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Long-Term Outcomes With Transcatheter Aortic Valve Replacement in Women Compared With Men

Evidence From a Meta-Analysis

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ABSTRACT

OBJECTIVES This study sought to examine long-term outcomes with transcatheter aortic valve replacement (TAVR) in women versus men.

BACKGROUND TAVR is commonly performed in women. Previous studies have shown conflicting results with respect to sex differences in outcomes with TAVR. In addition, short-term outcomes have primarily been reported.

METHODS Electronic search was performed until March 2017 for studies reporting outcomes with TAVR in women versus men. Random effects DerSimonian-Laird risk ratios were calculated. Outcomes included all-cause mortality and major cardiovascular events at short- (30 days) and long-term (>1 year) follow-up.

RESULTS Seventeen studies (8 TAVR registries; 47,188 patients; 49.4% women) were analyzed. Women were older but exhibited fewer comorbidities. At 30 days, women had more bleeding ($p < 0.001$), vascular complications ($p < 0.001$), and stroke/transient ischemic attack ($p = 0.02$), without difference in all-cause ($p = 0.19$) or cardiovascular mortality ($p = 0.91$) compared with men. However, female sex was associated with lower all-cause mortality at 1 year (risk ratio: 0.85; 95% confidence interval: 0.79 to 0.91; $p < 0.001$), and longest available follow-up (mean 3.28 ± 1.04 years; risk ratio: 0.86; 95% confidence interval: 0.81 to 0.92; $p < 0.001$), potentially caused by less moderate/severe aortic insufficiency ($p = 0.001$), and lower cardiovascular mortality ($p = 0.009$). The female survival advantage remained consistent across multiple secondary analyses. The risk of stroke, moderate/severe aortic insufficiency, and all-cause mortality seemed to vary based on the type of valve used; however, without significant subgroup interactions.

CONCLUSIONS Despite a higher upfront risk of complications, women derive a better long-term survival after TAVR compared with men. (J Am Coll Cardiol Intv 2017;■:■-■) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AI = aortic insufficiency

CI = confidence interval

MI = myocardial infarction

PPM = permanent pacemaker

RR = risk ratio

SAVR = surgical aortic valve replacement

TA-TAVR = transapical transcatheter aortic valve replacement

TAVR = transcatheter aortic valve replacement

TF-TAVR = transfemoral transcatheter aortic valve replacement

TIA = transient ischemic attack

Transcatheter aortic valve replacement (TAVR) is the recommended procedure for patients with symptomatic severe aortic stenosis who are at high risk or deemed inoperable for surgical aortic valve replacement (SAVR) (1,2). More recently, TAVR is being performed in intermediate-risk individuals as an alternative to SAVR (3,4). Multiple small observational studies suggested that women have worse short-term outcomes with TAVR; however, conflicting data on sex differences exist (5–11). A patient-level meta-analysis suggested that, compared with men, women undergoing TAVR had more major bleeding, vascular complications, and stroke at 30 days but lower mortality at 1 year (12).

Since the last meta-analysis that examined 1-year all-cause mortality (12), multiple studies reporting various clinical outcomes at long-term follow-up after TAVR have been published (13–21), including long-term risk of stroke, myocardial infarction (MI), cardiovascular mortality, and all-cause mortality. The conclusions of these recent studies are conflicting, resulting in more debate regarding the impact of sex on long-term outcomes after TAVR. Hence, we aim to perform an updated and comprehensive systematic review to examine the difference in short- and long-term clinical outcomes in women compared with men following TAVR.

METHODS

STUDY SEARCH AND ELIGIBILITY CRITERIA. The current meta-analysis was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (22), and is registered with the International Prospective Register for Systematic Reviews (PROSPERO: CRD42017060397). We searched PubMed, Cochrane Library, Web of Science, and EMBASE databases from inception until March 2017, without language restriction, using key words "sex," "gender," "men," "women," "male," "female," "transcatheter aortic valve replacement," and "transcatheter aortic valve implantation" both separately and in combination. Online Figure 1 illustrates the PRISMA flow diagram for our search strategy. Bibliographies of retrieved articles and prior meta-analyses were searched for additional studies not retrieved using the original search strategy.

Studies were included if they examined clinical outcomes in patients with aortic stenosis who underwent TAVR; and if they reported clinical outcomes of interest in women versus men within the main article, a subgroup, or pooled analysis, at a follow-up of 1 year or longer. Studies were excluded if outcomes were reported as hazard ratios rather than numerical events. Further data were requested from corresponding authors of included studies if not reported in the published articles.

DATA EXTRACTION. Four reviewers (M.S., R.N., N.V.K.P., and A.A.) extracted baseline study characteristics, patients' demographic, and clinical outcomes of interest from the retrieved studies. Any discrepancy was resolved by consensus of the authors. The number of events for clinical outcomes in both arms was tabulated at 30 days, 1 year, and long-term (>1 year) follow-up.

QUALITY ASSESSMENT. We performed quality assessment at both the study and outcome levels. Quality of the included studies was assessed using the Newcastle-Ottawa Scale for cohort studies (23). Grades of Recommendation, Assessment, Development and Evaluation tool was then used to assess quality of evidence at each outcome level as recommended by the Cochrane Handbook for Systematic Reviews of Interventions. This tool specifies 4 levels of quality (high, moderate, low, and very low) depending on the type of studies included in the assessment of each outcome.

OUTCOMES. The main outcome was all-cause mortality at 30 days, 1 year, and long-term (>1 year) follow-up. Secondary outcomes included stroke/transient ischemic attack (TIA), MI, and cardiovascular mortality at 30 days and at the longest available follow-up. Post-procedure complications of major bleeding, blood transfusion, major vascular access complications, moderate/severe aortic insufficiency (AI), acute kidney injury, and permanent pacemaker (PPM) implantation were also examined at 30 days.

STATISTICAL ANALYSIS. Descriptive analyses were conducted using frequencies for categorical variables and standardized means with standard deviations for continuous variables. Random-effects summary risk ratios (RR) using DerSimonian and Laird model were performed (24). Weighted mean follow-up durations for outcomes were calculated using sample size as the weight. Confidence intervals (CI) were calculated at 95% level for overall estimates effect. The p values were 2-tailed, and considered statistically significant if <0.05. Heterogeneity was evaluated using I^2 statistic, where values <25% indicate low heterogeneity, and >50% indicate high heterogeneity (25). Egger method was used to calculate publication bias (26). All analyses

TABLE 1 Characteristics of Included Studies

Study (Ref. #)	Year	Country	Type of Study	Total Population, n	Enrollment Start Date	Enrollment End Date	Single/ Multicenter	Follow-Up Duration, yrs	Balloon-/ Self-Expanding Valve, %	TF/Non-TF Access, %
Ontario Cardiac Registry (13)	2017	Canada	Prospective observational	999	2007	2013	Multicenter	3.50	54/46	71/29
Levi et al. (15)	2017	Israel	Prospective observational	560	2008	2016	Single	5.00	27/73	86/14
Brazilian TAVI Registry (14)	2017	Brazil	Prospective observational	819	2008	2015	Multicenter	1.36	27/73	94/6
STS/ACC TVT Registry (16)	2016	United States	Prospective observational	23,652	2011	2014	Multicenter	1.00	87/13	60/40
US CoreValve Trial Registry (17)	2016	United States	Retrospective from RCT	3,687	NR	NR	Multicenter	1.00	0/100	80/20
FRANCE 2 Registry (21)	2016	France	Prospective observational	4,201	2010	2012	Multicenter	3.00	67/33	74/26
PARTNER trial (18)	2016	United States/ Canada/Germany	Retrospective from RCT	2,559	2007	2012	Multicenter	1.00	100/0	58/42
PARTNER 2 Sapien 3 trial (19)	2016	United States/ Canada	Retrospective from RCT	1,661	2013	2014	Multicenter	1.00	100/0	NR
Woitek et al. (20)	2016	Germany	Prospective observational	2,004	2006	2015	Single	2.00	NR	NR
UK TAVI Registry (27)	2015	United Kingdom	Prospective observational	3,813	2007	2012	Multicenter	2.00	52/48	71/29
Yakubov et al. (28)	2015	United States	Prospective observational	489	NR	NR	NR	2.00	100/0	100/0
German TAVI Registry (29)	2014	Germany	Prospective observational	201	2009	2010	Multicenter	1.00	9/91	90/10
Italian CoreValve Registry (7)	2013	Italy	Prospective observational	659	2007	2009	Multicenter	1.10	0/100	90/10
D'Ascenzo et al. (6)	2013	Italy	Prospective observational	377	2007	2011	Multicenter	1.35	47/53	85/15
Hayashida et al. (9)	2012	France	Prospective observational	260	2006	2010	Single	1.00	85/15	65/35
Humphries et al. (8)	2012	Canada	Prospective observational	584	2005	2011	Multicenter	2.00	97/3	NR*
Tamburino et al. (30)	2011	Italy	Prospective observational	663	NR	NR	NR	1.00	0/100	90/10

*Access was mainly transfemoral.

NR = not reported; RCT = randomized clinical trial; STS/ACC = Society of Thoracic Surgeons/American College of Cardiology; TF = transfemoral.

were performed using STATA software version 14 (StataCorp, College Station, Texas).

SENSITIVITY AND SUBGROUP ANALYSES. For the main outcome of all-cause mortality, pre-specified sensitivity analyses were performed: 1) excluding intermediate-risk cohorts (i.e., limited to patients considered to be inoperable or at high-risk for SAVR by a heart team consensus); 2) limited to studies where transfemoral vascular access (TF-TAVR) was used in ≥70% of cohort; and 3) limited to studies reporting outcomes at ≥3 years. We performed a subgroup analysis based on the geographic location of centers where studies were conducted (i.e., centers at North and South America vs. centers at Europe, including Israel). Multiple subgroup analyses were further performed to compare outcomes based on the type of valve (balloon-expandable vs. self-expanding) used in ≥70% of study cohort. Interactions in subgroup analyses were evaluated by random-effects analysis, and p value for interaction was considered significant if <0.10.

META-REGRESSION ANALYSIS. Random effects meta-regression analyses were performed independently for both women and men to evaluate for any modification in outcome of all-cause mortality with baseline characteristics including age, European System for Cardiac Operative Risk Evaluation score, hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, peripheral arterial disease, history of MI, prior percutaneous coronary intervention, prior coronary artery bypass grafting, history of stroke, left ventricular ejection fraction, heart failure with New York Heart Association class III/IV symptoms, chronic kidney disease, vascular access used (TF-TAVR and transapical [TA]-TAVR), and type of valve used (balloon-expandable and self-expanding).

TABLE 2 Baseline Demographics in the Included Studies

	Total Patients	Women	Men	p Value
Age, yrs	36,160	82.7 ± 1.2	81.8 ± 1.4	0.0001
DM, %	36,160	34.9 ± 10.9	38.6 ± 12.3	0.0001
HTN, %	10,127	89.7 ± 9.3	87.9 ± 11.5	0.0004
AF, %	30,141	38.1 ± 1.0	42.1 ± 1.1	0.0004
Prior stroke, %	36,160	13.4 ± 6.5	15.4 ± 7.5	0.0001
Prior MI, %	10,067	16.6 ± 4.7	30.9 ± 10.6	0.0005
CAD, %	12,131	51.9 ± 19.7	74.4 ± 20.7	0.0004
PAD, %	33,256	28.2 ± 10.7	37.2 ± 11.5	0.0001
Prior PCI, %	32,193	29.9 ± 4.2	41.9 ± 4.8	0.0002
Prior CABG, %	34,757	15.9 ± 6.6	45.5 ± 13.9	0.0002
HF NYHA class III/IV, %	31,597	82.9 ± 6.5	80.8 ± 6.4	0.0001
Balloon-expandable valve, %	39,363	76.2 ± 38.7	72.7 ± 38.7	0.0001
Self-expandable valve, %	40,239	23.6 ± 38.4	26.1 ± 38.6	0.0001
Transfemoral access, %	37,702	62.7 ± 16.4	68.8 ± 13.7	0.0001
Transapical access, %	28,336	32.4 ± 17.5	26.8 ± 14.7	0.0001
LVEF, %	34,601	56.9 ± 2.9	50.7 ± 2.7	0.0002
CKD, %	9,505	30.6 ± 28.3	26.9 ± 25.6	0.0004
COPD, %	6,529	27.5 ± 10.7	33.9 ± 10.8	0.0006
EUROSCORE	11,924	20.3 ± 5.3	22.2 ± 5.7	0.0003

Values are n or weighted mean ± SD. AF = atrial fibrillation; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; EUROSCORE = European System for Cardiac Operative Risk Evaluation score; HF = heart failure; HTN = hypertension; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention.

RESULTS

CHARACTERISTICS OF THE INCLUDED STUDIES. As shown in Online Figure 1, our search yielded 1,625 studies. Nineteen studies met our inclusion criteria; 2 studies (10,11) were further excluded because only short-term outcomes were reported. Seventeen studies including 8 TAVR registries (6-9,13-21,27-30), with a total of 23,303 women and 23,885 men, were available for the final analysis. Eight studies were conducted in North/South American centers, and 9 in European centers. All studies included patients deemed inoperable or at high-risk for SAVR, except the PARTNER 2 Sapien 3 study, which included an intermediate-risk cohort as well (19). **Table 1** reports details of the included studies.

BASELINE CHARACTERISTICS OF THE INCLUDED COHORTS. Women were older compared with men (82.7 ± 1.2 vs. 81.8 ± 1.4 years; p = 0.0001); however, men had more comorbidities at baseline including diabetes mellitus, hypertension, atrial fibrillation, coronary artery disease, peripheral arterial disease, history of MI, prior percutaneous coronary intervention or coronary artery bypass grafting, and history of stroke. European System for Cardiac Operative Risk Evaluation score was significantly higher in men compared with women (p = 0.0003). Women had higher left ventricular ejection fraction (p = 0.0002) but had a higher prevalence of heart failure New York Heart Association III/IV symptoms (p = 0.0001) compared with men at baseline. Baseline patients' demographics are detailed in **Table 2**.

PROCEDURAL CHARACTERISTICS. The TF-TAVR approach was the most commonly used vascular access (75%) versus the TA-TAVR approach (20.4%). Women were more likely to have a TA-TAVR compared with men (23.7 ± 17.4% vs. 21.3 ± 14.7%; p = 0.0001). Six studies (8,9,16,18,19,28) used mainly balloon-expandable valves, another 6 studies used mainly self-expanding valves (7,14,15,17,29,30), and the remaining studies used both types without preference. Women were more likely to receive a balloon-expandable valves compared with men (76.2 ± 38.7% vs. 72.7 ± 38.7%; p = 0.0001).

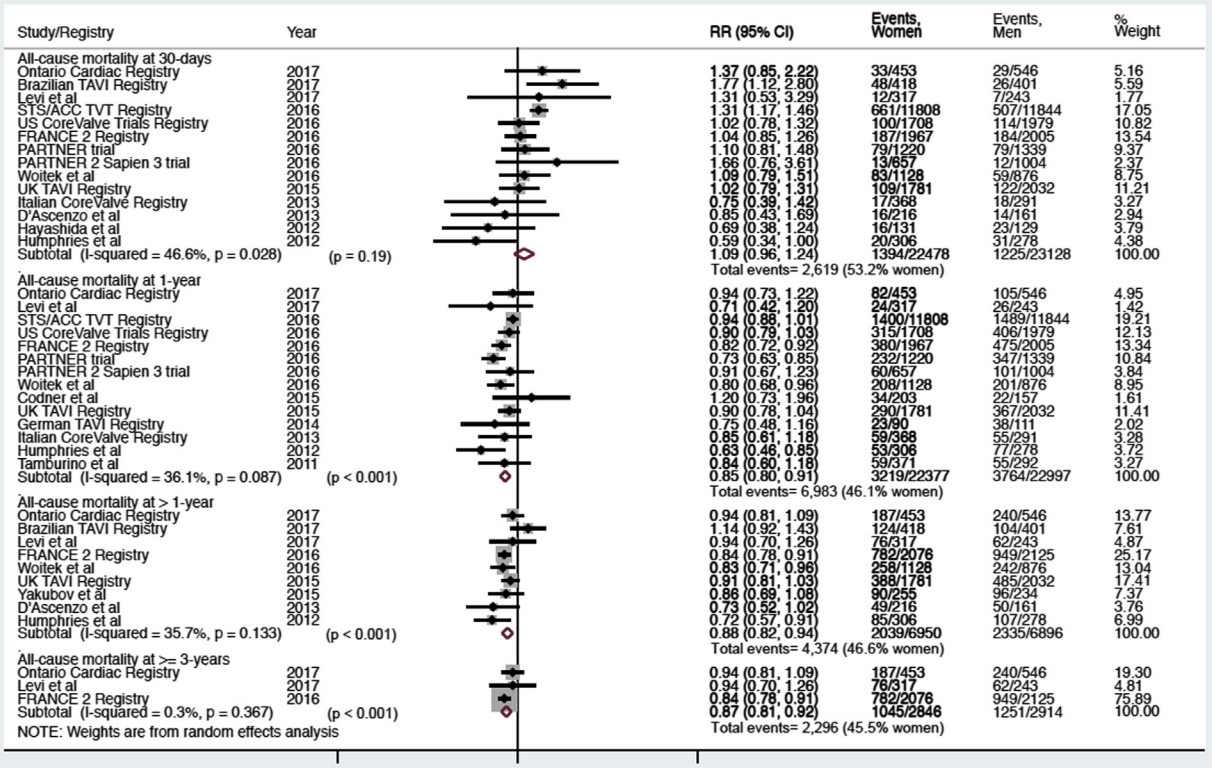
QUALITY ASSESSMENT AND RISK OF BIAS OF THE INCLUDED TRIALS. All trials were deemed at low risk of bias according to the Newcastle-Ottawa Scale (Online Table 1), and the body of evidence for the outcomes reached the level of high quality according to the Grades of Recommendation, Assessment, Development and Evaluation tool (Online Table 2). No risk of bias was demonstrated by the Egger test for any of the outcomes.

ALL-CAUSE MORTALITY. At 30 days, the incidence of all-cause mortality was similar in both women (6.5%; 95% CI: 5.34% to 7.59%) and men (6.2%; 95% CI: 4.87% to 7.57%) undergoing TAVR (RR: 1.09; 95% CI: 0.96 to 1.24; p = 0.19; I^2 = 47%). However, at 1 year female sex was associated with lower all-cause mortality (16.0%; 95% CI: 13.75% to 18.30%) compared with men (19.4%; 95% CI: 16.23% to 22.65; RR: 0.85; 95% CI: 0.79 to 0.91; p < 0.001; I^2 = 36%).

At long-term follow-up (mean, 2.58 ± 1.2 years), female sex continued to be associated with lower all-cause mortality (RR: 0.88; 95% CI: 0.82 to 0.94; p < 0.001; I^2 = 36%). In an analysis including only studies that reported outcomes at ≥3 years (total of 2,846 women and 2,914 men), women demonstrated greater survival compared with men (65.6%; 95% CI: 56.9% to 74.2%; vs. 61.7%; 95% CI: 51.77% to 71.60%; RR: 0.86; 95% CI: 0.81 to 0.92; p < 0.001; I^2 = 0%) at weighted mean follow-up of 3.28 ± 1.04 years (**Central illustration**).

SECONDARY OUTCOMES. Women undergoing TAVR were more likely to experience major bleeding

CENTRAL ILLUSTRATION **Summary Forest Plot of All-Cause Mortality in Women Versus Men at Short-, Intermediate-, and Long-Term Follow-Up After Transcatheter Aortic Valve Replacement**



Saad, M. et al. J Am Coll Cardiol Intv. 2017;■(■):■–■.

The relative size of the data markers indicates the weight of the sample size from each study. CI = confidence interval; RR = risk ratio; STS/ACC = Society of Thoracic Surgeons/American College of Cardiology.

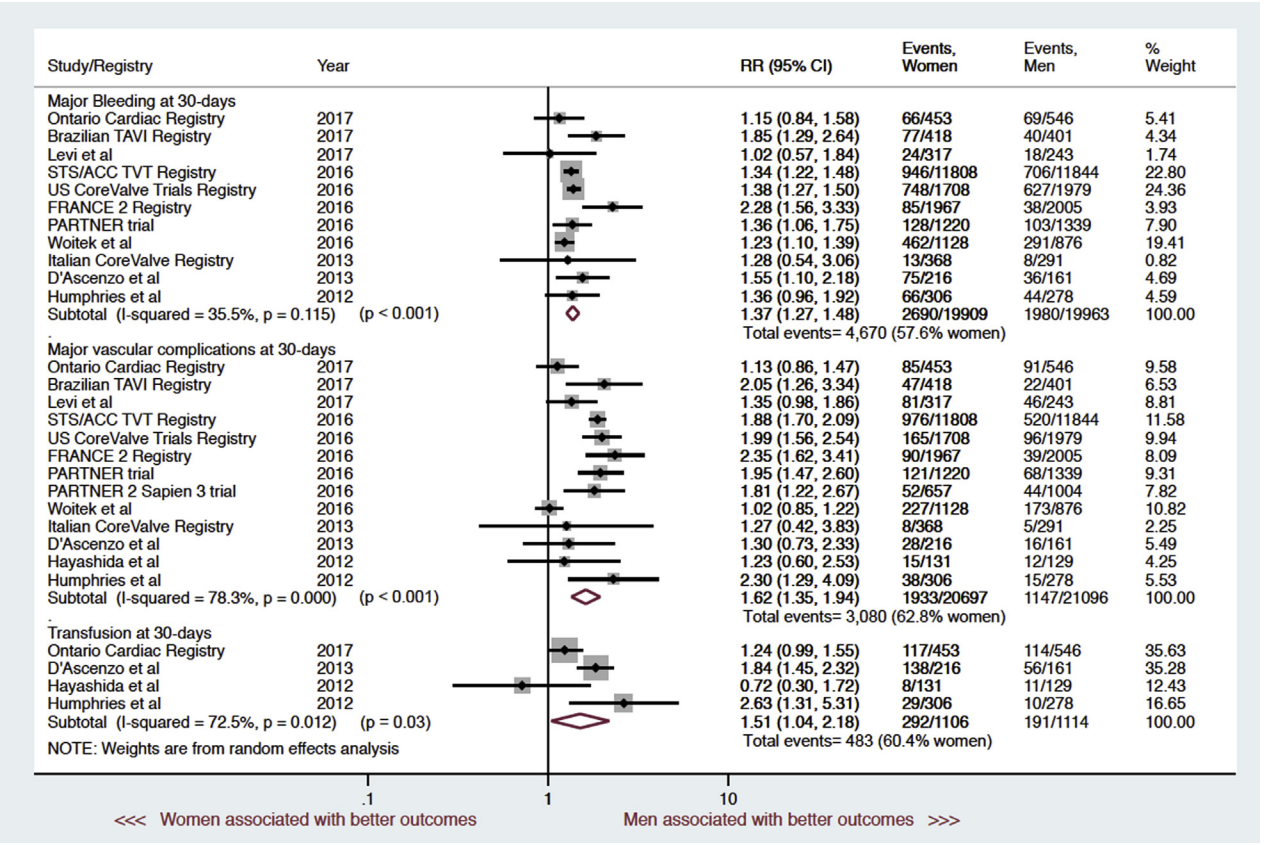
(RR: 1.37; 95% CI: 1.26 to 1.49; $p < 0.001$), vascular complications (RR: 1.62; 95% CI: 1.35 to 1.95; $p < 0.001$), and to require blood transfusion (RR: 1.51; 95% CI: 1.04 to 2.18; $p = 0.03$) compared with men at 30 days (Figure 1). Female sex was also associated with increased risk of stroke/TIA (RR: 1.28; 95% CI: 1.04 to 1.57; $p = 0.02$), and a trend toward increased MI (RR: 1.32; 95% CI: 0.99 to 1.77; $p = 0.06$). However, cardiovascular mortality was similar compared with men (RR: 1.01; 95% CI: 0.87 to 1.17; $p = 0.91$; $I^2 = 0\%$) (Figure 2).

Women were less likely to have moderate/severe AI (4.4% vs. 6.1%; RR: 0.65; 95% CI: 0.51 to 0.84; $p = 0.001$), and PPM placement (RR: 0.83; 95% CI: 0.70 to 0.98; $p = 0.03$) after TAVR compared with men. No difference was observed in the risk of acute kidney injury between both groups (RR: 0.92; 95% CI: 0.83 to 1.02; $p = 0.11$) (Figure 3).

At a mean follow-up of 1.1 ± 0.5 years, female sex was associated with lower cardiovascular mortality (RR: 0.80; 95% CI: 0.68 to 0.95; $p = 0.009$), despite having an increased risk of stroke/TIA (RR: 1.23; 95% CI: 1.06 to 1.43; $p = 0.006$) and similar risk of MI (RR: 0.96; 95% CI: 0.66 to 1.39; $p = 0.83$) compared with men (Figure 4).

SENSITIVITY, SUBGROUP, AND META-REGRESSION ANALYSES. After a sensitivity analysis excluding the intermediate-risk cohort of PARTNER 2 Sapien 3 study, women continued to have lower long-term all-cause mortality compared with men (RR: 0.87; 95% CI: 0.82 to 0.92; $p < 0.001$) (Online Figure 2).

FIGURE 1 Summary Forest Plot of Major Bleeding, Need for Transfusion, and Vascular Access Complications in Women Versus Men at 30 Days After Transcatheter Aortic Valve Replacement

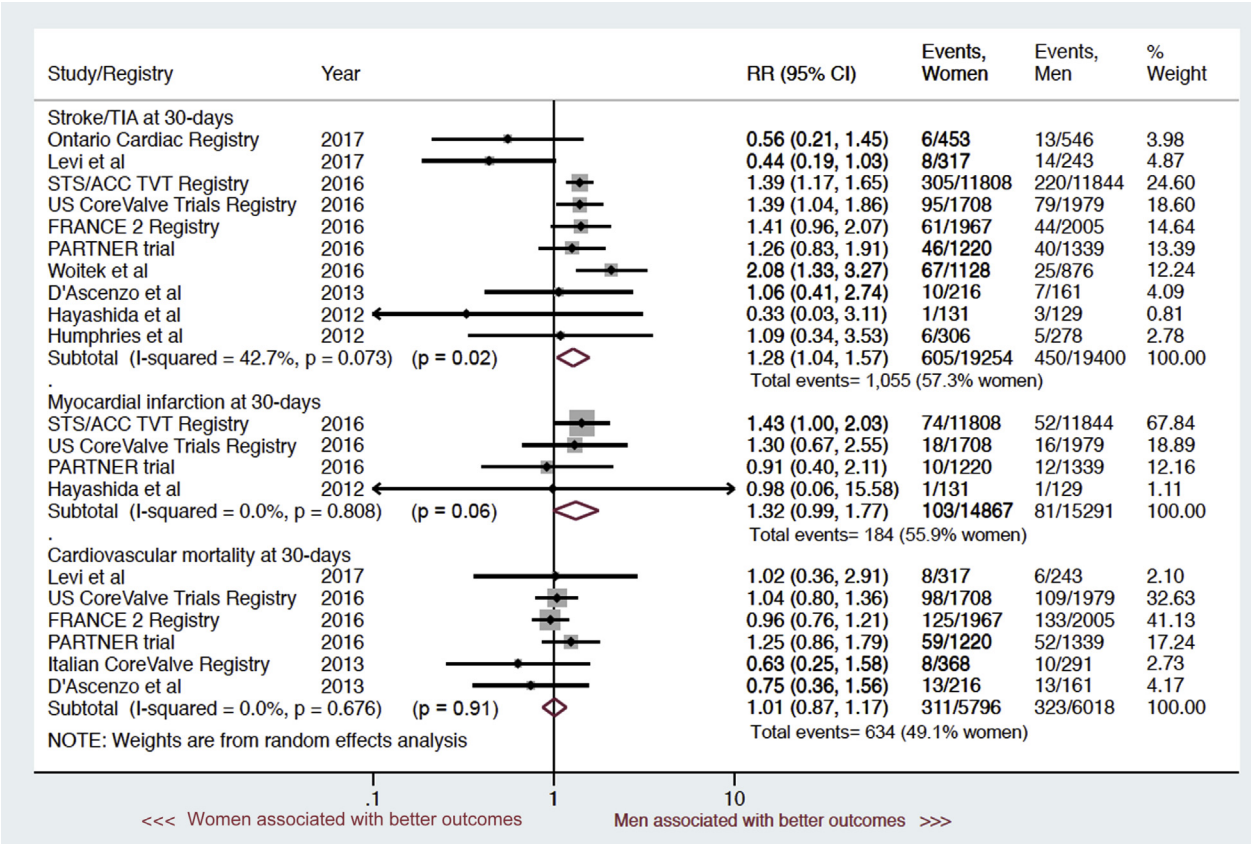


The relative size of the data markers indicates the weight of the sample size from each study. CI = confidence interval; RR = risk ratio; STS/ACC = Society of Thoracic Surgeons/American College of Cardiology.

This finding persisted on a sensitivity analysis including studies that performed TF-TAVR approach in ≥70% of the cohort (RR: 0.88; 95% CI: 0.83 to 0.93; $p < 0.001$) (Online Figure 3).

A subgroup analysis by geographic location of study centers continued to show a survival benefit in women compared with men in studies based in North/South America (RR: 0.89; 95% CI: 0.81 to 0.97; $p = 0.009$) and those based in Europe (RR: 0.85; 95% CI: 0.81 to 0.89; $p < 0.001$) (Online Figure 4). In a further subgroup analyses according to valve type, reduction in all-cause mortality in women compared with men was more evident with balloon-expandable valves (RR: 0.82; 95% CI: 0.72 to 0.93; $p = 0.003$), than with self-expanding valves (RR: 0.93; 95% CI: 0.84 to 1.02; $p = 0.13$); however, without a statistically significant interaction ($p_{interaction} = 0.13$) (Online Figure 5). When balloon-expandable valves were mainly used, a higher long-term risk of stroke was observed in women versus men (RR: 1.35; 95% CI: 1.16 to 1.56; $p < 0.0001$), compared with when self-expanding valves were mostly used (RR: 0.96; 95% CI: 0.44 to 2.06; $p = 0.91$), without statistically significant interaction ($p_{interaction} = 0.39$). Furthermore, the lower risk of moderate/severe AI with women versus men was more frequently observed with self-expanding valves (RR: 0.58; 95% CI: 0.37 to 0.91; $p = 0.02$), rather than balloon-expandable valves (RR: 0.72; 95% CI: 0.44 to 1.20; $p = 0.21$), but there was again no statistically significant interaction ($p_{interaction} = 0.53$). Meta-regression analysis demonstrated absence of modification in the outcome of all-cause mortality with different baseline characteristics in both groups (Online Table 3).

FIGURE 2 **Summary Forest Plot of Stroke/TIA, Myocardial Infarction, and Cardiovascular Mortality in Women Versus Men at 30 Days After Transcatheter Aortic Valve Replacement**



The relative size of the data markers indicates the weight of the sample size from each study. TIA = transient ischemic attack; other abbreviations as in Figure 1.

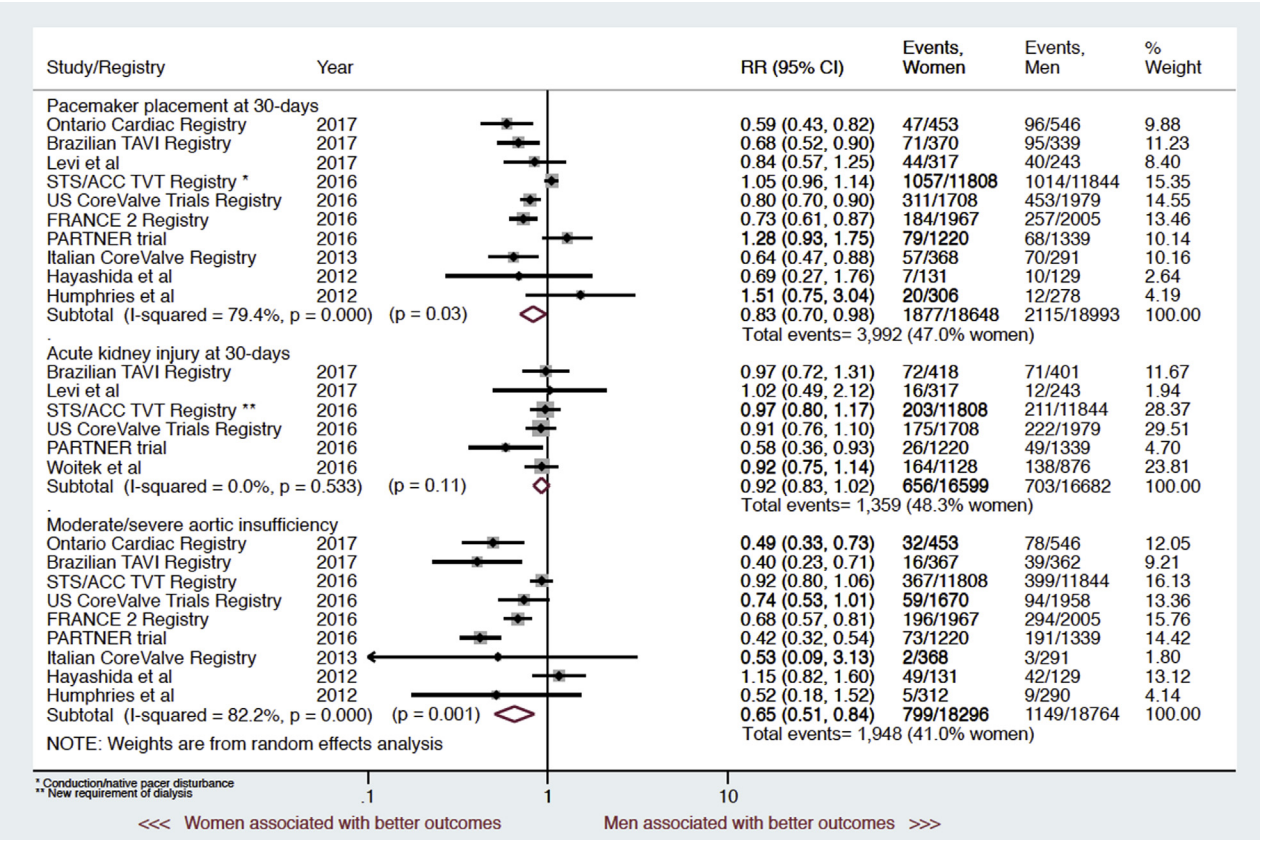
DISCUSSION

The current meta-analysis of 47,188 patients shows that women who underwent TAVR had better 1-year and long-term (3.28 ± 1.04 years) survival compared with men, despite a higher risk of early post-operative (30 days) bleeding and vascular complications, and a higher long-term risk of stroke.

LONG-TERM SURVIVAL IN WOMEN VERSUS MEN. There are several plausible explanations for improved long-term survival after TAVR in women. First, women had a lower risk of moderate/severe AI after TAVR in our study. More-than-mild AI after TAVR is a well-known risk factor for cardiovascular mortality (31–33). Smaller annular size in women reduces the incidence of prosthesis undersizing compared with men who tend to receive undersized valves and hence experience more paravalvular leaks (12,16,34). Furthermore, our study showed that women were more likely to receive balloon-expandable valves, whereas men were more likely to receive self-expanding valves. A reasonable explanation for this observation is that before the introduction of the 29-mm Sapien valve, only self-expanding valves were used for larger annular sizes. Because TAVR is based on sutureless anchoring of the prosthesis across the annulus, using more balloon-expandable valves in women could have contributed to optimal stent frame expansion and less moderate/severe AI compared with men (32).

Second, men in our analysis had significantly worse baseline vascular disease and comorbidities including hypertension, diabetes mellitus, coronary artery disease, prior revascularization, lower left ventricular ejection fraction, and higher European System for Cardiac Operative Risk Evaluation score compared with women. This finding is consistent with a prior patient-level analysis, and seems to be associated with worse long-term mortality (12).

FIGURE 3 Summary Forest Plot of Permanent Pacemaker Placement, Acute Kidney Injury, and Moderate/Severe Aortic Incompetence in Women Versus Men at 30 Days After Transcatheter Aortic Valve Replacement



The relative size of the data markers indicates the weight of the sample size from each study. Abbreviations as in Figure 1.

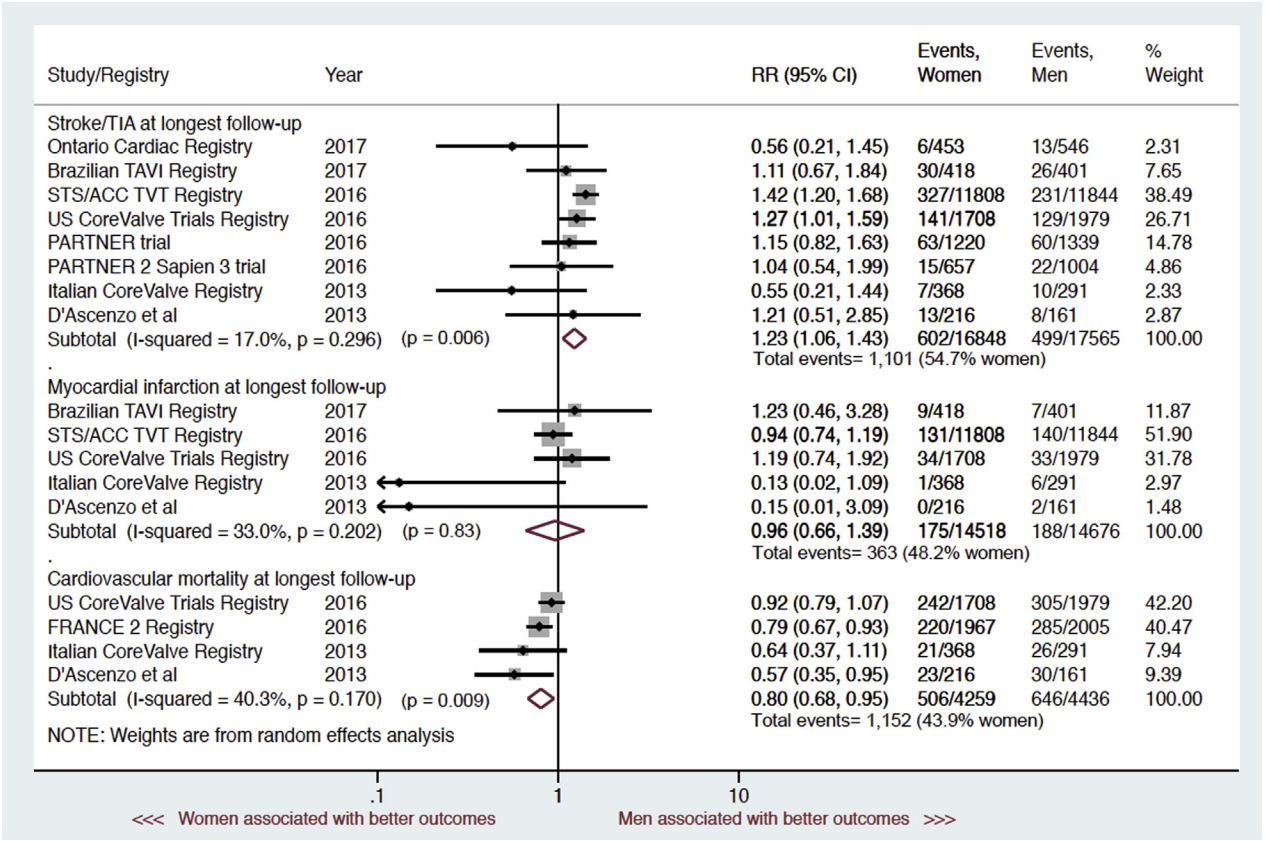
A third possible explanation is the sex-related difference in myocardial remodeling in response to pressure or volume overload. Compared with men, women's hearts tend to exhibit more favorable remodeling to hemodynamic stress caused by aortic stenosis, mainly through less fibrosis and collagen deposition, thus allowing a faster and better reversal of cardiac remodeling after TAVR (35-37).

The long-term survival advantage in women in our study did not seem to be affected by the increase in short-term bleeding or vascular complications, or the higher risk of stroke/TIA. Such survival advantage remained consistently observed along multiple sensitivity and subgroup analyses based on the included cohorts, vascular accesses, geographic variations, and type of valve used.

30 DAYS POST-TAVR COMPLICATIONS. In our study, female sex was associated with higher rates of major bleeding, vascular complications, and need for transfusion. This is in keeping with previous reports of women undergoing coronary interventions (38-40) and TAVR (17,18). Older age, lower body surface area, and smaller-diameter vessels likely contribute to this finding (12,41-43). In our study, women undergoing TAVR were significantly older compared with men (standardized mean difference: 0.69 years; 95% CI: 0.67 to 0.72; $p = 0.0001$). However, the increase in bleeding and vascular complications in women in the current study did not negate the long-term survival benefit compared with men.

The lower risk of PPM placement in women after TAVR in our study is difficult to explain based on gender, and is more likely a result of an increased number of self-expanding valves implanted in men compared with women in our population. Prior studies have shown a significant lower risk of PPM placement with balloon- versus self-expanding valves (44).

FIGURE 4 Summary Forest Plot of Stroke/TIA, Myocardial Infarction, and Cardiovascular Mortality in Women Versus Men at Long-Term Follow-Up After Transcatheter Aortic Valve Replacement



The relative size of the data markers indicates the weight of the sample size from each study. Abbreviations as in Figures 1 and 2.

SHORT- AND LONG-TERM RISK OF STROKE. Sex-related differences in the risk of stroke after TAVR remain controversial. Although some studies demonstrated a similar stroke risk at 30 days (8,16,18) and 1 year (19), 1 patient-level meta-analysis showed that women were more likely to experience stroke compared with men at 30-days post-TAVR (12). Our finding of an increased 30-day risk of stroke/TIA in women supports that analysis. To our knowledge, our meta-analysis is the first to report that such risk remains significantly higher in women at long-term follow-up (mean follow-up of 1.4 years). Despite the long-term survival advantage of TAVR in women compared with men, the increased risk of stroke should be carefully considered and therapies directed at stroke reduction should be implemented.

In a report from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies Registry, female sex was the single baseline variable associated with increased risk of stroke at 1-year (hazard ratio: 1.40; 95% CI: 1.15 to 1.71) (45). It remains unclear why women are at higher risk of stroke after TAVR, especially because male sex in most of these studies, including ours, was associated with worse baseline vascular comorbidities. One hypothesis could be that women, with a lower body surface area, make the valve delivery systems relatively bulkier in ascending aorta and aortic arch compared with men. In our study, the greater use of balloon-expandable valves in women could be another theory to explain this increased risk of stroke. It has been postulated that cerebral hypoperfusion caused by rapid ventricular pacing and transient outflow tract obstruction during balloon-expandable valve implantation may increase the risk of watershed infarcts (46).

Furthermore, access-related difference in the risk of stroke is unclear. TA-TAVR was shown to be a predictive factor for new-onset atrial fibrillation (47), and stroke (48). Women in our study were more likely to

have TA-TAVR compared with men. Minimizing ventricular pacing, avoiding balloon aortic valvuloplasty before deployment of the valve, restricting post-dilatation to underexpanded valves, and careful selection of valve size are potential methods to reduce both ischemic and embolic stroke post-TAVR (49), particularly in female patients. Whether women may specifically benefit from use of embolic protection devices during TAVR warrants investigation.

BALLOON-EXPANDABLE VERSUS SELF-EXPANDING VALVES. There are currently no conclusive data about differences in long-term outcomes with TAVR based on the type of valve implanted. In our study, we observed survival advantage for women with balloon-expandable rather than self-expanding valves; however, with no statistically significant interaction between subgroups. Similarly, our analysis showed that the difference in outcome of moderate/severe AI between both groups was less evident when balloon-expandable valves were mainly used; however, again without a significant subgroup interaction. This was previously demonstrated in a randomized clinical trial, where balloon-expandable valves were associated with higher success, and lower rates of more-than-mild AI compared with self-expanding valves (44).

Despite the observed differences in outcomes based on the type of valve used, our findings should be considered exploratory in the absence of statistically significant interaction among subgroups. Further randomized trials examining the relative benefit of a specific valve in women versus men may help unravel this finding.

ADVANTAGES AND LIMITATIONS OF OUR STUDY. The current study, including 8 TAVR registries from multiple countries, is the largest analysis aiming to provide physicians and their patients with real-world data about sex-specific outcomes of TAVR at the longest follow-up available in the literature to date. However, our study has several limitations. The main limitation is including observational data from studies and registries, subjecting our analysis to possible bias. We attempted to overcome this limitation through the performance of multiple sensitivity and subgroup analyses, and meta-regression analyses. Another limitation is the high heterogeneity in some outcomes; however, not including the main outcome of all-cause mortality. We performed random-effects summary RR to reduce the effect of such heterogeneity. Finally, lack of patient-level data in most of the studies precluded a more robust analysis.

CONCLUSIONS

Female sex is associated with a better long-term survival after TAVR compared with men; however, with a potential increased risk of stroke. Comprehensive discussion with patients and their families is encouraged regarding the potential impact of sex-specific anatomic and physiological differences on long-term outcomes with TAVR. Further large randomized trials are recommended to further explore these results.

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PERSPECTIVES

WHAT IS KNOWN? Compared with men, women undergoing TAVR are likely to have more major bleeding, vascular complications, and stroke at 30 days but lower mortality at 1 year. Sex-related differences in long-term outcomes with TAVR are unknown.

WHAT IS NEW? The current meta-analysis demonstrated that despite higher short-term complication rate in women undergoing TAVR, female sex is associated with a better long-term survival compared with men; however, with a potential increased risk of stroke.

WHAT IS NEXT? Large randomized trials comparing long-term TAVR outcomes in women with men are encouraged to further explore these results.

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KEY WORDS gender, sex, men, women, aortic valve replacement, TAVR

APPENDIX For supplemental tables and figures, please see the online version of this article.