Rate and Predictors of Permanent Pacemaker Implantation after Transcatheter Aortic Valve Implantation: Current Status

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Abstract: Transcatheter aortic valve implantation (TAVI) has become a safe and indispensable treatment option for patients with severe symptomatic aortic stenosis who are at high surgical risk. Recently, outcomes after TAVI have improved significantly and TAVI has emerged as a qualified alternative to surgical aortic valve replacement in the treatment of intermediate risk patients and greater adoption of this procedure is to be expected in a wider patients population, including younger patients and low surgical risk patients. However since the aortic valve has close spatial proximity to the conduction system, conduction anomalies are frequently observed in TAVI. In this article, we aim to review the key aspects of pathophysiology, current incidence, predictors and clinical association of conduction anomalies following TAVI.

Keywords: Transcatheter aortic valve implantation, pacemaker implantation, predictive factors, left bundle branch block, review, valve in valve transcatheter aortic valve implantation, electrophysiological study.

1. INTRODUCTION

Severe symptomatic aortic stenosis (AS) is a common and serious condition and surgical aortic valve replacement (SAVR) is the gold standard for the treatment of operable patients. Since Alain Cribier performed the first transcatheter aortic valve implantation (TAVI) in an inoperable patient in 2004, transcatheter valve intervention has become an established therapy for patients with AS. With increasing clinical experience and by using modern transcatheter heart valves, outcomes of TAVI have continuously improved. To date, TAVI has become a safe and indispensable treatment option for patients with severe symptomatic AS who are inoperable or at high and intermediate surgical risk [1, 2]. Furthermore, the rate of peri-procedural complications has decreased over time, and TAVI has been increasingly performed with a minimalist approach, evolving into a “routine practice” procedure. This provided the rationale for an extension of TAVI indications to younger and low surgical risk patients.

However, recently, unlike other procedural complications, the incidence of new-onset conduction anomalies (i.e., high degree atioventricular block (HAVB)) and new-onset left bundle branch block (LBBB) have failed to decrease [3, 4]. With the anatomical proximity of the atrio-ventricular (AV) node to the aortic annulus, conduction anomalies caused by calcification and mechanical trauma might result in HAVB with the subsequent requirement for requiring permanent pacemaker implantation (PPI).

Apart from these outcomes in patients with native aortic valve disease, TAVI was also identified early on as an elegant treatment option in patients with bioprosthetic valve failure, in contrast with SAVR with its potentially increased surgical trauma [5]. While so-called valve-in-valve TAVI has not been compared to conventional SAVR in randomised studies, it has been shown that it results in excellent outcomes in higher-risk elderly patients. Haemodynamic improvements are easily achieved in larger failing bioprostheses. However, in small prostheses, TAVI, in contrast to SAVR, results in higher transprosthetic gradients and can cause PPI [6].

This review aims to summarize the current evidence for the rate of PPI after TAVI (including second generation devices), PPI predictors, management of conduction anomalies after TAVI and timing of PPI. Moreover, we discuss the role of new on-set conduction anomalies on patient prognosis and current guidelines on pacemaker implantation after TAVI.
2. AORTIC VALVE AND THE CONDUCTION SYSTEM

The anatomy of the heart and its conduction system are intrinsically associated with the appearance of conduction anomalies after invasive procedures. On the right side, the AV node is located within the triangle of Koch (demarcated by the tendon of Todaro, the septal attachment of the tricuspid valve and the orifice of the coronary sinus). The AV node continues with the bundle of His piercing the membranous septum and penetrating to the left through the central fibrous body. On the left side, the conduction axis exists beneath the membranous septum and continues as left bundle branch which is intimately related to the base of the interleaflet triangle separating non coronary and right coronary leaflets of the aortic valve (Fig. 1). During TAVI procedure, conduction anomalies are primarily related to a mechanical trauma resulting in edema, hematoma and ischemia. Furthermore, Kawashima and Sato [7] identified an interindividual variability in the penetrating portion of the His bundle length and depth and interindividual variation in the location of the proximal portion of left bundle. They described three variants that determine the susceptibility to develop complete AV block or LBBB. They found in an autopsy series of 115 elderly patients, in 50% cases right sided AV bundle, in 30% cases a left-sided AV bundle and in 20% cases the bundle courses under the membranous septum just below endocardium. In the latter two variants, the AV bundle is particularly exposed to injury and consequently to develop conduction anomalies.

These relationships have important implications with the potential to induce abnormalities of conduction after percutaneous insertion of a new aortic valve.

3. CONDUCTION ABNORMALITIES: THE Achilles HEEL OF TAVI PROCEDURE

3.1. Pre-procedural Related Causes

In TAVI settings, damage may occur during the preparatory phases of the procedure including crossing the aortic valve, exchange and manipulation of various guide wires and bulky catheter systems in the left ventricular outflow tract (LVOT) which can determine temporary or permanent injury to the conduction axys. Furthermore, new conduction disturbances may occur also during the predilatation step, especially in the case of high balloon/aortic annulus ratio. It was shown that moderate predilatation performed with smaller valvuloplasty balloons is associated with a reduced PPI rate after CoreValve implantation; therefore, the authors proposed a two-hit model, where the first hit to the conduction
system is given by a large valvuloplasty balloon and is usually insufficient to determine an advanced conduction disturbance, whereas the second hit is given by valve deployment and may eventually lead to the final damage requiring PPI [8]. In line with these considerations, a recent meta-analysis [9] and the large UK TAVI registry suggest a signal towards lower PPI rate with direct TAVI [10]. Conversely a recent study including 2,721 subjects treated with Medtronic CoreValve System TAVI, PPI rate was numerically lower with pre-implantation balloon aortic valvuloplasty (pre-BAV), but the difference was not statistically significant [11]. However, as the decision to perform pre-BAV was left to the operator’s discretion in most published studies, a significant selection bias may have influenced these findings; only large randomised studies will clarify the impact of pre-BAV on conduction anomalies.

3.2. Device Related Causes

The susceptibility to AV block in the TAVI setting is in some degree device specific [12]. For early generation SA-PIEN devices (Sapien Edwards, Sapien XT) post TAVI PPI rate ranged from 2.3 % in the PARTNER EU trial [13] to 17.3% in the randomized controlled CHOICE trial [14]. In early generation of the Medtronic Corevalve, the PPI rate ranged from 16.3 % in the Italian Corevalve Registry [15] to 37.7 % in the CHOICE trial [14]. A recent systematic review [16] including 17139 patients treated new generation TAVI prostheses (Edwards Sapien 3 [17, 18], CoreValve Evolut R [19, 20], Accurate transcatheter heart valve system [21], Lotus valve [22, 23], Direct Flow Medical transcatheter aortic valve system [24, 25], Jena Valve [26], Portico transcatheter valve system [27, 28]) the risk of PPI remained low for the balloon expandable devices, conversely the risk seems to be reduced with the second generation self expandable CoreValve systems (Fig. 2).

Differences in the design and in the positioning technique may explain, at least in part, the higher rate of conduction anomalies with the Corevalve. In fact, it is delivered into the LVOT and this may result in more injury to the AV node and left bundle branches. Furthermore, the damage may be delayed because of the self expanding nature of the prosthesis and tissue edema. Whereas the Sapien valve is delivered intra-annularly and expanded by balloon inflation. A critical aspect of TAVI devices is the appropriate administration of the radial force that the transcatheter valve frame applies to the tissues of the LVOT. The radial force has to be sufficient.

![Fig. (2). Permanent PM rates with different devices.](image-url)
to ensure the valve anchoring, but should not interfere with the atrio-ventricular node and disturb the electrical conduction system. Tzamitis S. et al. [29] demonstrated that, for self-expanding valves, the radial force produced depends essentially on the LVOT diameter; while for balloon-expandable valves the force is dependent not only on the LVOT dimensions but also on the stiffness (calcifications) of the host tissues.

Also, the mechanically expanded Lotus valve implantation has been associated with a very high PPI rate (30%) and that was attributed to device oversizing as a consequence of availability in only two sizes (23 mm and 27 mm) [30]. Furthermore, the high PPI rate with Lotus could hypothetically be caused by (1) a higher radial force of the stented frame compared to other devices, which potentially forces the native annulus in a circular shape, and (2) the Lotus frame remains in contact with the wall of the LVOT throughout the process of foreshortening and locking, which could be more harmful to the conduction system [31].

It must be said that a large range of PPI rates across different studies reflects the heterogeneous populations and procedural features, thus limiting the generalizability of the results. Two additional issues should be considered in this setting. Firstly, patients with a prior pacemaker were included in some studies as “patients without new pacemaker”, resulting in an underestimation of the real incidence of PPI after TAVI. Secondly, the indication for PPI may have varied according to operator/center criteria, not always following current guidelines.

3.3. Peri-procedural Related Causes

3.3.1. Implantation Depth in LVOT

Device implantation depth within the LVOT is strongly associated with increased risk of PPI after TAVI, regardless of the prosthesis used. In a study by Mauri V. et al. [32], balloon expandable valves, in patients requiring PPI because of new-onset AV conduction anomalies, were implanted significantly deeper into the LVOT than in patients without the need for PPI. The rate of PPI was reduced from 19.2% to 9.2%, when ≤22% of the device frame was positioned into the ventricular side. A recent study showed that implantation depth was not a predictor for the need of PPI with the Edwards Sapien 3 valve [33]. Implantation depth as a risk factor for PPI has been described previously mainly in the context of TAVI with the CoreValve device, and the PPI rate could be reduced by aiming at a higher final valve position [34]. Furthermore, several studies suggest that maneuvers associated with an overstretching/overexpansion of the LVOT such as balloon predilatation or implantation of large devices in a smaller LVOT increase the risk of TAVI induced conduction anomalies [35, 36].

3.3.2. Post-dilatation After TAVI

Balloon post-dilatation (BPD) has been proposed as an option to reduce the degree of paravalvular aortic regurgitation (AR) by obtaining a better expansion of the stent containing the transcatheter valve.

In a study by Lange P et al., BPD, after CoreValve implantation, had no effect on the requirement for PPI. The reason for this observation might be the relatively short time period when the aortic annulus is exposed to high pressure from repeated valvuloplasty [37]. BPD after Edwards valve implantation ranges between 20-41% and shows no impact on PPI rate [38-40]. Some studies showed that BPD is not a predictor of PPI, but of new-onset LBBB [25, 41]. The use of a slightly larger balloon for BPD might translate into a greater mechanical stress on the ventricular septum and cause potential damage to the left bundle branch system.

3.3.3. Device Oversizing

The degree of prosthesis oversizing may lead to a higher incidence of PPI. Increasing TAVI to aortic annulus oversizing ratios using multislice computed tomography is known to reduce rates of paravalvular leak as the valve has a better fit in the annulus, however, it is also associated with an increase in PPI rate due to increased stress on the membranous septum, aortic annulus and LVOT complex [42].

Schroeter et al. found larger or significantly oversized prostheses to be an independent risk factor for PPI following TAVI with the Medtronic CoreValve bioprosthesis [43]. Leber et al. showed in a prospective study including patients undergoing Edwards Sapien XT device implantation, that the rate of postprocedural PPI tended to be lower in patients with ≤15% oversizing compared to those with >25% oversizing (5.3% vs. 16.7%, P<0.23) [44]. For SAPIEN 3 valve, the frequency and extent of paravalvular leakage are inversely related to the degree of oversizing with acceptable rates of paravalvular leakage being achieved at lower degrees of oversizing, whereas excessive oversizing increases the risk of new conduction anomalies and PPI [45, 46].

4. INCIDENCE OF CONDUCTION ANOMALIES AFTER TAVI

Most conduction anomalies in TAVI setting occur in the acute period (peri procedural or within 24 hours of the procedure). TAVI procedure is associated with both atrioventricular and intraventricular conduction disorders. New-onset LBBB is one of the most common complications after TAVI despite its highly variable incidence, estimated at 5% to 65% depending on the study [47, 48]. LBBB can be transient and hence disappear within the first few days in 19% to 34% of patients [49] but mostly persists at 30 days (62%) [50]. A small proportion of patients (2-8.6%) develop subacute LBBB [51, 52]. It can also be permanent and persist in 2 of 3 patients at 1 year or can appear up to 1 year after procedure in 0.8% of patients.

Like new-onset LBBB, HAVB appears mostly in the peri procedural setting; 60% of 96% of these anomalies occurred within 24 hours of TAVI [53, 54]. About 2% to 7% of patients experienced delayed HAVB ≥ 48 hours after TAVI [40, 55]. HAVB after TAVI may resolve over time and does not always require pacemaker placement. Several previous studies have examined recovery of conduction after TAVI, and their results showed a majority of patients recover conduction during follow-up [56-58]. The only predictors of a lack of recovery of the AVB are prior right bundle branch block (RBBB) [59], higher mean aortic valve gradients and postdilatation of the prosthesis.
Most of these studies were relatively small, with 15-30 pacemaker patients followed on average for ≤1 year. In these small cohorts, recovery of conduction was found in 52-71% of patients. Other studies have provided information about the recovery of conduction after TAVI by performing interrogations of the implanted pacemakers [21, 36, 60-62]. Although heterogeneity in defining pacemaker dependency and in the timing of pacemaker interrogation must be acknowledged, these studies provide further evidence that a significant proportion of conduction anomalies resolve during follow-up period. Pacemaker dependency rates ranged from 27% to 68%, and rates of intrinsic atrio-ventricular conduction increased from 25.9% at 7 days to 59.3% at 30 days. However, it should be stressed that the definition of pacemaker dependency may be inappropriate because even a <1% ventricular pacing rate may be due to paroxysmal HAVB and would, therefore, be enough to avoid sudden cardiac death. Furthermore, statistics on pacing should be used only if the device has been programmed in a mode with a preference for intrinsic rhythm. It is not possible to determine the exact time of rhythm recovery at pacemaker interrogation, because in several studies rhythm check was performed at significant days, usually 1,7 and 1 month or even later.

For early generation devices, conduction anomalies are more common after CoreValve System than Edwards Sapien valve [28]. Regarding new generation valves, a recent study compared early postprocedural and midterm evolution of atrioventricular and intraventricular conduction properties following implantation of the new generation Medtronic Evolut R prosthesis to the previous generation CoreValve system. The authors showed that Evolut R group more frequently had postprocedural PR interval and QRS prolongation at discharge in comparison with those in the CoreValve group. Incidences of 2:1 or greater AV block, new LBBB and permanent pacemaker were similar between both groups [63]. Recently, van Rosendael PJ et al. in a systematic review showed that PPI rates after new generation prosthesis remain low with balloon expandable prosthesis compared with early generation devices, whereas they have reduced with the new generation of self expandable CoreValve systems [15]. Recently published data from studies investigating the Lotus prostheses present a rate of postprocedural PPI similar to CoreValve. In the REPRISE II study, 28.6% of participants had a new pacemaker implanted during the perioperative period, mostly due to third-degree AVB [64].

5. PREDICTORS OF LBBB AND OF NEED PPI

5.1. Patient Related Predictors

Clinical characteristics associated with new on-set LBBB and with pacemaker need are preexisting conduction anomalies (RBBB, left anterior hemiblock, first degree AV block, longer baseline QRS duration) [39,65], male gender [51], previous valve surgery [66], presence of porcelain aorta, calcifications of the aortic valve [67], LVOT [68] and mitral annulus [53], diabetes [51]. Anatomical characteristics of the aortic annulus and the LVOT also play a role. Tzamtzis et al. [16] showed that for both balloon expandable and self expanding devices, the radial force exerted on the LVOT was higher for patients with smaller annuli. Furthermore, authors observed sex specific differences, with females having a smaller annulus, LVOT and sinus of Valsalva, whereas the dimensions of the ascending aorta were similar for both sexes. Toutouzas et al. suggested that a low LVOT/annulus ratio may cause greater tension and edema in the interventricular septum which would exacerbate underlying conduction disturbances and they found that a low LVOT/annulus ratio (<0.89) was a strong indicator of the need for pacemaker. PPI could be predicted by LVOT/annulus ratio with a sensitivity of 77.3% and a specificity of 73.9% [69].

Schewel et al. documented that severe tricuspid regurgitation at baseline is more often accompanied by a greater incidence of HAVB compared with lower levels tricuspid regurgitation. Probably because severe tricuspid regurgitation is the result of a late stage chronic AS and a significant predictor for developing a new HAVB after TAVI [70].

Previously it was mentioned that calcifications of the aortic valve are predictors of PPI. More specifically Spaziano et al showed that right coronary cuspid (RCC) calcium volume was an independent predictor of the need for new pacemaker, while non coronary cuspid (NCC) calcium was a negative predictor for PPI after TAVI [71]. The authors speculated that calcium distribution in the RCC may lead to a shift of the expanded prosthesis towards the area under the NCC, where the AV conduction system is located. Conversely, a high calcium burden in the NCC can act as a “shield”, protecting the AV conduction system, in a similar fashion as a bioprosthesis in the context of valve-in-valve procedures.

A preexisting right bundle branch block remains the strongest predictor of developing complete HAVB [72-74] (Table I).

5.2. Procedural Related Predictors

We have previously discussed balloon predilatation, self expandable CoreValve systems, balloon post-dilatation, device oversizing as causes of conduction anomalies and consequently predictors of PPI. Irrespective of prosthesis type, one of the most frequently identified procedural factor is the depth of device implantation, with deeper implantation being correlated with a higher risk of new conduction anomalies. Proposed cut off values for valve implantation depth predicting LBBB or PPI were 6.3 mm with the Edwards Sapien XT [75] and 7 mm or 25% of the stent frame in the LVOT with the Edwards Sapien 3 [19, 32, 58, 75] and ranged from 6 to 7.8 mm with the CoreValve system [76] and 5 to 6.7 mm with the Lotus valve [77].

Due to the sheath and delivery system sizes, the delivery route in TAVI is related to some complications. They are mostly vascular or bleeding complications, not conduction disturbances. In a study conducted by Salizzoni et al. only the transapical access was related to postprocedural LBBB occurrence [78].

5.3. The Role of Electrophysiological Study

Electrophysiological studies performed after TAVI have shown damage of the AV node, the His and the infra His system. In a study including 75 patients (88% treated with CoreValve and 14.7% treated with Edwards SAPIEN) underwent to pre and post TAVI electrophysiological study, the
δ interval (i.e. HV interval after TAVI minus the HV interval before TAVI) was the only independent predictor of HAVB in the study population and the subgroup with new LBBB, with an optimal cut off of ≥ 13 milliseconds [79]. Excluding results of pre TAVI electrophysiological study from the analysis, the only predictor of HAVB was the δ QRS duration (i.e. QRS duration after TAVI minus duration before TAVI) with an optimal cut off of 38 milliseconds. In the subgroup of patients with new onset LBBB, when data of pre TAVI electrophysiological study were excluded, the only predictor of HAVB was the HV interval after TAVI, with an optimal cut off of ≥ 65 milliseconds [62].

In another recent study including 84 patients (67% treated with CoreValve and 33% treated with Edwards SA-PIEN) the presence of persistent complete AV block during the procedure and post operative HAVB were the only factors associated with the need for PPI at follow up, whereas the serial measurement of the HV interval could not predict the need for PPI [80].

Therefore the role of the electrophysiological study is still controversial, particularly in patients with new on set LBBB.

6. CURRENT GUIDELINES

No official American College of Cardiology guidelines or position statements exist to date, and for all practical purposes, PPI is left to the discretion of the physician. The 2013 European Society of Cardiology guidelines recommend a period of clinical observation up to 7 days for recovery before proceeding with PPI in patients with persistent high degree or complete AV block post-surgery or post-TAVI in order to assess whether the conduction disturbance is transient or permanent (Class I recommendation; Level of Evidence C) [81]. Such a strategy of more prolonged ECG monitoring post TAVI prior to PPI is supported by the results of studies showing that a significant proportion of conduction anomalies resolves early within the post TAVI period, and there is an increased risk of late mortality or repeat hospitalizations for heart failure associated with cardiac pacing, particularly in patients with low ejection fraction and higher rates of pacemaker dependency [82]. However, this may delay ambulation and discharge and increase the risk of morbidity and mortality from immobility with temporary pacemaker in place. In case of complete AV block with a low rate of escape rhythm this observation period can be shortened since resolution is unlikely (Class I recommendation; Level of Evidence C) [81]. In patients with transient high-degree AV block or a new left bundle branch block, short-term mobile outpatient rhythm monitoring, along with avoidance of AV-nodal-blocking agents, might be indicated upon hospital discharge, with close follow-up for conduction recovery. With current knowledge and technology, it may still be justified to implant a pacemaker in patients who develop complete heart block because the median time to recovery might take several months. There is a lack of consensus and data regarding PPI in case of occurrence of TAVI related second degree atrio-ventricular block, bundle branch blocks or combination of atrio-ventricular block and bundle blocks, but most researchers recommend PPI.

Recent reports suggest that PPI not only increases the length of ICU and hospital stay post procedure but also can increase overall mortality and exacerbation of heart failure, therefore the role of pacemaker placement in TAVI is being more closely examined [83].

A review of the literature leaves more questions than answers. The role of pacemaker placement, the timing of placement, and prognosis of patients who require pacing are definitely issues that need to be addressed, with the identification of the patient with new conduction abnormalities post TAVI that requires device placement a close second.

7. IMPACT OF LBBB AND PPI IN MIDTERM MORTALITY

There are different clinical implications of PPI and LBBB after TAVI. A reduced left ventricular ejection fraction (LVEF) is common among patients after TAVI. This comorbidity is present in about 36% of patients scheduled for TAVI according to the UK TAVI registry [84]. Urena et al. showed that patients with either persistent LBBB or new pacemaker experienced a decrease in LVEF at 1 year post TAVI [45, 85]. Subanalyses of the PARTNER trial indicated that at 30 days after TAVI, previous PM correlated with a reduced probability of an increase of ≥10% in LVEF [86]. Regarding new LBBB, Tzikas et al. showed that 6 day after TAVI, patients with new conduction anomalies had a decrease in LVEF, whereas patients without new conduction anomalies had an increase in LVEF [87].

Given that LBBB and PPI appear to negatively affect LVEF and the absence of an improvement in LVEF results in poor prognosis and increased mortality, the benefit to risk profile of TAVI should be carefully evaluated in patients with baseline characteristics that may predispose them to TAVI induced conduction anomalies. Data on the impact of LBBB or PPI on mortality rates are not clear [64] (Table 2). LBBB causes electrical and mechanical dyssynchrony of the heart and various unfavorable hemodynamic effects. In a largest meta-analysis, Regueiro et al. pooled data from 8 studies (4756 patients) and failed to demonstrate a significant association between new LBBB and 1-year all cause mortality. In contrast, LBBB was associated with a greater risk of 1-year cardiac mortality [88].

Regarding clinical association of PPI with midterm mortality, while individual studies provided inconsistent results [89, 90], a report from the Society of Thoracic Surgeons Transcatheter Valve Therapy registry including 9785 patients, showed an increased risk in 1-year overall mortality among patients who had PPI after TAVI [91]. The negative effect of PPI on LVEF among TAVI patients may explain this finding. However, similar to LBBB, the association of PPI with midterm mortality remains controversial, by reason of differences in PPI indications, pacemaker dependency, and ventricular pacing rates across studies. Indeed, Watanabe et al. demonstrated an increased 1-year mortality among patients with baseline RBBB undergoing PPI, a subset of patients likely to exhibit high rates of ventricular pacing, supporting the hypothesis that long-term pacing has negative effects on midterm follow up [92].
Table 1. Impact of permanent pacemaker implantation after TAVI on mortality.

| Author (Supp. Refs.) | Valve Type | Total Population (n) | New Pacemaker Rate (%) | Conduction Disturbances Leading to Permanent Pacemaker Implantation | Follow up (Months) | Mortality Rate at Follow up | HR (Confidence Interval 95%) | Impact on All Cause Mortality |
|-----------------------|------------|----------------------|------------------------|---------------------------------------------------------------|-------------------|-----------------------------|-----------------------------|------------------------------|
| Urena et al. [25]     | Sapien     | 668                  | 4.3                    | -High degree AVB
  - Sinus node dysfunction with symptomatic bradycardia
  - Slow atrial fibrillation | 13 | 27.8 | 28.4 | 0.87 (0.55-1.37) | None (p=0.54) |
| Fadahunsi et al. [12]| CoreValve  | 9785                 | 6.7                    | -Conduction defects (not specified) | 12 | 24.1 | 19.6 | 1.31 (1.09-1.58) | Yes (p=0.003) |
| De Carlo et al. [26]  | CoreValve  | 275                  | 25.5                   | -High degree AVB | 12 | 12.5 | 11.8 | NR | None(p=0.90) |
| Buellesfeld et al. [27]| CoreValve | 305                  | 27.8                   | -High degree AVB | 12 | 19.4 | 18.0 | 1.06 (0.60-1.84) | None (p=0.77) |
| Carrabba et al. [28] | CoreValve  | 92                   | 33                     | -High degree AVB
  - Sinus node dysfunction with symptomatic bradycardia | 12 | NR | NR | 0.74 (0.18-3.02) | None (p=0.67) |
| Dizon et al. [29]     | Sapien     | 2531                 | 6.8                    | -High degree AVB
  - Sinus node dysfunction with symptomatic bradycardia | 12 | 26.3 | 20.0 | 1.38 (1.00-1.89) | Yes (p=0.05) |
| Pereira et al. [30]   | CoreValve  | 65                   | 32.8                   | -Third-degree AVB
  - Mobitz II second-degree AVB
  - AF with complete AVB
  - Trifascicular block | 12 | 26.3 | 24.3 | NR | None (p=0.111) |
| Giustino et al. [13]  | CoreValve  | 1062                 | 15.4                   | -High degree AVB | 12 | 28.7 | 21.8 | 1.11 (0.74-1.67) | None (p=0.62) |
| Urena et al. [31]     | CoreValve  | 1556                 | 25.5                   | -Third-degree or advanced second-degree AVB
  - Sinus node dysfunction with documented symptomatic bradycardia
  - Left bundle branch block with first degree AVB (at the discretion of the physician) | 22 | 20.6 | 22.2 | 1.02 (0.74-1.42) | None (0.89) |

(Table 1) Contd...
| Author (Supp. Refs.) | Valve Type | Total Population (n) | New Pacemaker Rate (%) | Conduction Disturbances Leading to Permanent Pacemaker Implantation | Follow up (Months) | Mortality Rate at Follow up | HR (Confidence Interval 95%) | Impact on All Cause Mortality |
|----------------------|------------|----------------------|------------------------|---------------------------------------------------------------|-------------------|---------------------------|-----------------------------|-----------------------------|
| Meredith et al. [32] | CoreValve  | 540                  | 28.4                   | -High degree AVB                                              | 24                | NR                        | NR                          | NR (p=0.58)                  |
| Gerckens et al. [33] | CoreValve  | 1015                 | 33.7                   | -High degree AVB                                              | 60                | NR                        | NR                          | NR (p=0.48)                  |
| Nadeem et al. [34]   | Sapien     | CoreValve            | 672                    | -Conduction anomalies (not specified)                         | 12                | 21.9                      | 15.4                        | 1.42 (0.99-2.05)             |

HR: Hazard Ratio; PPI: Pacemaker Implantation; AVB: Atrioventricular Block.

Table 2. Predictors of permanent pacemaker implantation after TAVI.

| Valve Type | Author (Supp. Refs.) | Year | N of Patients | New Pacemaker Incidence (%) | Multivariable Predictors | Odds Ratio | 95% Confidence Interval |
|------------|----------------------|------|--------------|-----------------------------|--------------------------|------------|------------------------|
| CoreValve  | De Carlo et al. [1]   | 2012 | 275          | 24                          | -Depth of implantation   | 1.2        | 1.03-1.3               |
|            |                      |      |              |                             | -RBBB                   | 3.7        | 1.5-9.2                |
|            |                      |      |              |                             | -Left anterior hemiblock | 2.3        | 1.1-5.1                |
|            |                      |      |              |                             | -Longer PR interval      | 1.02       | 1.0-1.04               |
| CoreValve  | Ledwoch et al. [2]    | 2013 | 1147         | 33.7                        | -No prior valve surgery  | 0.3        | 0.1-0.8                |
|            |                      |      |              |                             | -Porcelain aorta        | 1.6        | 1.1-2.4                |
|            |                      |      |              |                             | -CoreValve              | 2.9        | 1.7-4.7                |
| CoreValve  | Lange et al. [3]      | 2014 | 237          | 21.1                        | -RBBB                   | 46.7       | 8.8-249                |
|            |                      |      |              |                             | -Valvuloplasty balloon of 25 mm | 5.5    | 1.0-29.0               |
| CoreValve  | Mouillet et al. [4]   | 2015 | 833          | 30.3                        | -RBBB                   | 2.3        | 1.7-3.1                |
| Sapien     | Nazif et al. [5]      | 2015 | 1973         | 8.8                         | -RBBB                   | 7.0        | 4.9-10.1               |
|            |                      |      |              |                             | -Prosthesis diameter/LVOT diameter | 1.3/0.1 incre-ment | 1.1-1.5                |
|            |                      |      |              |                             | -Left ventricular end diastolic diameter | 0.68 per cm | 0.53-0.87              |
| Sapien     | Schymik et al. [6]    | 2015 | 634          | 10.8                        | -RBBB                   | 6.2        | 3.8-10.3               |
| Sapien XT  | Schymik et al. [6]    |      |              |                             | -Permanent atrial fibrillation | 1.8   | 1.1-2.6                |
| CoreValve  |                      |      |              |                             | -CoreValve              | 2.4        | 1.6-3.8                |
| Sapien     | Van Der Boon et al. [7]| 2015 | 549          | 13.3                        | -RBBB                   | 7.2        | 3.3-15.9               |
| Sapien XT  | Van Der Boon et al. [7]|      |              |                             |                      | 3.7        | 1.3-10.6               |
| CoreValve  |                      |      |              |                             | 14.4                    | 16.9       | 3.0-95.5               |
| Sapien 3   | Mauri et al. [8]      | 2016 | 229          | 14.4                        | -LVOT left coronary calcification >13.7 mm² | 4.7   | 1.6-14.1               |
|            |                      |      |              |                             | -RBBB                   | 15.7       | 5.7-43.5               |

(Table 2) Contd…
| Valve Type | Author (Supp. Refs.) | Year | N of Patients | New Pacemaker Incidence (%) | Multivariable Predictors | Odds Ratio | 95% Confidence Interval |
|------------|----------------------|------|---------------|-----------------------------|--------------------------|------------|------------------------|
| Sapien 3   | Sawaya et al. [9]    | 2016 | 283          | 17.3                       | • RBBB                   | 4.9        | 1.88-12.95             |
|            |                      |      |              |                             | • PR duration (per 10 ms increment) | 1.14       | 1.00-1.29              |
|            |                      |      |              |                             | • Device lack of coaxiality during implant (per 1 mm increment) | 1.13       | 1.00-1.29              |
| Sapien 3   | De Torres-Alba et al. [10] | 2016 | 162          | 19.1                       | • Implantation depth (% of stent length in the aorta) | 0.95       | 0.91-0.99              |
| Sapien 3   | Husser et al. [11]   | 2016 | 208          | 16                         | • RBBB                   | 11.9       | 3.4-42.0               |
|            |                      |      |              |                             | • Atrial fibrillation    | 3.9        | 1.5-10.1               |
|            |                      |      |              |                             | • Heart rate on admission | 0.9        | 0.90-0.97              |
|            |                      |      |              |                             | • Unspecified intraventricular conduction abnormality | 10.02      | 1.6-61.0               |
|            |                      |      |              |                             | • Chronic obstructive pulmonary disease | 4.6        | 1.5-14.4               |
|            |                      |      |              |                             | • Implantation depth at the non septal side | 1.06       | 1.06-1.12              |
| Sapien XT  | Fadahunsi et al. [12] | 2016 | 9785         | 6.7                        | • Age                    | 1.07/5 years | 1.01-1.2         |
| CoreValve  |                      |      |              |                             | • Prior conduct defect   | 1.9        | 1.6-2.3                |
|            |                      |      |              |                             | • CoreValve              | 7.6        | 6.0-9.6                |
| Sapien XT  | Giustino et al. [13]  | 2016 | 947          | 17.3                       | • Age                    | 1.08 per year | 1.04-1.12         |
| CoreValve  |                      |      |              |                             | • Male sex               | 1.7        | 1.1-2.7                |
|            |                      |      |              |                             | • Body mass index        | 1.08 per unit  | 1.02-1.13         |
|            |                      |      |              |                             | • Transfemoral access TAVI | 0.5        | 0.3-0.9                |
|            |                      |      |              |                             | • CoreValve              | 2.6        | 1.6-4.3                |
|            |                      |      |              |                             | • Balloon post dilatation | 9.2        | 5.5-15.5               |
| CoreValve  | Rodriguez-Olivares et al. [14] | 2016 | 302          | 22.5                       | • RBBB                   | 2.9        | 1.2-6.9                |
| Sapien XT  |                      |      |              |                             | • LVOT oversizing        | 1.03 per 1%  | 1.005-1.065        |
| Lotus      |                      |      |              |                             | • Depth of implantation  | 1.2 per mm  | 1.09-1.3              |
|             | Van Mieghehm et al. [15] | 2016 | 864          | 30                         | • RBBB                   | 3.3        | 1.8-5.9                |
|             |                      |      |              |                             | • STS score              | 1.03       | 1.00-1.05              |
| Sapien 3   | Gonska et al. [16]   | 2017 | 283          | 18.4                       | • First degree atrio ventricular block | 4.0        | 1.7-9.1                |
|            |                      |      |              |                             | • RBBB                   | 4.6        | 1.5-13.2               |
| Sapien 3   | Maeno et al. [17]    | 2017 | 240          | 14.6                       | • RBBB                   | 14.3       | 5.0-40.9               |
|            |                      |      |              |                             | • Non coronary cusp device landing zone calcium volume | 1.02       | 1.02-1.06             |
|            |                      |      |              |                             | • Difference between membranous septal length and valve implantation | 1.68       | 1.36-2.08              |
| Sapien XT  | Abramowitz et al. [18] | 2017 | 606          | 11.6                       | • Severe mitral annular calcification | 2.8        | 1.1-7.5                |
| Sapien3    |                      |      |              |                             | • RBBB                   | 6.9        | 3.3-14.6               |
| CoreValve  |                      |      |              |                             | • Medtronic CoreValve    | 4.9        | 1.4-16.9               |
| Sapien XT  | Al-Azzam et al. [19] | 2017 | 300          | 19.7                       | • RBBB                   | 4.5        | 1.6-8.6                |
| Sapien3    |                      |      |              |                             | • Medtronic CoreValve    | 4.1        | 1.5-11                 |
| Lotus      | Zaman et al. [20]    | 2017 | 93           | 28                         | • RBBB                   | 2.8        | 1.1-7.0                |
|            |                      |      |              |                             | • Depth of implantation below the non coronary cusp> 5 mm | 2.4        | 1.0                   |

(Table 2) Contd...
8. VALVE IN VALVE TRANSCATHETER AORTIC VALVE IMPLANTATION AND RISK OF PPI

The management of the aortic valve disease is changed with the advent of TAVI. Bioprosthetic valves have been increasingly employed over the last decade for surgical aortic valve replacement as the ageing patient population is preferring to avoid systemic anticoagulation. Redo-surgical aortic valve replacement (redo-SAVR) has been the gold standard for the treatment of failing bio-prostheses. However, it carries an inherent risk associated with a reoperative open heart surgery. In this setting, valve-in-valve transcatheter aortic valve implantation (ViV-TAVI) has evolved as a new alternative approach to redo-SAVR. A recent systematic review compared safety and efficacy of ViV-TAVI versus redo-SAVR for failed aortic bioprostheses and showed that ViV-TAVI was associated with lower PPI rates compared to redo-SAVR [93]. This finding is probably related to surgical excision of the previously implanted bioprostheses and longer manipulation of aortic annulus, which confers a higher risk of injury to the atroventricular node, whereas during ViV-TAVI, the failed bioprosthesis protects the conduction system from injury [6, 94]. Another recent meta-analysis between ViV-TAVI and redo-SAVR reported that PPI rates after ViV-TAVI ranged from 8.3% to 14%, which are lower to PPI rates after redo-SAVR [95], confirming previously reported data [76].

CONCLUSION

Conduction anomalies are a common complication of TAVI that may compromise the quality of life and prognosis of patients. Baseline RBBB, the use of some self-expanding valve systems and the depth of device implantation within the LVOT remain the main risk factors of conduction anomalies occurrence, but several factors are involved. The use of second generation transcatheter valve device can reduce a little the risk of conduction anomalies. Limiting the indications to PPI to those strictly recommended in guidelines reduces the need of PPI, and the risks and benefits of implementing a more prolonged period of electrocardiographic monitoring in the TAVI workflow need to be adequately assessed in prospective studies. Moreover, the optimal timing of PPI, the factors associated with development and recovery of conduction anomalies after TAVI, the role of “prophylactic” PPI in some cases of LBBB after TAVI, need to be elucidated in further studies.

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The authors declare no conflict of interest, financial or otherwise.

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**Table: Valve Type and Predictors**

| Valve Type | Author (Supp. Refs.) | Year | N of Patients | New Pacemaker Incidence (%) | Multivariable Predictors | Odds Ratio | 95% Confidence Interval |
|------------|----------------------|------|---------------|------------------------------|--------------------------|------------|------------------------|
| Lotus      | Dunontei et al. [21] | 2017 | 249           | 32                           | RBBB, LVOT area overstretch >10%, First degree atroventricular block, LVOT total calcium volume | 12.7       | 4.45-36.2              |
| Evolut R   | Gomes et al. [22]   | 2017 | 100           | 23.3                         | RBBB, Implantation depth (mm) | 4          | 1.9-4.7                |
| Sapien XT  | Gaede et al. [23]   | 2018 | 1198          | 14.7                         | RBBB, CoreValve           | 3.0        | 1.3-2.9                |
| Acurate neo| Kim et al. [24]     | 2018 | 500           | 10.2                         | RBBB, Oversizing          | 3.1        | 1.2-7.7                |

RBBB: Right Bundle Branch Block; LVOT: Left Ventricular Outflow Tract.
Rate and Predictors of Permanent Pacemaker Implantation

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218 Current Cardiology Reviews, 2019, Vol. 15, No. 3

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