Predictors of Conduction Disturbances after Transcatheter Aortic Valve Implantation with Balloon-expandable Valve for Bicuspid Aortic Valve Stenosis

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Abstract

Objective: The implantation depth and membranous septum (MS) length are established as the predictors of new-onset conduction disturbance (CD) after transcatheter aortic valve replacement (TAVR) for tricuspid aortic valve (TAV) stenosis. However, little is known about the predictors with bicuspid aortic valve (BAV). This study investigated the role of MS length and implantation depth in predicting CD following TAVR with a balloon-expandable valve in patients with BAV. Methods and results: This retrospective study analyzed 169 patients who underwent TAVR for BAV with balloon-expandable valve, and TAV cohort was established as a control group using propensity score (PS) matching. The primary endpoint was in-hospital new-onset CD (new-onset left bundle branch block or new permanent pacemaker implantation). New-onset CD developed in 37 patients (21.9%). Multivariate analysis revealed severe LVOT calcification (Odds ratio [OR]: 5.83, 95% confidence interval [CI]: 1.08 – 31.5, p = 0.0407) and implantation depth – MS length (OR: 1.30, 95% CI: 1.12 – 1.51, p = 0.0005) as the predictors of new-onset CD within BAV cohort. The matched comparison between BAV and TAV groups showed similar MS length (3.0 vs 3.2mm, p = 0.5307), but valves were implanted deeper in BAV than TAV group (3.9 vs 3.0mm, p < .0001). New-onset CD was more frequent in patients having BAV (22.3% vs 13.9%, p = 0.0458). Conclusion: The implantation depth - MS length, and severe LVOT calcification predicted new-onset CD following TAVR in BAV with balloon-expandable valve. High implantation technique could be considered to avoid new-onset CD in BAV anatomy.

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Disclosure statement

Dr. Miyashita has nothing to disclose. Dr. Moriyama is a clinical proctor of Edwards Lifesciences (SAPIEN) and Boston Scientific (ACURATE neo and LOTUS Edge). Dr. Yamanaka has nothing to disclose. Dr. Saito reports lecture fees from Edwards Lifesciences and Medtronic and is a clinical proctor of Edwards Lifesciences (SAPIEN) and Medtronic (Evolut). Dr. Lehtola has nothing to disclose. Dr. Piuhola reports a lecture fee from Edwards Lifesciences. Dr. Laine reports non-regulatory research grants from Teleflex and consulting fees from Edwards Lifesciences, Boston Scientific, and Medtronic.

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Abstract

Objective: The implantation depth and membranous septum (MS) length are established as the predictors of new-onset conduction disturbance (CD) after transcatheter aortic valve replacement (TAVR) for tricuspid aortic valve (TAV) stenosis. However, little is known about the predictors with bicuspid aortic valve (BAV). This study investigated the role of MS length and implantation depth in predicting CD following TAVR with a balloon-expandable valve in patients with BAV.

Methods and results: This retrospective study analyzed 169 patients who underwent TAVR for BAV with balloon-expandable valve, and TAV cohort was established as a control group using propensity score (PS) matching. The primary endpoint was in-hospital new-onset CD (new-onset left bundle branch block or new permanent pacemaker implantation). New-onset CD developed in 37 patients (21.9%). Multivariate analysis revealed severe LVOT calcification (Odds ratio [OR]: 5.83, 95% confidence interval [CI]: 1.08 – 31.5, p = 0.0407) and implantation depth – MS length (OR: 1.30, 95% CI: 1.12 – 1.51, p = 0.0005) as the predictors of new-onset CD within BAV cohort. The matched comparison between BAV and TAV groups showed similar MS length (3.0 vs 3.2mm, p = 0.5307), but valves were implanted deeper in BAV than TAV group (3.9 vs 3.0mm, p < .0001). New-onset CD was more frequent in patients having BAV (22.3% vs 13.9%, p = 0.0458).

Conclusion: The implantation depth - MS length, and severe LVOT calcification predicted new-onset CD following TAVR in BAV with balloon-expandable valve. High implantation technique could be considered to avoid new-onset CD in BAV anatomy.

Key words:

Aortic stenosis, Bicuspid aortic valve, Conduction disorder, Implantation depth, Membranous septum length, Transcatheter aortic valve replacement

Introduction

Transcatheter aortic valve replacement (TAVR) has been established as a treatment of symptomatic aortic stenosis (AS) (**1, 2**), and its benefit has been extended to low-surgical risk patients (**3, 4**). Bicuspid aortic valve (BAV) is estimated to have a prevalence of around 0.5% (**5**) and 0.8% in the male population (**6**

) and is associated with the risk of developing aortic stenosis due to underlying abnormal valve geometry and mechanical stress (**7**). Although AS patients with BAV were excluded from early pivotal randomized studies (**1 - 4**), the evidence concerning TAVR for BAV is important because of the high prevalence of BAV among younger AS patients. Recent studies have reported comparable prognosis, hemodynamic results, and the safety of TAVR for BAV stenosis as compared to tricuspid aortic valve (TAV) stenosis (**8 - 10**). In addition, a randomized study showed the safety of TAVR for BAV in comparison with surgical aortic valve replacement (SAVR) (**11**).

Conduction disturbance (CD) including new permanent pacemaker implantation (PPI) and complete left bundle branch block (LBBB) have been reported as major complications following TAVR, and they are also associated with the risk of increased mortality and hospital readmissions (**12 - 14**). To avoid TAVR-related CD, several techniques such as double-cusp-view implantation with self-expandable THV (**15**) and high implantation technique with balloon-expandable THV (**16**) have been proposed. In addition, membranous septum (MS) length represents an anatomic surrogate of the distance between the aortic annulus and the bundle of HIS, and MS length is inversely related to the risk of CD following TAVR (**17**). Moreover, other studies reported, that both MS length and implantation depth are associated with CD (**18, 19**). However, less is known about the impact of the implantation depth and the MS length on CD outcomes in bicuspid anatomy

This study aimed to investigate the impact of MS length and implantation depth in predicting CD following TAVR with balloon-expandable valve in patients with BAV.

Methods

Patient selection

This study was a retrospective registry from 3 centers (Helsinki University Hospital, Finland; Oulu University Hospital, Finland and Shonan Kamakura General Hospital, Japan). Patients with BAV stenosis who underwent TAVR were eligible for the study. Out of 195 eligible patients from 3 centers, 26 patients (intra-procedural death: 0, implantation failure: 2, poor CT image quality: 1, poor angiogram quality: 5, prior PPI: 17) were excluded from the analysis (**Figure 1**). After exclusion, 169 patients remained for further analysis. BAV morphology was confirmed by pre-procedural MDCT and determined using the Sievers classification (**20**). TAV cohort was established to compare with BAV cohort by using propensity score (PS) matching. The inclusion criteria of TAV cohort were patients with TAV stenosis who underwent TAVR at Helsinki university hospital. Exclusion criteria were the same as the BAV cohort. THV size was selected based on the integration of preprocedural MDCT assessment including annulus area size and inter-commissural distance (ICD) at 4mm above the annulus by the multidisciplinary heart team at the individual hospital. This study was conformed to the Declaration of Helsinki and approved by the Institutional Review Board in Helsinki.

Definition and outcome measures

The MS was defined as the thinnest part of the interventricular septum on the perpendicular annular plane image, and MS length was measured as the distance from the annular plane to the vertex of the muscular septum in stretched vessel image (**18**). Leaflet calcification and LVOT calcification severity were semi-quantitatively measured as previously defined (**21, 22**). The implantation depth was measured with fluoroscopy images by using institutional imaging software. The implantation depth was defined as the distance between the bottom of the non-coronary cusp (NCC) to the ventricular end of the valve stent frame in the final angiogram after the valve deployment (**Figure 2**). The angle of the image was normally perpendicular deployment view, but it can be adjusted by the attending physician.

To evaluate CD following TAVR, we set the primary endpoint as in-hospital new CD (new-onset LBBB or new PPI). The indication of PPI following TAVR was decided by the heart team at each hospital. Also, the hemodynamic outcome measured by ultrasound and in-hospital complications based on VARC-2 criteria (**23**) were collected. The preoperative risk was evaluated by calculating the Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) score. The baseline characteristics, procedural characteristics, complications,

and results were compared between the patients without CD and with CD following TAVR. Also, CD and hemodynamic results were compared between the 2 groups based on implantation depth and MS length (implantation depth > MS length and implantation depth [?] MS length groups).

Statistical analysis

Categorical variables are presented as counts and/or percentages and were compared using the chi-square test or Fischer's exact test if needed. Continuous variables are presented as the mean +- standard deviation and were compared using the Student's t-test or the Wilcoxon rank-sum test based on their distributions. To determine predictors of the endpoint, a logistic regression analysis including baseline and procedural covariates was used to obtain the odds ratio (OR) and 95% confidence interval (CI) for the development of endpoints. Variables with a p-value <0.1 on univariate analysis were included for the multivariate model. All statistical tests were two-tailed. A p-value <0.05 was considered statistically significant. To compare the BAV patient group and TAV group, the propensity score matching method was modeled with the following variables: age, gender, body mass index, NYHA class [?]3, STS PROM, hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, chronic kidney disease, prior coronary artery bypass graft surgery (CABG), right bundle branch block (RBBB), LBBB, first-degree atrioventricular block (AVB), left ventricular ejection fraction (LVEF), SAPIEN 3 ultra, approach site. Statistical analyses were performed using JMP version 14.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics, including baseline CD and anatomical characteristics, are shown in **Table 1** . The mean age was 76.8 +- 6.7 years old, 53% were female, and STS PROM was 3.2%. As ECG findings, 8.9% of patients had RBBB, 8.3% LBBB, and 24.9%first-degree atrio-ventricular block. The most prevalent anatomical type was the type 1 (158/169) 93.5%, the second common type was the type 0 (10/169) 5.9%, and one patient had the type 2 BAV (1/169) 0.6%. The mean MS length was 3.0 +- 2.0 mm. **Table 1** also presented patient characteristics comparison between the patient without (n = 132) and with CD (n = 37) after TAVR. There were significant differences in the prevalence of atrial fibrillation (without CD 25.8% vs. with CD 43.2%, p = 0.0394), prior stroke (7.6% vs. 21.6%, p = 0.0295), severe leaflet calcification (74.2% vs. 94.6%, p = 0.0060), and severe LVOT calcification (2.3% vs. 18.9%, p = 0.0011), but not in RBBB (8.3% vs. 10.8%, p = 0.6396), first degree AVB (22.7% vs. 32.4%, p = 0.2273), and MS length (3.1 +- 2.0 mm vs. 2.5 +- 2.0 mm, p = 0.1147).

Procedural characteristics and complications are shown in **Table 2** . There were significant differences in the implantation depth (3.4 +- 1.7 mm vs. 5.5 +- 3.0 mm, p < 0.0001), implantation depth - MS (0.3 +- 2.5 mm vs. 3.0 +- 3.9 mm, p < 0.0001), and patients with the implantation depth > MS length (55.3% vs. 78.4%, p = 0.0112). No significant difference was observed in the incidence of procedure-related complications.

Table 3 presents clinical and hemodynamic outcomes. In the whole bicuspid patient cohort, new PPI was required in 8.3% (14/169), and the incidence of new-onset LBBB or new PPI was 21.9% (37/169). The most common indication for PPI, was a complete AVB, 7 of 14 (50%), one patient (7.1%) had Mobitz type 2 AVB, two patients (14.3%) had tri-fascicular block and the remaining four patients (28.6%) had other indications for PPI. The duration from the TAVR to the PPI is shown in**Figure 3** . The other clinical and hemodynamic outcomes were not significantly different (**Table 3**). **Figure 4** shows that severe LVOT calcification and implantation depth – MS length were the independent predictors of new-onset CD in the multivariate logistic regression model (severe LVOT calcification: OR 5.83, CI 1.08 – 31.5, p = 0.0407; implantation depth -MS length: OR 1.31 per 1 mm, CI 1.13 – 1.52, p < 0.0001). The results of univariate analysis were shown in **Supplemental table 1** .

Supplemental table 2 presents multivariate analysis for new PPI after TAVR, which showed baseline RBBB, severe LVOT calcification, and implantation depth – MS length were the predictors of new PPI.**Supplemental table 3** represents the comparisons of CD and hemodynamic outcomes between the two groups based on implantation depth and MS length (implantation depth > MS length, and implantation depth [?] MS length groups). The incidence of new-onset CD was greater in implantation depth > MS group,

while the other hemodynamic outcomes were not significantly different.**Figure 5** plots the distribution of implantation depth and MS length, and the red color indicates the new-onset CD.

To compare the anatomical characteristics and outcomes between TAVR for BAV and TAV, PS matching was performed to balance the patient characteristics (**Table 4**), which resulted in well-balanced except for estimated glomerular filtration rate (eGFR) and aortic valve area (AVA). There were significant differences in annulus size (543.7 +- 96.0 mm2 vs. 505.5 +- 100.8 mm2, p = 0.005), but not in severe leaflet calcification (78.9% vs. 71.0%, p = 0.0994), severe LVOT calcification (6.0% vs. 7.2%, p = 0.6590), and MS length (3.0 +- 2.0 mm vs. 3.0 +- 2.1 p = 0.9038). As to procedural characteristics, matched BAV group underwent more pre-dilatation (61.5% vs. 28.9%, p < 0.0001), implanted the THV deeper (implantation depth: 3.9 +- 2.2 mm vs. 2.9 +- 1.0 mm, p < 0.0001), and had similar rate of procedural complications (**Table 5**). New CD was significantly greater in the patients with BAV than TAV (22.3% vs. 13.9%, respectively, p = 0.0458), and the other clinical and hemodynamic outcomes were not significantly different between the two groups (**Supplemental table 4**).

Discussion

This 3-center retrospective registry demonstrated 3 main findings: 1) implantation depth - MS length and severe LVOT calcification were independent predictors of new CD in BAV; 2) when comparing matched BAV and TAV group, MS length was not different, but the incidence of new CD was higher in the patients with BAV, 3) BAV anatomy resulted in a deeper valve implantation, which may explain the increased incidence of CD

Permanent pacemaker implantation rate

The PPI rate following TAVR for BAV has been reported from 8.0% to 18% regardless of the used THV (**8, 24**) and from 13.1% to 17.6% with balloon-expanding SAPIEN 3 THV (**11, 25, 26**). When comparing the incidence of PPI with tricuspid valve, the results were not consistent through the studies; one retrospective study showed a higher PPI rate in the BAV group (**5**), and the others demonstrated no significant differences between 2 groups (**8 – 10, 27**). The new PPI rate in the BAV group in our study was in the lower range of previous reports, which was still significantly greater in the matched comparison to TAV group. A possible explanation of low rate of new PPI could be the high implantation (implantation depth: 3.9 +- 2.2 mm), which was higher than that in the previous study (implantation depth: 5.5 +- 3.7mm). They reported 18% incidence of new PPI and 41% incidence of new PPI or new-onset LBBB (**24**). However, the other studies have not provided implantation depth, thus further studies on the relation between implantation depth and PPI rate in bicuspid aortic valve were warranted.

Predictors of new conduction disturbance in the BAV cohort

The current study revealed that the implantation depth – MS length and severe LVOT calcification were independent predictors of new CD following TAVR for BAV with SAPIEN 3. The findings on implantation depth and MS length were consistent with prior studies concerning BAV regardless of the THVs (**24**) and with TAV with self-expandable THV (**18**). In addition, the high implantation technique with balloon-expandable SAPIEN 3 THV achieved lower rate of new conduction disturbances. Furthermore, high implantation was considered safe and provided good hemodynamic results (**16**). Our study implicates the advantage of high implantation for BAV in terms of reducing CD. The comparison between deeper implantation depth (implantation depth < MS) and higher implantation depth (implantation depth [?] MS) showed a similar complication rate other than CD and similar hemodynamic outcomes.

The impact of LVOT calcification on new CD has been controversial. Although some studies did not find association with LVOT calcification and an increased risk of PPI (**28, 29**), the location of LVOT calcification has been reported as a predictor of PPI in the other studies (**19, 30**). LVOT calcification below NCC (**19**), LCC (**30**), and RCC (**30**) were individually reported as the predictor of new PPI. Our analysis revealed the overall LVOT calcification, regardless of the location, as a predictor of new CD, however, the distribution of calcification was not assessed.

Careful THV sizing and implantation strategy is implicated for the TAVR for BAV anatomy with severe LVOT calcification. The LVOT calcification may increase mechanical stress to the LVOT tissue and conduction system (**19, 30**). In theory, this problem might be solved with the high implantation technique because high-implanted THV would have less chance to interact with the conduction system nor the LVOT calcification.

Membranous septum length and bicuspid aortic valve

The current study demonstrated similar MS length in BAV and TAV patients, unlike the previous study that revealed shorter MS length in BAV than TAV (**24**). A possible explanation for this discrepancy is the difference in measuring the MS length (**18, 24**). We speculate that it is more difficult to control the deployment of the THV due to challenging anatomical features accompanied with BAV such as eccentric device landing zone calcification, asymmetric geometry of the cusps, and concomitant pathologies of the aorta (severe tortuosity, horizontal aorta, and aneurysms) (**31**). Thus, the implantation might be targeted deeper to avoid valve migration or embolization rather than high implantation when the device manipulation is difficult especially in a trans-femoral case. Also, variation of implantation depth was higher in the BAV group (0.59 vs 0.34), which might reflect the unstable control of implantation depth compared to TAV. Further studies demonstrating the relation between implantation depth and the safety or the efficacy of high implantation for BAV are warranted.

Limitations

First, this study had the typical limitation of a retrospective study. The indication of TAVR for bicuspid aortic valve instead of SAVR, the choice of THV type or size may differ among the centers. Second, there have been published two different methods of measuring MS, and the gold standard was still controversial. The results that MS was not significantly different between the 2 groups might be different when the other way is employed. Third, as to clinical outcomes other than CD, the results should be interpreted with care, since the study cohort excluded the patients who potentially develop complications. Two implantation failures and no intraprocedural death were excluded from the BAV cohort, and 2 implantation failures 2 intraprocedural death were excluded from TAV group. Fourth, PS matching was modeled with the TAV cohort from single-center, while the BAV cohort consisted of the patients from 3 centers. Also, even though the PS matching has balanced patient characteristics, several factors were not included in the model and unmeasured confound factors may not be eliminated.

Conclusion

The combination of the implantation depth at non-coronary cusp and membranous septum length, and severe LVOT calcification were significantly associated with new conduction disturbance following TAVR for bicuspid aortic stenosis with balloon-expandable valve. High implantation technique could be considered to avoid new-onset CD in BAV anatomy.

Data availability

The data that support the findings of this study are available from the corresponding author, ML, upon reasonable request.

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Figure Legends:

Figure 1. Study flow chart

The incidence and predictors of new-onset CD were identified from the BAV cohort (169 patients) and the incidence of new-onset CD was identified from the matched cohort (166 pairs).

AS = aortic stenosis; CD = conduction disturbance; CT = Computed Tomography; PPI = permanent pacemaker implantation; TAVR = transcatheter aortic valve replacement.

Figure 2. The measurement of implantation depth

Implantation depth was defined as the distance between the bottom of the non-coronary cusp to the ventricular end of the valve stent frame in the final angiogram. Implantation view (3 cusp view) was employed to measure the depth, but the attending physician can be adjusted it.

Figure 3. The duration from the TAVR to the pacemaker implantation.

This figure shows the duration from the TAVR to the permanent pacemaker implantation.

TAVR = transcatheter aortic valve replacement.

Figure 4. Multivariate analysis for new-onset conduction disturbance after TAVR.

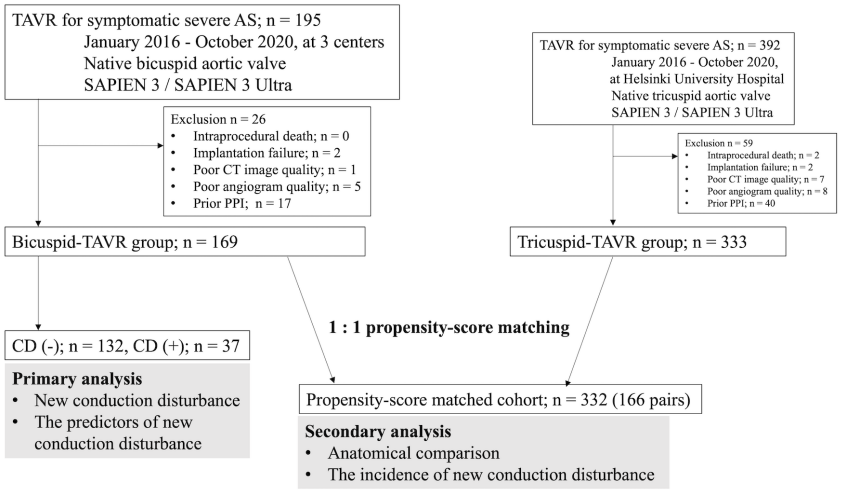
Multivariate analysis for new-onset conduction disturbance after TAVR. Univariate analysis was shown in **Supplemental table 1** .

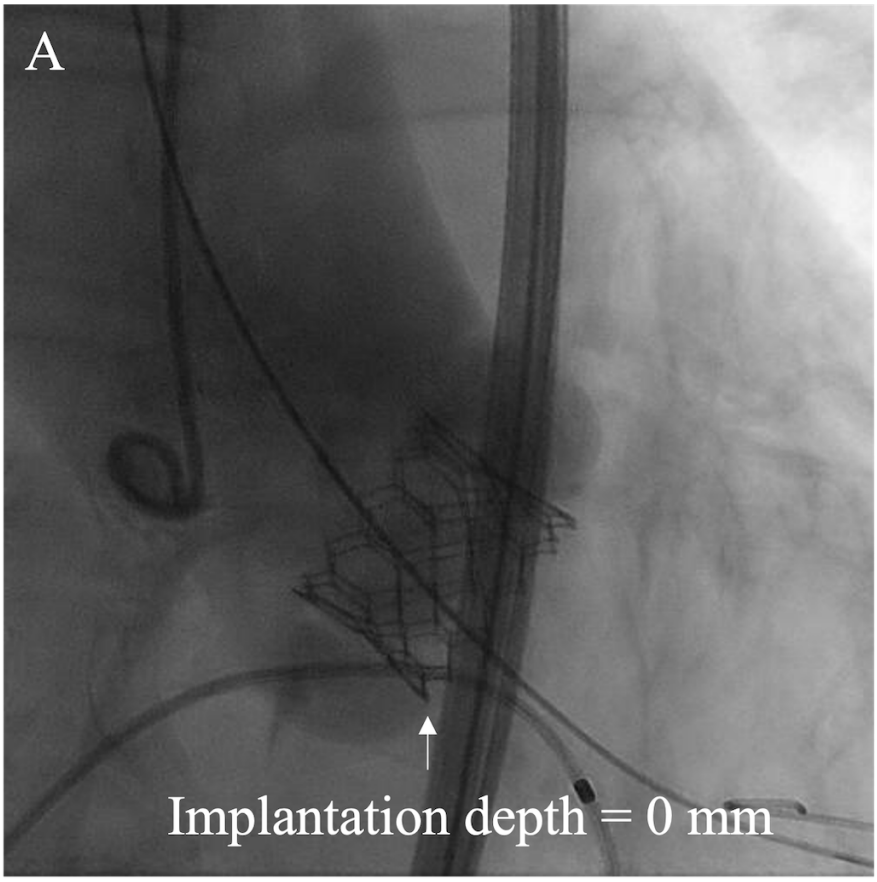
CABG = coronary artery bypass graft; CI = confidence interval; LVOT = left ventricular outflow tract; MS = membranous septum; TAVR = transcatheter aortic valve replacement.

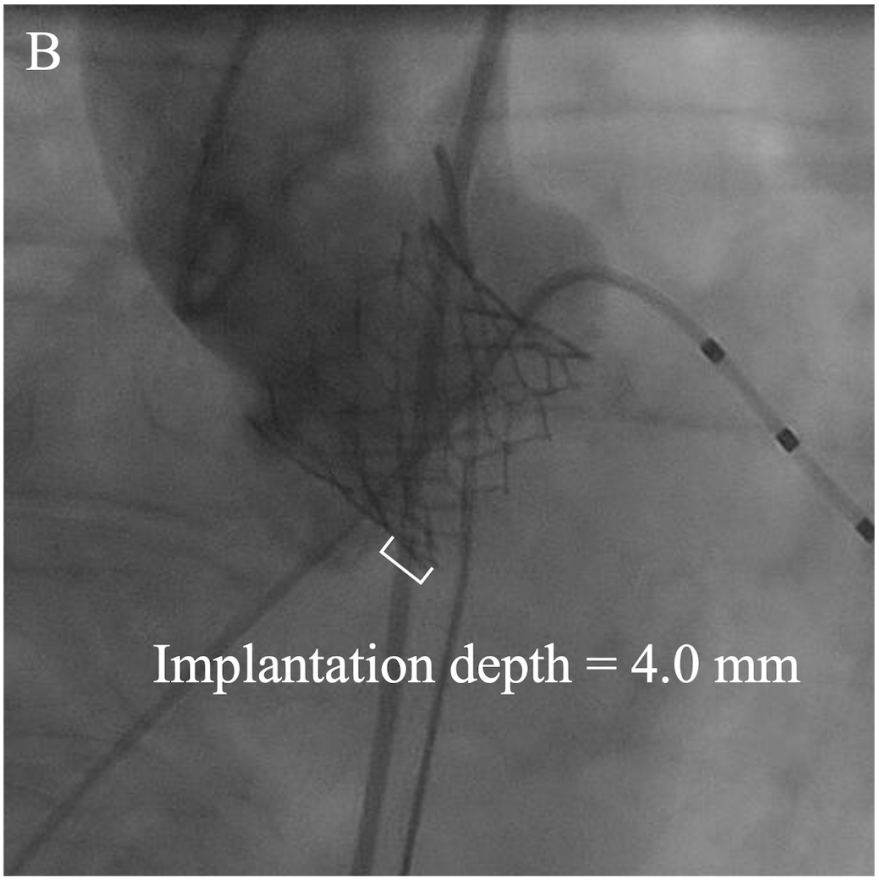
Figure 5. Plotting of the distribution of implantation depth and membranous septum length.

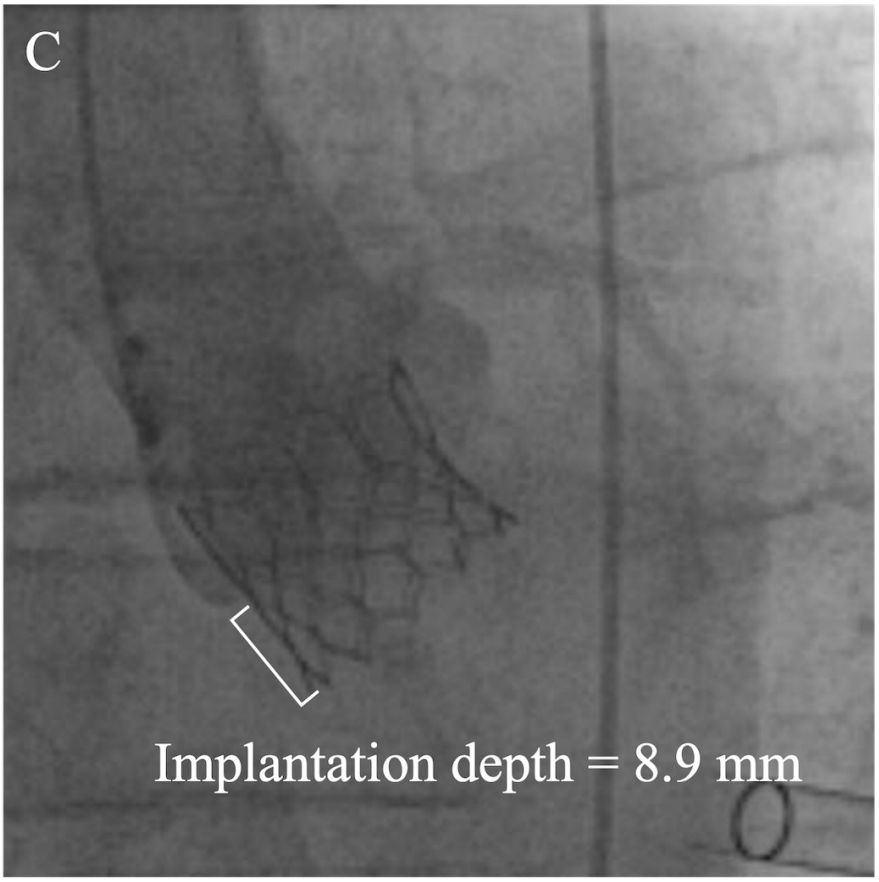
This figure plots the distribution of implantation depth and MS length, and the red color indicates the new-onset CD. The black line divided the patients into two groups (Implantation depth > MS and implantation depth [?] MS).

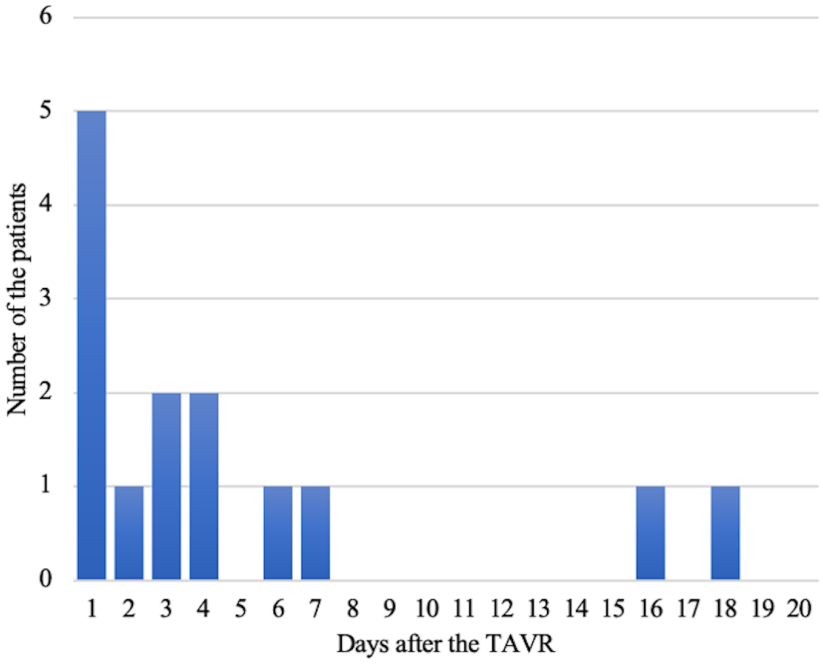
CD = conduction disturbance; MS = membranous septum length.

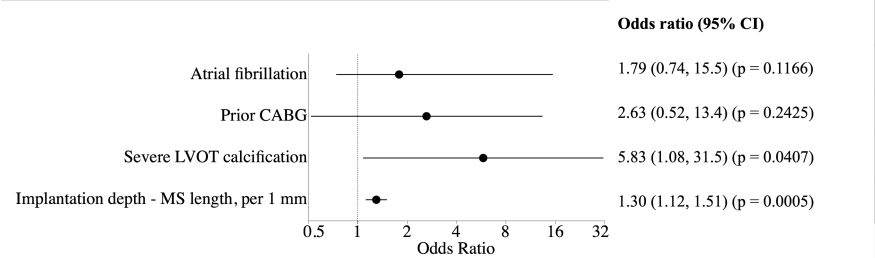


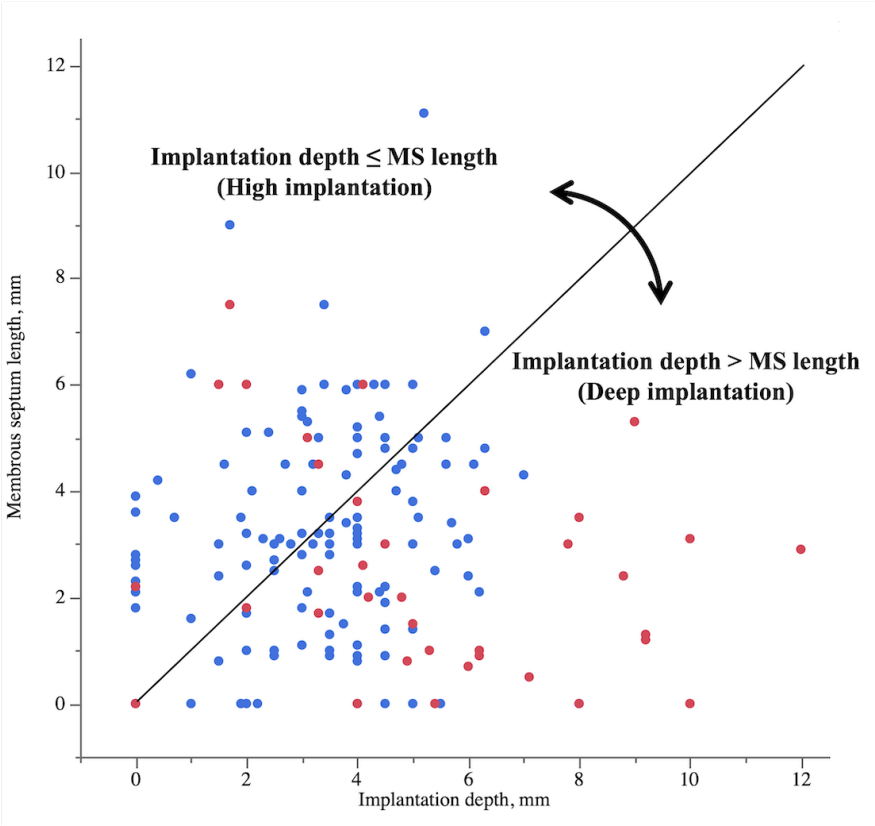












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