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SYSTEMATIC REVIEW AND META-ANALYSIS

Predictors of Permanent Pacemaker Implantation in Patients Undergoing Transcatheter Aortic Valve Replacement - A Systematic Review and Meta-Analysis

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BACKGROUND: As transcatheter aortic valve replacement (TAVR) technology expands to healthy and lower-risk populations, the burden and predictors of procedure-related complications including the need for permanent pacemaker (PPM) implantation needs to be identified.

METHODS AND RESULTS: Digital databases were systematically searched to identify studies reporting the incidence of PPM implantation after TAVR. A random- and fixed-effects model was used to calculate unadjusted odds ratios (OR) for all predictors. A total of 78 studies, recruiting 31 261 patients were included in the final analysis. Overall, 6212 patients required a PPM, with a mean of 18.9% PPM per study and net rate ranging from 0.16% to 51%. The pooled estimates on a random-effects model indicated significantly higher odds of post-TAVR PPM implantation for men (OR, 1.16; 95% CI, 1.04–1.28); for patients with baseline mobitz type-1 second-degree atrioventricular block (OR, 3.13; 95% CI, 1.64–5.93), left anterior hemiblock (OR, 1.43; 95% CI, 1.09–1.86), bifascicular block (OR, 2.59; 95% CI, 1.52–4.42), right bundle-branch block (OR, 2.48; 95% CI, 2.17–2.83), and for periprocedural atriorventricular block (OR, 4.17; 95% CI, 2.69–6.46). The mechanically expandable valves had 1.44 (95% CI, 1.18–1.76), while self-expandable valves had 1.93 (95% CI, 1.42–2.63) fold higher odds of PPM requirement compared with self-expandable and balloon-expandable valves, respectively.

CONCLUSIONS: Male sex, baseline atrioventricular conduction delays, intraprocedural atrioventricular block, and use of mechanically expandable and self-expanding prosthesis served as positive predictors of PPM implantation in patients undergoing TAVR.

Key Words: aortic disease ■ aortic valve ■ aortic valve implantation ■ aortic valve stenosis ■ atrioventricular block ■ pacemaker ■ transcathether aortic valve replacement

As the rheumatic etiology of aortic stenosis (AS) has significantly waned over time, age-related AS remains the most common valvular disease in the developed world.[1] Valve replacement is the only definite and effective treatment to improve survival in these patients, however, a multitude of coexisting comorbidities, including but not limited to chronic cardiac or pulmonary diseases, operative risks, extremes of age and poor physical health serve as barriers to surgical aortic valve replacement (SAVR). Transcatheter aortic valve replacement (TAVR) has recently emerged as a reasonable alternative to rescue these high-risk patients.[2] The first TAVR was performed in 2002, in France, on a 57-year-old man in whom SAVR was

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CLINICAL PERSPECTIVE

What Is New?

- This meta-analysis comprising 78 studies (31261 patients) provides a comprehensive analysis of the predictors of pacemaker implantation in patients undergoing transcathether aortic valve replacement.
- Male sex, baseline atrioventricular conduction delays, and the use of mechanically expandable and self-expanding prosthesis are associated with a higher need for permanent pacemakers after transcatheter aortic valve replacement.

What Are the Clinical Implications?

- Timely identification of these high-risk patients can alleviate the risk of periprocedural atrioventricular block and associated complications such as syncope and sudden cardiac death.

Nonstandard Abbreviations and Acronyms

AR	aortic regurgitation
CVA	cerebrovascular accident
FU	follow up
HB	heart block
MACCE	major adverse cardiac or cerebrovascular event
MCRS	Medtronic Corevalve Revealing System
MR	mitral regurgitation
NOP LBBB	new onset persistent left bundle-branch block
OCS	Observational Cohort Study
PPM	permanent pacemaker
RCT	randomized controlled trial
SAVR	surgical atrial valve replacement
SEV	self-expandable valve
TAVR	transcatheter aortic valve replacement
VIV	valve-in-valve

contraindicated due to multiple comorbidities.[3] Almost 20 years later, the data indicates that not only is it superior to medical therapy in patients with severe AS, but is also non-inferior to SAVR, even in low-risk patients.[4–6]

However, like any other therapeutic intervention, the advent of TAVR has presented its own set of challenges urging the need for a favorable risk-benefit estimation. With the widespread availability and expanded indication of TAVR to a lower-risk healthy population, there are concerns about the rising trend of procedural complications associated with TAVR. A frequent issue encountered with this procedure is conduction defects requiring permanent pacemaker (PPM) implantation.[7,8] The bundle of His and the bundle branches run in the vicinity of where the prosthesis is being placed. These conduction abnormalities arise primarily due to the proximity of the aortic annulus to the atrioventricular conduction system that gets manipulated during the procedure.[7] Data suggests that the prevalence of conduction defects post-procedure also depends upon the type of valve implanted during the TAVR procedure.[8] The 2 most common prostheses used are balloon-expandable Edwards Sapien Valve (ESV) and self-expanding Medtronic Corevalve Revealing System (MCRS) with a 5%–12% incidence of PPM implantation post-procedure in the former and 24%–33% in the latter.[9] Due to the manipulation of the old valve, aortic annulus dilatation and subsequent implantation of a prosthetic valve, conduction defects are common. In our study, we intend to identify various cardiac and non-cardiac predictors that lead to PPM implantation following TAVR. We also aim to gauge the risk of conduction abnormalities based on the type of prosthesis and access site used in TAVR.

METHODS

Data was obtained from published articles on the topic. All data can be obtained from the references mentioned in the supplementary file. The consolidated extracted data is available on demand.

Search Strategy

PubMed, Embase, Ovid, and Cochrane databases were queried with various combinations of keywords and medical subject headings (MeSH) to identify studies of interest. There were no time filters or language restrictions placed. Backward snowballing by screening the references of relevant articles were also performed to retrieve unidentified articles that were missed on the primary search. The MeSH used included 2 subsets: one for TAVR using the keywords "percutaneous prosthetic valve," "transcatheter aortic valve replacement," "TAVR," "transcatheter aortic valve implantation," "TAVI," "percutaneous approach," "minimal invasive aortic valve replacement," "transapical aortic valve replacement," and the other for PPM and heart block including "LAFB," "LPFB," "LBBB," "pacemaker implantation," "heart block," "conduction abnormalities," and "conduction delays." The 2 subsets of MeSH were systematically combined using Boolean operators. The final results from all possible combinations were downloaded into an EndNote library. All randomized control trials (RCT) and

observational cohort studies (OCS) until April 2021, were screened for relevance. Any OCS or RCT that assessed the post-TAVR rate of atrioventricular conduction or cardiac rhythm abnormalities and subsequent PPM implantation during the same hospitalization or within 30-days of TAVR procedure were included. To avoid the inclusion of duplicate data, we only selected the most contemporary data when overlapping study populations (according to the period of recruitment and participating institutions) were reported; however, we cautiously included all patients reporting different predictors from studies of overlapping populations. To measure the impact of the procedure on PPM implantation, all patients with prophylactic implantation of PPM before the TAVR procedure were excluded from the analysis.

Data Extraction

Raw data about the events of PPM implantation in different predictor comparison groups were extracted for analysis by the first 9 authors independently. Detailed study- and patient-level baseline characteristics including the type of study design; recruitment period, region, and follow-up duration; sample size, number of post-TAVR PPM implantations, sex, age, procedural risk assessment (by logistic EuroSCORE [European System for Cardiac Operative Risk Evaluation] or STS-PROM [Society of Thoracic Surgeons Predicted Risk of Mortality] score), and baseline comorbidities were abstracted. Additionally, data related to the access site (transfemoral versus trans subclavian, transapical versus transvascular), type of prosthesis (MCRS versus ESV versus LOTUS), inclusion criteria, and definition of outcomes were obtained from individual studies (Table S1). Finally, the post-TAVR indications for PPM implantation in each article were also extracted. Based on previous reviews, the following proposed potential predictors were selected: age, sex, baseline conduction abnormalities, anatomical features, access route, and valve types. Case reports, review articles, conference papers, and articles with insufficient data or no control arms were excluded. Patients with prior PPM implantation unrelated to TAVR were also excluded from our analysis. All data was validated by the corresponding author; in case of missing data authors of the original article were contacted. The detailed search map is given in Data S1.

Statistical Analysis

The statistical analysis was performed using the DerSimonian and Laird (DL) and Mantel Haenszel (MH) methods on random- and fixed-effects models, respectively. The unadjusted odds ratio (OR) for dichotomous outcomes of RCTs and OCS were calculated. The "test for overall effect" was reported as a z value corroborating the inference from the 95% confidence interval. To avoid the influence of study design on pooled estimates, a stratified analysis based on the type of study (OCS versus RCT) was performed. A subgroup analysis based on the type of implanted valve (mechanically expandable versus self-expanding versus balloon-expandable), access route (transfemoral versus trans subclavian), and procedure type (transapical versus transvascular) was also performed. Sensitivity analysis after exclusion of small studies with fewer than 200 patients was done to determine the impact of sample size on pooled estimates. Descriptive characteristics for continuous data were reported as mean and SD, whereas categorical variables were presented as frequencies and percentages. Higgins I-squared (I^2) statistical model was used to determine heterogeneity in outcomes of the included studies. The observed heterogeneity was regarded statistically significant if the I^2 statistics P value was <0.05. Publication bias was illustrated graphically using a funnel plot. The methodological quality assessment of the included RCTs was performed using the risk of bias-2 (RoB-2) tool and the Oxford quality scoring system (Jadad score). The Newcastle-Ottawa Scale was used for assessing non-randomized studies. The probability value of two-sided $P<0.05$ was considered statistically significant. All statistical analysis was performed using the Cochrane Review Manager (RevMan) version 5.3 and STATA software (version 16.0, STATA Corp., College Station, Texas).

Quality of the Included Studies

The overall quality of the included studies was high. The risk of bias-2 (RoB-2) tool used 5 different bias assessments: selection, detection, performance, attrition, and reporting. All 3 of the included RCTs in our meta-analysis were open-label, posing some theoretical risk to "allocation concealment," however, the overall risk of selection bias was reduced due to adequate randomization. Because most RCTs used an "intention to treat model" or had a lower loss at follow-up, the risk of attrition bias was minimal. Similarly, the risk of reporting, detection and performance bias was lower due to appropriate reporting and adequate blinding of outcome assessors, respectively. The RoB-2 plots are given in Figure 1. [10–12] The methodological quality of included RCTs was also high on the Jadad scale with a score >3 (Table S2). Observational studies were mostly matched in terms of clinical profile and demographics to curtail selection bias. The Newcastle-Ottawa Scale for assessing nonrandomized studies indicated the inclusion of high-quality observational studies (score >7) (Table S3).

RESULTS

Search Results

The initial search revealed 4118 articles. After the removal of irrelevant (1561) and duplicate (2109) items, 448 studies were selected for full-text review. Of these, 370 articles were excluded based on different reasons including: review articles (35), meta-analyses (41), insufficient data for analysis (162), duplicate population studies (47), no risk factors data (80), and other reasons (5). A total of 78 articles (3 RCTs, 75 observational studies) qualified for quantitative analysis. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram is shown in Figure 2 and the PRISMA checklist is given in Data S2.

Study Characteristics

A total of 31 261 patients undergoing TAVR from 78 studies were included, of these 6212 (19.8%) received PPM, while 25 049 (80.2%) did not require a PPM.[7,9–85] Most of the studies were from the United States and

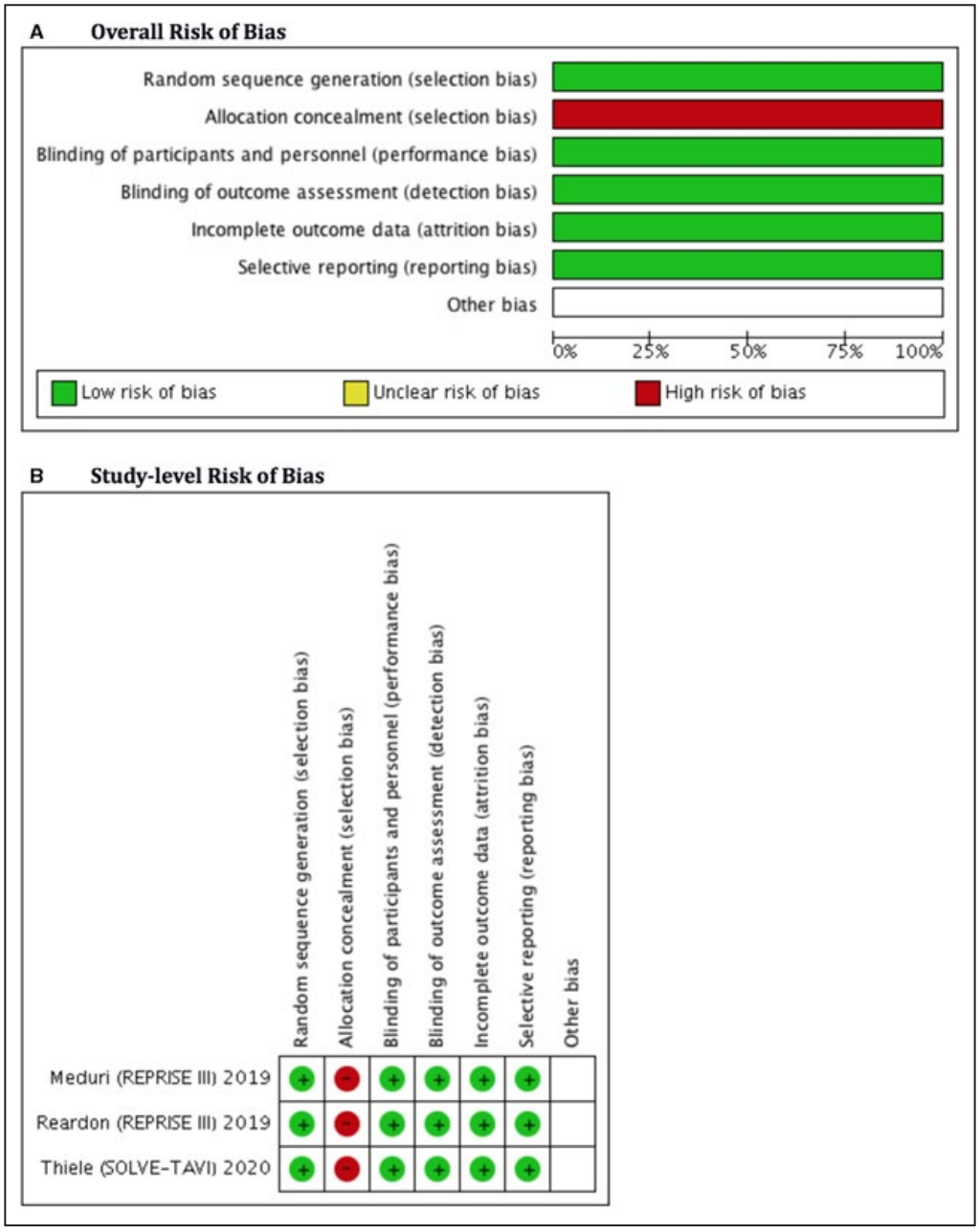

Figure 1. Overall (A) and study-level (B) methodological bias assessment of the included randomized clinical trials with the Cochrane risk of bias tool-2.

Europe. Two of the RCTs were multi-continental, recruiting patients from the US, Australia, Germany, and Brazil. All included studies were published between 2009 and 2020 with an average recruitment period of approximately 4 years. The mean age of the included population was 81±8 years, comprising on average 46% male patients. The proportion of PPM implantation across different baseline comorbidities was comparable between the 2 groups. The detailed baseline characteristics are given in Tables S4 and S5, while the procedure characteristics of TAVR are given in Table S6. The summary is illustrated in Figure 1. The overall study-level rate of post-TAVR PPM ranged from 0.16% to 51.1%. The need for PPM implantation across different baseline comorbidities was variable as shown in Table S7 and Figure 3. The etiology for PPM implantation was only mentioned in 19.9% of patients (n=1238/6212). Post-TAVR complete atrioventricular block was the most commonly observed indication for PPM implantation; other causes included bradycardia,

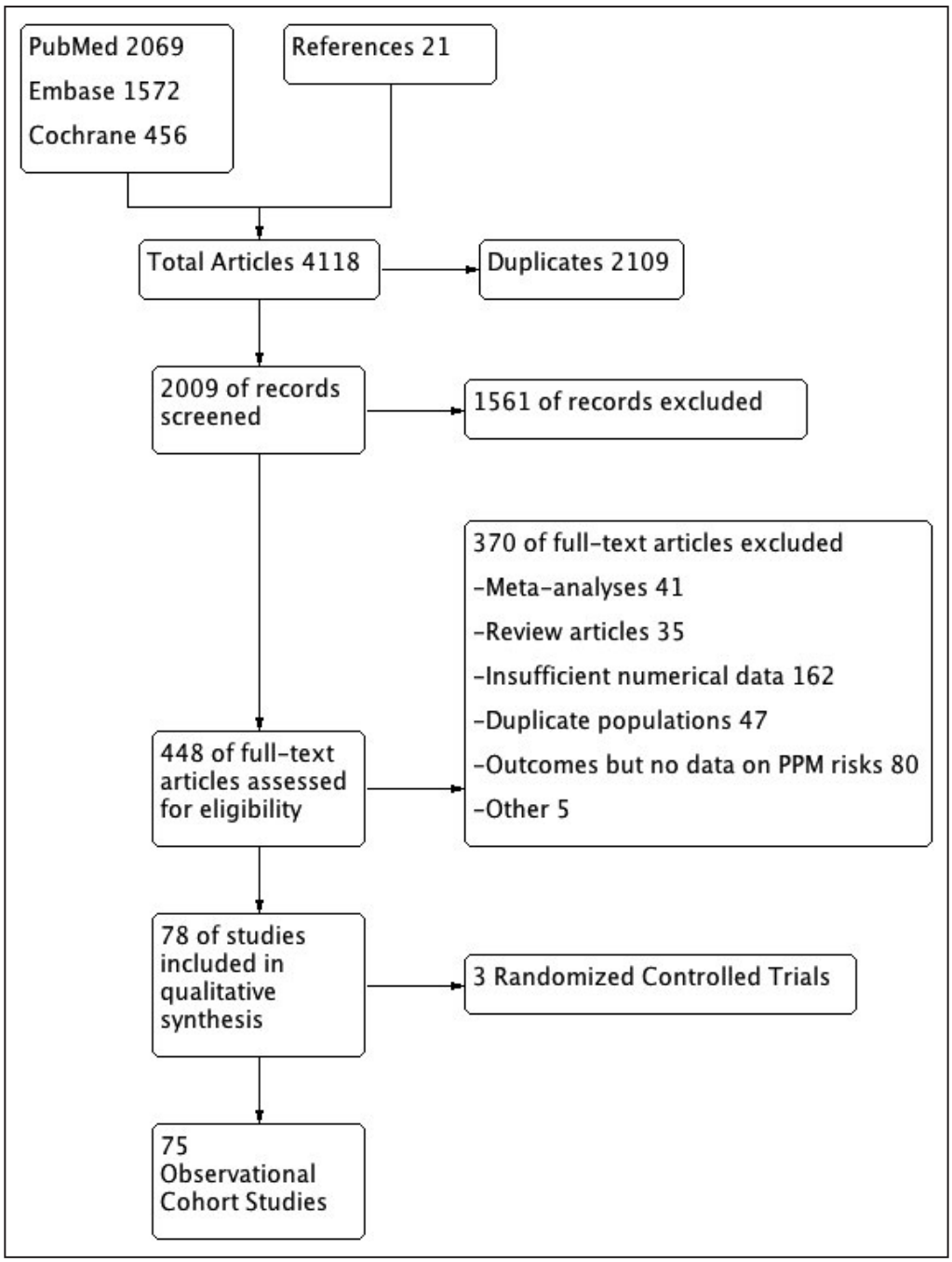

Figure 2. PRISMA flow diagram showing the included studies.

new-onset left bundle-branch block (LBBB), and trifascicular block (Table). Patients with a prior history of PPM before the index TAVR procedure were mostly excluded from the analysis of their respective study. Two studies (De-Carlo and Hamandi et al) had prophylactic PPM implantation before the TAVR procedure in 158 patients; these patients were excluded from the analysis. Most PPM implantations were performed during the same hospitalization or within 30-days of the TAVR procedure. Most studies employed a transfemoral approach for TAVR, while 31 studies used transapical access in about 32% of its population. Mechanical (LOTUS) self-expanding (MCRS and Evolut R) and balloon-expandable (ESV) aortic prosthesis were the major valves used in the included studies. MCRS was used in 55, while ESV and Lotus were used in 46 and 12 studies, respectively. The mean log EuroSCORE for patients among the included studies was around 18.9±10 and the mean Society of Thoracic Surgeons score was found to be 5.85. The overall follow-up duration ranged from 2 to 36 months, with a mean follow-up of 8.02 months (Tables S4 through S6).

Pooled Analysis of Overall Studies

Twenty-nine different potential predictors for the PPM implantation were evaluated. The number of patients having post-TAVR PPM implantation (n=6212) from all studies contributed to the pooled OR calculation for each predictor. On a random effects model of binary data, the aggregate odds for post-TAVR PPM implantation irrespective of the type of valve was higher in the male population compared with the female patients (OR, 1.16; 95% CI, 1.04–1.28). The baseline electrocardiographic conduction abnormalities, mobitz type-1 second-degree heart block (OR, 3.13; 95% CI, 1.64–5.93), mobitz type-2 second-degree heart block (OR, 3.89; 95% CI, 2.54–5.95), left anterior fascicular hemiblock (LAFB; OR, 1.43; 95% CI, 1.09–1.86), bifascicular block (OR, 2.59; 95% CI, 1.52–4.42), right bundle-branch block (RBBB; OR, 2.48; 95% CI, 2.17–2.83), and intraprocedural atrioventricular block (OR, 4.17; 95% CI, 2.69–6.46) were associated with significantly higher odds of PPM implantation. The baseline predictor variables that were not statistically significantly associated with PPM implantation were age (OR, 1.19; 95% CI, 0.95–1.49), first-degree heart block (OR, 1.09; 95% CI, 0.05–2.37), atrial fibrillation (AF; OR, 1.05; 95% CI, 0.93–1.20), left posterior fascicular hemiblock (LPFB; OR, 3.34; 95% CI, 1.1–11.13), left bundle branch block (LBBB; OR, 1.06; 95% CI, 0.87–1.29), severe pulmonary hypertension (OR, 1.78; 95% CI, 0.82–3.89), moderate/severe mitral regurgitation (MR; OR, 3.3; 95% CI, 0.59–18.32), unspecified heart failure; OR, 1.06; 95% CI, 0.72–1.55), and heart failure with preserved ejection fraction (OR, 1.01; 95% CI, 0.51–2.01). Of note, patients receiving 29 mm of prosthesis had significantly higher odds of PPM implantation compared with 23 mm prosthesis (OR, 1.49; 95% CI, 1.06–2.08). However, there appeared to be a statistically nonsignificant difference in the odds of PPM implantation between 23 mm versus 26 mm prosthesis (OR, 1.12; 95% CI, 0.62–2.03) and for patients with intraventricular septum size >11 mm (OR, 1.71; 95% CI, 0.17–17.41) and >22 mm (OR, 1.65; 95% CI, 0.55–4.93). The detailed valvular and anatomical variant estimates for PPM need are given Table S8.

Analysis of all predictors on a fixed-effects model mirrored the findings of the random-effects model with 2 exceptions; first-degree heart block (OR, 0.35; 95% CI, 0.30–0.40) was found to be associated with a significantly lower risk, while LBBB (OR, 1.29; 95% CI, 1.14–1.46) had significantly higher odds of need for PPM. The detailed forest plots for both random and fixed effects are given in Figures S1 through S16. The heterogeneity in the outcomes of these studies was I^2=0%, except for the studies comparing the RBBB and male populations, which showed significant heterogeneity (I^2=52% and I^2=74%, both P=<0.05), respectively (Figure 4). There was no significant difference in the odds of mortality in patients receiving PPM compared with those who did not receive PPM at 30 days and 1 year in 12 studies that included survival data (Figure 5).

On pooled analysis of continuous data, membranous septal length (MSL) was inversely, while the depth of prosthesis was directly, associated with the risk of PPM implantation. The mean MSL was 5.6 mm for patients requiring PPM implantation compared with 6.8 mm for those who did not require PPM, while the mean depth for prosthesis implantation for the former group was 6.86 mm compared with 5.34 mm in patients who did not require PPM (Figures S17 and S18).

Subgroup and Sensitivity Analyses

Overall, a head-to-head comparison based on the type of prosthesis favored the balloon-expandable valves irrespective of the prevalence of different predictors. On a random-effects model, the mechanically expandable valve (OR, 1.44; 95% CI, 1.18–1.76) and self-expanding valves (OR, 1.93; 95% CI, 1.42–2.63) had higher PPM requirements compared with the self-expanding and balloon-expandable valves, respectively. Based on a breakdown data of 16 studies, MCRS implantation was associated with significantly higher odds of PPM implantation compared with ESV (OR, 2.48; 95% CI, 1.91–3.22). By contrast, the LOTUS valve implantation was associated with higher odds (OR, 1.61; 95% CI, 1.23–2.1) of PPM implantation compared with MCRS. Compared with EVOLUT-R, the risk of PPM implantation was not significantly different in LOTUS and ESV (Table S9). There was no significant difference in the odds of PPM implantation

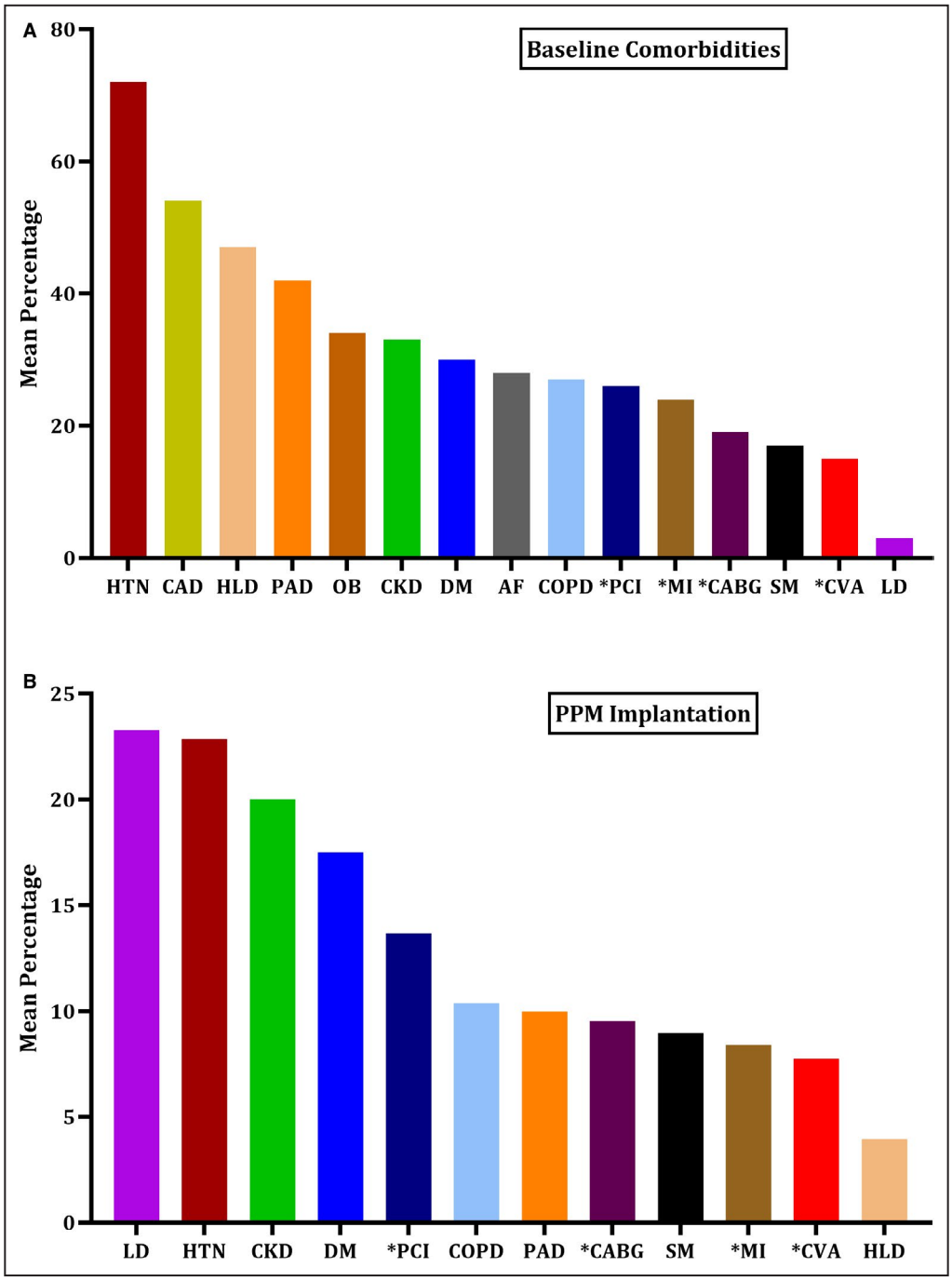

Figure 3. Percentages of patients with (A) different comorbidities and (B) those with and without permanent pacemaker (PPM) implantation across different baseline comorbidities.
A, Mean percentage of comorbidities. **B**, Proportion of comorbidities in PPM vs no-PPM groups. ACS indicates acute coronary syndrome; AF; atrial fibrillation; OB, obesity; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accidents; DM, diabetes; HLD, hyperlipidemia; HTN, hypertension; LD, Liver Disease; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SM, smoking. Asterisk denotes "prior history of".

in patients undergoing a transarterial versus transapical approach (OR 1.02; 95% CI, 0.1–10.1), transfemoral versus subclavian approach (OR 1.13; 95% CI, 0.6–2.1). These findings remained invariant on a fixed-effects model. The heterogeneity among these studies ranged from I^2=0% to I^2=54% (Figure 6, Figures S14 through S16).

Overall, a subgroup analysis based on the type of valve used, study design and access site mirrored the

Table 1. Periprocedural Causes of PPM Implantation in Patients Undergoing TAVR for Severe Aortic Stenosis

Periprocedural Events Leading to PPM in TAVR	No. of Patients	Percentage in the Known Causes
Third degree heart block	941	76%
LBBB	106	8.5%
Bradycardia	60	4.84%
Second degree AV block	45	3.63%
Second degree atrioventricular block associated with LBBB	36	2.9%
First degree atrioventricular block	35	2.82%
Tachy-Brady syndrome	34	2.58%
Symptomatic pause	5	0.40%
Sick sinus syndrome	9	0.72%
Alternating RBBB and LBBB	4	0.32%
Afib with slow response	4	0.32%
Afib with complete atrioventricular block	4	0.32%
Total	1238	100%

All percentages are calculated among the known causes (1238). The reason for PPM implantation was not reported in 4924 cases. Afib indicates atrial fibrillation; LBBB, left bundle-branch block; PPM, permanent pacemaker; RBBB, right bundle-branch block; TAVR, transcatheter aortic valve replacement.

overall findings with few exceptions. In contrast to the pooled analysis, the summary estimates suggested higher odds of PPM implantation in patients with first-degree heart block in MCRS (OR 1.95; 95% CI, 1.18–3.24). In concordance to the pooled analysis. Male sex (OR 1.33; 95% CI, 1.02–1.73), LAFB (OR 1.94, 95% CI, 1.11–3.38), intraprocedural atrioventricular block (OR 8.04; 95% CI, 3.53–18.29), and RBBB (OR 4.03; 95% CI, 2.47–6.56) remained the positive predictors of PPM implantation in a subset of patient undergoing MCRS-only. For ESV and Evolut-R valves, none of the previously mentioned predictors (except the intraprocedural atrioventricular block) appeared to have a significant influence on the need for PPM implantation. For individual valve types, we were able to assess only 5 to 10 predictors of PPM implantation (Table S9, Figures S19 through S21). More large scale studies are needed to determine the impact of other risk factors for PPM implantation across different valve types.

A sensitivity analysis on the "leave-one-out" strategy showed that the significantly lower odds of PPM implantation in patients with first-degree heart block on a fixed-effects model was driven by one study (Doshi et al) (Figure S22). There was no significant influence of any individual study on the pooled odds of PPM implantation across all other predictors (Figure S23 and S24). On a sensitivity analysis restricted to large studies of 200 patients or more, results remained consistent with the pooled results of the random-effects model. Moreover, the summary estimates of OCS-only (after exclusion of RCTs) and a subgroup analysis based on study design (OCS versus RCTs) also mirrored the results of the pooled analysis that included both OCS and RCT data (Table S10). The central illustration of all predictors is given in Figure 7 and the detailed study level PPM implantation rates for each predictor are given in Table S11.

Publication Bias

On the visual assessment of the funnel plots, no significant publication bias was detected for most of the predictors across all studies. Using the standard error, the vertical axis of the plot estimated the sample size of the study. Studies with a larger sample size were plotted on top and those with smaller populations appeared at the bottom of the plot. The horizontal spread indicated the individual effect size reflecting the overall power of the included studies. Our funnel plots were symmetrical, and most studies with low precision were spread evenly on both sides of the average line (Figure S25).

DISCUSSION

The present meta-analysis represents the most contemporary and largest evidence on the predictors of PPM implantation in patients with severe AS undergoing TAVR. Our findings revealed that male sex, pre-TAVR baseline atrioventricular conduction abnormalities (including mobitz type-1 second-degree heart block, LAFB, RBBB), and intraprocedural atrioventricular block were associated with higher odds of PPM implantation, irrespective of the type of prosthesis or choice of the access site. A stratified analysis based on the prosthesis design showed a 2.4-fold increased risk of PPM implantation with MCRS (self-expanding) compared with ESV (balloon-expandable), and 1.61 times higher odds of PPM-need in LOTUS (mechanically expandable) compared with MCRS. The overall odds of PPM implantation remained identical in patients aged >80 years versus the younger population and those having first-degree heart block, AF, prolonged PR-interval, LPFB and LBBB, when compared with their corresponding control groups who had an absence of these rhythm abnormalities. The type of approach (transapical versus transvascular) or choice of access site (transfemoral versus trans-subclavian) also had no impact on the risk of PPM implantation. Among the anatomical and valvular variants, the membranous septal length (MSL) was inversely, while the depth of prosthesis implantation was directly associated with the risk of PPM implantation. Larger devices (29 mm) had a higher risk of PPM implantation, while there was no impact of interventricular septum thickness, mitral regurgitation, or pulmonary hypertension on the need

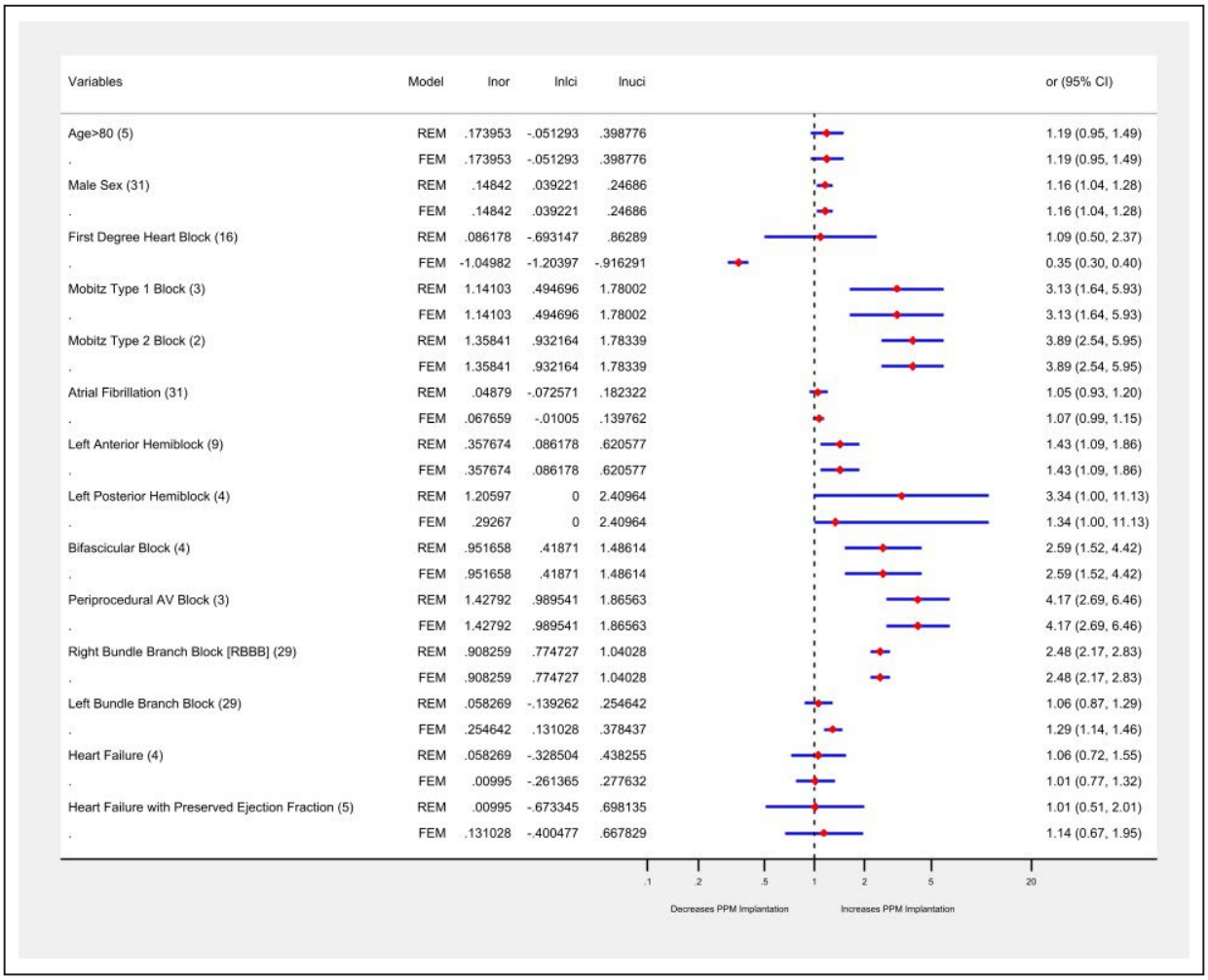

Figure 4. Forest plot showing pooled estimates of demographic and electrocardiographic factors as potential predictors of permanent pacemaker (PPM) implantation in patients undergoing TAVR using random effects model (REM) and fixed effects model (FEM).

The dotted black line indicates null line (odds ratio of 1), to the right of null line indicates increased odds of PPM implantation. For each predictor the number of studies is in the parenthesis, the blue line indicates confidence interval, and the diamond red box signifies the point estimate. Lnor indicates natural log of odds ratio; lnlci, natural log of lower confidence interval; lnuci, natural log of uppper confidence interval.

for PPM during TAVR. On subgroup analysis, only the MCRS data followed the results of the pooled analysis, indicating that the overall findings were mostly driven by the data obtained from patients receiving self-expanding valves. The major post-procedural etiology for PPM implantation was a periprocedural occurrence of high degree heart block, new-onset LBBB, or persistent bradycardia.

It is imperative to identify patients at an increased risk of PPM implantation before a TAVR procedure, as timely detection of high-risk patients can potentially prevent the occurrence of atrioventricular block and its associated complications (including syncope and sudden cardiac death). Also, patients with post-TAVR atrioventricular nodal abnormalities are prone to prolonged hospitalization, putting a high financial burden on the healthcare budget.[86] PPM predictors in this context can help in the effective allocation of limited resources. With all its benefits, PPM placement comes at the cost of loss of atrioventricular synchrony, lack of physiological heart rate control, and increased risk of bleeding and pocket infection.[87,88] Early detection of patients at high risk of PPM implantation and identification of prespecified predictors, therefore provides an opportunity to mitigate these risks and to favorably lower the harm-benefit ratio.

Among the measured predictors for PPM implantation, the demographic risk factors including age and sex are of paramount importance. Current evidence on sex-related differences in post-TAVR complications and the need for PPM is conflicting in recently published studies.[89,90]Our large-scale analysis shows a

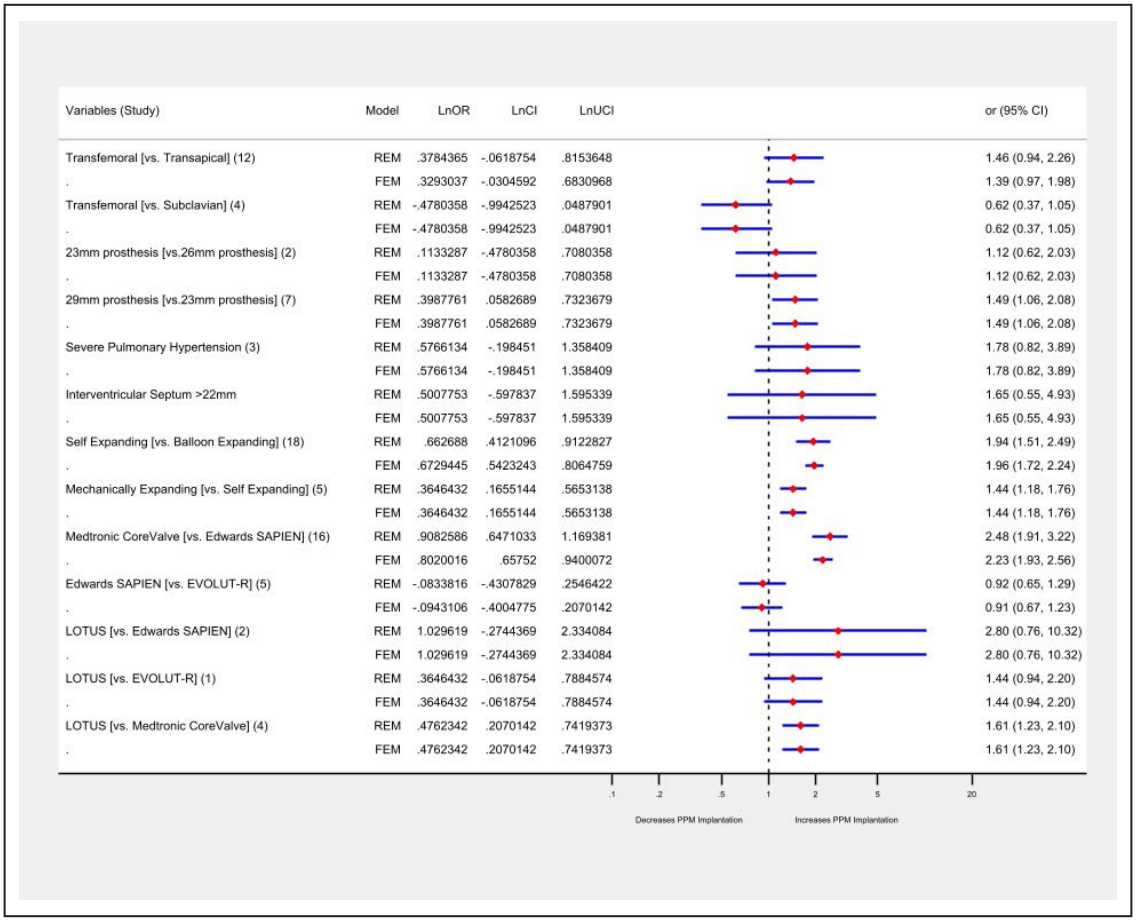

Figure 5. Forest plot showing pooled estimates of procedural factors as potential predictors of permanent pacemaker (PPM) implantation in patients undergoing transcatheter aortic valve replacement (TAVR) using random effects model (REM) and fixed effects model (FEM).

16% higher rate of PPM implantation in men. This can partly be explained by the relatively larger-sized bioprosthesis (>25 mm) they receive, but mostly because of the higher prevalence of baseline comorbidities, putting men at a greater risk of procedural complications.[63,90] Additionally, our results also revealed a numerically higher rate of PPM use (by 19%) in a population age >80 years, however, the difference did not reach statistical significance. These findings contrast the results of Ramkumar et al. and Ledwoch et al. studies, which denoted a significantly higher risk of post-TAVR PPM placement in octogenarians by 30% and 35%, respectively.[37,44] Amongst the cardiac predictors, the presence of a LAFB, bi-fascicular block and second degree atrioventricular block are known to be associated with higher chances of receiving a PPM after TAVR.[7–9] Our study echoes the same trend and expands these findings by demonstrating a 1.3-, 2.1-, and 3.1-fold increase in the odds of the need for PPM implantation in LAFB, bi-fascicular block and second degree atrioventricular block, respectively.[9] Regarding the baseline first-degree atrioventricular block, Dolci et al and Naveh et al showed an increased incidence of PPM placement at 1 year of TAVR.[46,91] By contrast, we believe that a first-degree atrioventricular block is a mere delay of atrioventricular conduction rather than a true block and that is why our study demonstrated no impact of first-degree heart block on the need for PPM implantation.

Studies have shown a higher incidence of post-TAVR atrioventricular blocks in patients with baseline conduction blocks, due to the manipulation of an already diseased conduction system.[37,44,46,61,73,92,93] Pre-procedure LBBB and RBBB resulted in up to 1.5 times greater risk of PPM implantation after TAVR.[92,93] In our study, RBBB conferred a 2.48 times greater risk of PPM implantation, much higher than the expected rise seen in previous studies. Intriguingly, baseline LBBB on our analysis did not increase the peri-procedural odds of atrioventricular block or the need for PPM implantation on a random-effects model. These effects were consistent across the different types of prosthesis and

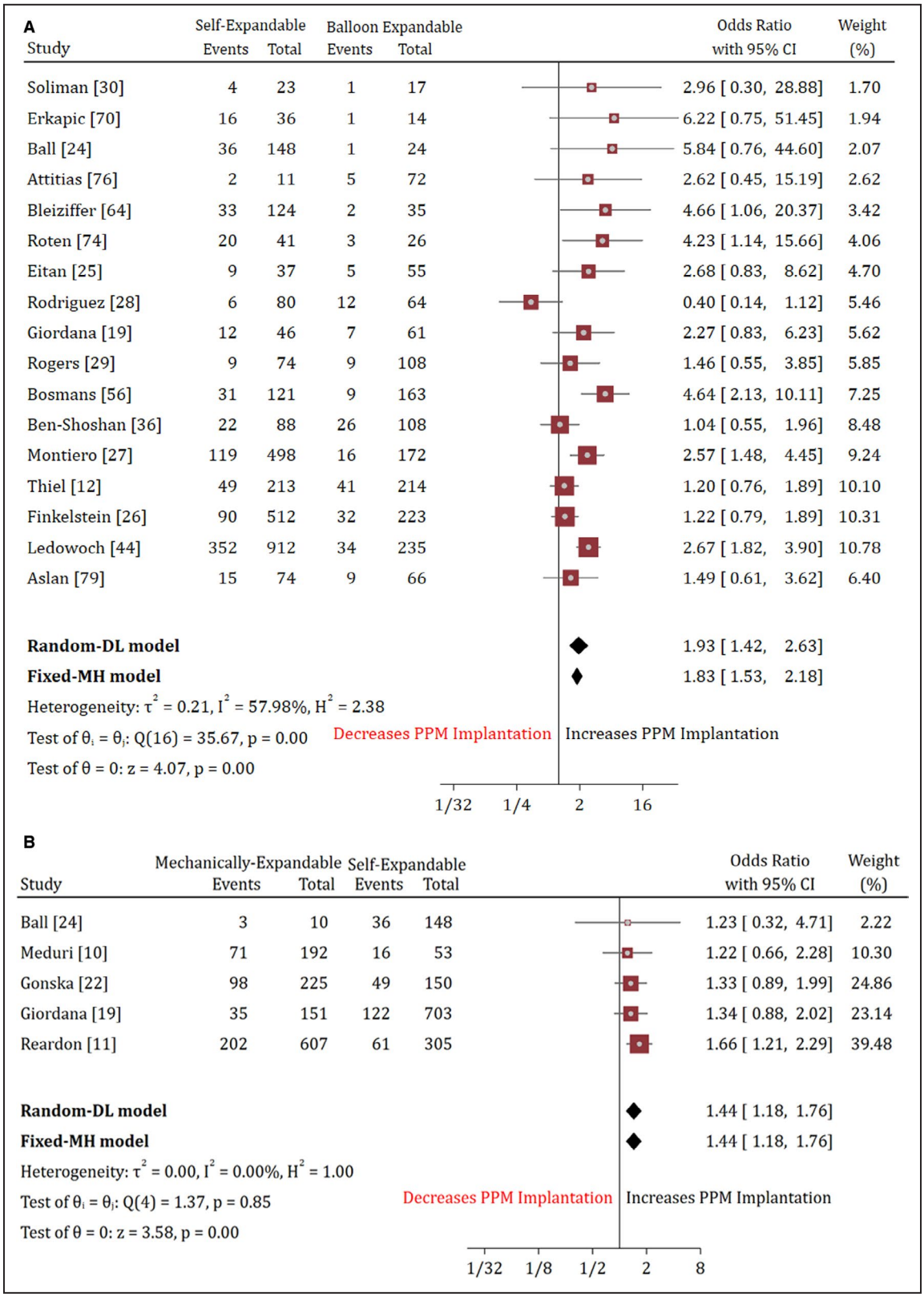

Figure 6. Forest plot showing the pooled estimate comparison of (A) self expanding vs balloon expandable and (B) mechanically expandable vs self-expanding.
DL indicates DerSimonian and Laird; MH, Mantel-Haenszel; PPM, permanent pacemaker.

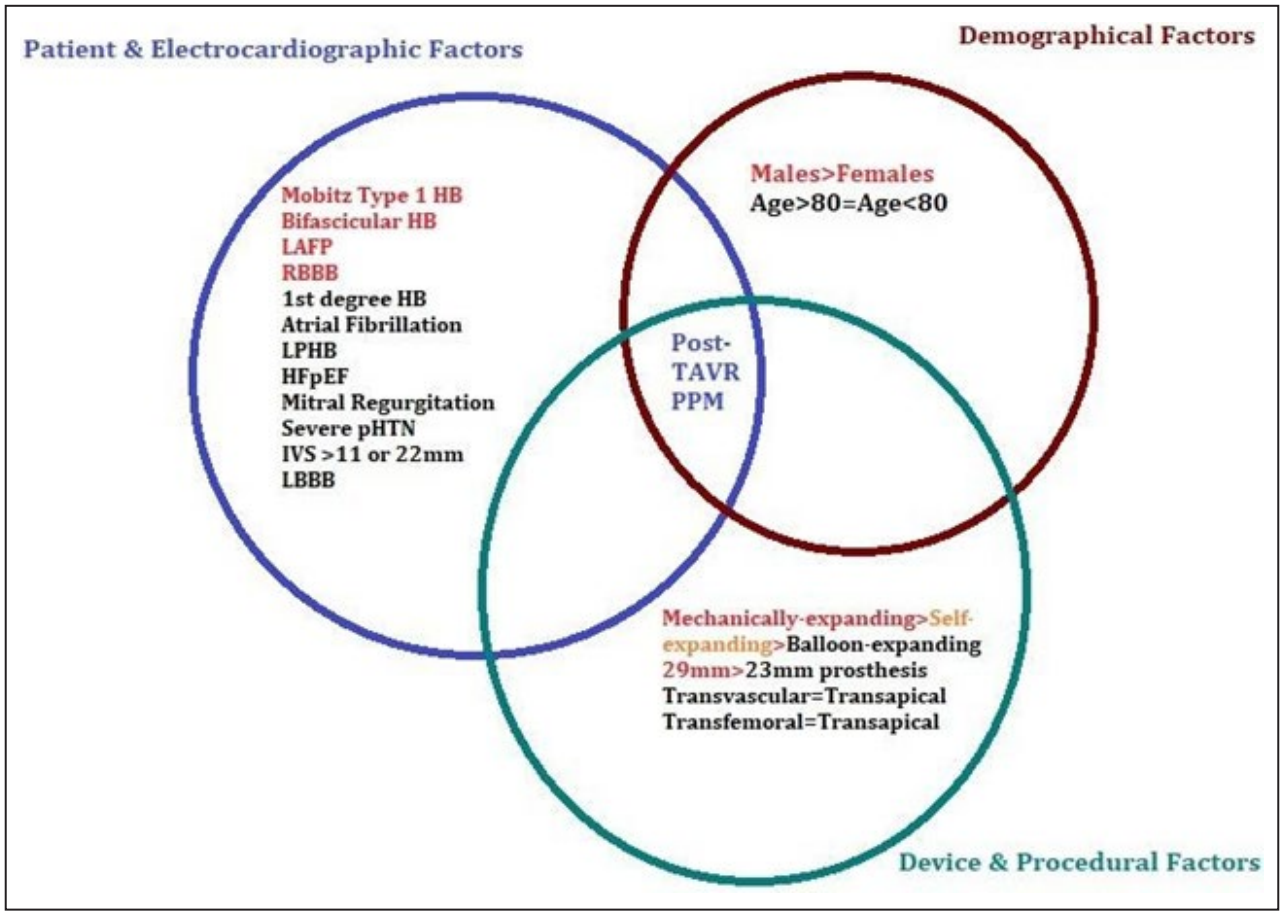

Figure 7. **Factors increasing the risk of PPM implantation post-TAVR (red text indicates a higher risk).**

access sites used for the TAVR procedure. When comparing the risk of atrial arrhythmias induced conduction abnormalities, we found that AF had no impact on the need for PPM implantation after TAVR. These findings were in line with the previous literature that also demonstrated an identical rate of need for PPM.[94] While a subset of the PARTNER registry showed that patients with sinus rhythm before TAVR and AF at discharge were twice more likely to get a PPM, patients with chronic AF had <6% risk of PPM, not significantly different from patients having no-AF at baseline.[94]

On review, we found 40 previous meta-analyses discussing the risk factors of PPM implantation, however in light of the current evidence the applicability of those studies is limited.[92,95–132] Most of these meta-analyses included a smaller number of previously published studies ranging from 4 to 41 articles, missing a large amount of contemporary data. The selection criteria and measured predictors were limited with respect to conduction abnormalities evaluated, indications for TAVR, and in some incidences inclusive of SAVR patients. More importantly, these studies had conflicting results. By contrast, our meta-analysis is the largest study (78 studies), including all patients who underwent TAVR for symptomatic AS (irrespective of the etiology), a wider range of demographics predictors, conduction abnormalities and procedural characteristics (29 predictors). Our study also provides a subgroup analysis on the type of valve and sensitivity analysis based on the sample size and study design. The detailed study-level characteristics and differences of our study from previous meta-analyses are given in Table S12.

Previous small-scale studies have also shown that atrioventricular conduction disturbances and a subsequent requirement for PPM were more common after the implantation of non-balloon expandable valves.[111,133] Our results validated these findings by demonstrating a 1.93 and 2.8 times higher rate of PPM implantation in the self-expanding and mechanically expandable prosthesis compared with the balloon-expandable valves. MCRS and LOTUS, being a self-expanding and mechanically expandable valve increases the risk of complete heart block due to deeper implantation into the aortic annulus, tissue edema, and sustained pressure on the conduction pathway (atrioventricular

node and left bundle branches).[73] These effects might be delayed in the balloon-expandable valves (ESV) due to the intermittent nature of expansion and lower risk of tissue impingement. Although relatively lower, the newer generation balloon-expandable prosthesis is not devoid of the risk of PPM implantation. A study by Bisson and colleagues noted that in an effort to decrease a paravalvular leak, the newer ESV comes with an outer skirt, increasing the odds of PPM implantation.[134] In contrast to the studies by Puls et al and Rouge et al that showed a higher prevalence of PPM implantation in transfemoral approach compared with trans subclavian access, we found no impact of the choice of the TAVR access site (transapical versus transvascular) and (transfemoral versus trans subclavian) on the need for PPM implantation.[38,135] To summarize, men, patients with baseline conduction abnormalities and those receiving the self-expanding or mechanically expandable prosthesis are at higher risk of PPM implantation after TAVR.

Limitations

Our study is constrained by the limitations of the included studies. A multivariate logistic regression model is required to control for potential confounders and to obtain an independent impact of the predictor. Patient-level data were missing to determine the adjusted odds of PPM predictors. For the same reason, we could not assess the impact of the procedure technique and could not account for the differential use of medications or other causes of atrioventricular conduction abnormalities. The impact of unmeasured confounding factors and operators' skills could not be measured. Although we selected a wide range of potential, previously proven predictors, the available data for some comparisons were sparse. Due to the lack of extended follow-up data the long-term effectiveness of PPM could not be evaluated. It is also important to note that the reasons for PPM implantation were variable in included studies, hence PPM implantation in our analysis should not be interpreted as a surrogate marker of atrioventricular conduction disturbances. The need for PPM in post-TAVR patients can be influenced by several economic and logistic factors out of the scope of the current study.

CONCLUSIONS

Patients with baseline conduction abnormalities, men, and those receiving mechanical- or self-expanding larger-sized prostheses for transcatheter aortic valve replacement are at an increased risk of pacemaker implantation. Given the clinical and economic impact of TAVR, interventionists should cautiously risk-stratify and identify patients at a high risk of the need for PPM.

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Supplementary Material

Data S1
Tables S1–S12
Figures S1–S25
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Supplemental Material

Data S1.

A. SEARCH STRATEGY and MAP:

(((((((((per-cutaneous aortic valve implantation AND cardiac pacemaker)) OR (per-cutaneous aortic valve implantation AND artificial pacemaker)) OR (per-cutaneous aortic valve implantation AND pacer)) OR (per-cutaneous aortic valve implantation AND pacemaker))) OR (((((g transcatheter aortic valve implantation AND cardiac pacemaker)) OR (g transcatheter aortic valve implantation AND artificial pacemaker)) OR (transcatheter aortic valve implantation AND pacer)) OR (g transcatheter aortic valve implantation AND pacemaker))) OR (((((tavr AND cardiac pacemaker)) OR (tavr AND artificial pacemaker)) OR (tavr AND pacer)) OR (tavr AND pacemaker)))) OR (((((((per-cutaneous aortic valve replacement AND cardiac pacemaker)) OR (per-cutaneous aortic valve replacement AND artificial pacemaker)) OR (per-cutaneous aortic valve replacement AND pacer)) OR (per-cutaneous aortic valve replacement AND pacemaker))) OR (((((transcatheter aortic valve replacement AND cardiac pacemaker)) OR (transcatheter aortic valve replacement AND artificial pacemaker)) OR (transcatheter aortic valve replacement AND pacer)) OR (transcatheter aortic valve replacement AND pacemaker))) OR (((((tavr AND cardiac pacemaker)) OR (tavr AND artificial pacemaker)) OR (tavr AND pacer)) OR (tavr AND pacemaker)))

PRISMA 2020 Checklist

Data S2.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 3, Supplementary page 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5,7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 4-5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 4-5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 4-5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 4,6,7

	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 5
Study characteristics	17	Cite each included study and present its characteristics.	Page 5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 5, Figure 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	S.Figure 1-21
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	S.Table 4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 6-7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 6-7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	S.Table 11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	S.Figure 25
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 6-7
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 7,8,9
	23b	Discuss any limitations of the evidence included in the review.	Page 9
	23c	Discuss any limitations of the review processes used.	Page 10
	23d	Discuss implications of the results for practice, policy, and future research.	Page 9
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	NA
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 1
Competing interests	26	Declare any competing interests of review authors.	Page 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 1

PRISMA 2020 Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

Table S1: Inclusion criteria of the included RCTs

Author/Study/Year/Ref	Inclusion Criteria	MACCE Components
Meduri (REPRISE III) 2019	Symptomatic Aortic Stenosis and STS predicted risk of Mortality >8%.	Cardiovascular Mortality, MI, Stroke, Conduction abnormality requiring new-pacemaker placement, Paravalvular leakage.
Thiele (SOLVE-TAVI) 2020	Symptomatic Aortic Stenosis, Age >75 years and high predicted surgical risk of Mortality defined as Logistic Euroscore >20% or STS score >10%.	Cardiovascular Mortality, MI, Stroke, Conduction abnormality requiring new-pacemaker placement, Paravalvular leakage.
Reardon (REPRISE III) 2019	Severe Native Aortic stenosis, and STS predicted risk of Mortality >8%	Cardiovascular Mortality, MI, Stroke, Conduction abnormality requiring new-pacemaker placement, Paravalvular leakage.

Table S2: Randomized studies quality assessment using the Oxford Quality Scoring System. (Jadad score ≥ 3 considered high quality)

Author/Study/Year/Ref	Rating Scale List		Jadad Score
Meduri (REPRISE III) 2019	Was the study described as random	Yes	3
	Was the randomization described and appropriate	Yes	
	Was the study described as double-blind	No	
	Was the method of double-blinding appropriate	No	
	Was there a description of dropouts and withdrawals	Yes	
Thiele (SOLVE-TAVI) 2020	Was the study described as random	Yes	3
	Was the randomization described and appropriate	Yes	
	Was the study described as double-blind	No	
	Was the method of double-blinding appropriate	No	
	Was there a description of dropouts and withdrawals	Yes	
Reardon (REPRISE III) 2019	Was the study described as random	Yes	3
	Was the randomization described and appropriate	Yes	
	Was the study described as double-blind	No	
	Was the method of double-blinding appropriate	No	
	Was there a description of dropouts and withdrawals	Yes	

Table S3: Quality Assessment of the included observational studies

Author/Study	Year	Representativeness of the exposed	Selection of the non exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Comparability of the cohort	Assessment of outcome	Enough follow-up duration	Adequate follow-up	Total score
Hamandi	2020	*	*	*	*	*	*	*	*	8
Kochman	2020	*	*	*	*	*	*	*	*	8
Sharma	2020	*	*	*	*	**	*	*	*	9
Ay	2019	*	*	*	*	**	*	*	*	9
Giordano	2019	*	*	*	*	**	*	*	*	9
Kaneko	2019	*	*	*	*	**	*	*	*	9
Karacop	2019	*	*	*	*	**	*	*	*	9
Ball	2018	*	*	*	*	**	*	*	*	9
Bhardwaj	2018	*	*	*	*	**	*	*	*	9
Doshi	2018	*	*	*	*	*	*	*	*	8
Eitan	2018	*	*	*	*	*	*	*	*	8
Finkelstein	2018	*	*	*	*	*	*	*	*	8
Gonska	2018	*	*	*	*	**	*	*	*	9
Yousif	2018	*	*	*	*	**	*	*	*	9
Enriquez-Rodriguez	2017	*	*	*	*	*	*	*	*	8
Monteiro	2017	*	*	*	*	**	*	*	*	9
Rogers	2017	*	*	*	*	*	*	*	*	8
Soliman	2017	*	*	*	*	**	*	*	*	9
Van Mourik	2017	*	*	*	*	*	*	*	*	8
Ben-Shoshan	2016	*	*	*	*	*	*	*	*	8
Kahraman	2016	*	*	*	*	**	*	*	*	9
Kley	2016	*	*	*	*	*	*	*	*	8
Ramkumar	2016	*	*	*	*	*	*	*	*	8
Sawaya	2016	*	*	*	*	*	*	*	*	8
Zaman	2016	*	*	*	*	**	*	*	*	9
Gauthier	2015	*	*	*	*	**	*	*	*	9
Rouge	2015	*	*	*	*	*	*	*	*	8
Boerlage-Van Dijk	2014	*	*	*	*	**	*	*	*	9
Simms	2013	*	*	*	*	**	*	*	*	9
Akin	2012	*	*	*	*	**	*	*	*	9
Bagur	2012	*	*	*	*	**	*	*	*	9
De Carlo	2012	*	*	*	*	**	*	*	*	9
Gilard	2012	*	*	*	*	*	*	*	*	8
Ledwoch	2012	*	*	*	*	*	*	*	*	8
Mouillet	2012	*	*	*	*	**	*	*	*	9
Muniz-Garcia	2012	*	*	*	*	**	*	*	*	9
Nuis	2012	*	*	*	*	**	*	*	*	9
Pulse	2012	*	*	*	*	*	*	*	*	8
Saia	2012	*	*	*	*	**	*	*	*	9
Salinas	2012	*	*	*	*	**	*	*	*	9
Schroeter	2012	*	*	*	*	**	*	*	*	9
Van der Boon	2012	*	*	*	*	**	*	*	*	9
Bosmans	2011	*	*	*	*		*	*	*	7
Calvi	2011	*	*	*	*	*	*	*	*	8
Chorianopoulos	2011	*	*	*	*	**	*	*	*	9
D'Ancona	2011	*	*	*	*	**	*	*	*	9
Ewe	2011	*	*	*	*	*	*	*	*	8
Fraccaro	2011	*	*	*	*	**	*	*	*	9
Guetta	2011	*	*	*	*	**	*	*	*	9
Khawaja	2011	*	*	*	*	**	*	*	*	9

Pilgrim	2011	*	*	*	*	*	*	*	*	8
Baan	2010	*	*	*	*	**	*	*	*	9
Bleiziffer	2010	*	*	*	*	**	*	*	*	8
Eltchnainoff	2010	*	*	*	*	**	*	*	*	9
Erkapic	2010	*	*	*	*	**	*	*	*	9
Ewe	2010	*	*	*	*	**	*	*	*	9
Ferriera	2010	*	*	*	*	**	*	*	*	9
Godino	2010	*	*	*	*	*	*	*	*	8
Haworth	2010	*	*	*	*	**	*	*	*	9
Lefevre	2010	*	*	*	*	*	*	*	*	8
Piazza	2010	*	*	*	*	*	*	*	*	8
Rodes-Cabau	2010	*	*	*	*	**	*	*	*	9
Roten	2010	*	*	*	*	**	*	*	*	9
Thielmann	2009	*	*	*	*	**	*	*	*	9
Aslan	2020	*	*	*	*	**	*	*	*	9
Hamdan	2015	*	*	*	*	**	*	*	*	9
Jilaihawi	2019	*	*	*	*	**	*	*	*	9
Matsushita	2020	*	*	*	*		*	*	*	7
Tretter	2019	*	*	*	*	**	*	*	*	9
Zaid	2020	*	*	*	*	**	*	*	*	9
Ahmad	2019	*	*	*	*		*	*	*	7

The methodological quality of retrospective or prospective observational studies was done using Newcastle–Ottawa scale (NOS) quality scale. Each asterisk/star in the Newcastle-Ottawa Scaling System (NOS) represents responses of the biases questionnaire. Each bias assessment part gets one star except comparability that gets a maximum of 2 stars. Each star counts towards the total score. Score <5 represents poor quality, 5-6 represents moderate quality and 7 to 9 are considered as high quality. Total of 30 studies had a NOS score >7 representing a high quality. Rest of the studies had moderate to poor quality owing to the ascertainment bias, comparability, and follow up limitations.

- Not Available or unable to extract

Table S4: The demographics of the population in all the included studies

Author	Year	Study	Country	Period	FU	Size	PPM	PPM %	Mean age	Male	EuroSCORE	STS	Valve type
Hamandi	2020	OCS	US	2012- 2016	12	424	110	25.9	82	52.9			Sapien, CoreValve, Evolut
Sharma	2020	OCS	US	2012-2016	1	226	25	11.1	81±7	50.4			Edwards Sapien
Thiele	2020	RCT	Germany	2016-2018		438	90	20.6	81.7 ± 5	48.9	4.10	4.90	Evolut R vs Sapien 3
Kochman	2020	OCS	Poland	2015-2016	24	24	6	30	75.3±7	50.0			lotus
Meduri	2019	RCT	US, Brazil, Australia	2014-2015	12	704	245	26.9	82±8	49.0	6.5± 5.7		LOTUS and CoreValve
Karacop	2019	OCS	Turkey	2013-2018	3	150	49	32.7	81±8	72.7	20.9±3.		CoreValve
Ay	2019	OCS	Turkey	2012-2017	27	274	25	9.1	78	37.2	20.85		ESV XR, Corevalve, Lotus
Kaneko	2019	OCS.	Germany	2015-2017		92	17	18.5	82±7	32.6	17±13		Evolut R
Reardon	2019	RCT	US,Europe,Australia	2014-2018	2	912	263	28.8	82.8	49.0		6.70	Corevalve vs Lotus
Giordan]	2019	OCS	Italy	2012-2018	1	1976	284	14.4	83.5	42.3	16.13	5.56	lotus, ESV, portico evolut,accurate, evol
Doshi	2018	OCS	US	2012-2014	12	8210	1949	23	81±8	52.3			Not mentioned
Bhardwaj	2018	OCS	US	2012-2016	12	383	44	11.5	83±8	50.9			Edward Sapien and CoreValve
Gonska	2018	OCS	Germany	2014-2016	12	612	168	27.5	80±6	47.1			Corevalve,ESV and Lotus Edge
Yousif	2018	OCS	Switzerland	2008-2014	12	546	103	18.9	81.35	48.5	21.4±15	6.60	Corevalce, ESV,Symetis, Ventor
Ball	2018	OCS	US	2012-2015		209	44	21.1		56.5			ESV, Lotus, CoreValve, Evolut
Eitan	2018	OCS	Germany	2014-2017		92	18	23	82.4	93.5	21.04	4.50	ESV & core valve
Finkelstei	2018	OCS	Israel	2012-2016		735	122	16.6	81	44.6		3.40	ESV corevalve
Monteiro	2017	OCS	Brazil	2008-2015	1	670	135	20.2	82±7	47.9	20.2±15		CoreValve and Sapien XT
Enriquez-R	2017	OCS	Spain		1	144	18	12.5	83 ± 6	47.9		6 ± 5	sapien corevalve
Rogers	2017	OCS	US	2013-2016		257	17	6.6	82 ± 8	49.4		6.96	sapien corevalve
Soliman	2017	OCS	Egypt	2013-2016	6	40	5	12.5	73.98± 8.	52.5			sapien medtronic
vanMourik	2017	OCS	Netherland	2010-2013	36	114	5	4.4	79.6±8.7	32.5	17.8±11	6.7± 5.	sapien
Kley	2016	OCS	Nehterland	2007-2013	12	240	25	10.4	81	0.0	23.2±14		Edward Sapien XT, Corevalve
Zaman	2016	OCS	Australia	2012-2015		95	27	27.4	83 ± 6	44.5		7.3± 8	Lotus
Kahraman	2016	OCS	Turkey	2012-2014	6	136	6	4.4	79.4	38.2	21.15		NA
Sawaya	2016	OCS	France	2010-2015	12	790	87	11	82.8 ± 7.1	47.9	17.70	6.0	sapien
Ben-Shoshan	2016	OCS	Israel	2014-2016	1	232	48	24.5	82.3 ± 6.1	46.1	5.3 ± 5.0	4.1	ESV, Medtronic
Ramkumar	2016	OCS	australia	2012-2015	1	104	25	24		46.2			lotus
Rouge	2015	OCS	France	2009-2015	6	150	18	12	82.6	45.3	21.67	9.65	ESV and Medtronic
Gauthier	2015	OCS		2009-2013		176	13	7.4	85	51.7	25.28		ESV, core valve and portico
Boerlage	2014	OCS	Netherland	2007-2011	12	121	23	19	80.5 ± 7.8	38.1	19.2 ± 12	4.5 ± 2	Corevalve
Simms	2013	OCS	UK	2008-2010	12	100	17	17	81±6	48.0			Medtronic CoreValve
Nuis	2012	OCS	Columbia, Nether	2005-2011	1	235	48	20.4	80±7	48.9	19.1±13	6.1± 5	medtronic
Pulse	2012	OCS	Germany	2008-2010	12	180	9	5	82.1 ± 5.4	30.0	27 ± 14		medtronic and sapien
Ledwoch	2012	OCS	Germany	2009- 2010	1	1147	386	33.7	82±6	40.8	20±13		Medtronic and sapien
Akin	2012	OCS	Germany	2007- 2008	0.2	45	23	51.1	81±6	40.0	21±16		Medtronic CoreValve
Bagur	2012	OCS	Canada	2005- 2010	1	411	30	7.3	81±11	42.8	26±17	9±6	Edward SAPIEN
De Carlo	2012	OCS	Italy	2007- 2010	12	275	66	24	82±6	46.6	23±14		Medtronic CoreValve

Gilard	2012	OCS	France	2010- 2011	3.8	3195	497	15.6	83±7	51.0	22±14	14±12	CoreValve and ESV
Muniz-Garcia	2012	OCS	Spain	2008- 2011		174	48	27.6	79±7	37.4	19±10	7±5	Medtronic CoreValve
Saia	2012	OCS	Italy	2008- 2010	12	60	17	28.3	82±6	43.3	23±13	9±7	Medtronic CoreValve
Salinas	2012	OCS	Spain		12	34	3	8.8	84	38.2	23.00		Edward SAPIEN
Schroeter	2012	OCS	Germany	2008-2009		88	32	36.4	80±6		23±12		Medtronic CoreValve
van der Boon	2012	OCS	Netherlands	2005- 2011	12	167	36	21.6	81±7	46.0	13.00		Medtronic CoreValve
Mouillet	2012	OCS	France	2007-2011	10	79	21	26.6	82±17	31.0	23±10		Medtronic CoreValve
Liang	2012	OCS	New Zealand	2008-2011	21	53	5	9.4	80±7	56.6	26±16	6±3	CoreValve and ESV
Pilgrim	2011	OCS	Switzerland	2007-2010	12	256	60	23.4	82.3 ± 6.2	56.3	40.6±16	6.2± 5.0	Medtronic and ESV
Bosmans	2011	OCS	Belgium	2010	12	328	40	12.2	83±6	46.0	28±16		CoreValve and ESV
D'Ancona	2011	OCS	Germany	2008- 2011	12	322	20	6.2	82±6	33.2	39±22	18±10	Edward SAPIEN
Ewe	2011	OCS	Netherlands		29	104	4	3.8	80.6±7.9	50.0	21±12	8.7± 3.6	Edward SAPIEN
Fraccaro	2011	OCS	Italy	2007- 2009	6	64	25	39.1	81±7	45.0	24±15		Medtronic CoreValve
Guetta	2011	OCS	Israel	2008-2010	3	70	28	40	83±5	37.0			Medtronic CoreValve
Khawaja	2011	OCS	UK	2007-2009		243	81	33.3	81±7	50.6			Medtronic CoreValve
Calvi	2011	OCS	Italy	2007- 2011	12	162	52	32.1	81±5	39.5	28±15		Medtronic CoreValve
Chorianopoulos	2011	OCS	Germany	2009- 2011	1	130	46	35.4	81±6	41.5	24±13.1		Medtronic CoreValve
Hayashida	2011	OCS	France	2006-2010	7	260	17	6.5	83.1±6.3	49.6	24.3±11.4		CoreValve and ESV
Bleiziffer	2010	OCS	Germany	2007- 2009	0.5	159	35	22	80.8±6.2	43.0	21.6±13		CoreValve and ESV
Eltchnainoff	2010	OCS	France	2009- 2009	1	244	29	11.9	82.3±7.3	56.6	25.6±1.1.4	18.9 ±12.8	CoreValve and ESV
Baan	2010	OCS	Netherland		1	34	7	0.2	80±8	53.0		5±3	Medtronic CoreValve
Ewe	2010	OCS	Nether, Sing, Italy		12	147	7	4.8	80±7	42.9	21.8±11		Edward SAPIEN
Ferriera	2010	OCS	Portugal	2007- 2009		32	8	25	81	34.0	23.9± 14.9		Medtronic CoreValve
Godino	2010	OCS	Italy	2007- 2010	6	137	23	0.16		53.3			CoreValve and ESV
Erkapic	2010	OCS	Germany	2008- 2009	0.4	50	17	34	80±6	46.0	20 ± 15		CoreValve and ESV
Haworth	2010	OCS	UK	2007-2008	5	33	8	24	81.5±6.7	57.0	24±15		Medtronic CoreValve
Piazza	2010	OCS	Netherlands	2005- 2009	6	91	17	18.7	81±7	42.9	16±9		Medtronic CoreValve
Rodes-Cabau	2010	OCS	Canada	2005-2009	8	339	17	5	81±8	44.8		9.8± 6.4	Edward SAPIEN
Roten	2010	OCS	Switzerland	2007-2008	2.6	67	23	34.3	83	46.0	23.00	6.00	CoreValve and ESV
Lefevre	2010	OCS	Europe	2007- 2008	12	130	3	2.3	82.1±5.5	44.6	30±13.7	11.6 ±6.5	Edward SAPIEN
Attias	2010	OCS	France	2006-2009	1	83	7	8.4	81±9	53.0	26±14	15±8	CoreValve and ESV
Petronio	2010	OCS	Italy	2007-2009	6	514	84	16.3	83	44.0	20.1		Medtronic CoreValve
Thielmann	2009	OCS	Germany	2005- 2008	12	39	4	10.3	81 ± 5	38.0	44.2 ±12.6	17.9 ±6	Edward SAPIEN
Aslan	2020	OCS	Turkey	2017-2020		140	24	17	78.8	36.4			Edward SAPIEN XT, Medtronic Corevalve evolut
Hamdan	2015	OCS	Israel	2015		73	21	29	79.8±6	45.0			CoreValve, Engager
Jilaihawi	2019	OCS	US	2016-2018	1	248	24	9.6	83.2±6	57.3		6.0± 2.9	Evolut R, Evolut Pro, XL
Matsushita	2020	OCS	France	2014-2018	3	242	114	47		38.4			Sapien 3, Evolut R
Tretter	2019	OCS	US	2013-2017	6	200	41	20.5	81±7.7	49.0		4.7± 2.8	Sapien XT, Sapien 3, LOTUS, CoreValve, Evolut R, Evolut
Zaid	2020	OCS	US	2015-2019	1	532	57	10.7	80.7±8	57.9		5.5	Sapien 3

Ahmad	2019	OCS	US	2019	1	269	17	6.3	79.7±8	50.6	6.2	Edward Sapien

Excluded patients with prophylactic PPM: Hamandi (126), De Carlo (32); Excluded patients with prior PPM: Kochman (4), Eitan (14), Ben-Shoshan 36, Meduri (160), Sharma (36), Doshi (62), D'Ancona (36), Chorianopoulos (32); OCS: Observational Cohort Study, RCT: Randomized Controlled Trial, FU: Follow up in years, STS: Society of Thoracic Surgeons Score

Table S5: The baseline comorbidities of the population in all the included studies (all numbers indicate percentages).

Author	AF	LBBB	RBBB	EF	Sm	DM	HTN	HLD	CKD	CVA	Ob	LC	PAD	MI	PCI	CABG	CAD	COPD
Hamandi		9																
Sharma		10	12			36	90						15		35	33	78	18
Thiele	45				4	38	91	41	82	12			13	9	37	1	56	14
Kochman	25					21	67			13			17	17	4	8	54	29
Meduri	29	8	12			31	92			13		1	28	17	31	24	71	17
Karacop				52	34	35	79	16		62			5				45	22
Ay	32			50		29	62	17					22	5		12	54	34
Kaneko	34	8	10			67	77	32	49					11				
Reardon	34			56						12								
Giordano																		
Doshi	44	9	3			28	79		37		14	2			3	1	7	
Bhardwaj	43	10	13		3	36	94						41	19	20	33		
Gonska	36			20		30			10	10				14		10	61	44
Yousif						24	74	38									55	
Ball	32	10	11			39	91										97	
Eitan	47	14				28	87	65		11			27	73	37	26	73	22
Finkelstei	29				6	4	85	71	64	17	66		10	51				9
Monteiro	14	14	11			32	75	49	76	7			17	14	34	15	11.6 ??	19
Enriquez-R	34					37	80	46	19				7	22				15
Rogers	38					33	88	86	31	7			20	60	25	22		36
Soliman					35	53	65		15	10			35	15	23	23		30
vanMourik	25					26	65	36	33	6		1	14	13	25	10	42	
Kley	18			52		29	75		22				50				63	31
Zaman	28	8	7			23	75			14				12				24
Kahraman	21					30	70	15					24	4		13	65	
Sawaya	27	2	4	54	3	25	64	46	2	8			25		25	10		18
Ben-Shoshan	32			56	23	40	88	76						16		14	56	10
Ramkumar	32					23	76			15			10			17	20	24
Rouge					31	28	59			13			17	11	29	19	47	16
Gauthier						20				20				72			72	30
Boerlage	31	12	12			28	50	12							30	12	51	36
Simms	29					28	23		19								61	21
Nuis	21					24	56		5				13	19	26	23		30
Pulse		7				36			61	12			31		28	15	67	32
Ledwoch	24					34	65		6	8			31	14	34	17		25
Akin	16	2	4		27	38	91			29			13			7	78	18
Bagur	23	8	5	54		29	79		60	24			30	45	42	33		28

De Carlo		14	12	52															
Gilard	26			53							10			21	16		18	48	25
Muniz-Garcia	32	17	17			37	76	52	17	16								33	
Saia		15	18	59		15	5			5					23		2	12	32
Salinas	50			56		41	68		9	14				15				47	
Schroeter	32	8	7	56														61	
van der Boon	25	8	10	51		22	55		5	21				10	23	24	24	46	26
Mouillet	25	20	9	49		18	68		25						24				20
Liang	32	15	9			26	57											72	
Pilgrim	26			56	16	24	78	60		9				25	18	23	21		
Bosmans	9																		
D'Ancona	29					29				24									
Ewe	21				37		60			12				43	23		40		27
Fraccaro	16	14	13	52					55	11		8		34				63	22
Guetta	27	24	16		16		83										23	54	
Khawaja	19	13	10																
Calvi	17	3		50	30	31	85	58		16					27	32	17		
Chorianopoulos	22	7	14							4								32	
Hayashida				50	7		71	49		13				34	15	30	2	64	37
Bleiziffer	26	17	4																
Eltchnainoff				51		27	69			10				734	23		25	41	
Baan	42	6	9			32	53	21								27	12	47	21
Ewe	20				35	25	77	46						35	18	22	19		
Ferriera	28					50	97									16	13	41	56
Godino						29	26		37	23				35	29	24	26		46
Erkapic	34	1	14	51		30	82											56	46
Haworth	18	9	21			9				17				21		23	23		9
Piazza	28	15	6																
Rodes-Cabau	34			55	6	23	74	71		23				35	51	29	34	69	
Roten	12	16	19	51		22	72											55	
Lefevre	25			53		32	74		42					34	21	25	32	60	42
Attias				52										28	13	19	22	51	33
Petronio		12	8		5	27	75			8				19	22	29	16		22
Thielmann				51		28	92		54	18				62	53	36	26	56	39
Aslan	21	38				36	61		28								21	64	
Hamdan	14	1	10			38	84	70							14	22	21	49	
Jilaihawi	17	6	15	65		31			24			2							26
Matsushita	31		15	57		30	85	56	42	13								38	
Tretter	31	7	17			31	90		29	9				19				67	21

Zaid							
Ahmad	37	5	45	91	21	32	

Table S6: Procedural characteristics and type of valves used across the included studies (all numbers indicate percentages).

Author	Apical access	Femoral access	MR-Pro ADM >/= 1.3 nmol/l	TAVR using ACURATE TA device	Medtronic Corevalve	Edward Sapien	Lotus	Transarterial vs transapical comparison (y or n)	Trans Subclavian vs Transfemoral (y or n)
Hamandi	12.7	84.5			9.8	86.9		y	n
Sharma	17.6	77.8				100		y	n
Thiele		100				50		n	n
Kochman		100					100	n	n
Meduri					33.8		66.1	n	n
Karacop		36.6(100%)			36.6			n	n
Ay		100			33.2	50	2.9	n	n
Kaneko		100			100				
Reardon					33.4		66.5		
Giordano		90.2		11.8	35.6	27.3	7.64	n	n
Doshi		79.6							
Bhardwaj		94.3			18		82		
Gonska		100			4.4	58.8	36.7	n	n
Yousif	14.4	84.4			50.5	48.4		y	n
Ball					70.8	11.5	4.8		
Eitan		100				59.7		n	n
Finkelstei		94.1			69.6	30.3		n	n
Monteiro		96.1			74.3	25.6		n	n
Enriquez-R		94.4				55.5		n	n
Rogers	2.3	90.6			28.8	71.2		y	n
Soliman					57.5	42.5		n	n
vanMourik		100				100		n	n
Kley	58.7	41.3			7.5	92.5		n	n
Zaman	1	98.9					100	n	n
Kahraman		100						n	n
Sawaya		63.9				100		n	n
Ben-Shoshan		100				53.4		n	n
Ramkumar	1	99					100	n	n
Rouge	48	52			8	91.3		y	n
Gauthier	33.5	66.5			3.4	93.1		y	n
Boerlage		100			100			N	N
Simms					100			n	n
Nuis		97			100			n	y
Pulse	53.9	46.1			13.3	86.6		y	n
Ledwoch	9.8	86.9			79.5	20.5		n	n
Akin		100			100			n	n
Bagur	45.7	54.3				83.7		y	n
De Carlo					100			n	n
Gilard	18.2	75.9			32.6	65.9		y	y
Muniz-Garcia		89.6			100			n	n
Saia		81.7			100			n	y
Salinas	8.9	91.1				100		y	n
Schroeter		100			100			n	n
van der Boon		91.6			100			n	y
Mouillet					100			n	n
Liang					71.7	28.3		n	n
Pilgrim	21.5	76.9			64			y	y
Bosmans	26.9	70.7			42.9	57		y	n
D'Ancona	100					100			
Ewe	56.7	43.3				100		y	n
Fraccaro		93.8			100			n	y
Guetta		100			100			n	n
Khawaja					100			n	n
Calvi		100			100			n	n
Chorianopoulos		100			100			n	n
Hayashida	31.9	65			14.6	85.4		y	y
Bleiziffer	23.2	72.9			78	22		n	n
Eltchnainoff	29.1	65.9			32	68		y	y
Baan					100			n	n
Ewe	49	51				100		y	n
Ferriera		100			100			n	n
Godino	10.9	78.1			20.4	57.7		y	y
Erkapic	28	72			72	28		y	
Haworth		100			100			n	n
Piazza		100			100			n	n
Rodes-Cabau	51	49				100		y	n

Roten	25	75	61.2	38.8		y	n
Lefevre	47	53		100		y	n
Attias		100	13.3	86.7		y	y
Petronio	10.5	89.5	100			n	y
Thielmann	61.5	38.5		100		y	
Aslan	0	100	52.9	47.1		n	n
Hamdan	8.2	80.8	91.7			n	n
Jilaihawi		99.6				n	n
Matsushita				74.4		n	n
Tretter			38	47	15	n	n
Zaid				100		n	n
Ahmad				100		n	n

***n=no, y=yes**

Table S7: Proportion of PPM implantation across different baseline comorbidities in the included studies

Variable	Total	PPM	PPM (%)	No PPM	No PPM (%)
Diabetes Mellitus	5904	1034	17.51	4870	82.49
Hypertension	14879	3401	22.86	11478	77.14
Hyperlipidemia	2634	104	3.95	2530	96.05
COPD	3034	314	10.35	2720	89.65
Prior CVA	1747	135	7.73	1612	92.27
CKD	5839	1168	20.00	4671	80.00
Liver Cirrhosis	215	50	23.26	165	76.74
PAD	2928	292	9.97	2636	90.03
Smokers	425	38	8.94	387	91.06
Prior MI	2776	233	8.39	2543	91.61
Prior PCI	2581	353	13.68	2228	86.32
Prior CABG	2453	234	9.54	2219	90.46

COPD- Chronic Obstructive Pulmonary Disease, CVA- Cerebrovascular Accident, CKD- Chronic Kidney Disease, PAD- Peripheral arterial disease, MI- Myocardial Infarction, PCI- Percutaneous coronary intervention, CABG- Coronary Artery Bypass graft

Table S8: Pooled estimates of anatomical and valvular predictors for PPM implantation in TAVR

Anatomical Variants		Valvular Variants	
23mm vs. 26mm prosthesis (2)	1.12 (0.62-2.03)	LOTUS vs. EvolutR	1.44 (0.94-2.20)
29mm vs. 23mm(7)	1.49 (1.06-2.08)	LOTUS vs. ESV	2.80 (0.76-10.32)
IV septum >22mm vs. <22mm (1)	1.65 (0.55-4.93)	LOTUS vs. MCRS	1.61 (1.23-2.1)
IV septum>11mm vs. <11mm (1)	1.71 (0.17-17.41)	P-HTN (>60mmHg) vs. No P-HTN (3)	1.78 (0.82-3.89)
LVOT>22mm vs. <22mm (1)	1.65 (0.55-4.93)	Severe MR vs. No MR (3)	3.30 (0.59-18.32)

Abbreviations: mm: millimeter, PPM- Permanent pacemaker, TAVR-Transaortic valve replacement, IV septum-interventricular septum, LVOT- Left ventricular outflow tract, P-HTN: Pulmonary hypertension, MCRS - Medtronic CoreValve Revalving System, ESV: Edwards SAPIEN valve,

Table S9: Predictors of PPM Implantation across different valve types

Variables	Medtronic CoreValve	Edward SAPIENS Valve	LOTUS	EVOLUT R
Comparison	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
Male vs. Female (MCV)	1.33 (1.02-1.73)	1.25(0.70-2.24)	-	2.14 (0.73-6.27)*
1st HB vs. No 1st HB	1.95 (1.18-3.24)	1.56 (0.20-11.8)	0.19 (0.04-0.89)*	1.47 (0.41-5.23)*
LBBB vs. No LBBB	0.99(0.66-1.48)	0.28 (0.03-2.39)	0.34 (0.04-2.86)*	0.29 (0.02-2.28)*
LAHB vs. No LAHB	1.94 (1.11-3.38)	1.95 (0.32-12.01)	-	-
LPHB vs. No LPHB	1.19 (0.05-29.88)	2.29(0.12-41.9)	-	-
RBBB vs. No RBBB	4.03 (2.47-6.56)	14 (0.51-387)*	1.01 (0.18-5.54)*	4.31 (1.02-18.22)*
Bifascicular Block	-	3.84 (0.67-21.9)	-	-
IPB vs. No IPB	8.04 (3.53-18.2)	12.83 (1.26-130)*	-	-
AF vs. No AF	1.39 (0.86-2.26)	0.70 (0.34-1.43)	0.12 (0.01-0.92)*	0.55 (0.16-1.85)*
Transfemoral vs. Subclavian	0.35 (0.09-1.31)	-	-	-
Transarterial vs. Transapical	-	1.11 (0.46-2.72)	-	-

***Less than 3 studies with small sample size were used to calculate these values**

Abbreviations: PPM- Permanent pacemaker, MCV- medtronic corevalve, HB- Heart block, LBBB- left bundle branch block, LAHB- Left anterior hemiblock, LPHB- Left posterior hemiblock, RBBB- Right bundle branch block, IPB- intraprocedural block, AF- atrial fibrillation

Table S10: Sensitivity and subgroup analysis based on sample size and study design

Variable	Sensitivity analysis based on sample size (<200 removed)	Sensitivity analysis based on study design (RCT removed)
Age	1.25 (0.98-1.60)	-
Male sex	1.47 (1.12-1.91)	-
First degree heart block	0.68 (0.14-3.30)	0.86 (0.27-2.80)
Mobitz type 1 2nd Degree Heart Block	6.77 (2.82-16.22)	-
Mobitz type 2 2nd Degree Heart Block	3.89 (2.54-5.95)	-
Atrial Fibrillation	1.08 (0.89-1.32)	-
Left Anterior Hemiblock	1.60 (1.17-2.18)	1.87 (1.19-2.93)
Left Posterior Hemiblock	1.23 (0.05-30.77)	-
Intraprocedural AV Block	8.04 (3.53-18.29)	-
Left bundle branch block	1.14 (0.84-1.55)	1.01 (0.76-1.35)
Right bundle branch block	4.12 (2.83-6)	4.21 (3.13-5.66)
Bifascicular Block	2.38 (1.94-6.01)	-
Heart Failure with Preserved Ejection Fraction	1.60 (0.88-2.91)	-
Transarterial Approach with Transapical Approach (Edward Sapien)	1.44 (0.34-6.04)	-
Transfemoral approach with Subclavian Approach (MCV)	0.84 (0.41-1.75)	-
Medtronic CoreValve with Edward SAPIEN	2.87 (1.96-4.21)	3.03 (2.57-3.56)
LOTUS valve with Medtronic CoreValve	1.76 (1.38-2.25)	1.75 (1.38-2.22)
Edward SAPIEN valve with Medtronic EvolutR valve	0.81 (0.58-1.14)	-

Table S11: Number of studies and patients with PPM and total patients across different predictors.

Variable	PPM/Predictor present	PPM/Predictor absent
Age >80 (n=5)		
Ledwoch	278/788	108/359
Kley	14/135	11/105
Ay	14/132	11/142
Kahraman	4/69	2/67
Ramkumar	7/23	18/81
Sex (male) (n=31)		
Monteiro	80/321	55/349
Meduri	122/345	123/359
Bharadwaj	20/195	24/188
Gonska	88/288	80/324
Karacop	35/109	14/41
Yousif	59/270	44/276
Kaneko	8/30	9/62
Boerlage-Van Dijk	6/40	17/65
Ball	25/118	19/91
Tretter	21/93	20/107
Ledwoch	174/468	212/679
Bleiziffer	13/68	22/91
Baan	2/14	5/13
Roten	13/31	10/36
D'Ancona	8/107	12/215
Fraccaro	15/29	10/35
Akin	10/18	13/27
Calvi	22/64	30/98
Bagur	14/176	16/235
De Carlo	37/128	29/147
Munoz-Garcia	21/65	27/109
Saia	8/24	9/36
Simms	10/48	7/52
van der Boon	19/77	17/90
Mouillet	7/25	14/54
Ahmad	11/136	6/133
Matsushita	45/94	69/148
Hamdan	7/33	14/40
Aslan	9/51	15/89
Zaid	31/308	26/224
Jilawahi	10/142	14/106
Hayashida	10/129	7/131
Atrial fibrillation (n=31)		
Monteiro	19/91	116/579
Doshi	925/3653	1086/4557
Meduri	78/202	167/502
Bharadwaj	11/163	33/220
Gonska	66/220	102/392
Kaneko	4/31	13/61
Zaman	3/19	23/76

Boerlage-Van Dijk	7/30	98/75
Ball	18/67	26/142
Matsushita	40/76	74/166
Hamadan	4/10	17/63
Ledwoch	103/277	283/870
Bleiziffer	9/41	26/118
Baan	4/10	3/17
Erkapic	5/17	12/33
Roten	4/8	19/59
D'Ancona	5/93	15/229
Calvi	11/27	41/135
Bagur	4/96	26/315
Chorianopoulos	6/29	40/101
Munoz-Garcia	14/56	34/118
Salinas	2/17	1/17
Schroeter	16/28	16/60
Simms	7/29	10/71
Aslan	6/29	18/111
Van der Boon	12/41	24/126
Roten	4/8	19/59
Mouillet	6/21	15/58
Tretter	13/61	28/139
Ahmad	8/99	9/170
Jilawahi	4/43	20/205
1st degree AV block (n=16)		
Monteiro	29/104	106/566
Doshi	127/2857	1822/5353
Meduri	25/56	220/648
Sharma	5/47	20/179
Kaneko	4/17	13/75
Zaman	8/23	18/192
Boerlage-Van Dijk	5/19	18/86
Hamadan	3/13	18/60
Baan	2/5	5/22
Tretter	2/22	27/187
Bleiziffer	7/22	28/137
Erkapic	4/10	13/40
Bagur	1/38	29/373
Jilawahi	4/29	20/219
Chorianopoulos	9/15	37/115
De Carlo	17/50	49/225
2nd degree Mobitz I AV block (n=3)		
Monteiro	1/1	134/669
Doshi	14/21	1935/8189
Liang	1/1	4/52
2nd degree Mobitz II AV block (n=2)		
Monteiro	0/1	135/669
Doshi	48/86	1963/8124
3rd degree AV block (n=4)		
Doshi	622/777	1351/7457
Karacop	49/49	0/101

Sharma	8/20	0/5
Liang	3/3	2/50
Left anterior hemiblock (n=9)		
Meduri	51/121	194/583
Sharma	7/34	18/192
Ball	2/7	42/202
Erkapic	4/8	13/42
Calvi	1/4	51/158
Bagur	3/29	27/382
De Carlo	18/46	48/229
Jilawahi	1/12	23/236
Van der Boon	5/19	31/148
Left posterior hemiblock (n=4)		
Sharma	2/3	23/223
Ball	0/1	44/208
Jilawahi	1/4	23/244
Van der Boon	0/1	36/166
Intraprocedural AV block (n=3)		
Sharma	13/30	12/196
Bleiziffer	18/37	17/122
Munoz-Garcia	22/34	26/140
Left bundle branch block (n=29)		
Monteiro	15/93	120/577
Doshi	260/731	1751/7479
Meduri	20/56	225/648
Bharadwaj	3/39	41/344
Hamandi	13/52	97/372
Sharma	1/23	24/203
Kaneko	0/7	17/92
Zaman	1/8	26/87
Boerlage-Van Dijk	1/14	22/91
Ball	28/100	16/109
Sawaya	0/14	43/230
Hamadan	1/9	12/72
Roten	1/11	22/56
Bleiziffer	7/27	28/132
Eltchnainoff	4/27	25/182
Baan	0/2	7/25
Erkapic	0/5	17/45
Haworth	1/3	7/27
Roten	1/11	22/56
Khawaja	14/32	67/211
Calvi	2/5	50/157
Bagur	1/33	29/378
Chorianopoulos	3/9	43/121
De Carlo	9/37	57/238
Saia	1/9	16/51
Schroeter	2/7	30/81
Jilawahi	0/14	24/234
Tretter	1/14	40/186
Van der Boon	3/14	33/153

Right bundle branch block (n=29)		
Monteiro	36/71	99/599
Doshi	96/220	1791/7990
Meduri	68/85	177/619
Bharadwaj	11/50	33/333
Sharma	10/28	15/198
Kaneko	4/9	13/83
Zaman	6/7	21/88
Boerlage-Van Dijk	5/11	18/94
Ball	11/23	33/186
Sawaya	12/29	31/215
Hamadan	4/7	17/66
Matsushita	19/35	95/207
Bleiziffer	3/6	32/153
Baan	0/2	7/25
Ferriera	4/7	4/20
Erkapic	6/7	11/43
Haworth	6/7	2/23
Piazza	5/5	12/75
Roten	10/13	13/54
Guetta	10/11	18/59
Khawaja	15/23	66/220
Bagur	7/20	23/391
Chorianopoulos	12/18	34/112
De Carlo	15/32	51/243
Saia	4/11	13/49
Van der Boon	11/17	25/150
Jilawahi	8/37	16/211
Tretter	18/34	23/166
Mouillet	3/7	18/72
Bifascicular block (n=4)		
Sharma	7/16	18/210
Ball	2/3	42/206
Jilawahi	2/8	22/240
Sawaya	12/45	31/199
23mm vs 26mm prosthesis (n=2_)		
D'Ancona	6/115	14/207
Bagur	16/187	14/223
23mm vs 29mm prosthesis (n=7)		
Akin	10/22	13/23
Saia	10/35	7/28
Fraccaro	12/36	13/28
Guetta	10/33	15/37
Boon	10/56	26/109
Chorianopoulos	12/46	34/84
Garcia	24/97	24/77
Severe Pulmonary Hypertension (n=3)		
Guetta	9/15	16/55
Munoz-Garcia	16/39	32/135
Calvi	26/83	26/79
Interventricular septum greater than 11mm (1)		

Guetta	24/66	1/4
Interventricular septum greater than 22mm (1)		
Guetta	8/18	17/52
Moderate/Severe MR (3)		
Akin	22/41	1/45
Boon	6/24	30/143
Bagur	9/104	21/307
MCRS vs. Edwards SAPIEN(n=16)		
Monteiro	119/498	16/172
Thiele	49/213	41/214
Ball	36/148	1/24
Soliman	4/23	1/17
Ledwoch	352/912	34/235
Bleiziffer	33/124	2/35
Godino	12/46	7/61
Erkapic	16/36	1/14
Roten	20/41	3/26
Bosmans	31/121	9/163
Gilard	252/874	243/1793
Liang	5/38	0/15
Attitias	2/11	5/72
Ben-Shoshan	22/88	26/108
Eltchnainoff	20/78	9/166
Rogue	6/12	12/135
LOTUS vs. MCV (n=4)		
Ball	3/10	36/148
Meduri	71/192	16/53
Gonska	98/225	49/150
Reardon	202/607	61/305
LOTUS vs. Evolut R (n=1)		
Giordana	35/151	122/703
LOTUS vs. Edwards SAPIEN (n=2)		
Ball	3/10	1/24
Giordana	35/151	72/541
Edwards SAPIEN vs. EVOLUT R (n=5)		
Eitan	10/50	8/28
Rodriguez	12/64	6/80
Rogers	9/108	9/74
Ben-Shoshan	26/108	22/88
Finklestein	32/223	90/512
Preserved LVEF (n=5)		
Simms	0/10	17/90
Fraccaro	10/39	53/313
Ewe	1/41	6/94
Ewe	0/97	2/50
Munoz-Garcia	8/23	40/151
Access route (transfemoral vs. transapical (n=12)		
Eltchnainoff	22/161	4/71
Sharma	21/176	4/40
Rodes-Cabau	6/168	11/177
Roten	20/50	3/17

Bosmans	35/232	5/88
Ewe	2/45	2/59
Lefevre	1/61	3/69
Bagur	15/223	15/188
Gauthier	10/66	3/59
Thielmann	4/14	0/20
Godino	17/107	3/15
Erkapic	16/36	1/14
Access route (transfemoral vs. subclavian) - MCRS (n=4)		
Petronio	74/460	10/54
Saia	10/49	7/11
Fraccaro	22/60	3/4
Eltchnainoff	22/161	3/12
Self-Expanding vs. Balloon-Expanding valves (n=18)		
Liang	5/38	0/15
Soliman	4/23	1/17
Erkapic	16/36	1/14
Ball	36/148	1/24
Attitias	2/11	5/72
Bleiziffer	33/124	2/35
Roten	20/41	3/26
Eitan	9/37	5/55
Rodriguez	6/80	12/64
Giordana	12/46	7/61
Rogers	9/74	9/108
Bosman	31/121	9/163
Ben-Shoshan	22/88	26/108
Montiero	119/498	16/172
Thiel	49/213	41/214
Finkelstein	90/512	32/223
Ledowoch	352/912	34/235
Aslan	15/74	9/66
Gilard	252/874	243/1793
Mechanically-Expandable vs. Self-Expanding Valves (n=5)		
Ball	3/10	36/148
Meduri	71/192	16/53
Gonska	98/225	49/150
Giordana	35/151	122/703
Reardon	202/607	61/305
Heart Failure (Unspecified) (n=4)		
Meduri	182/531	63/173
Bharadwaj	8/105	36/278
Ahmad	3/39	14/230
Kaneko	4/9	13/83
Pilgrim	12/37	48/219

Table S12: Characteristics of previously published meta analyses on the predictors of PPM implantation

Author	Year	S	PPM risk factors	Comparison arms	Model	Results
Erkapic	2011	32	Bradycardia, bifascicular block, RBBB	CVP VS ESP	Random and Fixed	Higher risk of PPM in CVP, with prior RBBB
Gozdek	2020	11	Lotus valve	Lotus Vs Sapiens 3	Random	Higher risk of PPM with Lotus
Zhan	2019	5	Access (transfemoral vs transaxial)	Transfemoral vs Transaxial	Random	No difference in PPM implantation with different access
Zafar	2020	4	Chest radiation in patients with thoracic malignancy	Hx of chest radiation vs no chest radiation	Random	No difference in PPM implantation in patients who received chest radiation
Xi	2019	20	Long term outcomes of TAVR and Self expandable prosthesis	Self expandable vs balloon expandable prosthesis	Random and Fixed	Self expandable prosthesis had 2.5 fold increased risk of PPM implantation compared to balloon expandable prosthesis
Siontis	2014	41	Age, sex, Afib, LBBB, RBBB,preserved EF, access route, first degree AV block, left anterior and posterior hemiblock, intraprocedural AV Block, medtronic vs edwards valve, PR >200	Predictors of pacemaker	Random	Male sex, intraprocedural AV block, baseline conduction abnormalities predicted PPM implantation
Shoar	2020	3	Preexisting LBBB	TAVR in patients with LBBB vs no LBBB	Random	LBBB has an increased risk of PPM after TAVR
Biondi	2014	4	Valve type (TAVR vs. SAVR risk factors)	CoreValve vs Sapien	Fixed	Higher PPM risk in CoreValve
Alperi	2020	35	Implantation depth, different types of valves and pre TAVR balloon aortic valvuloplasty	sapien3 vs Evolu R vs acurate neo vs portico	-	Pre-TAVR BAV has no impact. Sapien 3 and Acurate Neo valves had lowest risk for PPM. Deeper valve implantation and a shorter MS length has high risk
An lee	2020	27	SEV, BEV	SEV vs BEV in post TAVR	Random	Transcatheter aortic VIV, SEV was associated with larger postprocedural effective orifice area but higher rates of PPM.
Ando	2016	7	RBBB, self-expandable prosthesis valve, and depth of implantation	NO-LBBB vs Non NO LBBB (NO=New onset)	Random	LBBB after TAVI was associated with an increased rate of PPM
Faroux	2020	30	New onset persistent (NOP)-LBBB	NOP-LBBB	Random and Fixed	NOP-LBBB had increased risk of all-cause death and PPM at 1-year follow-up.
Fu	2019	15	PPM in TAVR	PPM in SAVR	Random	PPM implantation rate for TAVR is higher than SAVR at 1-year
Gozdek (duplicate, same as 3)	2020	11	Lotus valve	Sapien 3	Random	Lotus was associated with higher rate of PPM implantation
Haddad	2019	12	Core Valve	Jena Valve	Random	Early gen. Valve associated with increased PPM compared to new gen valves for TAVI in AR
Kanjanahattakij	2018	9	Bicuspid aortic valve (BAV) TAVR	Tricuspid valve TAVR	Random	No difference in pacemaker implantation, major bleeding, and major vascular complication
Khan	2017	12	TAVR	SAVR	Random	High PPM and paravalvular leaks in TAVR.

Khan	2020	7	TAVR	SAVR	Random	HIgh risk of PPM in TAVR
Khatri	2021	49	CoreValve, Transarterial route	CoreValve vs Edwards Sapien valve	Random	PPI was 5 times more common with the CoreValve than the Sapien valve
Lee	2020	31	Transaxillary route	Transaxillary vs direct aortic approach	Random	Direct aortic TAVR was associated with lower risks of permanent pacemaker implantation and valve malposition than transaxillaryTAVR
Li	2020	13	TAVR	SAVR	Random	No difference in PPM between TAVR and SAVR
Lou	2020	21	TAVR	TAVR vs SAVR	Random	TAVR had high complication, paravalvular leak, and PPM
Krasopolous	2016	8	CoreValve	Transfemoral Edwards Sapiens vs Transapical Edwards Sapiens vs CoreValve	Random	CoreValve implantation was associated with an increased risk of PPM
Liu	2018	3	TAVR	SAVR and Medical therapy	Fixed	No differences in the risk of PPM, myocardial infarction, acute kidney injury or endocarditis
Liu	2020	5	Nonagenarians	Younger patients	Random and Fixed	Nonagenarians had higher complications but no difference in PPM risk
Wagner	2019	19	TAVR	TAVR vs SAVR, BAV, and medical therapy	Random and Fixed	TAVR had lower risk of PPM compared to SAVR
Wang	2020	6	TAVR	SUAVR (sutureless aortic valve replacement)	Random and Fixed	No significant difference in need for PPM
Williams	2020	4	Sutureless and rapid-deployment aortic valve replacement (SURD-AVR)	Edwards Intuity (Edwards Lifesciences, California) valves	Random	PPM insertion rate was 8.2%.
Xie	2016	17	BAV pts with TAVR	non-BAV	Random and Fixed	No difference in the risk of PPM
Seimens	2016	4	Trans-arterial vs surgical apprach	TAVR vs SAVR	Random ized	TAVI had lower risk of PPM
Rosendael	2018	40	Pre-procedural conduction abnormalities including RBBB, prolonged PR interval, Atrial fibrilation and first degree AV block; LVOT calcification amount; Implantation depth.	Preprocedural anatomical and conduction abnormalities, present vs not present.	Random and Fixed	Electrical factor, calcification of the left ventricular outflow tract, balloon valvuloplasty and depth of implantation had increased risk of PPI.
Regueiro	2016	17	Pre-procedural conduction abnormalities. New onset LBBB post-TAVR	Edward SApiens vs Medtronic valve.	Fixed	New-onset LBBB had higher PPM risk
R Khan	2020	7	Undergoing TAVR. Moderate vs low surgical risk	TAVR vs SAVR.	Random ized	HIgh PPM in TAVR
Quintana	2019	5	BAV	TAV	Fixed	No difference of PPM in BAV and TAV
Panchal	2015	27	Valve type used for TAVR	Edwards vs Medronic Corevalve	Random and Fixed	PPM higher in Corevalve compared to EV

Nagaraja	2014	39	TAVR	TAVR vs SAVR	Random and Fixed	No difference in risk of PPM in TAVR and SAVR
Malik	2020	4	TAVR	TAVR vs SAVR	Random	HIgh risk of PPM in TAVR
Ma	2020	7	Chronic liver disease (CLD)	No CLD	Fixed	CLD has lower PPM risk
M Gozdek	2020	6	Valve type used for TAVR	Self expandable valve vs Balloon-expandable Valve	Random and Fixed	Lower risk of PPM in Accurate neo self expandable valve
Arora	2016	29	TAVR	SAVR	Random	Increase risk of PPM in TAVR.
Croix	2020	11	RBBB	TAVR in No RBBB	Fixed	RBBB had higher incidence of PPM & mortality at 30 days

SUPPLEMENTAL FOREST PLOTS FOR ALL STUDIES:

Figure S1: Forest Plot showing an individual and pooled OR of PPM Implantation in patients age>80

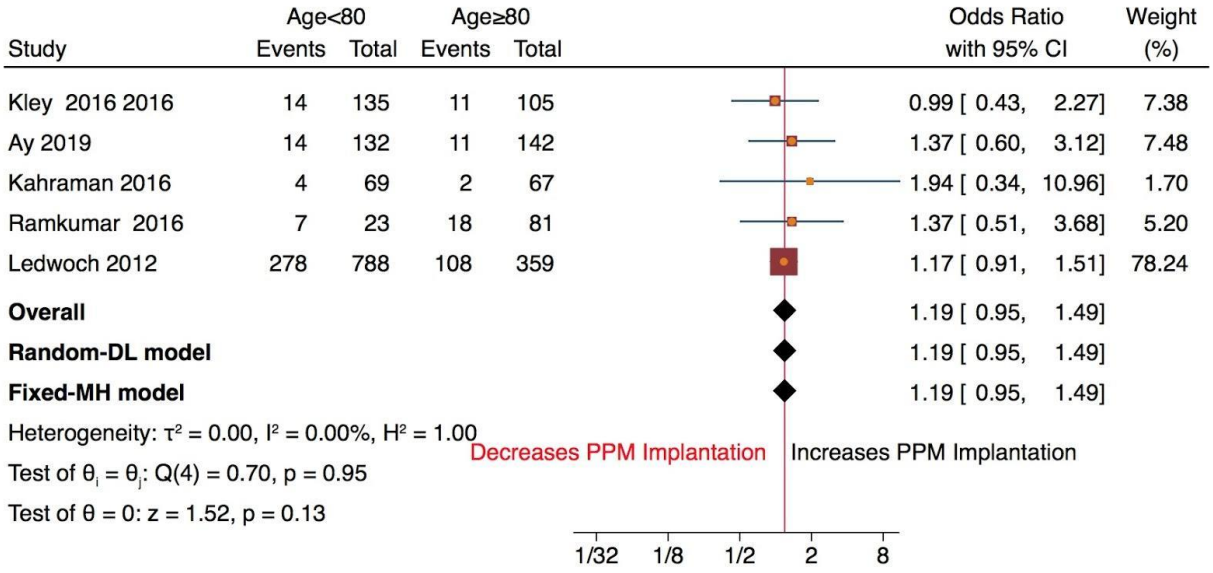

Figure S2: Forest Plot showing an individual and pooled OR of PPM Implantation in Male Patients

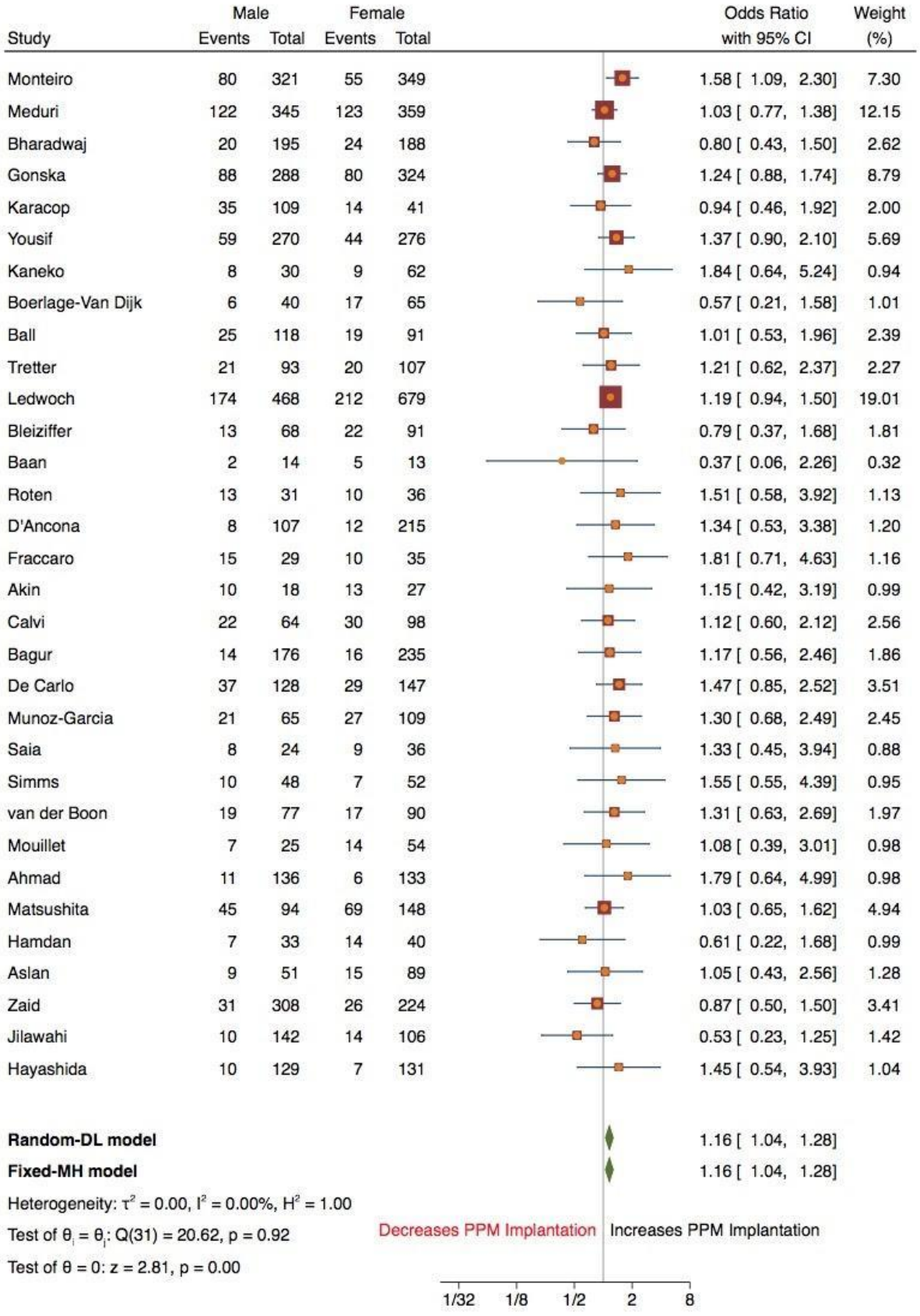

Figure S3: Forest Plot showing an individual and pooled OR of PPM Implantation with First Degree Heart Block

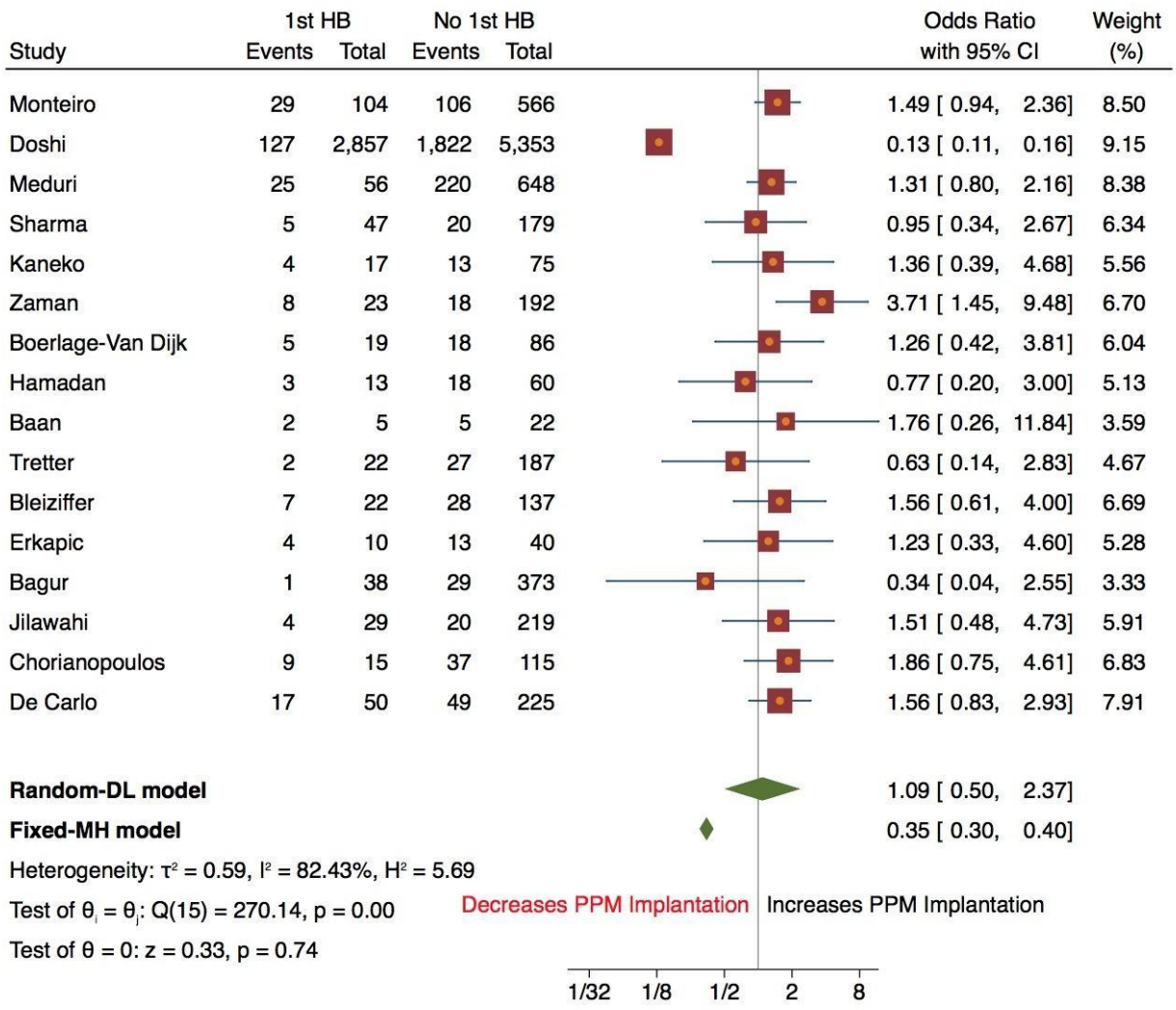

Figure S4: Forest Plot showing an individual and pooled OR of PPM Implantation with Mobitz type 1 2nd Degree Heart Block

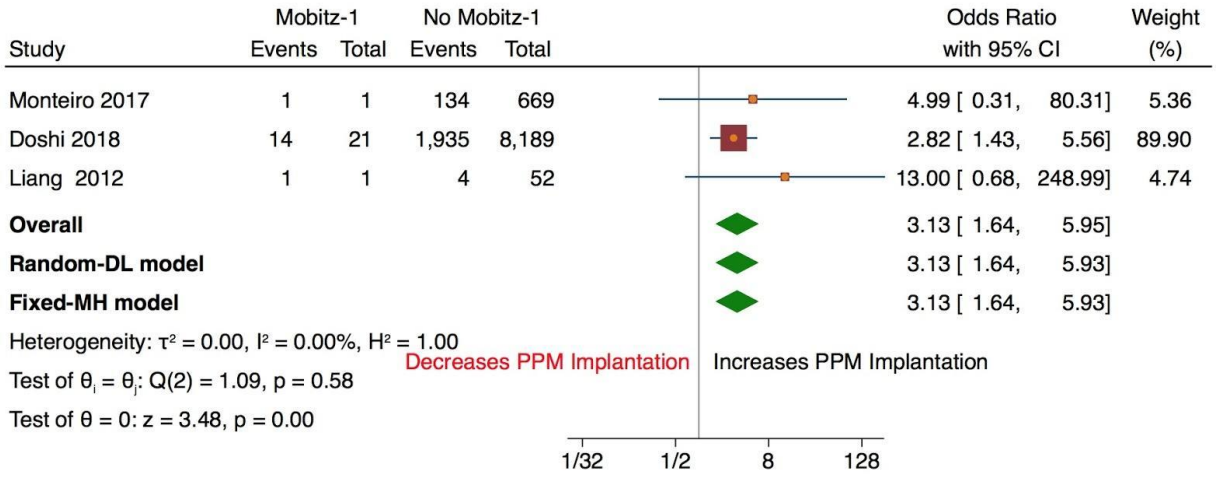

Figure S5: Forest Plot showing an individual and pooled OR of PPM Implantation with Atrial Fibrillation

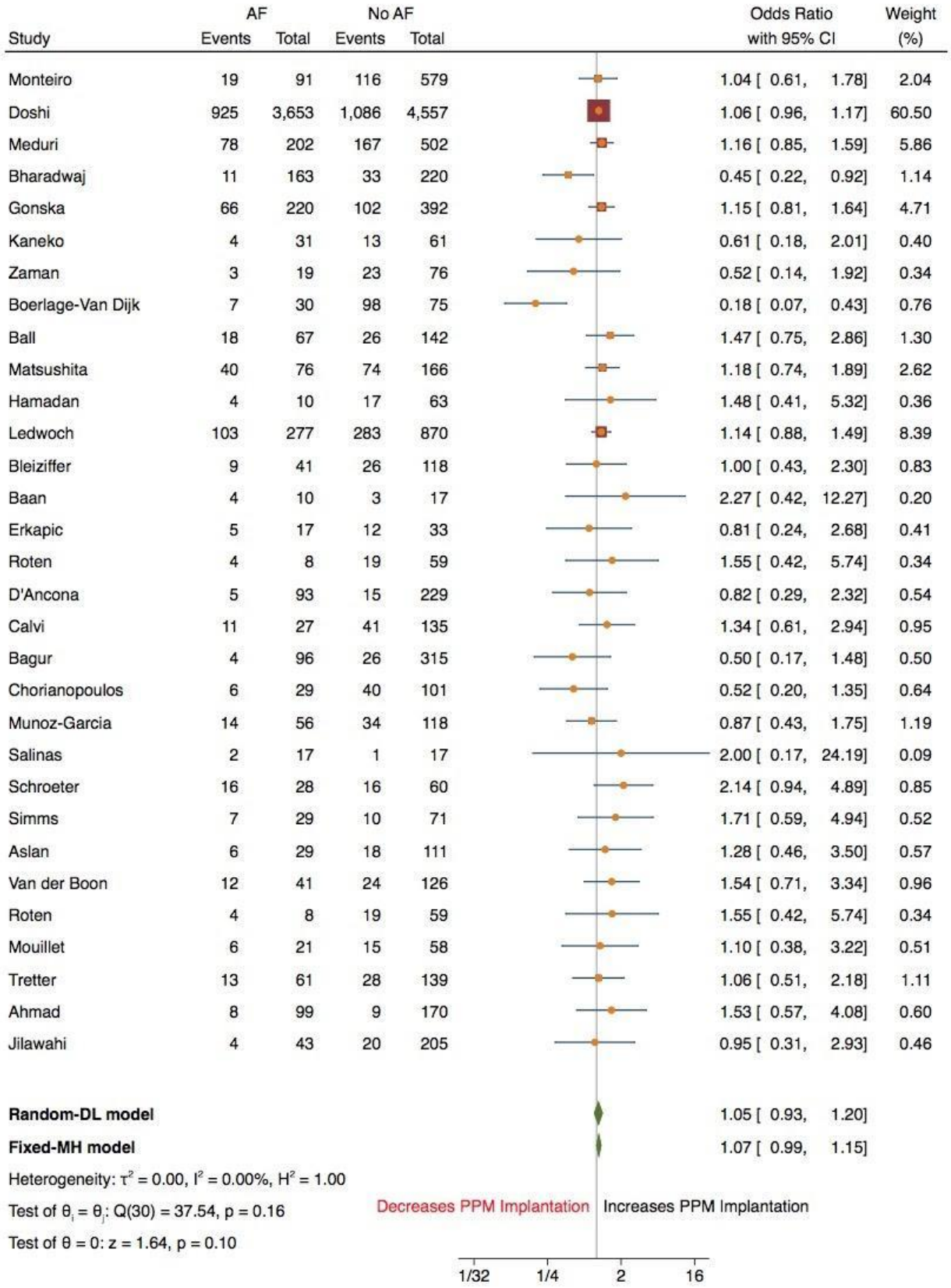

Figure S6: Forest Plot showing an individual and pooled OR of PPM Implantation with Left Anterior Fascicular Block (LAFB)

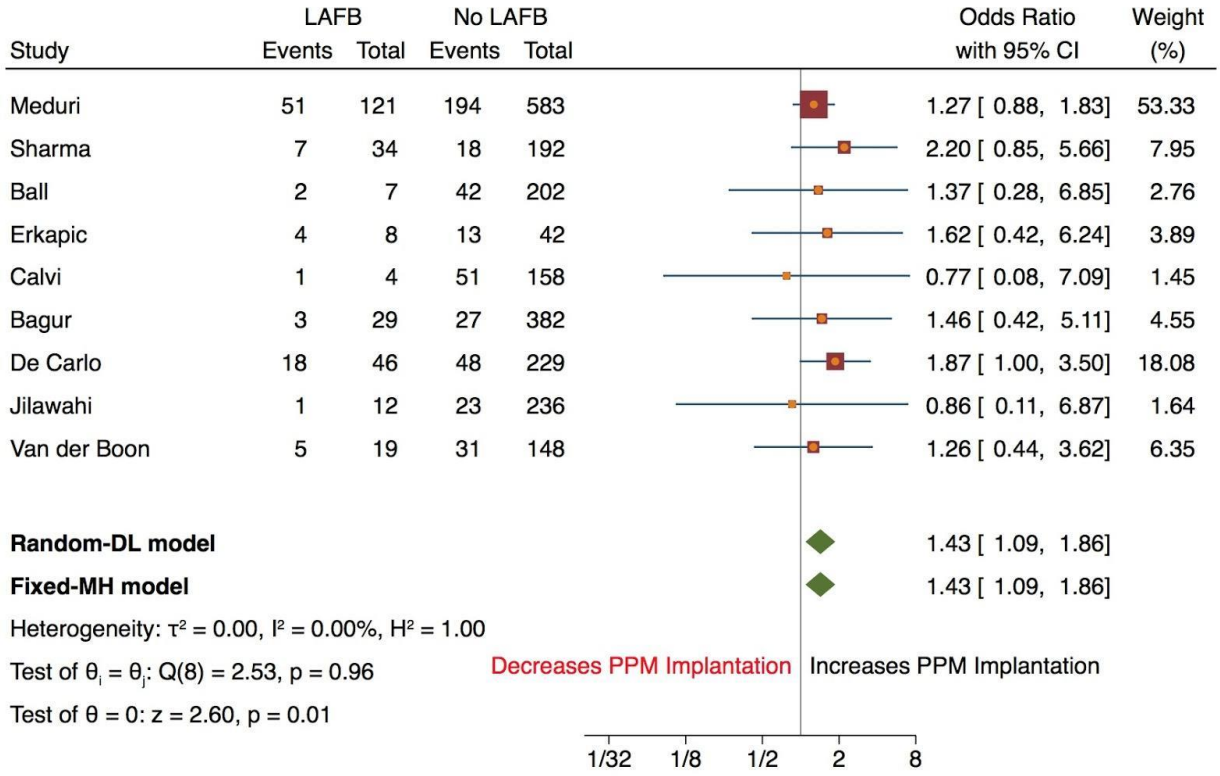

Figure S7: Forest Plot showing an individual and pooled OR of PPM Implantation with Left Posterior Fascicular Block (LPFB)

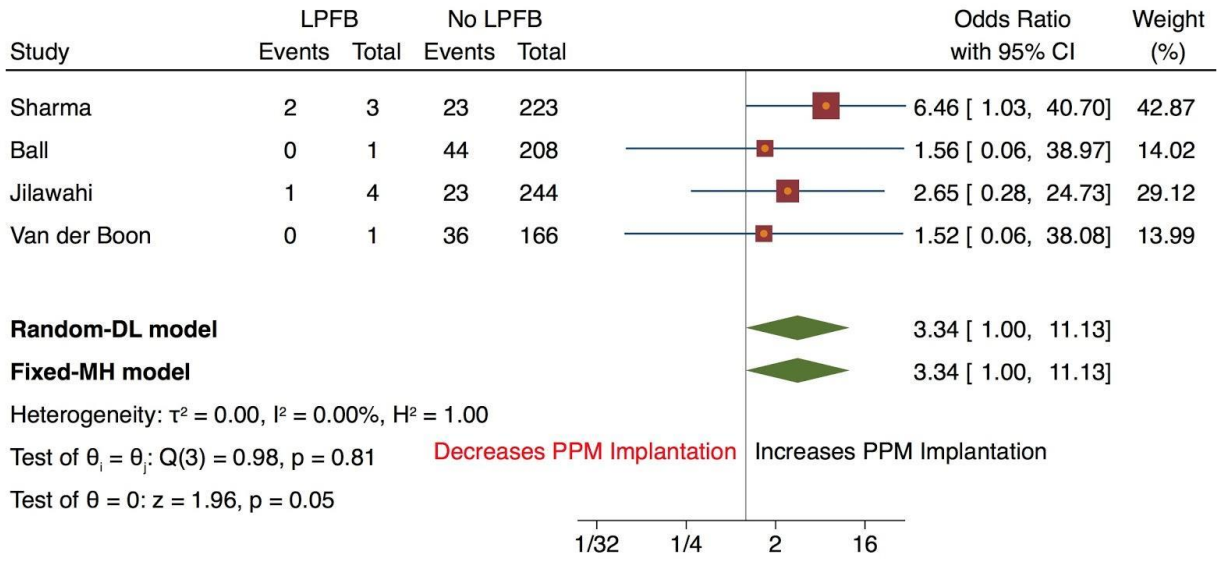

Figure S8: Forest Plot showing an individual and pooled OR of PPM Implantation with Intraprocedural AV Block

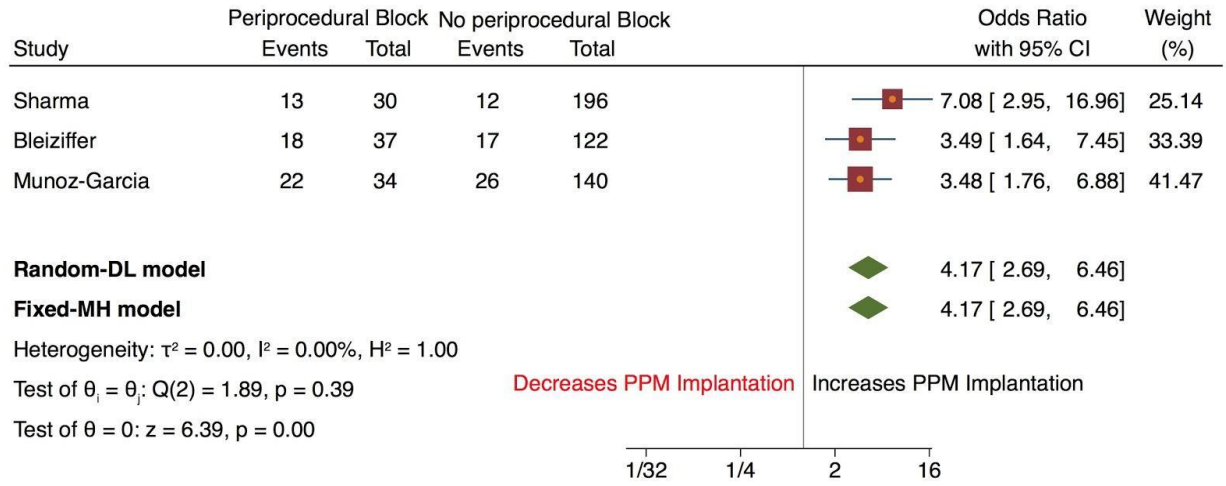

Figure S9: Forest Plot showing an individual and pooled OR of PPM Implantation with Left Bundle Branch block.

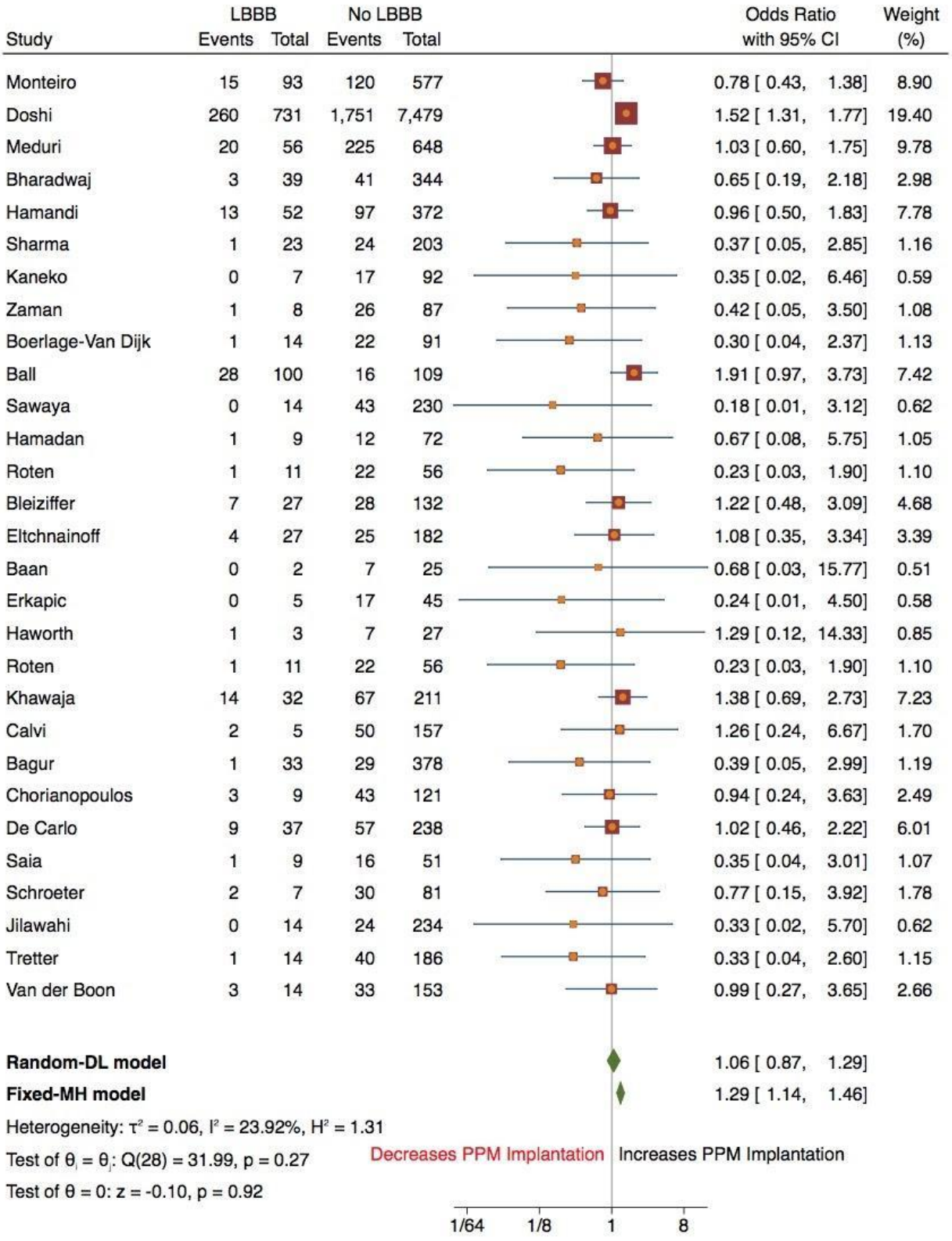

Figure S10: Forest Plot showing an individual and pooled OR of PPM Implantation with RBBB

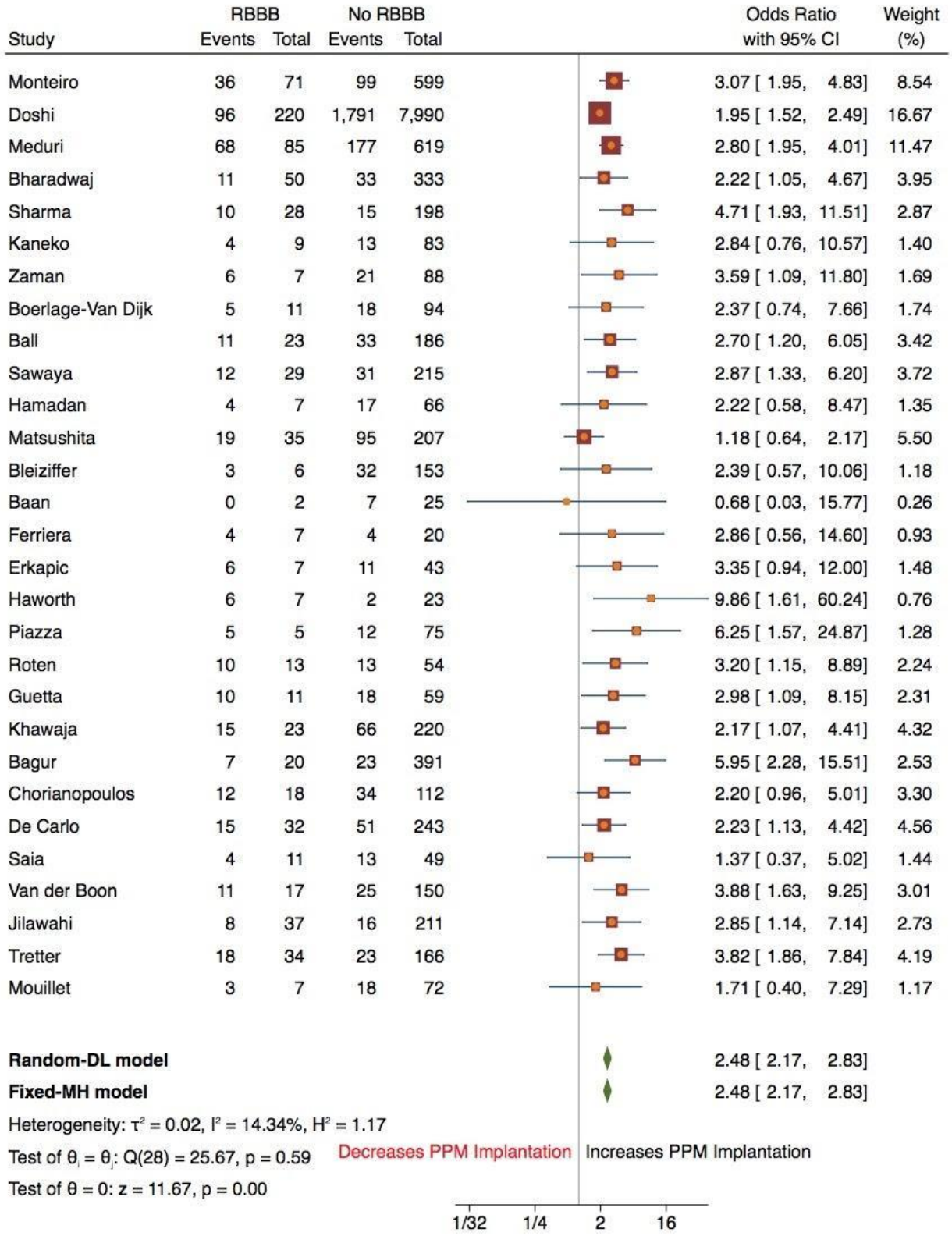

Figure S11: Forest Plot showing an individual and pooled OR of PPM Implantation with Bifascicular Block

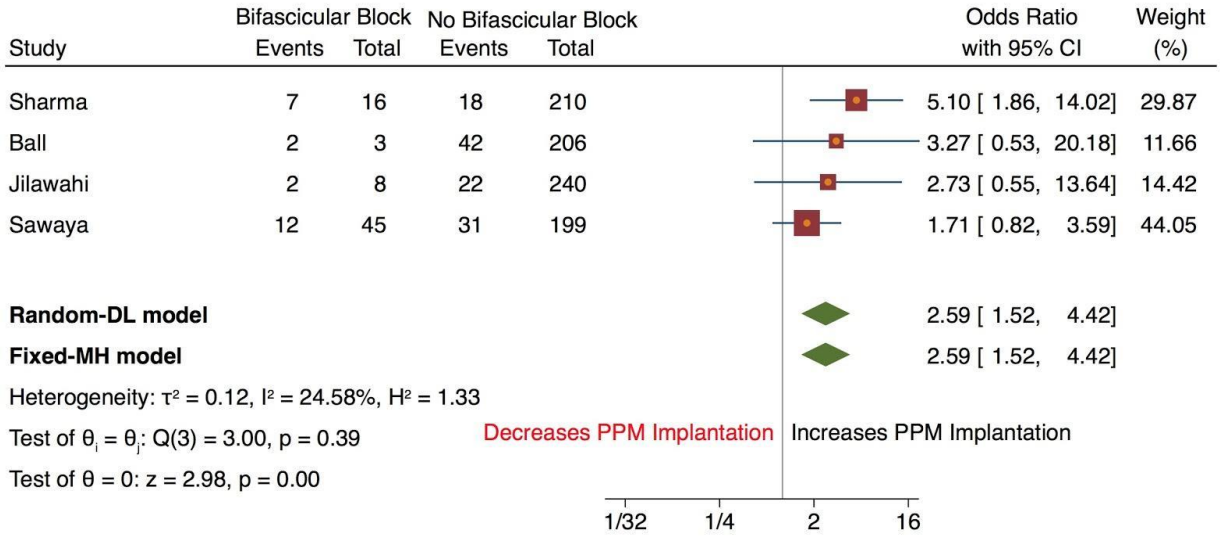

Figure S12: Forest Plot showing an individual and pooled OR of PPM Implantation in Heart Failure

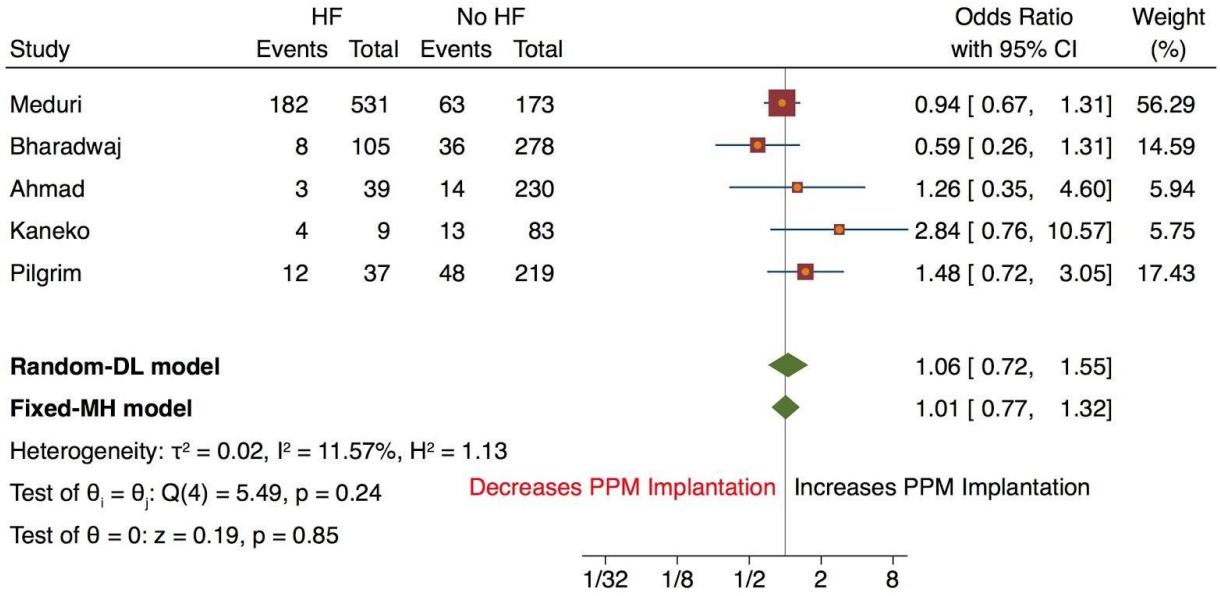

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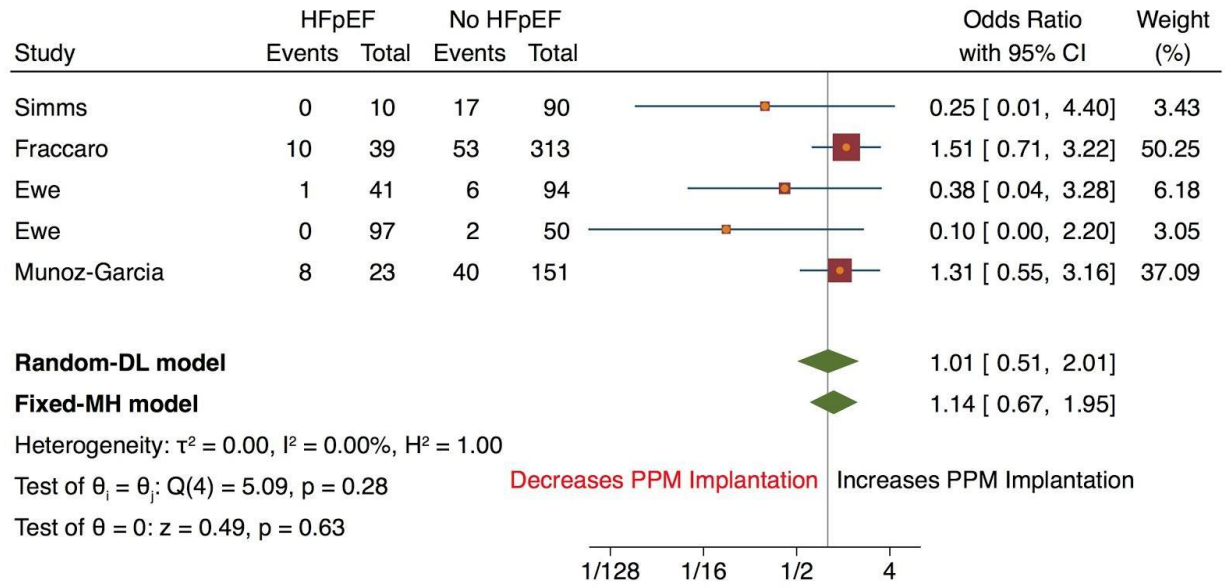
Figure S13: Forest Plot showing an individual and pooled OR of PPM Implantation in Heart Failure with Preserved Ejection Fraction.



Random-effects REML model

Figure S14: Forest Plot showing an individual and pooled OR of PPM Implantation comparing Transfemoral approach with Transapical Approach

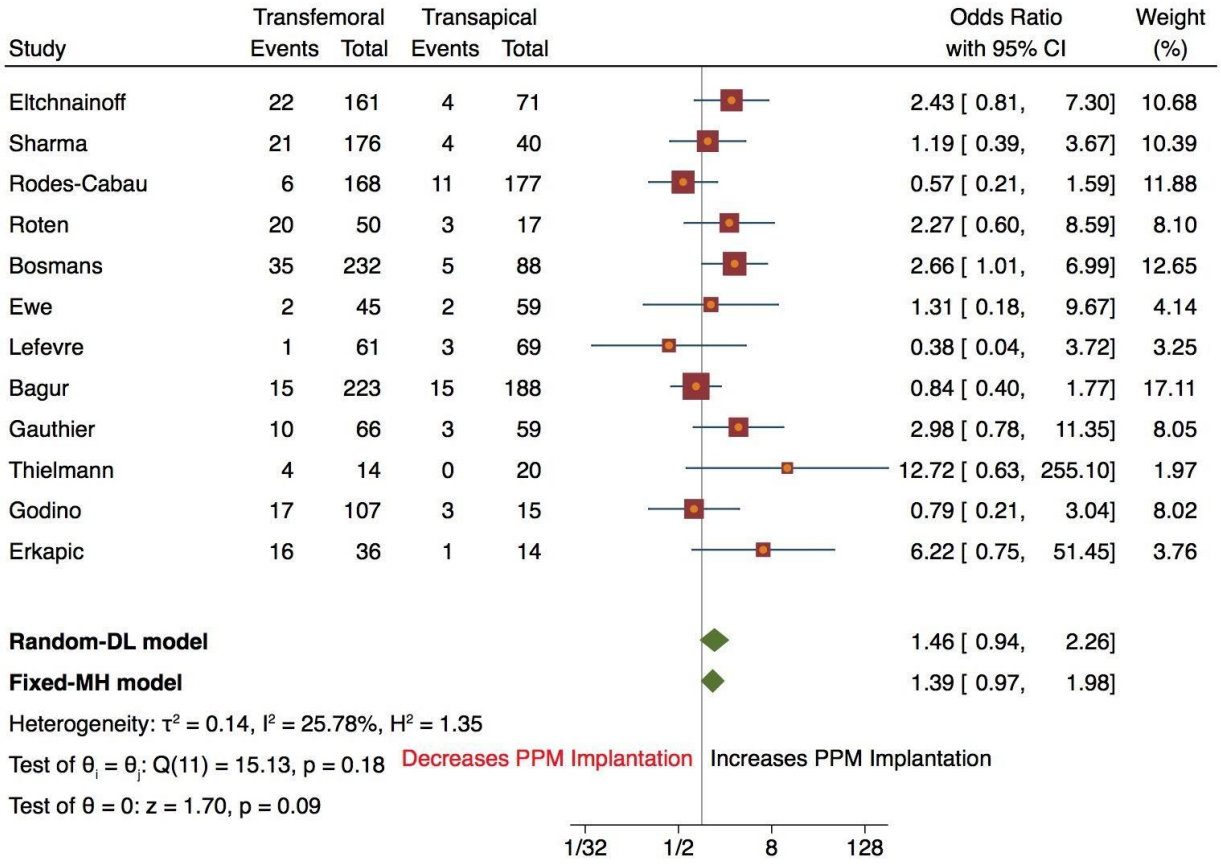


Figure S16: Forest Plot showing an individual and pooled OR of PPM Implantation comparing Transfemoral approach with subclavian approach

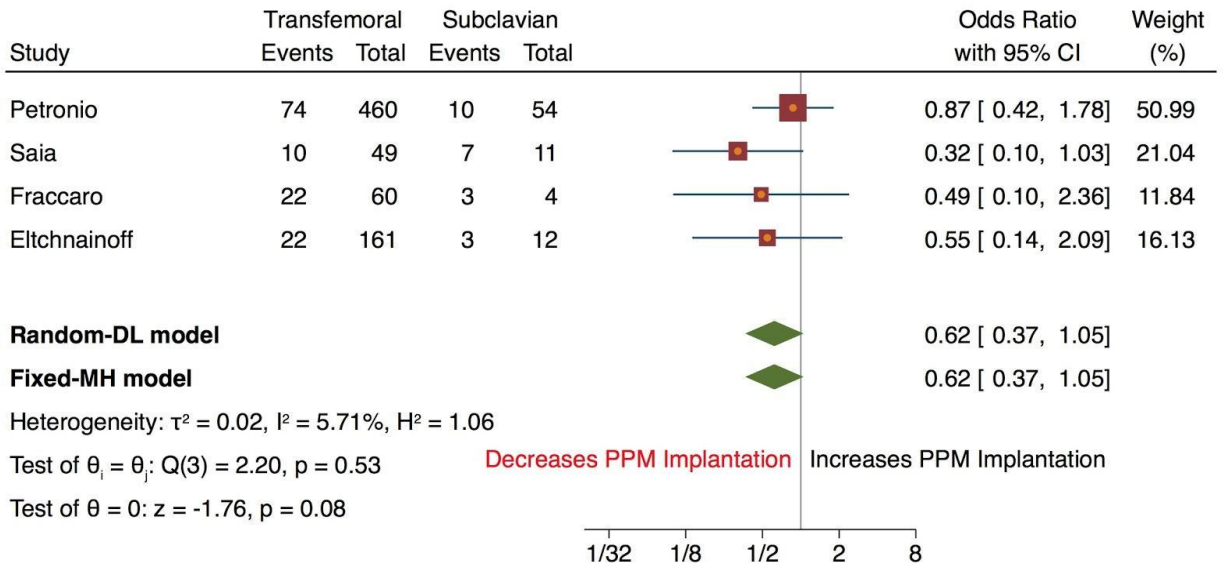


Figure S17: Forest plot showing the mean difference of implantation depth for patients with and without PPM

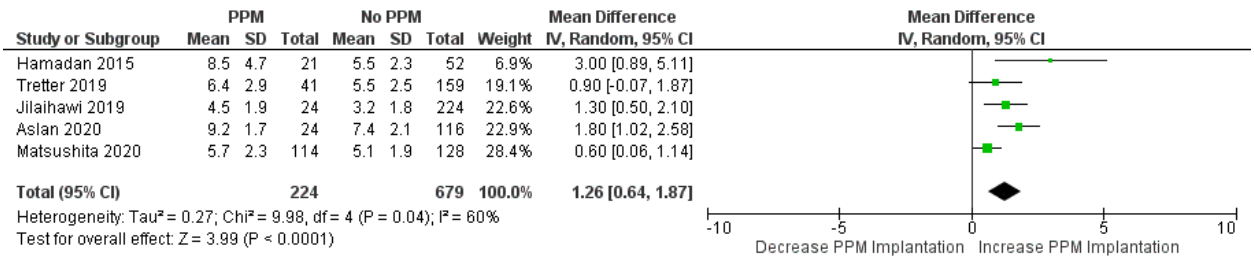


Figure S18: Forest plot showing the pooled mean membranous septal length for patients with and without PPM

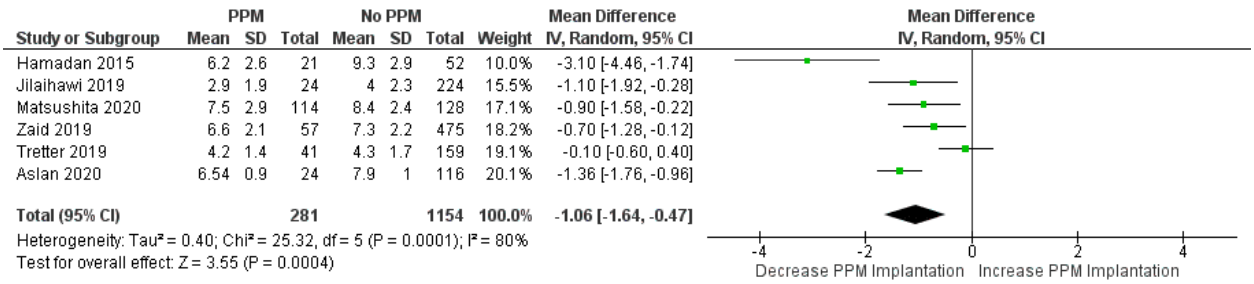


Figure S19:Forest Plot showing an individual and pooled OR of PPM Implantation comparing Medtronic CoreValve with Edwards SAPIEN valve

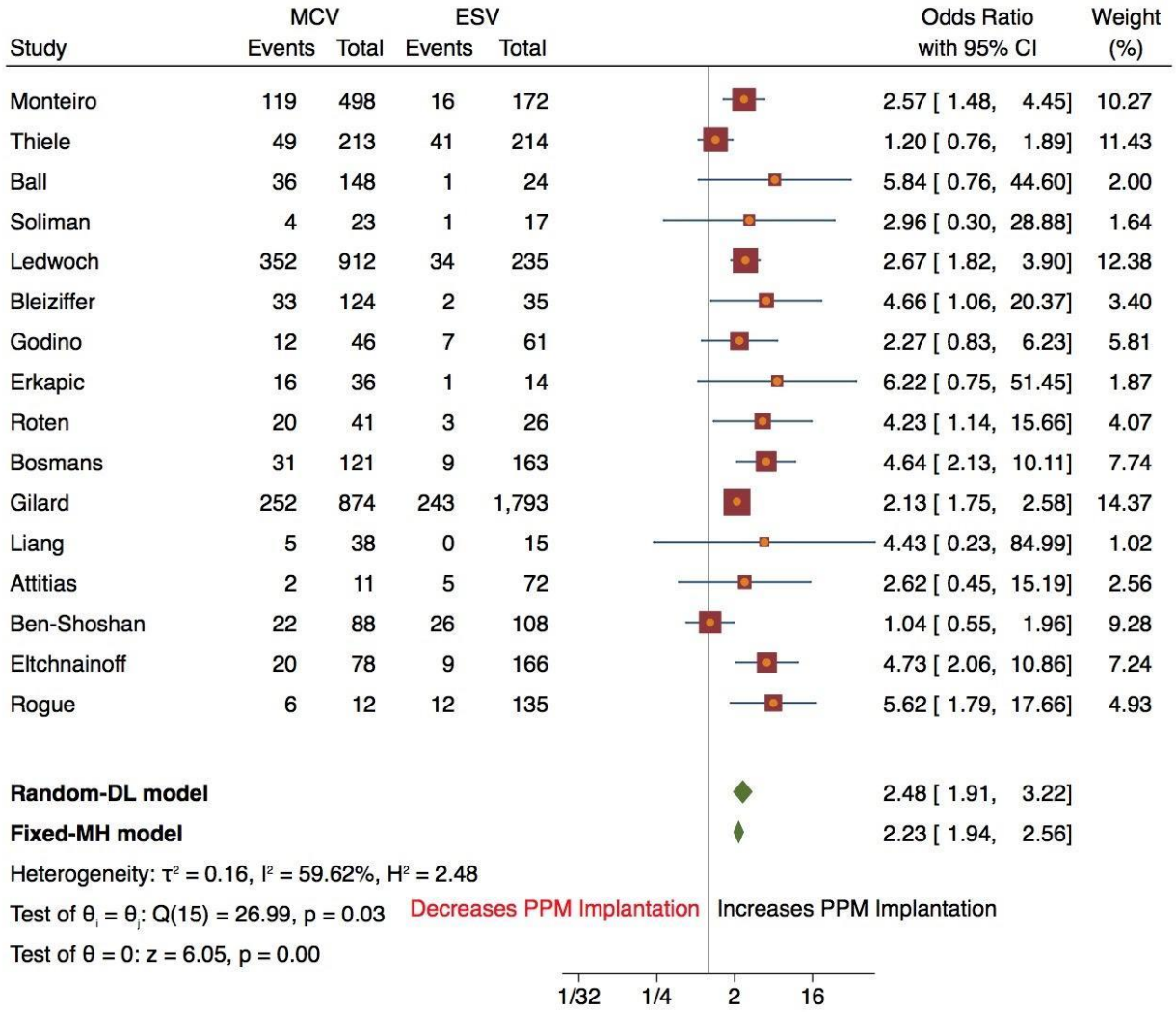


Figure S20: Forest Plot showing an individual and pooled OR of PPM Implantation comparing LOTUS valve with Medtronic CoreValve

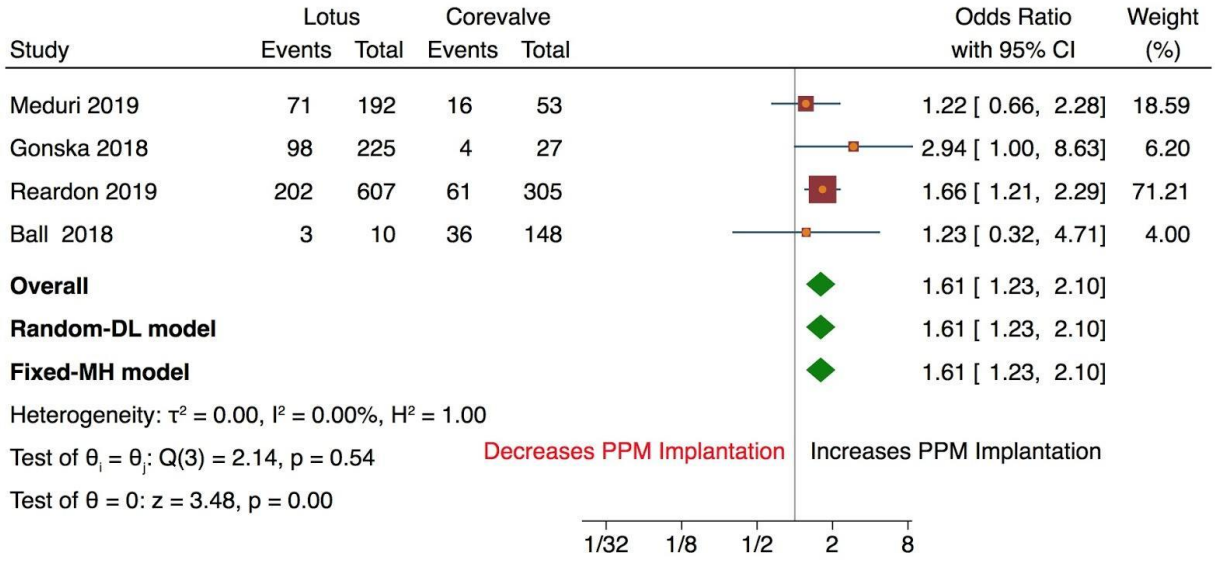


Figure S21: Forest Plot showing an individual and pooled OR of PPM Implantation comparing Edwards SAPIEN valve with Medtronic EvolutR valve

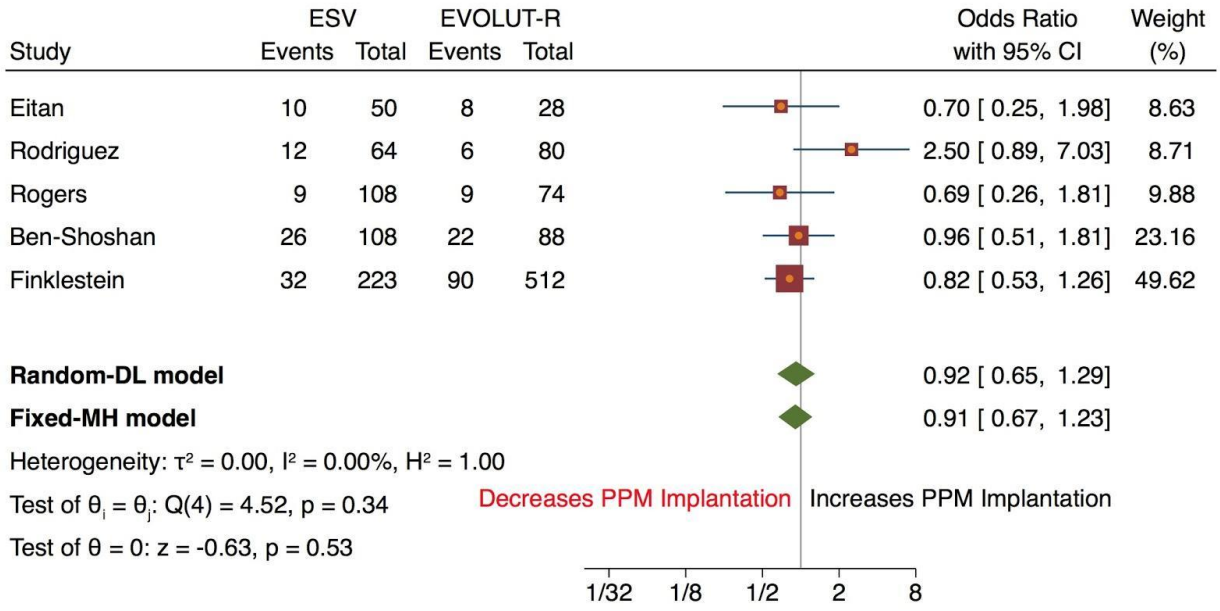


Figure S22: Sensitivity Analysis on the pooled estimate of PPM implantation in patients with First Degree HB.

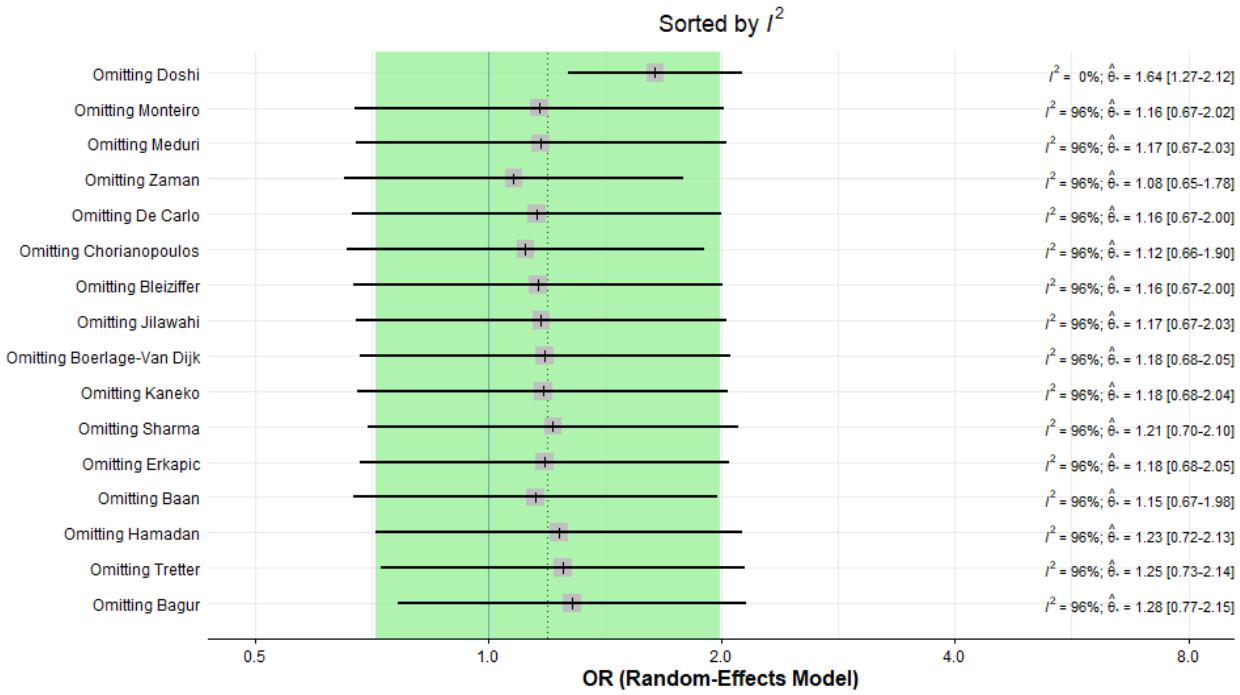


Figure S23: Sensitivity Analysis on the pooled estimate of PPM implantation in patients with RBBB.

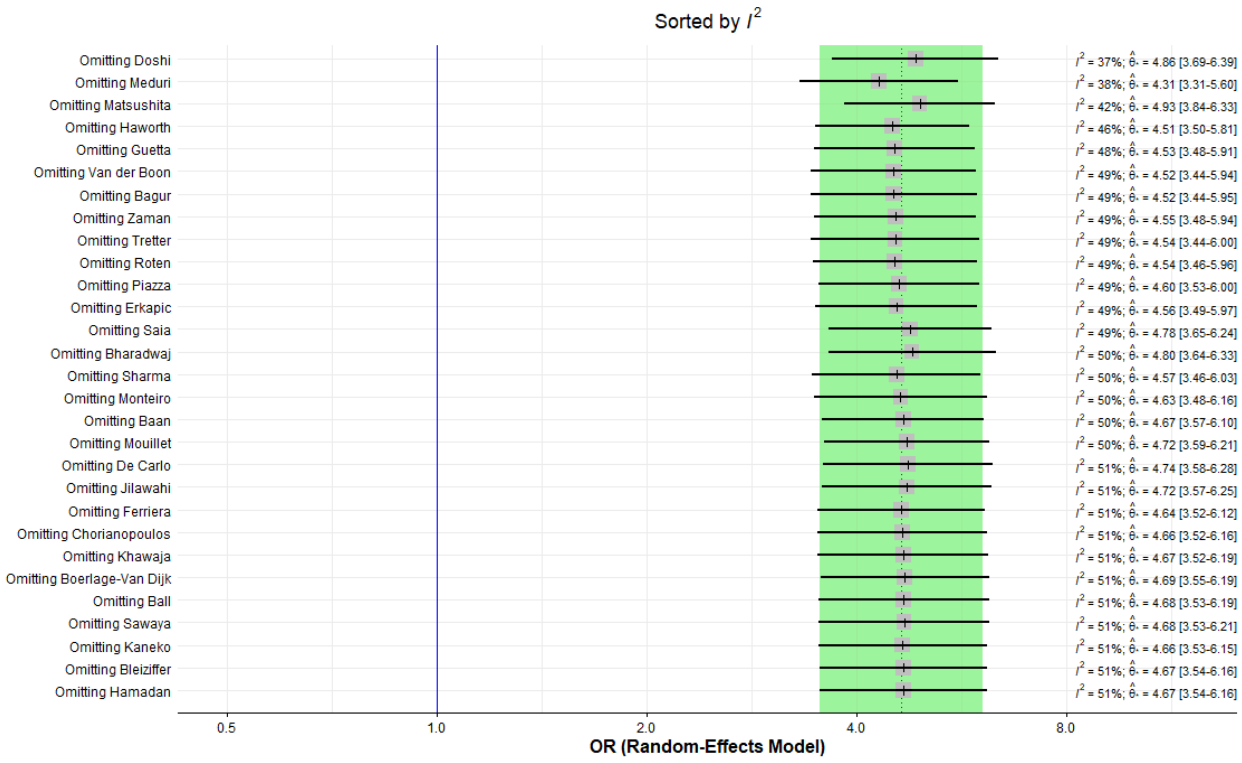


Figure S24: Sensitivity Analysis on the pooled estimate of PPM implantation in patients with LBBB.

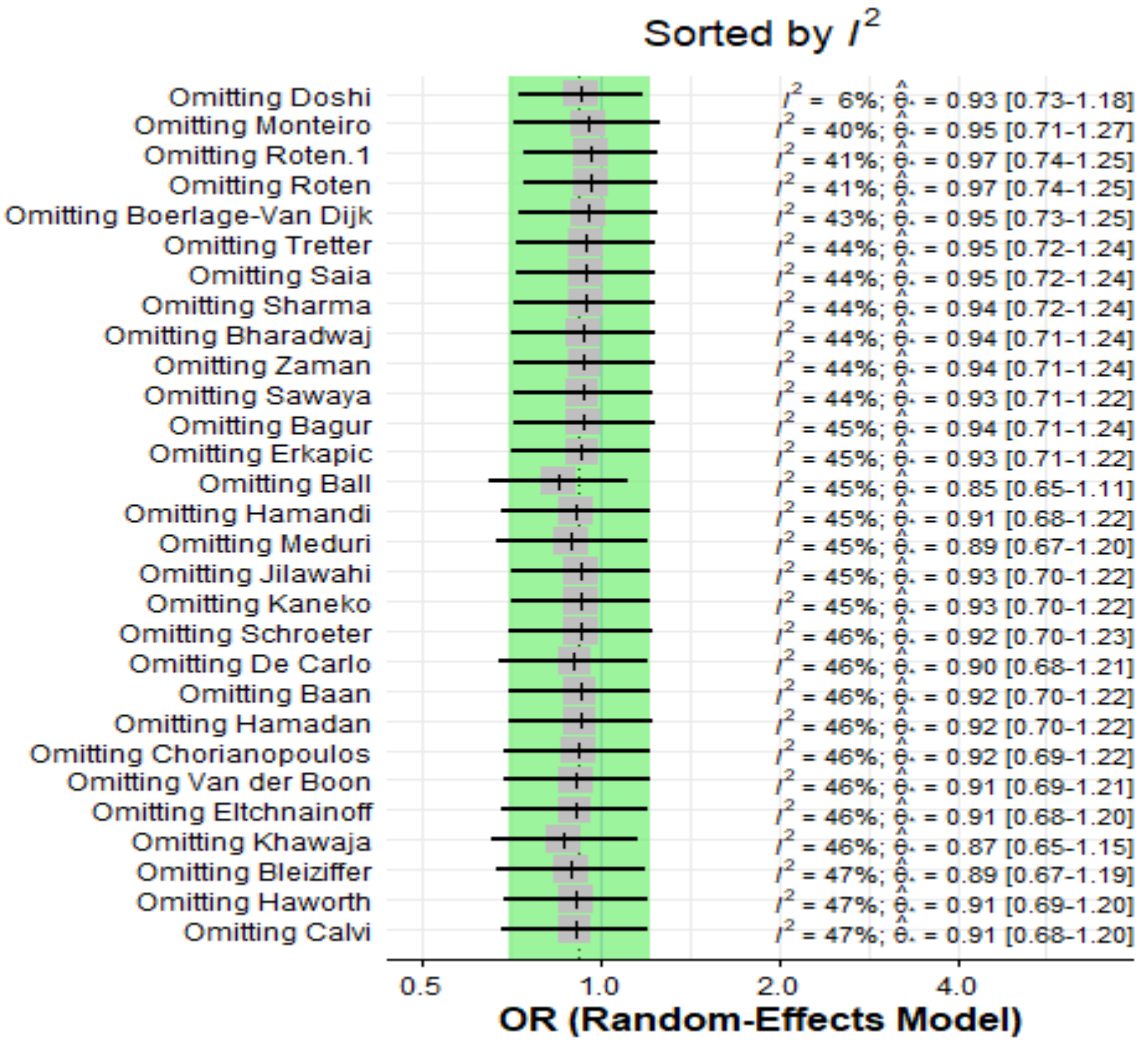


Figure S25: Funnel plot showing minimal publication bias comparing the pooled estimate of PPM predictor across studies for sex.