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Depth of valve implantation, conduction disturbances and pacemaker implantation with CoreValve and CoreValve Accutrak system for Transcatheter Aortic Valve Implantation, a multi-center study[☆]

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ABSTRACT

Background: Transcatheter Aortic Valve Implantation (TAVI) is now considered an indispensable treatment strategy in high operative risk patients with severe, symptomatic aortic stenosis. However, conduction disturbances and the need for Permanent Pacemaker (PPM) implantation after TAVI with the CoreValve prosthesis still remain frequent.

Methods and results: We aimed to evaluate the implantation depth, the incidence and predictors of new conduction disturbances, and the need for PPM implantation within the first month after TAVI, using the new Accutrak CoreValve delivery system (ACV), compared to the previous generation CoreValve (non-ACV). In 5 experienced TAVI-centers, a total of 120 consecutive non-ACV and 112 consecutive ACV patients were included (n = 232). The mean depth of valve implantation (DVI) was 8.4 ± 4.0 mm in the non-ACV group and 7.1 ± 4.0 mm in the ACV group (p = 0.034). The combined incidence of new PPM implantation and new LBBB was 71.2% in the non-ACV group compared to 50.5% in the ACV group (p = 0.014). DVI (p = 0.002), first degree AV block (p = 0.018) and RBBB (p < 0.001) were independent predictors of PPM implantation. DVI (p < 0.001) and pre-existing first degree AV-block (p = 0.021) were identified as significant predictors of new LBBB.

Conclusion: DVI is an independent predictor of TAVI-related conduction disturbances and can be reduced by using the newer CoreValve Accutrak delivery system, resulting in a significantly lower incidence of new LBBB and new PPM implantation.

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1. Introduction

Transcatheter Aortic Valve Implantation (TAVI) has become the treatment of choice for inoperable patients with severe, symptomatic aortic stenosis and a valuable alternative for those with high operative risk [1–3]. However, TAVI performed with the self-expanding Medtronic CoreValve[®] device (CV) is frequently complicated by new conduction disturbances and subsequent need for Permanent Pacemaker (PPM) implantation. Due to intrinsic properties of the delivery catheter, the use of the first generation 18Fr CV often resulted

in anatomically deep valve implantation. It has been hypothesized that trauma to the interventricular septum by deep insertion of the nitinol frame could impede the conduction tissue which it embeds, resulting in a high incidence of new Left Bundle Branch Block (LBBB) or complete AV-block after valve implantation [4,5]. This might explain the relatively high rate of new pacemaker implantation, as consistently reported by several TAVI registries [6,7].

The Accutrak delivery catheter for the CV has an additional stability layer by which friction forces are reduced, resulting in a more controlled and accurate positioning of the CV. Therefore it was hypothesized that using the Accutrak delivery catheter could result in a higher valve implantation, inflicting a milder trauma to surrounding structures and conduction tissue resulting in a decreased need of new pacemaker implantation. However, only few comparative data are available at present [8].

The pre-specified primary aim of this multi-center Accutrak conduction study was to evaluate the implantation depth, the incidence of new

[☆] Conflict of interest: José Maria Hernandez, Haim Danenberg, Victor Legrand, Peter den Heijer and Johan Bosmans are part-time clinical proctors for Medtronic CoreValve.

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conduction disturbances, and the need for and indications of PPM implantation within the first month after TAVI, using the new Accutrak CV delivery system (ACV), compared to the previous generation CV (non-ACV) in a consecutive “real world” patient population. In addition, we tried to identify predictors for new PPM implantation and new LBBB occurrence.

2. Methods

2.1. Study population

A total of 232 patients were included in 5 high-volume centers experienced in performing TAVI with the CV prosthesis between January 2008 and May 2011. All centers were asked to include the first 20 to 25 consecutive patients before and after implementation of the Accutrak delivery system after excluding 5 “learning curve” patients. Finally, each center included 17 to 25 consecutive non-Accutrak patients (non-ACV group) and afterwards 21 to 25 consecutive Accutrak patients (ACV group). All patients had severe symptomatic aortic valve stenosis, with (very) high operative risk. TAVI implantation was considered feasible by the local heart team, consisting of cardiologists, interventional cardiologists, cardiac surgeons and anaesthesiologists. All patients underwent TAVI with the CV prosthesis.

2.2. Data collection and processing

Age, gender, logistic EuroSCORE, the mean gradient of the aortic stenosis, Aortic Valve Area (AVA), presence of atrial fibrillation (AF), pre-existing LBBB and RBBB, pre-existing 1st degree AV-block and previous PM implantation were assessed in all patients. ECG was performed before, after, at hospital discharge and at 1 month follow-up after TAVI. Vascular access site and size of the prosthesis were assessed for all procedures. Depth of valve implantation (DVI) was assessed in a central core lab (Antwerp University Hospital) based on procedural final angiography performed immediately after TAVI. Blinded measurements were made by one operator (VC), to ensure consistency of the results, using IMPAX Cardiovascular Information System (Agfa Healthcare, Mortsel, Belgium) and CAAS system (Pie Medical Imaging, Maastricht, The Netherlands) software. First, an angiographic projection in which the three sinuses of the aortic valve were seen in the same plane (annular perpendicular view) was chosen as a reference. Secondly, the lower edges of the three cusps of the aortic valve were connected to form a reference line. Perpendicular to this line, the implantation depth of the CoreValve prosthesis was measured medial (interventricular septum) and lateral. The mean of these two measurements was considered the correct DVI in the left ventricular outflow tract. DVI was quantitatively measured in mm beneath the aortic annulus and a mean depth of 4–6 mm beneath the aortic annulus was considered “normal”. Fig. 1 shows a high (A) and low (B) TAVI implantation. Calibration was done using the 5 French pigtail-catheter as a reference. Intraclass correlation was used to test for reproducibility. A total of 15 random measurements were repeated with an intraclass correlation coefficient of 0.96. One center (Malaga) performed, in a similar way, their own measurements of DVI both in ACV patients and non-ACV patients, excluding possible bias.

New PPM-implantation was assessed until 30 days after the procedure and indications were classified according to the ESC-guidelines for PPM implantation [9].

2.3. Endpoints

The combined primary endpoint for the need for new PPM implantation and the occurrence of new LBBB (not requiring new PPM implantation), in the first month after TAVI, was compared between the ACV group and the non-ACV group. Secondly, DVI was compared between both groups and the relationship with significant conduction disturbances was assessed. Finally, possible predictors for the need of new PPM implantation and the occurrence of LBBB were analyzed.

2.4. Statistical analysis

Statistical analysis for the study was performed using SPSS software version 20.0 (IBM Corporation, New York). Categorical variables were expressed as percentages and were compared using Chi Square tests. Fisher's exact test was performed when applicable. Continuous variables were expressed as mean \pm SD and were compared using unpaired Student t-tests when normal distribution occurred. Mann–Whitney U-tests were used in case of abnormal distribution. Correlation between baseline characteristics and the CoreValve type were determined by binary logistic regression. All p-values were 2-sided and differences were considered statistically significant when $p < 0.05$.

3. Results

3.1. Baseline patient and procedural characteristics

A total of 232 consecutive patients – 120 non-ACV and 112 ACV patients – were included between May 2007 and December 2011. Baseline patient and procedural characteristics are presented in Table 1. No significant differences in baseline characteristics between the two patient groups could be detected. The mean age was 81.7 ± 6.0 years, mean logistic EuroSCORE was $22.2 \pm 14.3\%$ and mean AVA was 0.62 ± 0.16 cm [2], reflecting a typical TAVI population with severe aortic valve stenosis, old age and high risk for surgical valve replacement. Pre-procedural ECG-analysis demonstrated atrial fibrillation (AF) in 37 patients (15.9%). Eighteen patients had already a PPM (7.8%) and were excluded from analysis. RBBB was present in 26 patients (12.10%), LBBB in another 26 patients (12.1%) while 1st degree AV block was present in 33 patients (15.4%).

In the majority of patients TAVI was performed by femoral access (>90%). Subclavian access was used in only 12 patients (10%) in the non-ACV group and 8 patients (7%) in the ACV group. Three patients in the ACV group were treated by direct aortic access. Both 26 mm valve size and 29 mm valve size were used almost equally in both the non-ACV and ACV groups. The 23 mm and 31 mm CV devices were not yet widely available at the time of this study. Post dilatation was

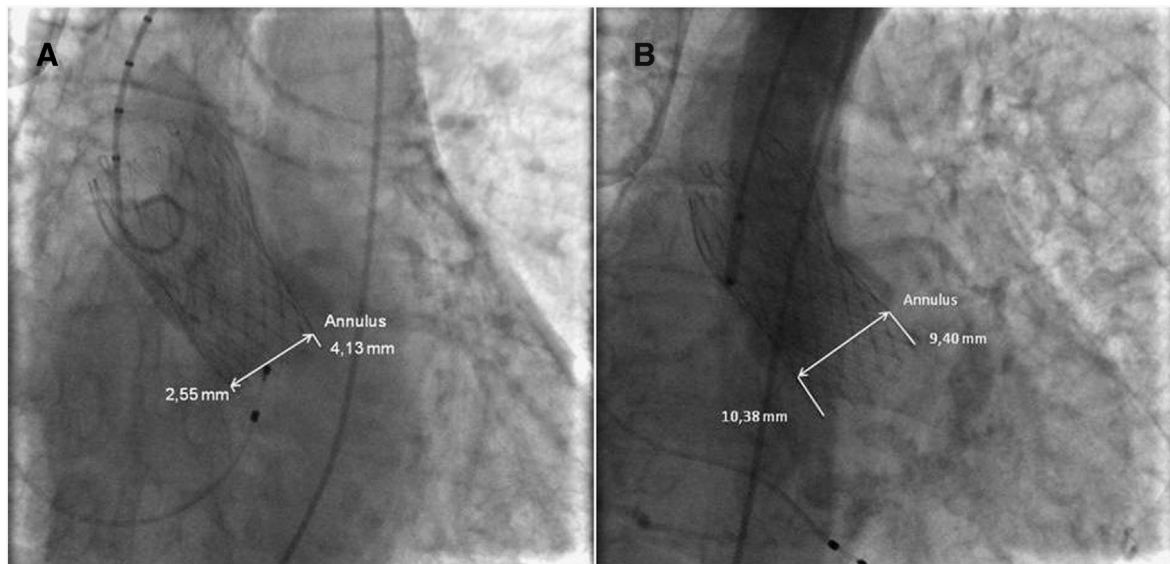


Fig. 1. Angiography in LAO of a fully deployed CoreValve after a high (A) and a low (B) implantation beneath the aortic annulus. Medial and lateral DVI (depth of valve implantation) is depicted.

Table 1
Baseline and procedural characteristics. Categorical and continuous variables.

	Non-AMCV (n = 120)	AMCV (n = 112)	Total (n = 232)	p-Value
Age (years) – mean ± SD	82.0 ± 5.2	81.4 ± 6.8	81.7 ± 6.0	0.412
Male – n (%)	56 (46.7)	45 (40.2)	101 (43.5)	0.319
Logistic EuroSCORE (%) – mean ± SD	21.1 ± 12.6	23.5 ± 15.9	22.2 ± 14.3	0.466
AVA (cm ²) – mean ± SD	0.64 ± 0.14	0.61 ± 0.18	0.62 ± 0.16	0.157
Mean gradient AV (mm Hg) – mean ± SD	47.7 ± 14.3	47.7 ± 13.1	47.7 ± 13.7	0.968
Previous AF – n (%)	16 (13.3)	21 (18.8)	37 (15.9)	0.245
Previous pacemaker – n (%)	10 (8.3)	8 (7.14)	18 (7.8)	0.735
RBBB – n (%)	14 (11.7)	12 (10.7)	26 (11.2)	0.832
LBBB – n (%)	15 (12.5)	11 (9.8)	26 (11.2)	0.528
1st degree AV block – n (%)	18 (15)	15 (13.4)	33 (14.2)	0.781
Transfemoral – n (%)	108 (90.0)	101 (90.2)	209 (90.1)	0.964
Transsubclavian – n (%)	12 (10.0)	8 (7.1)	20 (8.6)	0.438
Direct aortic – n (%)	0 (0)	3 (2.7)	3 (1.3)	0.111
26 mm CoreValve – n (%)	49 (40.8)	54 (48.2)	103 (44.4)	0.258
29 mm CoreValve – n (%)	71 (59.2)	58 (51.8)	129 (55.6)	0.205
Post dilatation – n (%)	20 (16.7)	24 (21.4)	44 (18.9)	0.324

AMCV: Accutrack Medtronic CoreValve; AVA: Aortic valve area; AF: Atrial fibrillation; RBBB: Right Bundle Branch Block; LBBB: Left Bundle Branch Block.

performed equally in both groups (16.7% in the non-ACV group and 21.4% in the ACV group).

3.2. Depth of valve implantation, conduction disturbances and pacemaker implantation

Table 2 summarizes the mean DVI and the incidence of new PPM implantations, new conduction disturbances and mortality at 30 days. The mean DVI was 8.4 ± 4.0 mm in the non-ACV group and 7.1 ± 4.0 mm in the ACV group (p = 0.034). In patients without PPM or LBBB before valve implantation, the combined incidence of new PPM implantation and new LBBB (primary endpoint) was 71.2% in the non-ACV group compared to 50.5% in the ACV group (p = 0.014). In the non-ACV group, 33 (32.3%) “pacemaker naïve” patients received PPM after valve implantation compared to 21 (21.4%) “pacemaker naïve” patients in the ACV group (p = 0.094). In the non-ACV group, 29 (33.3%) “LBBB-naïve patients” developed new LBBB without a need for new PPM at discharge, compared to 23 (26.4%) “LBBB-naïve patients” in the ACV group (p = 0.320). The occurrence of a new RBBB in “RBBB-naïve patients” was rare and did not differ between both groups (p = 1.000) nor did the occurrence of new 1st degree AV-block after valve implantation (p = 0.909). The 30 day all-cause mortality was low and not significantly different between the non-ACV group (6.7%) and the ACV group (5.4%).

Most pacemakers were implanted because of 3rd degree AV-block (67% in the non-ACV group and 76% in the ACV group) without any statistical difference in all classes of indications for pacemaker implantation (Table 3). Most PPMs were implanted in the first week after TAVI, both in the ACV and non-ACV groups.

Table 2
DVI, new Permanent Pacemaker (PPM) implantations, conduction disturbances and all-cause mortality, 30 days after TAVI.

	Non-AMCV	AMCV	Total	p-Value
DVI (mm) – mean ± SD	8.4 ± 4.0	7.1 ± 4.0	7.7 ± 4.1	0.034
New PPM + new LBBB – n (%) ^a	73 (76.8)	53 (56.9)	126 (67.0)	0.014
New PPM – n (%) ^b	32 (29.1)	21 (20.2)	53 (24.8)	0.082
New LBBB – n (%) ^a	41 (43.2)	32 (34.4)	73 (38.8)	0.053
New RBBB – n (%) ^c	1 (1.0)	4 (4.3)	5 (2.7)	0.368
New 1st degree AV block – n (%) ^d	13 (17.1)	15 (22.1)	28 (19.4)	0.742
All-cause 30 day mortality – n (%)	8 (6.7)	6 (5.4)	14 (6.0)	0.676

AMCV: Accutrack Medtronic CoreValve; PPM: Permanent Pacemaker; LBBB: Left Bundle Branch Block; RBBB: Right Bundle Branch Block; AV: Atrio Ventricular.

Bold values indicate significance at p < 0.05.

^a Patients with previous PPM or previous LBBB excluded (n = 188).

^b Patients with previous PPM excluded (n = 214).

^c Patients with previous PPM or previous RBBB excluded (n = 188).

^d Patients with previous PPM, 1st degree AV-block and AF excluded (n = 144).

The relationship between DVI and the need for new PPM implantation, for both the non-ACV and ACV groups, is presented in Table 4 and Fig. 2. The mean DVI in all patients (combined ACV and non-ACV) that required new PPM implantation (n = 54) was 8.9 ± 4.2 mm, which is significantly lower compared to those who did not need new PPM implantation with a mean DVI of 6.9 ± 3.8 mm (p = 0.002). In the non-ACV group this difference remains significant with a mean DVI of 9.4 ± 4.2 mm in patients receiving PPM implantation compared to 7.3 mm ± 3.7 in those who did not (p = 0.022). A trend remained also in the ACV group, with the mean DVI of 8.2 ± 4.2 mm in patients receiving pacemaker implantation compared to 6.6 mm ± 4.1 in those who did not (p = 0.115).

The relationship between DVI and new LBBB is also statistically significant with a lower implantation in the patients with a new LBBB (8.8 ± 3.5 mm) compared with those without a new LBBB (5.4 ± 3.5 mm). This difference remains statistically significant in both the non-ACV group and the ACV group (Table 5).

3.3. Predictors

In a univariate analysis of the total population of both ACV and non-ACV patients, pre-existing 1st degree AV block (p = 0.018), pre-existing RBBB (p < 0.001) and DVI (p = 0.002) were predictors of new PPM implantation at 30 days after TAVI (Table 6). In Table 7, a similar univariate analysis of the total study population is depicted for the occurrence of a new LBBB (only significant predictors and the use of the Accutrak catheter are shown). DVI and pre-existing 1st degree AV-block were identified as significant predictors.

4. Discussion

The pre-specified primary aim of this multi-center conduction study was to evaluate the implantation depth, the incidence of new conduction disturbances, and the need for and indications of PPM implantation

Table 3
Indications for new PPM implantation after TAVI.

	Non-ACV (n = 32)	ACV (n = 21)	Total (n = 53)	p-Value
3rd degree AV block – n (%)	21 (65.6)	16 (76.2)	37 (69.8)	0.412
New LBBB – n (%)	3 (9.4)	3 (14.3)	6 (11.3)	1.000
New 1st degree AV block – n (%)	1 (3.1)	0 (0)	1 (1.9)	0.625
1st degree AV block + LBBB – n (%)	4 (12.5)	0 (0)	4 (7.5)	0.143
Significant bradycardia – n (%)	3 (9.4)	2 (9.5)	5 (9.4)	0.755

PPM: Permanent Pacemaker; ACV: Accutrack CoreValve; AV: Atrio Ventricular; LBBB: Left Bundle Branch Block.

Table 4
Depth of valve implantation (DVI) versus PPM.

	DVI – no PPM Mean ± SD (mm)	DVI – PPM Mean ± SD (mm)	p-Value
Non-ACV	7.3 ± 3.7	9.4 ± 4.2	0.022
ACV	6.6 ± 4.1	8.2 ± 4.2	0.115
Total	6.9 ± 3.8	8.9 ± 4.2	0.002

PPM: Permanent Pacemaker; ACV: Accutrack CoreValve.
Bold values indicate significance at $p < 0.05$.

within the first month after TAVI, using the new Accutrack CV delivery system, compared to the previous generation CV in a consecutive “real world” patient population. In addition, we aimed to identify predictors of the occurrence of new PPM implantation and new LBBB. The main findings of this study can be summarized as follows:

- (1) The incidences of new PPM implantation and new LBBB are confirmed to be high after TAVI, especially when using the “old generation” non-Accutrack 18Fr CV prosthesis.
- (2) The mean depth of valve implantation is confirmed to be a strong predictor, for both new PPM implantation and new LBBB after TAVI.
- (3) The mean depth of valve implantation is significantly reduced using the “new generation” Accutrack 18Fr CV prosthesis.
- (4) The implementation of the “new generation” Accutrack 18Fr CV prosthesis significantly reduced the incidence of the combined endpoint of new PPM implantation and new LBBB after TAVI.

New conduction disturbances after TAVI remain a major limitation, especially with the self-expanding CV, with a reported incidence of PPM implantation varying between 16 and 40% [10–13]. PPM implantation holds certain procedural risks, especially in an old and frail population such as the one that undergoes TAVI (in casu pneumothorax, bleeding, infection, etc.). Moreover, longstanding RV-pacing on itself can induce heart failure [14], or prevent left ventricular recovery. Furthermore, the occurrence of conduction disturbances not requiring PPM implantation after TAVI is high as well. In particular, LBBB has recently been reported to be associated with worse clinical outcome [15]. Trauma to the IV-septum and subsequently to the conduction tissue it embeds, induced by the relatively deep implanted valve frame, is considered to be a major determinant for the new conduction disturbances occurring after TAVI [16]. Awareness of this post procedural

Table 5
Depth of valve implantation (DVI) versus new LBBB.

	DVI – no LBBB mean ± SD (mm)	DVI – LBBB mean ± SD (mm)	p-Value
Non-ACV	6.15 ± 2.97	8.79 ± 4.09	0.022
ACV	4.97 ± 3.78	8.82 ± 2.92	<0.001
Total	5.40 ± 3.52	8.81 ± 3.51	<0.001

LBBB: Left Bundle Branch Block; ACV: Accutrack CoreValve.
Bold values indicate significance at $p < 0.05$.

complication and its underlying pathophysiology has resulted in caution and attempts by operators to perform a safer and thus higher valve implantation. However proper valve positioning has been shown to be relatively challenging using the “old generation” CoreValve.

Several predictors for PPM implantation after TAVI have been identified, mostly in studies restricted by a relatively small sample size. Pre-existing RBBB, depth of valve implantation, hypertrophy of the interventricular septum and pre-existing 1st degree AV-block have previously been identified as predictors for the need for new PPM implantation after TAVI [5,17,18]. In this relatively large, multi-center study, not only depth of valve implantation, but also pre-existing RBBB and pre-existing 1st degree AV-block confirmed to be strong predictors of the need for new PPM implantation. Better control of depth of valve implantation, especially for the CV, is therefore of great clinical relevance in the prevention of conduction disturbances after TAVI.

There is no clear methodological consensus on how to measure most accurately DVI below the annulus. In the single center study by Muñoz-García et al. [19], the distance from the non-coronary cusp to the distal extreme of the prosthesis, based on angiography after TAVI, was considered to be the implantation depth. Using this methodology, the Accutrack delivery system was associated with less deep prosthesis implantation in the left ventricular outflow tract, which could be related to the lower rate of PPM requirement. Also Piazza et al. [20] demonstrated that the mean distance between the proximal end of the CV prosthesis and the lower edge of the non-coronary sinus was significantly shorter in patients who did not need PPM implantation. On the other hand, Tchetché et al. [8] defined DVI as the maximal distance between the intraventricular end of the prosthesis and the aortic annulus at the level of the non-coronary cusp and the left anterior coronary cusp. In this study, evaluating exclusively the Accutrack system, the mean DVI was 4.9 ± 2 mm. In our actual study, we defined DVI as the mean of the distance from the nadir of the non-coronary and left coronary sinus to the ventricular edge of the frame, demonstrating that DVI is an independent predictor of TAVI-related conduction disturbances and can be reduced by using the newer CoreValve Accutrack delivery system. However, although different methodologies are reported for quantifying depth of valve implantation, complicating interpretation of absolute implantation depths, a consistent relation between DVI and occurrence of new conduction disturbances is confirmed by most authors.

Table 6
Predictors of new PPM implantation – univariate analysis.
Bold values indicate significance at $p < 0.05$.

	No new PPM	New PPM	p-Value
AVA (cm ²) – mean ± SD	0.61 ± 0.16	0.65 ± 0.17	0.122
Male – n (%)	54 (37)	27 (50)	0.096
Pre-existing AVB I – n (%)	17 (14.4)	13 (31)	0.018
Pre-existing LBBB – n (%)	21 (14.5)	4 (7.4)	0.181
Pre-existing RBBB – n (%)	5 (3.4)	19 (35.2)	<0.001
DVI (mm beneath annulus) – n (%)	6.87 ± 3.92	8.94 ± 4.19	0.002
Accutrack – n (%)	77 (52.7)	21 (38.9)	0.082

PPM: Permanent Pacemaker; AVA: Aortic Valve Area; AVB: Atrio Ventricular Block; LBBB: Left Bundle Branch Block; RBBB: Right Bundle Branch Block; DVI: depth of valve implantation.
Bold values indicate significance at $p < 0.05$.

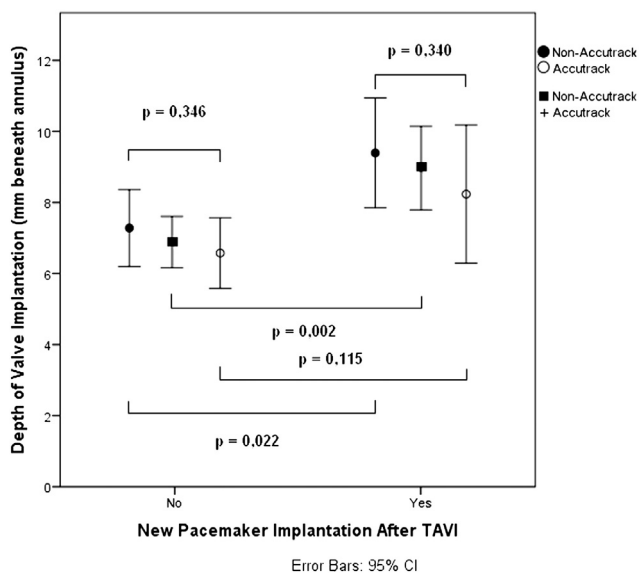


Fig. 2. Depth of valve implantation in patients with and without the need for new Pacemaker implantation. Clustered error bars of Accutrack patients, non-Accutrack patients and the combination of both Accutrack and non-Accutrack patients are shown.

Table 7

Predictors of new LBBB – univariate analysis.

	No new LBBB	New LBBB	p-Value
DVI (mm beneath annulus) – n (%)	5.4 ± 3.52	8.81 ± 3.51	< 0.001
Pre-existing AVB I – n (%)	3 (5.4)	9 (20.5)	0.021
Accutrak – n (%)	42 (60)	23 (44.2)	0.084

LBBB: Left Bundle Branch Block; DVI: depth of valve implantation; AVB: Atrio Ventricular Block.

Bold values indicate significance at $p < 0.05$.

To the best of our knowledge, the actual Accutrak study is the first multicenter comparative study, performed in 5 high-volume TAVI centers, in which depth of valve implantation, both of the “old” and “new generation” 18Fr CV, is measured by a blinded core lab and related to the occurrence of new conduction abnormalities and new PPM implantation.

4.1. Study limitations

The present study is of observational nature with the inherent limitations of such a design. However, all patients in all centers have been included consecutively, without exclusion, representing a “real world” situation. In addition, the fact that all patients in the Accutrak group were treated later in time, compared to those treated with the older system, could have created a bias because the concept of DVI, being potentially responsible for conduction disturbances, may have resulted in attempts of operators to implant higher and thus safer in later procedures, independent of the new delivery device. We tried to minimize this potential bias by including the last patients treated with the previous delivery system and the first patients treated with the Accutrak delivery system in every center, reducing the difference in time to a minimum.

We also did not implement data about the valve/annulus ratio, an additional potential risk factor for post procedural conduction disturbances because in different centers, different imaging techniques were used for valve sizing.

A higher valve implantation could hypothetically result in more severe aortic regurgitation although we found no significant difference in our study. But since assessment of aortic regurgitation, in our study, was done with visual assessment at final angiography only, we did not implement these data in our study.

Also the use of a combined endpoint of new PPM implantation and new LBBB (without PPM implantation) can appear heterogeneous but both reflect very similar CV related conduction abnormalities and are important predictors of morbidity and even mortality, so can be taken in account together.

5. Conclusion

The incidences of TAVI-related new LBBB and new PPM implantation remain high with the Medtronic CoreValve system. DVI is a significant predictor for PPM implantation and new LBBB. The newer Accutrak delivery catheter can significantly reduce DVI, resulting in

a significantly lower incidence of new LBBB and new PPM implantation. Further equivocal improvements in the conceptual design are needed to reduce complications if further indications for TAVI are to be extended.

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