New Pacemaker Implantation in Patients undergoing Transcatheter Valve Replacement: a systematic review and meta-analysis

Hilaryano Ferreira (✉ hilaryano.ferreira@hff.min-saude.pt)

Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal

Humberto Morais

Hospital Militar Principal/Instituto Superior, Luanda, Angola

Ana Rita Ferreira

Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal

Francisco Madeira

Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal

Carlos Morais

Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal

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Abstract

Background

Permanent pacemaker (PPM) implantation remain a common finding after Transcatheter aortic valve replacement (TAVR). Overall rate of PPM implantation after TAVR varies and is related to various factors and is highly variable. The purpose of this review is to evaluate the incidence of new permanent pacemaker implant at 1 year irrespective of valve brand manufacturer, vascular access used, deployment technique/mechanism. Secondary outcomes included all-cause mortality, 30-day, 1-year mortality, and cardiovascular mortality.

Methods

We performed a systematic search for studies that reported the incidence of PPM implantation after TAVR. Data on study, patient, and procedural characteristics were abstracted. Risk ratios (RRs); odds ratio (OR) and 95% confidence intervals were calculated by use of random effects models.

Results

14 studies were included, totalling 25,967 TAVR patients, mean age 80.15 ± 6.91 years, 52.9% being male, 26.3% of which required PPM implantation 1-year after intervention ($p = 0.00001$; RR 115.16).

Conclusions

Various factors impact the risk for pacemaker implantation after TAVR and one quarter of the patients undergo new permanent pacemaker implant at 1-year post undergoing TAVR.

Introduction

Aortic valve replacement (AVR) is the mainstay of treatment of symptomatic severe aortic stenosis (AS). Transcatheter aortic valve implantation (TAVI; or transcatheter aortic valve replacement [TAVR]) is now more a safe and feasible alternative to surgical aortic valve replacement (SAVR), especially in high surgical risk patients.^{1,2} Among procedural complications including arrhythmias (eg, conduction abnormalities and atrial fibrillation) may arise. Risk factors such as atrioventricular block, pre-existing right bundle branch block, new left bundle branch block and use of a CoreValve (versus SAPIEN valve) have been associated need for new permanent pacemaker (PPM) implantation.^{3,4} Post-TAVR overall new PPM implantation rate varies and is related to pre-procedural and intra-procedural factors. Some studies reported rates of new PPM or intracardiac defibrillator implant of about 8–17 percent.^{5–7} Other studies report incidence as high as 21–42.5 percent.^{8,9}

Current data regarding the impact of TAVR on conduction system, new PPM requirement on mortality is still conflicting.

In this meta-analysis we tend to evaluate the incidence of new permanent pacemaker implant at 1 year irrespective of valve brand manufacturer, vascular access used, deployment technique/mechanism (auto-expandable vs mechanical). Secondary outcomes included all-cause mortality, 30-day, 1-year mortality, and cardiovascular mortality.

Methods

Overview

We did a systematic review and meta-analysis of studies on prevalence and outcomes of arrhythmic mitral annular disjunction. The review is reported according to PRISMA guidelines.

Search strategy, selection criteria, and data extraction

We electronically searched the PUBMED databases with no starting date through June, 2021. The search included MeSH term ['TAVR' and 'pacemaker'] according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, PRISMA. No language restrictions were applied. Additional search strategy included limiting the search applying filters: 'Clinical Trials' and published in the last 5 years.

Abstracts and potentially relevant full texts were reviewed independently by two authors (HF and HM) with any conflicts resolved by consensus. Case-control studies, cohort studies, and brief reports were not eligible for inclusion (prespecified by search strategy). Case reports, studies without comparison groups, narrative or systematic literature reviews, preprint papers, and studies reporting on overlapping populations were excluded. The following data were extracted: author's name, publication date, study design, study population, follow-up period.

A total of fourteen (14) studies were included in the meta-analysis.^{10–23}

Primary outcomes included (rate of new pacemaker implantation in patients undergoing transcatheter aortic valve replacement at 1 year). We intended to evaluate the primary outcome irrespective of valve brand manufacturer, vascular access used, deployment technique/mechanism (auto-expandable vs mechanical). Secondary outcomes included (all-cause mortality at 1-year, 30-day mortality, and cardiovascular mortality). We planned to record any additional patients' outcomes identified. Where papers described service configuration or resource-use changes without clinical outcomes, we excluded them from the analysis.

Quality appraisal

The quality appraisal was established according to Le Floch and colleagues' criteria, by two independent assessors (HF and HM).²⁴ This tool appraises the quality of the study based on the following questions: Did this article give an answer to the research question? Did the article focus clearly on the research question? Was the methodology appropriate? Do you believe the results? (Can it be due to chance, bias or confounding?). To be included, the article had to score "yes" on every question.

Statistical analysis

Quantitative meta-analysis was done for an outcome when more than one study presented relevant data. We excluded individual outcomes from studies reporting no adverse outcomes in one or both groups, and studies not satisfying the normality assumption for continuous variables.

A random-effects estimate of the pooled odds of each outcome was generated with use of the Mantel-Haenszel method. Between-study heterogeneity was explored using the I^2 statistic, with substantial heterogeneity defined as an I^2 value greater than 50%. We reported p values and the amount of accounted heterogeneity for each covariate. Potential publication bias was assessed with Egger's test and funnel plots for visual inspection when sufficient studies ($n > 10$) were available. Statistical analyses were performed using the Revman software package (Review Manager, Version 5.4. Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration).

Results

Characterization of the study population:

Twenty-five thousand nine hundred and sixty-seven patients totalled from the fourteen studies included. The characteristics of the patients are shown in Table 1. The average age was 80.15 ± 6.91 years, 52.9% being male.

The prevalence of reported hypertension and coronary artery disease was high 76.6% and 59.7%, respectively; diabetes was reported in 30.2%. Of the studies that reported the prevalence of heart failure was 49.3%. Pre-procedural risk was assessed by the logistic EuroSCORE or the STS-PROM score in the majority of included studies, although in 5 studies, did not report on the risk score.

Primary outcome:

The overall prevalence of new permanent pacemaker implantation occurred in 6844 (26.3%) of the 25,967 patients ($p = .00001$) (RR 115.16 [95%CI 29.80-415.10]; $I^2 = 69\%$). Figure 1

Secondary outcomes:

All-cause mortality was reported in thirteen studies^{10-21,23} totalling 25875 patients. All-cause mortality occurred in 1613 (6.2%) patients (OR 51.84 [95%CI 11.35-236.68]). Table 2 30-day mortality rate reported by 8 studies^{10-15,19,21} occurring in 104 (2.4%) of the 4287 patients (OR 30.47 [95%CI 9.58-96.87]).

One-year mortality rate reported by 8 studies^{10-15,21,21} occurred in 398 (9.2%) of the 4287 patients (OR 94.44 [95%CI 30.06-296.71]).

Cardiovascular mortality reported in 9 studies^{10-13,15,18,19,20,21} occurring in 806 (3.2%) of the 25004 patients (OR 94.57 [95%CI 26.46-337.99]).

Discussion

Post-TAVR conduction disturbances such as new onset left bundle branch block (LBBB) are still the one of the main setbacks of the procedure. It may occur within the first 24 hours post-procedure, even though most events acutely during valve expansion, new-onset LBBB may occur before valve implantation, during guidewire insertion and balloon predilation.^{25,26}

The results of the present studies showed that about one quarter (26.3%) implanted permanent pacemaker (PPM) at 1-year. Previous studies report a 1-year implant rate between 5-20%.^{27,28} Recent published data from the MARE study reports an annual rate of PPM implantation of 7.3%.²⁹

New LBBB may occur beyond 6 months and at 1-year in about 57% of the patients, and in up to 2.9% of patients beyond 1-year.^{30,31} In this study we did not assess the clinical predictors of as it was not in our scope and there have been reported by other studies. Diabetes mellitus, previous coronary artery bypass graft, female sex, the amount of calcification of the aortic valve, and pre-existing conduction abnormalities (e.g. prolonged QRS duration) have been identified as risk factors new onset LBBB.^{32,33,34}

In the present analysis we sought to investigate the incidence of post-TAVR PPM implant, irrespective of valve brand, deployment mechanism and/or vascular access because previous studies reports on incidence are highly variable. Previous studies assessing the rate of PPM post-TAVR using first generation valves range from 2-51%.³⁵

There have been some contradictory data regarding mortality in patients with TAVR and new PPM, suggesting a possible correlation and increased mortality.^{36,37} In our meta-analysis we did not assess the correlation between PPM on mortality as we did not have access to individual patient data and subgroups. As so, we evaluated overall mortality rates. However, a meta-analysis showed that PPI post-TAVR was not associated with any increased risk of all-

cause mortality at 1 year (RR, 1.03; 95% CI, 0.9–1.18), furthermore there was a trend towards a protective effect on cardiac death was observed (RR, 0.78; 95% CI, 0.60–1.03).³⁸

Study Limitations

The current study had following limitations: 1) there were several clinical variables, but we did not aim to systematically examine them. 2) Follow-up data as well as clinical outcomes related to PPM were not reported in most of the studies. Thus, we could not address the clinical long-term effectiveness of PPM implantation in these patients. 3) A clear indication/diagnosis leading to pacemaker implantation was not possible assess in most of the studies.

Conclusions

Various factors impact the risk for pacemaker implantation after TAVR and although there's

Still conflicting data regarding the incidence, this study showed that at least one quarter of the patients undergo new permanent pacemaker implant at 1-year post undergoing TAVR. Adverse effects of new pacemaker on morbidity and mortality after TAVR, as well as long term mortality must be evaluated in by further research to improve risk-stratification and better identify predictors of poor outcome.

Declarations

Authors contributions:

Study design/data analysis (HF), re-checking of data collected (HM/ARF), Drafting article (HF), Critical revision of article article approval of article (FM/CM).

Conflicts of interest

The authors have no conflicts of interest to declare.

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Tables

Table.1 Study and Patients characteristics at baseline

VE PATIENT TERISTICS	Popma et al	Reardon et.al	Gleason 2018 et.al	Waksman et.al	Deharo et.al	Feldman et.al	Akodad et.al	Yamashita et.al	Lei et.al	Gleason 2017 et.al	Toutouzas et.al	Søndergaard et.al	Sager et.al	Seeger et.al
Study type (active/prospective)	Prospective	Prospective	Prospective	Prospective	Retrospective	Prospective	Prospective	Retrospective	Retrospective	Retrospective	Prospective	Prospective	Retrospective	Prospective
N	725	863	391	200	20 397	912	211	189	71	404	171	941	92	400
Age, mean/SD	74.0±5.9	79.9±6.2	83.2±7.1	73.6 ± 6.1	82.55±6.77	82.85±7.3	83±9	83.9±5.5	71.9 ± 5.8	80.5± 8.9	81.7±7.17	82.4±5.9	86±9	80.7±6.1
Sex (male), n (%)	65.1	498 (57.6)	207(52.9)	123 (61.5)	10883 (53.4)	449 (49.2)	129 (61.1%)	70 (37)	32 (45.1)	248 (61.3)	90 (52.6)	322 (34.3)	46 (50)	176 (44)
Medical History														
Hypertension, n (%)	614 (84.8)	801 (92.7)	372 (95.1)	171 (85.5)	16553 (81.2)	NR	137 (64.9)	NA	32 (45.1)	376 (93.0)	NR	759 (80.7)	81 (88)	NR
Diabetes, n (%)	228 (31.4)	295 (34.1)	136 (34.8)	61 (30.5)	6044 (29.6)	286 (31.3)	79 (37.4)	59 (31.2)	14 (19.7)	174 (43.0)	56 (32.7)	278 (29.6)	34 (37)	121 (30.2)
Epidemia, n (%)	NR	NR	NR	NR	9579 (47)	NR	NR	120 (63.4)	NR	NR	NR	NR	NR	NR
Acute use, n (%)	NR	NR	NR	NR	1688 (8.3)	NR	NR	NR	NR	248 (61.3)	NR	NR	57 (62)	NR
Stroke Failure, n (%)	NR	824 (95.4)	373 (95.4)	NR	11020 (54)	NR	NR	NR	NR	393 (97.2)	NR	125 (13.3)	71 (77.2)	NR
Coronary Artery Disease, n (%)	120 (16.4)	541 (62.6)	295 (75.4)	44 (23)	12593 (61.7)	657 (72)	104 (49.2)	NR	25 (35.2%)	334 (82.6)	78 (45.6)	473 (50.3)	NR	256 (64)
Scores														
STS PROM [†]	1.9±0.7	4.4±1.5	7.3 ± 3.0	1.8 ± 0.5	NR	6.7±4.0	NR	7.45±4.75	7.0±3.6	9.76±5.7	NR	5.8±4.8	NR	7.4±5.2
EuroSCORE [‡]	NR	11.9±7.6	17.7 ± 13.0	NR	NR	6.5 ± 5.5	2.6±2	NR	NR	20±14.65	24.3±10.68	15.7±11.3	NR	NR
SYNTAX [‡]	1.9±3.7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Angiography Results [§]														
Transcatheter aortic-valve gradient, mmHg (SD)	47.0±12.1	47.2 ± 14.3	NR	NR	NA	44.24 ±12.83	27.75 ±40	47.05±14.65	NR	NR	48.31±14.88	49.7±15.3	NR	36.0±16.5
Transcatheter aortic-valve area, cm2 (SD)	0.8±0.2	0.8 ± 0.2	NR	NR	NA	0.69 ± 0.19	0.75 ± 0.9	0.70±0.18	NR	NR	0.67±0.15	0.7±0.3	NR	0.79±0.29
Transcatheter aortic-valve ejection fraction, % (SD)	61.7±7.9	NR	NR	63.5 ± 7.5	NA	NR	60 ±10	58.5 ±8.5	NR	NR	50.46±9.79	57.4±11.6	NR	54±14.4

* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding. TAVR transcatheter aortic-valve replacement. † The Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) provides an estimate of the risk of death at 30 days among patients undergoing surgical aortic-valve replacement on the basis of several demographic and procedural variables. ‡ Logistic EuroSCORE range from 0 to 100%, with higher scores indicating greater surgical risk and a score of 20% indicating very high risk; ‡ The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score is a measure of the severity and extent of coronary artery disease. Low SYNTAX scores (<18) are associated with a higher success rate with PCI, scores between 18 and 27 with an intermediate success rate, and scores higher than 27 with a low success rate. § These data were reported by the studies.

Table.2 Secondary Outcomes

Outcome	N studies reporting	n/N	Odds Ratio (M-H, Random, 95% CI)
All-cause mortality	13	1613/25875	51.84 [11.35, 236.68]
30-day mortality	8	104/4287	30.47 [9.58, 96.87]
1-year mortality	8	398/4287	94.44 [30.06, 296.71]
Cardiovascular mortality	9	806/25004	94.57 [26.46, 337.99]

Figures

Figure 1

Primary Outcome

Supplementary Files

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- [PRISMAFlowDiagram.png](#)
- [GraphicalAbstract.png](#)