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SYSTEMATIC REVIEW AND META-ANALYSIS

Do Women Require Less Permanent Pacemaker After Transcatheter Aortic Valve Implantation? A Meta-Analysis and Meta-Regression

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BACKGROUND: Limited clinical evidence and literature are available about the potential impact of sex on permanent pacemaker implantation (PPI) after transcatheter aortic valve implantation (TAVI). The aim of this work was to evaluate the relationship between sexes and atrioventricular conduction disturbances requiring PPI after TAVI.

METHODS AND RESULTS: Data were obtained from 46 studies from PubMed reporting information about the impact of patient sex on PPI after TAVI. Total proportions with 95% CIs were reported. Funnel plot and Egger test were used for estimation of publication bias. The primary end point was 30-day or in-hospital PPI after TAVI, with odds ratios and 95% CIs extracted. A total of 70 313 patients were included, with a cumulative proportion of 51.5% of women (35 691 patients; 95% CI, 50.2–52.7). The proportion of women undergoing TAVI dropped significantly over time ($P<0.0001$). The cumulative PPI rate was 15.6% (95% CI, 13.3–18.3). The cumulative rate of PPI in women was 14.9% (95% CI, 12.6–17.6), lower than in men (16.6%; 95% CI, 14.2–19.4). The risk for post-TAVI PPI was lower in women (odds ratio, 0.90; 95% CI, 0.84–0.96 [$P=0.0022$]). By meta-regression analysis, age ($P=0.874$) and ventricular function ($P=0.302$) were not significantly associated with PPI among the sexes. Balloon-expandable TAVI significantly decrease the advantage of women for PPI, approaching the same rate as in men ($P=0.0061$).

CONCLUSIONS: Female sex is associated with a reduced rate of PPI after TAVI, without influence of age or ventricular function. Balloon-expandable devices attenuate this advantage in favor of women. Additional investigations are warranted to elucidate sex-based differences in developing conduction disturbances after TAVI.

Key Words: permanent pacemaker ■ sex ■ transcatheter aortic valve implantation ■ women

Transcatheter aortic valve implantation (TAVI) is a well-established therapeutic approach for patients with aortic stenosis at high and intermediate surgical risk.[1] Considerable advances in procedural techniques tend to extent TAVI indications to patients with a lower surgical risk.[2] However, atrioventricular conduction disturbances requiring PPI after TAVI continue to impact the benefit of this approach.[3,4] Sex-specific variations in the electrophysiological structure of the heart or other hormonal processes may cause differences in postoperative conduction disturbances leading to PPI.[5] A better patient selection and identification of preoperative risk factors for progression of conduction

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CLINICAL PERSPECTIVE

What Is New?

- Permanent pacemaker implantation (PPI) remains a frequent complication after transcatheter aortic valve implantation.
- A discriminative impact of sex has been observed in transcatheter aortic valve implantation outcomes, in favor of women, without specifically addressing the issue of postoperative PPI according to patient sex.
- This meta-analysis involving 35 691 women among a cohort of 70 313 patients is the first study to demonstrate a positive impact of female sex on postoperative PPI-related complication after transcatheter aortic valve implantation, with a beneficial risk reduction of 10%, independently of age or ventricular function.

What Are the Clinical Implications?

- Valve type may play an additional role; using a balloon-expandable valve in women increases the risk of PPI, reaching the same probability of PPI as in male patients.
- Further studies are required to understand the underlying mechanisms of postoperative conduction disturbances leading to PPI according to patient sex.

Nonstandard Abbreviations and Acronyms

PPI	permanent pacemaker implantation
TAVI	transcatheter aortic valve implantation

disturbances and subsequently PPI seem decisive to extent TAVI indications.[6] Current data about the impact of sex on PPI after TAVI remain controversial.[7] Female patients undergoing TAVI tend to have better outcomes than men[8,9] but specific investigations about PPI after TAVI according to sex have not been conducted: meta-analyses reporting on sex equality after TAVI do not often conclude about PPI according sex.[8–10] Siontis and colleagues[11] identified male sex as preprocedural predictor of PPI after TAVI but a recent meta-analysis showed that post-operative need for PPI was similar across sexes.[8] Women tend to have less comorbidities than men at baseline[10,12,13] but PPI creates more complications to women than men: pneumothorax and pocket haematoma after PPI are significantly more frequent in female patients.[14] Enhancing preventive measures for post-operative PPI, optimizing management of conduction disturbances post-TAVI and implementing data on sex differences in PPI after TAVI in clinical practice appear to be crucial.[15,16] Therefore, we performed a meta-analysis of published studies that reported sex-specific data on PPI after TAVI aiming to clarify the independent prognostic role of sex in patients undergoing PPI after TAVI.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files.

Research Strategy

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines and the Cochrane Collaboration, Quality of Reporting Meta-analyses (QUOROM). A broad, computerized literature search was performed to identify all relevant studies from PubMed database. The PubMed database was searched entering the following keywords: "Pacemaker, Artificial" [Mesh] OR pacemaker implantation AND "Transcatheter Aortic Valve Replacement" [Mesh] OR transcatheter aortic valve replacement AND "Female Sex" [Mesh] OR female gender. We restricted the research to publications in English language. Last access on database was on June 1, 2020. The search was limited to studies in human recipients.

Eligibility Criteria and Studies Selection

Review inclusion criteria were: patients aged >18 years (I), series with >250 patients (II) and reports providing a description of pacemaker status of the treated population (III). Furthermore, articles with no possible extraction of data sex were excluded. Systematic review and meta-analyses were not taken into account. Studies describing cardiac surgery procedures were excluded. We restricted the research to English publications.

Data Extraction

All potentially relevant studies were reviewed in details to check their adhesion to the inclusion criteria. A total of 877 records were initially screened at the title and abstract level, with 222 papers fully reviewed for eligibility. Title and abstracts of all retrieved articles were independently reviewed by two researchers (J.R. and M.D.M.) to identify studies fulfilling the inclusion criteria. Controversial findings were solved by the intervention of a third reviewer (R.L.). There were no duplicate data. Ultimately, 46 studies were identified and provided data for the research analysis. The process of study selection is illustrated in (Figure S1.)

Statistical Analysis

Calculation of an overall proportion from studies reporting a single proportion was performed using a meta-analytic approach by means of *metaprop* function of *meta-package* in RStudio. A logit-transformation was performed as suggested by Warton and Hui[17] to calculate CIs for individual study results, Clopper-Pearson approach was used; DerSimonian-Laird estimator was used to estimate the between-study variance.[18] Total proportion with 95% CI was reported. Funnel plot and Egger test were used for estimation of publication bias. Primary endpoint was 30-day or in-hospital PPI after TAVI, with odds ratios (ORs) and 95% CIs extracted from 46 studies. Statistical pooling of OR was performed using a random effect model with 95% CIs. Forest plots were used to plot the effect size, either for each study or overall. We calculated the I^2 statistics (0–100%) to explain the between-study heterogeneity, with $I^2 \leq 25\%$ suggesting more homogeneity, $25\% < I^2 \leq 75\%$ suggesting moderate heterogeneity, and $I^2 > 75\%$ suggesting high heterogeneity.[19,20] If the null hypothesis was rejected, a random effects model was used to calculate pooled effect estimates. If the null hypothesis was not rejected, a fixed effects model was used to calculate pooled effect estimations[18]; 95% CI was also reported. Forest plots were used to plot the effect size, either for each study or overall. Publication bias was evaluated by graphical inspection of funnel plot; estimation of publication bias was quantified by means of Egger linear regression test.[21] In case of moderate or high heterogeneity, influence analysis was performed with different approaches. Baujat plot[22] and leave-one-out sensitivity analysis were performed by iteratively removing one study at a time to confirm that our findings were not driven by any single study. Meta-regression analysis was performed, reporting results as *P* value. One study removed analysis was performed as sensitivity analysis. Meta-package in RStudio version 1.1.463 (2009–2018) was used.

RESULTS

Study, Participants and Proportion of Women

We included a total of 70 313 patients from 46 studies, published from January 2005 to October 2018. Baseline characteristics of patients are reported in Table 1.[23–68] Among the patients included in the analysis, there were 35 691 women with a cumulative proportion of 51.5% (95% CI, 50.2%–52.7%) (Figure S2). Heterogeneity was high (I^2=88.6%; 95% CI, 85.6%–90.9%]). No publication bias was found (Egger test *P* value 0.3362). The proportion of women dropped significantly over time (*P*<0.0001) (Figure 1).

Type of Valves and Proportion of Women

Splitting the studies according to the percentage of women included, 4 categories were obtained: <50%, 50% to 54%, 55% to 59%, and ≥60%. In the latter group of studies, balloon expanding valves were less implanted than the others. Conversely, self-expanding valves were highly implanted in those studies with higher proportion of women (Table S1). Mechanical expanding valves were used less commonly in this meta-analysis (only 8 studies) and in most of cases was the only valve used.

Permanent Pacemaker Implantation Details

Pacemaker-related details in the selected studies are reported in Table 2.[23–68] Cumulative rate of PPI was 15.6% (95% CI, 13.3%–18.3%) (Figure 2). Heterogeneity was high (I^2=98.6%; 95% CI, 98.4%–98.7%]). No publication bias was found (Egger test *P* value 0.8759). The pooled analysis showed that women had lower risk for post-TAVI PPI than men (OR, 0.90; 95% CI, 0.84–0.96 [*P*=0.0022]) (Figure 3). Heterogeneity was moderate (I^2=38.5%; 95% CI, 12.1%–57.0%). No publication bias was found (Figure S3), Egger test *P* value was 0.1234. Baujat plot (Figure S4) showed that overall heterogeneity was becasuse of few studies but the leave-one-out analysis (Figure S5) showed that the overall estimation was not driven by any single study.

Meta-Regression: Influence of Age, Ventricular Function, Balloon-Expandable TAVI, and Patient Risk

Meta-regression analysis showed no effect of age (*P*=0.874), and ventricular function (*P*=0.302) on different PPI rate between women and men (Figure S6A and S6B). Balloonexpandable TAVI showed a significant effect of sex difference in terms of PPI rate (*P*=0.0061) (Figure S6C), meaning that the higher the percentage of balloon-expandable implanted, the lower the difference in terms of risk between women and men. Mean value of risk score reported in each study was used to define the cohort as at high or intermediate risk. Hence, intermediate risk was defined as EuroSCORE (European System for Cardiac Operative Risk Evaluation) II between 4 and 9 or STS PROM (Society of Thoracic Surgeons Predicted Risk of Mortality) between 4 and 8. High risk was defined when Logistic EuroSCORE I was >20%, STS PROM was ≥8, or EuroSCORE II was >9. Finally, 30 studies included high-risk patients and 16 intermediate-risk

Table 1. Baseline Characteristics of the Included Studies (n=46)

Authors	Year	Study Design (n of Centers)	Sample Size, n of Patients	Patient Age, y	STS Risk Score, %	Inclusion Period	Valve Type	Follow-Up, mo*	Approach for TAVI	Mortality at 30 d, %
D'Ancona et al[23]	2011	Prospective (1)	322	80.5	16.1	April 2008–March 2011	100% BE	36	Na	5.7
Buellesfled et al[24]	2012	Retrospective (2)	305	82.6	Na	August 2007–March 2010	90% MCV/10% ES	12	Na	6.5
Humphries et al[25]	2012	Retrospective (2)	641	82.5	7.5	January 2005–September 2011	Na	10	Na	8.7
Hayashida et al[26]	2012	Prospective (1)	260	83.1	Na	October 2006–December 2010	14.6% SE/85.4% BE	7	65% Transfemoral/31.9% transapical/3.1% trans-subclavian	15
De Carlo et al[27]	2012	Retrospective (3)	275	82.4	Na	September 2007–July 2010	100% MCV	12	Na	3
Buja et al[28]	2013	Retrospective (13)	659	81	Na	June 2007–December 2009	100% SE	13	90% Transfemoral/10% trans-subclavian	Na
Ledwoch et al[29]	2013	Prospective (22)	1147	82	Na	January 2009–June 2010	80% MCV/20% ES	1	Surgical 10%/transapical 10%/direct aortic 0.6%/ transfemoral 87%/ transaxillary 3%/ transarterial 89%	7
Gensas et al[30]	2014	Retrospective (18)	353	82	14.4	January 2008–February 2012	85.8% SE/14.2% BE	60	Na	Na
Urena et al[31]	2014	Retrospective (8)	1556	80.5	7.5	January 2005–February 2013	55.1% BE/44.9% SE	22	Na	7
Dizon et al[32]	2015	Retrospective (21)	2531	84.5	11.6	March 2007–March 2009	100% BE	12	Na	Na
Mouillet et al[33]	2015	Retrospective (29)	833	82	14.1	January 2010–October 2011	100% SE	8	Na	9.3
Nazif et al[34]	2015	Retrospective (21)	1973	84.5	11.4	May 2007–September 2011	100% BE	12	Na	6.6
Fadahunsi et al[35]	2016	Retrospective (388)	9785	84	7	November 2011–September 2014	88.7% BE/11.3% SE	12	59.1% Transfemoral/0.5% trans-subclavian, transaxillary/30.8% transapical/7.5% transaortic/2.1% others	5.6
Giustino et al[36]	2016	Retrospective (4)	947	81.5	8.8	November 2005–December 2011	47.9% BE/52.1% SE	14	85.2% Transfemoral/7.4% transaxillary/1.5% transaortic/9.2% transapical	6.1
Rodriguez-Olivares et al[37]	2016	Retrospective (1)	302	81	Na	November 2005–January 2015	67.2% SE/21.2% BE/11.6% ME	Na	Na	Na
Gonska et al[38]	2017	Retrospective (1)	283	79.9	6.7	Na	100% ES	Na	Na	Na

(*Continued*)

Table 1. Continued

Authors	Year	Study Design (n of Centers)	Sample Size, n of Patients	Patient Age, y	STS Risk Score, %	Inclusion Period	Valve Type	Follow-Up, mo*	Approach for TAVI	Mortality at 30 d, %
Monteiro et al[39]	2017	Retrospective (22)	670	81.8	10.7	January 2008–January 2015	74% MCV/26% ES	Na	96% Transfemoral/4% others	Na
Van Gils et al[40]	2017	Retrospective (4)	306	83	6.3	May 2008–February 2016	38.2% SE/34.7% SE/27.1% ME	12	Na	7
Raelson et al[41]	2017	Retrospective (1)	578	85.5	Na	March 2009–December 2014	21% SE/79% BE	1	Na	Na
Dumonteil et al[42]	2017	Retrospective (14)	250	84	6.3	October 2012–May 2014	100% ME	12	100% Transfemoral	4
Chamandi et al[43]	2018	Prospective (9)	1692	81.5	10.9	May 2009–February 2015	50.3% BE/49.7% SE	48	Na	42.3
Gaede et al[44]	2018	Retrospective (1)	1025	81.9	Na	2010–2015	Na	2.4	Na	Na
Bhardwaj et al[45]	2018	Retrospective (1)	383	83	9	January 2012–July 2016	82% BE/18% SE	9	84% Transfemoral	Na
De-Torres-Alba et al[46]	2018	Retrospective (1)	606	81.6	Na	January 2014–January 2017	100% BE	Na	Na	Na
Mangieri et al[47]	2018	Retrospective (1)	611	84.4	6.9	October 2007–July 2015	51.7% BE/33.7% SE	12	Na	Na
Gonska et al[48]	2018	Prospective (1)	612	80.4	6.5	February 2014–September 2016	58.8% BE/36.7% ME/4.4% SE	12	Na	1.3
Marzahn et al[49]	2018	Retrospective (1)	856	80.5	Na	July 2008–May 2015	37.4% SE/57.8% BE/4.8% ME	12	100% Transfemoral	Na
Schewel et al[50]	2018	Retrospective (1)	563	81.2	5	July 2008–January 2016	100% BE	Na	8.9% Transapical/87.1% transfemoral/transaortic 1.6%/transaxillary 2.4%	Na
Doshi et al[51]	2018	Retrospective (Na)	5163	81.1	Na	January 2012–December 2014	Na	Na	Na	Na
Vejpongsa et al[52]	2018	Retrospective (Na)	18 400	81.2	Na	January 2012–December 2013	Na	Na	Transfemoral 75.5%/24.5% transapical	Na
Sannino et al[53]	2018	Retrospective (2)	910	81.5	7.5	January 2012–July 2016	59% BE/41% SE	12	88.2% Transfemoral/7.6% transapical/3.2% transaortic/1% transubclavian	2.9
Doshi et al[54]	2018	Retrospective (Na)	8148	82.5	Na	January 2012–December 2014	Na	Na	Na	Na
Nadeem et al[55]	2018	Retrospective (1)	672	81.4	7.4	2011–2017	Na	12	Na	Na
Pellegrini et al[56]	2019	Retrospective (3)	709	81	Na	January 2014–January 2016	100% BE	Na	100% Transfemoral	1.6
Pellegrini et al[57]	2019	Retrospective (3)	283	80.8	6	January 2014–January 2016	100% SE	12	100% Transfemoral	Na

(*Continued*)

Table 1. Continued

Authors	Year	Study Design (n of Centers)	Sample Size, n of Patients	Patient Age, y	STS Risk Score, %	Inclusion Period	Valve Type	Follow-Up, mo*	Approach for TAVI	Mortality at 30 d, %
Costa et al[58]	2019	Prospective (1)	1116	82	4.4	June 2007–February 2018	61.8% SE/27.2% BE/0.5% ME/10.5% others	72	97% Transfemoral/3% others	3.9
Dolci et al[59]	2019	Retrospective (1)	266	80	Na	February 2014–February 2018	100% BE	12	84% Transfemoral/16% transapical	Na
Meduri et al[60]	2019	Prospective (1)	704	82.5	6.6	Na	34% SE/66% ME	12	Na	Na
Husser et al[61]	2019	Prospective (7)	296	81	Na	January 2014–July 2017	66.9% BE/33.1% SE	1	Na	4
Ahmad et al[62]	2019	Retrospective (1)	269	79.5	6.2	December 2012–April 2018	100% BE	Na	Na	Na
Ahmad et al[63]	2019	Retrospective (1)	382	80.5	6.9	December 2012–April 2018	100% BE	1	86.6% Transfemoral/6% transaortic/6% transapical/0.8% transiliac/0.5% trans-subclavian	Na
Cresse et al[64]	2019	Retrospective (1)	386	83	Na	April 2008–June 2017	Na	Na	Na	Na
Wang et al[65]	2019	Prospective (1)	298	80	Na	December 2015–June 2018	78% BE/22% SE	Na	99.6% Transfemoral	Na
Maeno et al[66]	2019	Retrospective (1)	659	83	Na	January 2013–December 2015	85% BE/15% SE	19.1	Na	2.6
Du et al[67]	2020	Retrospective (1)	256	76.5	7.1	March 2013–October 2018	Na	12	Na	3.3
Shivamurthy et al[68]	2020	Retrospective (1)	917	80	Na	November 2011–February 2017	Na	Na	89.7% Transfemoral/10.3% transapical	Na

BE indicates balloon-expandable; ES, Edwards Sapien; MCV, medtronic core valve; ME, mechanically expandable; Na, not available; SE, self-expandable; STS, Society of Thoracic Surgeons; and TAVI, transcatheter aortic valve implantation.

*Follow-up is reported as mean or median as given by the authors.

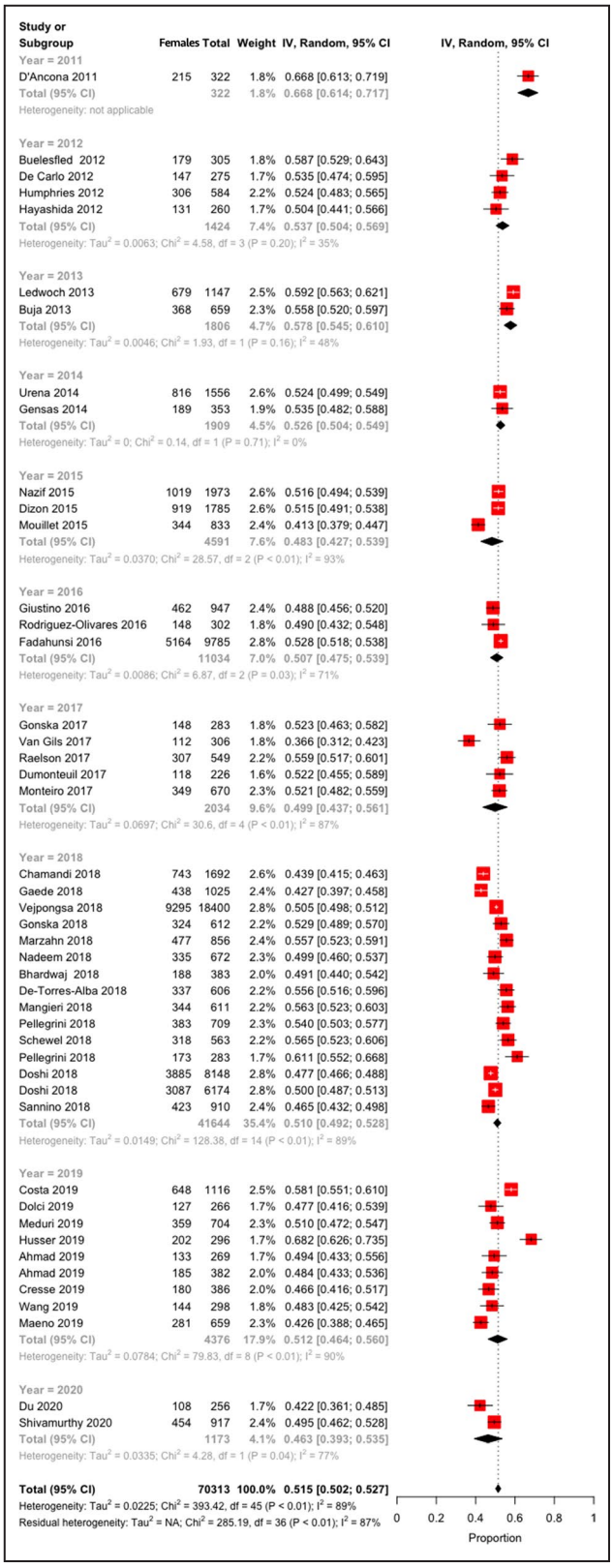

Figure 1. Forest plot pooling proportions of women according to year of publication.
IV indicates interval variable.

patients. No influence of pacemaker rate was found on the basis of cohort risk (*P*=0.9024) (Figure S6D).

DISCUSSION

This is the first meta-analysis to demonstrate the impact of sex on new PPI after TAVI. Our study is derived from 46 studies reporting clinical outcomes in 70 313 patients receiving TAVI. The most important findings of our study can be summarized as follows: (1) the proportion of women undergoing TAVI significantly decreases during the last 10 years; (2) female sex has 10% lower risk for PPI after TAVI than men, with no influence of age or ventricular function (3) the use of a balloon-expandable valve in women reduces the advantage of female sex in term of PPI post-TAVI.

Nowadays, women represent more than 50% of the patients undergoing TAVI.[69] Female patients eligible for TAVI have a lower burden of comorbidities.[8,10,26] Interestingly, we found that the proportion of women involved in the studies decreased during the last 10 years. We found no explanation for such a result and this information deserves further investigation. However, even if our study showed a decreasing trend in female submitted to TAVI procedure, a longer life-expectancy of female sex might foresee that the proportion of women undergoing TAVI will increase in the future.[70] Gathering these 2 aspects, we can reasonably extrapolate that women should be potential future low-risk patients who should benefit from TAVI. Therefore, decreasing complications as PPI is decisive to define the best therapeutic strategy for women with aortic stenosis.

Current evidence about the prognostic role of sex in outcomes after TAVI is poor, and the issue of atrioventricular conduction disturbances requiring PPI across sexes is rarely debated.[25,26,53] Recent studies showed favorable outcomes in female patients after TAVI,[10,53,71] without emphasizing the issue of post-operative PPI. Male sex was already identified as predictive factor for PPI after TAVI[11] even if other investigations reported no differences in PPI across sexes.[7,28] In this study, we found that women were 10% less at risk for PPI after TAVI procedure, confirming higher PPI rates in men reported by other studies.[28,72,73] This sex-based difference in post-operative PPI is often related to the favorable baseline characteristics of the women undergoing TAVI, explaining the better outcomes in the female cohort.[8,28] Nevertheless, data from feminine registry as WIN-TAVI[74] investigated anatomic risk-factors specific to women in PPI after TAVI and showed that right coronary cusp calcium volume was an independent predictor for PPI, while non-coronary cusp calcium has no incidence on atrio-ventricular conduction disturbances

Table 2. Pacemaker-Related Details in the Selected Studies

Authors	Indications for PPI	Timing of PPI, d*	PPI Rate, %	Multivariate Predictors of PPI	Association With PPI
D'Ancona et al[23]	Na	4	32	Age*	Na
Buellesfled et al[24]	62.2% AVB/21.4% Others/16.3% bradycardia	3	28	Na	Na
Humphries et al[25]	Na	Na	5.5	Na	Na
Hayashida et al[26]	Na	Na	6.5	Na	Na
De Carlo et al[27]	70% AVB/3% SSS/27% others	4	24	Lower MCV implantation below aortic annulus* RBBB* Left anterior hemiblock* Longer PR interval*	Na
Buja et al[28]	Na	Na	19	Na	Na
Ledwoch et al[29]	Na	Na	33.7	Absence of prior valve surgery* MCV* Porcelain aorta*	Na
Gensas et al[30]	Na	Na	25.2	Preexisting RBBB* Baloon predilatation* MCV use*	Na
Urena et al[31]	75.3% AVB/7.1% SSS/7.9% Bradycardia/9.6% others	3	15.4	Na	PPI protective factor for the occurrence of unexpected (sudden or unknown) death* Negative effect on LVF over time*
Dizon et al[32]	79% AVB/7.3% SSS	Na	8.8	Na	PPI and 1-y mortality*
Mouillet et al[33]	Na	Na	30.3	Na	Na
Nazif et al[34]	79% AVB/17.3% SSS	3	8.8	Preexisting RBBB* Prosthesis to LV outflow tract diameter ratio* LV end-diastolic diameter*	Longer duration of hospitalization* Higher rates of repeat hospitalization and mortality or repeat hospitalization at 1 y*
Fadahunsi et al[35]	Na	3	6.7	Na	PPI and higher mortality and composite of mortality or HF at 1 y*
Giustino et al[36]	Na	Na	15.4	Na	PPI+postprocedural aortic regurgitation=negative impact on survival and LVF recovery* PPI and valvular balloon postdilatation and device oversizing*
Rodriguez-Olivares et al[37]	Na	Na	22.5	Na	More LV outflow tract oversizing associated with higher PPI*
Gonska et al[38]	85.1% AVB/10.1% Bradycardia/4.8% others	Na	24.4	Na	PPI without significant impact on survival or combined end point of major adverse events within 1 y*
Monteiro et al[39]	Na	Na	20.1	Previous RBBB* Mean aortic gradient >50 mm Hg* MCV*	Na
Van Gils et al[40]	99% AVB/1% SSS	2	41	LOTUS valve* Higher BMI before TAVI*	RBBB at baseline associated with higher PPI*
Raelson et al[41]	82% AVB	3	9	Na	Na
Dumonteil et al[42]	88.9% AVB/5.9% others	3	32	Baseline RBBB* LV outflow tract overstretch >10%*	Trend lower PPI rate at 30 d with shallower (≤5 mm) implant depth*
Chamandi et al[43]	76.7% AVB/5.6% SSS/3.1% Bradycardia/14.6% others	2	19.8	Na	PPI higher rates of rehospitalization for HF and combined end point of mortality or hHFrehospitalization* PPI lesser improvement in LVF over time, particularly in patients with reduced LVF before TAVI*
Gaede et al[44]	90% AVB/8% SSS/2% Bradycardia	4	14.7	Preexisting RBBB* MCV prosthesis*	Predictors of lack of recovery of AVB Prior RBBB* Higher mean aortic valve gradient* Postdilatation of the prosthesis*

(*Continued*)

Table 2. Continued

Authors	Indications for PPI	Timing of PPI, d*	PPI Rate, %	Multivariate Predictors of PPI	Association With PPI
Bhardwaj et al[45]	Na	Na	11.5	PPI with short-term reduction in QoL without long-term implications*	Na
De-Torres-Alba et al[46]	96% AVB/1.4% Bradycardia/2.6% others	Na	12.5	Na	Na
Mangieri et al[47]	84% AVB/8.4% Bradycardia	0.3	8.8	Na	Na
Gonska et al[48]	94.2% AVB/3.8% Bradycardia/2% others	4.3	18.4	Baseline first-degree AVB* Preprocedural complete RBBB*	Na
Marzahn et al[49]	89% AVB/5.5% Bradycardia/4.1% SSS/1.4% others	Na	16.9	Na	Na
Schewel et al[50]	Na	Na	10.8	Na	Na
Doshi et al[51]	Na	Na	24	Female sex* AF* LBBB* AVB*	Na
Vejpongsa et al[52]	Na	2	9.9	Na	Na
Sannino et al[53]	Na	Na	18.4	Na	Na
Doshi et al[54]	Na	Na	25.5	Na	Na
Nadeem et al[55]	Na	Na	21.7	Na	PPI more likely to have HF admissions* PPI trend toward increased mortality*
Pellegrini et al[56]	71.3% AVB/5.2% SSS/23.5% Bradycardia	Na	16.2	Increase in prosthesis oversizing*	Na
Pellegrini et al[57]	71.5% AVB/3.5% SSS/25% Bradycardia	Na	10	Higher EuroSCORE*	Na
Costa et al[58]	84.8% AVB/4.1%SSS/11% others	Na	13	Na	PPI associated with increased 6 y mortality* Baseline RBBB higher chance of being dependent at follow-up*
Dolci et al[59]	80%AVB/11% Bradycardia/9% others	4	13	Baseline RBBB* QRS width immediately after TAVI*	Na
Meduri et al[60]	90% AVB/6% Bradycardia/4% others	2	28.4	Baseline RBBB* Mean depth of valve implantation*	Medically treated diabetes mellitus in patients with LOTUS valve*
Husser et al[61]	80.2% AVB/16.4% Bradycardia/3.4% SSS	Na	39.2	Na	If RBBB, lower PPI with Neo than Edwards Sapien 3*
Ahmad et al[62]	Na	1.3	6.3	Na	Higher hemoglobin* 29-mm Valve* Prior conduction defects*
Ahmad et al[63]	Na	Na	5	Na	Na
Cresse et al[64]	Na	4	6.7	Na	RBBB, LBBB, △PR >40 ms associated with PPI*
Wang et al[65]	Na	Na	7.7	Na	Na
Maeno et al[66]	77.9% AVB/11.5% SSS/10.6% Bradycardia	Na	15.8	Na	Na
Du et al[67]	89.5% AVB	8.7	14.8	Na	Na
Shivamurthy et al[68]	Na	Na	9.8	Na	Na

Values are number (percentage), mean=SD, or median (interquartile range) as appropriate. △ indicates change; AF, atrial fibrillation; AVB, atrioventricular block; BMI, body mass index; Edwards Sapien 3 valve (Edwards Lifesciences); EuroSCORE, European System for Cardiac Operative Risk Evaluation; HF, heart failure; LBBB, left bundle branch block; LOTUS valve (Boston Scientific Corporation); LV, left ventricular; LVF, left ventricular function; MCV, Medtronic CoreValve (Medtronic); Na, not available; PPI, permanent pacemaker implantation; QoL, quality of life; RBBB, right bundle branch block; SSS, sick sinus syndrome; and TAVI, transcatheter aortic valve implantation.

*Follow-up is reported as mean or median as given by the authors.

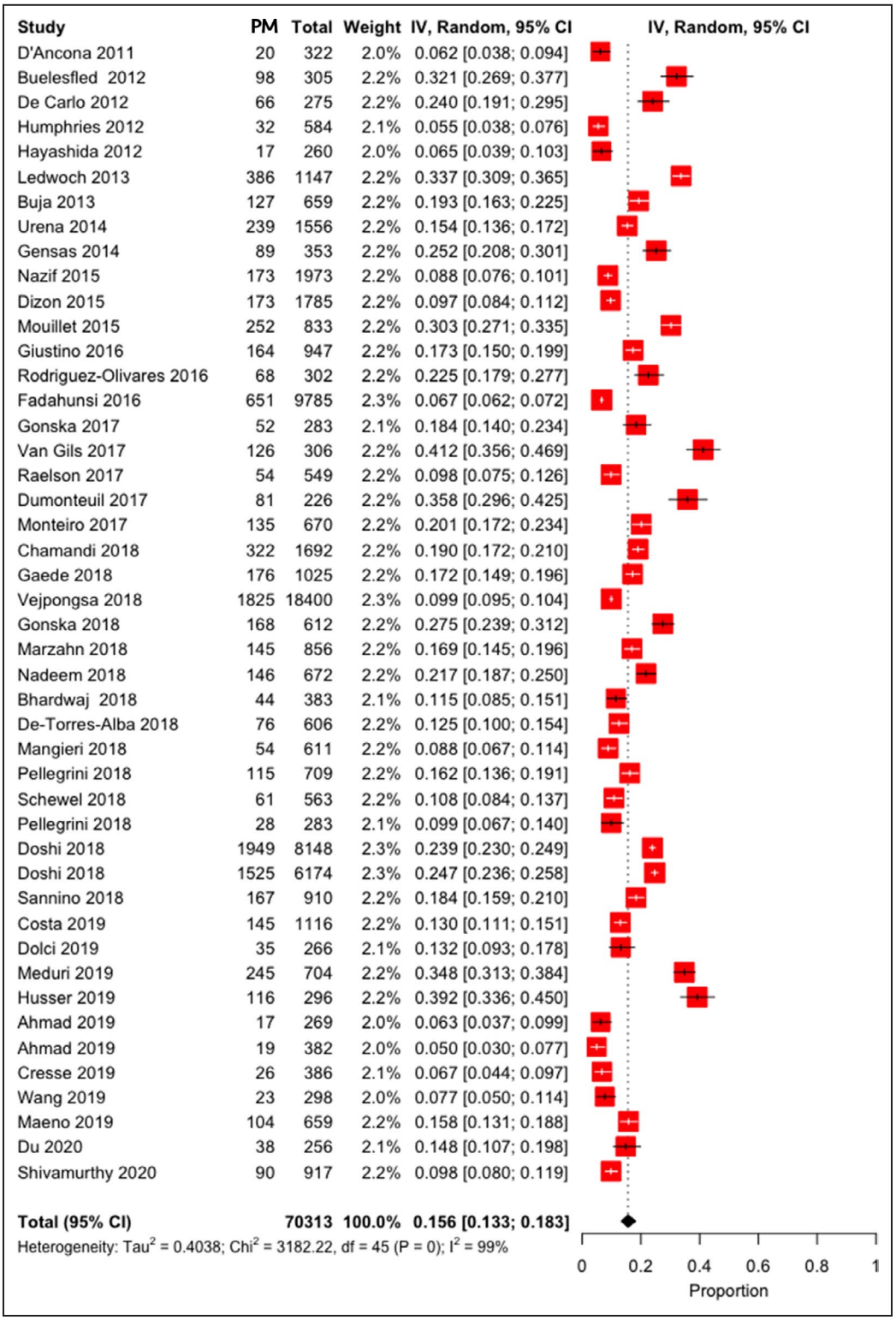

Figure 2. Forest plot pooling rate of postprocedure pacemaker implantation in 46 studies.[23–68]
IV indicates interval variable.

leading to PPI. Moreover, women with severe aortic stenosis have smaller aortic root dimensions compared with men, even after correction for body size and height.[75] The use of smaller devices and the lower need for eventual procedural balloon dilatation because of the smaller aortic root dimensions can explain

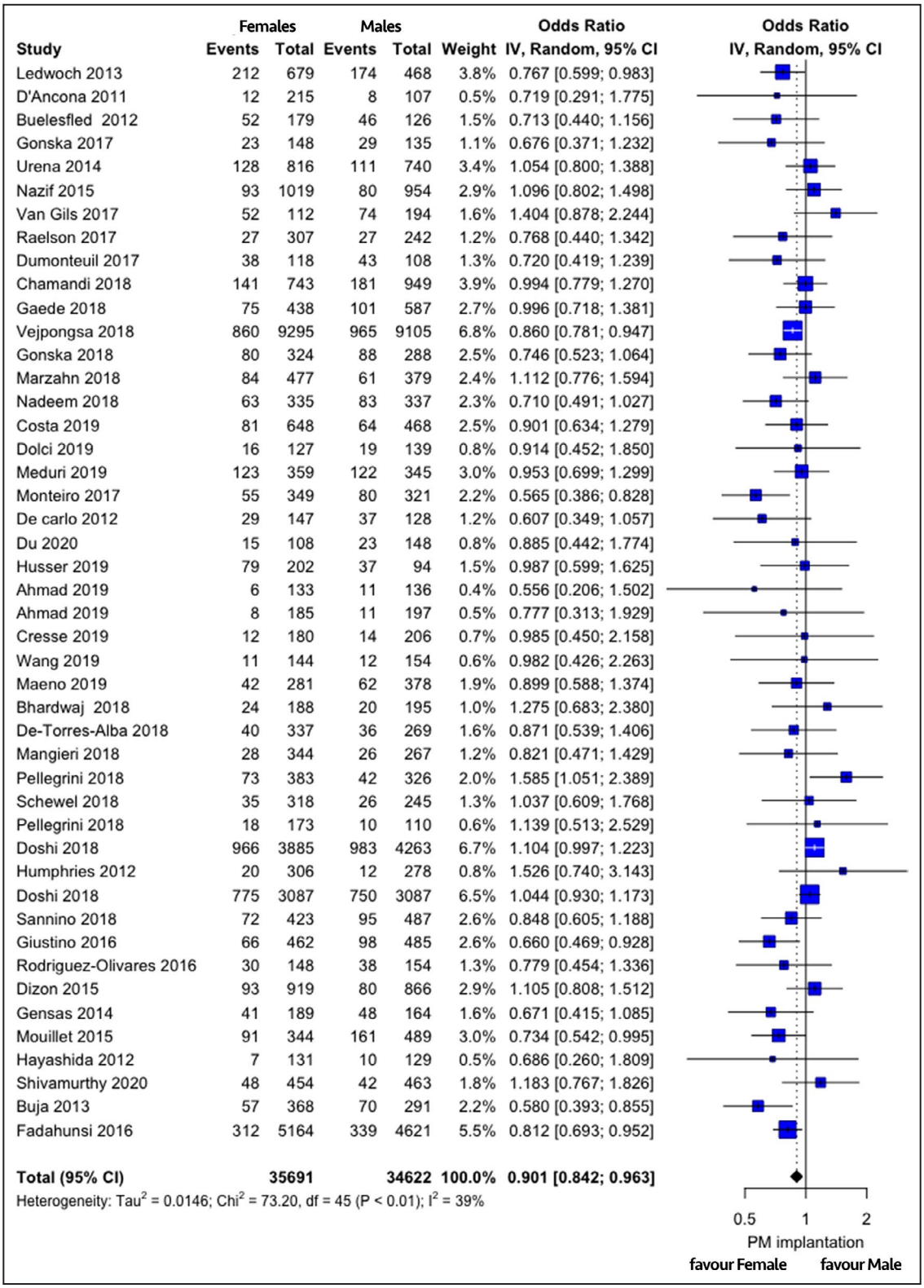

Figure 3. Forest plot comparing the effect of sex on the rate of postprocedure pacemaker implantation.[23–68]
IV indicates interval variable.

the lower rate of PPI in women,[76] making women less likely to undergo PPI post-TAVI, independently from age or ventricular function, as highlighted in this study.

Interestingly, we found that using a balloon-expandable valve could attenuate the advantage of women on post-operative PPI, reaching thus the

same risk as men. Generally, self-expandable devices are more described as predictive factors for PPI after TAVI than balloon-expandable devices, also in women.[11,77] However, the recent SOLVE-TAVI (Second-Generation Self-Expandable Versus Balloon-Expandable Valves and General Versus Local Anesthesia in TAVI) trial[78] showed that newer generation of self-expandable and balloon-expandable valve are equivalent in postoperative PPI, emphasizing that individual valve anatomy can lead to specific preferences in some patients. Thiele et al[78] reported a higher rate of postoperative PPI, probably related to the restrictive use of only 2 specific devices (Evolut R and Sapien 3), while the heterogeneity of the devices reported in this meta-analysis may have flattened the rate of PPI, explaining a lower rate of such outcome. Smaller annulus size in women can create a likely higher degree of oversizing, a potentially condition for higher postoperative rate of PPI, especially with balloon-expandable valves.[56]

Limitations

This investigation presents some limitations. First, although the present meta-analysis is based on published studies, publication bias still remains a weakness. Furthermore, on the 37 retrospective studies and the 9 prospective studies included, only 1 study was randomized. Second, the heterogeneity among studies was moderate, but no particular study determined the final results, which give us confidence in our statistic model. Nevertheless, no standard approach was defined with respect to the indications for PPI among studies and this heterogeneity should also be a source of variability in rate of PPI after TAVI. Third, lower sample studies were excluded from the final analysis, which may let us miss some information. Fourth, all studies did not include both in-hospital PPI and PPI after discharge to 30 days. Finally, this was a study-level meta-analysis. An analysis of individual patient data may provide further insights.

CONCLUSIONS

Female patients undergoing TAVI are at lower risk for PPI after TAVI, without influence of age or ventricular function. Balloon-expandable devices blunt this advantage in favor of women. Further studies are required to reduce the need for postoperative PPI, as well as further developments regarding prosthesis design and patient selection in order to offer a patient-tailored approach.

ARTICLE INFORMATION

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Supplementary Material

Table S1
Figures S1–S6

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SUPPLEMENTAL MATERIAL

Table S1. Proportion of prosthesis used by percentage of females included in each study.

	Percentage of female				
Type of prosthesis	Female <50%	Female 50-54%	Female 55-59%	Female≥60%	p-value
BE	68.2% (58.4- 76.6)	65.2% (43.7- 81.9)	54.4% (33.9- 73.6)	45.1% (12.2- 82.9)	<0.001
SE	29.6% (21.5- 39.2)	14.2% (6.6- 27.9)	41.1% (24.1- 60.7)	54.9% (17.1- 87.7)	0.0455

BE = Balloon-Expandable; SE = Self-Expandable

Figure S1. Flowsheet of the included studies.

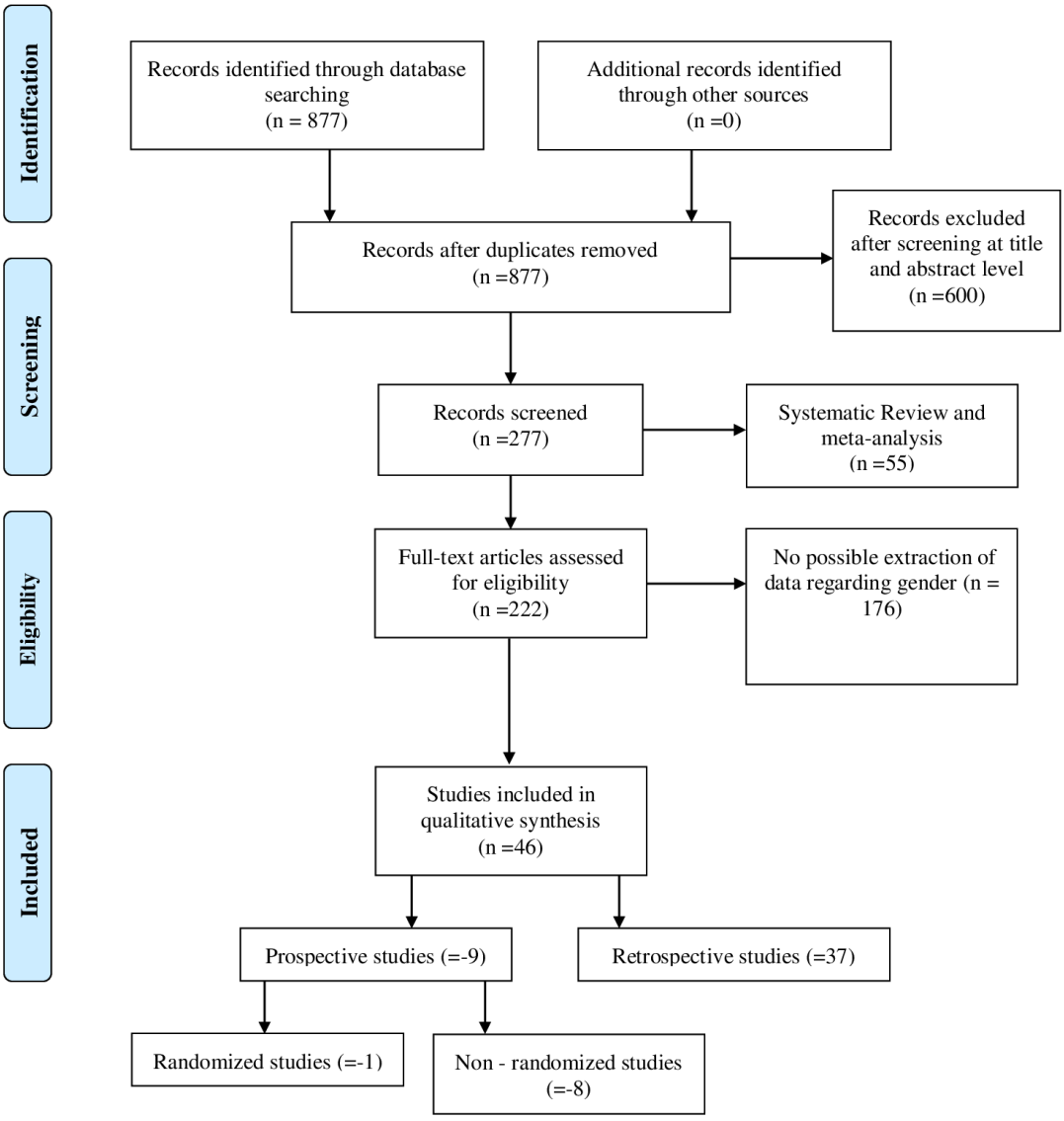
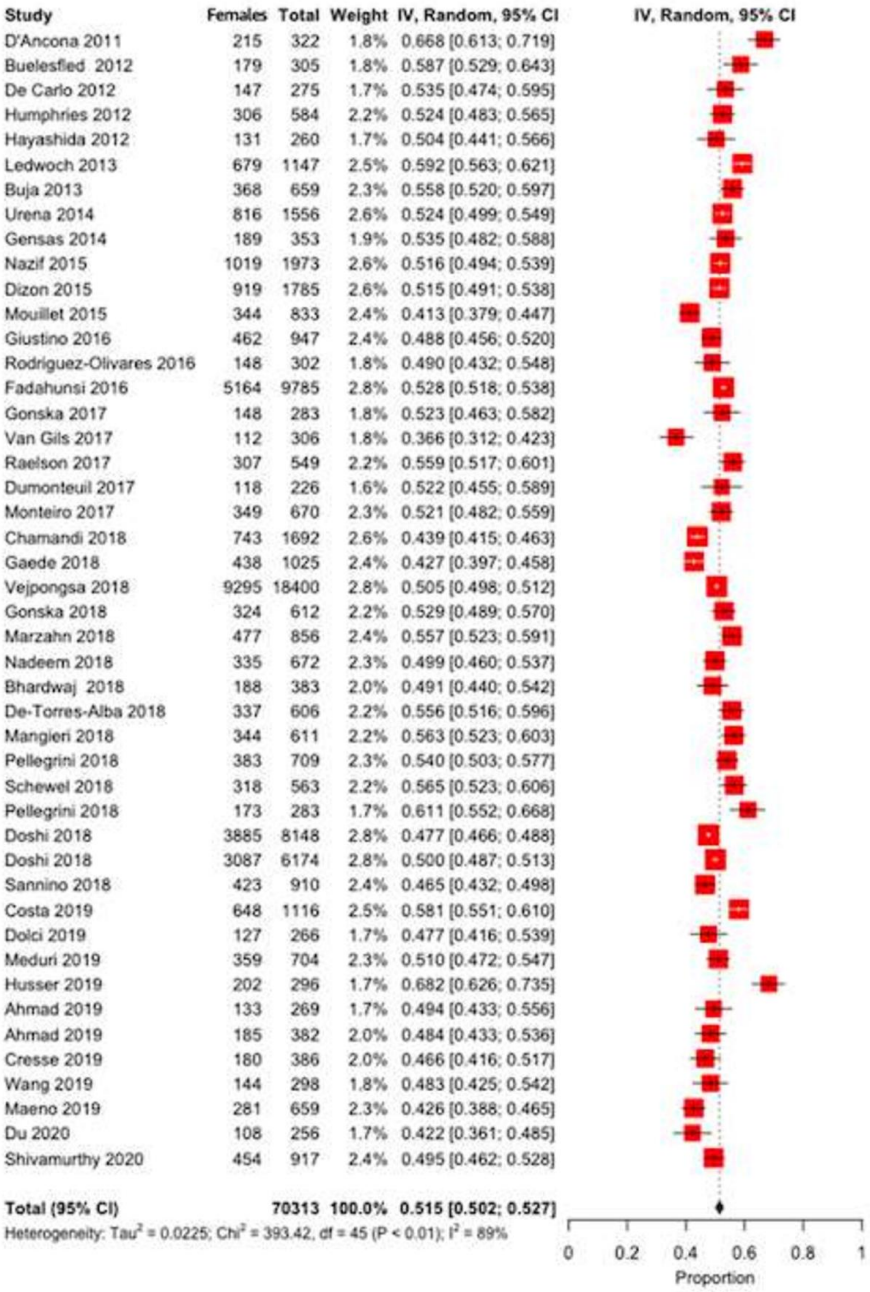


Figure S2. **Forest plot pooling proportion of females in 46 studies (23-68).**



IV = interval variable; 95%CI = confidence interval.

Figure S3. Funnel plot: odds ratio for pacemaker implantation versus its standard error.

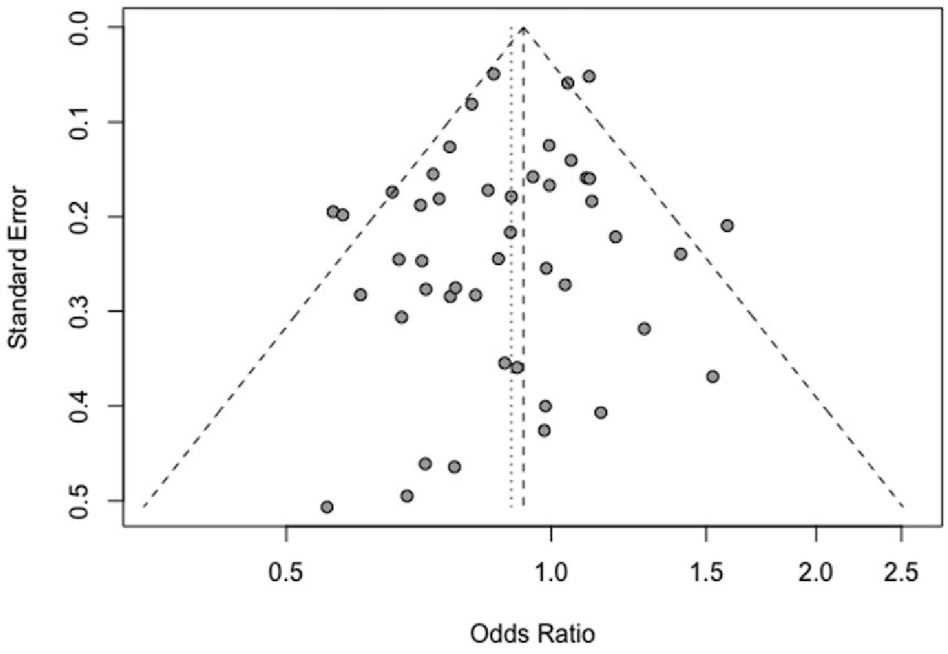
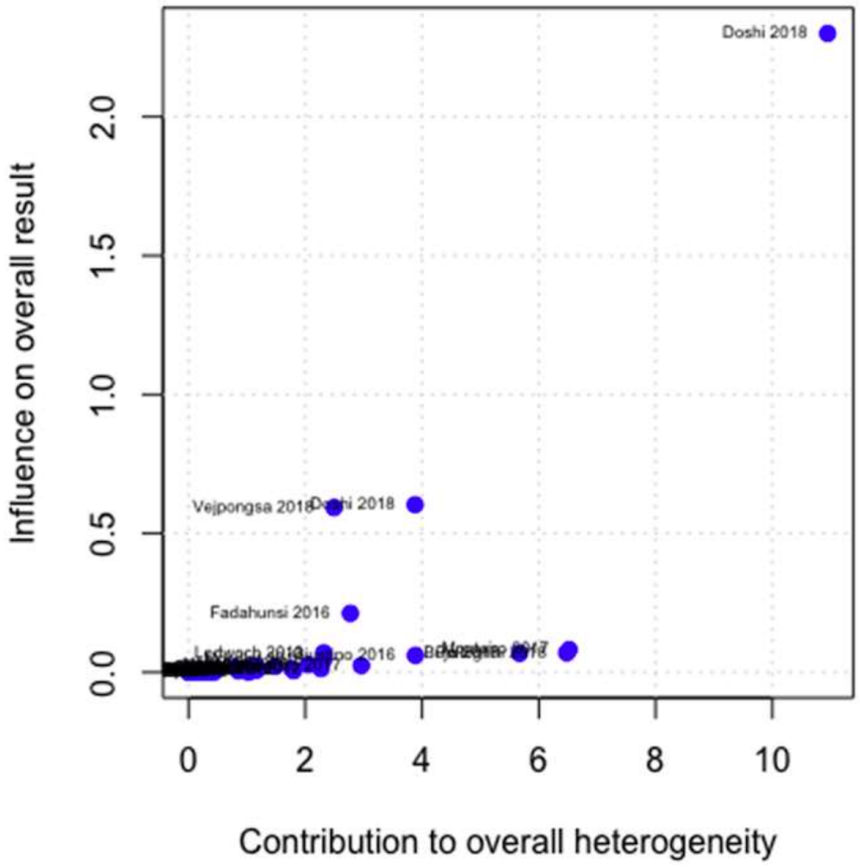
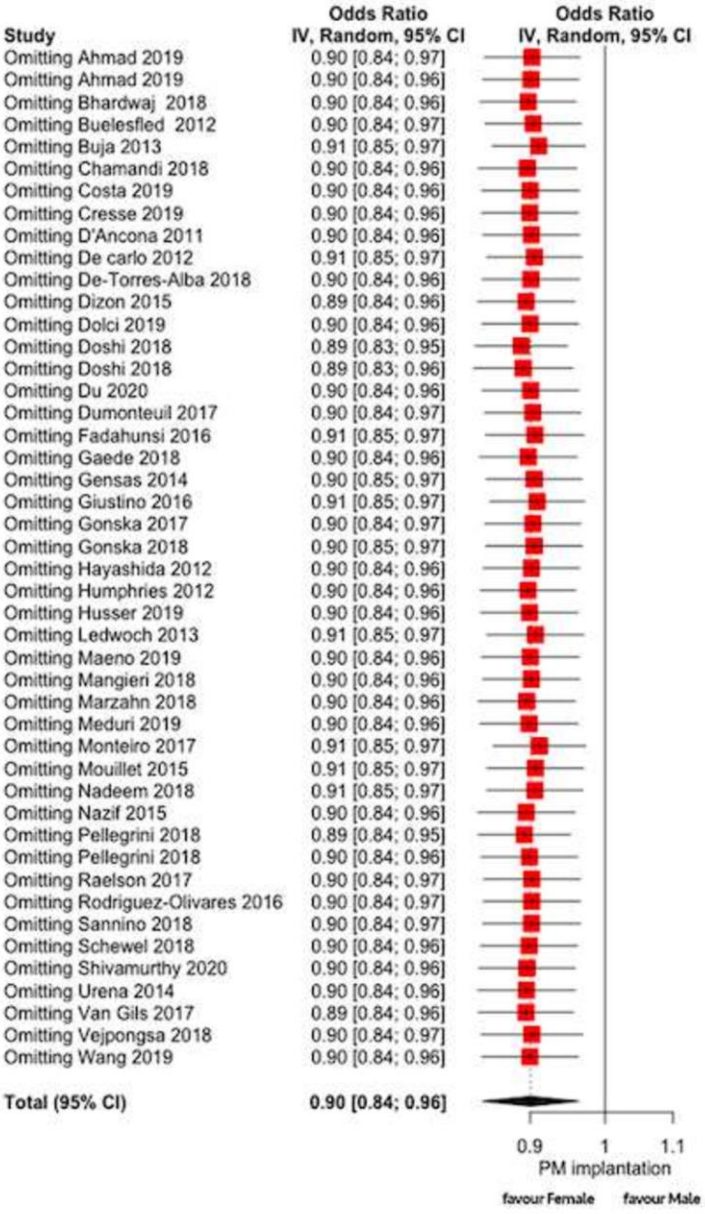


Figure S4. **Baujat plot.**



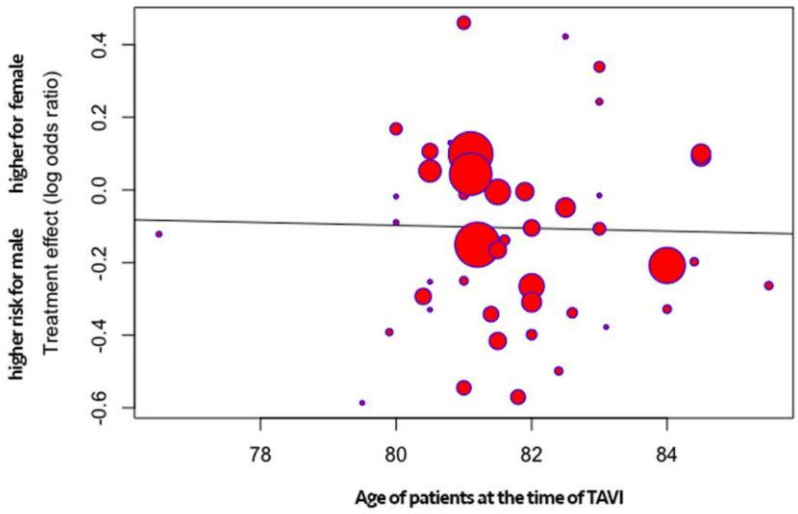
Overall heterogeneity was due to few studies

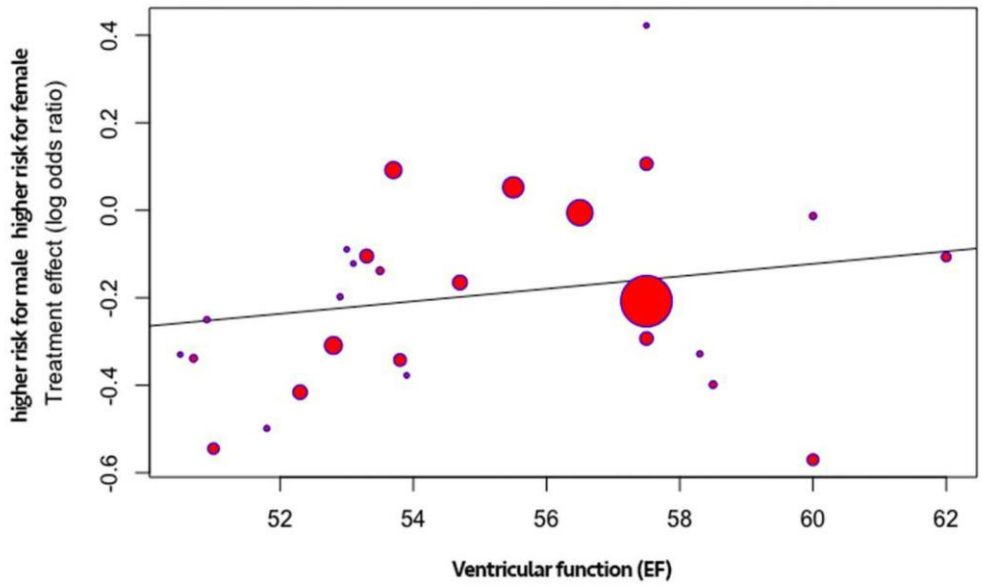
Figure S5. Forest plot leave one-out analysis comparing the effect of sex on the rate of post-procedure pacemaker implantation (23-68).

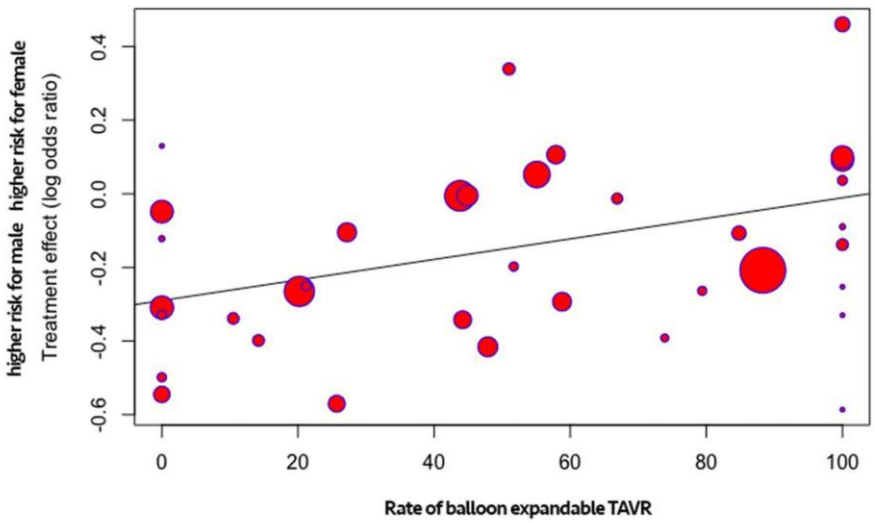


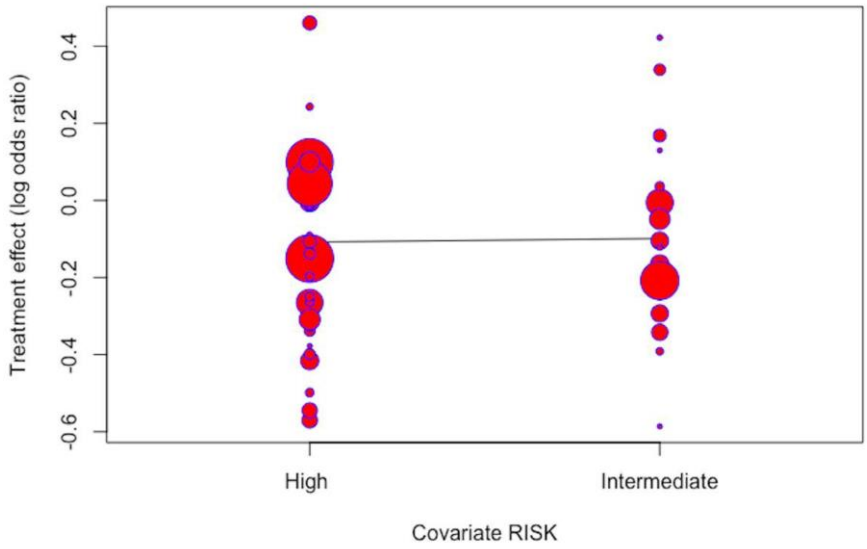
IV = interval variable; 95%CI = confidence interval.

Figure S6. **Bubble plots: influence of age on risk for post procedure pacemaker implantation on the basis of sex** (Panel A); influence of ventricular function on risk for post procedure pacemaker implantation on the basis of sex (Panel B); influence of balloon expandable prosthesis on risk for post procedure pacemaker implantation on the basis of sex (Panel C); influence of the patient risk on risk for post procedure pacemaker implantation on the basis of sex (Panel D).




higher risk for male higher risk for female
Treatment effect (log odds ratio)
-0.6
-0.4
-0.2
0.0
0.2
0.4
52
54
56
58
60
62
Ventricular function (EF)


higher risk for male higher risk for female
Treatment effect (log odds ratio)
-0.6
-0.4
-0.2
0.0
0.2
0.4
0
20
40
60
80
100
Rate of balloon expandable TAVR


Treatment effect (log odds ratio)
0.4
0.2
0.0
-0.2
-0.4
-0.6
High
Intermediate
Covariate RISK