

Permanent pacemaker insertion in patients with conduction abnormalities post transcatheter aortic valve replacement: a review and proposed guidelines

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Abstract: Conduction abnormalities are a common and serious complication of transcatheter aortic valve replacement (TAVR) with well-established predictive factors. Current guidelines are not concrete, leaving several questions unanswered about indications, timing and risks of pacemaker implantation post-TAVR. In this review article, we discuss current guidelines, predictors of pacemaker implantation, clinical implications of this procedure and our recommendations for reducing the pacemaker implantation rate post-TAVR.

Keywords: Transcatheter aortic valve replacement (TAVR); pacemaker; guidelines

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Introduction

More patients with aortic stenosis (AS) are now undergoing transcatheter valve replacement than ever before. The Placement of Aortic Transcatheter Valves (PARTNER2) data (1) has prompted intermediate risk patients to be included in the recent American Heart Association and American College of Cardiology joint guidelines for transcatheter aortic-valve replacement (TAVR) (2), while trials for low risk patients (3) are currently ongoing.

However, TAVR-related rates of conduction abnormalities remain higher than those who undergo surgical aortic valve replacement (SAVR) and permanent pacemaker (PPM) implantation is not without its short and long-term risks. The exact indications, timing and long-term outcomes of PPM implantation remain unclear necessitating this comprehensive review of current guidelines and clinical practices in this rapidly evolving area.

AS and current management

AS is a common cause of valvular heart disease present in almost 7% of patients older than 65 (3). It is estimated that by 2025, 1.3 million people in Europe and 1 million people in the United States will develop severe AS. In fact, these numbers are expected to double by the year 2050 (4). AS is a slow and progressive disease, but when symptomatic, it associated with up to 50% mortality in 2 years if untreated (5,6). Over the decades, SAVR has improved survival in patients with symptomatic severe AS (7,8).

However, up to 30% patients with severe symptomatic AS are unable to undergo SAVR due to multiple comorbid conditions, advanced age, and severe left ventricle dysfunction. Hence, TAVR has become an alternative for AS patients deemed high risk for SAVR and now for intermediate risk patients as well (9).

The recent update to the American Heart Association

and American College of Cardiology joint guidelines for valvular heart disease have designated a Class I recommendation for TAVR in high risk patients and Class IIa recommendation for intermediate risk surgical patients with AS (6). This promises to increase the numbers of patients suitable for TAVR worldwide. Improved operator experience and volume, better patient selection, improved pre-TAVR imaging, and improvement in the valve prosthesis and delivery systems has reduced the complications such as paravalvular leak (PVL), stroke, vascular complications, and conduction abnormalities (10).

Conduction abnormalities; a prevalent complication of TAVR

Conduction abnormality and need for PPM continues to be much higher for TAVR than with SAVR (11) and may prove its Achilles heel in the near future as it is applied to a large population of lower risk, younger patients.

The PARTNER2 trial showed that 30-day rates of PPM implantations in balloon expandable valve (BEV) and SAVR were 8.5% and 6.9% respectively (1) proving the higher rate of PPM implantation in TAVR patients. Historically, the incidence of PPM implantation has been significant; estimated at 3.2% with SAVR, compared to as high as 25% with TAVR using Medtronic self-expanding CoreValve (SEV) and approximately 7% with BEV (12,13). The higher incidence of conduction abnormalities in the self-expanding valve is due to differences in stent design and the radial force exerted on sensitive cardiac tissue: SEV has a rigid and longer nitinol stent usually implanted deeper in the left ventricular outflow tract (LVOT) and causing more inflammation to surrounding tissue (14,15).

However, TAVR has continued to improve, the current generation Medtronic Evolut R SEV have almost halved the PPM implantation (from 25% to <17% for SEV) (16). This has to do with its improved design and innovation as compared to the older generation CoreValve.

The new CoreValve® Evolut R™ (Medtronic, Minneapolis, MN, USA) uses a 14-Fr in-line sheath system, with fully repositionable and recapturable features.

The new built-in InLine sheath allows for the whole system to be inserted into a patient without the need for a separate access sheath. The InLine sheath and the EnVeO R™ delivery system have significantly reduced the overall profile and are compatible with vessel sizes 5 mm and larger. The smaller profile increases the pool of patients who are able to receive this new generation valve. Compared to the

old generation system, the new fully repositionable and recapturable properties of this newer generation valve have improved stability while reducing PVL and PPM rates.

The two recent studies which reported outcomes using the new generation SEV confirm improvement in several procedural indices; Kalra *et al.* (17) reported a periprocedural success rate of 91.3% and a 30-day mortality rate of 2.3%. Importantly, the pacemaker implantation was 14.7%. Similar outcomes were reported with 16.4% of patients requiring PPM in the Evolut R U.S. Study (18); and in 13.3% of patients requiring PPM in the Evolut R US IFU trial (19).

New generation BEV succeeded in reducing PVL (20), another complication of TAVR, by incorporating a longer stent design in the Balloon expandable Edwards™ Sapien S3 valve. This initially led to a significant increase in PPM implant rates with a single center study showing increase in PPM implantation from 12% in Sapien XT to 19% in Sapien S3 (21).

This has since been corrected by *Edwards Lifesciences* who changed the instructions for use in regard to device positioning to reduce PPM rates. After the alteration, patients with S3-TAVR had lower PPM rates. Several studies with early experience in the use of Edwards Sapien 3 was responsible for this discovery. De Torres-Alba *et al.* (22) showed that a deeper position of the S3 in the LVOT is independently associated with a higher PPM implantation after TAVR.

From their result with a large study group (n=206) they found that PPM implantation rate was significantly reduced by higher implantation height, intending a shorter extension of the stent into the LVOT by increasing the percentage of the stent in the aorta to approximately >70%.

Following this strategy, the cohort of patients in whom the mean implantation height was 75%/25% aortic/ventricular, had a PPM implantation rate of 12.3% which was roughly the same as in the previous Edwards Sapien XT group.

Schweg *et al.* (23) also replicated these results showing that in patients with a marker distance <2 mm (“low implantation”), the PPM rate was 32%, whereas in patients with a distance 2 mm (“high Implantation”), the rate was only 4.7% [OR of 0.1 (0.03–0.37, P<0.001)]. Importantly, this higher implantation did not lead to increased PVL.

AS is a commonly which associated with pre-existing conduction tissue disease. The direct trauma, ischemia, hemorrhage and compression during valve replacement places these patients at further risk (24).

Recovery of conduction tissue and pacemaker independence has been shown in approximately 50% recipients at 12 months follow up after BEV TAVR (9). Hence, recognizing the predictors of persistent conduction abnormalities following TAVR is paramount to establishing guidelines for PPM implantation post procedure.

Predictors of PPM implant post TAVR

Multivariate studies define some clear-cut predisposing factors for conduction abnormalities associated with TAVR. Anatomical factors including a small LVOT diameter, a baseline thick Interventricular septum (>17 mm), and a non-coronary cusp thickness (>8 mm) were highly predictive of PPM in clinical studies (25,26). Mauri *et al.* identified the volume of LVOT calcification below the level of the left and right coronary cusps as another independent predictor of the need for a PPM (27,28).

Pre-existing conduction tissue disease also plays an important role in conduction abnormalities associated with TAVR. A baseline right bundle branch block (RBBB) has been shown in several studies to be a prime predictor for post-TAVR PPM implantation (1,9,29-32), this is due to the “double-knockout effect”: patients with prior RBBB who undergo TAVR and suffer damage to their left bundle branch (LBBB) or Bundle of His fibers that run along the membranous septum and LVOT are more likely to suffer high grade conduction abnormalities including complete heart blocks (CHB).

Increasing TAVR to aortic annulus oversizing ratios using multislice computed tomography (MSCT) is known to reduce rates of PVL as the valve has a better fit in the annulus, however, it is also associated with an increase in pacemaker implantation rate due to increased stress on the membranous septum, aortic annulus and LVOT complex.

Leber *et al.* (33) showed in a prospective study that the rate of postprocedural PPMs tended to be lower in patients with <15% oversizing compared to those with >25% oversizing (5.3% vs. 16.7%, $P<0.23$). A more recent study by Husser *et al.* (34) using Edwards Sapien 3 valves also showed a statistically higher PPM implantation rate in patients with out of range valve oversizing (OR: 3.489; 95% CI: 1.236–9.848; $P=0.018$).

Baseline and post-procedural first degree AV Blocks (AVB) as well as a left anterior hemiblock have been studied as predictors of long term dependency on PPM, however have not qualified as independent predictors of advanced conduction abnormality post-TAVR (35). An implantation

depth of less than 6 mm and newer designs that allow implantation higher in the LVOT also show a lower trend in conduction abnormalities and PPM implants (6,8,29). A short membranous septum is believed to be an additional risk for heart block, and this risk can be determined by a pre-TAVR implant risk stratification (36).

Pre-TAVR assessment of the aortic annulus, calcification, and size of the membranous septum with cardiac MRI and/or gated CT angiogram has been shown to accurately predict PPM implantation (37). The need for pre-dilatation balloon valvuloplasty and post-implant dilatation have not been identified as potential contributing factors as it is believed the impact of the dilatation on the conduction tissue is transient and short lived (38). Access site does not seem to play a role in PPM implantation; there was no significant difference between the transfemoral approaches compared to the transapical approach in a single center study (39).

Clinical implications of conduction abnormalities post-TAVR

Outcomes of patients who have develop new onset LBBB after TAVR has been an area of interest with varying conclusions. Only one study by Houthuizen *et al.* (40) showed increased mortality in these patients although this study looked at all new LBBB rather than persistent LBBB. Most of the other studies showed a trend toward increased hospitalization (41,42), a lack of left ventricular ejection fraction (LVEF) improvement (41,42), and poorer functional class at follow-up (42), whilst other studies did not find significant differences in NYHA class (41,43) nor hospitalizations for heart failure (42,43). Importantly however a new study by Urena *et al.* showed increased PPM placement in patients with post procedural LBBB (42).

In conclusion the post procedural complications of LBBB after TAVR remain unclear, but the recent finding of increased PPM implantation should alert us to follow those patients carefully.

Clinical implication of PPM in TAVR

Implantation of pacemakers especially with right ventricular pacing have been shown to cause reduction in ejection fraction over time and lead to worsened cardiac output due to interventricular dyssynchrony (44-46). Pacemaker implantation post TAVR procedure has been shown to increase length of hospitalization, cost of overall procedure,

and expose patients to potential complications of PPM implantation such as pneumothorax and bleeding (9,29,47).

Urena *et al.* in an analysis of 1,556 TAVR recipients (858 SEV and 698 BEV) revealed no long-term outcomes or mortality (11) confirmed by a German study of 1,147 TAVR patients (48). Of note, ventricular conduction defect results in negative inotropic state and right ventricular pacing mimics LBBB, which can also deteriorate left ventricular (LV) function and hold a prognostic connotation especially in those TAVR recipients that have baseline LV dysfunction. Such cases should be evaluated for cardiac resynchronization therapy (CRT) with implantation of biventricular pacemaker and LV function trends followed for further understanding the impact of such intervention on the LV function (49-51).

There have been several studies on long term clinical outcomes in patients who receive pacemaker implantation post-TAVR that did not show any significant differences, however Biner *et al.* (52) showed attenuated improvement in LVEF and reduced right ventricular index of myocardial performance, while Nazif *et al.* (9) showed an increased PPM implantation was associated with significantly higher repeat hospitalization and mortality or repeat hospitalization, lastly a retrospective study by Fadahunsi *et al.* showed higher cumulative incidence of HF admission, mortality, composite of mortality or HF admission (29).

Current status

Our review of the literature raises some serious unanswered questions. Are all patients undergoing TAVR being risk stratified appropriately in keeping with the above predictors regarding the need for PPM post-TAVR? Can procedural factors be stringently controlled to minimize advanced conduction abnormality post TAVR? Are patients being monitored optimally for resolution of TAVR related conduction abnormalities prior to PPM implantation, especially given that half of TAVR patients with PPM are no longer dependent? Most importantly, it is incumbent on us now to diligently develop guidelines for risk stratification, procedure selection, monitoring and recommending PPM implantation in TAVR patients in light of the intermediate-risk patients now being at the receiving end.

Currently, peri-procedural high degree AVB and CHB are indications for PPM implantation (53). Expert recommendations point toward 24–48 hours post-TAVR monitoring be done prior to a final disposition, with the transvenous temporary pacemaker left in place post

procedure (43).

No official American College of Cardiology guidelines or position statements exist to date, and for all practical purposes, PPM implantation is left to the discretion of the physician. The European Society of Cardiology has recommended that PPM implants be considered only in patients with CHB and high grade AVB if they persist after 7 days of observation post TAVR or SAVR (Class I recommendation; Level of Evidence C) (54). However, this will delay ambulation and discharge and increase risk of morbidity and mortality from immobility with temporary pacemaker in place.

With more questions than guidelines, we propose that careful pre-procedure risk stratification and post procedure monitoring be carried out in the high-risk patients with pre-existing RBBB, heavily calcified LVOT and short membranous septum, as they present the highest risk of persistent CHB. In such patients, we propose procedural modification such as using the BEV and a high depth of implantation. We encourage further studies to test the predictive ability of cardiac electrophysiology testing using delta-HV interval ≥ 13 ms and an HV interval ≥ 65 ms in patients with new onset left bundle branch block after TAVR (55).

While further prospective studies are required to develop precise guidelines, we recommend that patients with a transient high grade AVB or a new LBBB should be followed closely with avoidance of negatively chronotropic medications and continued ambulatory rhythm monitoring, including implantable loop recorder as is currently being evaluated by the MARE study (46), to assess development of persistent advanced conduction abnormality.

Summary of our recommendations

Pre-procedural recommendations

Screening with pre procedural EKGs in all patients, incorporating membranous septum height measurement as part of routine pre TAVR planning, patients with 1st, 2nd or 3rd degree AVB should be more carefully followed peri-procedurally, and patients with higher calcium volume in the area below the LVOT right or left coronary cusp should also be classified as high risk. All patients with high risk of PPM implantation post procedure must be informed in details about these risks before TAVR and presented with the alternative of surgical valve replacement, if appropriate.

The known increased risk with SEV should prompt

the use of BEV if appropriate regardless of which valve is preferred in an interventional center. Finally, employing pacemaker implantation predictive scores may also be useful in choosing patients (56).

Intraprocedural recommendations

Patients who were noted to have transient intraprocedural CHB, required a great deal of post balloon dilatation to reduce PVL, underwent greater depth of valve implantation or underwent an unusually difficult or long procedure which required a second valve, or patients in whom aortic valve trauma or inflammation is suspected, should have the transvenous PPM left in place for at least 48 hours with cardiac electrophysiology consult compulsory for these patients and on testing for recovery of normal rhythm followed by PPM placement if recovery does not occur.

Post procedure recommendations

We discourage hospital discharge without implantation of PPM in patients with persistent CHB or unstable high grade AV block i.e., second degree AV block (mobitz type 2) as there is a higher risk of mortality in these patients. We advocate early discharge with leadless temporary pacemaker and continuous monitoring in high risk patients with widening QRS interval and new LBBB post procedure (57).

We also recommend very close follow up in patients who had RBBB at baseline on pre-procedure EKG but did not require PPM implantation after TAVR, as recent studies have shown an increase in mortality in these patients due to latent CHB and/or sudden cardiac death (58,59).

Conclusions

TAVR has become a mainstay in the treatment for intermediate and high risk patients with ongoing studies in low risk patients. Conduction abnormalities are a common and serious complication of TAVR with well-established predictive factors. There is need for more research to improve current surgical techniques to avoid PPM implantation and improve the current valve design to eliminate this problem.

Current guidelines are not concrete, leaving several questions unanswered about indications, timing and risks of PPM implantation post-TAVR. We propose careful selection of intermediate surgical risk patients for TAVR

who have high risk for PPM implantation, leaving the transvenous pacemaker lead wire in place in patients with high risk conduction abnormalities for 48 hours, and close follow-up with EKG clinics or holter monitors in patients discharged without PPM insertion who are at low or intermediate risk, respectively.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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