Impact of New-Onset Left Bundle Branch Block and Periprocedural Permanent Pacemaker Implantation on Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Replacement

A Systematic Review and Meta-Analysis

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Background—Available data on the clinical impact of new-onset left bundle branch block (LBBB) and permanent pacemaker implantation (PPI) after transcatheter aortic valve replacement (TAVR) remains controversial. We aimed to evaluate the impact of (1) periprocedural new-onset LBBB or PPI post-TAVR on cardiac mortality and all-cause 1-year mortality and (2) new-onset LBBB on the need for PPI at 1-year follow-up.

Methods and Results—We performed a systematic search from PubMed and EMBASE databases for studies reporting raw data on new-onset LBBB post-TAVR and the need for PPI or mortality at 1-year follow-up, or on 1-year mortality according to the need for periprocedural PPI post-TAVR. Data from 17 studies, including 4756 patients (8 studies) and 7032 patients (11 studies) for the evaluation of the impact of new-onset LBBB and periprocedural PPI post-TAVR were sourced, respectively (with 2 studies used for both outcomes). New-onset LBBB post-TAVR was associated with a higher risk of PPI (risk ratio [RR], 2.18; 95% confidence interval [CI], 1.28–3.70) and cardiac death (RR, 1.39; 95% CI, 1.04–1.86) during follow-up, as well with a tendency toward an increase in all-cause mortality (RR, 1.21; 95% CI, 0.98–1.50). Periprocedural 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), yet a tendency toward a protective effect on cardiac death was observed (RR, 0.78; 95% CI, 0.60–1.03).

Conclusions—New-onset LBBB post-TAVR is a marker of an increased risk of cardiac death and need for PPI at 1-year follow-up. The need for PPI early post-TAVR did not increase the risk of death. **(*Circ Cardiovasc Interv*. 2016;9:e003635. DOI: 10.1161/CIRCINTERVENTIONS.115.003635.)**

Key Words: aortic valve stenosis ■ bundle branch block ■ cardiac conduction defect ■ mortality ■ pacemaker, artificial ■ transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) is now an established treatment option for patients with aortic stenosis who are considered to be at high or prohibitive surgical risk.[1] Substantial improvements in technology, patient selection, and refined procedural techniques have provided the basis for TAVRs expansion toward treating a lower surgical risk aortic stenosis population.[2] However, the ocurrence of some periprocedural complications remain a concern.

Conduction disturbances and the need for permanent pacemaker implantation (PPI) frequently complicate TAVR. Importantly, the incidence of such complications has not changed significantly over time, with potentially a slightly rising incidence after the introduction of newer generation transcatheter valves.[3] Although the factors associated with conduction abnormalities and PPI post-TAVR are well described,[4] data on its clinical impact remain controversial. Studies evaluating the impact on mortality of new-onset left bundle branch block (LBBB) or need for periprocedural PPI post-TAVR have yielded conflicting results.[5–8] The current systematic review and meta-analysis was thus aimed at assessing (1) the impact of new-onset LBBB post-TAVR on the need for PPI, all-cause death, and cardiac death and (2) the impact of periprocedural PPI post-TAVR on all-cause and cardiac death.

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WHAT IS KNOWN

- Conduction disturbances and the need for PPI are frequent complications of TAVR, data on its clinical impact remain highly controversial, and studies evaluating the effect on mortality of new-onset LBBB or need for periprocedural PPI post-TAVR have yielded conflicting results.

WHAT THE STUDY ADDS

- Our study showed an increased risk of PPI and cardiac death at 1-year follow-up in those patients with new-onset LBBB post-TAVR and no impact of PPI post-TAVR on cardiac or all-cause death at follow-up.

Methods

Search Strategy

A systematic review of the published data on new-onset LBBB in TAVR recipients and on the need for PPI after TAVR was conducted in accordance to the guidance and the reporting items specified the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[9] A computerized search was performed to identify all relevant studies from PubMed and EMBASE databases. MeSH terms used were: TAVR; heart block; pacemaker, artificial; electrode, implanted. Keywords used were: percutaneous aortic, transcatheter aortic, transcatheter aortic valve implantation, conduction, block, bundle, AV, and pacemaker. The search strategy is outlined in the Data Supplement. Databases were last accessed on May 31, 2015. Citations were screened at the title and abstract level and retrieved as full text if they reported on outcome after new-onset LBBB or the need of periprocedural PPI post-TAVR.

Study Selection

Studies were included if the following criteria applied: (1) original design and (2) reported data on mortality or the need of PPI during follow-up after new-onset LBBB post-TAVR, or reported data on mortality based on the need of periprocedural PPI after TAVR. When 2 similar studies were reported from the same institution or author, the most recent publication or the publication with most information was included in the analysis. Case reports or studies published in a non-English language were excluded.

Data Extraction

We extracted data of the patients and studies using a standardized data abstraction sheet. Two investigators (A.R. and O.A.J.A.) conducted the literature search, selection and data extraction in duplicate. Any discrepancies were resolved by consensus, when needed, with a third investigator (J.R.C.).

Outcome

The end points that were pooled for the group of new-onset LBBB post-TAVR patients were (1) risk of PPI at 1 year, (2) risk of cardiac mortality at 1 year, and (3) risk of all-cause mortality at 1 year. In addition, the following end points were pooled for the group of periprocedural PPI post-TAVR: (1) risk of cardiac mortality at 1 year and (2) risk of all-cause mortality at 1 year.

Statistical Analysis

Crude risk ratio (RR) was the principal summary measure. RRs were retrieved or directly calculated with the corresponding 95% confidence interval (CI) for each end point and entered into the primary analysis. Consistency across the studies was assessed with the I^2 index.[10] For variables exhibiting mild heterogeneity ($I^2 \leq 25\%$), pooled estimates were derived with the Mantel–Haenszel fixed-effects models. For variables exhibiting significant heterogeneity, pooled estimates were derived using the DerSimonian and Laird random effects model.[11] To assess the potential effect of publication bias, we inspected funnel plots for asymmetry and used the Harbord test[12] as a formal statistical test. An exploratory meta-regression analysis was performed to examine a potential association between end points with the type of valve implanted during the procedure. Descriptive characteristics are presented as mean SD or median (interquartile range) when appropriate for continuous variables and frequencies and percentages for categorical variables. Statistical analyses were performed in STATA software (version 13.0, STATA Corp, College Station, TX) and RevMan (version 5.3.5, Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration).

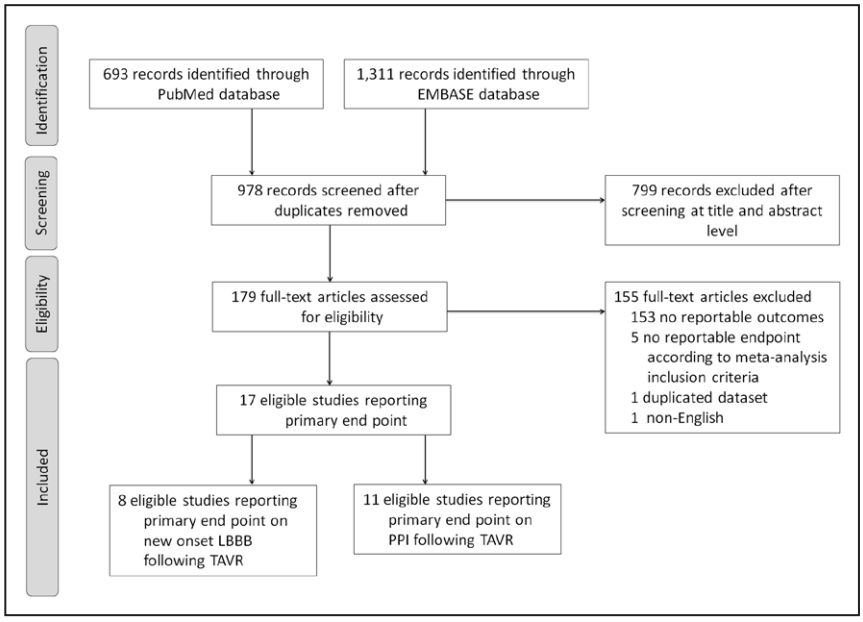

Figure 1. Flow diagram of selected studies. Flow diagram, based on the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) statement, of studies selected for evaluating the clinical impact of new-onset left bundle branch block (LBBB) and periprocedural permanent pacemaker implantation (PPI) post transcatheter aortic valve replacement (TAVR).

Results

A PubMed search identified 693 reports, whereas an EMBASE search uncovered 1311, yielding 978 records which were reviewed at the title and abstract level after exclusion of duplicates. Of those, 179 articles were selected and assessed for eligibility at full-text level. Five studies (5612 patients) were excluded from the quantitative synthesis because of missing data on the primary end point, despite reporting different outcomes based on the presence of new-onset LBBB or the need of PPI post-TAVR.[13–17] Finally, 17 studies were included for assessing primary end points, and of those, 8 studies were deemed eligible for assessing the outcome of patients with new-onset LBBB post-TAVR,[5,6,18–24] whereas 11 studies were deemed eligible for assessing the outcome of patients with PPI post-TAVR.[5,7,8,17–19,25–31] Figure 1 shows the PRISMA flow diagram. Quantitative synthesis was performed on 4756 patients to assess the clinical impact of new-onset LBBB post-TAVR and on 7032 patients to assess the clinical impact of periprocedural PPI post-TAVR.

Impact of New-Onset LBBB After TAVR on the Risk of Death and PPI

Eight studies were used to evaluate the impact of new-onset LBBB post-TAVR on 3 different end points: (1) 1-year risk of PPI, (2) 1-year cardiac mortality, and (3) 1-year all-cause mortality. Among the selected studies, the study of Nazif et al[22] was unique in that it included patients from a randomized clinical trial (The Placement of Aortic Transcatheter Valve [PARTNER trial]), although these data were not exclusive because it also included patients from a registry. All remaining studies were observational registries. With the exception of the study from Houthuizen et al,[21] new-onset LBBB was defined as appearing post-TAVR, and remaining until hospital discharge. The rate of new-onset LBBB at discharge ranged from 13.3% to 37%. Despite this relative consistency in the inclusion criteria, exclusion criteria varied significantly between studies. In regard to ECG analyses, Nazif et al[22] were the only investigators who used an independent core laboratory for defining LBBB. In addition, Urena et al[20] extended the follow-up period beyond 1 year (median follow-up 13 months, interquartile range: 3–27 months), consequently out of 29 events from the previous study were included in the current meta-analysis. Study and population characteristics are shown in Tables 1 and 2.

The risk of PPI after TAVR in patients with new-onset LBBB was estimated by analyzing 5 studies (3363 patients with LBBB; self-expandable valve [SEV] 28.4% versus balloon-expandable valve [BEV] 71.6%). The rate of PPI 1 year post-TAVR was 17.5%, (range, 5.2%–35.9%), including 55 patients who required PPI before discharge from the analysis of Urena et al,[20] and 61 patients who required PPI within 48 hours after TAVR from the analysis of Testa et al.[6] The rate of advanced atrioventricular block (AVB, as an indication for PPI during follow-up) varied from 78% to 89% in patients with new-onset LBBB, and in patients without LBBB the range was between 22.4% and 80% (Table I in the Data Supplement). The pooled result demonstrated a higher risk of PPI after 1-year follow-up for patients with new-onset LBBB (RR, 2.18; 95% CI, 1.28–3.70; $P<0.01$; Figure 2A). Heterogeneity across studies was observed ($I^2=81\%$), and a potential publication bias was evident with the Harbord test

Table 1. Characteristics of Selected Studies for Evaluating the Clinical Impact of New-Onset LBBB After TAVR

Reference	Year	Region	Centers	Sample Size	Inclusion Period	New-Onset LBBB Definition	Exclusion Criteria	Periprocedural Events Criteria
Carrabba et al[18]	2015	Italy	1	92	N/A	At discharge	Dead during first week of procedure, previous PPI or LBBB	VARC-2
Schymik et al[19]	2015	Germany	1	634	May 2008 to April 2012	At discharge (included also if LBBB and PPI before discharge)	Previous PPI or bundle branch block	N/A
Urena et al[20]	2014	Canada, Spain	4	668	N/A	At discharge or if LBBB and die before discharge	Previous PPI or LBBB, PPI before discharge	VARC-2
Houthuizen et al[21]	2014	International	4	476	January 2006 to July 2011	Persistent after 12 mo of follow-up or last available ECG	Previous PPI or LBBB, PPI within 30 days after TAVR	N/A
Nazif et al[22]	2014	International	25	1151	N/A	At discharge or within 7 days of procedure	Previous conduction disturbance or PPI. Paced rhythm on discharge or 7-day ECG	PARTNER trial and registry
Franzoni et al[23]	2013	Italy	1	238	November 2007 to November 2011	Postprocedural	Previous PPI or bundle branch block	N/A
Testa et al[6]	2013	Italy	9	818	June 2007 to April 2011	At discharge	Previous PPI or LBBB. PPI within 48 h after TAVR	VARC
Houthuizen et al[5]	2012	Netherlands	8	679	November 2005 to December 2010	Postprocedural	Previous PPI or LBBB, postprocedural PPI	N/A

LBBB indicates left bundle-branch block; N/A, not available; PPI, permanent pacemaker implantation; TAVR, transcatheter aortic valve replacement; and VARC, Valve Academic Research Consortium.

Table 2. Clinical and Procedural Characteristics of the Population From Selected Studies for Evaluating the Clinical Impact of New-Onset LBBB After TAVR

Reference	Year	Valve Type (%)	LBBB at Discharge (%)	Age, y	Male (%)	Logistic EuroSCORE
Carrabba et al[18]	2015	MCRS (100)	37.0	81±6.3	52	20±14
Schymik et al[19]	2015	ESV (81) MCRS (19)	31.1	82±4.5	38	22±13
Urena et al[20]	2014	ESV (100)	11.8	79±10	49	21±14
Houthuizen et al[21]	2014	ESV (53) MCRS (47)	28.7	81 (77–85)	44	16 (10–25)
Nazif et al[22]	2014	ESV (100)	10.5	84±7	43	25±16
Franzoni et al[23]	2013	ESV (63) MCRS (37)	26.5	79±7	50	22±15
Testa et al[6]	2013	MCRS (100)	22.5	82±6	44	23±11
Houthuizen et al[5]	2012	ESV (43) MCRS (57)	N/A*	81 (77–85)	47	16 (10–25)

ESV indicates Edwards Sapien valve; LBBB, left bundle-branch block; MCRS, Medtronic CoreValve revalving system; N/A, not available; and TAVR, transcatheter aortic valve replacement.

*Post discharge LBBB not available; 34.2% rate of LBBB after TAVR.

(P=0.031). After excluding studies with <200 patients, we did not observe a significant change in the RR (RR, 2.01; 95% CI, 1.10–3.67; P=0.02), whereas heterogeneity remained high (I^2=82%). A random effects meta-regression analysis was not performed because of the limited number of studies. To evaluate the potential effect of valve type (BEV versus SEV), a stratified analysis was performed, removing studies that included patients treated only with an SEV. The pooled risk of PPI of 3 studies[19,20,22] including 2453 patients (SEV 4.9% versus BEV 95.1%) was still significantly higher for patients with new-onset LBBB (RR, 2.75; 95% CI, 1.34–5.62; P<0.01). The pooled risk of PPI of the 2 studies that included patients treated exclusively with SEV[6,18] (910 patients) was greater, although it did not reach statistical significance, (RR, 1.74; 95% CI, 0.64–4.75; P=0.28), largely because of a lack of statistical power.

After pooling the results from 5 studies[5,6,21–23] (3554 patients: SEV 28.4% versus BEV 71.6%), the presence of new-onset LBBB post-TAVR was associated with a greater risk of 1-year cardiac death, with an RR of 1.39 (95% CI, 1.04–1.86; P=0.03; Figure 2B). Heterogeneity between studies was moderate (I^2=32%) and the Harbord test did not reveal any significant asymmetry (P=0.189). The pooled risk did not vary significantly when omitting studies with <200 patients in a sensitivity analysis (RR, 1.43; 95% CI, 1.04–1.96; P=0.03). Because of a limitation in the number of included studies, we did not perform a meta-regression analysis to evaluate the association between the risk of cardiac death and the type of valve.

The risk of 1-year all-cause death was evaluated from 8 studies[6,18–23,32] that included 4756 patients (SEV 36.5% versus BEV 63.5%). The overall pooled RR was 1.21 (95% CI, 0.98–1.50; P=0.07; Figure 2C). Inconsistency across studies was moderate (I^2=50%), and no asymmetry was detected with the Harbord test (P=0.757). The pooled risk did not vary significantly when omitting studies with <200 patients in a sensitivity analysis (RR, 1.22; 95% CI, 0.98–1.52; P=0.08), with and mild increase in heterogeneity (I^2=50% to I^2=56%). No association was found between the type of valve and the risk of 1-year all-cause death on a random effects meta-regression analysis (P=0.720). In a sensitivity analysis, we pooled the adjusted hazard ratios from 4 studies[5,18–20] (2191 patients) and did not observe any increase risk of global death in patients with new-onset LBBB post-TAVR (1.38, 95% CI, 0.84–1.93; P=0.21; I^2=77.2%).

Impact of Periprocedural PPI After TAVR on the Risk of Death

Eleven studies were used to evaluate the impact of periprocedural PPI after TAVR on mortality. All studies except for Nazif et al[7] were observational in nature. Criteria for PPI were described in 8 studies (61%). Five studies used either the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rythm Society (HRS)[8,18] or the European Society of Cardiology (ESC) guidelines.[19,29,31] Complete AVB was the most frequent indication for PPI after TAVR, with the exception of Pereira et al,[31] who reported a higher rate of Mobitz II second degree AVB than complete AVB (42% versus 21%). Dual-chamber pacemaker was the most frequently implanted device. With the exception of 2 studies, the rate of right ventricular stimulation was not reported. In the analysis of the PARTNER trial and registry, the authors reported that 50.5% of patients who required PPI had evidence of right ventricular pacing in the ECG performed 1-year follow-up.[7] Similarly, Pereira et al[31] reported a cumulative ventricular pacing requirement of 49.5% in the pacemaker interrogation after 12 months of the procedure. Characteristics of the studies and population are shown in Tables 3 and 4. Detailed information about the indications for PPI and type of device can be found in the Table II in the Data Supplement.

The risk of 1-year all-cause death was pooled from 11 studies[5,7,8,19,25–31] that included 7032 patients. The RR was 1.03 (95% CI, 0.9–1.18; P=0.64; Figure 3A). Heterogeneity between studies was not significant (I^2=0%). No asymmetry

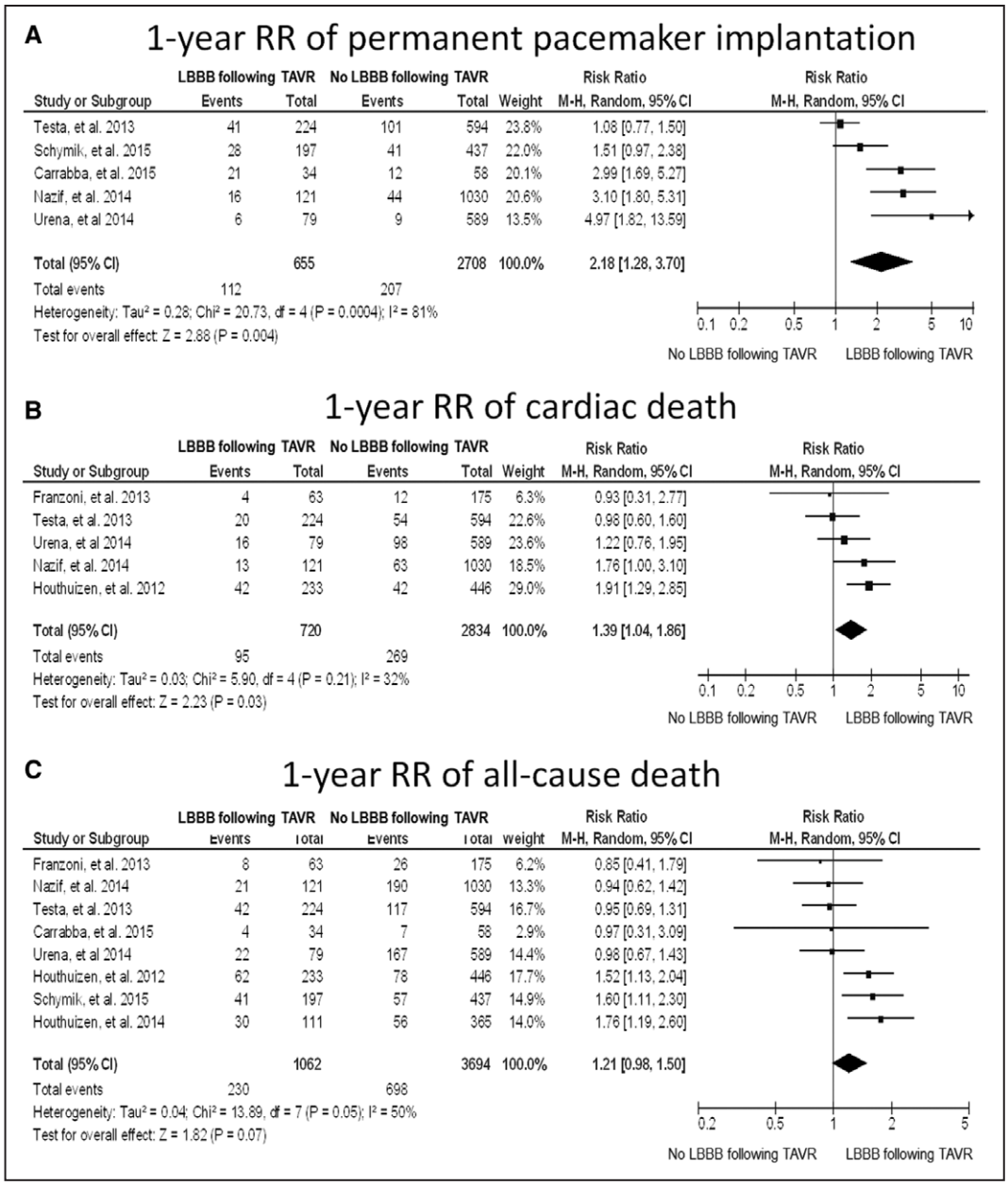

Figure 2. Risk of permanent pacemaker implantation, cardiac death, and all-cause death in patients with new-onset left bundle branch block (LBBB) after transcatheter aortic valve replacement (TAVR). **A**, Risk of permanent pacemaker implantation according to the occurrence of new-onset LBBB after TAVR.[6,18–20,22] **B**, Risk of cardiac death according to the occurrence of new-onset LBBB after TAVR.[5,6,20,22,23] **C**, Risk of all-cause death according to the occurrence of new-onset LBBB after TAVR.[5,6,18–23] CI indicates confidence interval; and RR, risk ratio.

was detected with the Harbord test (P=0.472). The pooled risk did not varied significant when omitting studies with <200 patients in a sensitivity analysis (RR, 1.02; 95% CI, 0.89–1.18; P=0.75; I^2=0%). No association was found between the type of valve and the risk of 1-year all-cause death on a random effects meta-regression analysis (P=0.305).

The risk of 1-year cardiac death was pooled from 3 studies[7,8,22] (n=4362). A borderline, nonsignificant, potentially protective effect of PPI on cardiac death was observed (RR, 0.77; 95% CI, 0.58–1.01; P=0.06). Heterogeneity across studies was low (I^2=0%; Figure 3B). No asymmetry was observed with the Harbord test (P=0.235). Because of a limitation in the number of included studies for this end point, we did not perform a meta-regression analysis to evaluate the association between cardiac death and the type of valve.

Discussion

The results of the present meta-analysis can be summarized as follows: (1) new-onset LBBB post-TAVR seems to significantly increase the risk of cardiac death and need for PPI at 1-year follow-up and (2) periprocedural PPI seemed not to associate with an increased risk of death (global or cardiac) within the year after TAVR.

New conduction disturbances represent a frequent post-TAVR complication. The reported rate of new-onset LBBB

Table 3. Characteristics of Selected Studies for Evaluating the Clinical Impact of Periprocedural PPI After TAVR

Reference	Year	Region	Centers	Sample Size	Inclusion Period	PPI Implantation Criteria	Periprocedural Events Criteria
Kawaguchi et al[25]	2015	France	1	160	February 2010 to June 2012	N/A	N/A
Nazif et al[7]	2015	International	25	1937	N/A	High-degree AVB, sick sinus syndrome, and symptomatic bradycardia	PARTNER trial and registry
Mouillet et al[26]	2015	France	29	833	January 2010 to October 2011	N/A	N/A
Schymik et al[19]	2015	Germany	1	634	May 2008 to April 2012	ESC 2013 Guidelines	N/A
Urena et al[8]	2014	International	8	1556	January 2005 to February 2013	ACC/AHA/HRS 2008 Guidelines	VARC-2
Biner et al[27]	2014	Israel	1	230	N/A	Pre-TAVR right BBB, post-TAVR high-degree AVB, alternating BBB, or new left-BBB with PR segment ≥280 ms	N/A
Pereira et al[31]	2013	Portugal	1	58	August 2007 to May 2011	ESC 2007 Guidelines	VARC
Houthuizen et al[5]	2012	Netherlands	8	797	November 2005 to December 2010	N/A	N/A
Buellesfeld et al[28]	2012	Germany, Switzerland	2	305	August 2007 to March 2010	High-degree AVB, new left BBB with PR segment ≥300 ms, or atrial fibrillation with inadequate escape rhythm	VARC
De Carlo et al[29]	2012	Italy	3	275	September 2007 to July 2010	ESC 2007 Guidelines	N/A
D'Ancona et al[30]	2011	Germany	1	322	April 2008 to March 2011	High-degree AVB or symptomatic bradycardia	N/A

ACC indicates American College of Cardiology; AHA, American Heart Association; AVB, atrioventricular block; BBB, bundle-branch block; ESC, European Society of Cardiology; HRS, Heart Rythm Society; N/A, not available; PARTNER, Placement of Aortic Transcatheter Valve; PPI, permanent pacemaker implantation; TAVR, transcatheter aortic valve replacement; and VARC, Valve Academic Research Consortium.

post-TAVR is ≈27%, ranging from 9% to 65% after the self-expanding CoreValve system implantation, or ≈11% (4%–18%) postballoon-expandable Edwards valve implantation.[33] With reference to PPI, the reported rate of PPI after TAVR is ≈17% (range 18%–49%) after self-expanding CoreValve implantation and ≈6% (0%–12%) after balloon-expandable Edwards valve implantation. Despite the fact that the incidence of these conduction disturbances and PPI has slowly decreased over time,[3] this effect seems to be limited to patients receiving a SEV and is partially related to significant reductions in valve implantation depths and improvement in the delivery systems.[34] Furthermore, the incidence of major periprocedural complications post-TAVR has decreased dramatically in recent times after the adoption of new valve technologies. However, early results show a lack of reduction, or even an increase in the rate of conduction system disturbances associated with these so-called new-generation valves.[3] Specifically, an increase rate of PPI has been reported with the use of the third-generation balloon-expandable Edwards valve when compared with the previous Edward valve generations. This finding has been attributed to the incorporation of an external fabric cuff in the inferior part of the valve intended to minimize paravalvular leak. A higher (more aortic) valve depth implantation of this new-generation valve might help in preventing the higher risk of PPI.[35] Furthermore, no significant decreases in the incidence of new conduction system disturbances is expected with the novel generatino devices, as no additional features have been specifically designed to reduce the risk of these conduction system-based complications.

Impact of New-Onset LBBB on the Risk of PPI and Death

A higher rate of PPI at 1-year follow-up among patients with new-onset LBBB was observed in the present meta-analysis. The rate of PPI after TAVR across the various studies used in the present meta-analysis was relatively low, and this can be explained by the frequent use of a BEV. The increased risk of complete AVB with SEV has been previously described.[4] The continuous radial force of the nitinol stent in the SEV and the potential for deeper implantation leading to persistent AV node and LBB mechanical compression and injury have been postulated to explain these between-valve differences in PPI rates. Another possible factor that could partially explain a higher risk of PPI was a lower threshold for treating patients with new-onset LBBB. However, when evaluating the reasons for PPI in patients with new-onset LBBB post-TAVR, close to 80% of the patients, who underwent PPI

Table 4. Clinical and Procedural Characteristics of the Population from Selected Studies for Evaluating the Clinical Impact of PPI After TAVR

Reference	Year	Valve Type (%)	PPI at Discharge (%)	Age, y	Male (%)	Logistic EuroSCORE
Kawaguchi et al[25]	2014	ESV (34) MCRS (66)	17.5	83±7	55	22±17
Nazif et al[7]	2015	ESV (100)	8.8	84±7	47	26±16
Mouillet et al[26]	2015	MCRS (100)	30.2	82±7	59	21±14
Schymik et al[19]	2015	ESV (81) MCRS (19)	10.8	82±4	38	22±13
Urena et al[8]	2014	ESV (55) MCRS (45)	15.4*	80±8	47	20±14
Biner et al[27]	2014	ESV (13) MCRS (87)	25.2	83±5	38	26±14
Pereira et al[31]	2013	MCRS (100)	33.0	79±6	46	23±13
Houthuizen et al[5]	2012	ESV (43) MCRS (57)	14.8	N/A	N/A	N/A
Buellesfeld et al[28]	2012	ESV (10) MCRS (90)	32.1*	83±6	43	25±15
De Carlo et al[29]	2012	MCRS (100)	24.0	82±6	47	23±14
D'Ancona et al[30]	2011	ESV (100)	5.9	81±7	36	38±21

ESV indicates Edwards Sapien valve; MCRS, Medtronic CoreValve revalving system; N/A, not available; PPI, permanent pacemaker implantation; and TAVR, transcatheter aortic valve replacement.

*PPI within 30 days after TAVR.

had documented advanced AVB. The ongoing Ambulatory Electrocardiographic Monitoring for the Detection of High-Degree Atrio-Ventricular Block in Patients With New-Onset Persistent Left Bundle Branch Block After Transcatheter Aortic Valve Implantation (MARE) study (NCT02153307) with ambulatory ECG monitoring up to 3 years could help us to identify the subgroup of patients that could progress from LBBB to complete AV block after TAVR, requiring PPI during follow-up.

In our study, patients with new-onset LBBB had a higher risk of cardiac death after 1-year of follow-up. The increased risk of death could be attributed to 3 physiopathological mechanisms: (1) the increased risk of ventricular arrhythmias in patients with reduced ejection fraction and ventricular dyssynchrony or (2) the progression to advanced AVB or (3) the combination of LBBB-induced intraventricular dyssynchrony and subsequent systolic dysfunction, followed by clinical heart failure.

The presence of LBBB is known to be a marker of poor long-term survival in the general population[36] and in patients with cardiac disease.[37] LBBB produces an intraventricular dyssynchrony that results in deterioration of left ventricle (LV) systolic and diastolic function,[38] it is also known that the effect of LBBB is dominant over the presence of cardiomyopathy, on the deterioration of LV function.[39] This negative effect on ventricular function has been observed also in patients that develop LBBB post-TAVR. The consequences of intraventricular dyssynchrony are not limited to the mechanical function of the ventricle, as they can be an important factor in ventricular arrhythmogenesis. Kutyifa et al[40] demonstrated that improved synchrony might translate into a reduction of ventricular arrhythmic events in patients with LBBB by a more homogeneous LV mechanical activation followed by electric resynchronization per se. In addition, constant mechanical compression of the conduction system by the transcatheter valve could be responsible for the progression of LBBB to complete AV block,[41] increasing the risk of sudden cardiac death in patients without a permanent pacemaker. Also, new-onset persistent LBBB after TAVR may be a marker of greater vulnerability toward the occurrence and progression of conduction disturbances irrespective of the procedure.

Although there was an increased risk of cardiac death associated with new-onset LBBB post-TAVR, there was, however, no difference in the risk of all-cause death. Several points need to be considered to explain these findings. The population included in the studies had a high baseline risk morbidity and mortality risk, and this high prevalence of severe noncardiac comorbidities could have translated into high incidence of death from noncardiac causes in both groups, and the effect of LBBB could have been masked. We decided to use the RRs as a risk measure, although some studies reported the adjusted hazard ratio. The decision was based on the fact that the number of patients included in studies who reported the adjusted hazard ratio was limited, and that the covariables used for the adjustment were not comparable between studies. Despite this, there was not a higher risk of all-cause death in patients with new-onset LBBB after performing a meta-analysis of the studies that reported an adjusted hazard ratio.

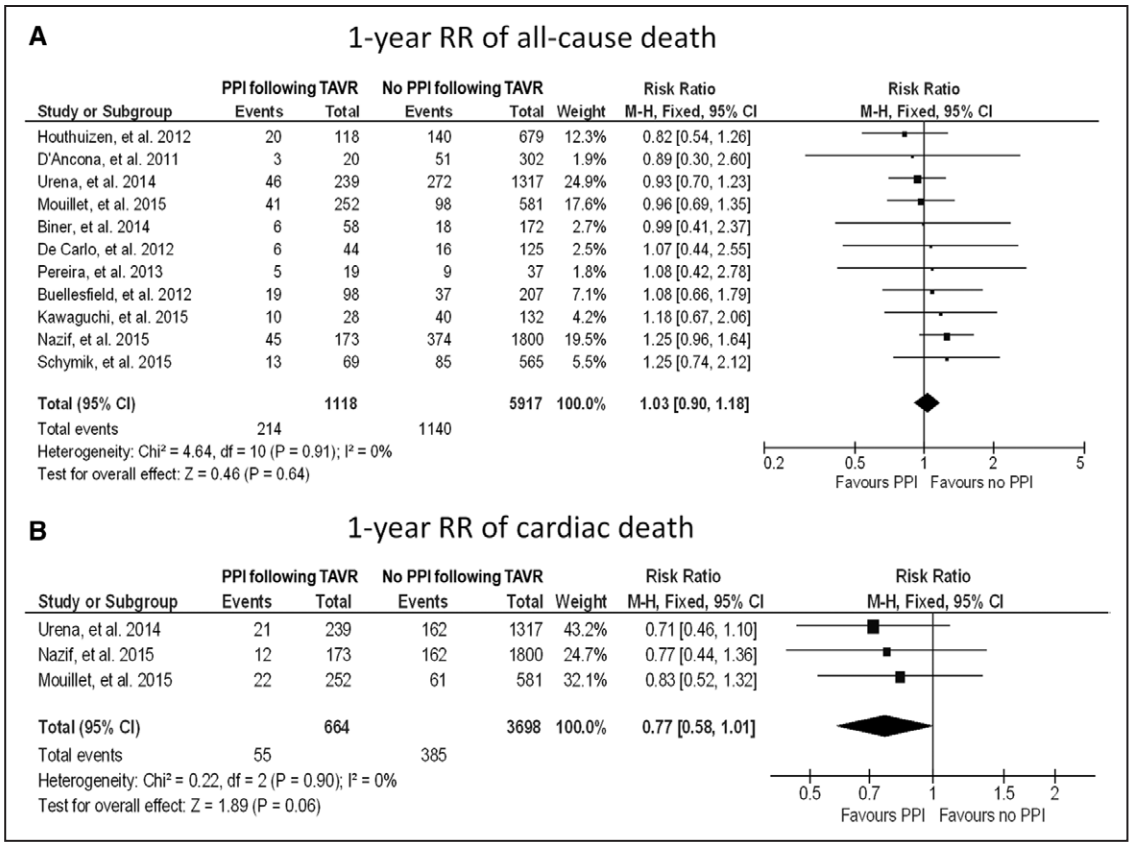

Figure 3. Risk of cardiac death and all-cause death in patients with periprocedural permanent pacemaker implantation (PPI) after transcatheter aortic valve replacement (TAVR). **A**, Risk of all-cause death according to the need for periprocedural PPI after TAVR.[5,7,8,19,25–29,31] **B**, Risk of cardiac death according to the need for periprocedural PPI after TAVR.[7,8,26] CI indicates confidence interval; and RR, risk ratio.

Impact of Periprocedural PPI After TAVR on the Risk of Death

The present meta-analysis failed to show an increased risk of death in patients who received a PPI after TAVR. In fact, there was a tendency toward a protective effect from cardiac death in the year after the procedure. As previously discussed, patients with new-onset LBBB post-TAVR may have harbored a higher risk of cardiac death partially because of progression toward complete AVB and sudden death,[36] which could have been prevented by PPI. It is known that the need for pacing increases the risk of heart failure and late mortality.[42] This detrimental impact on heart failure and mortality depend on the cumulative time of ventricular pacing. However, information on the requirement of ventricular pacing was available only from 2 of 11 studies included in the present meta-analysis. In both of these studies, approximately half of the patients did not require ventricular pacing after 1-year of follow-up. The percentage of ventricular pacing is similar to those reported in other studies who were not included in the present analysis.[16] This suggests that in a significant proportion of patients complete AVB present on TAVR at discharge resolved over time, as complete AVB was the most frequent indication for PPI. It has been further suggested that the deleterious impact of PPI might differ between different subgroups of patients. Although the majority of patients with a standard indication for PPI remain clinically stable over time, patients with low LV ejection fraction and LBBB notionally possess a higher risk of hospitalization or death because of heart failure.[43] Thus, the deleterious effect of ventricular pacing over time in patients undergoing TAVR could be masked by the severity of comorbidities and concomitant structural heart disease, as well as the immediate hemodynamic improvement after valve implantation.[8] However, it is also known that after an early increase in LV ejection fraction post-TAVR, PPI implantation is associated with reduced LV ejection fraction at 6 months,[8] although this lack of improvement does not seem to affect clinical outcomes after 2 years of follow-up.[27] Finally, a much longer time period may be necessary to detect a negative effect of PPI on cardiovascular and global outcomes.[44]

Study Limitations

Several limitations of the present meta-analysis warrant consideration. Our findings derive mainly from observational studies with retrospective analysis. The pooled analysis for each end point was obtained from a limited number of studies because of a high variability when reporting clinical outcomes associated with the exposure to PPI or new-onset LBBB after TAVR. Heterogeneity across studies was high when we analyzed the risk of death and PPI associated with new-onset LBBB post-TAVR. However, the results remained similar after a sensitivity analysis that excluded smaller studies or with the use of a fixed-effects model.

In conclusion, the present meta-analysis provides evidence that the development of LBBB post-TAVR correlates

with a greater risk of cardiac death and need for PPI within the year after the procedure. However, the need for PPI post procedurally had no impact on cardiac and all-cause death rates, and a trend toward a protective effect on cardiac death was observed. Conduction disturbances post-TAVR remains an ongoing problem because of its high incidence and negative clinical impact. Further efforts are important to identify the factors associated with the progression of conduction disturbances to appropriately risk stratify patients and provide an optimal treatment.

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References

1. Rodés-Cabau J. Transcatheter aortic valve implantation: current and future approaches. *Nat Rev Cardiol*. 2012;9:15–29. doi: 10.1038/nrcardio.2011.164.
2. Wenaweser P, Stortecky S, Schwander S, Heg D, Huber C, Pilgrim T, Gloekler S, O'Sullivan CJ, Meier B, Jüni P, Carrel T, Windecker S. Clinical outcomes of patients with estimated low or intermediate surgical risk undergoing transcatheter aortic valve implantation. *Eur Heart J*. 2013;34:1894–1905. doi: 10.1093/eurheartj/eht086.
3. Urena M, Rodés-Cabau J. Managing heart block after transcatheter aortic valve implantation: from monitoring to device selection and pacemaker indications. *EuroIntervention*. 2015;11(suppl W):W101–W105. doi: 10.4244/EIJV11SWA30.
4. Siontis GC, Jüni P, Pilgrim T, Stortecky S, Büllesfeld L, Meier B, Wenaweser P, Windecker S. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. *J Am Coll Cardiol*. 2014;64:129–140. doi: 10.1016/j.jacc.2014.04.033.
5. Houthuizen P, Van Garsse LA, Poels TT, de Jaegere P, van der Boon RM, Swinkels BM, Ten Berg JM, van der Kley F, Schalij MJ, Baan J Jr, Cocchieri R, Brueren GR, van Straten AH, den Heijer P, Bentala M, van Ommen V, Kluin J, Stella PR, Prins MH, Maessen JG, Prinzen FW. Left bundle-branch block induced by transcatheter aortic valve implantation increases risk of death. *Circulation*. 2012;126:720–728. doi: 10.1161/CIRCULATIONAHA.112.101055.
6. Testa L, Latib A, De Marco F, De Carlo M, Agnifili M, Latini RA, Petronio AS, Ettori F, Poli A, De Servi S, Ramondo A, Napodano M, Klugmann S, Ussia GP, Tamburino C, Brambilla N, Colombo A, Bedogni F. Clinical impact of persistent left bundle-branch block after transcatheter aortic valve implantation with CoreValve Revalving System. *Circulation*. 2013;127:1300–1307. doi: 10.1161/CIRCULATIONAHA.112.001099.
7. Nazif TM, Dizon JM, Hahn RT, Xu K, Babaliaros V, Douglas PS, El-Chami MF, Herrmann HC, Mack M, Makkar RR, Miller DC, Pichard A, Tuzcu EM, Szeto WY, Webb JG, Moses JW, Smith CR, Williams MR, Leon MB, Kodali SK; PARTNER Publications Office. Predictors and clinical outcomes of permanent pacemaker implantation after transcatheter aortic valve replacement: the PARTNER (Placement of AoRtic TraNscathetER Valves) trial and registry. *JACC Cardiovasc Interv*. 2015;8(1 pt A):60–69. doi: 10.1016/j.jcin.2014.07.022.
8. Urena M, Webb JG, Tamburino C, Muñoz-García AJ, Cheema A, Dager AE, Serra V, Amat-Santos IJ, Barbanti M, Immè S, Briales JH, Benitez LM, Al Lawati H, Cucalon AM, García Del Blanco B, López J, Dumont E, Delarochellière R, Ribeiro HB, Nombela-Franco L, Philippon F, Rodés-Cabau J. Permanent pacemaker implantation after transcatheter aortic valve implantation: impact on late clinical outcomes and left ventricular function. *Circulation*. 2014;129:1233–1243. doi: 10.1161/CIRCULATIONAHA.113.005479.
9. Panic N, Leoncini E, de Belvis G, Ricciardi W, Boccia S. Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. *PLoS One*. 2013;8:e83138. doi: 10.1371/journal.pone.0083138.
10. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. The Cochrane Collaboration, 2011. http://www.cochrane-handbook.org. Accessed May 1, 2015.
11. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
12. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med*. 2006;25:3443–3457. doi: 10.1002/sim.2380.
13. Urena M, Webb JG, Eltchaninoff H, Muñoz-García AJ, Bouleti C, Tamburino C, Nombela-Franco L, Nietlispach F, Moris C, Ruel M, Dager AE, Serra V, Cheema AN, Amat-Santos IJ, de Brito FS, Lemos PA, Abizaid A, Sarmento-Leite R, Ribeiro HB, Dumont E, Barbanti M, Durand E, Alonso Briales JH, Himbert D, Vahanian A, Immè S, Garcia E, Maisano F, del Valle R, Benitez LM, García del Blanco B, Gutiérrez H, Perin MA, Siqueira D, Bernardi G, Philippon F, Rodés-Cabau J. Late cardiac death in patients undergoing transcatheter aortic valve replacement: incidence and predictors of advanced heart failure and sudden cardiac death. *J Am Coll Cardiol*. 2015;65:437–448. doi: 10.1016/j.jacc.2014.11.027.
14. Gensas CS, Caixeta A, Siqueira D, Carvalho LA, Sarmento-Leite R, Mangione JA, Lemos PA, Colafranceschi AS, Caramori P, Ferreira MC, Abizaid A, Brito FS Jr; Brazilian Registry in Transcatheter Aortic Valve Implantation Investigators. Predictors of permanent pacemaker requirement after transcatheter aortic valve implantation: insights from a Brazilian registry. *Int J Cardiol*. 2014;175:248–252. doi: 10.1016/j.ijcard.2014.05.020.
15. Ledwoch J, Franke J, Gerckens U, Kuck KH, Linke A, Nickenig G, Krülls-Münch J, Vöhringer M, Hambrecht R, Erbel R, Richardt G, Horack M, Zahn R, Senges J, Sievert H; German Transcatheter Aortic Valve Interventions Registry Investigators. Incidence and predictors of permanent pacemaker implantation following transcatheter aortic valve implantation: analysis from the German transcatheter aortic valve interventions registry. *Catheter Cardiovasc Interv*. 2013;82:E569–E577. doi: 10.1002/ccd.24915.
16. Fraccaro C, Buja G, Tarantini G, Gasparetto V, Leoni L, Razzolini R, Corrado D, Bonato R, Basso C, Thiene G, Gerosa G, Isabella G, Iliceto S, Napodano M. Incidence, predictors, and outcome of conduction disorders after transcatheter self-expandable aortic valve implantation. *Am J Cardiol*. 2011;107:747–754. doi: 10.1016/j.amjcard.2010.10.054.
17. Adamo M, Fiorina C, Curello S, Maffeo D, Chizzola G, Di Matteo G, Mastropierro R, Nardi M, Cervi E, De Cicco G, Chiari E, Curnis A, Bonardelli S, Coletti G, Manzato A, Metra M, Ettori F. Role of different vascular approaches on transcatheter aortic valve implantation outcome: a single-center study. *J Cardiovasc Med (Hagerstown)*. 2015;16:279–285. doi: 10.2459/JCM.0000000000000252.
18. Carrabba N, Valenti R, Migliorini A, Marrani M, Cantini G, Parodi G, Dovellini EV, Antoniucci D. Impact on left ventricular function and remodeling and on 1-year outcome in patients with left bundle branch block after transcatheter aortic valve implantation. *Am J Cardiol*. 2015;116:125–131. doi: 10.1016/j.amjcard.2015.03.054.
19. Schymik G, Tzamalis P, Bramlage P, Heimeshoff M, Würth A, Wondraschek R, Gonska BD, Posival H, Schmitt C, Schröfel H, Luik A. Clinical impact of a new left bundle branch block following TAVI implantation: 1-year results of the TAVIK cohort. *Clin Res Cardiol*. 2015;104:351–362. doi: 10.1007/s00392-014-0791-2.
20. Urena M, Webb JG, Cheema A, Serra V, Toggweiler S, Barbanti M, Cheung A, Ye J, Dumont E, DeLarochellière R, Doyle D, Al Lawati HA, Peterson M, Chisholm R, Igual A, Ribeiro HB, Nombela-Franco L, Philippon F, Garcia del Blanco B, Rodés-Cabau J. Impact of new-onset persistent left bundle branch block on late clinical outcomes in patients undergoing transcatheter aortic valve implantation with a balloon-expandable valve. *JACC Cardiovasc Interv*. 2014;7:128–136. doi: 10.1016/j.jcin.2013.08.015.
21. Houthuizen P, van der Boon RM, Urena M, Van Mieghem N, Brueren GB, Poels TT, Van Garsse LA, Rodés-Cabau J, Prinzen FW, de Jaegere P. Occurrence, fate and consequences of ventricular conduction abnormalities after transcatheter aortic valve implantation. *EuroIntervention*. 2014;9:1142–1150. doi: 10.4244/EIJV9I10A194.
22. Nazif TM, Williams MR, Hahn RT, Kapadia S, Babaliaros V, Rodés-Cabau J, Szeto WY, Jilaihawi H, Fearon WF, Dvir D, Dewey TM, Makkar RR, Xu K, Dizon JM, Smith CR, Leon MB, Kodali SK. Clinical

implications of new-onset left bundle branch block after transcatheter aortic valve replacement: analysis of the PARTNER experience. *Eur Heart J*. 2014;35:1599–1607. doi: 10.1093/eurheartj/eht376.
23. Franzoni I, Latib A, Maisano F, Costopoulos C, Testa L, Figini F, Giannini F, Basavarajaiah S, Mussardo M, Slavich M, Taramasso M, Cioni M, Longoni M, Ferrarello S, Radinovic A, Sala S, Ajello S, Sticchi A, Giglio M, Agricola E, Chieffo A, Montorfano M, Alfieri O, Colombo A. Comparison of incidence and predictors of left bundle branch block after transcatheter aortic valve implantation using the CoreValve versus the Edwards valve. *Am J Cardiol*. 2013;112:554–559. doi: 10.1016/j.amjcard.2013.04.026.
24. Urena M, Mok M, Serra V, Dumont E, Nombela-Franco L, DeLarochellière R, Doyle D, Igual A, Larose E, Amat-Santos I, Côté M, Cuéllar H, Pibarot P, de Jaegere P, Philippon F, Garcia del Blanco B, Rodés-Cabau J. Predictive factors and long-term clinical consequences of persistent left bundle branch block following transcatheter aortic valve implantation with a balloon-expandable valve. *J Am Coll Cardiol*. 2012;60:1743–1752. doi: 10.1016/j.jacc.2012.07.035.
25. Kawaguchi AT, D'Allessandro C, Collet JP, Cluzel P, Makri R, Leprince P. Ventricular conduction defects after transcatheter aortic valve implantation: a single-institute analysis. *Artif Organs*. 2015;39:409–415. doi: 10.1111/aor.12393.
26. Mouillet G, Lellouche N, Yamamoto M, Oguri A, Dubois-Rande JL, Van Belle E, Gilard M, Laskar M, Teiger E. Outcomes following pacemaker implantation after transcatheter aortic valve implantation with CoreValve(®) devices: Results from the FRANCE 2 Registry. *Catheter Cardiovasc Interv*. 2015;86:E158–E166. doi: 10.1002/ccd.25818.
27. Biner S, Michowitz Y, Leshem-Rubinow E, Topilsky Y, Ben-Assa E, Shimiaie J, Banai S, Keren G, Steinvil A, Finkelstein A. Hemodynamic impact and outcome of permanent pacemaker implantation following transcatheter aortic valve implantation. *Am J Cardiol*. 2014;113:132–137. doi: 10.1016/j.amjcard.2013.09.030.
28. Buellesfeld L, Stortecky S, Heg D, Hausen S, Mueller R, Wenaweser P, Pilgrim T, Gloekler S, Khattab AA, Huber C, Carrel T, Eberle B, Meier B, Boekstegers P, Jüni P, Gerckens U, Grube E, Windecker S. Impact of permanent pacemaker implantation on clinical outcome among patients undergoing transcatheter aortic valve implantation. *J Am Coll Cardiol*. 2012;60:493–501. doi: 10.1016/j.jacc.2012.03.054.
29. De Carlo M, Giannini C, Bedogni F, Klugmann S, Brambilla N, De Marco F, Zucchelli G, Testa L, Oreglia J, Petronio AS. Safety of a conservative strategy of permanent pacemaker implantation after transcatheter aortic CoreValve implantation. *Am Heart J*. 2012;163:492–499. doi: 10.1016/j.ahj.2011.12.009.
30. D'Ancona G, Pasic M, Unbehaun A, Hetzer R. Permanent pacemaker implantation after transapical transcatheter aortic valve implantation. *Interact Cardiovasc Thorac Surg*. 2011;13:373–376. doi: 10.1510/icvts.2011.274456.
31. Pereira E, Ferreira N, Caeiro D, Primo J, Adão L, Oliveira M, Gonçalves H, Ribeiro J, Santos E, Leite D, Bettencourt N, Braga P, Simões L, Vouga L, Gama V. Transcatheter aortic valve implantation and requirements of pacing over time. *Pacing Clin Electrophysiol*. 2013;36:559–569. doi: 10.1111/pace.12104.
32. Muñoz-García AJ, Hernández-García JM, Jiménez-Navarro MF, Alonso-Briales JH, Rodríguez-Bailón I, Peña-Hernández J, Fernández-Pastor J, Domínguez-Franco AJ, Barrera-Cordero A, Alzueta-Rodríguez J, de Teresa Galván E. Changes in atrioventricular conduction and predictors of pacemaker need after percutaneous implantation of the CoreValve®. Aortic valve prosthesis. *Rev Esp Cardiol*. 2010;63:1444–1451.
33. van der Boon RM, Nuis RJ, Van Mieghem NM, Jordaens L, Rodés-Cabau J, van Domburg RT, Serruys PW, Anderson RH, de Jaegere PP. New conduction abnormalities after TAVI–frequency and causes. *Nat Rev Cardiol*. 2012;9:454–463. doi: 10.1038/nrcardio.2012.58.
34. Muñoz-García AJ, Hernández-García JM, Jiménez-Navarro MF, Alonso-Briales JH, Domínguez-Franco AJ, Fernández-Pastor J, Peña Hernández J, Barrera Cordero A, Alzueta Rodríguez J, de Teresa-Galván E. Factors predicting and having an impact on the need for a permanent pacemaker after CoreValve prosthesis implantation using the new Accutrak delivery catheter system. *JACC Cardiovasc Interv*. 2012;5:533–539. doi: 10.1016/j.jcin.2012.03.011.
35. Tarantini G, Mojoli M, Purita P, Napodano M, D'Onofrio A, Frigo A, Covolo E, Facchin M, Isabella G, Gerosa G, Iliceto S. Unravelling the (arte)fact of increased pacemaker rate with the Edwards SAPIEN 3 valve. *EuroIntervention*. 2015;11:343–350. doi: 10.4244/EIJY14M11_06.
36. Zhang ZM, Rautaharju PM, Soliman EZ, Manson JE, Cain ME, Martin LW, Bavry AA, Mehta L, Vitolins M, Prineas RJ. Mortality risk associated with bundle branch blocks and related repolarization abnormalities (from the Women's Health Initiative [WHI]). *Am J Cardiol*. 2012;110:1489–1495. doi: 10.1016/j.amjcard.2012.06.060.
37. Zannad F, Huvelle E, Dickstein K, van Veldhuisen DJ, Stellbrink C, Køber L, Cazeau S, Ritter P, Maggioni AP, Ferrari R, Lechat P. Left bundle branch block as a risk factor for progression to heart failure. *Eur J Heart Fail*. 2007;9:7–14. doi: 10.1016/j.ejheart.2006.04.011.
38. Xiao HB, Lee CH, Gibson DG. Effect of left bundle branch block on diastolic function in dilated cardiomyopathy. *Br Heart J*. 1991;66:443–447.
39. Zhou Q, Henein M, Coats A, Gibson D. Different effects of abnormal activation and myocardial disease on left ventricular ejection and filling times. *Heart*. 2000;84:272–276.
40. Kutyifa V, Pouleur AC, Knappe D, Al-Ahmad A, Gibinski M, Wang PJ, McNitt S, Merkely B, Goldenberg I, Solomon SD, Moss AJ, Zareba W. Dyssynchrony and the risk of ventricular arrhythmias. *JACC Cardiovasc Imaging*. 2013;6:432–444. doi: 10.1016/j.jcmg.2012.12.008.
41. Saji M, Murai T, Tobaru T, Tabata M, Takanashi S, Takayama M. Autopsy finding of the Sapien XT valve from a patient who died suddenly after transcatheter aortic valve replacement. *Cardiovasc Interv Ther*. 2013;28:267–271. doi: 10.1007/s12928-012-0153-9.
42. Dewland TA, Pellegrini CN, Wang Y, Marcus GM, Keung E, Varosy PD. Dual-chamber implantable cardioverter-defibrillator selection is associated with increased complication rates and mortality among patients enrolled in the NCDR implantable cardioverter-defibrillator registry. *J Am Coll Cardiol*. 2011;58:1007–1013. doi: 10.1016/j.jacc.2011.04.039.
43. Mazza A, Bendini MG, Leggio M, Riva U, Ciardiello C, Valsecchi S, De Cristofaro R, Giordano G. Incidence and predictors of heart failure hospitalization and death in permanent pacemaker patients: a single-centre experience over medium-term follow-up. *Europace*. 2013;15:1267–1272. doi: 10.1093/europace/eut041.
44. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, Lamas GA; Mode Selection Trial Investigators. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation*. 2003;107:2932–2937. doi: 10.1161/01.CIR.0000072769.17295.B1.

Impact of New-Onset Left Bundle Branch Block and Periprocedural Permanent Pacemaker Implantation on Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis

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Supplemental Material

Search Strategy

Database: Medline <1946 to 2015 June 1>

((Transcatheter Aortic Valve Replacement[MESH Terms]) OR (Percutaneous aortic) OR (Transcatheter aortic) OR TAVI OR TAVR) AND ((heart block[MeSH Terms] OR conduction OR block OR bundle OR AV) OR (pacemaker, artificial[MESH Terms] OR electrode, implanted[MESH Terms] OR pacemaker))

Database: Embase <1946 to 2015 June 1>

ID	Search
#1	Transcatheter aortic valve implantation
#2	Heart block
#3	Conduct disorder
#4	Heart bundle branch block
#5	Pacemaker
#6	Electrode implant
#7	#2 OR #3 OR #4
#8	#5 OR #6
#9	#7 OR #8
#10	#1 AND #9
#11	#10 AND [embase]/lim NOT [01-06-2015]/sd

Supplemental Table 1. Study characteristics. Impact on PPI in patients with new onset LBBB following TAVI

Author. Ref.	Indication of PPI after TAVI	Advanced AVB as indication for PPI	Reason for PPI after discharge	Time for PPI following TAVI
Carrabba, et al[1]	Third-degree or second-degree advanced AVB that was not expected to resolve Sinus node dysfunction with documented symptomatic bradycardia	New onset LBBB 18 (85.7%) No LBBB 13 (22.4%)	New onset LBBB 1 Patient with complete AVB No LBBB 1 Patient for slow AF	N/A
Schymik, et al[2]	According to guidelines, no extra especifications	N/A	N/A	N/A
Urena, et al[3]	Third-degree or second-degree advanced AVB that was not expected to resolve Sinus node dysfunction with documented symptomatic bradycardia	New onset LBBB 8 (89%) No LBBB 8 (40%)	New onset LBBB 8 (89%) advanced AVB No LBBB 8 (40%) advanced AVB	Median time 5 months (IQR:5 to 38 months)
Houthuizen, et al[4]	N/A	N/A	N/A	N/A
Nazif, et al[5]	High-degree AVB, sick sinus syndrome, and symptomatic bradycardia	N/A	N/A	N/A
Testa, et al[6]	N/A	New onset LBBB 95% within 30 days 78% at 1 year No LBBB 96% within 30 days 80% at 1 year	N/A	N/A

AVB indicates Atrioventricular block; LBBB, left bundle branch block; N/A, not-available; TAVI, transcatheter aortic valve implantation

Supplemental Table 2. Indications for PPI and type of device

Author. Ref.	Indications for PPI	Type of device
Kawaguchi, et al[7]	N/A	N/A
Nazif, et al[8]	Complete AVB in 79% Sick sinus syndrome 17.3%	Dual-chamber in 75.5% Single-chamber in 19.7% ICD or biventricular ICD in 1.2%
Mouillet, et al[9]	High-grade AVB in 30.3%	N/A
Schymik, et al[2]	N/A	N/A
Urena, et al[10]	Complete AVB in 75.3% Left BBB+ first-degree AVB in 9.6% Symptomatic bradycardia in 7.9% Sick sinus syndrome in 7.1%	Single-chamber in 40% Dual-chamber in 60%
Biner, et al[11]	Complete AVB in 62% Left BBB + prolonged PR in 32.3% Alternating BBB in 3.4%	N/A
Pereira, et al[12]	Mobitz II second-degree ABV in 42% Third-degree AVB in 21% AF with complete AVB in 21% Trifascicular block in 16%	Dual-chamber in 68% Single-chamber in 32%
Houthuizen, et al[13]	N/A	N/A
Buellesfeld, et al[14]	High-degree AVB in 62.2% Left BBB + prolonged PR in 21.4% Slow AF in 16.3%	N/A
De Carlo, et al[15]	Complete AVB in 71.3% Left BBB + prolonged PR in 10.6% Left BBB + slow atrial tachycardia in 7.6% Mobitz II second-degree AVB in 4.3% Sick sinus syndrome in 3% Left BBB + low LVEF in 3%	N/A
D'Ancona, et al[16]	N/A	N/A

AF indicates Atrial fibrillation; AVB, Atrioventricular block; BBB, bundle branch block; ICD, Implantable cardioverter-defibrillator; LVEF, left-ventricle ejection fraction; N/A, not-available.

Supplemental References

1. Carrabba N, Valenti R, Migliorini A, Marrani M, Cantini G, Parodi G, Dovellini EV, Antoniucci D. Impact on Left Ventricular Function and Remodeling and on 1-Year Outcome in Patients With Left Bundle Branch Block After Transcatheter Aortic Valve Implantation. *Am J Cardiol*. 2015;116:125-131
2. Schymik G, Tzamalis P, Bramlage P, Heimeshoff M, Würth A, Wondraschek R, Gonska B-D, Posival H, Schmitt C, Schröfel H, Luik A. Clinical impact of a new left bundle branch block following TAVI implantation: 1-year results of the TAVIK cohort. *Clin Res Cardiol*. 2015;104:351–362.
3. Urena M, Webb JG, Cheema A, Serra V, Toggweiler S, Barbanti M, Cheung A, Ye J, Dumont E, DeLarochellière R, Doyle D, Al Lawati HA, Peterson M, Chisholm R, Igual A, Ribeiro HB, Nombela-Franco L, Philippon F, Garcia del Blanco B, Rodés-Cabau J. Impact of new-onset persistent left bundle branch block on late clinical outcomes in patients undergoing transcatheter aortic valve implantation with a balloon-expandable valve. *JACC Cardiovasc Interv*. 2014;7:128–136.
4. Houthuizen P, van der Boon RMA, Urena M, Van Mieghem N, Brueren GBR, Poels TT, Van Garsse LAFM, Rodés-Cabau J, Prinzen FW, de Jaegere P. Occurrence, fate and consequences of ventricular conduction abnormalities after transcatheter aortic valve implantation. *EuroIntervention.* 2014;9:1142–1150.
5. Nazif TM, Williams MR, Hahn RT, Kapadia S, Babaliaros V, Rodés-Cabau J, Szeto WY, Jilaihawi H, Fearon WF, Dvir D, Dewey TM, Makkar RR, Xu K, Dizon JM, Smith CR, Leon MB, Kodali SK. Clinical implications of new-onset left bundle branch block after transcatheter aortic valve replacement: analysis of the PARTNER experience. *Eur Heart J*. 2014;35:1599–1607.
6. Testa L, Latib A, De Marco F, De Carlo M, Agnifili M, Latini RA, Petronio AS, Ettori F, Poli A, De Servi S, Ramondo A, Napodano M, Klugmann S, Ussia GP, Tamburino C, Brambilla N, Colombo A, Bedogni F. Clinical impact of persistent left bundle-branch block after transcatheter aortic valve implantation with CoreValve Revalving System. *Circulation.* 2013;127:1300–1307. 5
7. Kawaguchi AT, D'Allessandro C, Collet JP, Cluzel P, Makri R, Leprince P. Ventricular conduction defects after transcatheter aortic valve implantation: a single-institute analysis. *Artif Organs*. 2015;39:409–415.
8. Nazif TM, Dizon JM, Hahn RT, Xu K, Babaliaros V, Douglas PS, El-Chami MF, Herrmann HC, Mack M, Makkar RR, Miller DC, Pichard A, Tuzcu EM, Szeto WY, Webb JG, Moses JW, Smith CR, Williams MR, Leon MB, Kodali SK. Predictors and clinical outcomes of permanent pacemaker implantation after transcatheter aortic valve replacement: the PARTNER (Placement of AoRtic TraNscathetER Valves) trial and registry. *JACC Cardiovasc Interv*. 2015;8:60–69.
9. Mouillet G, Lellouche N, Yamamoto M, Oguri A, Dubois-Rande J-L, Van Belle E, Gilard M, Laskar M, Teiger E. Outcomes following pacemaker implantation after transcatheter aortic valve implantation with CoreValve(®) devices: Results from the FRANCE 2 Registry. *Catheter Cardiovasc Interv*. 2015; 86:E158-166
10. Urena M, Webb JG, Tamburino C, Muñoz-García AJ, Cheema A, Dager AE, Serra V, Amat-Santos IJ, Barbanti M, Immè S, Briales JHA, Benitez LM, Al Lawati H, Cucalon AM, García Del Blanco B, López J, Dumont E, Delarochellière R, Ribeiro HB, Nombela-Franco L, Philippon F, Rodés-Cabau J. Permanent pacemaker implantation after transcatheter aortic valve implantation: impact on late clinical outcomes and left ventricular function. *Circulation*. 2014;129:1233–1243.
11. Biner S, Michowitz Y, Leshem-Rubinow E, Topilsky Y, Ben-Assa E, Shimiaie J, Banai S, Keren G, Steinvil A, Finkelstein A. Hemodynamic impact and outcome of permanent pacemaker implantation following transcatheter aortic valve implantation. *Am J Cardiol*. 2014;113:132–137.
12. Pereira E, Ferreira N, Caeiro D, Primo J, Adão L, Oliveira M, Gonçalves H, Ribeiro J, Santos E, Leite D, Bettencourt N, Braga P, Simões L, Vouga L, Gama V. Transcatheter

aortic valve implantation and requirements of pacing over time. *Pacing Clin Electrophysiol*. 2013;36:559–569.
13. Houthuizen P, Van Garsse LAFM, Poels TT, de Jaegere P, van der Boon RMA, Swinkels BM, Ten Berg JM, van der Kley F, Schalij MJ, Baan J, Cocchieri R, Brueren GRG, van Straten AHM, den Heijer P, Bentala M, van Ommen V, Kluin J, Stella PR, Prins MH, Maessen JG, Prinzen FW. Left bundle-branch block induced by transcatheter aortic valve implantation increases risk of death. *Circulation*. 2012;126:720–728.
14. Buellesfeld L, Stortecky S, Heg D, Hausen S, Mueller R, Wenaweser P, Pilgrim T, Gloekler S, Khattab AA, Huber C, Carrel T, Eberle B, Meier B, Boekstegers P, Jüni P, Gerckens U, Grube E, Windecker S. Impact of permanent pacemaker implantation on clinical outcome among patients undergoing transcatheter aortic valve implantation. *J Am Coll Cardiol*. 2012;60:493–501.
15. De Carlo M, Giannini C, Bedogni F, Klugmann S, Brambilla N, De Marco F, Zucchelli G, Testa L, Oreglia J, Petronio AS. Safety of a conservative strategy of permanent pacemaker implantation after transcatheter aortic CoreValve implantation. *Am Heart J*. 2012;163:492–499.
16. D'Ancona G, Pasic M, Unbehaun A, Hetzer R. Permanent pacemaker implantation after transapical transcatheter aortic valve implantation. *Interact Cardiovasc Thorac Surg*. 2011;13:373–376.