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RESEARCH ARTICLE

Impact of Gender on Outcomes of Transcatheter edge to edge mitral valve repair: A Meta-analysis.

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Abstract

Background: Gender disparities in outcomes after mitral valve surgery are well known. There are only few studies reporting the influence of gender on outcomes following transcatheter edge to edge repair (TEER) of the mitral valve using MitraClip (MC). In this meta-analysis, we describe outcomes by gender after mitral valve TEER.

Methods: Studies reporting gender specific outcomes in patients treated with MC were reviewed from January 2010 to February 2022. Outcomes evaluated include all-cause mortality, New York Heart Association (NYHA) class, readmission for heart failure and residual mitral regurgitation (MR) at the longest follow up. Pooled odds ratio (OR) and 95% confidence interval (CI) were calculated using random effects models.

Results: Seventeen studies with 33,747 patients (19,303 males and 14,444 females) were included. There was no difference in all-cause mortality (OR: 1.00, 95% CI: [0.90-1.12], p=0.93), residual MR (OR: 0.59, 95% CI: [0.34-1.02], p=0.06) or readmission for heart failure (OR: 1.04, 95% CI: [0.69-1.57], p=0.83). However, NYHA class III/IV was more frequent in female patients as compared to male patients at the end of follow up (OR: 0.62, 95% CI: [0.51-0.74], p<0.00001).

Conclusions: Our meta-analysis, the largest to date, suggests that female patients have worse NHYA functional class after TEER without any difference in all-cause mortality, readmissions for heart failure or residual MR when compared to male patients.

Introduction

Valvular heart disease is considered a major public health problem, with mitral regurgitation (MR) being the most common[1]. Surgical mitral valve repair or replacement is indicated in severe MR causing symptoms or cardiomyopathy[2]. However, about half of the patients with severe MR are deemed poor surgical candidates due to operative risks secondary to advanced age and multiple comorbidities. Therefore, for carefully selected patients with high operative risk, transcatheter edge-to-edge mitral valve repair (TEER) with MitraClip (MC) is an appealing and less invasive therapeutic modality that has become part of practice guidelines[3]. While percutaneous repair of mitral valve has shown to be safe in EVEREST II trial[4], patient treated with TEER with MC had persistent reduction in both deaths and heart failure hospitalization at 5 years[5].

The decision to undergo mitral valve repair surgically or percutaneously, depends on the individual patient factors, such as valve morphology, degree of the mitral stenosis and co-morbid conditions rather than the gender. While gender disparity in outcomes of patients undergoing mitral valve surgery is well documented, there is a paucity of outcome data on gender-related differences in patients undergoing TEER. It has also been reported that more men undergo mitral valve surgery and women tend to have less favorable post-operative clinical outcomes in terms of recurrent heart failure[6]. On the other hand, the studies that address TEER outcomes based on gender are very few and the data is very conflicting. Therefore, we performed a meta-analysis and sought to provide comprehensive evaluation of the impact of gender on the clinical outcomes or TEER in patients with severe MR.

Methods

Data sources and search strategy

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[7] guidelines were followed to conduct and report this meta-analysis (Figure 1). We searched electronic databases of PubMed, EMBASE and Cochrane Central Register of Clinical Trials with no language restriction from inception through February 2023 using the search terms: "MitraClip" OR "Edge to Edge MitraClip" AND "Gender specific outcomes". Two investigators (UM and PG) independently performed the database search and agreed on final study selection. In addition, a manual search was performed for relevant references from the selected articles and published reviews.

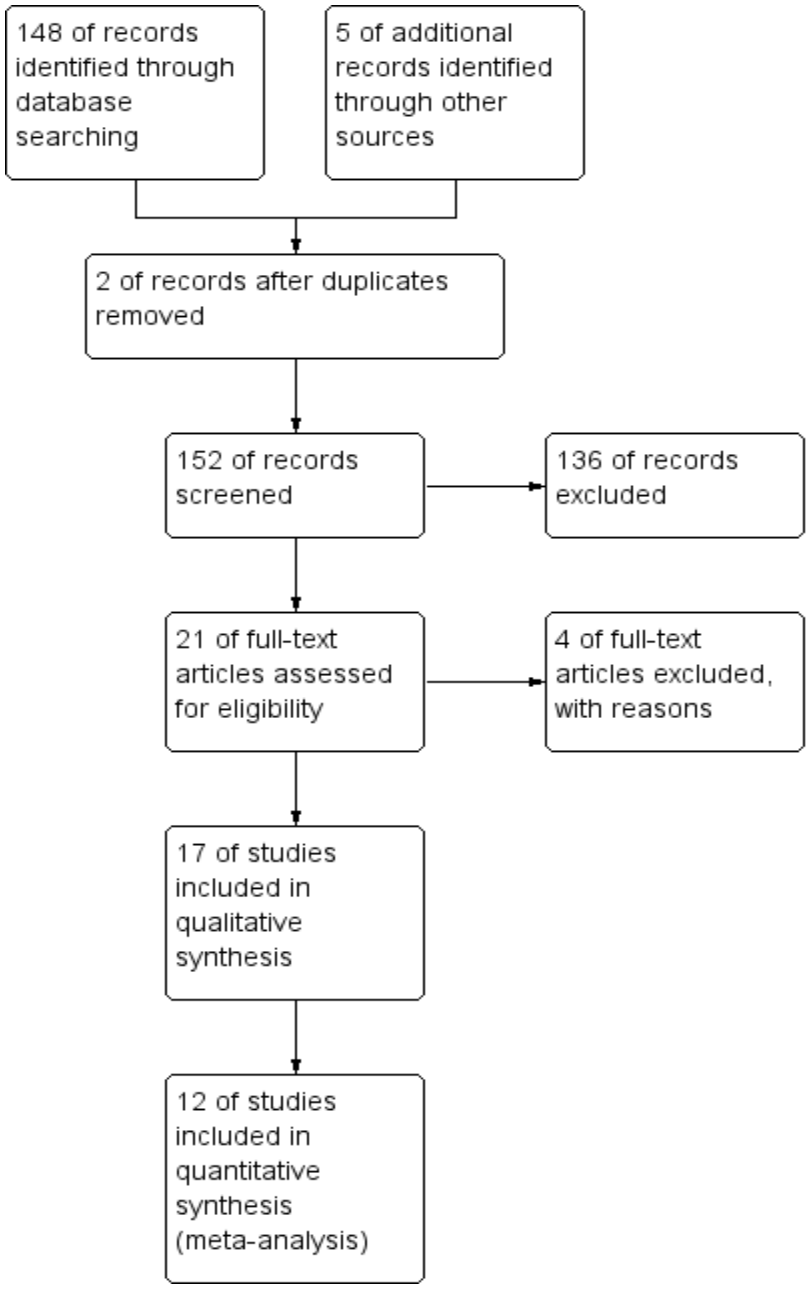

Figure 1: PRISMA Flow

Study selection

Randomized trials and observational studies (retrospective and prospective) reporting gender-based outcomes of all-cause mortality, mitral regurgitation severity, NYHA class for heart failure and readmission for heart failure in patients with TEER were included. Studies were excluded if they lacked a control group, reported hazard or odds ratio, had inadequate data on baseline characteristics and were in non-English language with no English translation.

Table 1: Baseline characteristics

Study	Type	Follow up	Number of Patients		Age	DM (%)		HTN (%)		CAD (%)		CKD (%)		LVEF (%)	
			Male	Female		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Attizzani 2015	OBS	12	106	65	72	34	37	75	74	43	20	43	56	35	39
Estevez-Loureiro 2015	OBS	16.1	109	64	76	26	11	62	61	46	20	NS		42	48
Gafoor 2016	OBS	12	362	205	74	NS		NS		NS		NS		62% had <40%	37% had <40%
Schluter 2013	OBS	13.1	227	134	75	NS		NS		NS		NS		NS	
Tigges 2016	OBS	12	362	230	75	33	20	70	74	73	50	63	80+O19:P19	39	47
Werner 2019	OBS	12	501	327	76	29	35	79	77	81	74	49	32	40% had <30%	22% had <30%
Stone 2018	RCT	24	393	221	71	37		80		51		NS		31%	
Giordano 2015	OBS	12	39	48	76	80	50	85	72	61	23	39	32	33	44
Doshi 2017	OBS	7.5 days	302	219	73	24	19	69	65	NS		NS		NS	
Gotzmann 2017	OBS	12	25	21	76	47		69		60		NS		42	
Franzen 2011	OBS	6.1	38	12	70	NS		NS		NS		NS		10	
Bardeleben 2019	OBS	60	8149	5426	78	31		53		65		51		NS	
Park 2021	OBS	13	788	445	73	33		75		NS		NS		33	40
Kosmidou 2021	RCT	24	393	221	72	36	39	82	78	84	53	61	50	32	32
Paulus 2020	OBS	28 days	42	37	76	25		52		47		51		45	
Khan 2020	OBS	NS	8080	7184	80	11	10	50	49	68	51	43	30	NS	
Baldi 2018	OBS	12	41	13	72	39		26		37		69		33	

DM: Diabetes Mellitus, HTN: Hypertension, CAD: Coronary artery disease, CKD: Chronic kidney disease, LVEF: Left ventricular ejection fraction, NS: Not specified in the study.

Data extraction

From selected studies, data were independently extracted by two investigators (UM and PG) and cross verified by a third investigator (JD). We obtained data on study characteristics (study design, patient selection, inclusion and exclusion criteria, follow-up duration, number of patients, endpoints), patient characteristics (age, sex, race, co-morbidities, medications and indication for mitral valve repair), and outcomes of mortality, NYHA class, MR severity and readmission for heart failure. For MR severity, data with MR grades of 3 and above at maximum reported follow up was extracted for analysis. Data for NYHA class reporting only III and IV was extracted and included in meta-analysis.

Outcomes

All-cause and cardiovascular mortality, residual mitral regurgitation, NYHA class and readmission for heart failure after TEER were the major outcomes investigated in this meta-analysis.

Statistical analysis

We performed statistical analyses with Review Manager (RevMan 5.4). Odds ratio (OR) with 95% confidence interval (CI) was calculated using number of events and total number of patients. Pooled ORs ratios and 95% CIs were calculated using the more conservative DerSimonian and Laird random-effects model[8]. All tests were 2-sided and a p-value less than 0.05 was deemed significant. Heterogeneity was assessed by the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. $I^2 > 50\%$ was considered significant heterogeneity.

Results:

Search Results:

Literature search produced 242 articles. After removing the duplicate articles and excluding the irrelevant articles, 17 studies[9-25] with 33,747 patients (19,303 males and 14,444 females) were included in the meta-analysis. Sixteen studies were available as full text and 1 study[18] was available as abstract only. Average follow up duration was 16 months (ranging 6.1-60 months).

All-cause mortality:

Fourteen studies[9-17,19,21-23] with 33,076 patients (18,894 males and 14,182 females) were included in the analysis. There was no difference in all-cause mortality based on gender in patients undergoing mitral valve TEER OR: 1.00, 95% CI: [0.90-1.12], p=0.93) Figure 2.

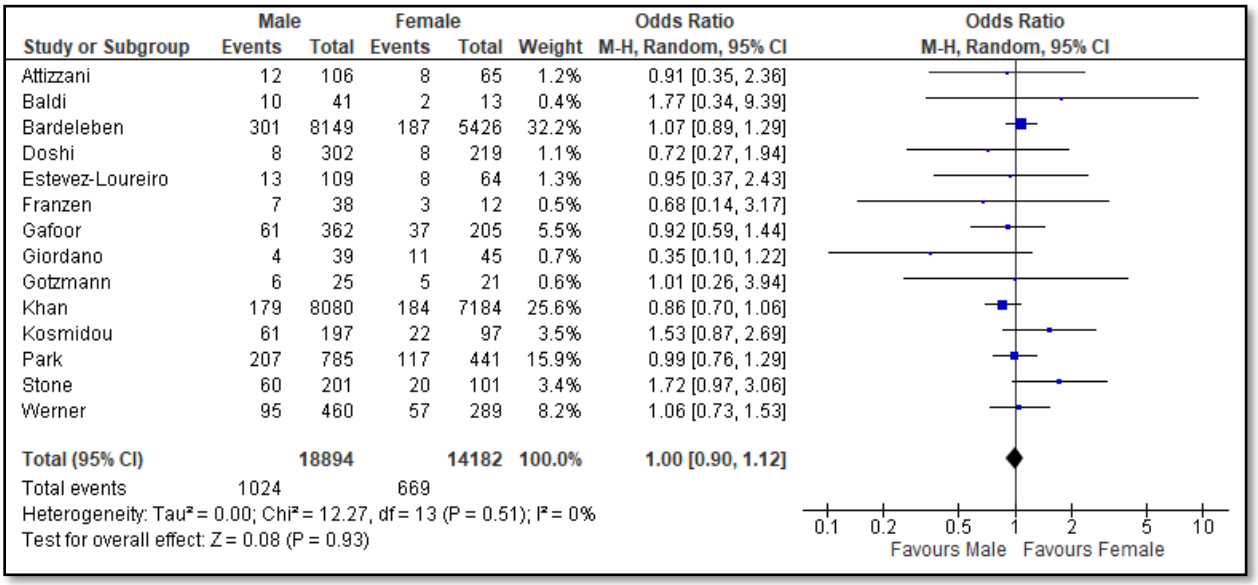

Figure 2: Forest plot showing no difference in all-cause mortality between male and females.

Residual Mitral Regurgitation:

Seven studies[9,10,13,15,18,20,24] with 1,544 patients (952 males, 592 females) were included in the meta-analysis (Figure 3). There was no difference in residual mitral regurgitation at follow up (OR: 0.59, 95% CI: [0.34-1.02], p=0.06). A sensitivity analysis excluding the abstract[18] did not alter the results (OR: 0.68, 95% CI: [0.35-1.32], p=0.26).

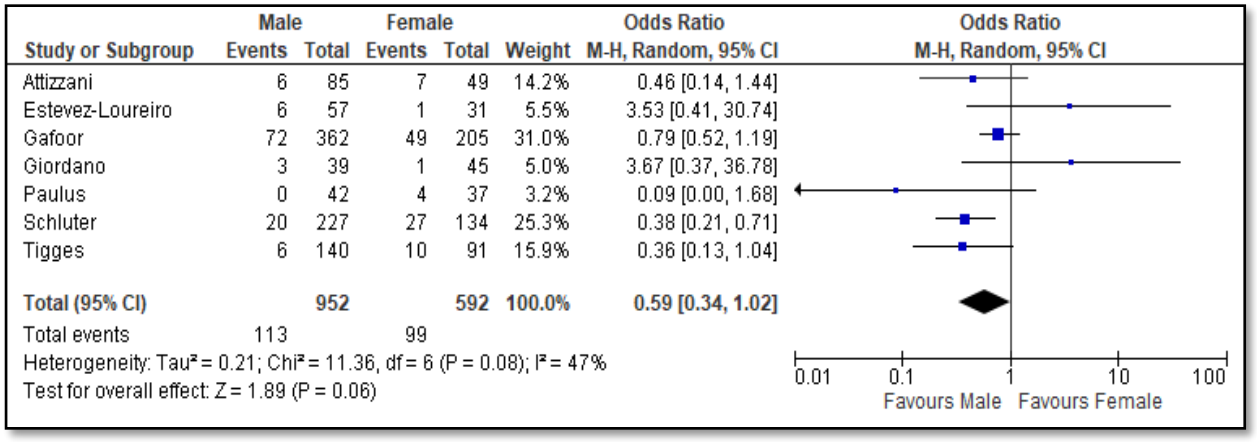

Figure 3: Forest plot showing no difference in residual MR between male and females

NYHA Class:

Seven studies[10,13,15,18,20,22,24] with 2,350 patients (1,469 males, 881 females) were included in this meta-analysis (Figure 4). NYHA class was significantly higher in female patients as compared to male patients at the end of follow up (OR: 0.62, 95% CI: [0.51-0.74], p<0.00001). A sensitivity analysis excluding the abstract did not alter the results (OR: 0.62, 95% CI: [0.52-0.76], p<0.00001).

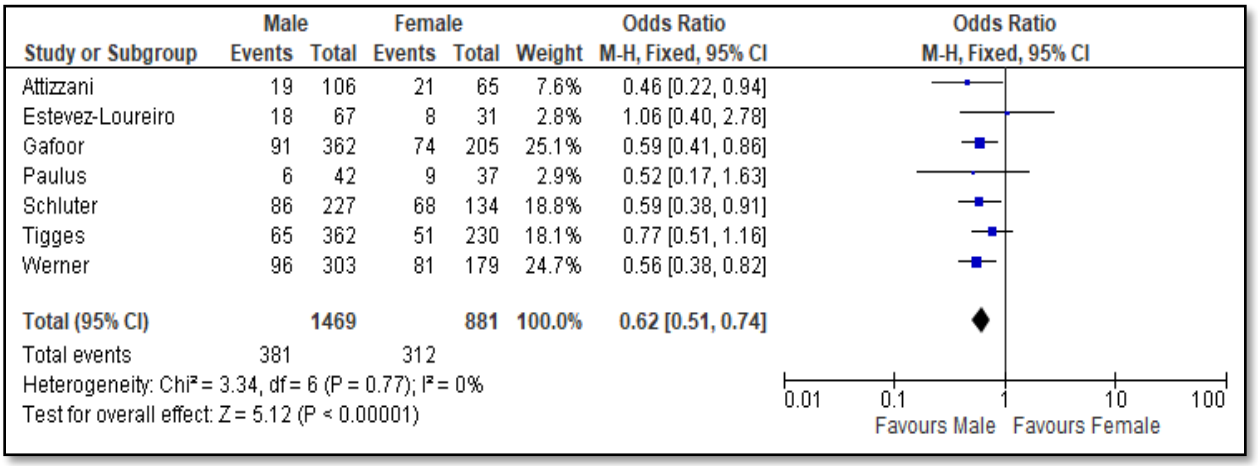

Figure 4: Forest plot showing higher NYHA functional class in females at follow up

Readmission Rate:

Seven studies[9,10,13,18,19,22,25] with 1,894 patients (1207 males, 687 females) reported readmission rate for heart failure and were included in the analysis (Figure 5). There was no difference in readmission rate between the groups (OR: 1.04, 95% CI: [0.69-1.57], p=0.83). A sensitivity analysis excluding the abstract did not alter the results (OR: 0.89, 95% CI: [0.62-1.29], p=0.55).

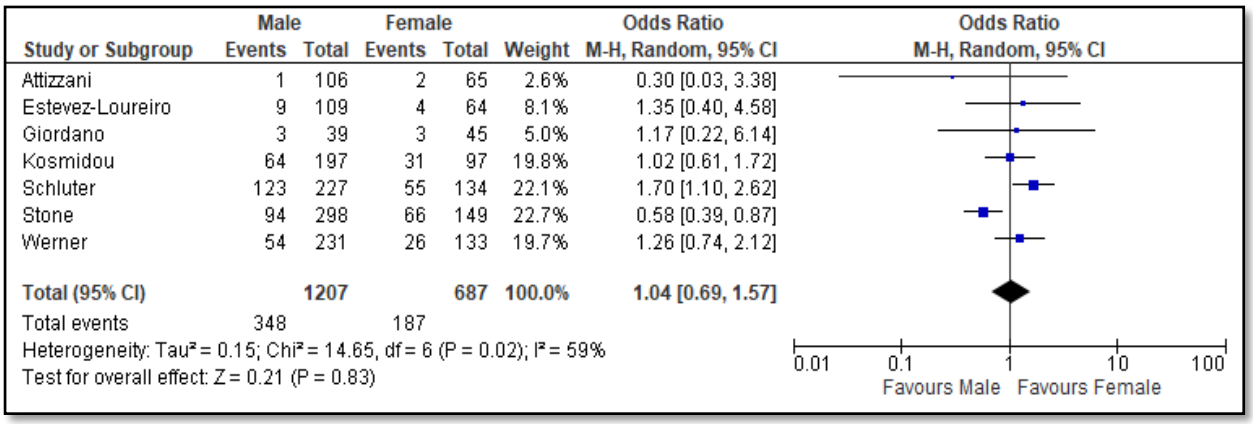

Figure 5: Forest plot showing no difference in readmission rate for hospitalization between male and females.

Discussion

Female gender is known to be a predictor of adverse outcomes after surgical mitral valve replacement largely due to advanced age at presentation, worse baseline characteristics and higher incidence of mitral valve replacement as opposed to repair[26]. There can be other explanations for poor surgical outcome in female patients including smaller body surface area, which correlates with a smaller mitral valve annular area that may account for this difference. Moreover, female patients are more prone to have unfavorable valvular anatomy including calcification and degenerative changes at the valvular level.[27] making the repair challenging. A study by Vassileva et al.[26] demonstrated higher long-term mortality in female patients after surgical repair of the mitral valve (4.2% versus 3.5%). This difference was thought to be mainly because of worse baseline risk profile of women compared with men, as the mortality rate was similar between the groups after risk adjustment. While there is paucity of data on gender-based outcomes after TEER, the pooled data allowed us to explore various aspects related to the gender differences and their potential influence on the effectiveness of the TEER with MC. In our meta-analysis which is the largest to date, we found no difference in all-cause mortality, residual MR and readmission for heart failure based on gender after TEER. However, differences were seen in heart failure symptoms post-procedure, with NYHA class III/IV significantly higher in female patients.

A prospective study by Tigges et al[20], showed better survival in females at 2 years follow up after TEER, however, the study included a

male dominant cohort with higher comorbidities. As pointed in their study, the male gender was not found to be the predictor of mortality in multivariate analysis, supporting the fact that mortality was not directly related to the procedure itself. This is in contrast to study performed by Attizzani et al[10], that also included male subjects with worse baseline clinical characteristics and yet found no significant gender-based differences in all-cause mortality after TEER. Additionally, their results did not change after adjusting their Kaplan-Meier estimates for baseline characteristics, further consolidating the notion of no gender-based mortality difference after TEER. These findings are in accordance with our meta-analysis that also suggests similar all-cause mortality in females and males after mitral valve repair with TEER and stresses the appropriateness of TEER as a treatment option regardless of gender.

Several studies have reported substantial clinical improvement after TEER, as well as considerable MR reduction immediately post procedure and at long term follow up. Both genders appear to benefit equally based on these studies[10,13]. However, in our meta-analysis, female patients had significantly higher NYHA functional class III/IV at follow up. Moreover, male gender showed a statistically non-significant trend towards improvement in residual MR (p=0.09), which might possibly explain why female patients had poor NYHA class at follow up. On the other hand, readmission for heart failure symptoms, which is an important gauge of procedural success of TEER, was not significantly different between males and females, which is in line with the findings of several studies included in our metanalysis.

It is important to note, however, that there are caveats in the interpretation of the significant difference in NYHA class between males and females in our meta-analysis. NYHA classification is subjective, and to some extent, is dependent on patient's expectation post-procedure. Furthermore, there is insufficient data to indicate whether increased HF symptoms at follow up are due to residual MR or increased gradients post MC, especially that the difference in the degree of MR reduction between the two groups was not statistically significant. Nonetheless, appropriately powered studies comparing the gender differences among patients treated with TEER will help clarify the findings of our meta-analysis.

Limitations:

While our meta-analysis provides valuable insights into the gender differences associated with the transcatheter edge to edge repair with MitraClip, there are certain limitations that need to be acknowledged. One limitation of our meta-analysis is that it was predominantly based on observational studies. Therefore, there might have been confounding factors that were not accounted for in our study. Another limitation is that many of the included studies did not report all outcomes evaluated in our meta-analysis. Hence, more studies evaluating all potential outcomes are still needed. A third limitation is that NYHA classification is subjective and can

be poorly reproducible. Therefore, the finding of worse NYHA class after TEER in female patients should be taken with caution. Finally, Chamber dimensions before and after the procedure were not reported uniformly and the available data were insufficient to perform a meta-analysis.

Conclusion:

Our meta-analysis shows no gender-based difference in all-cause mortality, MR grade and HF readmission rate after transcatheter edge to edge mitral valve repair. However, improvement in NYHA functional class was less significant in female patients at follow up. Randomized trials are needed to elucidate our findings

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