Systematic Review

Overcoming the transcatheter aortic valve replacement Achilles heel: conduction abnormalities—a systematic review

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Background: Transcatheter aortic valve replacement (TAVR) has been shown to be a good alternative to surgery for treating severe symptomatic aortic stenosis (AS) across the whole range of surgical risk patients. Whereas most periprocedural TAVR complications have significantly decreased over time, conduction disturbances remain high. Approaches to decrease this shortcoming are under continuous investigation.

Methods: We conducted a systematic review focusing on modifiable factors impacting post-TAVR conduction disturbances, such as balloon aortic valvuloplasty (BAV), type of new-generation transcatheter valve and implantation depth (ID). Search strategies were based on the best available evidence from each study. Primary endpoints were post-TAVR need of permanent pacemaker implantation (PPI) and new onset left bundle branch block (NOLBBB).

Results: Data from 35 studies with a total of 29,982 patients were analyzed. BAV did not negatively impact PPI rates after TAVR. In propensity-matched and randomized trials, the Evolut R valve was associated with higher rates of PPI compared to the Sapien 3 valve (25% *vs.* 19.2% in propensity-matched studies; 22.9% *vs.* 19% in a randomized trial). The Acurate Neo valve was associated with the lowest PPI rate in observational studies (10.4%), but a PPI rate similar to Sapien 3 was reported in a randomized trial (10% *vs.* 9%). The Portico valve system was associated with a higher PPI risk (PPI rate of 21.9% and 27.7% in propensity-matched and randomized studies, respectively). ID and its relation with the membranous septum (MS) length predicted post-TAVR conduction disturbances, particularly with Evolut R and Sapien 3 valves.

Conclusions: Pre-TAVR BAV did not increase the risk of conduction disturbances post-TAVR. Among the new-generation transcatheter valve systems, Sapien 3 and Acurate Neo valves were associated with the lowest PPI rates followed by the Evolut and Portico valves. A deeper valve implantation and a shorter MS length determined an increased risk of conduction disturbances post-TAVR.

Keywords: Transcatheter aortic valve replacement (TAVR); pacemaker; left bundle branch block; conduction disturbances

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Introduction

Transcatheter aortic valve replacement (TAVR) is a well-established therapy for treating patients with severe symptomatic aortic stenosis (AS). Most recent clinical guidelines on valvular heart disease management have broadened its indications according to the results of several randomized clinical trials (1-4). Moreover, recent data on low surgical risk patients have shown TAVR outcomes to be equivalent or superior to standard surgical aortic valve replacement (SAVR) (5,6). However, TAVR still faces important shortcomings, and procedural-related conduction disturbances are currently considered its main Achilles heel. Permanent pacemaker implantation (PPI) as well as new onset left bundle branch block (NOLBBB) after TAVR have

been shown to be independent predictors of all-cause death and heart failure hospitalization (7). PPI incidence has been high in TAVR registries (~15%), with the transcatheter approach exhibiting higher PPI rates than SAVR in most observational and randomized studies (3-8).

The aim of this systematic review was to offer the most up-to-date evidence on new-onset bradyarrhythmia and conduction disturbances with new-generation TAVR devices, focusing on modifiable procedural factors that may play a role on the aforementioned outcomes.

Methods

Search strategy

A systematic review of available data reporting outcomes on conduction disturbances post-TAVR was performed in accordance with the guidance and the reporting items specified on the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (9). Three main subjects were considered: pre-TAVR balloon aortic valvuloplasty (BAV), type of valve selection, and prosthesis implantation depth (ID). A computerized search was performed on PubMed and Embase databases in order to identify any relevant entry, as well as manual search of primary studies references (backward snowballing). TAVR in patients with previous aortic bioprostheses (valve-in-valve procedures), as well as TAVR indications beyond severe AS, were out of the scope of this review. We limited our search to studies including new-generation TAVR devices: Acurate neo (Boston Scientific, Natick, MA, USA); Evolut R or Evolut PRO (Medtronic, Minneapolis, MN, USA); Portico (St. Jude Medical, Saint Paul, MN, USA) and Sapien 3 (Edwards Lifesciences, Irvine, CA, USA). Databases were last accessed January 31st 2020, and studies were included if they were published in English. Data were extracted using a standardized data abstraction sheet. Two investigators (AA and GM) conducted the literature search, selection and data extraction in duplicate. Any discrepancies between these two investigators were resolved by a third investigator (JRC). Clinical characteristics, as well as in-hospital and/or 30-day outcomes on new PPI or NOLBBB were collected as reported by authors. The Newcastle-Ottawa scale was used for quality assessment of non-randomized studies selected (Table S1).

The search strategy was conducted differently according to the variable robustness of evidence available to address each research question.

Balloon aortic valvuloplasty prior to TAVR

Only observational propensity-matched studies and randomized clinical trials using new-generation devices were included. For studies including both early and new-generation valves, only those in which the latter represented more than 80% of the whole cohort, or if a separate analysis for new-generation valves was carried out, were selected. The following key terms were used: transcatheter aortic valve replacement/implantation valvuloplasty; transcatheter aortic valve replacement/implantation predilation. A flow diagram illustrating BAV selection process is available in Figure S1.

Direct valve type comparison

Only observational propensity-matched studies and randomized clinical trials using new-generation devices were included. Studies including both early and new-generation valves were selected if either the latter represented more than 80% of the whole cohort, or if a separate endpoint analysis for new-generation valves was carried out. The following key terms were used: transcatheter aortic valve replacement/implantation comparison; transcatheter aortic valve replacement/implantation selection; Sapien 3 Evolut; Sapien 3 Acurate Neo; Evolut Acurate Neo; Sapien 3 Portico; Evolut Portico.

Implantation depth

Observational studies reporting any association (whether positive, negative or null) between ID and post-TAVR conduction abnormalities. Studies should include at least 100 new-generation valve recipients. The following key terms were used: transcatheter aortic valve replacement/implantation pacemaker; transcatheter aortic valve replacement/implantation predictors. After title and abstract revision, as well as duplicity elimination, the following terms were used: “depth”, “height” and “pacemaker”.

Endpoints

Primary outcomes of the systematic review were short-term new PPI and NOLBBB, whether at hospital discharge or at 30-day follow-up, as reported by the authors.

Statistical analysis

Continuous variables were expressed as mean ± SD. Global cohort values were reported as weighted mean (95% confidence interval) or frequency (percentage). Weighted

mean was calculated according to the total number of patients in each study (weight = n). Data originated from propensity-matched investigations were analyzed separately from the evidence derived from clinical trials. Data analyses were performed using the STATA software (v14.0; StataCorp).

Results

Balloon aortic valvuloplasty prior to TAVR

PubMed and Embase searches identified 176 and 353 records, respectively. After title and abstract revision, as well as duplicity elimination, 5 studies fulfilled the criteria and were selected (10-14). Clinical characteristics and outcomes were collected as reported by the authors and are summarized in *Table 1*. Quantitative data from Spaziano *et al*. (11) were reported as weighted means since the BAV group was subdivided in selective and systematic predilation.

Overall, 2,412 patients were evaluated, 1,231 undergoing direct TAVR and 1,181 with a pre-BAV approach. Clinical characteristics and conduction disturbances are depicted in *Table 1*. Most patients received either a Sapien 3 (84.9%) or Evolut R (11.6%) valve. Only 2.6% of the cohort received an early-generation valve such as CoreValve (Medtronic, Minneapolis, MN, USA) or Lotus (Boston Scientific, Natick, MA, USA).

Rates of new PPI after TAVR were similar between those undergoing BAV versus patients with direct valve implantation. No information regarding NOLBBB was reported in these studies. The only randomized data, reported by Toutouzas *et al*. (14). showed no differences between the two strategies in self-expandable prosthesis recipients (30-day new PPI 32.8% in direct TAVR *vs*. 27.5% in BAV pre-TAVR, P=0.54). Studies focusing exclusively on balloon-expandable devices reported either non-significant differences, like Abramowitz *et al*. (10) (odds ratio 1.11, 95% CI: 0.44–2.80), or even a higher rate of PPI in patients undergoing the direct TAVR approach (13.9% *vs*. 10.4%, P=0.032) (13). Spaziano *et al*. (11) reported a lack of statistically significant differences after a separate evaluation of systematic predilation *vs*. direct TAVR (30-day new PPI: 4% *vs*. 27%, respectively, P=0.16) and selective predilation *vs*. direct TAVR (30-day new PPI: 18% *vs*. 18% direct TAVR, P=0.94).

Global results showed similar rates of 30-day new PPI between both strategies: 16% with direct-TAVR and 13.2% in the previous BAV group.

Direct valve type comparison

PubMed and Embase searches identified 606 and 2,374 records, respectively. After title and abstract revision, as well as duplicity elimination, 12 studies fulfilled the pre-specified criteria and were finally selected.

Sapien 3 vs. Evolut R/PRO

Data from 5 different studies (4 observational propensity-matched and 1 randomized trial) were included. Propensity-matched studies are summarized in *Table 2*. Overall, 23,965 patients were evaluated, 12,006 and 11,959 Sapien 3 and Evolut R/PRO recipients, respectively. Rates of new PPI across propensity-matched studies were slightly higher when using the Evolut R/PRO valve in comparison with the Sapien 3 valve (23.8% Evolut *vs*. 18.4% Sapien 3). Three out of 5 studies reported significant differences regarding 30-day or post-procedural new PPI, all of them favoring the Sapien 3 valve (15,17,18). Contrarily, the only randomized trial (19) did not find any differences in PPI rates between the two valves (22.9% Evolut R *vs*. 19% Sapien 3, P=0.34) (*Figure 1*). The only study reporting data on NOLBBB after TAVR showed no significant differences between valve types after propensity matching (26.7% Evolut R *vs*. 24.8% Sapien 3, P=0.75) (16).

Sapien 3 vs. Acurate Neo

Data from 5 different studies (4 observational propensity-matched and 1 randomized trial) were included. The main characteristics of propensity-matched studies are summarized in *Table 3*. A total of 2,194 patients were evaluated, 1,250 Sapien 3 and 944 Acurate Neo recipients. Overall incidence of new PPI was 15.6% for Sapien 3 and 10.4% for Acurate Neo across the propensity-matched studies. No data was available on NOLBBB.

One of the observational studies included exclusively patients with previous right bundle branch block (RBBB) and without previous PPI (21). Two of the observational studies reported higher PPI rates with Sapien 3: 15.5% *vs*. 9.9% Acurate Neo, P=0.02 (all-comers) (20); and 43.9% Sapien 3 *vs*. 29.6% Acurate Neo, P=0.02 (RBBB patients) (21); whereas the other matched studies reported numerically higher rates but not-statistically significant differences: 15.2% Sapien 3 *vs*. 12% Acurate Neo, P=0.068 (24); and 16.4% Sapien 3 *vs*. 10.6% Acurate Neo, P=0.24 (23). Conversely, a recently published randomized trial showed no differences in PPI rates between valves (9% Sapien 3 *vs*. 10% Acurate Neo, P=0.76), mainly driven by a much lower incidence of new PPI after Sapien 3

Table 1 Propensity-matched and randomized studies evaluating the impact of pre-TAVR balloon aortic valvuloplasty on conduction disturbances

Study	Cohorts	Patients (N)	Age	STS	Previous PM	Previous RBBB	Post-TAVR PPI	Type of study	Devices
Abramowitz *et al*. (10)	Direct	119	82±7.9	6.4±3.3	15 (12.6)	NR	12 (11.5)	Propensity-matched	Sapien 3
	BAV	126	82.1±7.8	6.3±2.7	22 (17.5)	NR	18 (17)		
Spaziano *et al*. (11)	Direct	116	*83.5 (83.1–83.8)	*5.2 (5–5.4)	15 (12.9)	15/91 (16.5)	19 (20.9)	Propensity-matched	Sapien 3
	BAV	58	*84 (83.7–84.3)	*5.8 (5.7–5.9)	5 (8.6)	6/47 (12.8)	6 (11.3)		
Giordano *et al*. (12)	Direct	139	82.6±5.8	7.9±7.9	13 (9.4)	NR	15 (10.8)	Propensity-matched	Acurate Neo (5.1%); CoreValve (10%); Evolut R (45.9%); Sapien 3 (30.2%); Portico (3.7%); Lotus (5.1%)
	BAV	139	83.1±6.3	11.5±11.9	27 (19.5)	NR	12 (8.6)		
Dumonteil *et al*. (13)	Direct	772	81.7±6.7	6±5.9	88 (11.4)	77 (18.4)	107 (13.9)	Propensity-matched	Sapien 3
	BAV	772	81.6±6.6	7.8±8.3	89 (11.5)	70 (18.4)	80 (10.4)		
Toutouzas *et al*. (14)	Direct	85	81.3±6.9	NR	18 (21.2)	NR	22 (32.8)	Randomized trial	Evolut R 83.6%; Evolut PRO 4.7%; CoreValve 11.7%
	BAV	86	82.1±7.4	NR	17 (19.8)	NR	19 (27.5)		
Overall*	Direct	1,231	82 (81.9–82.1)	6.51 (6.4–6.6)	149/1,231 (12.1)	92/863 (10.7)	175/1,094 (16.0)	–	Sapien 3: 2,047/2,412 (84.9%); Evolut R/PRO: 279/2,412 (11.6%); Acurate Neo: 13/2,412 (0.5%); Portico: 10/2,412 (0.4%); CoreValve: 50/2,412 (2.1%); Lotus: 13/2,412 (0.5%)
	BAV	1,181	82.2 (82.1–82.3)	7.61 (7.58–7.62)	160/1,181 (13.6)	76/819 (9.3)	135/1,023 (13.2)		

Values are mean ± SD or n (%) except as noted. *, values are weighted mean (95% confidence interval) or n/N (%). BAV, balloon aortic valvuloplasty; Direct, direct TAVR without previous balloon aortic valvuloplasty; NR, not reported; PM, pacemaker; PPI, permanent pacemaker implantation; RBBB, right bundle branch block; TAVR, transcatheter aortic valve replacement.

implantation in comparison with previous observational studies (*Figure 1*).

Evolut PRO vs. Acurate Neo

Only one study met the inclusion criteria, the NEOPRO (A Multicenter Comparison of Acurate NEO Versus Evolut PRO Transcatheter Heart Valves) registry. After propensity-score matching, a total of 251 pairs were compared, without significant differences in baseline characteristics between Evolut PRO and Acurate Neo groups. The incidence of new PPI post-procedure was similar between groups (11% Acurate neo *vs.* 12.8% Evolut PRO, P=0.565). Results are displayed in *Table 4*.

Portico vs. Sapien 3 and Portico vs. commercially available prosthesis

Portico and Sapien 3 were compared in a propensity-matched study including 177 patients (*Table 4*). No statistically significant differences were observed between groups in terms of new PPI (21.9% Portico *vs.* 17.5% Sapien 3, P>0.05). On the other hand, a randomized trial involving 732 TAVR recipients demonstrated higher rates of new PPI after Portico implantation in comparison with a pool of commercially available, mainly balloon-expandable,

Table 2 Propensity-matched studies comparing the incidence of new-onset conduction disturbances between Sapien 3 and Evolut R/PRO valves

Study	Cohorts	Patients (N)	Age	STS	Previous PM	Previous RBBB	Post-TAVR PPI	NOLBBB	Type of study
Enríquez-Rodríguez *et al*. (15)	Sapien 3	80	82±6	6.2±5	NR	NR	6 (7.5)	NR	Propensity-matched
	Evolut R	64	84±5	5.8±5	NR	NR	12 (19.0)	NR	
Finkelstein *et al*. (16)	Sapien 3	126	82	3.2	18 (14.3)	NR	– (12.8)	31 (24.8)	Propensity-matched
	Evolut R	126	82	3.2	16 (12.8)	NR	– (12.8)	34 (26.7)	
Vlastra *et al*. (17)	Sapien 3	1,122	81.5±7.1	6.3	NR	NR	89 (8.9)	NR	Propensity-matched
	Evolut R	1,091	81.3±7.1	6.6	NR	NR	186 (18.1)	NR	
Deharo *et al*. (18)	Sapien 3	10,459	83.04±6.6	NR	2,101 (20.1)	NR	– (20.5)	NR	Propensity-matched
	Evolut R	10,459	83.09±6.4	NR	2,091 (20.0)	NR	– (25.9)	NR	
Overall*	Sapien 3	11,787	82.8 (82.8-82.9)	6 (5.95–6.05)	2,119/10,585 (20.0)	–	[19.22]	31/126 (24.8)	–
	Evolut R	11,740	82.9 (82.9-90)	6.22 (6.17-6.28)	2,107/10,585 (19.9)	–	[25.01]	34/126 (26.7)	–

Values are mean ± SD or n (%) except as noted. *, values are weighted mean (95% confidence interval) or n/N (%). Values within [ ] represent the weighted mean of post-TAVR new PPI incidence across studies. NOLBBB, new onset left bundle branch block; NR, not reported; PM, pacemaker; PPI, permanent pacemaker implantation; RBBB, right bundle branch block; TAVR, transcatheter aortic valve replacement.

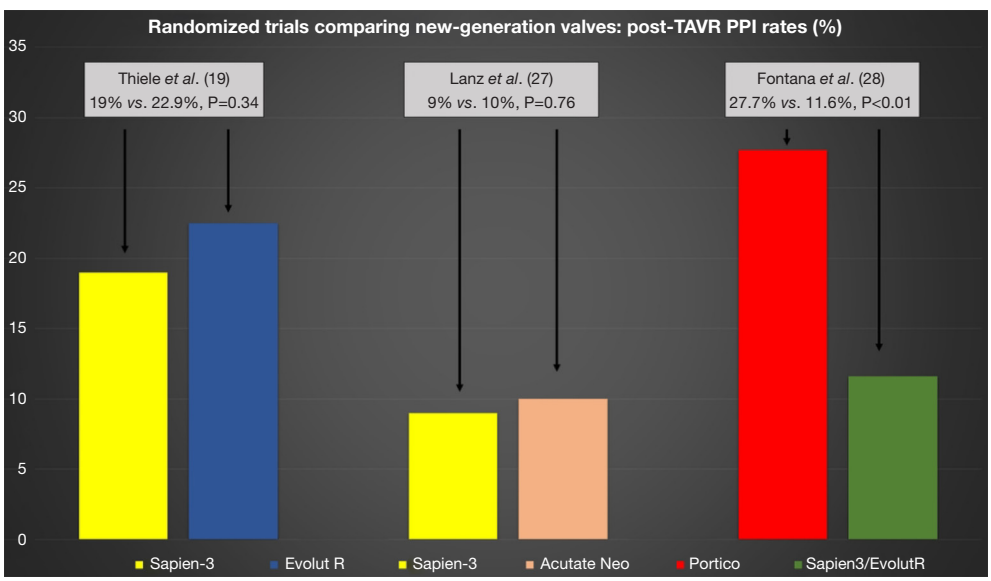

Figure 1 Pacemaker rates on randomized trials with direct comparison between new-generation TAVR devices. TAVR, transcatheter aortic valve replacement.

Table 3 Propensity-matched studies comparing the incidence of new-onset conduction disturbances between Edwards Sapien 3 and Acurate Neo valves

Variables	Husser *et al*. (20)		Husser *et al*. (21)		Mauri *et al*. (22)		Schaefer *et al*. (23)		Overall*	
	Sapien 3	Acurate	Sapien 3	Acurate	Sapien 3	Acurate	Sapien 3	Acurate	Sapien 3	Acurate
Patients (N)	622	311	65	65	92	92	104	104	883	572
Age	81±6	81±6	82 [77–86]#	81 [77–84]#	81.9±5.3	82.8±6.5	81.2±6.2	81.7±5.5	81.2 (81.1–81.2)	81.4 (81.4–81.5)
STS	NR	NR	NR	NR	NR	NR	5.4±3.6	5.8±3.8	5.4	5.8
Previous PM	62 (10)	28 (9)	0	0	NR	NR	NR	NR	62/687 (9)	28/376 (7.4)
Previous RBBB	51 (8.2)	26 (8.4)	65 [100]	65 [100]	NR	NR	NR	NR	116/687 (16.9)	91/376 (24.2)
Post-TAVR PPI	87 (15.5)	28 (9.9)	29 (44.6)	15 (23.1)	14 (15.2)	11 (12)	17 (16.4)	11 (10.6)	a) 147/821 (17.9) [17.7]	a) 65/544 (11.9) [11.9]
									b) 118/756 (15.6) [15.6]	b) 50/479 (10.4) [10.4]
NOLBBB	NR	NR	NR	NR	NR	NR	NR	NR		

Values are mean ± SD or n (%) except as noted. *, values are weighted mean (95% confidence interval) or n/N (%). #, values are median (interquartile range); a), post-TAVR new PPI rates considering all studies; b) post-TAVR new PPI rates excluding Husser *et al*. [2], as they were selected according to pre-procedure RBBB. Values are median (interquartile range). Values within [ ] represent the weighted mean of post-TAVR new PPI incidence across studies. NOLBBB, new onset left bundle branch block; NR, not reported; PM, pacemaker; PPI, permanent pacemaker implantation; RBBB, right bundle branch block; TAVR, transcatheter aortic valve replacement.

Table 4 Propensity-matched studies comparing Evolut R/PRO vs. Acurate Neo and Portico *vs*. Sapien 3 providing conduction disturbance rates

Variables	Evolut R/PRO *vs*. Acurate Neo Pagnesi *et al*. (25)		Portico *vs*. Sapien 3 Mas-Peiro *et al*. (26)	
	Evolut PRO	Acurate	Portico	Sapien 3
Patients (N)	251	251	104	73
Age	81.6±6.1	81.4±6.5	81.8±4.9	81.5±7.3
STS	5.25±3.7	5.08±3.05	3.9±2.2	3.9±2.9
Previous PM	23 (9.2)	21 (8.4)	13 (15.5)	10 (13.7)
Previous RBBB	NR	NR	NR	NR
Post-TAVR PPI	29 (12.8)	25 (11.0)	20 (21.9)	11 (17.5)
NOLBBB	NR	NR	NR	NR

Values are mean ± SD or n (%). NOLBBB, new onset left bundle branch block; NR, not reported; PM, pacemaker; PPI, permanent pacemaker implantation; RBBB, right bundle branch block; TAVR, transcatheter aortic valve replacement.

valves (27.7% Portico *vs*. 11.6% commercially available) (*Figure 1*). The main characteristics and results from randomized trials comparing new-generation valves are displayed in *Table 5*.

Implantation depth

PubMed and Embase searches identified 958 and 2,284 records, respectively. After title and abstract revision as well as, duplicity elimination, 17 studies fulfilled the inclusion criteria and were selected. Overall, 1,784 Sapien 3, 421 Evolut R/PRO, 1,070 Acurate Neo and 298 Portico recipients were evaluated (*Tables 6*,*7*). The aortic angiography imaging immediately after valve deployment was the main technique used to measure ID (stent depth bellow the annulus in mm).

Table 5 Randomized studies comparing new-generation transcatheter valves

Variables	Thiele *et al*. (19)		Lanz *et al*. (27)		Fontana *et al*. (28)	
	Sapien 3	Evolut R	Sapien 3	Acurate Neo	Portico	Commercially available; (65% BEP; 35% SEP%); Sapien: 4 (1%); Sapien XT: 25 (7%); Sapien 3: 206 (57%); CoreValve: 15 (4%); Evolut R: 90 (25%); Evolut PRO: 22 (6%)
Patients (N)	219	219	367	372	371	361
Age	81.5±5.7	81.7±5.3	83±3.9	82.6±4.3	83±7.6	83.7±7
STS	7.6±7.4	7.7±7.2	3.4	3.7	6.4	6.6
Previous PM	23 (10.5)	24 (11.0)	36 (9.8)	43 (11.6)	57 (15.4)	63 (17.5)
Previous RBBB	NR	NR	NR	NR	NR	NR
Post-TAVR PPI	41/214 (19.2)	49/213 (23.0)	34/364 (9.3)	37/368 (10.0)	87/314 (27.7)	35/298 (11.7)
NOLBBB	NR	NR	NR	NR	NR	NR

Values are mean ± SD or n (%). BEP, balloon-expandable prosthesis; NOLBBB, new onset left bundle branch block; NR, not reported; PM, pacemaker; PPI, permanent pacemaker implantation; RBBB, right bundle branch block; SEP, self-expandable prosthesis; TAVR, transcatheter aortic valve replacement.

The Sapien 3 was the valve with the largest body of evidence regarding ID. Two studies reported the lack of significant association between ID and pacemaker requirement (30,35), and six studies showed an association between ID and either new PPI or a combination of PPI and any new conduction disturbance. Of note, 2 studies found an interaction between the ID and membranous septum (MS) length: one study showed a significant association between any conduction disturbance and two anatomical measures (MS length and the difference between the MS and ID) (41), and another study reported a directly proportional association between new PPI and ID (42).

Few studies evaluated the association between Evolut R/PRO ID and conduction disturbances. One study involving 100 patients showed a significant correlation between ID and post-TAVR PPI rates (29). Recently, results on ID and MS length in 248 Evolut R/PRO patients were reported. The overall incidence of PPI was 9.7%. The PPI rate increased as MS length decreased, and only the use of a larger Evolut valve size (34 mm) and a negative difference between ID and MS (deeper valve implantation than the length of the MS) were independently associated with PPI (OR 8.04; 95% CI: 2.58–25.04). A valve implantation technique taking into consideration the MS length (targeting a valve ID < MS length) was prospectively evaluated in 100 patients, resulting in a much lower valve ID, which translated into a significant decrease in PPI rate, from 9.7% to 3% (44).

On the other hand, none of the four Acurate Neo studies evaluating the predictors of conduction disturbances showed an association prosthesis ID and PPI. Lastly, studies involving the Portico valve have revealed heterogeneous findings (one study showed a higher PPI rate in patients with deeper valve implantation, and other studies reported a lack of association between PPI and ID) (*Table 6*).

Discussion

The main findings from our systematic review on modifiable factors influencing the occurrence of conduction disturbances after TAVR can be summarized as follows: First, BAV does not seem to play any relevant role on post-procedural new PPI rate with new-generation devices. Second, a consistently slightly higher rate of PPI was observed in Evolut R/PRO recipients in comparison with balloon-expandable Sapien 3 ones. Third, Acurate Neo and Sapien 3 valves have been the new-generation prosthesis associated with the lowest PPI incidence, with controversial results between observational and randomized studies. Fourth, despite showing less consistency within Acurate Neo and Portico studies, ID and its relation with the MS length are anatomical and procedural landmarks that play a significant role in post-TAVR conduction disturbance rates. Fifth, considerable absence of data remains regarding NOLBBB among the main TAVR studies.

Table 6 New-generation device studies with n>100 evaluating the association between implantation depth and new-onset conduction abnormalities post-TAVR

Study	Number of patients	Valve (n if more than one)	ID assessment technique	Endpoint evaluated	Comparison performed	Risk or difference
Gomes *et al.* (29)	200	CoreValve: 100; Evolut R: 100	NR	PPI	Multivariate regression analysis: PPI as dependent variable	OR: 1.2 (P<0.001) for every mm of ID
Sawaya *et al.* (30)	790	Sapien XT: 507 Sapien 3: 283	Angiographically: mm below septal side of the frame	PPI	Post-TAVR PPI *vs.* non-PPI groups	5.3± 2.4 *vs.* 5.0± 2.6 mm; P=0.67
De Torres-Alba *et al.* (31)	162	Sapien 3	Angiographically [aortic/ventricular stent extension (%)]	PPI	Post-TAVR PPI *vs.* non-PPI groups	72/28 *vs.* 67/23; P=0.032
Husser *et al.* (32)	208	Sapien 3	Angiographically (% of frame height below the aortic annulus)	PPI and/or new or worsened CA	Post-TAVR PPI/CA *vs.* non-PPI/CA	29%±8% *vs.* 25%±7%; P=0.003
Mauri *et al.* (33)	229	Sapien 3	Angiographically (% of frame height below the aortic annulus)	PPI	PPI rate below and above ID median	7% *vs.* 21.9%; P=0.001
Schwerg *et al.* (34)	131	Sapien 3	Angiographically: mm between central marker and aortic cusp	PPI	High implantation group (>2 mm) *vs.* low implantation group (<2 mm)	OR 9.7 (2.7–35.6)
Gonska *et al.* (35)	335	Sapien 3	Angiographically: mm below NCC	PPI	Post-TAVR PPI *vs.* non-PPI	6.7±2.59 *vs.* 6.39±2.48 mm; P=0.43
Mauri *et al.* (24)	212	Acurate Neo	Angiographically: mm below NCC	PPI	Post-TAVR PPI *vs.* non-PPI	5.3±1.9 *vs.* 5.8±2.0 mm; P=0.24
Kim *et al.* (36)	500	Acurate Neo	Angiographically: mm below NCC	PPI	Post-TAVR PPI *vs.* non-PPI	6 mm *vs.* 6 mm; P=0.15
Toggweiler *et al.* (37)	175	Acurate Neo	Angiographically: mm below NCC	Any new CA	Any new-CA group *vs.* non new-CA	4.5±1.5 *vs.* 4.1±1.5 mm; P=0.34
Pellegrini *et al.* (38)	283	Acurate Neo	Angiographically: mm below NCC	PPI and/or new onset LBBB/ RBBB	PPI/newLBBB/ new RBBB *vs.* non abnormalities	7.2±2.4 *vs.* 6.9±1.6; P=0.397
Mas-Peiro *et al.* (39)	100	Portico	Angiographically	PPI	% of PPI patients over and below mean ID	81.3% *vs.* 18.7%; P = NR
Walther *et al.* (40)	198	Portico	Angiographically: mm below NCC	PPI	Post-TAVR PPI *vs.* non-PPI	6.35±2.11 *vs.* 6.07±2.28; P=0.50

CA, conduction abnormality; ID, implantation depth; LBBB, left bundle branch block; NCC, non-coronary cusp; NR, not reported; OR, odds ratio; PPI, permanent pacemaker implantation; RBBB, right bundle branch block; TAVR, transcatheter aortic valve replacement.

Table 7 New-generation device studies with n>100 evaluating the association between implantation depth, membranous septum length and new onset conduction abnormalities post-TAVR

Study	Number of patients	Valve (n if more than one)	MS length assessment	ID assessment	Endpoint	Predictors evaluated	Results
Maeno *et al*. (41)	240	Sapien 3	Standard coronal	Angiographically (mm below NCC)	PPI	MS length (for every mm longer)	OR 0.63 (0.5–0.8). Multivariate analysis.
			Full MS length			ID (for every mm deeper)	OR 1.9 (1.5–2.5). Univariate analysis. No association in multivariate
						ΔMSID (MS-ID, result express for every mm of distance decrease)	OR 1.68 (1.4–2.1). Multivariate analysis.
Oestreich *et al*. (42)	102	Sapien 3	Oblique to AA plane	Angiographically (mm below NCC)	PPI/LBBB	MS length (PPI/LBBB group *vs*. non-PPI/LBBB)	7.9±2 mm *vs*. 7.2±2 mm; P=0.20
			MS length below AA			ID (PPI/LBBB group *vs*. non-PPI/LBBB)	5 mm (IQR:4-9) *vs*. 4 mm (IQR:3-6); P=0.03
						ΔMSID (PPI/LBBB group *vs*. non-PPI/LBBB)	0.5±4 mm *vs*. 1.1±4 mm; P=0.48
Tretter *et al*. (43)	200	Sapien XT/Sapien 3: 94	Oblique to AA plane	Angiographically (mm below NCC)	PPI	MS length (for every mm longer)	OR 0.91 (0.60 to 1.38). Univariate analysis.
		CoreValve/Evolut R/ Evolut PRO: 73	MS length below AA			ID (for every mm deeper)	OR 1.62 (1.01 to 2.61). Univariate analysis.
		Lotus: 30				ΔMSID (MS-ID, result express for every mm of distance increase)	OR 0.61 (0.38 to 0.99). Univariate analysis.
Jilaihawi *et al*. (44)	248	Evolut R: 71	Oblique to AA plane	Angiographically (mm below NCC)	PPI	MS length (cut-off 5 mm)	OR 11.73 (1.50–92.02). Multivariate analysis
		Evolut PRO: 149	MS length below AA			ΔMSID (ID > MS length)	OR 8.04 (2.58–25.04). Multivariate analysis.
		Evolut 34 XL: 28					

ΔMSID, difference between membranous septum length and implantation depth; AA, aortic annulus; ID, implantation depth; LBBB, left bundle branch block; MS, membranous septum; NCC, non-coronary cusp; OR, odds ratio; PPI, permanent pacemaker implantation; RBBB, right bundle branch block; TAVR, transcatheter aortic valve replacement.

Balloon aortic valvuloplasty

The most important studies evaluating BAV with new-generation prosthesis (propensity-matched with more than 700 patients per group and a randomized trial) supported the lack of association between BAV and PPI post-TAVR. Dumonteil *et al*. (13) reported a higher PPI rate with the direct TAVR approach, with no clear explanation for that finding. It is out of the aim of this study to provide general conclusions on BAV apart from conduction disturbances. Therefore, considering the insight provided by this systematic review, BAV utilization should rely on other factors beyond PPI and/or conduction disturbance risk.

Valve type comparison

In light of the results of the present meta-analysis, the Acurate Neo and Sapien 3 seemed to be the new-generation valves associated with the lowest incidence of post-TAVR conduction disturbances, whereas the Evolut R/PRO valve exhibited slightly higher PPI rates. However, it should be highlighted

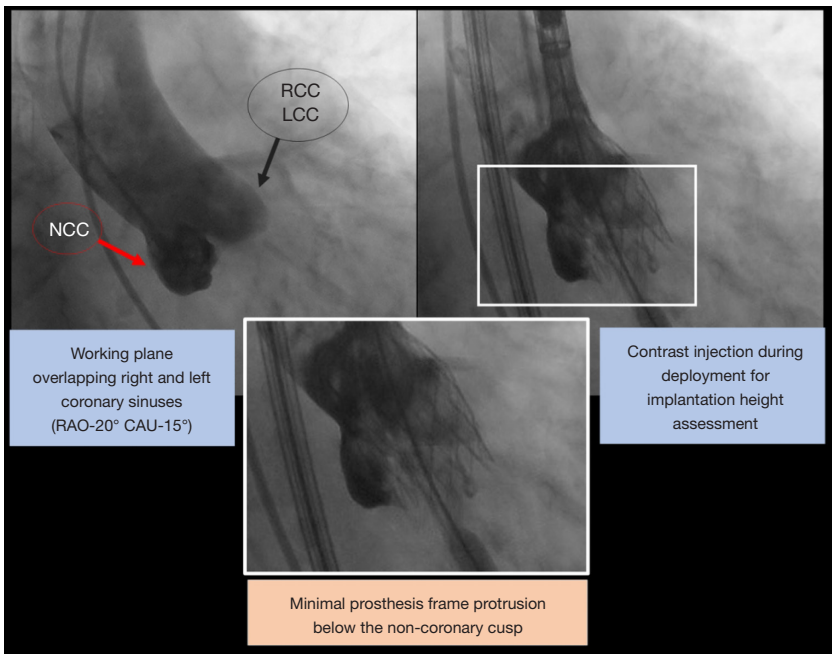

Figure 2 New angiography working plane intended for limiting valve implantation depth. Superior left: aortography demonstrating right and left coronary sinuses overlapping (RCC and LCC black-encircled) opposite to the non-coronary sinus (NCC red-encircled). Superior right: Evolut R 29 mm deployment in the same working plane. Inferior: magnification demonstrating null frame protrusion below the non-coronary cusp.

that the gap between the Sapien and Evolut valves regarding PPI rates has notably decreased since the early-TAVR experience (8,45), with a current difference of around 5% in PPI rate favoring the balloon-expandable valve system. On direct comparison between Acurate Neo and Sapien 3 valves, a trend towards a higher PPI rate with Sapien 3 was observed in propensity-matched studies, but a randomized trial showed a similar PPI rate between valve types (9% Sapien 3 and 10% Acurate Neo). Thus, controversy remains regarding the risk of conduction disturbances between these valves, with current data not allowing for a clear position in favor of any of them. Acurate Neo and Evolut were compared on a propensity-matched cohort without significant differences, and results from the randomized SCOPE II (Safety and Efficacy Comparison of Two TAVI Systems in a Prospective Randomized Evaluation II) trial are eagerly awaited to shed more light on this topic. On the other hand, the Portico valve was associated with higher PPI rates in comparative studies with other new generation valves.

Implantation depth

Although less consistent in studies involving Acurate Neo and Portico patients, ID represents a modifiable factor impacting the occurrence of conduction disturbances post-TAVR. It should be underscored that there was a substantial variability among studies on ID technique assessment and the methods linking ID and conduction disturbances. This is probably due to the lack of any specific consensus regarding ID assessment and the absence of an established cut-off point determining an increased risk of conduction disturbances. MS length has also been assessed by a variety of approaches. In our opinion, MS length below the aortic annular plane may be the most reliable landmark, since it considers the potential degree of interaction between the prosthesis frame and conduction tissue, which may be reduced by an "as-high-as-possible" implant. Interestingly, a new approach has been recently adopted in many centers in order to achieve a higher valve implant. Briefly, this approach considers an innovative angiography working plane during valve deployment in which both the right and left coronary sinuses are overlapped, thus isolating the non-coronary cusp (*Figure 2*). This might facilitate the deployment of the distal frame of the prosthesis just below or even at the same level as the aortic annular plane, which would translate into a decrease in ID. Future studies are

warranted to validate the safety and efficacy of this new valve implantation technique.

Limitations

This study has the limitations inherent to a systematic review that collects only information described in the publications. Thus, relevant information may have been omitted. Moreover, this systematic review focused exclusively on modifiable factors which may play a role on the occurrence of conduction disturbances, and non-modifiable factors (e.g., RBBB) were not included. Finally, other important topics like pre- and post-procedural ECG monitoring, PPI indications and management of conduction disturbances, which may be variable and add significant heterogeneity, were not considered (46).

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Footnote

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