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Review Article

Aortic Valve and Left Ventricular Outflow Tract Calcium Distribution and Conduction Outcomes After Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis

Princess Neila Litkouhi, BMed, MD [a,b], Karan Rao, BMed, MPH, MD [a,b], Alexandra Baer, BSN, MSHM [a], Peter S. Hansen, MBBS, PhD [a,b], Ravinay Bhindi, MBBS, MSc, PhD [a,b,*]

[a] Department of Cardiology, Royal North Shore Hospital, Sydney, New South Wales, Australia
[b] School of Medicine, University of Sydney, Camperdown, Australia

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ABSTRACT

Permanent pacemaker implantation (PPMI) is an important complication following transcatheter aortic valve replacement (TAVR). The influence of valvular and subvalvular calcium and its distribution between aortic leaflets on the risk of PPMI following TAVR remains unclear. We performed a systematic review of the aortic valve complex (AVC) calcium by leaflet, left ventricular outflow tract (LVOT) calcium by leaflet, total AVC calcium, total LVOT calcium, and mitral annular calcium and its association with post-TAVR atrioventricular block, left bundle branch block, and new PPMI. The search strategy included five databases identifying 893 articles. A total of 34 studies with 11,528 patients were included for qualitative analysis, and seven studies totaling 1056 patients were suitable for quantitative analysis. On meta-analysis, left coronary cusp calcium and right coronary cusp calcium were significant predictors of PPMI, while noncoronary cusp (NCC) calcium was not predictive (left coronary cusp: mean difference: 21.05 mm^3, 95% CI: 5.92-36.19, $p < 0.001$; right coronary cusp: mean difference: 46.02 mm^3, 95% CI: 1.84-90.21, $p = 0.04$, and NCC: mean difference: 0.19 mm^3, 95% CI: −0.32 to 0.50, $p = 0.10$). On qualitative review, LVOT calcium in the NCC region was the leaflet most commonly predictive of post-TAVR conduction outcomes. Total AVC, total LVOT calcium, and mitral annular calcium had no convincing association with post-TAVR conduction outcomes. The distribution of calcium rather than its total volume was associated with post-TAVR conduction abnormalities. Heterogeneity in methodology and implantation techniques between studies limits the clinical significance of these findings.

ABBREVIATIONS

AV, atrioventricular; AVC, aortic valve complex; HGAVB, high-grade atrioventricular block; LBBB, left bundle branch block; LCC, left coronary cusp; LVOT, left ventricular outflow tract; NCC, noncoronary cusp; PPMI, permanent pacemaker implantation; RBBB, right bundle branch block; RCC, right coronary cusp; TAVR, transcatheter aortic valve replacement.

Introduction

Transcatheter aortic valve replacement (TAVR) is an established treatment for patients with symptomatic aortic stenosis. High-grade atrioventricular block (HGAVB), specifically Mobitz II, and third-degree atrioventricular (AV) block have an incidence of 10% to 21% following TAVR and often require permanent pacemaker implantation (PPMI).[1] It has been proposed that the transcatheter heart valve (THV), when deployed may exert a unidirectional mechanical pressure onto the AV conduction system and contribute to new HGAVB after TAVR. High calcium burden in the aortic valve complex (AVC) and left ventricular outflow tract (LVOT) may compound mechanical pressures exerted by the THV and increase the risk of HGAVB.[2] Resolution of initial post-procedural conduction abnormalities in the days after TAVR for some

* Address correspondence to: Ravinay Bhindi, MBBS, MSc, PhD, Department of Cardiology, Royal North Shore Hospital, Reserve Rd, St Leonards, Sydney, New South Wales 2065.
E-mail address: ravinay.bhindi@sydney.edu.au (R. Bhindi).

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patients supports other theories whereby postprocedural edema and inflammation leads to a transient AV conduction impairment.[3] There is conjecture regarding the individual associations of noncoronary cusp (NCC), right coronary cusp (RCC), and left coronary cusp (LCC) calcium volumes and conduction abnormalities after TAVR. No specific distribution of calcium between leaflets has been established as the highest risk for PPMI requirement after TAVR. Existing studies present mixed findings with no consensus. There has also been recent literature to suggest mitral annular calcification (MAC), while not directly part of the AVC, may contribute to conduction abnormalities after TAVR. It is hypothesized that higher volumes of MAC may increase the risk of conduction abnormalities due to its proximity to the anterior aspect of the AV node. A comprehensive systematic review and meta-analysis of the latest available data has not yet been performed.

Materials and Methods

We performed a systematic review and meta-analysis of published studies that investigated whether there was an association between the distribution of calcium within the AVC and LVOT and the development of HGAVB, left bundle branch block (LBBB), or PPMI after TAVR. As a secondary aim, we performed a systematic review of studies investigating total AVC calcium, total LVOT calcium, and MAC and its association with HGAVB, LBBB, or PPMI after TAVR.

The systematic review and meta-analysis were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (ID CRD42023417976).

Study Selection

A broad search strategy was developed (Supplementary Figure 1) to identify studies that examined preprocedural AVC and/or LVOT calcium and its association with postprocedural conduction disturbances or PPMI in patients after TAVR. Five databases were included: EMBASE, MEDLINE, PUBMED, Scopus, and Wed of Science. The search was performed on 17 April 2023, and restricted to publications available in the English language.

Independent reviewers (P.L. and K.R.) performed title and abstract screening. Potentially eligible articles were reviewed in full text for final inclusion, with disagreements resolved by consensus with a third independent reviewer (R.B.). Abstracts, conference presentations, and review articles were excluded. Studies from 2014 and prior were excluded due to use of older generation THVs no longer commercially available.

Data Extraction and Synthesis

A standardized data collection template was used for data extraction, including recruitment timing, sample size, mean age, sex, bicuspid valve incidence if reported and other baseline demographics, existing conduction abnormalities (left and right bundle branch block [LBBB, RBBB], prior permanent pacemaker [PPM], prior first-degree atrioventricular block [AVB]), type of valve used, calcium volumes and distributions including preset Hounsfield unit (HU) thresholds for measurement and methodology of measurement, outcome measure, follow-up period, whether conduction was the primary outcome, and study findings.

Meta-analysis was performed on studies with quantitative data that was compatible with forest plot creation. Studies with calcium measurements separated based on PPMI status and presented in mean and SDs were able to be included in forest plot analysis. Studies with data presented in medians and interquartile ranges were first assessed for normal distribution or significant skew. Studies with a normal distribution of data were converted to mean and SD values, and studies with skewed data were excluded from meta-analysis.[4] In the case of one study, where calcium measurements were reported for the PPMI group and the whole cohort, raw data values for the non-PPMI group were manually calculated.[5]

Quality of Included Studies and Risk of Bias

The quality of included studies and risk of bias were independently assessed using the Newcastle Ottawa Scale for cohort studies. Studies were graded out of a maximum possible score of 9 and were classified as "Poor" quality (0-2 points), "Fair" quality (3-5 points) or "Good/High" quality (6-9 points).[6]

Statistical Analysis

Data analysis was conducted in Review Manager Version 5.4.1. Mean differences in calcium volumes were compared using random effect and generic inverse variance models. Significance was set as $p \leq 0.05$. Interstudy heterogeneity (I^2 statistic) was classified as low ($I^2 < 25\%$), moderate (I^2: 25%-50%), or high ($I^2 > 50\%$).[7]

Results

Study Selection

Our search strategy yielded a total of 893 articles, and an additional seven articles were identified manually. After duplicates were removed (n = 143), a total of 757 articles were retrieved for title and abstract screening. Seventy articles were determined eligible for full text review. A total of 34 studies were included after full text review for qualitative analysis. The other 36 studies were excluded in full text review for the following reasons: surgical valve, not TAVR (n = 2), abstract or conference presentation (n = 2), study date of 2014 or earlier (n = 2), calcium was not a studied predictor (n = 7), conduction was not a studied outcome (n = 16), conduction was reported within a composite morbidity measure but not individually reported (n = 5), and both calcium and conduction data were reported but not analyzed (n = 2).

Quantitative meta-analysis was able to be performed on seven studies. The other 27 studies were incompatible with meta-analysis for the following reasons: AVC calcium measurements by leaflets were not available (n = 18), calcium data grouped based on conduction outcome were not available (n = 6), and study data were significantly skewed, prohibiting the accurate derivation of mean and SD (n = 3). Study selection is summarized in Figure 1.

Study Characteristics

Thirty-four studies totaling 11,528 patients were included for review. Characteristics for all included studies were summarized (see Results tables). Pre-existing RBBB was controlled for as a confounder variable in 15 studies, excluded from the study cohorts in two studies, and had no explicit mention in 17 studies. PPMI was the primary conduction outcome in 30 (88%) studies. A subset of 10 studies included the following additional conduction outcomes: LBBB (n = 10), PR and QRS prolongation (n = 2), HGAVB (n = 7), or PPMI dependence for right ventricular pacing at one month follow-up (n = 1). Patients with prior PPM were excluded from the study cohort in 24 studies, not excluded from the study cohort in 6 studies, and had no explicit mention in four studies. All included studies derived their calcium measurements from computed tomography images.

A subset of seven studies totaling 1056 patients were included in the meta-analysis, and detailed patient characteristics of this cohort are summarized in Table 1. Specifically, all seven studies excluded patients with a prior PPM, and the incidence of pre-existing RBBB was 8.3%. The split of valve types used were mostly balloon-expandable valves (45.9%), followed by self-expandable valves (36.6%), and a smaller cohort of

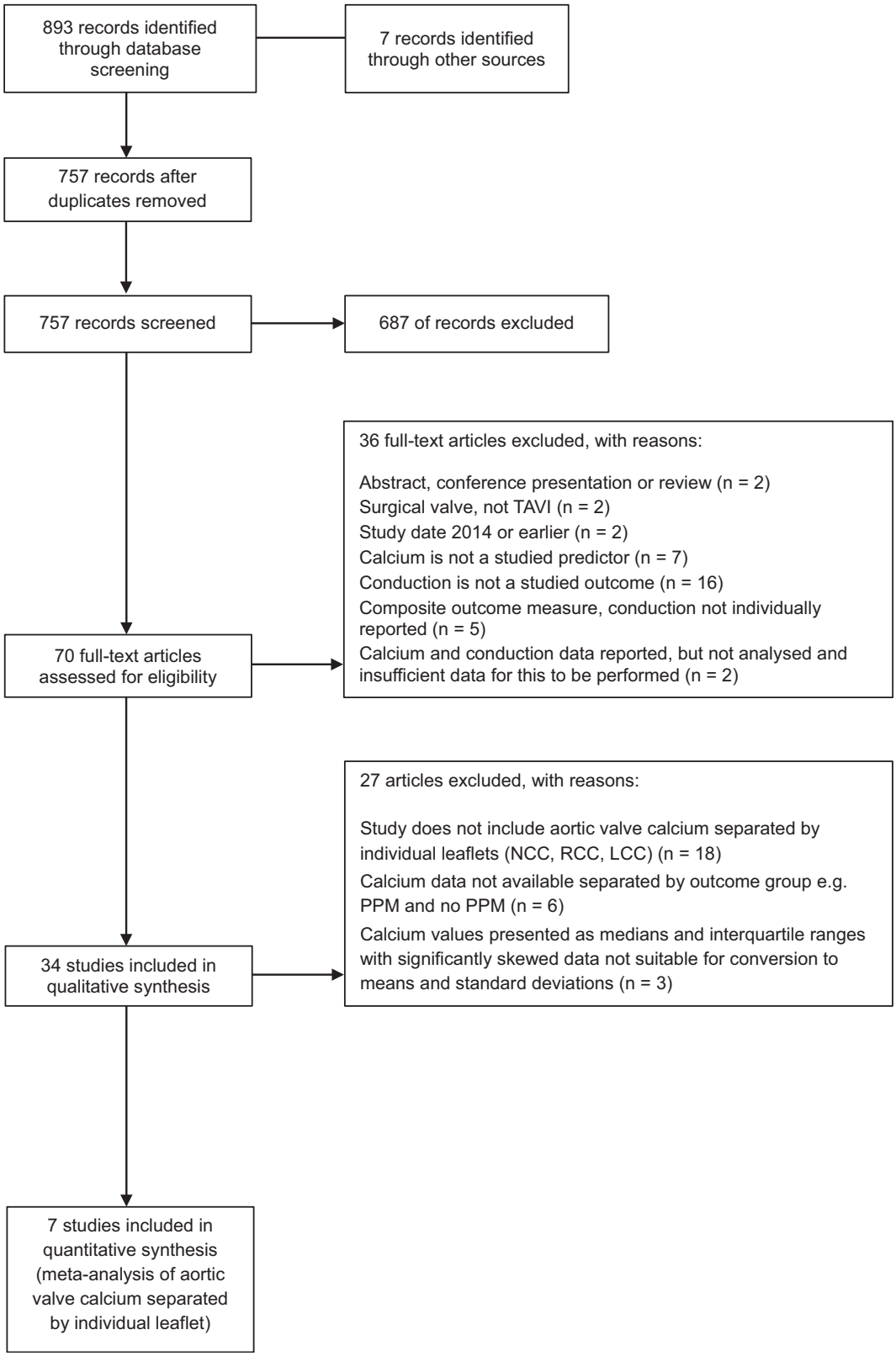

Figure 1. Study selection.
Abbreviations: LCC, left coronary cusp; NCC, noncoronary cusp; PPMI, permanent pacemaker implantation; RCC, right coronary cusp; TAVI, transcatheter aortic valve implantation.

Table 1
Patient characteristics

	Pooled	Fujita, 2016[8]	Gonska, 2017[9]	Kebler, 2017[10]	Mauri, 2018[11]	Schaefer, 2021[12]	Sharma, 2020[13]	Veulemans, 2020[14]
Sample size	1056	162	283	183	194	79	25	130
Baseline demographics								
Age (y) (M ± SD)	81.4 ± 6.0	82 ± 5	79.9 ± 6.2	81.1 ± 5.1	82.1 ± 5.2	79.8 ± 7.1	81.6 ± 7.5	80.4 ± 6.2
Sex (female) (n [%])	559 (52.9%)	96 (59.3%)	149 (52.7%)	103 (56.3%)	156 (73.6%)	32 (40.5%)	12 (49.6%)	11 (8.5%)
BMI (M ± SD)	26.3 ± 6.0	26.1 ± 4.7	27.5 ± 4.8	26.3 ± 8.1	27.6 ± 5.5	27.2 ± 5.5	21.5 ± 7.5	26.6 ± 4.0
EuroScore 1 (M ± SD)	15.4 ± 12.0	21.3 ± 10.6	14.2 ± 12.8	13.0 ± 11.5	14.3 ± 10.4	12.1 ± 8.8	ND	21.9 ± 14.0
STS-PROM (M ± SD)	6.4 ± 3.0	5.7 ± 2.1	6.7 ± 3.9	6.6 ± 5.0	ND	ND	ND	ND
EF (%) (M ± SD)	48.3 ± 13.0	51 ± 10	ND	ND	ND	52 ± 14	39.6 ± 13.5	ND
NYHA III/IV (n [%])	355 (33.6%)	ND	233 (82.7%)	ND	ND	29 (36.7%)	ND	93 (71.5%)
CAD (n [%])	650 (61.5%)	97 (59.9%)	168 (59.4%)	108 (59.0%)	124 (64.0%)	43 (54.4%)	19 (76.0%)	91 (70.0%)
HTN (n [%])	522 (49.4%)	144 (88.9%)	ND	ND	180 (93.0%)	59 (74.7%)	20 (80.0%)	119 (91.5%)
DM (n [%])	302 (28.6%)	43 (26.5%)	89 (29.7%)	44 (24.0%)	64 (33.0%)	13 (16.5%)	12 (48.0%)	37 (28.5%)
Baseline conduction								
Prior PPM (n [%])	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	ND	0 (0.0%)	0 (0.0%)
Prior AF (n [%])	314 (29.7%)	ND	116 (41.0%)	61 (33.3%)	72 (34.0%)	ND	8 (32.0%)	57 (43.8%)
Prior RBBB (n [%])	88 (8.3%)	20 (12.3%)	20 (7.1%)	13 (7.1%)	14 (7.2%)	ND	10 (40.0%)	11 (8.5%)
Prior LBBB (n [%])	94 (8.9%)	20 (12.3%)	26 (9.3%)	17 (9.3%)	15 (7.7%)	ND	1 (4.0%)	15 (11.5%)
Valve characteristics								
Self-expandable valve (n [%])	387 (36.6%)	63 (38.9%)	0 (0%)	0 (0%)	194 (100.0%)	0 (0.0%)	0 (0.0%)	130 (100.0%)
Balloon-expandable valve (n [%])	486 (45.9%)	99 (61.1%)	283 (100.0%)	0 (0.0%)	0 (0.0%)	79 (100.0%)	25 (100.0%)	0 (0.0%)
Mechanically expandable valve (n [%])	183 (17.3%)	0 (0.0%)	0 (0.0%)	183 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oversizing mean (M ± SD)	12.1 ± 10.7	15.5 ± 6.5	7.9 ± 13.5	8.4 ± 9.1	ND	ND	9.3 ± 13.8	23.1 ± 4.9
Implantation depth (M ± SD)	5.6 ± 2.2	5.2 ± 1.5	6.7 ± 2.4	ND	5.7 ± 2.0	ND	ND	5.1 ± 3.0

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; EF, ejection fraction; HTN, hypertension; LBBB, left bundle branch block; ND, no data; NYHA, New York Heart Association; PPM, permanent pacemaker; RBBB, right bundle branch block; STS-PROM, Society of Thoracic Surgeons, Patient Risk of Mortality.

patients who received the no longer commercially available, mechanically expandable valves (17.3%).

Quality of Included Studies and Risk of Bias Assessment

All studies scored the highest classification "Good/High" quality on Newcastle Ottawa Scale assessment (Table 2). There were 18 out of 34 studies that recorded the maximum possible score of nine. Variation in score was predominately due to some studies not controlling for confounders or including participants who had the outcome measure at baseline prior to TAVR.

AVC Leaflet Calcium and Conduction After TAVR

Of 14 studies identified that examined AVC calcium by leaflet, six studies did not find any association of specific leaflet calcium distribution and conduction outcomes after TAVR.[10,11,20,29,30,38] In the remaining eight studies, LCC calcium was reported as a significant predictor of conduction outcomes in four studies,[8,14,24,28] RCC calcium in four studies,[9,12,28,40] and NCC calcium in four studies.[9,13,24,28] Multiple studies identified more than one AVC leaflet as a significant predictor of conduction outcomes. In total, on qualitative review, no single AVC leaflet appeared to be associated with conduction outcomes more commonly than the other AVC leaflets (Table 3).

Meta-Analysis of AVC Leaflet Calcium and Conduction After TAVR

Our meta-analysis of AVC leaflet calcium and conduction outcomes after TAVR found that LCC and RCC calcium volumes were significantly higher in patients with PPMI after TAVR compared to patients without PPMI after TAVR, while there was no significant difference in NCC calcium volumes between the two groups. LCC calcium volume was significantly different between patients with and without PPMI after TAVR in pooled analysis and reported a mean volume difference of 21.05 mm^3 (95% CI: 5.92-36.19, $p < 0.001$, $I^2 = 0\%$) (Figure 2) with a low level of interstudy heterogeneity. RCC calcium volume was significantly different between patients with and without PPMI after TAVR in pooled analysis and reported a mean volume difference of 46.02 mm^3 (95% CI: 1.84-90.21, $p = 0.04$, $I^2 = 62\%$) (Figure 3) with a high level of interstudy heterogeneity. NCC calcium volume was not significantly different between patients with and without PPMI after TAVR in pooled analysis and reported a mean volume difference of 0.19 mm^3 (95% CI: −0.32 to 0.50, $p = 0.10$, $I^2 = 30\%$) (Figure 4) with a moderate level of interstudy heterogeneity. Figure 5 presents a visual representation of the comparative contributions of leaflet calcium on associations with PPMI requirement after TAVR.

LVOT Leaflet Calcium and Conduction After TAVR

Of eight studies that investigated LVOT calcium separated by leaflet and conduction outcomes after TAVR, two studies did not find calcium in any of the LVOT leaflet regions to be significant predictors of conduction outcomes.[12,14] In the remaining six studies, leaflet LVOT calcium was a significant predictor of conduction outcomes in the NCC region in five studies,[18,28,30,37,38] RCC region in two studies,[30,37] and LCC region in two studies.[11,30] There was insufficient compatible data among the studies investigating LVOT calcium by leaflet area to perform any meta-analysis (see Table 4).

Total AVC Calcium and Conduction After TAVR

Out of 20 studies that investigated total AVC calcium and conduction outcomes after TAVR, total AVC calcium was a significant predictor for

Table 2
Quality assessment of included studies according to the Newcastle-Ottawa Scale (NOS)

Study	Selection				Comparability	Outcome			Total score	Classification
	Represents exposed cohort	Selection of the nonexposed cohort	Ascertains exposure	Outcome was not present at start of study	Comparison of cohorts	Assessment of outcome	Long enough follow-up	Adequacy of follow-up		
Abramowitz, 2017[15]	*	*	*	*	**	*	*	*	9	Good/High
Al-Azzam, 2017[16]	*	*	*	*	**	*	*	*	9	Good/High
Ancona, 2017[17]	*	*	*		*	*	*	*	7	Good/High
Ancona, 2020[18]	*	*	*	*	**	*	*	*	9	Good/High
Brodov, 2019[19]	*	*	*	*	**	*	*	*	9	Good/High
Dowling, 2022[20]	*	*	*	*		*	*	*	7	Good/High
Esposito, 2022[21]	*	*	*		**	*	*	*	8	Good/High
Fujita, 2016[8]	*	*	*	*	**	*	*	*	9	Good/High
Gamet, 2020[22]	*	*	*	*		*	*	*	7	Good/High
Gonska, 2017[9]	*	*	*	*	**	*	*	*	9	Good/High
Hein-Rothweiler, 2017[23]	*	*	*	*	**	*	*	*	9	Good/High
Iacovelli, 2021[24]	*	*	*	*		*	*	*	7	Good/High
Jochheim, 2019[25]	*	*	*	*	**	*	*	*	9	Good/High
Kebler, 2017[10]	*	*	*	*	**	*	*	*	9	Good/High
Kim, 2018[26]	*	*	*		**	*	*	*	8	Good/High
Lak, 2022[27]	*	*	*			*	*	*	6	Good/High
Maeno, 2017[28]	*	*	*	*	**	*	*	*	9	Good/High
Mahon, 2021[29]	*	*	*	*	**	*	*	*	9	Good/High
Mauri, 2016[30]	*	*	*	*	**	*	*	*	9	Good/High
Mauri, 2018[11]	*	*	*	*	**	*	*	*	9	Good/High
Medranda, 2022[31]	*	*	*			*	*	*	6	Good/High
Milo, 2023[32]	*	*	*			*	*	*	6	Good/High
Musallam, 2022[33]	*	*	*			*	*	*	6	Good/High
Oestreich, 2017[34]	*	*	*	*		*	*	*	7	Good/High
Okuno, 2021[35]	*	*	*	*	**	*	*	*	9	Good/High
Piayda, 2020[36]	*	*	*	*	**	*	*	*	9	Good/High
Pollari, 2019[37]	*	*	*	*	**	*	*	*	9	Good/High
Pollari, 2022[38]	*	*	*		**	*	*	*	8	Good/High
Rodriguez-Olivares, 2016[39]	*	*	*	*	**	*	*	*	9	Good/High
Schaefer, 2021[12]	*	*	*			*	*	*	6	Good/High
Sharma, 2020[13]	*	*	*	*		*	*	*	7	Good/High
Spaziano, 2018[40]	*	*	*		**	*	*	*	8	Good/High
Veulemans, 2020[14]	*	*	*	*	**	*	*	*	9	Good/High
Waldschmidt, 2022[41]	*	*	*		**	*	*	*	8	Good/High

*Represents one point.
**Represents two points.
A blank cell or 0 * represents scoring 0 points for that question.

Table 3
Characteristics of included studies investigating aortic valve complex (AVC) calcium by leaflet

	Study type	Study time period	Sample size	Type of valve	Calcium measurement	Hounsfield threshold (HU)	Manual adjustment of threshold?	Conduction as primary outcome?	Prior RBBB	Controlled for RBBB?	Prior LBBB
Dowling, 2022[20]	Obs, R	March 2017-February 2021	80	SEV: 100.0%	Cubic millimeters	–	–	+	16.3%	+	0.0%
Fujita, 2016[8]	Obs, R	July 2012-December 2013	162	BEV: 60.1%. SEV: 39.9%	Cubic millimeters	500 HU	+	+	12.3%	+	12.3%
Gonska, 2017[9]	Obs, P	–	283	BEV: 100.0%	Cubic millimeters	850 HU	0	+	7.1%	+	26.1%
Iacovelli, 2021[24]	Obs, P	–	48	BEV: 100.0%	Cubic millimeters	850 HU	0	+	8.3%	0	8.3%

	Prior PPMI	PPMI analyzed?	PPMI rate (%)	PPMI with HGAVB as indication (%)	LBBB analyzed?	Other conduction parameter?	Follow-up period	Summary of findings
Dowling, 2022[20]	0.0%	+	26.3%	81.0%	+	HGAVB	In hospital	Leaflet calcium and PPMI: AUC, 0.47; 95% CI, 0.34-0.61; $p = 0.47$ Leaflet calcium and conduction disturbance composite: not predictive (statistics not provided).
Fujita, 2016[8]	0.0%	+	9.9%	93.8%	0	0	In hospital	LCC and PPMI: 14.8% vs. 4.9%, $p = 0.035$ NCC and PPMI: 11.1% vs. 8.6%, $p = 0.60$ RCC and PPMI: 11.1% vs. 8.6%, $p = 0.60$
Gonska, 2017[9]	0.0%	+	18.4%	90.4%	0	0	In hospital	LCC and PPMI: $p = 0.2$ NCC and PPMI: $p = 0.01$ RCC and PPMI: $p < 0.01$
Iacovelli, 2021[24]	0.0%	0	10.4%	100.0%	0	PR and QRS prolongation	30 d	LCC and QRS prolongation: OR 1.015, $p = 0.027$. LCC and PR prolongation: OR 1.003, $p = 0.422$. NCC and QRS prolongation: OR 1.010, $p = 0.019$. NCC and PR prolongation: OR 1.003, $p = 0.174$. RCC and QRS prolongation: OR 1.020, $p = 0.052$. RCC and PR prolongation: OR 1.004, $p = 0.331$.

	Study type	Study time period	Sample size	Type of valve	Calcium measurement	Hounsfield threshold (HU)	Manual adjustment of threshold?	Conduction as primary outcome?	Prior RBBB	Controlled for RBBB?	Prior LBBB
Maeno, 2017[28]	Obs, P	November 2013-December 2015	240	BEV: 100.0%	Cubic millimeters	850 HU	0	+	19.2%	+	8.8%
Mahon, 2021[29]	Obs, R	January 2014-November 2017	227	SEV: 100.0%	Agatston scoring	–	–	+	–	0	–
Mauri, 2016[30]	Obs, P	August 2013-January 2016	229	BEV: 100.0%	Cubic millimeters	500 HU	+	+	3.9%	+	4.8%

	Prior PPMI	PPMI analyzed?	PPMI rate (%)	PPMI with HGAVB as indication (%)	LBBB analyzed?	Other conduction parameter?	Follow-up period	Summary of findings
Maeno, 2017[28]	0.0%	+	14.6%	80%	0	0	In hospital	LCC and PPMI: 78.0 mm^3 vs. 42.2 mm^3, $p = 0.004$. NCC and PPMI: 110.2 mm^3 vs. 65.5 mm^3, $p = 0.03$. RCC and PPMI: 69.5 mm^3 vs. 28.8 mm^3, $p < 0.001$.
Mahon, 2021[29]	0.0%	0	22.5%	–	0	PR and QRS prolongation	In hospital	LCC and PPMI (OR: 1.03, 95% CI: 0.99-1.07) and PR prolongation ($p = 0.28$) and QRS prolongation ($p = 0.41$). NCC and PPMI (OR: 1.02, 95% CI: 0.98-1.06) and PR prolongation ($p = 0.13$) and QRS prolongation ($p = 0.99$). RCC and PPMI (OR: 1.01, 95% CI: 0.97-1.06) and PR prolongation ($p = 0.61$) and QRS prolongation ($p = 0.40$).
Mauri, 2016[30]	0.0%	+	14.4%	90.9%	0	0	In hospital	LCC and PPMI: $p = 0.075$ NCC and PPMI: $p = 0.056$ RCC and PPMI: $p = 0.200$

	Study type	Study time period	Sample size	Type of valve	Calcium measurement	Hounsfield threshold (HU)	Manual adjustment of threshold?	Conduction as primary outcome?	Prior RBBB	Controlled for RBBB?	Prior LBBB
Mauri, 2018[11]	Obs, R	March 2014-February 2017	194	SEV: 100.0%	Cubic millimeters	500 HU	+	+	7.2%	+	7.7%
Pollari, 2022[38]	Obs, R	January 2012-June 2017	569	BEV: 70.7%. SEV: 8.4%. Other: 20.9%	Cubic millimeters	500 HU	+	+	10.7%	+	10.0%
Schaefer, 2021[12]	Obs, R	March 2019-January 2020	79	BEV: 100.0%	Cubic millimeters	500 HU	0	0	–	–	–
Sharma, 2020[13]	Obs, R	March 2012-October 2016	25	BEV: 100.0%	Cubic millimeters	550 HU	+	+	40.0%	0	4.0%

	Prior PPMI	PPMI analyzed?	PPMI rate (%)	PPMI with HGAVB as indication (%)	LBBB analyzed?	Other conduction parameter?	Follow-up period	Summary of findings
Mauri, 2018[11]	0.0%	+	10.3%	90.0%	0	0	In hospital	LCC and PPMI: 128 mm^3 vs. 149 mm^3 (d = 0.20). NCC and PPMI: 210 mm^3 vs. 264 mm^3 (d = 0.19). RCC and PPMI: 130 mm^3 vs. 106 mm^3 (d = 0.05).
Pollari, 2022[38]	0.0%	0	7.9%	100.0%	+	HGAVB, new or worsening BBB	In hospital	LCC, NCC, RCC, and new BBB, transient or permanent AVB: not associated in univariate and multivariate analysis (statistics not provided).
Schaefer, 2021[12]	–	+	7.6%	–	0	0	30 d	LCC and PPMI: 246.0 mm^3 vs. 253.3 mm^3, $p = 0.89$ NCC and PPMI: 422.5 mm^3 vs. 389.7 mm^3, $p = 0.57$ RCC and PPMI: 273.7 mm^3 vs. 467.6 mm^3, $p = 0.02$
Sharma, 2020[13]	0.0%	+	11.1%	80.0%	0	PPM dependence at follow-up	30 d	LCC and PPM dependence at 30 d: $p = 0.29$. NCC and PPM dependence at 30 d: $p = 0.01$ (NCC calcium volume >239.2 mm^3 was strongly predictive of PPM dependence at 30 d). RCC and PPM dependence at 30 d: $p = 0.81$.

	Study type	Study time period	Sample size	Type of valve	Calcium measurement	Hounsfield threshold (HU)	Manual adjustment of threshold?	Conduction as primary outcome?	Prior RBBB	Controlled for RBBB?	Prior LBBB
Spaziano, 2018[40]	Obs, R	January 2013-December 2015	547	BEV: 38.0%. SEV: 46.3%. Other: 15.7%	Cubic millimeters	–	–	0	–	0	–
Veulemans, 2020[14]	Obs, P	March 2017-September 2019	130	SEV: 100.0%	Agatston scoring	600 HU	0	+	8.5%	+	11.5%

	Prior PPMI	PPMI analyzed?	PPMI rate (%)	PPMI with HGAVB as indication (%)	LBBB analyzed?	Other conduction parameter?	Follow-up period	Summary of findings
Spaziano, 2018[40]	8.6%	0	15.5%	–	0	0	30 d	LCC and PPMI: No comment made; presumably analyzed as per study methods. NCC and PPMI: HR = 0.78 per 100 mm^3 increment; 95% CI: 0.66-0.92; $p = 0.004$ RCC and PPMI: HR = 1.18 per 100 mm^3 increment; 95% CI: 1.01-1.38; $p = 0.04$
Veulemans, 2020[14]	0.0%	0	23.1%	96.7%	0	0	72 h	RCC, NCC, and LCC calcium were not associated with PPMI as continuous measures: statistics not provided. Leaflet calcium separated by median and patients in sinus rhythm only included, LCC calcium and PPMI: univariate (OR: 4.31, 95% CI 1.10-16.93, $p = 0.036$) and multivariate analysis (OR: 16.12, 95% CI 1.74-149.67, $p = 0.014$). NCC and RCC not significant predictors (statistics not provided).

Abbreviations: AUC, area under the curve; BEV, balloon-expandable valve; HGAVB, high-grade atrioventricular block; HU, Hounsfield unit; LBBB, left bundle branch block; LCC, left coronary cusp; NCC, noncoronary cusp; Obs, P, observational, prospective; Obs, R, observational, retrospective. PPMI, permanent pacemaker implantation; OR, odds ratio; RBBB, right bundle branch block; RCC, right coronary cusp; SEV, self-expandable valve.

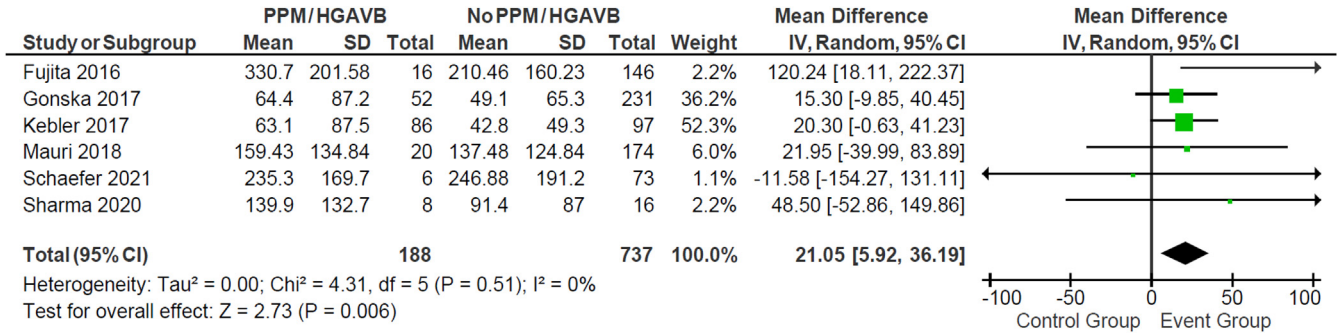

Figure 2. Meta-analysis of LCC calcium and permanent pacemaker implantation.
Abbreviations: HGAVB, high grade atrioventricular block; LCC, left coronary cusp; PPM, permanent pacemaker.

conduction outcomes in six studies[9,13,23,24,28,36] and in the remaining 14 studies, total AVC calcium was not reported as a significant predictor for conduction outcomes[8,10–12,14,16,20–22,26,29,32,38,39] (see Supplementary Table 1).

Total LVOT Calcium and Conduction After TAVR

Out of 19 studies that investigated total LVOT calcium and its association with conduction outcomes after TAVR, five studies found total LVOT calcium to be a significant predictor for conduction outcomes[18,25,28,31,34] and the remaining 14 studies did not find total LVOT calcium to be a significant predictor of conduction outcomes[8–14,20,24,26,29,33,39,41] (see Supplementary Table 2).

Mitral Annulus Calcium and Conduction After TAVR

There were five studies identified that investigated MAC and its association with conduction outcomes after TAVR. Of these five studies, three studies found that in patients with none compared to any MAC, there was no significance difference in the rate of PPMI[17,27,35] or LBBB after TAVR.[27] In the fourth study, severe MAC compared to no MAC was associated with a higher risk of PPMI, but not when any MAC was compared to no MAC.[15] In the fifth study, higher MAC was found in patients with a composite conduction outcome of LBBB and HGAVB[19] (see Supplementary Table 3).

All Calcium Measures and Associations With LBBB After TAVR

A subset of 12 studies investigated LBBB as a conduction outcome. Of four studies that investigated AVC calcium by leaflet and LBBB, three studies did not find AVC calcium in any leaflet predictive of LBBB, and one study found LCC and RCC calcium predicted QRS prolongation after TAVR. Of two studies that investigated LVOT calcium by leaflet and LBBB, the first study did not find LVOT calcium in any leaflet to predict new or worsening bundle branch block, but the second study found LVOT calcium in the NCC region was predictive of LBBB. Of six studies that investigated total AVC calcium and LBBB, four studies did not find total AVC calcium predictive of LBBB, and two studies found total AVC predicted LBBB. Of four studies that investigated total LVOT calcium and LBBB, three studies did not find total LVOT calcium predictive of LBBB, and one study found total LVOT calcium predicted LBBB. Of two studies investigating MAC and LBBB, one study found MAC was predictive of a composite conduction outcome that included LBBB, and the other study found MAC was not predictive of LBBB alone (see Supplementary Table 4).

Discussion

This systematic review and meta-analysis provide a comprehensive evaluation of the role of calcium and its distribution within the AVC, LVOT, and mitral annulus in predicting conduction abnormalities and the risk of PPMI after TAVR. The main findings were as follows: (1) in the AVC, LCC, and RCC calcification were associated with HGAVB after TAVR; (2) in the LVOT, NCC calcification was associated with HGAVB after TAVR; and (3) total calcium volumes in the AVC, LVOT, and mitral annulus regions were not associated with conduction outcomes after TAVR.

In greater detail, our meta-analysis found that patients with new HGAVB after TAVR had a higher volume of LCC (21.05 mm^3, $p < 0.001$) and RCC calcification (46.02 mm^3, $p = 0.04$) compared to patients without HGAVB after TAVR. There was no difference found between the two groups with respect to NCC calcification (0.19 mm^3, $p = 0.10$). The association between RCC calcification and HGAVB after TAVR had a higher level of heterogeneity with a wider confidence interval, compared to the LCC calcification. However, while both LCC and RCC calcium were statistically significant in the prediction of conduction outcomes for TAVR patients, there was debatable clinical significance,

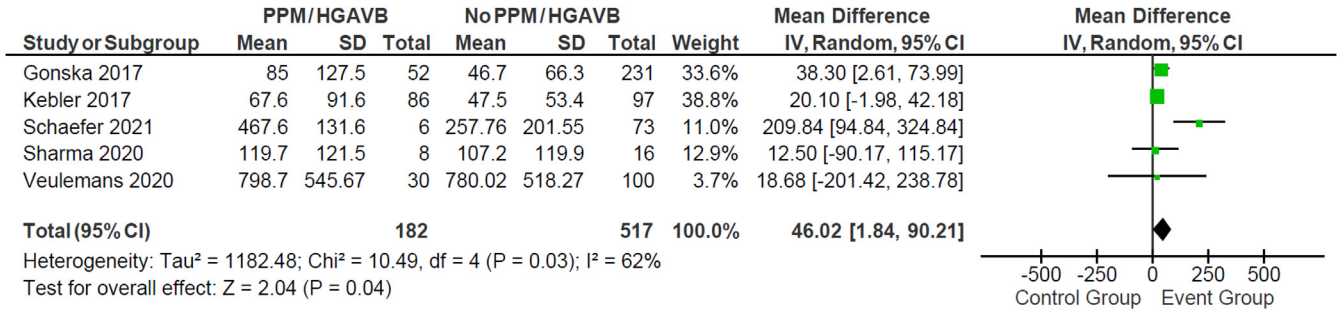

Figure 3. Meta-analysis of RCC calcium and permanent pacemaker implantation.
Abbreviations: HGAVB, high grade atrioventricular block; PPM, permanent pacemaker; RCC, right coronary cusp.

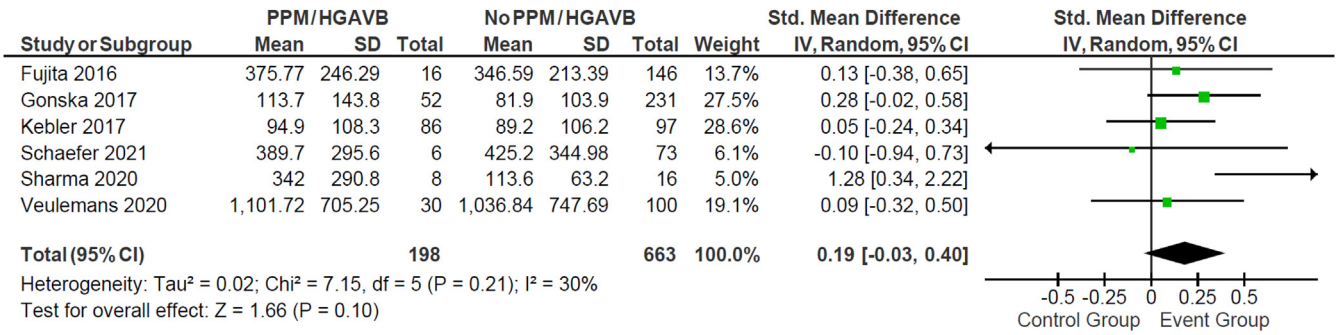

Figure 4. Meta-analysis of NCC calcium and permanent pacemaker implantation.
Abbreviations: HGAVB, high grade atrioventricular block; NCC, noncoronary cusp; PPM, permanent pacemaker.

given the differences in mean calcium volumes at these leaflets were small (21.07 mm^3 and 46.12 mm^3, respectively).

Asymmetric calcium burden with the greatest calcification in the LCC has been concluded to be a leading risk factor for PPMI in a prior systematic review.[42] The present study provides a quantitative corroboration. The LCC is anatomically opposite the His bundle, which runs within the membranous septum located in the interleaflet triangle between the NCC and RCC. Subsequently, the magnified role of LCC calcium in post-TAVR conduction disease may be associated with an increased force placed on these oppositional anatomical structures.[42] Other authors have suggested that the proximity of RCC and NCC calcium to the membranous septum could conversely provide a protective shielding from the implanted valve, which LCC calcium would not provide.[2] The small mean differences in calcium volume across all three leaflets found between patients with and without HGAVB after TAVR may be explained by these multiple concurrent, and at times oppositional, mechanisms underpinning the effect of calcium in THV deployment.

Meta-analysis of differential LVOT calcium by leaflets was not possible due to insufficient compatible data and heterogeneity in calcium measurements within the included studies. However, our systematic review of studies suggested that LVOT calcium corresponding to the NCC region was most strongly associated with conduction outcomes after TAVR. This could be explained by the anatomical location of the membranous septum, positioned at the NCC and RCC within the subvalvular apparatus. The membranous septum contains the Bundle of His, an important pathway of AV conduction that gives rise to the left and right bundle branches.[43] This would support the hypothesis of some authors that heavy calcium in the RCC and NCC potentiates the forces exerted by the THV onto the conduction system, or via effects of local calcium encroaching onto the adjacent His bundle.[2]

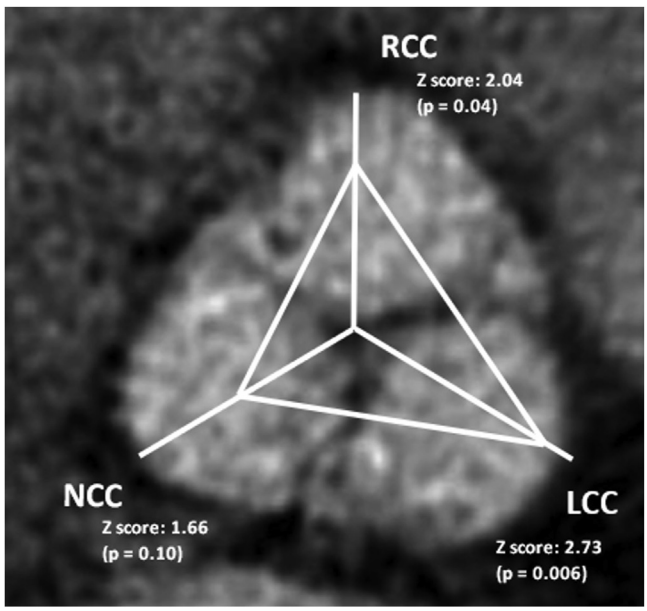

Figure 5. Comparative effects of calcium in aortic valve leaflets on high-grade atrioventricular block and permanent pacemaker implantation after TAVR.
Abbreviations: LCC, left coronary cusp; NCC, noncoronary cusp; RCC, right coronary cusp; TAVR, transcatheter aortic valve replacement.

On systematic review of studies related to total AVC and total LVOT calcium, these calcium measurements did not appear to be predictive of conduction outcomes or need for PPMI after TAVR. This is likely to be because the combined measurements do not capture the specific and varied mechanisms associated with calcium volume at different leaflets, as previously discussed.

On systematic review of studies related to MAC, it did not appear to be predictive of conduction outcomes or need for PPMI after TAVR; however, the number of studies was limited. MAC is hypothesized to be related to conduction outcomes after TAVR due to the proximity of the mitral annulus to the anterior aspect of the AV node.[15] Alternatively, given both MAC and AVC calcium deposition occur secondary to systemic atherosclerosis, MAC may function as a surrogate marker of valvular and subvalvular calcium burden and indirectly predict conduction outcomes after TAVR.[44] Increased MAC volumes have previously been associated with cardiovascular disease and mortality more broadly.[45] MAC has only recently become of interest to investigators, and it may be pre-emptive to draw conclusions regarding the association of MAC with conduction outcomes after TAVR until more studies have been performed.

New persistent LBBB occurs in approximately 20% of patients after TAVR.[46] Anatomically, the left bundle branch is a superficial structure that passes through the LVOT, the membranous interventricular septum, and then the muscular septum toward the left ventricle.[43] This explains why a pre-existing RBBB is the strongest predictor of PPMI,[47] as in such patients, the development of a new LBBB will precipitate complete AV block. LBBB has been associated with increased mortality among TAVR patients[48] and, more broadly, in patients with cardiovascular diseases such as heart failure or acute myocardial infarction.[49] Among the subset of studies that investigated new LBBB as a conduction outcome, we found no trend to suggest calcium in the AVC, LVOT, or MAC, based on either volume or distribution, was predictive of LBBB specifically after TAVR. However, the number of studies that have investigated calcium volume parameters and LBBB was small. Future studies with more detailed measurement of conduction outcomes such as new, persistent LBBB or length of QRS prolongation, are warranted.

It is important to note the limitations of this review. There was marked heterogeneity in study design and reporting of data between studies. For example, a variety of HU cut-offs were used to measure calcium volume (predominately ranging from 500-850 HU), while some studies included additional adjustment for luminal attenuation or had individualized HU cut-offs for each patient. Studies inconsistently controlled for confounders, particularly pre-existing RBBB, the strongest

Table 4
Characteristics of included studies investigating left ventricular outflow tract (LVOT) calcium by leaflet

	Study type	Study time period	Sample size	Type of valve	Calcium measurement	Hounsfield threshold	Manual adjustment of threshold?	Conduction as primary outcome?	Prior RBBB	Controlled for RBBB?	Prior LBBB
Ancona, 2020[18]	Obs, R	January 2014-June 2017	357	BEV: 25%. SEV: 34.0%. Other: 41%.	Grading of MSCT images	–	–	+	–	+	–
Maeno, 2017[28]	Obs, P	November 2013-December 2015	240	BEV: 100.0%	Cubic millimeters	850 HU	0	+	19.2%	+	8.8%
Mauri, 2016[30]	Obs, P	August 2013-January 2016	229	BEV: 100.0%	Cubic millimeters	500 HU	+	+	3.9%	+	4.8%

	Prior PPMI	PPMI analyzed?	PPMI rate (%)	PPMI with HGAVB as indication (%)	LBBB analyzed?	Other conduction parameter?	Follow-up period	Summary of findings
Ancona, 2020[18]	0.0%	+	23.6%	–	0	0	In hospital	LVOT (NCC) and PPMI: OR 2.45, 95% CI 1.19-5.07, $p = 0.02$ LVOT (RCC) and PPMI: OR 1.41, 95% CI 0.52-3.78, $p = 0.49$ LVOT (LCC) and PPMI: OR 1.20, 95% CI 0.66-2.16, $p = 0.55$
Maeno, 2017[28]	0.0%	+	14.6%	80%	0	0	In hospital	LVOT (NCC) and PPMI: 0.8 mm^3 vs. 0.0 mm^3, $p < 0.001$ LVOT (RCC) and PPMI: 0.0 mm^3 vs. 0.0 mm^3 LVOT (LCC) and PPMI: 0.0 mm^3 vs. 0.0 mm^3
Mauri, 2016[30]	0.0%	+	14.4%	90.9%	0	0	In hospital	LVOT (NCC) and PPMI: 16.1 mm^3 vs. 7.0 mm^3, $p = 0.035$ (multivariate: OR 0.8, $p = 0.736$) LVOT (RCC) and PPMI: 6.6 mm^3 vs. 0.3 mm^3; $p = 0.014$ (multivariate: OR 4.7, $p = 0.005$) LVOT (LCC) and PPMI: 23.7 mm^3 vs. 0.3 mm^3, $p < 0.001$ (multivariate: OR 3.7, $p = 0.016$)

	Study type	Study time period	Sample size	Type of valve	Calcium measurement	Hounsfield threshold	Manual adjustment of threshold?	Conduction as primary outcome?	Prior RBBB	Controlled for RBBB?	Prior LBBB
Mauri, 2018[11]	Obs, R	March 2014-February 2017	194	SEV: 100.0%	Cubic millimeters	500 HU	+	+	7.2%	+	7.7%
Pollari, 2019[37]	Obs, R	July 2009-October 2016	342	BEV: 100.0%	Cubic millimeters	500 HU	+	+	8.8%	+	10.5%
Pollari, 2022[38]	Obs, R	January 2012-June 2017	569	BEV: 70.7%. SEV: 8.4%. Other: 20.9%	Cubic millimeters	500 HU	+	+	10.7%	+	10.0%
Schaefer, 2021[12]	Obs, R	March 2019-January 2020	79	BEV: 100.0%	Cubic millimeters	500 HU	0	0	–	–	–
Veulemans, 2020[14]	Obs, P	March 2017-September 2019	130	SEV: 100.0%	Agatston scoring	600 HU	0	+	8.5%	+	11.5%

	Prior PPMI	PPMI analyzed?	PPMI rate (%)	PPMI with HGAVB as indication (%)	LBBB analyzed?	Other conduction parameter?	Follow-up period	Summary of findings
Mauri, 2018[11]	0.0%	+	10.3%	90.0%	0	0	In hospital	LVOT (LCC) (volume above median) and PPMI: OR 5.0, 95% CI 1.5-17.1, $p = 0.010$ LVOT (NCC and RCC) and PPMI: Not a significant predictor (no statistics provided)
Pollari, 2019[37]	0.0%	+	7.6%	100.0%	+	HGAVB, new or worsening BBB	In hospital	LVOT (RCC) and transient HGAVB: OR 1.16, 95% CI: 1.02-1.3, $p = 0.02$ LVOT (NCC) and permanent HGAVB and PPMI: OR 1.06, 95% CI: 1-1.1, $p = 0.03$ No other LVOT calcium regions were found to be associated with any conduction outcomes.

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Table 4 (*continued*)

Pollari, 2022[38]	0.0%	0	7.9%	100.0%	+	HGAVB, new or worsening BBB	In hospital	LVOT (NCC) and permanent HGAVB requiring PPMI: OR 1.6, 95% CI: 1-2 – 2.1, $p < 0.01$. LVOT (NCC) and new or worsening BBB: OR 1.3, 95% CI: 1-1.6, $p = 0.008$ LVOT calcium in the LCC and RCC was not associated with any conduction outcomes.
Schaefer, 2021[12]	–	+	7.6%	–	0	0	30 d	LVOT (NCC) and PPMI: 15.9 mm^3 vs. 21.3 mm^3, $p = 0.70$ LVOT (RCC) and PPMI: 7.9 mm^3 vs. 18.1 mm^3, $p = 0.29$ LVOT (LCC) and PPMI: 12.3 mm^3 vs. 3.8 mm^3, $p = 0.58$
Veulemans, 2020[14]	0.0%	0	23.1%	96.7%	0	0	72 h	LVOT (NCC) and PPMI: 0 mm^3 vs. 0 mm^3, $p = 0.542$ LVOT (RCC) and PPMI: 0 mm^3 vs. 0 mm^3, $p = 0.256$ LVOT (LCC) and PPMI: 0 mm^3 vs. 0 mm^3, $p = 0.661$

Abbreviations: BEV, balloon-expandable valve; HGAVB, high-grade atrioventricular block; HU, hounsfield unit; LBBB, left bundle branch block; LCC, left coronary cusp; LVOT, left ventricular outflow tract; MSCT, multistage computer tomography; NCC, noncoronary cusp; Obs, P, observational, prospective; Obs, R, observational, retrospective; OR, odds ratio; PPMI, permanent pacemaker implantation; RBBB, right bundle branch block; RCC, right coronary cusp; SEV, self-expandable valve.

predictor of PPMI after TAVR.[47] Many studies used PPMI as a surrogate end point for development of conduction disease post-TAVR but failed to clarify if there were other indications unrelated to the THV such as sick sinus syndrome. Thresholds for PPMI varied from center to center, particularly for patients with transient HGAVB or new persistent LBBB. Finally, the length of follow-up varied between studies. Some studies had shorter follow-up periods of 72 hours[14] or hospital discharge,[38] and other studies had longer follow-up periods of 30 days.[31] Due to the risk of delayed high-grade AV block, studies with shorter follow-up periods may have underestimated the overall incidence of conduction abnormalities.

Another key limitation was the impact of procedural factors that affect conduction outcomes after TAVR and could not be controlled for. For example, newer implantation techniques such as cusp overlap and higher implantation depths have reduced pacemaker requirement in self-expanding valves.[50] Although we excluded studies from 2014 and earlier, the included studies did not specify their implantation techniques. Anatomical factors such as a horizontal aorta have also been reported to affect final implantation position and can contribute to conduction disease.[51] Proceduralists may have made pre-emptive decisions based on preprocedural calcium, such as valve selection or implantation depth, which limits the ability to draw conclusions from the post-TAVR conduction outcomes.

Future studies require stricter confounder control and standardized procedural techniques to better establish the relationship between calcium burden and conduction after TAVR. More detailed and continuous monitoring of conduction for an extended period would also help better assess both immediate and delayed conduction outcomes. An Australian study, CONDUCT-TAVR (ACTRN 12621001700820), may help to provide an answer by utilizing an implantable loop recorder to provide follow-up data for patients up to one year following TAVR.

Conclusions

In summary, we presented a comprehensive review investigating the role of calcium volume and distribution in the AVC, LVOT, and mitral annulus in predicting HGAVB and PPMI after TAVR. Total calcium volume in the AVC, LVOT, and mitral annulus were not associated with conduction outcomes after TAVR. LCC, RCC, and NCC-LVOT calcium distributions had a slightly higher risk of HGAVB and PPMI after TAVR compared to other calcium distributions, but this was unlikely to be of clinical significance. Significant heterogeneity between studies was an important limitation of the review.

ORCIDs

Princess Neila Litkouhi https://orcid.org/0000-0002-2616-3524

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Supplementary Material

Supplemental data for this article can be accessed on the publisher's website.

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