Clip It or Let It: The Efficacy of Mitral Valve Transcatheter Edge-to-Edge Repair Versus Conservative Treatment in Reducing Mortality Among Patients With Ischemic Mitral Regurgitation

Published online: 11 November 2024
https://doi.org/10.69944/pjc.67f06d54cc
https://pjc.philheart.org
ISSN: 0115-1029
e-ISSN: 2815-2123
Volume 52 Issue 2

Giovanni A. Vista, MD | Marivic V. Vestal, MD | Von Jerick B. Tenorio, MD
Department of Adult Cardiology, Perpetual Succour Hospital - Cebu Heart Institute, Gorordo Avenue, Cebu City

Correspondence:
Giovanni A. Vista, MD
E-mail address: giovistalano124@gmail.com

Abstract

BACKGROUND: Despite revascularization and optimal medial therapy (OMT) residual ischemic mitral regurgitation (IMR) continues in a self-aggravating vicious cycle to affect prognosis and survival adversely. Mitral valve surgery in combination with coronary artery bypass graft remains a subject of debate due to the absence of a net overall benefit. Mitral valve transcatheter edge-to-edge repair (M-TEER) has been gaining grounds as a viable option from observational studies, but results from randomized controlled trials (RCTs) have yielded mixed results. Thus, this study was conducted to determine whether the current collective data support the efficacy of M-TEER with OMT versus OMT alone in patients with clinically significant IMR.

METHODS: A literature search from PubMed/MEDLINE, Cochrane Review Central, Clinical Trials Registry, ResearchGate, Mendeley, and Google Scholar for relevant RCTs and observational studies was conducted and reviewed independently by three reviewers. Published and unpublished studies indexed from inception until 2023 were included. The pooled estimates for the primary outcome of all-cause mortality and secondary outcomes of cardiac mortality and heart failure hospitalizations were measured using R Studio statistical software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS: Seven eligible studies (five observational and two RCTs) allocated 1610 IMR patients to M-TEER + OMT (n = 942) or OMT alone (n = 668). The effect estimate using random-effects model demonstrated M-TEER with OMT to significantly reduce 1-year (odds ratio [OR], 0.67; 95% confidence interval [CI], 0.52–0.86; $P = 0.002$) and 2-year (OR, 0.50; 95% CI, 0.38–0.67; $P < 0.00001$) all-cause mortality. Cardiac mortality (OR, 0.58; 95% CI, 0.27–1.23; $P = 0.15$) and heart failure hospitalization (OR, 0.45; 95% CI, 0.18–1.13; $P = 0.09$) did not reach statistical significance between the treatment arms.

CONCLUSION: In patients with IMR, M-TEER on top of OMT was able to afford a 2-year all-cause mortality advantage.

KEYWORDS: ischemic mitral regurgitation, mitral valve transcatheter edge-to-edge repair, optimal medical therapy

INTRODUCTION

Rationale

Ischemic mitral regurgitation (IMR) is a consequence of the modifications of geometry of the left atrium and/or ventricle brought about by the complex pathophysiology of ischemic cardiomyopathy.[1–3] Remodeling-led papillary muscle displacement can instigate apical mitral valve displacement, subsequent incomplete valve coaptation, and mitral regurgitation (MR) brought about by imbalance between the tethering forces, which is influenced by papillary muscle position and orientation and left ventricle (LV)–to–left atrium gradient–driven closing forces.[4]

The spectrum of IMR encompasses transient MR during exercise in the background of normal baseline LV function, MR associated with hibernating myocardium, and those developing

post–myocardial infarction.[5] Although IMR can occur acutely during a myocardial infarction, this meta-analysis focused only on chronic IMR.[6,7]

Mortality risk of chronic IMR is directly related to the severity of MR, regardless of the baseline characteristics and degree of ventricular dysfunction. As opposed to primary MR, even a mild IMR is associated with increase in heart failure risk and reduced survival in 5 years.[8]

Optimization of medical therapy (OMT) using renin-angiotensin system inhibition with angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, angiotensin receptor/neprilysin inhibitor, aldosterone antagonists, and β-blockers is the universal first step recommended by the guideline bodies. Their positive modulation on LV remodeling benefits patients with IMR only up to a certain point as MR severity progression is inevitable.

Mitral valve surgery alone or in combination with coronary artery bypass graft (CABG), on the other hand, remains a subject of debate due to the absence of a net overall benefit.[9]

Left ventricular dyssynchrony in patients with left bundle-branch block and widened QRS duration (>150 milliseconds) can also further impair LV function and interfere with mitral valve closure and contribute to IMR. Cardiac resynchronization therapy (CRT) has been known to decrease the severity of MR.[10] However, only select patients are eligible for CRT, and even with optimization in device programming, residual MR can still prevail.

Even after revascularization and/or CRT, residual MR remains a formidable therapeutic challenge as IMR, regardless of severity, continues in a self-aggravating vicious cycle to adversely affect prognosis and survival.[3,11]

Percutaneous mitral valve repair or mitral valve transcatheter edge-to-edge repair (M-TEER) is a novel option for chronic IMR.[12] It has been gaining grounds as a viable option from observational studies, but results from randomized controlled trials (RCTs) (COAPT and MITRA-FR)[13,14] have yielded conflicting results. Thus, this study was conducted to determine whether the current collective data support the efficacy of M-TEER with OMT versus OMT alone in patients with clinically significant IMR.

RESEARCH QUESTION

Among patients with IMR, how effective is M-TEER with OMT in reducing death compared with OMT alone?

OBJECTIVES

General Objective

To determine the efficacy of M-TEER with OMT versus OMT alone in reducing mortality among IMR patients.

Specific Objectives

1. To describe the baseline characteristics of patients with IMR.
2. To compare the 1-year all-cause mortality among IMR patients treated with M-TEER plus OMT versus OMT alone.
3. To compare the 2-year all-cause mortality among IMR patients treated with M-TEER repair plus OMT versus OMT alone.
4. To determine the cardiac mortality among IMR patients treated with M-TEER plus OMT versus OMT alone.
5. To determine the heart failure hospitalization (HFH) among IMR patients treated with M-TEER plus OMT versus OMT alone.

MATERIALS AND METHODS

This meta-analysis was performed according to a predetermined protocol outlined by PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis) using standard systematic review procedures.

Eligibility Criteria

Type of Studies: All studies including RCTs and observational studies evaluating M-TEER with OMT versus OMT alone among IMR patients were included.

Population: Studies were limited to chronic IMR patients who were given OMT with or without M-TEER.

Language: Publications in English language was considered.

Types of Intervention: Mitral valve transcatheter edge-to-edge repair with OMT versus OMT alone among IMR patients.

Time frame: The publication status restrictions were imposed. Published and unpublished studies indexed from inception until 2023 were included.

Type of Outcome Measures

Primary Outcome

1. One-year all-cause mortality
2. 2-Year All-cause Mortality

Secondary Outcome

1. Cardiac mortality
2. HFH

Exclusion Criteria

All abstract, review, and letters to the editor were excluded.

Operational Definition of Terms

- Mitral Regurgitation: A condition caused by the retrograde flow of blood from the LV into the left atrium through the mitral valve. For this meta-analysis, only those with moderate to severe MR based on the regurgitant volume and effective regurgitant orifice area were included.
- Ischemic Mitral Regurgitation: A subtype of secondary/functional MR, which is a complication of ischemic heart disease. This meta-analysis focused on postinfarction chronic MR that

is brought about by papillary muscle displacement and mitral valve leaflet tethering.
- Transcatheter Mitral Valve Repair: A minimally invasive procedure aimed at treating mitral valve regurgitation patients with high surgical risk.

Search Methods for Identification of Studies

Three reviewers independently searched both published and unpublished studies. Studies were identified by searching through electronic databases PubMed/MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed), Cochrane Review Central (http://www.cochranelibrary.com), Clinical Trials Registry (https://clinicaltrials.gov), ResearchGate (https://www.researchgate.net), Mendeley (https://www.mendeley.com), and Google Scholar (http://scholar.google.com), indexed from inception up to 2023, using the following search terms: "Transcatheter Mitral Valve Repair" OR "TMVr" OR "Percutaneous Mitral Valve Repair" OR Mitral Valve "Transcatheter Edge-to-edge Repair" OR "M-TEER" AND "Ischemic Mitral Regurgitation" OR "Functional Mitral Regurgitation" OR "Secondary Mitral Regurgitation." Reference lists of original articles identified were also hand searched for additional eligible studies. Only data accessible in peer-reviewed journals were included to minimize potential sources of bias and inaccuracy.

Data Collection and Data Analysis

Study Selection and Appraisal of Study Quality

Each title and abstract of individual studies were screened initially to exclude irrelevant reports. Eligibility assessment was executed independently, and potentially relevant studies were retrieved. In case of disagreement, discrepancies were resolved by reaching a consensus between reviewers. The reviewers started with a large number of identified records and then sequentially excluded records according to the eligibility criteria. Those who passed the eligibility criteria were reviewed its full text publication.

Quality assessment of the studies was accomplished using Cochrane Collaboration's Risk-of-Bias Tool. The Critical Appraisal Skills Programme RCT standard checklist was also utilized to assess the quality of evidence (Figure 1).

An extensive search was made via PubMed/MEDLINE, Cochrane Review Central, Clinical Trials Registry, ResearchGate, Mendeley, Google Scholar, and reference lists of relevant trial databases, which yielded 120 articles. After an eligibility assessment, only seven study trials were included in the final analysis.

Data Extraction and Management

Data from different relevant studies were extracted by two independent reviewers to an electronic data collection form. Full manuscripts of all potentially relevant studies were obtained from an eligible published and unpublished trial. The following data were extracted: author's name, year of publication, study design, study duration, population size, intervention, follow-up duration, and outcomes. The included studies were independently reviewed by two separate reviewers (G.V. and V.T.). Disagreements between data extractors/review authors were resolved after a thorough review and discussion of the eligibility criteria with third-party technical and content experts (M.V. and S.C., respectively) before getting into a consensus.

Assessment of Risk of Bias

Methodological quality assessment using ROBINS-I (Risk of Bias In Non-randomized Studies of Intervention) tool and the revised Cochrane RoB 2 (Risk-of-Bias Tool for Randomized Trials) was independently performed by two of the authors. Risk of bias was assessed by performing a full-text review of each included study and identifying statements that describes a particular domain. Any disagreement was resolved by consensus (Figures 2A, B).

Measures of Effect

For incidence of 1-year all-cause mortality, 2-year all-cause mortality, cardiac mortality, and HFH, the outcome measures were presented using odds ratio (OR) together with 95% confidence intervals (CIs). For dichotomous data (events and nonevents), Mantel-Haenszel was used for pooling effect sizes from individual studies.

Moreover, a χ^2 test was used to test the association between the studies, and after that, a pooled analysis was performed. Risk-of-bias assessment was used for the RCTs included in this study.

Cochran *Q* test was used to measure if there was a significant association between the studies (test for heterogeneity), and I^2 statistic was used to measure the degree of their association (level of heterogeneity).

Heterogeneity refers to the variation in study outcomes (events or mean) between studies. *Q* test was calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method. *Q* was distributed as a χ^2 statistic with degrees of freedom *k* (number of studies) minus 1.

I^2 statistic was also used alongside the Cochran *Q* test. I^2 statistic describes the percentage of variation across the studies that are due to heterogeneity rather than chance (Higgins and Thompson, 2002: Higgins et al, 2003)

$$I^2 = 100\% \times \frac{Q - df}{Q}$$

I^2 statistic was interpreted as follows:

- 0%–25%: heterogeneity is low
- 25%–50%: heterogeneity is moderate
- >50%: heterogeneity is high

Missing values were neither replaced nor estimated. Null hypotheses were rejected at 0.01 α level of significance. $P < 0.01$ is rejected.

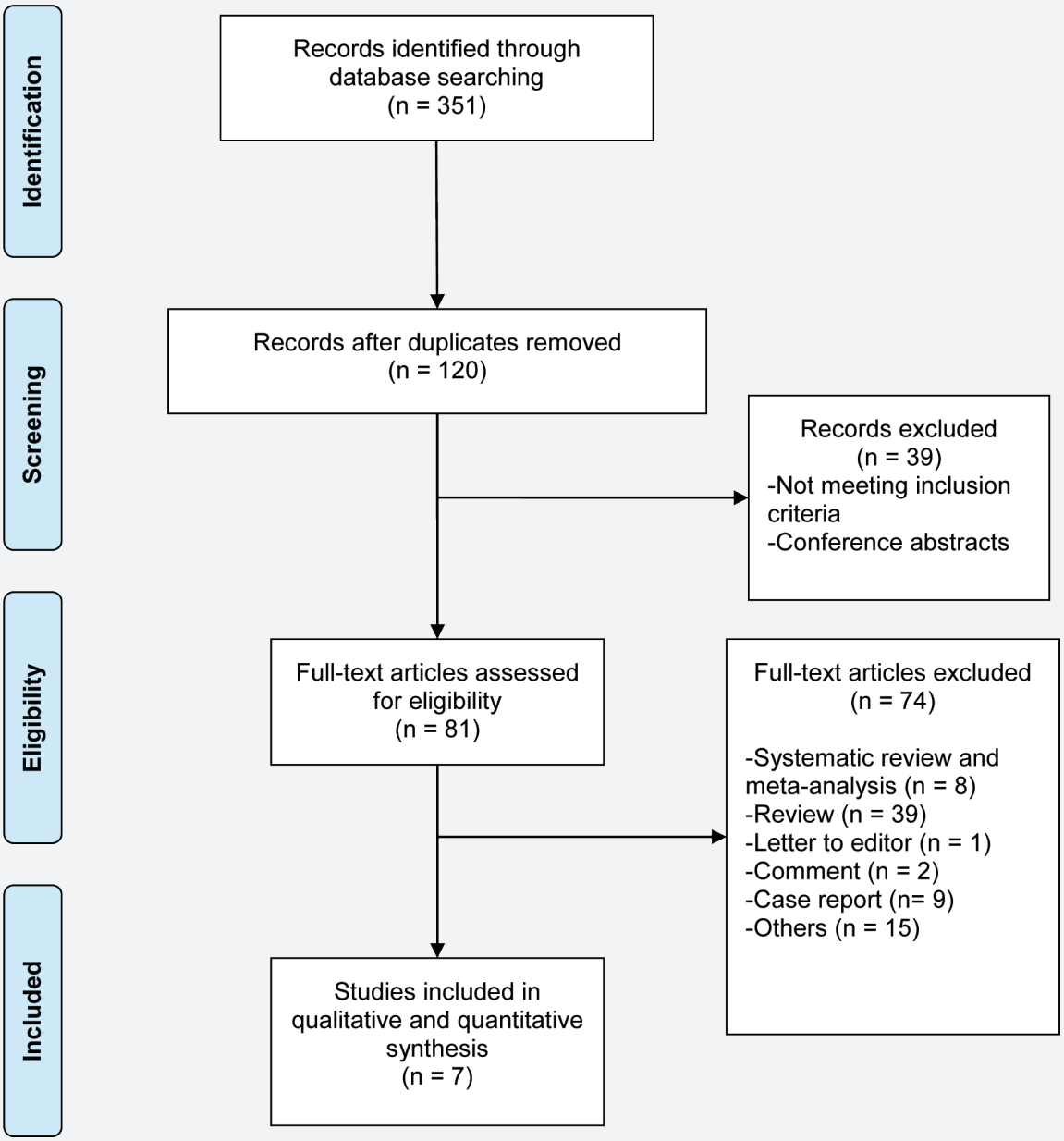

Figure 1. PRISMA flow diagram of study selection. Abbreviations: PRISMA, Preferred Reporting Items for Systematic review and Meta-Analysis.

RESULTS

Study Selection and Characteristics

A total of 1610 chronic IMR patients from the two RCTs and five observational studies were allocated to M-TEER + OMT (n = 942) versus OMT (n = 668) treatment arms (Table 1). Patients were followed up for 12 months (four studies) and 24 months or longer (three studies).

The study population (Table 2) was septuagenarians, with male and female sex distribution of 63% and 37% respectively. Almost half of the subjects underwent revascularization procedures (percutaneous coronary intervention or CABG) prior to randomization. Forty-two percent had a prior myocardial infarction. All patients had heart failure with reduced ejection fraction with a mean left ventricular ejection fraction of 34.8% ± 3.4%, New York Heart Association (NYHA) class II–IV, and a moderate to severe IMR, and almost half had atrial fibrillation. The eligible studies were conducted before the era of sodium glucose cotransporter 2 inhibitors, and the patients were given the prevailing guideline–directed medical therapy of that time. There was a very low utilization of angiotensin receptor/neprilysin inhibitor of only 2%, whereas loop diuretics use was up to 36%. Although not all studies provided data, patients were at intermediate to high surgical risk based on the mean Society of Thoracic Surgeons score of 8.6 and EuroSCORE II of 6.4.

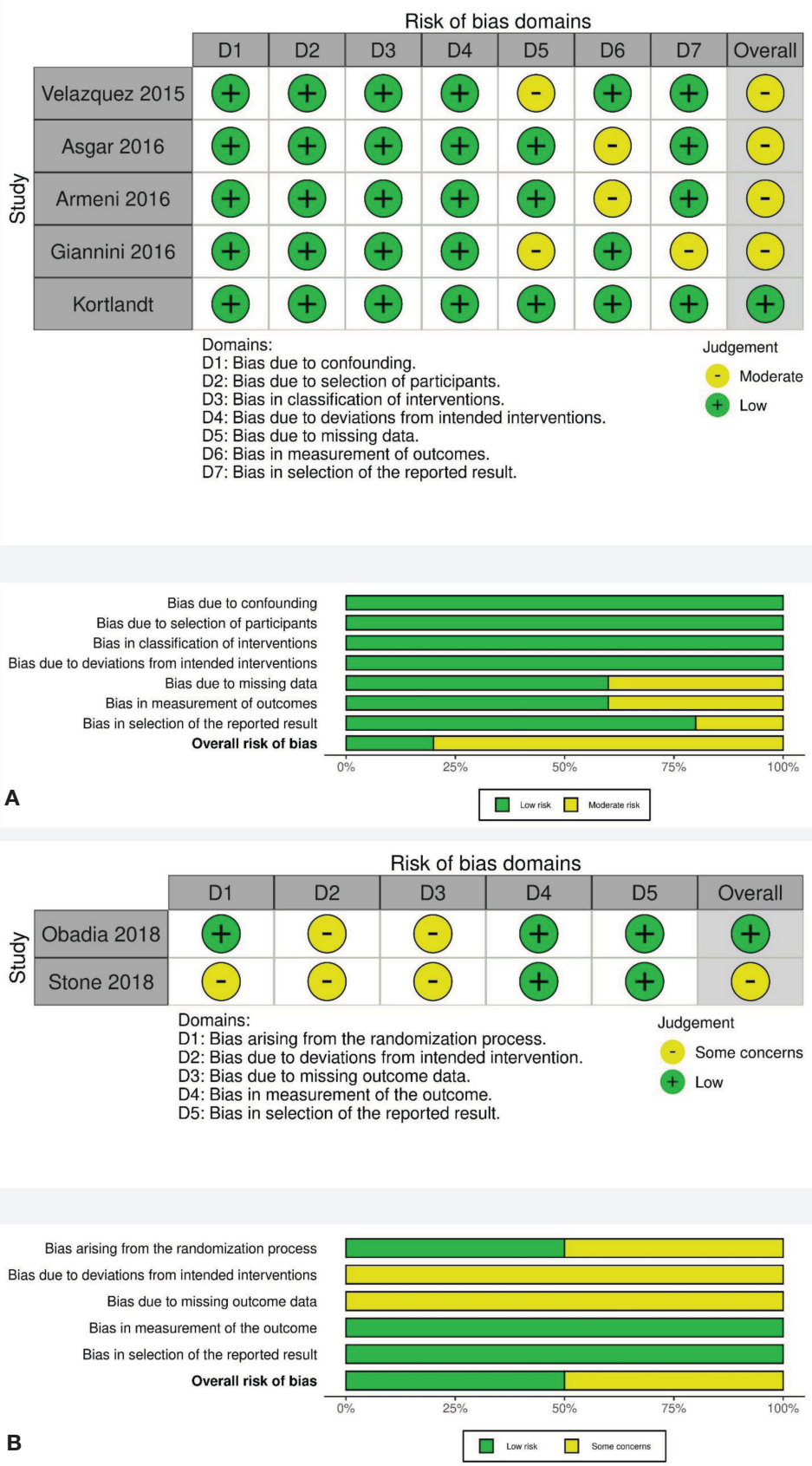

Figure 2. A. Risk of bias in nonrandomized studies. **B**. Risk of bias in randomized controlled trials.

Table 1. Characteristics of the Included Studies

STUDY / YEAR	STUDY DESIGN	STUDY DURATION	SIZE	INTERVENTION	FOLLOW-UP	OUTCOME
Obadia 2018[13]	RCT Multicenter	2013-2017	304	M-TEER + OMT vs. OMT alone	12 months	Primary: composite of death from any cause or unplanned hospitalization for HF at 12 months Secondary: death from any cause, unplanned hospitalization for HF, death from CV causes, and survival free from MACE (a composite of death, stroke, MI, or unplanned hospitalization for HF)
Stone 2018[14]	RCT Multicenter	2012-2017	614	M-TEER + OMT vs. OMT alone	24 months	Primary: all hospitalization for HF within 24 months Secondary: MR grade ≤2, all-cause mortality at 12 months, composite of death and recurrent HF hospitalization, change in QOL, change in 6-min walk test distance, all-cause hospitalization, NYHA functional class, change in LVEDV, all-cause mortality at 24 months, composite of all-cause death, stroke, MI, or non-elective CV surgery
Velazquez 2015[15]	Observational, Multicenter	2005-2011	478	M-TEER OMT vs. OMT alone	12 months	Primary: all-cause mortality
Asgar 2016[16]	Observational, Single center	2010-2013	92	M-TEER + OMT vs. OMT alone	36 months	Primary: all-cause mortality, life expectancy, QALYs, and costs and the incremental cost-effective ratio
Armeni 2016[17]	Observational, Multicenter	2007-2012	383	M-TEER + OMT vs. OMT alone	12 months	Primary: 12-month mortality Secondary: rehospitalization at 12 months, NYHA class improvement, HRQoL
Giannini 2016 [18]	Observational, Single center	2009-2015	120	M-TEER + OMT vs. OMT alone	12 months	Primary: all-cause mortality Secondary: cardiovascular death and rehospitalization due to HF
Kortlandt 2018 [19]	Observational, Multicenter	2009-2016	863	M-TEER + OMT vs. OMT alone	24 months	Primary: all-cause mortality

Abbreviations: CV, cardiovascular; HF, heart failure; HRQoL, health-related quality of life; LVEDV, left ventricular end-diastolic volume; MACE, major adverse cardiovascular events; MI, myocardial infarction; MR, mitral regurgitation; M-TEER, mitral valve transcatheter edge-to-edge repair; NYHA, New York Heart Association; OMT, optimal medical therapy; QALY, quality-adjusted life-year; QOL, quality of life; RCT, randomized controlled trial.

Table 2. Baseline Characteristics of Study Participants

	Total / Ave.	Obadia 2018		Stone 2018		Velazquez 2015		Asgar 2016		Armeni 2016		Giannini 2016		Kortlandt 2018	
	N = 2854	M-TEER + OMT	OMT	M-TEER + OMT	OMT	M-TEER + OMT	OMT	M-TEER + OMT	OMT	M-TEER + OMT	OMT	M-TEER + OMT	OMT	M-TEER + OMT	OMT
		n=152	n=152	n=302	n=312	n=239	n=239	n=50	n=42	n=232	n=151	n=60	n=60	n=568	n=295
Age (years)	72.59±1.7	70.1±10.1	70.6±9.9	71.7±11.8	72.8±10.5	73.7±10.5	73.7±11.0	75.4±9.1	68.2±15.5	71±10.0	71±11.0	74±8.0	76±8.0	74±10.45	74.1±11.73
Male	1800 (63.07)	120	107	201	192	143	130	37	33	171	112	42	38	321	153
BMI (kg/m2)	18.76±12.8	-	-	27	27.1	27.3	27	-	-	26	25	25	26	26	26.3
Comorbid conditions:															
HPN	1703 (59.67)	-	-	243	251	210	195	29	24	191	74	39	32	285	130
Diabetes	896 (31.39)	50	39	106	123	94	105	21	13	67	44	17	18	131	68
Dyslipidemia	512 (17.93)	-	-	166	163	-	-	-	-	140	43	-	-	-	-
CAD	774 (27.11)	95	85	-	-	-	-	39	30	-	-	27	35	325	138
Stroke	346 (12.12)	-	-	56	49	34	36	-	-	19	12	1	0	87	52
COPD	479 (16.78)	-	-	71	72	22	23	-	-	58	31	15	12	113	62
CKD	937 (32.83)	22	19	214	227	64	62	-	-	-	-	29	20	213	67
Atrial Fibrillation	1383 (48.45)	49	48	173	166	137	139	29	27	77	50	21	26	316	125
Previous MI	1210 (42.39)	75	52	156	160	124	109	-	-	105	75	22	23	218	91
Previous Revacularization															
Previous PCI	566 (19.83)	-	-	130	153	-	-	20	14	-	-	17	21	167	44
Previous CABG	820 (28.73)	-	-	121	126	144	132	26	20	-	-	14	16	172	49
LV Ejection Fraction (%)	34.8 ± 3.4	33.3±6.5	32.9±6.7	31.3±9.1	31.3±9.6	41.5±12.0	42±10.7	38.3±15.8	31.8±13.6	34±13.0	32±10.0	33±34.5	34±34.0	37.2±14.69	33.9±14.24
MR grade															
3	2162 (75.75)	-	-	148	172	239	239	29	32	232	151	27	30	568	295
4	682 23.90)	152	152	154	139			21	10			33	21		
NYHA															
II	561 (19.66)	56	44	129	110	-	-	1	31	-	-	-	-	78	112
III	1524 (53.40)	82	96	154	168	187	190	16	9	-	-	36	39	402	145
IV	249 (8.72)	14	12	18	33			33	0	-	-	8	6	88	37
STS score (mean)	3.66±4.9	-	-	7.8	8.5	9.9	13.8	-	-	-	-	-	-	7.8	3.5
EuroSCORE II (mean)	2.74±3.4	6.6	5.9	-	-	-	-	-	-	-	-	5	7	8.0	5.8
Medications															
ACEi	524 (18.36)	-	-	138	115	-	-	22	18	125	106	-	-	-	-
ARBs	241 (8.44)	-	-	66	72	-	-	14	11	51	27	-	-	-	-
ACEi/ARBS	301 (10.55)	111	113	-	-	-	-	-	-	-	-	42	35	-	-
ARNI	53 (1.86)	14	17	13	9	-	-	-	-	-	-	-	-	-	-
Beta-blockers	1272 (44.57)	134	138	275	280	-	-	43	35	158	128	40	41	-	-
Aldosterone agonists	838 (29.36)	86	80	153	155	-	-	25	26	153	98	35	27	-	-
Diuretics	1035 (36.26)	151	149	270	277	-	-	44	36	-	-	56	52	-	-
Statins	564 (19.76)	-	-	189	189	-	-	-	-	123	63	-	-	-	-

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; M-TEER, mitral valve transcatheter edge-edge repair; NYHA, New York Heart Association; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons

Study Outcomes

One-Year All-Cause Mortality

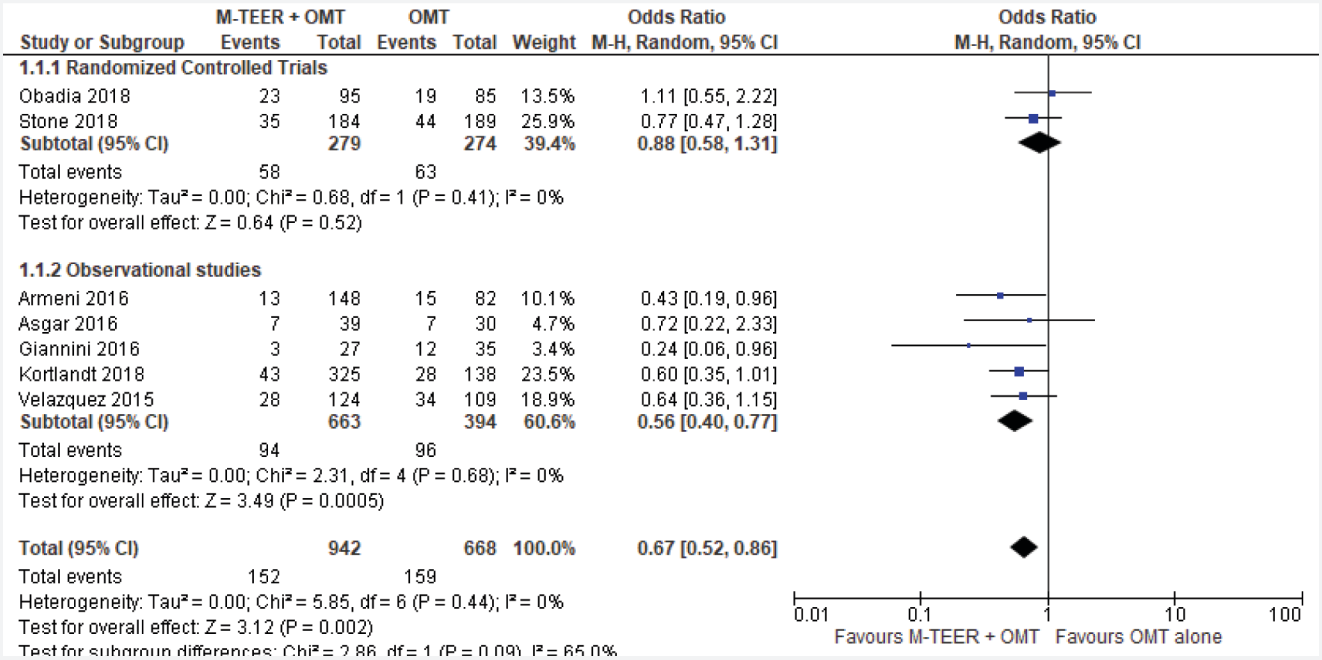

Figure 3. Forest plot comparing the 1-year all-cause mortality between mitral valve transcatheter edge-to-edge repair with optimal medical therapy and optimal medical therapy alone in patients with chronic ischemic mitral regurgitation patients.

At 12 months, the rate of the primary all-cause mortality outcome was 152/942 (16%) in the intervention group and 159/668 (23%) in those on OMT alone (Figure 3). Although the pooled estimates using random-effects model demonstrated a significant 37% (OR, 0.67; 95% CI, 0.52–0.86; $P = 0.002$, $I^2 = 0\%$) mortality risk reduction afforded by M-TEER + OMT, it is apparent that the RCTs by Stone et al[14] and Obadia et al[13] showed no significant mortality difference (OR, 0.88; 95% CI, 0.58–1.31; $P = 0.52$, $I^2 = 0\%$) between the treatment arms (Figure 4).

In contrast, the survival advantage of M-TEER + OMT at the 24th month was consistent from both the RCTs and observational studies. The rate of mortality outcome between M-TEER + OMT versus OMT alone were 139/575 (24%) and 162/392 (41%), respectively. These effected a significant 50% reduction in the 2-year all-cause mortality (OR, 0.5; 95% CI, 0.38–0.67; $P = 0.03$, $I^2 = 0\%$), favoring the intervention arm.

Cardiac Mortality

Only the RCTs by Obadia et al[13] and Stone et al,[14] as well as the observational study of Giannini et al,[18] looked into the cardiac mortality outcome, and the corresponding rates were 62/306 (20%) and 92/309 (30%) for the treatment arms, respectively.

The pooled estimates of cardiac mortality reduction showed a trend favoring the intervention arm, but this did not reach statistical significance (OR, 0.58; 95% CI, 0.27–1.23; $P = 0.15$, $I^2 = 66\%$).

Heart Failure Hospitalization

The event rates for unplanned hospitalization for heart failure were 130/345 (38%) versus 201/339 (59%) for the respective treatment arms, although there is also a trend of HFH reduction favoring M-TEER + OMT (OR, 0.45; 95% CI, 0.18–1.13; $P = 0.09$, $I^2 = 85\%$).

DISCUSSION

Ischemic MR is a sequela of left ventricular dysfunction of a prior MI and hibernating myocardium due to valvular consequences of increased tethering forces or reduced closing forces.[1,2,20] It is a common complication of coronary artery disease and portends a dismal prognosis.[7,8,21] It often affects the posterior leaflet and may be due to restricted leaflet motion in systole, isolated annular dilation, and/or excessive leaflet motion (Carpentier types IIIa, I, and II, respectively).[1,2]

Two-Year All-Cause Mortality

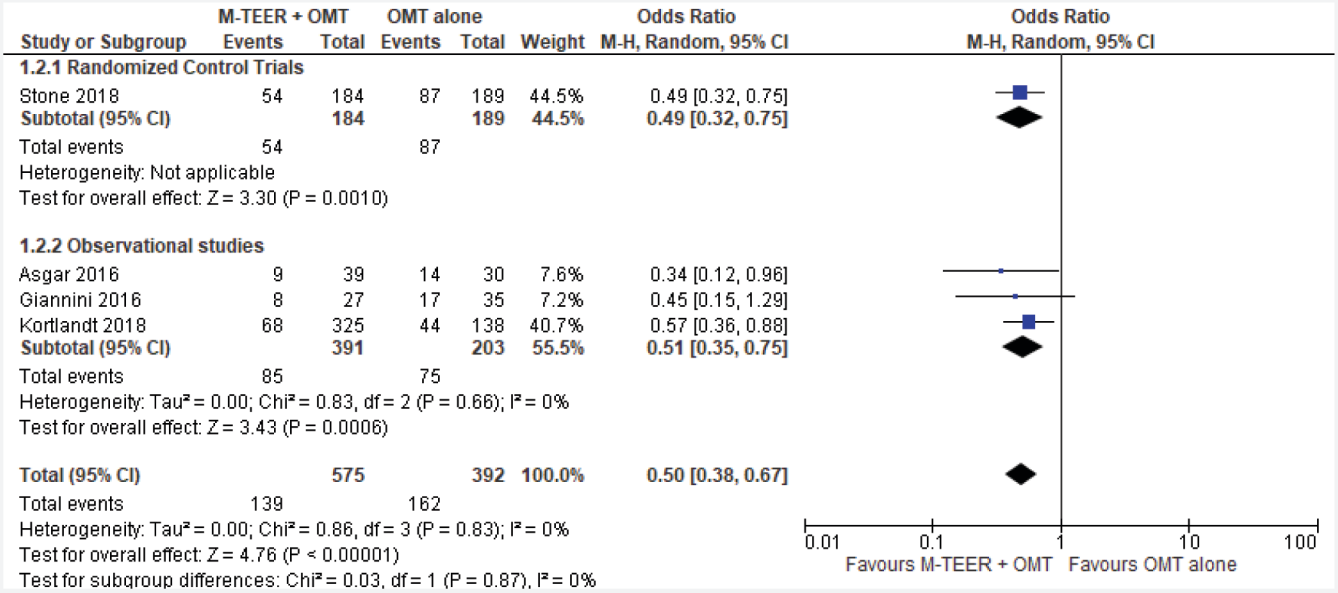

Figure 4. Forest plot comparing the 2-year all-cause mortality between mitral valve transcatheter edge-to-edge repair with optimal medical therapy and optimal medical therapy alone in patients with chronic ischemic mitral regurgitation patients.

Because of the absence of a net overall benefit, mitral valve surgery alone or in combination with CABG remains debatable as a treatment option for IMR. Alternative strategies are continuously pursued.[9]

A revolutionary option of transcatheter mitral clip device implantation for symptomatic, at least moderate IMR has been gaining grounds in the demographic of IMR with high operative risks.

Our meta-analysis on M-TEER + OMT in IMR patients showed significant reduction in 1- and 2-year all-cause mortality of 37% and 50%, respectively. With the COAPT and MITRA -FR RCTs having conflicting results, our meta-analysis was driven by the observational studies. Still, an overall statistical advantage of greater than 10% reduction in all-cause mortality is promising in a disease with historically poor prognosis.

However, the difference in the secondary endpoints of HF hospitalization and cardiac mortality did not reach statistical significance, albeit showing a trend to benefit favoring the intervention. The lack of benefit of M-TEER on the secondary outcomes suggests that the underlying ischemic cardiomyopathy may be the principal determinant of these outcomes. And a "sicker" population studied (older age group of septuagenarians, the low average left ventricular ejection fraction of 34.8%, predominantly NYHA class III to IV, and intermediate to high surgical risks) may decrease the potential benefit of M-TEER in reducing these endpoints. Given a relatively higher HFH event rate (130/345 [38%]), it is possible the M-TEER may have been performed late in the course of heart failure progression.

Another plausible explanation is the fact that M-TEER offers only an incomplete correction of MR. Although MR severity may be downgraded, the fact remains that residual MR, regardless of severity, is still significantly associated with poorer outcomes.[22]

Both the estimate analyses of the secondary outcomes of cardiovascular mortality and HFH yielded a very high heterogeneity I^2 of 66% and 85%, respectively (Figures 5 and 6). A Pearson test for independence was performed to determine the potential source of heterogeneity. Male sex, all the preexisting comorbidities (HPN, DM, coronary artery disease, prior stroke, chronic kidney disease, chronic obstructive pulmonary disease, atrial fibrillation), previous MI, prior revascularization procedure, NYHA III and IV, and angiotensin-converting enzyme inhibitor usage all reached statistical significance (Table 3). These imply that the frequency of these variables was significantly different from study to study, and thus, these are potential sources of the reported high heterogeneity.

LIMITATIONS OF THE STUDY

This meta-analysis has several limitations that should be considered. First, this meta-analysis is composed of RCTs and observational study data. Potential biases are more

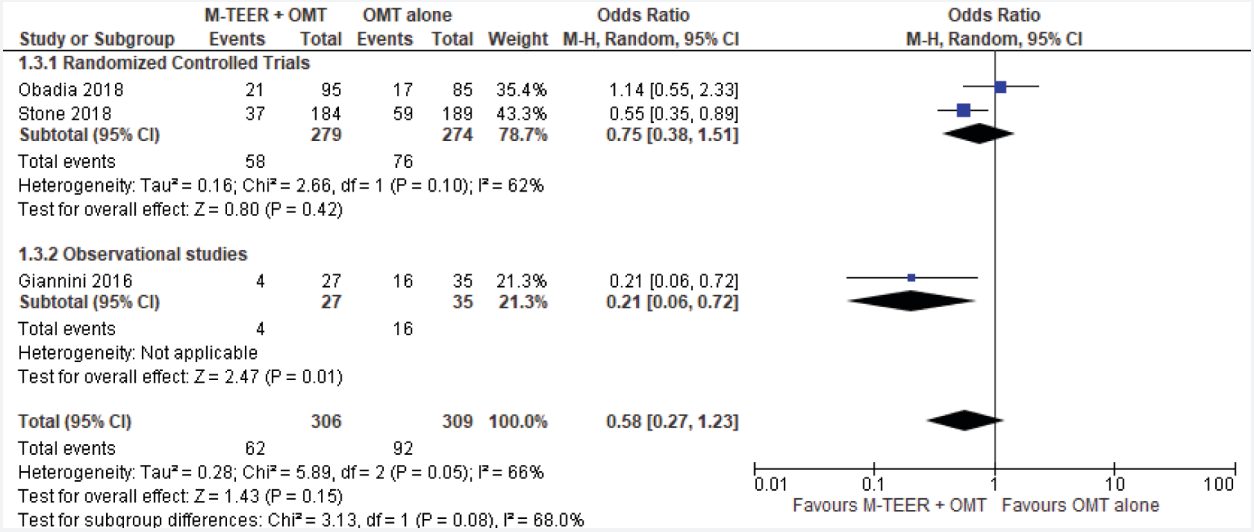

Figure 5. Forest plot comparing the cardiac mortality between mitral valve transcatheter edge-to-edge repair with optimal medical therapy and optimal medical therapy alone in ischemic mitral regurgitation patients.

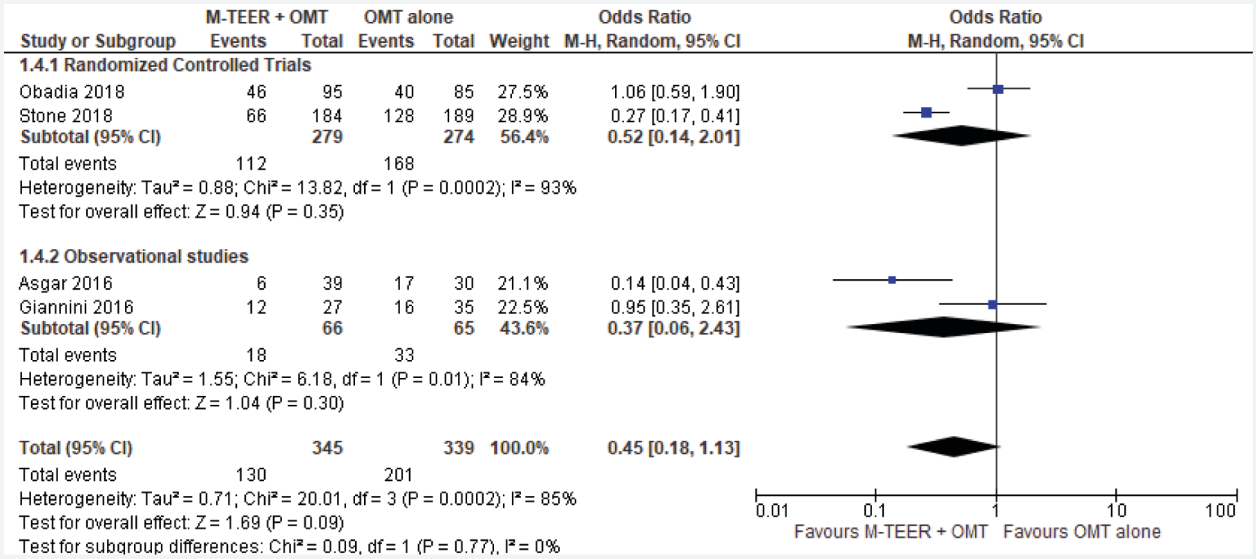

Figure 6. Forest plot comparing the heart failure hospitalization between mitral valve transcatheter edge-to-edge repair with optimal medical therapy and optimal medical therapy alone in ischemic mitral regurgitation patients.

likely to arise from observational studies compared with RCTs. Treatment selection bias is a major limitation of most observational studies; thus, it may affect the validity of the study considering that patients who receive most treatment were those who have the worse condition. In addition, observational studies possess inherent bias due to its lack of randomization of patients to treatment strategies. Therefore, results of this meta-analysis should always be cautiously interpreted considering the above limitations.

CONCLUSION

This meta-analysis showed that M-TEER on top of OMT conferred a reduction advantage in a 2-year all-cause mortality among patients with IMR. Although the collective data may be driven by observational studies, the overall statistical advantage still holds promise in a disease with historically poor prognosis. More large-scale phase III trials are needed to further validate the benefit of M-TEER in this demographic.

Table 3. Pearson Test for Independence

Variables	Total / Ave.	Obadia 2018	Stone 2018	Velazquez 2015	Asgar 2016	Armeni 2016	Giannini 2016	Kortlandt 2018	P VALUE
	N = 2854	N=304	N=614	N=478	N=92	N=383	N=120	N=863	
Age (mean +/- sd)	72.59 +/-1.7	70.35 +/-0.4	72.25 +/-0.8	73.7 +/-0	71.8 +/-5.1	71 +/-0	75 +/-1.4	74.05 +/-0.1	0.4232
Male (n (%))	1800 (63%)	227 (75%)	393 (64%)	273 (57%)	70 (76%)	283 (74%)	80 (67%)	474 (55%)	0.0000*
BMI (mean)	18.76 +/-12.8	-	27.05 +/-0.1	27.15 +/-0.2	-	25.5 +/-0.7	25.5 +/-0.7	26.15 +/-0.2	0.406
Comorbid conditions:N(%)									
HPN	1703 (60%)	-	494 (80%)	405 (85%)	53 (58%)	265 (69%)	71 (59%)	415 (48%)	0.0000*
Diabetes	896 (31%)	89 (29%)	229 (37%)	199 (42%)	34 (37%)	111 (29%)	35 (29%)	199 (23%)	0.0000*
Dyslipidemia	512 (18%)	-	329 (54%)	-	-	183 (48%)	-	-	0.0000*
CAD	774 (27%)	180 (59%)	-	-	69 (75%)	-	62 (52%)	463 (54%)	0.0000*
STROKE	346 (12%)	-	105 (17%)	70 (15%)	-	31 (8%)	1 (1%)	139 (16%)	0.0000*
COPD	479 (17%)	-	143 (23%)	45 (9%)	-	89 (23%)	27 (23%)	175 (20%)	0.0000*
CKD	937 (33%)	41 (13%)	441 (72%)	126 (26%)	-	-	49 (41%)	280 (32%)	0.0000*
Atrial Fibrillation	1383 (48%)	97 (32%)	339 (55%)	276 (58%)	56 (61%)	127 (33%)	47 (39%)	441 (51%)	0.0000*
Previous MI	1210 (42%)	127 (42%)	316 (51%)	233 (49%)	-	180 (47%)	45 (38%)	309 (36%)	0.0000*
Prev Revascularization									
Previous PCI	566 (20%)	-	283 (46%)	-	34 (37%)	-	38 (32%)	211 (24%)	0.0000*
Previous CABG	820 (29%)	-	247 (40%)	276 (58%)	46 (50%)	-	30 (25%)	221 (26%)	0.0000*
LVEF% (SD)	34.75 +/-3.4	33.1 +/-0.3	31.3 +/-0	41.75 +/-0.4	35.05 +/-4.6	33 +/-1.4	33.5 +/-0.7	35.55 +/-2.3	0.4232
MR grade									
3	2162 (76%)	-	320 (52%)	478 (100%)	61 (66%)	383 (100%)	57 (48%)	863 (100%)	0.9933
4	682 (24%)	304 (100%)	293 (48%)		31 (34%)		54 (45%)		0.9933
NYHA									
II	561 (20%)	100 (33%)	239 (39%)	-	32 (35%)	-	-	190 (22%)	0.4232
III	1524 (53%)	178 (59%)	322 (52%)	377 (79%)	25 (27%)	-	75 (63%)	547 (63%)	0.0000*
IV	249 (9%)	26 (9%)	51 (8%)		33 (36%)	-	14 (12%)	125 (14%)	0.0000*
STS score (mean)	3.66 +/-4.9	-	8.15 +/-0.5	11.85 +/-2.8	-	-	-	5.65 +/-3	0.3679
EuroSCORE II (mean)	2.74 +/-3.4	6.25 +/-0.5	-	-	-	-	6 +/-1.4	6.9 +/-1.6	0.3679
Medications									
ACEi	524 (18%)	-	253 (41%)	-	40 (43%)	231 (60%)	-	-	0.0122*
ARBs	241 (8%)	-	138 (22%)	-	25 (27%)	78 (20%)	-	-	0.4499
ACEi/ARBS	301 (11%)	224 (74%)	-	-	-	-	77 (64%)	-	0.9921
ARNI	53 (2%)	31 (10%)	22 (4%)	-	-	-	-	-	0.9998
Beta-blockers	1272 (45%)	272 (89%)	555 (90%)	-	78 (85%)	286 (75%)	81 (68%)	-	0.2499
Aldosterone agonists	838 (29%)	166 (55%)	308 (50%)	-	51 (55%)	251 (66%)	62 (52%)	-	0.5952
Diuretics	1035 (36%)	300 (99%)	547 (89%)	-	80 (87%)	-	108 (90%)	-	0.5442
Statins	564 (20%)	-	378 (62%)	-	-	186 (49%)	-	-	0.4334

**p-value < 0.05, significant;Kruskal-Wallis test for continuous and Chi-Square test for categorical*

REFERENCES

1. Vahanian A, Beyersdorf F, Praz F, et al, ESC/EACTS Scientific Document Group 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2022;43(7):561–632. doi:10.1093/eurheartj/ehab395.
2. Varma PK, Krishna N, Jose RL, Madkaiker AN. Ischemic mitral regurgitation. *Ann Card Anaesth* 2017;20(4):432–439. https://doi.org/10.4103/aca.ACA_58_17.
3. Hickey MS, Smith LR, Muhlbaier LH, et al. Current prognosis of ischemic mitral regurgitation. Implications for future management. *Circulation* 1988;78(3 pt 2):I51–I59.
4. Godley RW, Wann LS, Rogers EW, Feigenbaum H, Weyman AE. Incomplete mitral leaflet closure in patients with papillary muscle dysfunction. *Circulation* 1981;63(3):565–571. doi:10.1161/01.cir.63.3.565.
5. Fehrenbacher G, Schmidt DH, Bommer WJ. Evaluation of transient mitral regurgitation in coronary artery disease. *Am J Cardiol* 1991;68(9):868–873. doi:10.1016/0002-9149(91)90401-6.
6. Hennessey B, Sabatovicz N Jr, del Trigo M. Acute ischaemic mitral valve regurgitation. *J Clin Med* 2022;11(19):5526. doi:10.3390/jcm11195526.
7. Lamas GA, Mitchell GF, Flaker GC, et al. Clinical significance of mitral regurgitation after acute myocardial infarction. Survival and Ventricular Enlargement Investigators. *Circulation* 1997;96(3):827–833. doi:10.1161/01.cir.96.3.827.
8. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation* 2001;103(13):1759–1764. doi:10.1161/01.cir.103.13.1759.
9. Goldstein D, Moskowitz AJ, Gelijns AC, et al, CTSN. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. *N Engl J Med* 2016;374(4):344–353. doi:10.1056/NEJMoa1512913.
10. Ypenburg C, Lancellotti P, Tops LF, et al. Mechanism of improvement in mitral regurgitation after cardiac resynchronization therapy. *Eur Heart J* 2008;29(6):757–765. doi:10.1093/eurheartj/ehn063.
11. Barzilai B, Gessler C Jr, Pérez JE, Schaab C, Jaffe AS. Significance of Doppler-detected mitral regurgitation in acute myocardial infarction. *Am J Cardiol* 1988;61(4):220–223. doi:10.1016/0002-9149(88)90919-8.
12. Daimon M, Shiota T, Gillinov AM, et al. Percutaneous mitral valve repair for chronic ischemic mitral regurgitation: a real-time three-dimensional echocardiographic study in an ovine model. *Circulation* 2005;111(17):2183–2189. doi:10.1161/01.CIR.0000163547.03188.AC.
13. Obadia JF, Messika-Zeitoun D, Leurent G, et al, MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018;379(24):2297–2306. doi:10.1056/NEJMoa1805374.
14. Stone GW, Lindenfeld J, Abraham WT, et al, COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;379(24):2307–2318. doi:10.1056/NEJMoa1806640.
15. Velazquez EJ, Samad Z, Al-Khalidi HR, et al. The MitraClip and survival in patients with mitral regurgitation at high risk for surgery: a propensity-matched comparison. *Am Heart J* 2015;170(5):1050.e3–1059.e3. doi:10.1016/j.ahj.2015.08.004.
16. Asgar AW, Khairy P, Guertin MC, et al. Clinical outcomes and economic impact of transcatheter mitral leaflet repair in heart failure patients. *J Med Econ* 2017;20(1):82–90. doi:10.1080/13696998.2016.1227828.
17. Armeni P, Boscolo PR, Tarricone R, et al. Real-world cost effectiveness of MitraClip combined with medical therapy versus medical therapy alone in patients with moderate or severe mitral regurgitation. *Int J Cardiol* 2016;209:153–160. doi:10.1016/j.ijcard.2016.01.212.
18. Giannini C, Fiorelli F, de Carlo M, et al. Comparison of percutaneous mitral valve repair versus conservative treatment in severe functional mitral regurgitation. *Am J Cardiol* 2016;117(2):271–277. doi:10.1016/j.amjcard.2015.10.044.
19. Kortlandt F, Velu J, Schurer R, et al. Survival after MitraClip treatment compared to surgical and conservative treatment for high-surgical-risk patients With mitral regurgitation. *Circ Cardiovasc Interv* 2018;11(6):e005985. doi:10.1161/CIRCINTERVENTIONS.117.005985.
20. Piérard LA, Carabello BA. Ischaemic mitral regurgitation: pathophysiology, outcomes and the conundrum of treatment. *Eur Heart J* 2010;31(24):2996–3005. doi:10.1093/eurheartj/ehq411.
21. Serri K, Bouchard D, Demers P, et al. Is a good perioperative echocardiographic result predictive of durability in ischemic mitral valve repair? *J Thorac Cardiovasc Surgery* 2006;131(3):565.e2–573.e2. doi:10.1016/j.jtcvs.2005.09.037.
22. Buzzatti N, de Bonis M, Denti P, et al. What is a "good" result after transcatheter mitral repair? Impact of 2+ residual mitral regurgitation. *J Thorac Cardiovasc Surg* 2016;151(1):88–96. doi:10.1016/j.jtcvs.2015.09.099.