disturbance. LBBB n=114, 1st degree n=74

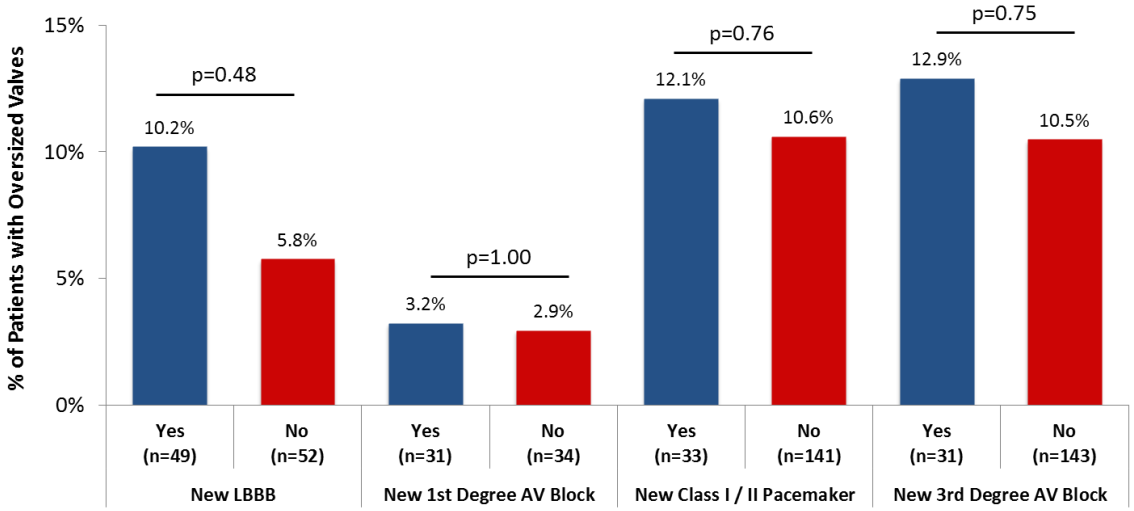
Figure 3.

Fig 3A.



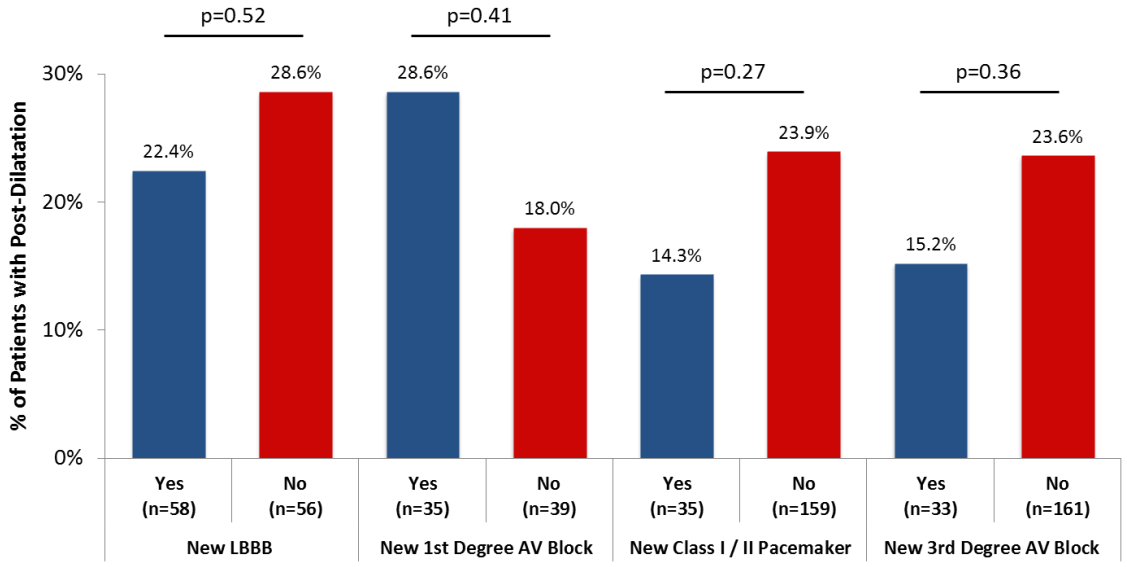
pooled t-test p values, standard error is shown as error bars
New pacemaker at 30 days, new conduction disturbance is defined as a conduction disturbance not present at baseline which developed within 30 days of TAVI
3rd Degree AV Block data from CEC adjudication, LBBB and 1st Degree AV Block from core lab adjudication
Implant depth defined as the distance from the lower edge of the non-coronary leaflet to the ventricular edge of the frame

Fig 3B.



pooled t-test p values
New pacemaker at 30 days, new conduction disturbance is defined as a conduction disturbance not present at baseline which developed within 30 days of TAVI
*Oversizing occurs when a valve is implanted in an annulus that is smaller than the range defined by the CoreValve sizing guide
% Oversizing = 100 x ([Perimeter of CoreValve– CT Derived Perimeter of the Annulus] / CT Derived Perimeter of the Annulus)
3rd Degree AV Block data from CEC adjudication, LBBB and 1st Degree AV Block from core lab adjudication

Fig 3C.



Fisher's Exact Test p values
New pacemaker at 30 days, new conduction disturbance is defined as a conduction disturbance not present at baseline which developed within 30 days of TAVI
3rd Degree AV Block data from CEC adjudication, LBBB and 1st Degree AV Block from core lab adjudication

Table 1. Baseline Patient Characteristics

Characteristic*	All Patients (N=200)
Age - years	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 grafting	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%)
Prior porcelain aorta	4/191 (2.1%)
Hyperlipidemia	92/194 (47.4%)

*Categorical variables are reported as counts and percentages, and continuous variables as means and standard deviations.

Table 2. Baseline Imaging and ECG Characteristics

Characteristic*	All Patients (N=200)
Electrocardiogram	
PQ interval, msec	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	42.0±14.4 (167)
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)

*Categorical variables are reported as counts and percentages, and continuous variables as means and standard deviations (n).

Abbreviations: LVEF, left ventricular ejection fraction; AV, atrioventricular; IV, interventricular; LBBB, left bundle branch block; RBBB, right bundle branch block; LAFB, left anterior fascicular block; LPFB, left posterior fascicular block.

Table 3: Safety Outcomes at 30 Days

	Implanted Patients* **(N=194)**
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%]

*Kaplan-Meier rates are reported with counts and 95% confidence intervals.

†Kaplan-Meier rates defined according to the Valve Academic Research Consortium-2 definitions.

‡Calculated as a percentage out of 117 patients with echocardiograms available at 30 days.

Table 4: Incidence and Timing of Conduction Disturbances

Visit*	LBBB	RBBB	LAFB	LPFB	1st Degree AV Block	3rd Degree AV Block
Baseline	11/192	12/192	21/192	1/192	45/185	0/185
	(5.7%)	(6.3%)	(10.9%)	(0.5%)	(24.3%)	(0.0%)
Post-TAVI	85/169	13/169	18/169	1/169	57/156	2/156
	(50.3%)	(7.7%)	(10.7%)	(0.6%)	(36.5%)	(1.3%)
24 hours	83/169	7/169	12/169	0/169	53/155	2/155
	(49.1%)	(4.1%)	(7.1%)	(0.0%)	(34.2%)	(1.3%)
48 hours	70/147	8/147	8/147	0/147	56/128	4/128
	(47.6%)	(5.4%)	(5.4%)	(0.0%)	(43.8%)	(3.1%)
7 days	74/149	6/149	12/149	0/149	67/135	0/135
	(49.7%)	(4.0%)	(8.1%)	(0.0%)	(49.6%)	(0.0%)
30 days	43/135	8/135	14/135	0/135	43/127	0/127
	(31.9%)	(5.9%)	(10.4%)	(0.0%)	(33.9%)	(0.0%)

*Available 12-lead ECG data at each visit, adjudicated by the core lab. Data reported as number of events out of number of interpretable ECGs at the given time point, followed by percentages.

Abbreviations: TAVI, transcatheter aortic valve replacement; LBBB, left bundle branch block; RBBB, right bundle branch block; LAFB, left anterior fascicular block; LPFB, left posterior fascicular block; AV, atrioventricular.