1-30-2022

Sex differences in outcomes of transcatheter edge-to-edge repair with MitraClip: A meta-analysis

Lina Ya'qoub
Henry Ford Health, lyaqou1@hfhs.org

Mohamed Gad

Nadeen N. Faza

Katherine J. Kunkel
Henry Ford Health, kkunkel2@hfhs.org

Rawan Ya'acoub

See next page for additional authors

Recommended Citation

Ya'Qoub L, Gad M, Faza NN, Kunkel KJ, Ya'acoub R, Villablanca P, Bagur R, Alasnag M, Eng M, and Elgendy IY. Sex differences in outcomes of transcatheter edge-to-edge repair with MitraClip: A meta-analysis. Catheter Cardiovasc Interv 2022.

Authors
Lina Ya'qoub, Mohamed Gad, Nadeen N. Faza, Katherine J. Kunkel, Rawan Ya'acoub, Pedro Villablanca, Rodrigo Bagur, Mirvat Alasnag, Marvin H. Eng, and Islam Y. Elgendy

Received: 22 September 2021 | Revised: 2 January 2022 | Accepted: 17 January 2022

DOI: 10.1002/ccd.30110

ORIGINAL STUDIES

WILEY

Sex differences in outcomes of transcatheter edge-to-edge repair with MitraClip: A meta-analysis

Lina Ya'Qoub MD[1] | Mohamed Gad MD[2] | Nadeen N. Faza MD[3] | Katherine J. Kunkel MD[1] | Rawan Ya'acoub PharmD[4] | Pedro Villablanca MD[5] | Rodrigo Bagur MD, PhD[6] | Mirvat Alasnag MD[7] | Marvin Eng MD[5] | Islam Y. Elgendy MD[8]

[1]Division of Interventional Cardiology, Henry Ford Hospital, Detroit, Michigan, USA

[2]Department of Internal Medicine, Cleveland Clinic, Cleveland, Ohio, USA

[3]Department of Cardiology, DeBakey Heart and Vascular Center, Houston, Texas, USA

[4]Department of Clinical Pharmacology, The University of Jordan, Amman, Jordan

[5]Divsion of Structural Heart Disease, Henry Ford Hospital, Detroit, Michigan, USA

[6]Division of Cardiology, London Health Sciences Centre, Ontario, London, Canada

[7]Division of Interventional Cardiology, King Fahd Armed Forces Hospital, Jeddah, Saudi Arabia

[8]Department of Medicine, Weill Cornell Medicine, Doha, Qatar, Qatar

Correspondence

Islam Y. Elgendy, MD, Department of Medicine, Weill Cornell Medicine, Education City, Qatar Foundation, Doha, Qatar.
Email: iyelgendy@gmail.com

Abstract

Background: Transcatheter edge-to-edge repair (TEER) with MitraClip improves outcomes among select patients with moderate–to-severe and severe mitral regurgitation; however, data regarding sex-specific differences in the outcomes among patients undergoing TEER are limited.

Methods: An electronic search of the PubMed, Embase, Central, and Web of Science databases for studies comparing sex differences in outcomes among patients undergoing TEER was performed. Summary estimates were primarily conducted using a random-effects model.

Results: Eleven studies with a total of 24,905 patients (45.6% women) were included. Women were older and had a lower prevalence of comorbidities, including diabetes, chronic kidney disease, and coronary artery disease. There was no difference in procedural success (odds ratio [OR]: 0.75, 95% confidence interval [CI]: 0.55–1.05) and short-term mortality (i.e., up to 30 days) between women and men (OR: 1.16, 95% CI: 0.97–1.39). Women had a higher incidence of periprocedural bleeding and stroke (OR: 1.34, 95% CI: 1.15–1.56) and (OR: 1.57, 95% CI: 1.10–2.25), respectively. At a median follow-up of 12 months, there was no difference in mortality (OR: 0.98, 95% CI: 0.89–1.09) and heart failure hospitalizations (OR: 1.07, 95% CI: 0.68–1.67). An analysis of adjusted long-term mortality showed a lower incidence of mortality among women (hazards ratio: 0.77, 95% CI: 0.67–0.88).

Conclusions: Despite a lower prevalence of baseline comorbidities, women undergoing TEER with MitraClip had higher unadjusted rates of periprocedural stroke and bleeding as compared with men. There was no difference in unadjusted procedural success, short-term or long-term mortality. However, women had lower adjusted mortality on long-term follow-up. Future high-quality studies assessing sex differences in outcomes after TEER are needed to confirm these findings.

KEYWORDS

MitraClip, outcomes, percutaneous mitral valve repair, sex differences, transcatheter edge-to-edge mitral valve repair

Abbreviations: CI, confidence interval; HR, hazards ratio; MR, mitral regurgitation; OR, odds ratio; TEER, transcatheter edge-to-edge repair.

1 | INTRODUCTION

Transcatheter edge-to-edge mitral valve repair (TEER), using MitraClip, is a therapeutic option for select patients with symptomatic moderate-to-severe or severe (Grade 3+ or 4+) mitral regurgitation (MR), whether functional or degenerative.[1–8] In the 2020 American College of Cardiology/American Heart Association (ACC/AHA) valvular heart disease guidelines, TEER is given a class IIa recommendation for severe primary MR among patients with prohibitive or high-risk for surgery together with feasible anatomy and life expectancy of at least 1 year.[2] Similarly, TEER is endosed as a Class IIa recommendation for symptomatic cardiomyopathy patients and chronic severe secondary MR despite optimal guideline-directed medical therapy (GDMT).[2]

Few studies have assessed the sex differences in the clinical profile and outcomes of TEER.[3–16] While some studies showed that women and men undergoing TEER do not share a similar clinical profile, studies also showed conflicting findings regarding the outcomes after TEER. For example, some studies suggested that women have a higher risk of short-term mortality and bleeding,[6,9] but these findings were not replicated in other studies.[3–5] To better address this knowledge gap, we aimed to conduct a comprehensive meta-analysis to compare the outcomes between women and men undergoing TEER with MitraClip.

2 | METHODS

2.1 | Data sources

An electronic search of the MEDLINE, Embase, Central, and Web of Science was performed from inception until November 2021 without language restriction, using the keywords: “mitral valve clip,” “MitraClip,” “MVR”, or “percutaneous mitral valve repair,” and “sex” or “gender” (Table S1). Bibliographies of the included studies, relevant review articles, and meta-analyses were manually searched for any potential missed studies. The major cardiovascular conferences and proceedings, including the ACC and AHA scientific sessions, were also screened for any abstracts addressing this topic. This meta-analysis was registered with the International Prospective Register for Systemic Reviews (CRD42021236447) and conducted according to the meta-analysis of observational studies in the epidemiology group and the preferred reporting items for systematic reviews and meta-analyses guidelines.[17,18] The data that support the findings of this study are available from the corresponding author upon reasonable request.

2.2 | Selection criteria

Randomized clinical trials, prospective and retrospective cohort studies, as well as case-control studies, comparing sex-specific outcomes among adults undergoing TEER, were included. To be eligible, studies were required to report sex-specific outcomes between women and men. Studies not reporting sex-specific outcomes were excluded. If a study population was utilized in more than one publication, we included the study with the largest population or the one with the longest available follow-up.

2.3 | Data extraction

Data including study design, baseline characteristics, clinical outcomes of both unadjusted and maximally adjusted data when available were independently extracted by two authors (Lina Ya'Qoub and Rawan Ya'acoub). Any discrepancy was resolved by consensus among the authors.

2.4 | Outcomes

The outcomes assessed in this study were classified as short-term (i.e., up to 30 days), and long-term (i.e., reported at the longest available duration of follow-up). Short-term outcomes included: all-cause mortality, stroke, bleeding, and procedural success rate. The definition of stroke and bleeding was according to the individual studies. Procedural success was defined as residual MR of Grade 2 or less.[3–14] The long-term outcomes included: all-cause mortality, heart failure (HF) hospitalization, and residual MR of ≥Grade 3 on subsequent imaging.

2.5 | Quality assessment

The Newcastle–Ottawa scale was used to assess the risk of bias of each study included. A study was considered of high quality if achieved 7 out of 9 points. The scale is based on three main components: selection of the case/control and their representativeness, comparability of cases and controls based on design and analysis, and ascertainment of exposure and outcome.[19] A study is awarded a star for each component in the selection and exposure sections and a maximum of two stars in the comparability section.

2.6 | Statistical analysis

All descriptive analyses were conducted using weighted means and ranges for continuous variables and weighted frequencies for categorical variables with the weight corresponding to the sample size of each study. For each outcome, an unadjusted summary odds ratio (OR) was calculated using the reported events. Both unadjusted and adjusted outcomes were calculated by the random-effects model using the Der–Simonian and Laird model. A secondary analysis using the fixed-effects model was also conducted. The degree of statistical heterogeneity was evaluated by I^2 statistics. A sensitivity analysis excluding the largest study was conducted to determine its effect on the summary estimates. Publication bias was not assessed since the number of included studies for each outcome was <10 studies.[20] All analyses were considered statistically significant if the $p < 0.05$ and all effect sizes were calculated with a 95% confidence interval (CI). The statistical analysis was conducted using R studio software (2020; Integrated Development for R and RStudio, Inc.).

3 | RESULTS

3.1 | Included studies

The initial search yielded 2218 articles, of which 2205 were excluded on the revision of the titles and abstracts. Among the remaining 13 studies, 3 studies were driven from the National Inpatient Sample database,[11,15,16] thus we included the study with the largest sample size.[11] Eleven studies with 24,905 patients were included in the final analysis. Of which, 11,346 were females (45.6%) and 13,559 were males (54.4%).[3–14] The study flow diagram is summarized in Figure 1.

The study characteristics are summarized in Table 1. The included studies were from Europe, United States, and Canada. One study was a secondary analysis of a randomized clinical trial,[14] and the rest were observational studies.[3–7,9–14] Eight of the studies were multicenter, while the remainder were single-center studies (Table 1). The follow-up duration ranged from in-hospital to 24 months (weighted median follow-up duration was 12 months).

Overall, six studies were determined as high quality by the Newcastle–Ottawa scale while the other five were considered as low-intermediate quality. In this scale index, the domains of highest susceptibility to bias were exposure/outcome followed by comparability (Table S2).

The baseline characteristics of the included subjects are shown in Table 2. The mean Society of Thoracic Surgery score was 6.2, and the mean logistic EuroSCORE was 21.1 (Table 2). In most studies, women were older, had higher mean ejection fraction and higher rates of New York Heart Association Class III/IV HF at baseline. Risk profile in men differed, with overall higher rates of certain comorbidities, such as diabetes mellitus, chronic kidney disease, coronary artery disease, or prior myocardial infarction than women (Table 2).

The proportions of functional and degenerative MR were different among the studies.[3,4,6,10,12–14] Gafoor et al.[6] included a high proportion of patients with functional MR (68% among women and 86% among men). Paulus et al.[10] included 92.4% with secondary MR and 7.6% with MR of mixed etiology. In the study by Villablanca et al.,[12] 87.5% of patients had degenerative MR, while functional MR rate comprised 17.6% of patients. Two other studies reported the proportion of patients with functional MR, 75.4% among women and 82.1% among men in one study,[3] and 48% among women and 58% among men in the other.[4]

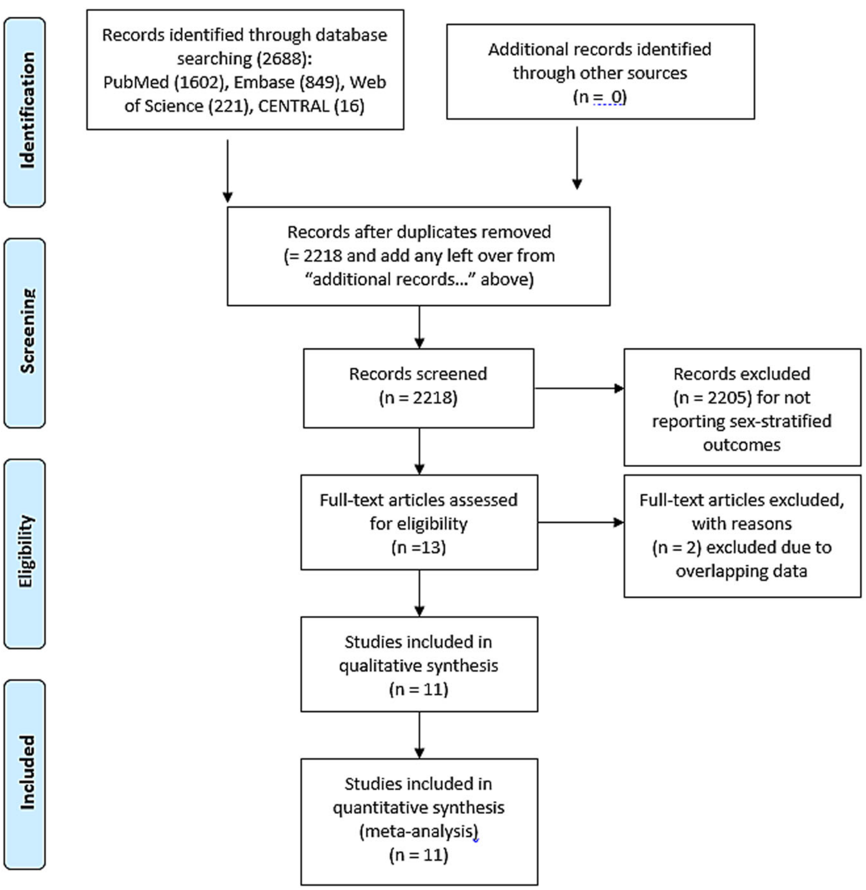

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram summarizing the search strategy and included studies [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Characteristics for each study included in the analysis

Study (References)	Year published	Study type	Single/ multicenter	Countries	Enrollment period	Females	Males	Follow-up, months
Attizzani et al.[3]	2015	Prospective	Single-center	Italy	2008–2013	65	106	12
Estevez-Loureiro et al.[4]	2015	Retrospective	Multicenter	UK, Denmark, Sweden	2009–2012	64	109	16
Giordano et al.[5]	2015	Retrospective	Multicenter	Italy	NR	45	39	12
Gafoor et al.[6]	2016	Prospective	Multicenter	Europe	2008–2011	205	362	12
Tigges et al.[7]	2016	Prospective	Single-center	Germany	2008–2015	230	362	24
Werner et al.[9]	2019	Prospective	Multicenter	Germany	2010–2013	327	501	12
Paulus et al.[10]	2020	Retrospective	Single-center	Germany	2011–2019	37	42	1
Khan et al.[11]	2020	Retrospective	Multicenter	US	2010–2017	7184	8080	0
Villablanca et al.[12]	2021	Retrospective	multicenter	US	2013–2017	2523	2772	12
Park et al.[13]	2021	Retrospective	Multicenter	Europe	2008–2018	445	788	24
Kosmidou et al.[14]	2021	Prospective	Multicenter	US	2012–2017	221	393	24

Abbreviations: NR, not reported; US, United States.

3.2 | Short-term outcomes

Eight studies reported short-term mortality with a total of 23,608 patients (46.0% women).[3–6,9,11–13] There was no difference in the incidence of all-cause mortality between women and men (OR: 1.16, 95% CI: 0.97–1.39; I^2 = 11%). The secondary analysis with a fixed-effect model demonstrated comparable findings (Figure 2A). The sensitivity analysis excluding the largest study showed consistent findings (OR: 1.17, 95% CI: 0.85–1.61; I^2 = 24%) (Supporting Information Figure Panel A).[11] Analysis of the three studies which reported adjusted short-term mortality showed no difference in the adjusted short-term mortality (adjusted hazard ratio [HR]: 1.11, 95% CI: 0.94–1.33) (Figure 4A).[11–13]

A total of six studies reported periprocedural stroke events with 22,254 patients (46.5% women).[3,4,6,9,11,12] There was no clear definition for stroke in these studies with the exception of Villablanca et al.[12] defining stroke as per the Valve Academic Research Consortium 2 criteria as "duration of a focal or global neurological deficit ≥24 h; or <24 h if available neuroimaging documents a new hemorrhage or infarct; or the neurological deficit results in death." Compared with men, women had higher odds of unadjusted stroke (OR: 1.57, 95% CI: 1.10–2.25; I^2 = 0%). The analysis using the fixed-effect model showed consistent findings (Figure 2B). The sensitivity analysis excluding the largest study showed comparable findings (OR: 1.20, 95% CI: 0.74–1.96; I^2 = 0%) (Supporting Information Figure Panel B).[11]

Four studies reported periprocedural bleeding events with a total of 6816 patients (45.5% women).[3,6,9,12] There was no uniform definition for bleeding across the studies. Gafoor et al.[6] reported "bleeding complications," Attizini et al.[3] reported "blood transfusion," and Werner et al.[9] reported "transfusion or major bleeding." Villablanca et al.[12] defined major bleeding as per the Mitral Valve Academic Research Consortium criteria: a drop in the hemoglobin of 3.0 g/dl or requiring transfusion of 3 units of whole blood or packed red blood cells. Women had higher unadjusted rates of bleeding compared with men (OR: 1.34, 95% CI: 1.15–1.56; I^2 = 0%). The secondary analysis with the fixed-effect model demonstrated comparable findings (Figure 2C).

Seven studies provided sex-specific procedural success rates for 3648 patients (37.9% women).[3–7,9,13] Overall, there was no difference in procedural success rate (OR: 0.75, 95% CI: 0.55–1.05; I^2 = 0%). The analysis using the fixed-effect model showed consistent findings (Figure 2D).

3.3 | Long-term outcomes

Eight studies reported sex-specific long-term mortality, with a total of 8499 patients (43.6% women),[3–6,9,12–14] while five studies reported adjusted mortality.[5,6,12–14] There was no difference in the incidence of unadjusted mortality (OR: 0.98, 95% CI: 0.89–1.09; I^2 = 0%) (Figure 3A). Women had lower incidence of all-cause mortality using the maximally adjusted summary estimates (adjusted HR: 0.77, 95% CI: 0.67–0.88; I^2 = 0%) (Figure 4B). The analysis using the fixed-effect model showed consistent findings.

Five studies reported HF hospitalizations with a total of 1180 patients (44.2% women).[3–5,9,14] There was no difference in the incidence of HF hospitalization (OR: 1.07, 95% CI: 0.68–1.67; I^2 = 40%) (Figure 3B).

Seven studies reported residual MR (Grade 3 or 4) on follow-up, with a total of 6913 patients (45.0% women).[3,4,6,7,12–14] There was no difference in the incidence of residual MR (OR: 1.13, 95% CI: 0.85–1.49; I^2 = 24%) (Figure 3C).

TABLE 2 Baseline characteristics of patients undergoing TEER using MitraClip in each of the studies

Study (References)	Mean age (y)		Hypertension (%)		Diabetes Mellitus (%)		Prior MI (%)		CVD (%)		Ejection fraction, mean		Chronic kidney disease (%)		Baseline NYHA III/IV (%)		Baseline +3/+4 MR (%)		Mean STS score (%)	Mean Euro-score (%)
	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M		
Attizzani et al.[3]	74.0	70.3	73.8	74.5	36.9	34.0	20	42.5	NR	NR	38.4	34.6	55.4	43.4	83.1	80.2	95.4	98.1	6.58	NR
Estevez-Loureiro et al.[4]	78.9	73.5	64.1	60.6	10.9	25.7	20	46	NR	NR	48.1	42.8	NR	NR	96.9	94.5	NR	NR	NR	18.9
Giordano et al.[5]	78	73	71.1	84.6	22.2	41.0	22.7	60.5	NR	NR	44	33	31.1	38.5	100	100	80	92.3	4.6	NR
Gafoor et al.[6]	76	72	NR	NR	NR	NR	21	38	44	73	NR	NR	34.1	46.1	83.9	81.2	97.1	98.1	NR	23.15
Tigges et al.[7]	76	74.4	73.9	70.2	19.6	32.9	21.8	40.4	50.4	73.5	46.5	39	45.7	63.5	NR	NR	NR	NR	4.25	21.2
Werner et al.[9]	77	74.2	61.2	64.7	33.3	27.7	21.9	31.2	66.7	83.9	NR	NR	29.7	47.3	87.2	85.8	87.8	88.2	8.3	24.45
Paulus et al.[10]	76	76	62.2	69.0	27.0	35.7	NR	NR	48.6	69	49	42	54.1	73.8	97.2	92.9	100	100	NR	19.5
Khan et al.[11]	80	79	48.6	50.0	9.7	11.1	NR	NR	51.4	67.5	NR	NR	30.2	42.9	NR	NR	NR	NR	NR	NR
Villablanca et al.[12]	83	82	85.8	86.7	22.9	27.3	19.7	31	39.7	62.3	58	53	2.3[a]	3.4[a]	85.7	82.3	19.3	13.9	6.2	NR
Park et al.[13]	76	72	64.9	66.2	24.7	31.3	18.9	30.6	NR	NR	40	33	79	69	87.4	88.3	94.6	95.4	NR	21
Kosmidou et al.[14]	69.5	73.8	77.8	81.9	38.9	36.4	36.7	59.8	52.5	84	31.6	31.1	50.2	60.6	66.5	57.7	100	100	NR	NR

Abbreviations: CVD, cardiovascular disease; MI, myocardial infarction; MR, mitral regurgitation; NR, not reported; NYHA, New York Heart Association; STS Society of Thoracic Surgery; TEER, transcatheter edge-to-edge repair.

[a]End-stage renal disease on dialysis.

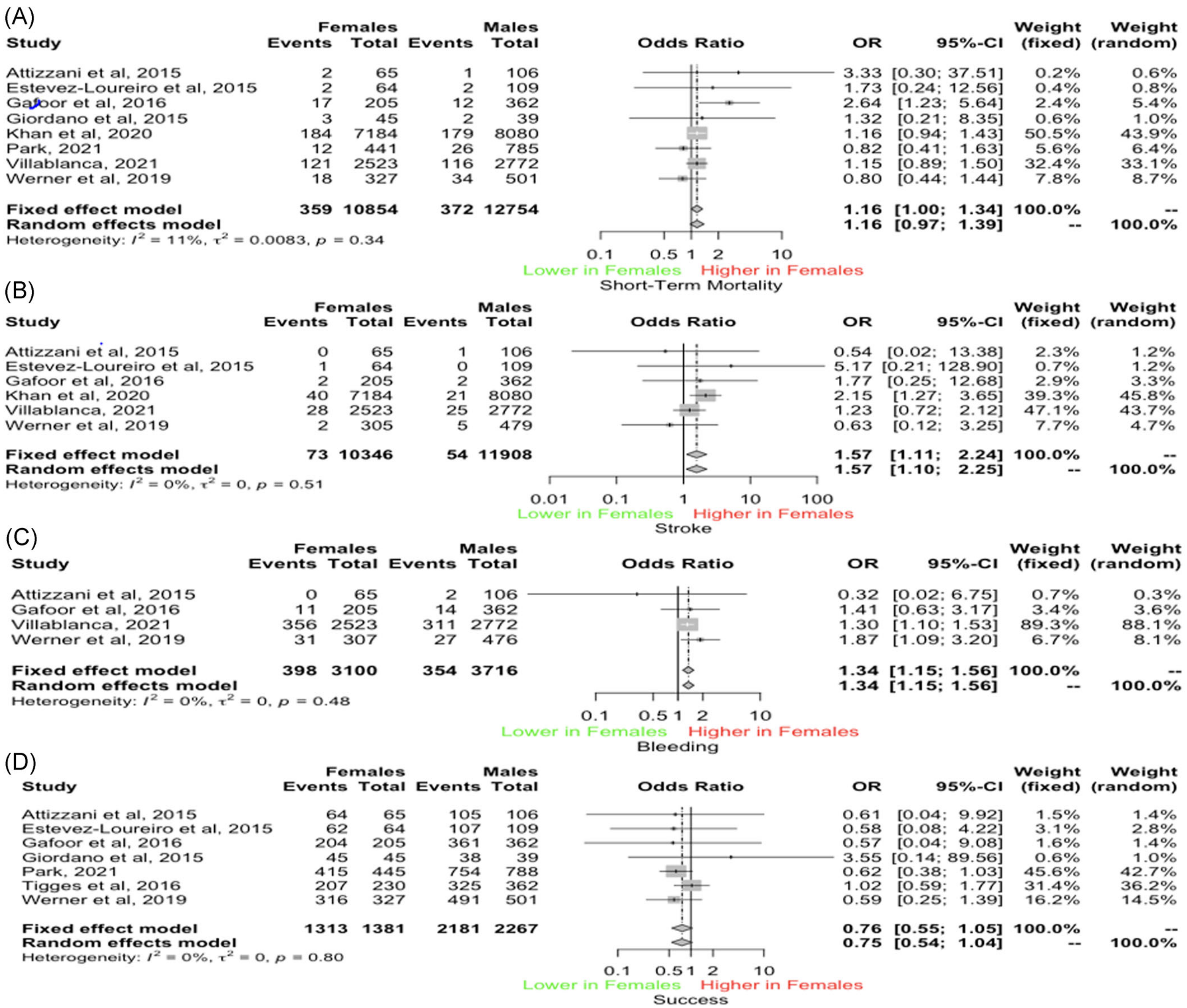

FIGURE 2 Forest plot of short-term outcomes, including (A) mortality, (B) periprocedural stroke, (C) bleeding, and (D) procedural success rate. CI, confidence interval; OR, odds ratio [Color figure can be viewed at wileyonlinelibrary.com]

Six studies reported HF hospitalization or mortality with a total of 1264 patients (44.9%).[3–6,9,14] There was no difference in the incidence of HF or mortality (OR: 1.05, 95% CI: 0.79–1.39; I^2 = 42%) (Figure 3D).

4 | DISCUSSION

In this meta-analysis of 11 studies with 24,905 patients, we examined the sex differences in clinical profile and outcomes among patients undergoing TEER with MitraClip. The salient findings of this meta-analysis were: i) there was no difference in the rates of procedural success rate and short-term mortality between women and men; ii) women appear to have a higher rate of periprocedural bleeding and stroke, despite having a lower prevalence of comorbidities such as coronary artery disease, chronic kidney disease and diabetes mellitus at baseline; and iii) there was no difference between women and men in the unadjusted mortality and HF hospitalization at a median follow-up of 12 months. However, women had a lower incidence of adjusted mortality.

Moderate-to-severe and severe MR, whether functional or degenerative, is associated with an increased risk of HF hospitalizations and mortality.[1–8] Studies have shown that mitral valve repair, using surgery or transcatheter techniques for patients who are not candidates for surgery or at high risk for surgery, improves outcomes.[3–14] As such, TEER using MitraClip is now classified as a reasonable option for a subset of patients in the 2020 ACC/AHA valvular heart disease guidelines.[2] The endovascular valve edge-to-edge repair study (EVEREST II) trial was the first trial to show the efficacy and safety of TEER using MitraClip for MR compared with surgery.[1] Subsequently, the Cardiovascular Outcomes Assessment of the MitraClip

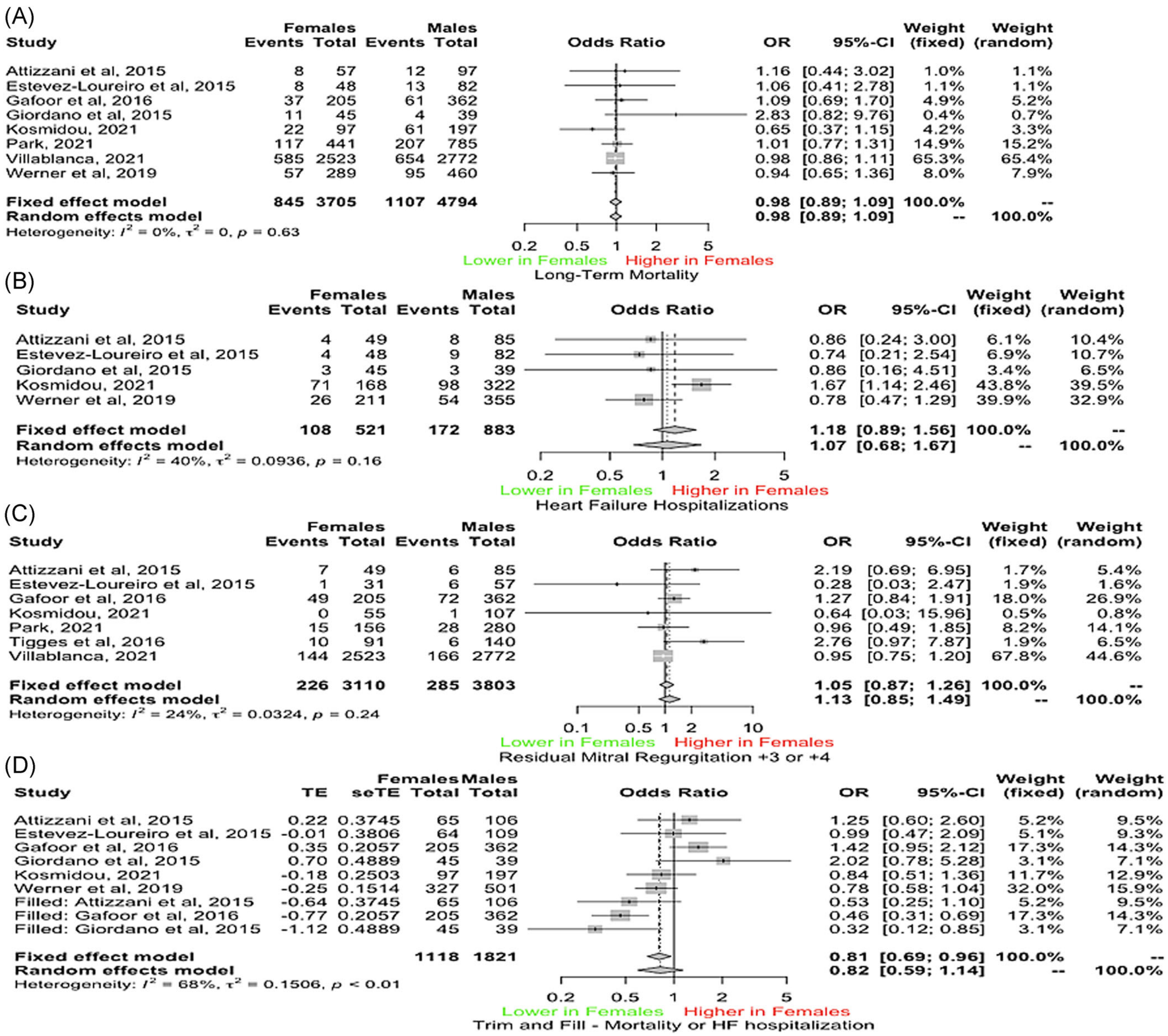

FIGURE 3 Forest plot showing odds ratio (OR) of studies reporting long-term outcomes (A) mortality, (B) heart failure (HF) hospitalization, (C) residual significant mitral regurgitation (Grade +3 or +4), and (D) mortality or HF hospitalization. CI, confidence interval [Color figure can be viewed at wileyonlinelibrary.com]

Percutaneous Therapy (COAPT) trial demonstrated a long-term survival benefit of TEER with MitraClip over guideline directed medical treatment alone for secondary MR among symptomatic patients despite maximally tolerated medical therapy.[8] In a sex-specific analysis of the COAPT study, TEER improved clinical outcomes compared with guideline directed medical treatment alone, irrespective of sex. However, the impact of TEER in reducing HF hospitalization was less pronounced among women compared with men beyond 1 year.[14] In this context, our meta-analysis showed no difference between men and women in the unadjusted long-term mortality or HF hospitalization at 12 months. Using the maximally adjusted summary estimates, women appeared to have a lower incidence of long-term mortality. However, the interpretation of this finding is limited given that this analysis was driven by five studies, and one study contributed to the main weight of that analysis.

Some studies suggest that the benefit of TEER is mainly observed among patients with "disproportionate" MR (i.e., patients with higher regurgitant volume relative to left ventricular end-diastolic volume).[21–26] However, this alone does not completely account for the difference in the outcomes after TEER.[21] A secondary analysis of the COAPT trial suggested that the effective regurgitant orifice area to the left ventricular end-diastolic dysfunction may not be the best factor associated with TEER benefit in regard to all-cause mortality and HF hospitalizations.[27] Additionally, some authors suggested that sex might influence the outcomes following TEER; as women tend to

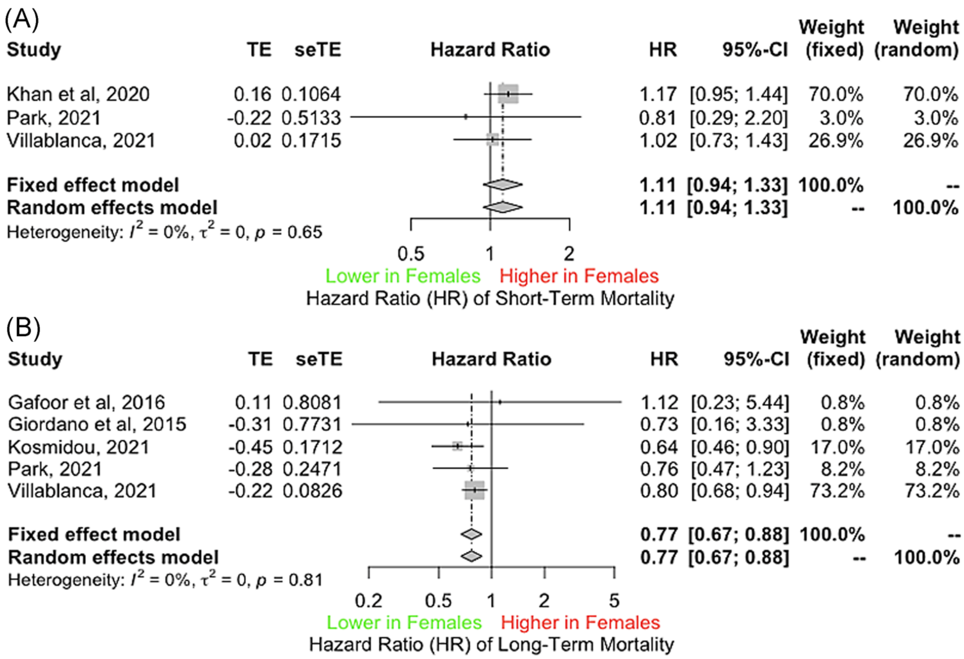

FIGURE 4 Forest plot of hazard ratios for adjusted short-term (A) and long-term (B) mortality. Khan et al.[11] adjusted for age and other comorbidities: HF, CAD, coagulopathy, diabetes (with complications), hypertension (HTN), PVD, pulmonary hypertension, renal failure, smoking, prior percutaneous coronary intervention (PCI), and prior coronary artery bypass graft (CABG). Park et al.[13] adjusted for body surface area (BSA); body mass index; PCI; CABG; transient ischemic attack (TIA); chronic obstructive pulmonary disease (COPD); or atrial fibrillation (A fib) or atrial flutter (A flutter); left ventricular ejection fraction (LVEF); left ventricular end-diastolic volume; left ventricular end-systolic volume; effective regurgitant orifice area; and mitral regurgitation. Villablanca et al.[12] adjusted for age, race, BSA, prior myocardial infarction, prior revascularization, prior cardiac operations, HTN, diabetes mellitus, any A fib or A flutter, prior stroke or TIA, prior peripheral arterial disease, carotid stenosis, dialysis, severe chronic lung disease, home oxygen, immunocompromised status, endocarditis, current/recent smoker, New York Heart Association functional Class IV, glomerular filtration rate, hemoglobin, LVEF, left ventricular systolic internal dimension, left ventricular diastolic internal dimension, left main stenosis of 50% or more, triple vessel disease, hostile chest, porcelain aorta, prior mitral valve procedure, prior nonmitral valve procedure, mitral etiology (degenerative vs. functional), mean mitral valve gradient, mitral leaflet calcification, mitral annular calcification, aortic insufficiency (moderate/severe vs. other), procedural acuity (elective vs. urgent vs. shock or inotropes or assist device vs. emergency or salvage or cardiac arrest) and years performing procedure. Giordano et al.[5] adjusted for the following factors: age, height, BSA, prior myocardial infarction, prior percutaneous coronary intervention, prior CABG, prior arrhythmia device implantation, ischemic cardiomyopathy, COPD, and LVEF. Gafoor et al.[6] adjusted for age, renal disease, and COPD. CAD, coronary artery disease; CI, confidence interval; HF, heart failure; PVD, peripheral vascular disease [Color figure can be viewed at wileyonlinelibrary.com]

have significantly smaller left ventricles thus higher rates of disproportionate MR relative to their small left ventricles.[21] Persistent sex differences in left ventricular size even after adjusting for body surface area suggest that the use of sex-specific echocardiographic values may potentially improve the identification of women that are most likely to benefit from TEER.[21–26]

Mitral valve prolapse is more frequently encountered among women.[25] In addition, MR secondary to atrial dilation and remodeling (also known as "atrial MR") is more common among women, and it is unclear whether TEER is beneficial for this specific entity.[21,28] It is worth mentioning that women's enrollment in the landmark TEER trials has been low. Women comprised approximately one-third of patients in the TEER group in both the EVEREST II and COAPT trials, and even lower in the MIRTA-FR trial (around 21%).[1,8,29] In addition, only one of these landmark trials reported sex-specific data in the clinical profile and outcomes of patients undergoing TEER. Our findings highlight the importance of recruiting a greater proportion of women and reporting sex-specific data in future trials to bridge this critically important knowledge gap.[30]

Studies have shown that women tend to have a higher risk of bleeding and stroke following percutaneous cardiac procedures, including transcatheter aortic valve replacement and percutaneous coronary interventions.[31–36] Not only do women tend to have an increased risk for peri-procedural stroke, but also tend to have worse recovery after stroke compared with men.[30,32] Consistent with other studies, this analysis showed that women had higher rates of peri-procedural stroke.[30,32] The higher rates of stroke could be attributed to the older age of women, as well as the higher incidence of atrial arrhythmias, including atrial fibrillation, which is more common in women, and could have potentially attributed to the higher rate of stroke; however, this information was not reported by most of the included studies.[29,31] Additionally, our analysis was consistent with prior studies showing higher rates of bleeding in women following cardiac procedures.[31–34] This might have also been attributed to the older age women as well as the lower body weight among women.[31]

Importantly, there was no difference in the long-term mortality between women and men, despite women having higher rates of periprocedural complications, including stroke and bleeding. Nevertheless, future studies addressing these potential confounders to assess sex-specific outcomes are needed to understand the true impact of sex on these complications following TEER.[37]

5 | LIMITATIONS

This analysis should be interpreted in the context of some limitations. First, the majority of the studies included in this analysis are nonrandomized studies. Second, individual-patient data were not available, precluding adjustment for differences in clinical or anatomical variables or comparisons of severity or risk across the cohorts. Third, most outcomes (except short and long-term mortality) were unadjusted since the individual studies did not report these adjusted outcomes, raising concern for potential confounding and selection bias. Fourth, there was no clear definition for stroke or bleeding by most of the studies. Fifth, there was some degree of variation in the follow-up between the studies. Sixth, the impact of medications, including guideline directed medical treatment for HF and antithrombotic medications, could not be assessed since these were not reported by the studies. Lastly, the echocardiographic parameters and type of MR at baseline were not consistently reported in most studies. In addition, there were no core labs to validate the reported results in the registries. As such the impact of the baseline echocardiographic measurements could not be assessed.

6 | CONCLUSION

In this meta-analysis of 11 studies reporting sex-specific outcomes for patients undergoing TEER, we found that there was no difference in procedural success, short-term mortality, or long-term outcomes between women and men undergoing TEER with MitraClip. Women had a lower prevalence of baseline comorbidities, but higher rates of periprocedural stroke and bleeding. Women had a lower incidence of adjusted long-term mortality. Future high-quality studies assessing sex-specific outcomes following TEER using MitraClip are needed.

CONFLICT OF INTERESTS

Dr. Islam Y. Elgendy has a conflict of interest unrelated to this manuscript content including receiving research grants from Caladrius Biosciences, Inc. The remaining authors have no conflict of interests.

ORCID

Rodrigo Bagur http://orcid.org/0000-0003-1888-9429
Islam Y. Elgendy http://orcid.org/0000-0001-9853-7591

REFERENCES

1. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med*. 2011;364(15): 1395-1406. doi:10.1056/NEJMoa1009355
2. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2021;143:e35-e71. doi:10.1161/CIR.0000000000000932
3. Attizzani GF, Ohno Y, Capodanno D, et al. Gender-related clinical and echocardiographic outcomes at 30-day and 12-month follow-up after MitraClip implantation in the GRASP registry. *Catheter Cardiovasc Interv*. 2015;85(5):889-897.
4. Estévez-Loureiro R, Settergren M, Winter R, et al. Effect of gender on results of percutaneous edge-to-edge mitral valve repair with MitraClip system. *Am J Cardiol*. 2015;116(2):275-279. doi:10.1016/j.amjcard.2015.04.019
5. Giordano A, Indolfi C, Baldi C, et al. Comparison of men versus women undergoing transcatheter mitral valve repair with MitraClip. *Journal of Cardiology and Therapy*. 2015;2(2):285-290. http://www.ghrnet.org/index.php/jct/article/view/1152
6. Gafoor S, Sievert H, Maisano F, et al. Gender in the ACCESS-EU registry: a prospective, multicentre, non-randomised post-market approval study of MitraClip® therapy in Europe. *EuroIntervention*. 2016;12(2):e257-e264. doi:10.4244/EIJV12I2A40
7. Tigges E, Kalbacher D, Thomas C, et al. Transcatheter mitral valve repair in surgical high-risk patients: gender-specific acute and long-term outcomes. *BioMed Res Int*. 2016;2016:3934842. doi:10.1155/2016/3934842
8. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018; 379(24):2307-2318. doi:10.1056/NEJMoa1806640
9. Werner N, Puls M, Baldus S, et al. Gender-related differences in patients undergoing transcatheter mitral valve interventions in clinical practice: 1-year results from the German TRAMI registry. *Catheter Cardiovasc Interv*. 2020;95(4):819-829. doi:10.1002/ccd.28372
10. Paulus MG, Meindl C, Böhm L, et al. Predictors of functional improvement in the short term after MitraClip implantation in patients with secondary mitral regurgitation. *PLoS ONE*. 2020;15(5): e0232817. doi:10.1371/journal.pone.0232817
11. Khan MZ, Zahid S, Khan MU, Khan SU, Munir MB, Balla S. Gender disparities in percutaneous mitral valve repair (from the National Inpatient Sample). *Am J Cardiol*. 2020;132:179-181. doi:10.1016/j.amjcard.2020.07.021
12. Villablanca P, Vemulapalli S, Stebbins A, et al. Sex-based differences in outcomes with percutaneous transcatheter repair of mitral regurgitation with the MitraClip system: transcatheter valve therapy registry from 2011 to 2017. *Circ Cardiovasc Interv*. 2021;14(11): e009374. doi:10.1161/CIRCINTERVENTIONS.120.009374
13. Park SD, Orban M, Karam N, et al. Sex-Related clinical characteristics and outcomes of patients undergoing transcatheter edge-to-edge repair for secondary mitral regurgitation. *JACC Cardiovasc Interv*. 2021;14(8):819-827. doi:10.1016/j.jcin.2020.12.042
14. Kosmidou I, Lindenfeld J, Abraham WT, et al. Sex-specific outcomes of transcatheter mitral-valve repair and medical therapy for mitral regurgitation in heart failure. *JACC Heart Fail*. 2021;9(9):674-683. doi:10.1016/j.jchf.2021.04.011
15. Elbadawi A, Elzeneini M, Thakker R, et al. Sex differences in in-hospital outcomes of transcatheter mitral valve repair (from a National Database). *Am J Cardiol*. 2020;125(9):1391-1397. doi:10.1016/j.amjcard.2020.01.013
16. Doshi R, Shlofmitz E, Vadher A, Shah J, Meraj P. Impact of sex on short term in-hospital outcomes with transcatheter edge-to-edge

mitral valve repair. *Cardiovasc Revasc Med*. 2018;19(2):182-185. doi:10.1016/j.carrev.2017.07.002

17. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA*. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008
18. Sideri S, Papageorgiou SN, Eliades T. Registration in the international prospective register of systematic reviews (PROSPERO) of systematic review protocols was associated with increased review quality. *J Clin Epidemiol*. 2018;100:103-110. doi:10.1016/j.jclinepi.2018.01.003
19. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;259:603-605. doi:10.1007/s10654-010-9491-z
20. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629
21. Shah SV, Bavry AA, Kumbhani DJ. Transcatheter mitral valve edge-to-edge repair for secondary mitral regurgitation: why sex matters. *Circulation*. 2021;143(7):621-623. doi:10.1161/CIRCULATIONAHA.120.052345
22. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation. A new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *JACC Cardiovasc Imaging*. 2019;12:353-362. doi:10.1016/j.jcmg.2018.11.006
23. Orban M, Karam N, Lubos E, et al. Impact of proportionality of secondary mitral regurgitation on outcome after transcatheter mitral valve repair. *JACC Cardiovasc Imaging*. 2021;14:715-725. doi:10.1016/j.jcmg.2020.05.042
24. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16:233-270. doi:10.1093/ehjci/jev014
25. Avierinos JF, Inamo J, Grigioni F, Gersh B, Shub C, Enriquez-Sarano M. Sex differences in morphology and outcomes of mitral valve prolapse. *Ann Intern Med*. 2008;149(11):787-795. doi:10.7326/0003-4819-149-11-200812020-00003
26. Giustino G, Overbey J, Taylor D, et al. Sex-based differences in outcomes after mitral valve surgery for severe ischemic mitral regurgitation: from the cardiothoracic surgical trials network. *JACC Heart Fail*. 2019;7(6):481-490. doi:10.1016/j.jchf.2019.03.001
27. Lindenfeld J, Abraham WT, Grayburn PA, et al. Association of effective regurgitation orifice area to left ventricular end-diastolic volume ratio with transcatheter mitral valve repair outcomes. A secondary analysis of the COAPT trial. *JAMA Cardiol*. 2021;6:427-436. doi:10.1001/jamacardio.2020.7200
28. Dziadzko V, Dziadzko M, Medina-Inojosa JR, et al. Causes and mechanisms of isolated mitral regurgitation in the community: clinical context and outcome. *Eur Heart J*. 2019;40(27):2194-2202. doi:10.1093/eurheartj/ehz314
29. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379(24):2297-2306. doi:10.1056/NEJMoa1805374
30. Elgendy IY, Van Spall HGC, Mamas MA. Cardiogenic shock in the setting of acute myocardial infarction: history repeating itself? *Circ Cardiovasc Interv*. 2020;13(3):e009034. doi:10.1161/CIRCINTERVENTIONS.120.009034
31. Mehta LS, Beckie TM, DeVon HA, et al. Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation*. 2016;133(9):916-947. doi:10.1161/CIR.0000000000000351
32. Itchhaporia D. Transcatheter aortic valve replacement in women. *Clin Cardiol*. 2018;41(2):228-231. doi:10.1002/clc.22912
33. Heer T, Hochadel M, Schmidt K, et al. Sex differences in percutaneous coronary intervention-insights from the coronary angiography and PCI registry of the German Society of Cardiology. *J Am Heart Assoc*. 2017;6(3):e004972. doi:10.1161/JAHA.116.004972
34. Reeves MJ, Bushnell CD, Howard G, et al. Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol*. 2008;7(10):915-926. doi:10.1016/S1474-4422(08)70193-5
35. Saati A, AlHajri N, Ya'Qoub L, Ahmed W, Alasnag M. Peripheral vascular disease in women: therapeutic options in 2019. *Curr Treat Options Cardiovasc Med*. 2019;21(11):68. doi:10.1007/s11936-019-0769-5
36. Ya'Qoub L, Lemor A, Dabbagh M, et al. Racial, ethnic, and sex disparities in patients with STEMI and cardiogenic shock. *JACC Cardiovasc Interv*. 2021;14(6):653-660. doi:10.1016/j.jcin.2021.01.003
37. Ya'Qoub L, Faza NN, Khalique O. Intraprocedural cardiac complications of transcatheter aortic and mitral valve interventions: "the eyes do not see what the mind does not know." *Cardiovasc Revasc Med*. 2021;S1553-8389(21):00245-1. doi:10.1016/j.carrev.2021.05.001

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Ya'Qoub L, Gad M, Faza NN, et al. Sex differences in outcomes of transcatheter edge-to-edge repair with MitraClip: a meta-analysis. *Catheter Cardiovasc Interv*. 2022;1-10. doi:10.1002/ccd.30110