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# Transcatheter edge-to-edge mitral valve repair *versus* medical therapy for secondary mitral regurgitation: a meta-analysis of randomized controlled trials

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**Abstract**

Secondary mitral regurgitation (SMR) is associated with increased hospitalizations and mortality. Clinical trials comparing mitral valve transcatheter edge-to-edge repair (M-TEER) with guideline-directed medical therapy (GDMT) show conflicting results, but the RESHAPE-HF2 trial offers new insights.

This study aims to assess the M-TEER effect in addition to GDMT in reducing all-cause mortality, cardiovascular death, and heart failure hospitalizations (HHF) in patients with SMR when compared to GDMT alone. On September 2, 2024, PubMed, Cochrane CENTRAL, Scopus, and Web of Science were searched for randomized controlled trials comparing M-TEER in addition to GDMT with GDMT in SMR patients with heart failure. A study-level random-effects meta-analysis was conducted using trial-reported point estimates.

Seven records from three trials (COAPT, MITRA-FR, RESHAPE-HF2) involving 1426 participants were included. At 24 months, M-TEER (using MitraClip®) significantly reduced the first HHF [hazard ratio (HR) 0.66, 95% confidence interval (CI) 0.45-0.96] and all HHF (HR 0.63, 95% CI 0.49-0.81). However, no significant reduction was observed in all-cause mortality (HR 0.76, 95% CI 0.57-1.01) or cardiovascular death (HR 0.77, 95% CI 0.56-1.06). The intervention group had more patients in New York Heart Association class I/II at 12 and 24 months, but no significant improvement in 6-minute walk test performance at 12 months.

High trial heterogeneity requires careful interpretation of pooled estimates. Differences in medical therapy and patient characteristics likely affected outcomes across trials. While M-TEER demonstrates benefits in reducing HHF, its effectiveness in reducing mortality remains inconclusive. The degree of left ventricular enlargement may have influenced outcomes, underscoring the importance of careful patient selection.

**Key words:** mitral regurgitation, mitral valve repair, chronic heart failure.

## Introduction

Mitral regurgitation (MR) is the most common valvular heart disease in patients with heart failure (HF), with secondary mitral regurgitation (SMR) being the most prevalent type. SMR is often associated with atrial enlargement, left ventricular (LV) remodelling, and dysfunctional papillary muscles, all of which worsen the prognosis of HF patients by increasing mortality and hospitalization related to heart failure rates [1].

Historically, SMR was considered a marker of advanced LV dysfunction, raising doubts about whether addressing this secondary condition would improve clinical outcomes. Non-randomized surgical experiences provided little optimism [2]. In 2018, two randomized controlled trials (COAPT and MITRA-FR) directly addressed this issue by comparing mitral valve transcatheter edge-to-edge repair (M-TEER) using the MitraClip® device against medical therapy alone in patients with severe SMR, yielding contradictory results [3,4].

Currently, for patients with significant symptomatic SMR that persists despite guideline-directed medical therapy (GDMT), including cardiac resynchronization therapy, who are not eligible for surgery and do not require coronary revascularization, M-TEER should be considered if they have favourable mitral anatomy [5,6].

Recently, the RESHAPE-HF2 trial [7] provided new evidence, prompting us to conduct a systematic review with meta-analysis to compare mortality and hospitalization effects of M-TEER in addition to GDMT versus GDMT alone in patients with symptomatic HF and moderate to severe SMR.

## Methods

### *Search strategy and selection criteria*

This study was conducted as per the PRISMA statement [8] and registered with PROSPERO (CRD42024591866).

On 2nd September 2024, a systematic search using PubMed, Cochrane Central Register of Controlled Trials, Scopus and Web of Science was conducted. The search encompassed broad terms referring to "transcatheter mitral valve repair" and "heart failure" (Full query in *Supplementary Table 1*). The references' lists of the included studies and relevant reviews were searched for additional publications. Eligible studies satisfied the following inclusion criteria: (1) randomized controlled trials (RCT) that enrolled (2) adult patients with HF and SMR (3) randomized to undertake M-TEER and GDMT or GDMT alone, (4) and report on mortality or hospitalizations. No restrictions were applied for publication status or publication language.

The search records were screened by two independent reviewers at the abstract level. Following the elimination of duplicates and ineligible publications, relevant abstracts were

retrieved in full text. The full text was accessed and selected independently against inclusion criteria by the same two reviewers. Any disagreements were resolved with a third researcher.

### *Data extraction and outcomes of interest*

Two reviewers independently extracted data from each eligible study, using a standardized data extraction form with information regarding study and patient characteristics, medical or device therapy at baseline, pre- and post-procedure echocardiographic features, and outcomes at 12 and 24 months.

Clinical outcomes of mortality (death by any cause and cardiovascular death), first and all hospitalizations related to heart failure and major adverse cardiovascular events were the main outcomes of interest. Secondary outcomes were changes in 6-minute walk test from baseline to follow-up, New York Heart Association (NYHA) functional classification and quality of life assessed by validated tools.

### *Risk of bias*

The risk of bias in each study has been assessed using the Cochrane risk of bias tool for RCTs. The presence of publication bias could not be performed because only 3 studies were included.

### *Statistical analysis*

A study-level meta-analysis was conducted based on point estimates and 95% confidence intervals (CIs) or standard deviations (SDs) reported in the individual trials, employing an intention-to-treat approach. All estimates were calculated using a random-effects model based on the DerSimonian and Laird method. The effect measure for continuous data was the mean difference (MD) with 95% CIs, while NYHA functional class assessments at 12 and 24 months were expressed as risk ratios (RR) with 95% CI. Continuous variables, as well as hazard ratios (HR), were analysed using the generic inverse variance method, while NYHA functional class assessments at 12 and 24 months were weighted using the Mantel-Haenszel method.

Estimates of mean and standard deviation for metanalyses were performed when only median and interquartile range (IQR) was reported using methodology previously described [9-11].

Heterogeneity was tested and quantified using Chi-squared test and $I^2$ statistics. Thresholds of $I^2$ statistic of 25% (low), 50% (moderate) and 75% (large) were defined, and a p-value of 0.10 was used to determine statistical significance [12].

A leave-one-out sensitivity analysis was performed for the primary outcomes. Statistical analysis was conducted using Review Manager (RevMan) software, version 5.3 (Copenhagen:

The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). The statistical level of significance was two-tailed p-value < 0.05.

## Results

### *Study selection and characteristics*

Literature search (Figure 1) retrieved a total of seven records referring to three randomized, multicentric, clinical trials [3,4,7] (COAPT, MITRA-FR and RESHAPE-HF2). Four of the records [13-16] identified reported results from the studies, throughout different follow-up periods.

Table 1 summarizes the characteristics of the included trials. The recruitment period of the included studies spanned from 2012 to 2023, primarily in European centres, except for the COAPT trial, which was carried out in North America. Across all studies, a total of 1,426 participants were included. Eligible patients were required to have SMR with signs and symptoms of HF despite receiving optimal medical therapy, and for whom mitral valve surgery was not recommended. A total of 1,426 participants were included across all studies. Patients eligible were required to have SMR with signs and symptoms of HF despite optimal medical therapy and not in whom mitral valve surgery was not recommended. The inclusion criteria for MR varied between trials as in COAPT MR severity was defined according to the American Society of Echocardiography (ASE) [17], while in MITRA-FR and RESHAPE-HF2 assessment was based on the European Association of Echocardiography (EAE) criteria [18], which adopts a lower threshold for defining severe MR. All three trials involved the implantation of the MitraClip® in the intervention group, with 659 receiving the device. All studies had a low risk of bias according to the Cochrane risk of bias tool for RCTs (*Supplementary Table 2*).

### *Clinical baseline characteristics of patients*

Table 2 summarizes the baseline characteristics of patients enrolled across all trials. Participants had similar age across trials. The proportion of men varied, with the COAPT trial having fewer men (64.0%) compared to RESHAPE-HF2 (80.4%) and MITRA-FR (74.7%).

The COAPT trial reported higher prevalence rates of hypertension and coronary artery bypass graft surgery compared to RESHAPE-HF2 (80.5% vs. 52.5% and 40.2% vs. 26.3%, respectively). Diabetes mellitus was present in 29.3% of patients in MITRA-FR and up to 37.3% in COAPT, while atrial fibrillation/atrial flutter was less prevalent in MITRA-FR (33.6%) compared to COAPT (55.2%) and RESHAPE-HF2 (48.1%). The glomerular filtration rate (GFR) in the intervention group was 50.9 ± 28.5 mL/min in COAPT, 48.8±19.7 mL/min in MITRA-FR, and highest in RESHAPE-HF2, 54.9±19.0 mL/min.

Ischemic cardiomyopathy was observed with similar prevalence across trials: COAPT (60.7%), MITRA-FR (59.4%), and RESHAPE-HF2 (64.2%).

Upon enrolment, fewer patients in the COAPT trial were on neurohormonal modulation with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor-neprilysin inhibitors (ARNI) compared to MITRA-FR and RESHAPE-HF2 (67.3% vs. 84.8% and 87.9%, respectively). The lower adherence to ARNI in COAPT may attributed to the trial's enrolment period, which began before the clinical benefits of ARNI were established, whereas RESHAPE-HF2 had the highest proportion of patients on ARNI. Similarly, the use of sodium-glucose cotransporter-2 inhibitors (SGLT2i) was not recommended at the time of the COAPT and MITRA-FR trials. RESHAPE-HF2 also demonstrated higher prevalence rates of beta-blocker and mineralocorticoid receptor antagonist (MRA) use compared to COAPT and MITRA-FR (beta-blockers: 95.8% vs. 90.4% and 89.5%; MRA: 82.2% vs. 50.2% and 54.8%). Cardiac resynchronization therapy was more prevalent in COAPT compared to MITRA-FR and RESHAPE-HF2 (36.5% vs. 26.7% and 28.8%, respectively).
Upon enrolment, about 60.8% of patients in COAPT, 67.1% in MITRA-FR, and 75.4% in RESHAPE-HF2 had significant symptomatic heart failure (NYHA class III/IV) (*Supplementary Table 3*).

***Echocardiographic baseline characteristics of patients***

The RESHAPE-HF2 enrolled patients with less severe MR, followed by MITRA-FR and COAPT. In the intervention group the effective regurgitant orifice area (EROA) was highest in the COAPT trial (0.41±0.15 $cm^2$), followed by MITRA-FR (0.31±0.1 $cm^2$), and lowest in RESHAPE-HF2 (0.23 [IQR: 0.20; 0.30] $cm^2$).
Meanwhile, smaller ventricles, as measured by left ventricular end-diastolic volume (LVEDV), were observed in the COAPT trial (194.4±69.2 mL) and in RESHAPE-HF2 patients (median 200 [IQR: 153; 249] mL) compared to those in MITRA-FR (258.8±71.1 mL) (Table 3). Left ventricular ejection fraction (LVEF) was similar between studies, around 31%.
After M-TEER, most patients improved significantly MR grade across all trials.

***Primary outcomes***

The COAPT trial demonstrated significant reductions in both all-cause mortality and first HHF with benefits persisting through 5 years of follow-up [3,14,16]. Similarly, the RESHAPE-HF2 trial yielded significant reductions in first and all (first and recurrent) HHF over 24 months but failed to reach a statistically significant reduction in mortality [7,15]. In contrast, MITRA-FR found no significant benefit of M-TEER in reducing death or HHF within 24 months [13].
When pooled together, patients with SMR receiving GDMT in combination with M-TEER did not demonstrate a significant reduction in all-cause mortality (HR 0.76, 95% CI 0.57–1.01) or cardiovascular (CV) death (HR 0.77, 95% CI 0.56–1.06) within 24 months of follow-up,

compared to those receiving GDMT alone (Figure 2 A,B). However, the M-TEER group demonstrated a significant reduction in first HHF (HR 0.66, 95% CI 0.45–0.96) and in all HHFs (HR 0.63, 95% CI 0.49–0.81) within 24 months (Figure 2 C,D). Although there was a trend toward reduction, the effect did not reach statistical significance for the composite endpoint of all-cause mortality and first HHF (HR 0.71; 95% CI 0.51–1.00) (Figure 2E).

***Secondary outcomes***

At 12 months, both COAPT [3] and RESHAPE-HF2 [7,15] demonstrated a statistically significant higher proportion of patients in NYHA class I/II in the intervention group compared to the control group, a result not observed in MITRA-FR [4]. However, this trend was not maintained at 24 months in RESHAPE-HF2 [15], with only COAPT continuing to show a significant difference [14,16]. In meta-analysis patients treated with M-TEER in addition to GDMT were significantly more likely to have NYHA class I/II status at 12 months (RR 1.25, 95% CI 1.04–1.50) and 24 months (RR 1.28, 95% CI 1.05–1.56) (Figure 3 A,B).

Regarding the change in six-minute walk test distance from baseline to 12 months, significant improvements were observed in both the COAPT and RESHAPE-HF2 trials [3,7], but not in MITRA-FR [4]. However, when pooled together, the overall estimate did not show a significant difference (MD 26.31, 95% CI -3.71–56.33) (Figure 3C). A sensitivity analysis that pooled the 12-month endpoint value for MITRA-FR, instead of the change from baseline (to avoid using estimated mean and SD), also did not reveal significant differences (*Supplementary Table 4*).

COAPT demonstrated significant improvements in quality of life in the intervention group, with these benefits persisting through 5 years of follow-up [3,14,16], a finding also observed in the 12-month follow-up of the RESHAPE-HF2 trial [7]. In contrast, MITRA-FR failed to show improvements in quality of life at 12 months, a trend that continued at 2 years [4,13].

## Discussion

The RESHAPE-HF2 trial has provided new insights into the role of M-TEER in the management of SMR. It offers evidence on the safety and efficacy of the MitraClip®, complementing the findings from the COAPT and MITRA-FR trials [3,4,7].

The reduction in mortality and CV death observed in the COAPT trial, along with a non-significant but notable trend in reduced all-cause mortality and CV death in RESHAPE-HF, positions the MITRA-FR findings as an outlier compared to the other two trials. This pattern also extends to HHF, where COAPT and RESHAPE-HF showed significant reductions, but MITRA-FR did not.

Pooled estimates revealed significant reductions in HHF but no significant effect on death but the heterogeneity across trials calls for cautious interpretation, and the reasons for these outcome variations need to be elucidated.

***Discussing the outcomes: RESHAPE-HF2 patients as a third distinct population***

Differences in study designs and patient characteristics likely explain the discordant results. Patients in the RESHAPE-HF2 trial constituted a distinct group compared to COAPT and MITRA-FR.

Patients enrolled in RESHAPE-HF2 may have been less ill than those in COAPT and MITRA-FR, as indicated by higher GFR values and lower natriuretic peptide concentrations, suggesting lower LV end-diastolic pressure and less congestion. Another hypothesis that can be considered is that RESHAPE-HF patients were treated at an earlier stage of disease evolution, particularly in comparison with MITRA-FR patients.

***The relationship between mitral regurgitation severity and left ventricular chamber size***

The RESHAPE-HF2 population primarily consisted of patients with moderate-to-severe SMR, unlike COAPT and MITRA-FR, which included patients with more severe SMR. Despite similar mean LVEF (around 31%) across the trials, COAPT patients had a mean LVEDV of 192.7 mL and a mean EROA of 0.40 $cm^2$, indicating less LV remodelling but severe MR [3]. This suggests that in COAPT, MR was a major driver of HF and addressing MR with M-TEER led to significant improvements in primary and secondary outcomes [19].

In contrast, MITRA-FR included patients with a significantly larger mean LVEDV of 257.2 mL and a smaller mean EROA of 0.31 $cm^2$. This cohort did not benefit from M-TEER in terms of mortality and HHF reduction, highlighting the limitations of M-TEER in the context of advanced LV remodeling [4,13]. Current evidence suggests that the benefits of M-TEER may be limited in patients with severely dilated LV (LVEDV >220 mL) [20].

The results of RESHAPE-HF2 fall between those of COAPT and MITRA-FR but are closer to COAPT. RESHAPE-HF2 enrolled symptomatic HF patients with a mean LVEDV of 202 mL and less severe MR (mean EROA of 0.25 $cm^2$), with only 14% of patients having an EROA >0.40 $cm^2$ (compared to 48% in COAPT [3]) and 23% having an EROA <0.20 $cm^2$ [7]. Interestingly, in RESHAPE-HF2, there was no apparent relationship between the severity of baseline MR, as assessed by EROA tertiles, and the 2-year relative reduction in HHF rates and composite of HHF rates and all-cause mortality with M-TEER [7,15]. Although these subgroups are too small for definitive conclusions, whether the lack of benefit in the MITRA-FR trial is solely due to the degree of LV dilation or involves other factors remains unclear.

It is important to highlight that direct numerical comparison of SMR grade severity across trials is limited due to the different definitions used by each trial. COAPT defined 3+ or 4+ MR according to the ASE criteria [17], whereas MITRA-FR and RESHAPE-HF2 relied on the EAE criteria [18]. While both organizations recommend integration of multiple qualitative and quantitative measures from transthoracic echocardiography to determine MR severity, the EROA (and regurgitant volume) thresholds vary.

After COAPT, an EROA threshold of 0.30 $cm^2$ became widely adopted for considering SMR treatment with M-TEER [5,6]. Prior to RESHAPE-HF2, there was no credible evidence that treating MR with EROA less than 0.30 $cm^2$ was beneficial. A previous randomized trial found that treating with ischemic SMR (EROA 0.20 to 0.40 $cm^2$), undergoing coronary- artery bypass graft reduced MR severity but did not improve clinical or structural cardiac outcomes [21]. In contrast, RESHAPE-HF2, where most patients had an EROA of less than 0.30 $cm^2$, saw and improvement in reduction of HHF in symptomatic HF patients on M-TEER group [7]. While RESHAPE-HF2 supports M-TEER for patients with an EROA greater than 0.20 $cm^2$, further trials are necessary to determine whether this threshold is optimal for identifying patients who benefit from this procedure.

Interpreting these trial outcomes requires understanding the relationship between MR severity and LV chamber size. Combining the three trials suggests that the ability to impact clinical outcomes diminishes as LV size increases beyond a certain threshold, though the exact threshold remains undefined (Figure 4).

***The role of right ventricle function and tricuspid regurgitation***

It is important to note that both COAPT and RESHAPE-HF2 trials excluded patients with severe TR and significant RV dysfunction, as well as those with elevated pulmonary pressures suggesting potential RV strain. In COAPT, the mean right ventricular systolic pressure (RVSP) was 44.0±13.4 mmHg (n=253) in the M-TEER group and 44.6±14.0 mmHg (n=275) in the GDMT group. Additionally, patients with pulmonary artery systolic pressure (PASP) exceeding 60 mmHg were excluded.

In contrast, the MITRA-FR trial allowed patients with concomitant TR or RV dysfunction. Notably, PASP higher than 50 mmHg was observed in over 50% of the participants included (57.9% in M-TEER and 66.7% in GDMT) and moderate to severe TR was present in 20.1% and 16.3% of patients, respectively.

The inclusion of patients with severe TR and RV dysfunction in MITRA-FR could potentially result in worse outcomes compared to COAPT and RESHAPE-HF2. These conditions linked to poorer overall prognosis could have reduced the apparent advantages of the M-TEER when compared to GDMT in MITRA-FR trial.

***The role of guideline-directed medical therapies***

HF GDMT can significantly reduce SMR severity through reverse LV remodelling and improve outcomes, especially in patients with significant LV enlargement [22].

The COAPT trial's strict eligibility requirements ensured patients were on maximally tolerated GDMT with minimal changes during follow-up [3]. In contrast, MITRA-FR did not monitor medication adherence, raising questions about whether varying treatments between groups may have contributed to better-than-expected outcomes in the control arm [4]. As for the RESHAPE-HF2 trial, conducted over more than eight years, evolving background therapies were observed, but GDMT use was not tracked during follow-up, leaving the impact of medication changes on HF outcomes unclear [5,23].

In fact, a greater proportion of patients in RESHAPE-HF2 received GDMT compared to those in COAPT and MITRA-FR. Notably, about one-third of the COAPT cohort had died by the 2-year follow-up, a higher mortality rate when compared to RESHAPE-HF2 (38% vs. 31.7%) [3,7]. This difference may be attributed to the different time periods in which the trials were conducted, leading to variations in GDMT that reflect advancements in treatment over the years.

The current landscape of HF management has shifted towards rapid sequencing or even simultaneous initiation of all four pillars of GDMT — ARNIs, beta-blockers, MRAs, and SGLT2is — reflecting a more aggressive and multipronged approach. These newer therapies have demonstrated significant benefits, including LV reverse remodeling that may optimize valve geometry and improve SMR, potentially enhancing the efficacy of M-TEER. Particularly, ARNIs have proven to be more effective than valsartan alone in reducing SMR in patients whose LVEDV and EROA were similar to those in RESHAPE-HF2 [24]. Dapagliflozin has been shown to reduce the extent of mitral regurgitation and improve myocardial remodeling in SMR [25]. Moreover, Vericiguat, a soluble guanylate cyclase stimulator, further expands treatment options for patients with HF with reduced ejection fraction, as evidenced by the VICTORIA trial [26]. Its effects in reducing LV filling pressures, promoting reverse LV remodeling, and alleviating pulmonary hypertension address key pathophysiological contributors to SMR severity.

It is important to also emphasize that SMR is a heterogeneous condition with diverse phenotypes that may respond differently to GDMT and M-TEER [27]. In this context, M-TEER may play a key role in improving hemodynamic stability, which could facilitate the up-titration of HF medications, allowing patients to tolerate higher doses of these beneficial therapies.

Cardiac resynchronization therapy (CRT) plays a pivotal role in improving outcomes in HF patients with desynchrony. In COAPT, CRT was used in 38.1% of M-TEER and 34.9% of GDMT patients, with similar rates in MITRA-FR (30.5%) and RESHAPE-HF2 (26.6%),

highlighting its broad implementation alongside GDMT. Post-hoc analyses of landmark CRT trials report a 23–35% SMR reduction within 3–6 months in advanced HF patients [28-31]. CRT improves valve geometry and reduces SMR severity by coordinating left ventricular contractions, which may reduce the need for M-TEER in some patients. It could also enhance outcomes in those undergoing M-TEER by addressing residual SMR and desynchrony.
These factors emphasize the interplay between intensive GDMT regimens, CRT and M-TEER in managing HF and SMR. Future studies should focus on the impact of these therapies on SMR, both as standalone treatments and in combination with interventions like M-TEER [20].

***Functional status***

The evaluation of functional status using both the NYHA classification and the six-minute walk test (6MWT) revealed conflicting results. Patients undergoing M-TEER were more likely to achieve NYHA class I/II status at 12 and 24 months, indicating a generally positive impact of the intervention on functional status. However, the results from the 6MWT distance were less conclusive.
While the improvement in NYHA classification suggests benefits, this measure is subjective, poorly reproducible, and a flawed surrogate for functional status. Furthermore, the estimated heterogeneity measures ($I^2$ = 75% at 12 months and $I^2$ = 65% at 24 months) were high, rendering the pooled estimates less robust and highlighting the need for cautious interpretation. In contrast, the 6MWT provides a more objective assessment of functional capacity, but high heterogeneity also poses challenges in the reliability of estimated effects.

***Procedural safety and efficacy of mitral valve transcatheter edge-to-edge repair***

The three studies reported a low complication rate, with the device being successfully implanted in more than 90% of patients, underscoring the procedure's feasibility [3,4,7].
Post-intervention, M-TEER effectively reduced MR, with the COAPT trial demonstrating the greatest reduction compared to MITRA-FR and RESHAPE-HF2. This higher effectiveness in COAPT may be attributed to the selection of patients with more severe MR, making them more likely to benefit from the intervention [3].
While MV repair durability appears to be consistent for at least 12 months across all trials, the MITRA-FR trial, unlike COAPT and RESHAPE-HF2 [3,7], lacked consistent echocardiographic follow-up, potentially undermining the reliability of its results [4].

***Surgery versus mitral valve transcatheter edge-to-edge repair***

Current European guidelines only recommend M-TEER in patients not eligible for surgery [5]. Before RESHAPE-HF2, the benefit of M-TEER over medical therapy was not well established.

Recently, another study, MATTERHORN, published simultaneously with RESHAPE-HF2, compared mitral valve surgery to M-TEER. In this trial, M-TEER was found to be noninferior to mitral valve surgery regarding a composite of death, rehospitalization for HF, stroke, reintervention, or implantation of a left ventricular assist device at 1 year (16.7% vs. 22.5%) [32].

However, this trial included different patients, with much higher LVEF (43%), lower EROA (0.22 $cm^2$), smaller ventricles (LVEDV of 164.6 ml) than any of the included trials in this meta-analysis. Also, nearly half of the patients had MR due to ventricular tethering rather than annular dilation [32]. These characteristics suggest that RESHAPE-HF2 cohort may be less advanced in their disease progression, and thus surgery might be a better option. Additionally, MATTERHORN had a 1-year follow-up which besides being too short to fully appreciate the benefits of surgery when comparing with M-TEER, makes it direct comparations with RESHAPE-HF2, COAPT and MITRA-FR challenging**.**

***Emerging technologies in transcatheter mitral valve therapy***

Other technologies, including transcatheter mitral valve replacement (TMVR) and annuloplasty systems (e.g., Cardioband), are under development. TMVR offers to completely abolish MR, which is rarely achieved with an isolated M-TEER procedure alone, but faces challenges such as LVOT obstruction and procedural complexity. The SUMMIT (NCT03433274) and APOLLO (NCT03242642) trials are evaluating the safety and efficacy of TMVR in patients with severe MR, with preliminary results showing promise. Annuloplasty systems address annular dilation, a common mechanism of SMR but require further validation. While promising, these techniques need longer-term data to define their role alongside M-TEER.

***Limitations***

The main limitations of this meta-analysis stem from its reliance on study-level data, which restricts detailed comparisons across trials. Significant heterogeneity exists in patient populations, MR severity, and left ventricular remodelling across COAPT, MITRA-FR, and RESHAPE-HF2, complicating direct comparisons. While metaregression could theoretically help explore the influence of these variables, its utility in this context was constrained by the limited number of included studies (N=3), reducing statistical power and limiting meaningful subgroup analyses.

In contrast, a patient-level meta-analysis could overcome many of these limitations. By leveraging individual patient data, it would allow for more granular adjustments for baseline characteristics, exploration of treatment-effect modifiers, and nuanced modeling of

interactions between variables. This approach could clarify the extent to which differences in patient selection, MR severity thresholds, or variations in left ventricular remodeling contribute to the heterogeneity in trial outcomes and enhance the validity of cross-trial comparisons.

**Conclusions**

This meta-analysis of three main trials indicates that M-TEER with MitraClip®, combined with GDMT, benefits HF patients with moderate to severe SMR by reducing first and all HHF within 24 months. Although there was a trend towards a reduction in all-cause mortality, CV death and a composite of all-cause mortality and first HHF, it did not reach statistical significance. Additionally, this meta-analysis highlights that the success of M-TEER may rely on careful patient selection, taking into account LV enlargement and MR severity within a robust GDMT framework.

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Online supplementary material:
Supplementary Table 1. Full search query.
Supplementary Table 2. Assessment of risk of bias utilizing Cochrane risk of bias tool for randomized controlled trials.
Supplementary Table 3. Baseline characteristics of study population.
Supplementary Table 4. Sensitivity analysis of six-minute walk test distance at 12 months of follow-up sensitivity analysis.

**Table 1. Characteristics of the included studies.**

| Study | Countries and No. of centres | Recruitment period | Inclusion/exclusion criteria | No. patients | Primary endpoint |
|---|---|---|---|---|---|
| COAPT, 2018 Stone et al. | Canada, United States (78 centres) | Dec 2012 – Jun 2017 | Inclusion criteria:<br>- Secondary mitral regurgitation (EROA >0.3 $cm^2$; regurgitant volume >45 ml; regurgitation fraction >40%)<br>- Heart failure with LVEF 20-50<br>- NYHA II-IV after GDMT<br>Exclusion criteria:<br>- Candidates for cardiac surgery | 614 | - Hospitalizations for heart failure within 24 months.<br>- Freedom from device-related complications at 12 months |
| MITRA-FR, 2018 Obadia et al. | France (37 centres) | Dec 2013 – Mar 2017 | Inclusion criteria:<br>- Secondary mitral regurgitation (EROA >0.2 $cm^2$ or regurgitation volume >30 mL)<br>- Heart failure with LVEF 15-40%<br>- NYHA II-IV after GDMT<br>Exclusion criteria:<br>- Candidates for cardiac surgery | 304 | - Composite of death or unplanned hospitalization for heart failure at 12 months. |
| RESHAPE-HF2, 2024 Anker et al. | Czechia, Denmark, Germany, Greece, Italy, Portugal, Poland, Spain, United Kingdom (30 centres) | Mar 2015 – Oct 2023 | Inclusion criteria:<br>- Secondary mitral regurgitation* grade 3+ or grade 4+<br>- Heart failure with LVEF 20-50% and with a hospitalization for heart failure within 90 days or an elevated plasma natriuretic peptide concentration<br>Exclusion criteria:<br>- Candidates for cardiac surgery<br>- PCI, AF ablation, cardiovascular surgery within 90 days | 505 | - Rate of the composite of first or recurrent hospitalization for heart failure or cardiovascular death during 24 months<br>- Rate of first or recurrent hospitalization for heart failure during 24 months<br>- Change from baseline to 12 months in the score on the KCCQ-OS |

GDMT: guideline-directed medical therapy; KCCQ-OS: Kansas City Cardiomyopathy Questionnaire–Overall Summary; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association functional class. * Mitral valve regurgitation grade defined by the European Association of Echocardiography in RESHAPE-HF2 trial.

**Table 2. Characteristics of the patients at baseline.**

| | COAPT Trial | | MITRA-FR Trial | | RESHAPE-HF2 Trial | |
|---|---|---|---|---|---|---|
| | **Intervention** | **Control** | **Intervention** | **Control** | **Intervention** | **Control** |
| Age, year – (n) | 71.7±11.8 (302) | 72.8±10.5 (312) | 70.1±10.1 (152) | 70.6±9.9 (152) | 70.0±10.4 (250) | 69.4±10.7 (255) |
| Male – no./total no. (%) | 201/302 (66.6) | 192/312 (61.5) | 120/152 (78.9) | 107/152 (70.4) | 195/250 (78.0) | 211/255 (82.8) |
| Body mass index – (n) | 27.0±5.8 (302) | 27.1±5.9 (312) | - | - | 27.0±4.3 (250) | 26.7±4.3 (255) |
| Medical and surgical history – no./total no. (%) | | | | | | |
| Hypertension | 243/302 (80.5) | 251/312 (80.4) | - | - | 141/255 (56.4) | 127/255 (49.8) |
| Diabetes | 106/302 (35.1) | 123/312 (39.4) | 50/152 (32.9) | 39/152 (25.7) | 91/250 (36.4) | 85/255 (33.3) |
| Previous MI | 156/302 (51.7) | 160/312 (51.3) | 75/152 (49.3) | 52/152 (34.2) | 144/255 (57.6) | 135/255 (52.9) |
| Previous PCI | 130/302 (43.0) | 153/312 (49.0) | 71/152 (46.7)* | 64/151 (42.4)* | 118/250 (47.2) | 125/255 (49.0) |
| Previous CABG | 121/302 (40.1) | 126/312 (40.4) | | | 69/250 (27.6) | 64/255 (25.1) |
| ICM | 184/302 (60.9) | 189/312 (60.6) | 95/152 (62.5) | 85/151 (56.3) | 162/250 (64.8) | 162/255 (63.5) |
| History of AF or AFL | 173/302 (57.3) | 166/312 (53.2) | 49/142 (34.5) | 48/147 (32.7) | 118/250 (47.2) | 125/255 (49.0) |
| Previous stroke/TIA | 56/302 (18.5) | 49/312 (15.7) | - | - | 29/250 (11.6) | 30/255 (11.8) |
| History of COPD | 71/302 (23.5) | 72/312 (23.1) | - | - | 34/250 (13.6) | 37/255 (14.5) |
| GFR – (n) | 50.9±28.5 (299) | 47.8±25.0 (302) | 48.8±19.7 (152) | 50.2±20.1 (152) | 54.9±19.0 (250) | 56.7±23.3 (255) |
| HHF in previous year | 176/302 (58.3) | 175/312 (56.1) | 55/152 (36.2)† | 63/152 (41.4)† | 165/250 (66.0) | 168/255 (65.9) |
| Therapy used at baseline – no./total no. (%) | | | | | | |
| ACEI/ARB | 204/302 (67.5) | 187/312 (59.9) | 111/152 (73.0) | 113/152 (74.3) | 190/250 (76.0) | 186/255 (72.9) |
| ARNI | 13/302 (4.3) | 9/312 (2.9) | 14/140 (10.0) | 17/140 (12.1) | 40/250 (16.0) | 28/255 (11.0) |
| Beta-blocker | 275/302 (91.1) | 280/312 (89.7) | 134/152 (88.2) | 138/152 (90.8) | 238/250 (95.2) | 246/255 (96.5) |
| SGLT2i | N/A | N/A | N/A | N/A | 24/250 (9.6) | 22/255 (8.6) |
| Diuretic | 270/302 (89.4) | 277/312 (88.8) | 151/152 (99.3) | 149/152 (98.0) | 239/250 (95.6) | 243/255 (95.3) |
| MRA | 153/302 (50.7) | 155/312 (49.7) | 86/152 (56.6) | 80/151 (53.0) | 200/250 (80.0) | 215/255 (84.3) |
| Oral Anticoagulant | 140/302 (46.4) | 125/312 (40.1) | 93/152 (61.2) | 93/152 (61.2) | 163/250 (65.2) | 152/255 (59.6) |
| ICD | 91/302 (30.1) | 101/312 (32.4) | 48/151 (31.8) | 57/152 (37.5) | 75/250 (30.1) | 103/255 (40.4) |
| CRT | 115/302 (38.1) | 109/312 (34.9) | 46/151 (30.5)‡ | 35/152 (23.0)‡ | 77/249 (30.9) | 68/255 (26.6) |
| NYHA class I/II – no./total no. (%) | 130/302 (43.0) | 110/311 (35.4) | 56/152 (36.8) | 44/152 (28.9) | 59/250 (23.6) | 65/255 (25.5) |
| 6MWT distance, m – (n) | 249.6±123.8 (302) | 234.5±123.5 (312) | 301±126 (120) | 319±127 (103) | 300 [220; 382] (250) | 310 [200; 378] (255) |
| EQ5D scale score – (n) | - | - | 51.5±19.2 (143) | 53.2±16.6 (128) | - | - |
| KCCQ-OS score – (n) | 53.2±22.8 (302) | 51.6±23.3 (312) | - | - | 42.2 [28.3; 62.0] (250) | 44.3 [25.8; 64.2] (255) |
| BNP, pg/ml – (n) | 1014.8±1086.0 (208) | 1017.1±1212.8 (209) | 765 [417; 1281] (66) | 835 [496; 1258] (60) | 556 [312; 1018] (61) | 406 [231; 874] (62) |
| NT-proBNP, pg/ml – (n) | 5174.3±6566.6 (74) | 5943.9±8437.6 (85) | 3407 [1948; 6790] (75) | 3292 [1937; 6343] (72) | 2651 [1630; 4918] (191) | 2816 [1306; 5496] (193) |
| STS risk score, % – (n) | 7.8±5.5 (302) | 8.5±6.2 (312) | - | - | - | - |
| EuroSCORE II, % – (n) | - | - | 6.6 [3.5; 11.9] (152) | 5.9 [3.4; 10.4] (152) | 5.3 [2.7; 8.9] (250) | 5.3 [2.9; 9.0] (255) |

Continuous values are given as means ± standard deviation or median [interquartile range]. 6MWT: 6-min walk test; ACEI: angiotensin converting enzyme inhibitor; AF: atrial fibrillation; AFL: atrial flutter; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BNP: B-type natriuretic peptide; CABG: coronary-artery bypass graft; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronization therapy; GFR: estimated glomerular filtration rate (ml/min/1.73 $m^2$); HHF: hospitalization related to heart failure; ICD: implantable cardioverter defibrillator; ICM: ischemic cardiomyopathy; KCCQ-OS: Kansas City Cardiomyopathy Questionnaire–Overall summary; MI:

myocardial infarction; MRA: mineralocorticoid receptor antagonist; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; SGLT2i: Sodium-glucose cotransporter 2 inhibitor; STS: Society of Thoracic Surgeons; TIA: transient ischemic attack. * Reported as coronary revascularization. † At least two hospitalizations related to heart failure. ‡ Cardiac resynchronization therapy defibrillator

**Table 3. Echocardiographic characteristics of the patients at baseline.**

| | COAPT Trial | | MITRA-FR Trial | | RESHAPE-HF2 Trial | |
|---|---|---|---|---|---|---|
| | Intervention | Control | Intervention | Control | Intervention | Control |
| LVESV, ml – (n) | 135.5±56.1(281) | 134.3±60.3 (294) | - | - | 137 [100; 173] (250) | 140 [104; 176] (255) |
| LVEDV, ml – (n) | 194.4±69.2 (281) | 191.0±72.9 (294) | 258.8±71.1 (152)* | 255.6±62.9 (152)* | 200 [153; 249] (250) | 206 [158; 250] (255) |
| LVEF, % – (n) | 31.3±9.1 (281) | 31.3±9.6 (294) | 33.3±6.5 (152) | 32.9±6.7 (152) | 32 [26; 37] (250) | 31 [25; 37] (255) |
| EROA, $cm^2$ – (n) | 0.41±0.15 (289) | 0.40±0.15 (302) | 0.31±0.1 (152) | 0.31±0.11 (152) | 0.23 [0.20; 0.30] (250) | 0.23 [0.19; 0.29] (255) |
| <0.30 $cm^2$– no./total no.(%) | 0/302 (0)† | 0/302 (0)† | 77/152 (50.7) | 80/152 (52.6) | 151/235 (46.5)‡ | 168/243 (69.1)‡ |
| Regurgitant volume, ml – (n) | 28.8±17.0 (124) | 25.0±15.3 (136) | 45±13 (152) | 45±14 (152) | 35.4 [28.9; 43.9] (250) | 35.6 [28.2; 42.5] (255) |
| Post-intervention or at discharge mitral valve regurgitation grade – no./total no. (%)§ | | | | | | |
| Grade 1+ | 214/260 (82.3%) | N/A | 93/123 (75.6) | N/A | 181/243 (74.5) | N/A |
| Grade 2+ | 33/260 (12.7%) | N/A | 20/123 (16.3) | N/A | 43/243 (17.7) | N/A |
| Grade 3+ | 9/260 (3.5%) | N/A | 4/123 (3.3) | N/A | 10/243 (4.1) | N/A |
| Grade 4+ | 4/260 (1.5%) | N/A | 6/123 (4.9) | N/A | 9/243 (3.7) | N/A |

Continuous values are given as means ± standard deviation or median [interquartile range]. LVESV: Left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; EROA: effective regurgitant orifice area; LVEDV: left ventricular end-diastolic volume. * Converted from indexed value using a mean of body surface area of 1.9 $m^2$. † Mitral valve regurgitation grade I and II defined by American Society of Echocardiography. ‡ Effective regurgitant orifice area less than 0.27 $cm^2$. § Mitral valve regurgitation grade defined by the American Society of Echocardiography in COAPT trial and by the European Association of Echocardiography in MITRA-FR and RESHAPE-HF2.

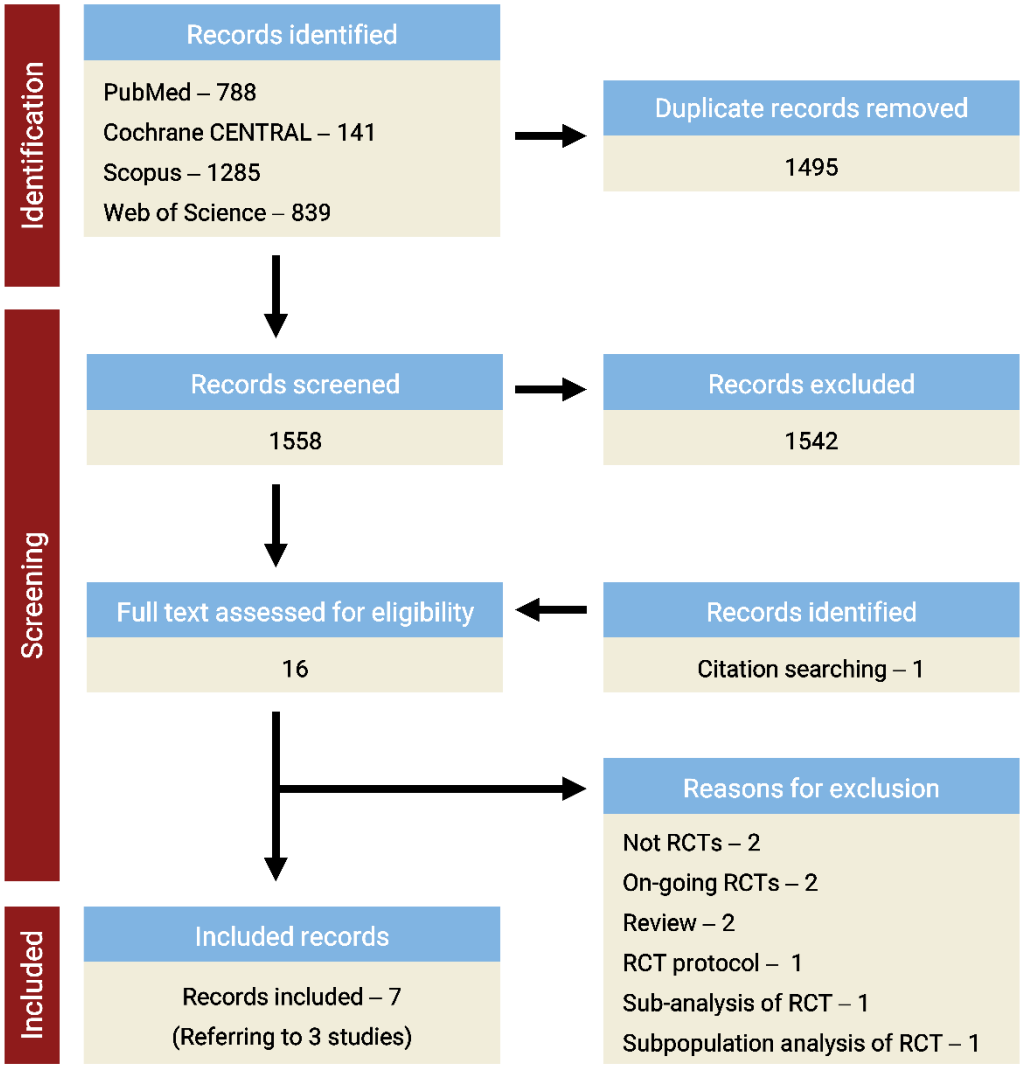



**Figure 1. PRISMA flowchart. Study identification and selection process through the different stages of the systematic review. Cochrane CENTRAL: Cochrane Central Register of Controlled Trials; RCT: randomized controlled trials.**

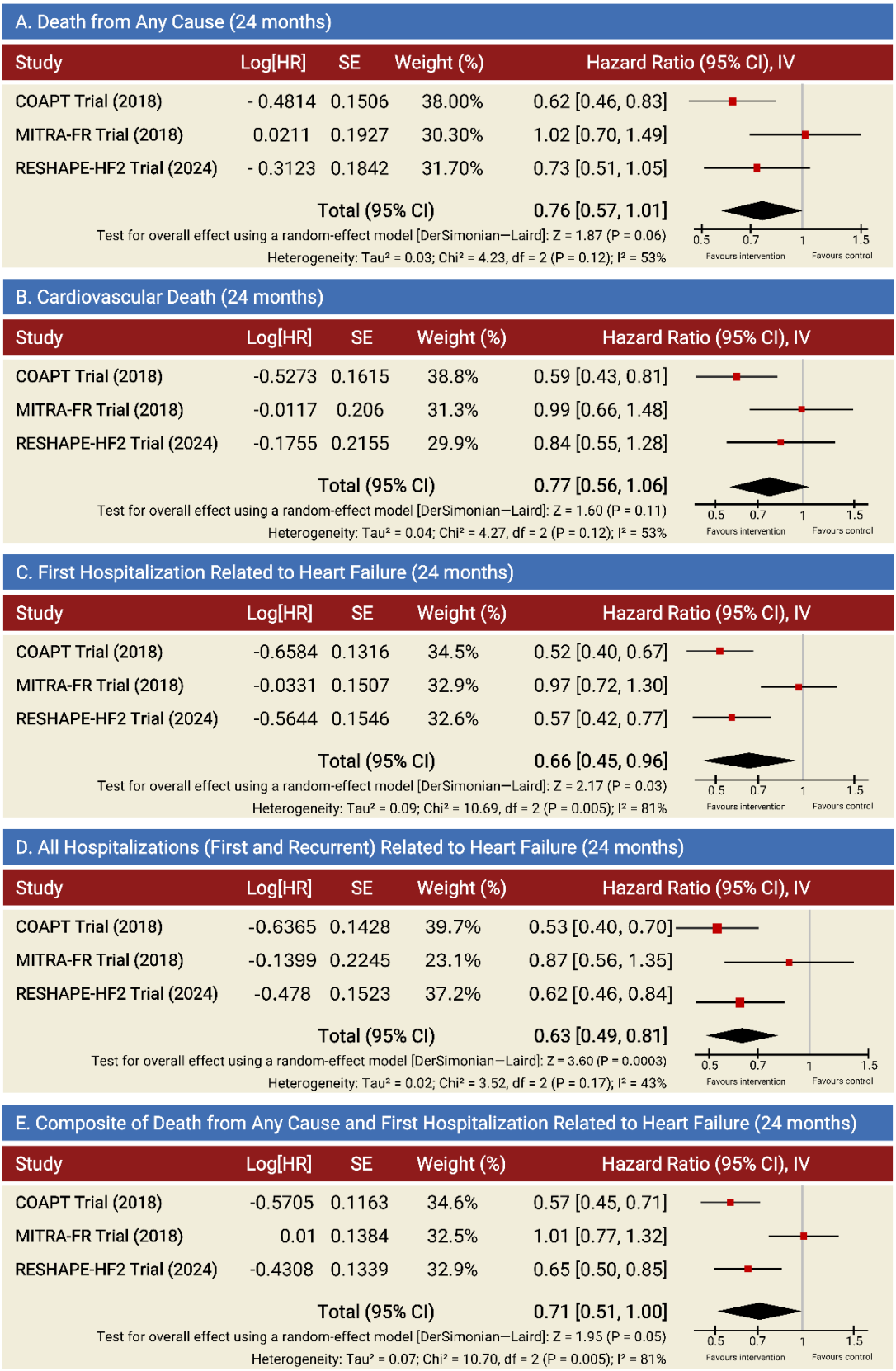



**Figure 2. Primary outcomes of meta-analysis. Generic inverse variance random-effects model based on the DerSimonian and Laird method. Data pooled from: COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial; MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial; and RESHAPE-HF2 (A Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation) trial. The effect estimates are reported as hazard ratios. CI: confidence interval; HR: hazard ratio; IV: inverse variance.**

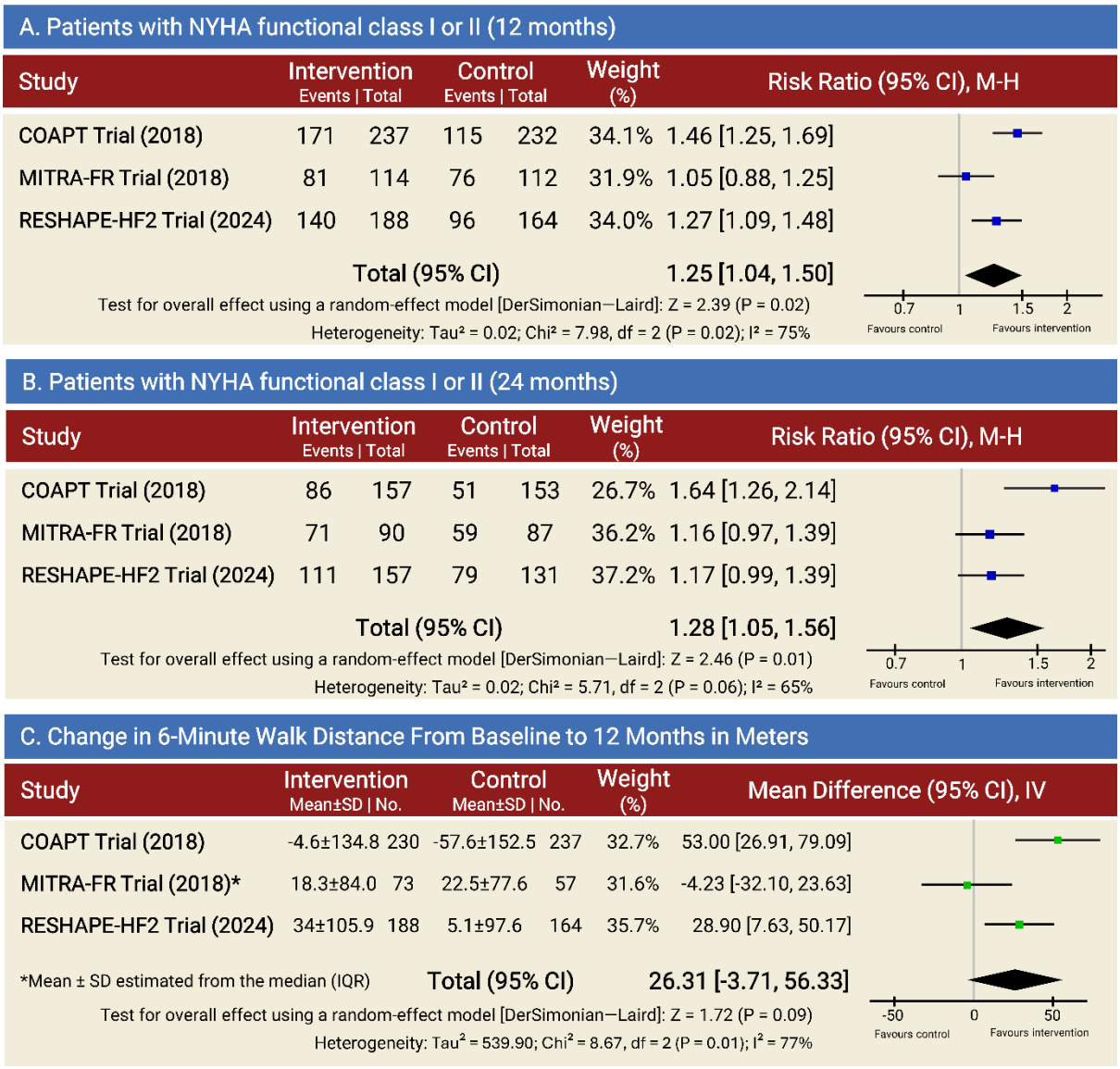
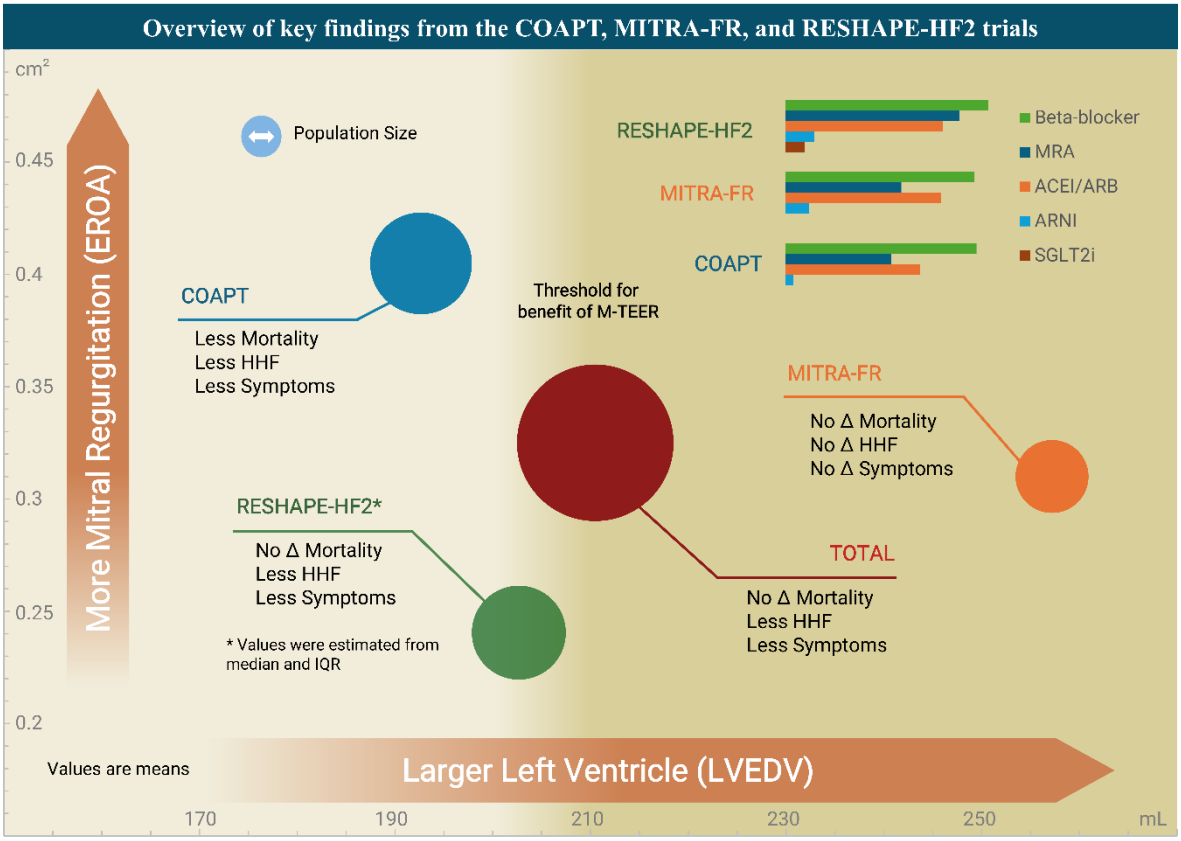



**Figure 3. Secondary outcomes of meta-analysis. Random-effects meta-analysis based on the DerSimonian and Laird method with data pooled from: COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial; MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial; and RESHAPE-HF2 (A Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation) trial. The risk ratios for patients with NYHA functional class I or II (A-B) were weighted using the Mantel-Haenszel method. The effect measure for the change in 6-minute walk test distance (C) was mean difference and weighted using the generic inverse variance method. IQR: interquartile range; IV: inverse variance; M-H: Mantel-Haenszel method; NYHA: New York Heart Association; SD: standard deviation.**




*ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; EROA: effective regurgitant orifice area; HHF: hospitalization related to heart failure; IQR: interquartile range; LVEDV: left ventricular end-diastolic volume; M-TEER: percutaneous edge-to-edge mitral valve repair; MRA: mineralocorticoid receptor antagonist; SGLT2i: Sodium-glucose cotransporter 2 inhibitor;*

**Figure 4. Exploring the relationship between effective regurgitant orifice area (EROA), left ventricular end-diastolic volume (LVEDV), and clinical outcomes. The data suggest that patient selection, particularly regarding LVEDV, may influence the observed benefits of transcatheter mitral valve repair. The outcomes and therapy optimization should be interpreted within the context of each study's population and criteria.**