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ORIGINAL RESEARCH

Transcatheter edge-to-edge repair plus guideline-directed medical therapy versus guideline-directed medical therapy alone for symptomatic functional mitral regurgitation: a comprehensive, up-to-date meta-analysis of randomised trials

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ABSTRACT

BACKGROUND: Transcatheter edge-to-edge repair (TEER) is among the treatments for functional mitral regurgitation (FMR), but its benefits over guideline-directed medical therapy (GDMT) alone are discordant. We conducted a meta-analysis of randomised trials comparing long-term outcomes between these treatment strategies.

AIMS: We aimed to compare long-term clinical outcomes between TEER plus GDMT and GDMT alone in symptomatic moderate-to-severe FMR.

METHODS: Major electronic databases were searched for randomised trials comparing TEER plus GDMT with GDMT alone in FMR. The primary outcome was death or first hospitalisation due to heart failure at 24 months. The key secondary outcome was first hospitalisation due to heart failure at 24 months. Summary hazard ratios (HRs) with 95% confidence intervals (CIs) were computed by mixed-effects Cox models based on reconstructed time-to-first event individual patient data and random-effects models based on study-level data.

RESULTS: Three randomised trials (MITRA-FR, COAPT, and RESHAPE-HF2) were included, for a total of 1,422 patients assigned to TEER plus GDMT (n=703) or GDMT alone (n=719). The primary outcome was significantly lower in the TEER plus GDMT group compared with the GDMT-alone group by one-stage analysis (HR 0.72, 95% CI: 0.56-0.92; p=0.010). However, the two-stage analysis marginally failed to confirm this result (HR 0.72, 95% CI: 0.51-1.00; p=0.052) and showed substantial heterogeneity (I^2=80.3%; p=0.006). Hospitalisation due to heart failure was significantly lower in the TEER plus GDMT group, regardless of the statistical method used (one-stage: HR 0.65, 95% CI: 0.48-0.88; p=0.006; two-stage: HR 0.66, 95% CI: 0.45-0.96; p=0.031). However, heterogeneity was substantial (I^2=81.2%; p=0.005). All-cause death and cardiovascular death at 24 months were not significantly different between treatment groups but became significant after excluding MITRA-FR in the leave-one-out analysis.

CONCLUSIONS: In symptomatic moderate-to-severe FMR, TEER plus GDMT significantly reduces death or hospitalisation due to heart failure and hospitalisation due to heart failure at 24 months.

KEYWORDS: heart failure; mitral insufficiency; mitral regurgitation; mitral repair; transcatheter edge-to-edge repair; valve disease

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Mitral regurgitation (MR) is a highly prevalent valvular heart disease that, when in its advanced stages and left untreated, results in reduced quality of life, heart failure, and increased mortality[1]. In recent years, transcatheter edge-to-edge repair (TEER) has emerged as a promising, minimally invasive interventional treatment for patients with symptomatic moderate-to-severe functional mitral regurgitation (FMR) who are not suitable for surgery because of high operative risk[2]. TEER involves creating a double orifice in the mitral valve by approximating the leaflets with a clip, which is delivered under transoesophageal echocardiographic guidance through the interatrial septum via the femoral vein[2,3].

Despite the increasing use of TEER, the predictability of results and sustained efficacy over time in decreasing major adverse cardiovascular events remain uncertain[4]. This uncertainty arises from the limited number of randomised controlled trials conducted to date, which have produced inconsistent results regarding the benefits of TEER plus guideline-directed medical therapy (GDMT) compared with GDMT alone[4]. The inconsistency of outcomes across trials has been attributed to differences in patient selection criteria, particularly left ventricular volume and systolic function, mitral regurgitation mechanism and severity, heart failure stage, and comorbidities[4,5]. Additionally, differences in study design, sample size, and definitions may have further made the interpretation of results challenging, raising questions about the generalisability of findings[2,5].

In the context of this controversial background, the results of RESHAPE-HF2 have recently enhanced the amount of available data from randomised trials[6]. A simultaneous study-level meta-analysis has summarised available data without providing multiple analyses and proper exploration of between-trial heterogeneity[7]. A comprehensive evaluation of the existing evidence from randomised trials would delineate the role of TEER for FMR and indicate future directions.

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Impact on daily practice

In patients with symptomatic functional mitral regurgitation on optimal guideline-directed medical therapy, transcatheter edge-to-edge repair (TEER) reduces the long-term incidence of the composite endpoint of death or hospitalisation due to heart failure and the rate of heart failure-related hospitalisation. Despite the substantial heterogeneity driven by the MITRA-FR trial, which emphasises the need for patient selection, the consistent risk reductions observed in COAPT and RESHAPE-HF2 confirm that TEER achieves superior long-term outcomes over guideline-directed medical therapy.

Methods

This study follows the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) of randomised clinical trials **(Supplementary Table 1)**. The protocol was registered with PROSPERO (CRD42024583172). No institutional review board approval was required for this type of study.

SEARCH STRATEGY AND DATA EXTRACTION

Randomised clinical trials evaluating the effectiveness and safety of TEER plus GDMT compared with GDMT alone for the treatment of symptomatic moderate-to-severe FMR were systematically searched across major electronic databases (PubMed, Scopus, Web of Science, and Embase). Eligible trials had to include at least one of the following outcomes within a follow-up period of at least 12 months: the composite of death and hospitalisation for heart failure, death, hospitalisation for heart failure, cardiovascular death, and other study-defined major adverse cardiovascular events (MACE). The search strategy for each database is detailed in **Supplementary Table 2**. Retrieved reports were independently screened at the title and abstract level by two reviewers under the supervision of a senior reviewer. The remaining reports were subsequently evaluated in full text by the same reviewers with identification of the trials that could be included in the meta-analysis. Relevant information on the design, TEER system, clinical and procedural characteristics, definitions, and clinical outcomes of trials ultimately included for qualitative assessment and quantitative synthesis was extracted and collected using electronic spreadsheets. Before performing the statistical analysis, the quality of each trial was evaluated by the Risk of Bias 2 tool.

OUTCOMES

The prespecified primary outcome was the composite of death or first hospitalisation due to heart failure at 24 months. The key secondary outcome was first hospitalisation due to heart failure at 24 months. Other secondary outcomes, analysed at the follow-up of 24 months, included all-cause death, cardiovascular death, and first or recurrent hospitalisation due to heart failure. In more detail, while hospitalisations due to heart failure were evaluated primarily as time-to-first event, in a supplementary analysis, both first and recurrent events were considered. Finally, the composite of death or first hospitalisation due to heart failure was also evaluated at the longest available follow-up (5 years). Further details on the outcomes and the criteria used are provided in **Supplementary Table 3**.

STATISTICAL ANALYSIS

The meta-analysis was conducted by frequentist random-effects models with inverse variance weighting and restricted maximum likelihood estimation of between-trial variance (τ^2). Differences between outcomes in the two groups were reported by hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Conventional CIs were complemented with 95% CIs after Hartung-Knapp correction to assess the robustness of conclusions. Heterogeneity between trials was graded using

Abbreviations

FMR functional mitral regurgitation **GDMT** guideline-directed medical therapy **TEER** transcatheter edge-to-edge repair

the I^2 statistic and formally tested by the Q test. Forest plots were generated to display the distribution of trial-level and summary estimates and illustrate the relative contribution of each trial to the pooled effect. In the context of random-effects models, 95% prediction intervals were calculated according to the t-distribution with k–2 degrees of freedom to provide a predicted range of the true effect size in a new study.

The primary and key secondary outcomes were assessed by one-stage mixed-effects penalised partial likelihood semiparametric frailty models based on reconstructed time-to-first event individual patient data[8-10]. The models included a random intercept allowing for a different baseline risk across trials and a random slope accounting for treatment effect variations across trials. Kaplan-Meier curves from the combined data of all three trials were generated to illustrate the cumulative distribution of events between treatment groups over 24 months. The proportional hazards assumption was verified by the Grambsch-Therneau test and scaled Schoenfeld residuals.

Leave-one-out sensitivity analyses were conducted to evaluate the influence of individual trials on the pooled estimates. The use of funnel plots to address potential small-study effects and publication bias and formal testing for asymmetry by the Egger's test were prespecified if the number of trials was deemed sufficient for employing these assessments. Statistical analyses were conducted using R, version 4.3.2 (R Foundation for Statistical Computing).

Results

The search and selection of trials are shown in **Supplementary Figure 1** and **Supplementary Table 2**. A total of three randomised controlled trials (MITRA-FR, COAPT, and RESHAPE-HF2)[6,11-15] **(Supplementary Appendix 1)** were included in the meta-analysis, encompassing a combined population of 1,422 patients with symptomatic FMR, of whom 703 were assigned to TEER plus GDMT and 719 to GDMT alone. The main characteristics of the trials are presented in **Table 1**, **Table 2**, **Supplementary Table 3**, and **Supplementary Table 4**.

Table 1. Design of the included trials.

	MITRA-FR (2019)[11,13]	COAPT (2019)[12,14]	RESHAPE-HF2 (2024)[6,15]
Sample size	304	614	505
(TEER vs GDMT)	(152 vs 152)	(302 vs 312)	(250 vs 255)
Study population	Heart failure and FMR	Heart failure and FMR	Heart failure and FMR
Accrual period, years	3.3	4.5	8.7
Centres	37	78	30
Patients/site	8.2	7.8	16.8
Patients/site/year	2.5	1.8	1.9
Countries	France	United States	Czech Republic, Denmark, Germany, Greece, Italy, Poland, Portugal, Spain, United Kingdom
Clinical inclusion criteria	NYHA II-IV Not a candidate for surgery ≥1 hospitalisation(s) due to heart failure <12 months	NYHA II-IVa ≥1 hospitalisation(s) due to heart failure <12 months or BNP ≥300 pg/mL or NT-proBNP ≥1,000 pg/mL after GDMT Not a candidate for surgery	NYHA II-IV ≥1 hospitalisation(s) due to heart failure <12 months or BNP ≥300 pg/mL or NT-proBNP ≥1,000 pg/mL after GDMT Surgery is not preferable
Echocardiographic inclusion criteria	Grade 3+ or 4+ FMR EROA >20 mm^2 and/or RV >30 mL/beat LVEF 15-40%	Grade 3+ or 4+ FMR LVEDD ≤70 mm LVEF 20-50%	Grade 3+ or 4+ FMR LVEF 15-35% and NYHA II or LVEF ≤45% and NYHA III-IV
GDMT	At the investigator's discretion	Stable maximal doses of GDMT and cardiac resynchronisation therapy	GDMT with no dose changes except diuretics for ≤2 weeks
TEER system	MitraClip	MitraClip	MitraClip
Hypothesis	Superiority	Superiority	Superiority
Primary outcomes	Death or hospitalisation due to heart failure at 12 months	Hospitalisation due to heart failure at 24 months Device-related complications at 12 months	Cardiovascular death or hospitalisation due to heart failure at 24 months Hospitalisation due to heart failure at 24 months Change in KCCQ at 12 months
Key secondary outcomes	All-cause death, hospitalisation due to heart failure, and cardiovascular death at 12 months	All-cause death or hospitalisation due to heart failure, and cardiovascular death at 24 months	All-cause death, hospitalisation due to heart failure, and cardiovascular death at 24 months
Maximum available follow-up	24 months	60 months	24 months

BNP: B-type natriuretic peptide; EROA: effective regurgitant orifice area; FMR: functional mitral regurgitation; GDMT: guideline-directed medical therapy; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; RV: regurgitant volume; TEER: transcatheter edge-to-edge repair

Table 2. Baseline characteristics across trials.

Baseline characteristics	MITRA-FR (2019)[11]		COAPT (2019)[12]		RESHAPE-HF2 (2024)[6]	
	TEER (152)	GDMT (152)	TEER (302)	GDMT (312)	TEER (250)	GDMT (255)
Age, years	70.1±10.1	70.6±9.9	71.7±11.8	72.8±10.5	70.0±10.4	69.4±10.7
Female	32 (21.1)	45 (19.6)	101 (33.3)	120 (38.5)	55 (22.0)	44 (17.2)
NYHA III-IV	96 (63.1)	108 (71.1)	172 (57.0)	201 (64.6)	191 (76.4)	189 (74.1)
NT-proBNP, pg/mL	3,407 (1,948-6,790)	3,292 (1,937-6,343)	5,174.3±6,566.6	5,943.9±8,437.6	2,651 (1,630-4,918)	2,816 (1,306-5,496)
Ischaemic cardiomyopathy	95 (62.5)	85 (56.3)	184 (60.9)	189 (60.6)	162 (64.8)	167 (65.4)
eGFR, mL/min/1.73m^2	48.8±19.7	50.2±20.1	50.9±28.5	47.8±25.0	54.9±19.0	56.7±23.3
Atrial fibrillation	49 (34.5)	48 (32.7)	173 (57.3)	166 (53.2)	118 (47.2)	125 (49.0)
EuroSCORE II	6.6 (3.5-11.9)	5.9 (3.4-10.4)	–	–	–	–
STS score	–	–	7.8±5.5	8.5±6.2	–	–
EROA, cm^2	0.31±0.10	0.31±0.11	0.41±0.15	0.40±0.15	0.23 (0.20-0.30)	0.23 (0.19-0.29)
RV, mL	45±13	45±14	–	–	35.4 (28.9-43.9)	35.6 (28.2-42.5)
LVEDV, mL	255.6±63	258.8±71	194.4±69.2	191.0±72.9	200 (153-249)	206 (158-250)
LVEF, %	33.3±6.5	32.9±6.5	31.3±9.1	31.3±9.6	32 (27-36)	31 (25-37)
Loop diuretics	151 (99.3)	149 (98.0)	270 (89.4)	277 (88.8)	239 (95.6)	243 (95.3)
ACEi/ARB	111 (73.0)	113 (74.3)	204 (67.8)	187 (60.0)	190 (76.0)	186 (72.9)
ARNi	14 (10.0)	17 (12.1)	13 (4.3)	9 (2.9)	40 (16.0)	28 (11.0)
MRA	86 (56.6)	80 (53.0)	153 (50.7)	155 (49.7)	200 (80.0)	215 (84.3)
Beta blockers	134 (88.2)	138 (90.8)	275 (91.1)	280 (89.7)	238 (95.2)	246 (96.5)
SGLT2i	0 (0)	0 (0)	0 (0)	0 (0)	24 (9.6)	22 (8.6)
CRT	46 (30.5)	35 (23.0)	115 (38.1)	109 (34.9)	77 (30.9)	68 (26.7)

Continuous variables are summarised as mean±standard deviation or median (interquartile range), as appropriate. Categorical variables are summarised as counts (proportions). ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNi: angiotensin receptor-neprilysin inhibitor; COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; CRT: cardiac resynchronisation therapy; eGFR: estimated glomerular filtration rate; EROA: effective regurgitant orifice area; EuroSCORE: European System for Cardiac Operative Risk Evaluation; GDMT: guideline-directed medical therapy; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; MITRA-FR: Percutaneous Repair with the MitraClip Device for Severe Secondary Mitral Regurgitation; MRA: mineralocorticoid receptor antagonist; NT-proBNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association; RESHAPE-HF2: Randomised Study of the MitraClip Device in Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation 2; RV: regurgitant volume; SGLT2i: sodium-glucose co-transporter-2 inhibitor; STS: Society of Thoracic Surgeons; TEER: transcatheter edge-to-edge repair

Some characteristics, primarily sex, left ventricular end-diastolic volume, FMR severity, atrial fibrillation, and GDMT showed heterogeneity across trials. Specifically, patients in COAPT and in RESHAPE-HF2 presented with smaller left ventricular end-diastolic volumes (194±69 mL vs 191±73 mL in COAPT; 200±24 mL vs 206±23 mL in RESHAPE-HF2) than those in MITRA-FR (255.6±63 mL vs 258.8±71 mL). The ischaemic aetiology of FMR was predominant, identified in almost two-thirds of patients in each trial, with high prevalences of prior revascularisation and coronary artery bypass grafting. The effective regurgitant orifice area was largest in COAPT (0.41 cm^2), followed by MITRA-FR (0.31 cm^2) and RESHAPE-HF2 (0.23 cm^2). Atrial fibrillation was less prevalent in MITRA-FR (33.6%) compared with COAPT (55.2%) and RESHAPE-HF2 (48.1%). New York Heart Association (NYHA) Class III-IV was the most frequent, ranging from 63.1-71.1% in the MITRA-FR trial to 76.4-74.1% in the RESHAPE-HF2 trial. Loop diuretic use was prescribed to almost all patients, ranging from 89.1% in COAPT to 98.7% in MITRA-FR. COAPT had a lower proportion of patients on angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor-neprilysin inhibitors (67.3%) compared with MITRA-FR (84.8%) and RESHAPE-HF2 (87.9%). Consistently, beta blockers and mineralocorticoid receptor antagonists were more prevalent in RESHAPE-HF2 (95.8% and 82.2%, respectively) compared with MITRA-FR (89.8% and 54.8%, respectively) and COAPT (90.4% and 50.2%, respectively). Sodium-glucose co-transporter 2 inhibitor use was reported only in RESHAPE-HF2, as it entered clinical practice for heart failure treatment after the other two trials had been completed. The quality of trials was high overall and, except for a possible bias due to the unfeasibility of masking, there were no significant concerns **(Supplementary Figure 2)**.

PRIMARY OUTCOME

At the 24-month follow-up, TEER plus GDMT was associated with a significant reduction in death or hospitalisation due to heart failure compared with GDMT

alone by one-stage analysis (HR 0.72, 95% CI: 0.56-0.92; p=0.010) based on reconstructed time-to-first event individual patient data **(Figure 1)**. The reconstructed 2-year rate of survival free from events was 51.3% in the TEER plus GDMT group and 38.1% in the GDMT-alone group **(Figure 1)**. However, the two-stage random-effects analysis without and with 95% CI correction showed a non-significant difference between groups (random-effects: HR 0.72, 95% CI: 0.51-1.00; p=0.052; random-effects with 95% CI correction: HR 0.72, 95% CI: 0.34-1.50; p=0.192) **(Figure 1)**. While the relative weight of each trial was balanced, between-trial heterogeneity was substantial (I^2=80.3%; p=0.006), mainly due to the substantial differences in the effects of the COAPT (HR 0.57, 95% CI: 0.45-0.71; p<0.001) and RESHAPE-HF2 trials (HR 0.65, 95% CI: 0.50-0.85; p<0.001), supporting a benefit of TEER plus GDMT over GDMT alone, and the effect of the MITRA-FR trial (HR 1.01, 95% CI: 0.77-1.34; p=0.944), indicating no significant difference between the treatment groups **(Figure 1)**. The high heterogeneity resulted in a prediction interval crossing the null, highlighting the uncertainty in the effect size of a new trial according to the available information **(Figure 1)**. These findings were outlined by the leave-one-out analysis, in which heterogeneity was no longer detectable after removal of the MITRA-FR trial **(Supplementary Figure 3)**. The exclusion of either the COAPT trial or the RESHAPE-HF2 trial produced largely non-significant differences between treatment groups **(Supplementary Figure 3)**.

SECONDARY OUTCOMES

The key secondary outcome of first hospitalisation for heart failure at 24 months was significantly reduced in patients assigned to TEER plus GDMT compared with

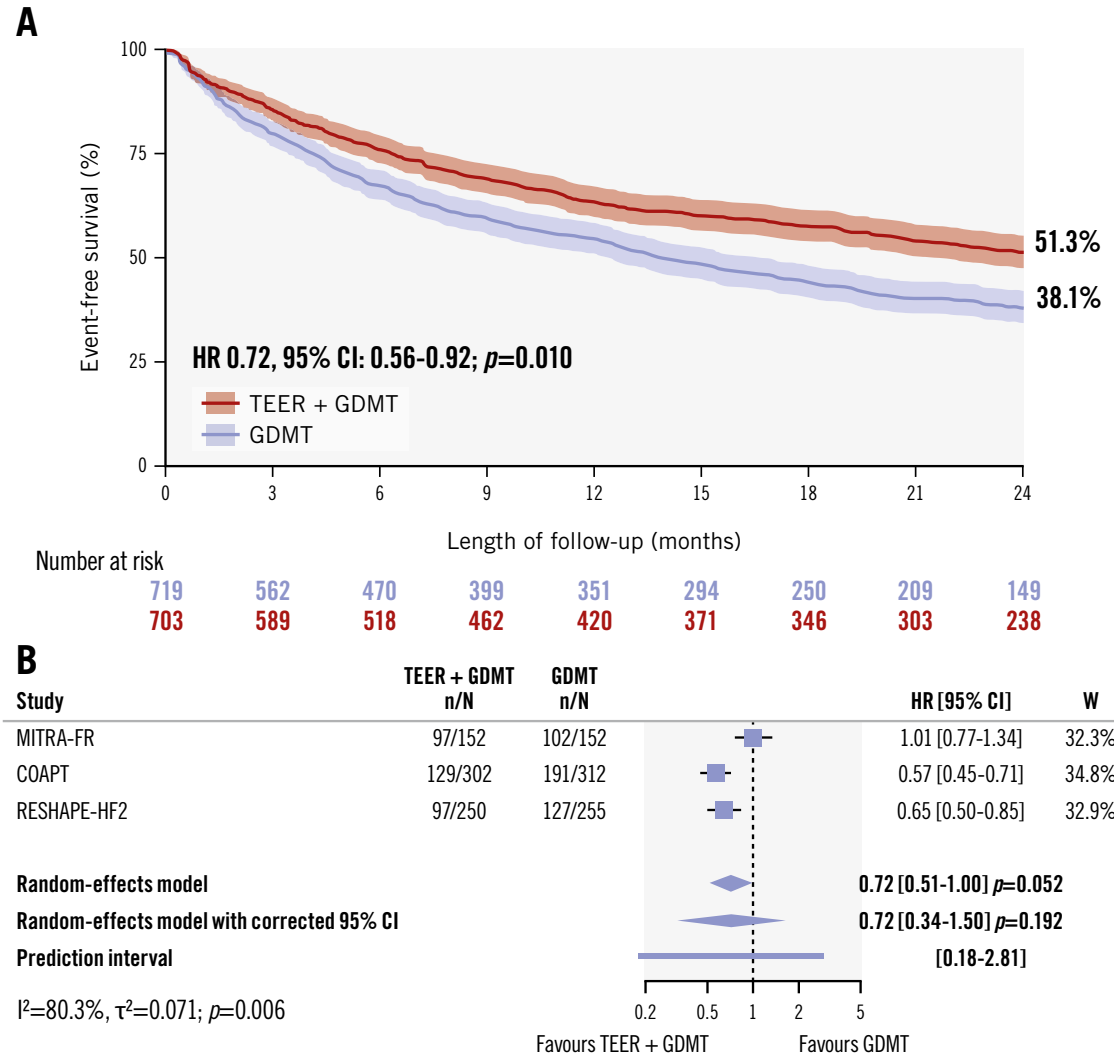


Figure 1. *All-cause death or hospitalisation due to heart failure between TEER plus GDMT and GDMT alone. A) Event-free survival by the Kaplan-Meier method after combination of reconstructed time-to-event individual patient data and the one-stage meta-analysis results. B) Two-stage meta-analysis results without and with 95% confidence interval correction by the Hartung-Knapp method and the prediction interval. CI: confidence interval; GDMT: guideline-directed medical therapy; HR: hazard ratio; TEER: transcatheter edge-to-edge repair; W: weight*

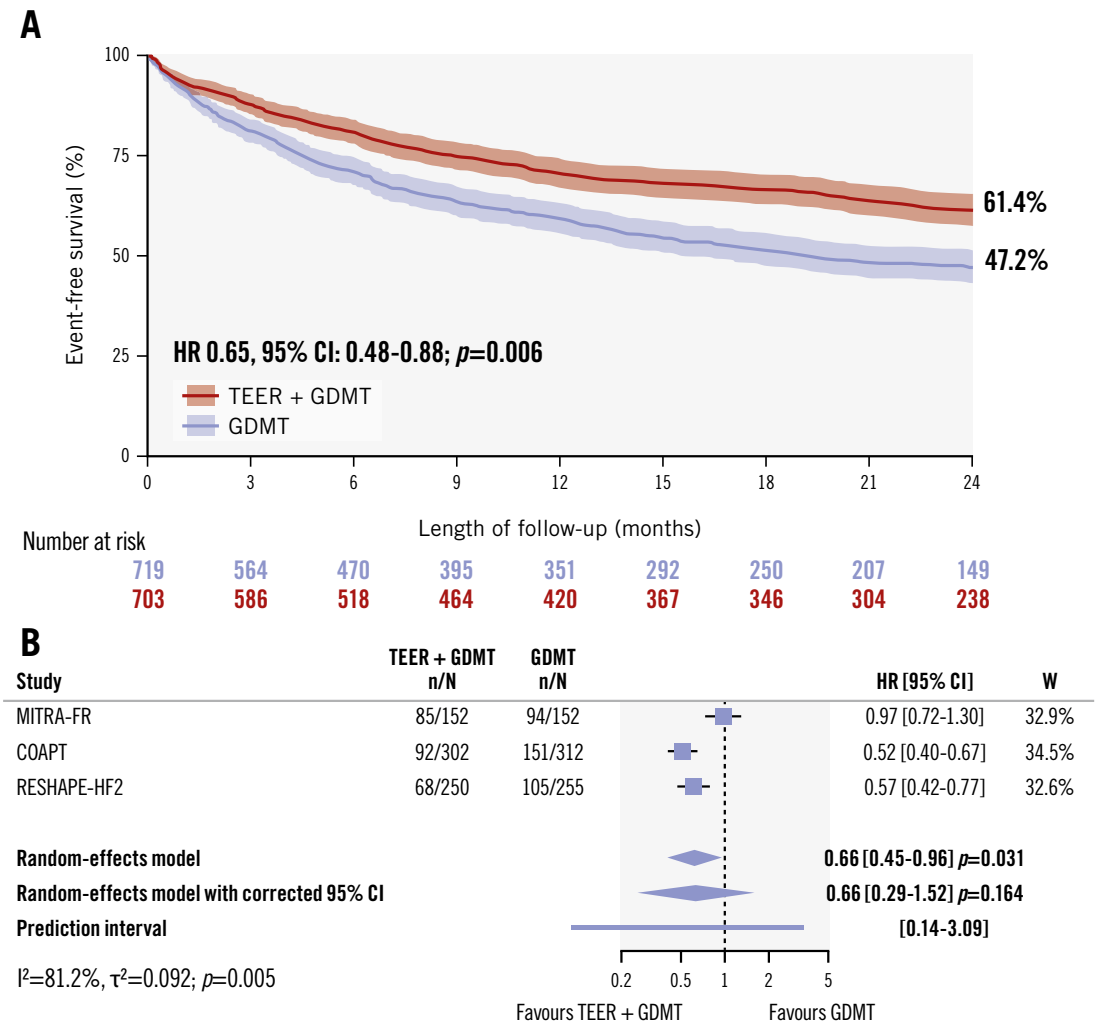


Figure 2. *Hospitalisation due to heart failure between TEER plus GDMT and GDMT alone. A) Event-free survival by the Kaplan-Meier method after combination of reconstructed time-to-event individual patient data and the one-stage meta-analysis results. B) Two-stage meta-analysis results without and with 95% confidence interval correction by the Hartung-Knapp method and the prediction interval. CI: confidence interval; GDMT: guideline-directed medical therapy; HR: hazard ratio; TEER: transcatheter edge-to-edge repair; W: weight*

those assigned to GDMT alone by one-stage analysis (HR 0.65, 95% CI: 0.48-0.88; p=0.006) based on reconstructed time-to-first event individual patient data **(Figure 2)**. The reconstructed 2-year survival free from hospitalisation due to heart failure was 61.4% in the TEER plus GDMT group and 47.2% in the GDMT-alone group **(Figure 2)**. The two-stage analysis showed consistent results (HR 0.66, 95% CI: 0.45-0.96; p=0.031) **(Figure 2)**. However, after conservative correction of the 95% CI by the Hartung-Knapp method, the difference between treatments was no longer significant (HR 0.66, 95% CI: 0.29-1.52; p=0.164) as a result of the substantial between-trial heterogeneity (I^2=81.2%; p=0.005) **(Figure 2)**. The 95% prediction interval crossed the null, highlighting the uncertainty in the predicted effect size of a new trial according to the available information **(Figure 2)**. The leave-one-out analysis confirmed that the exclusion of either the COAPT trial or the RESHAPE-HF2 trial led to non-significant differences between treatment groups, and the exclusion of the MITRA-FR trial rendered heterogeneity no longer detectable **(Supplementary Figure 3)**.

Death was not significantly different between treatment groups (HR 0.76, 95% CI: 0.57-1.01; p=0.056), though there was a numerical trend toward a mortality reduction in patients assigned to TEER plus GDMT compared with those assigned to GDMT alone **(Figure 3)**. Between-trial heterogeneity was moderate (I^2=52.0%; p=0.124) and, after excluding MITRA-FR, there was a significant reduction in death associated with TEER plus GDMT compared with GDMT alone (HR 0.66, 95% CI: 0.53-0.83; p<0.001) **(Supplementary Figure 3)**. Cardiovascular death was not significantly different between patients assigned to TEER plus GDMT compared with those assigned to GDMT alone (HR 0.77, 95% CI: 0.56-1.06; p=0.110), though a numerical trend was observed towards a cardiovascular mortality reduction associated with TEER plus GDMT compared with GDMT alone **(Figure 3)**. Between-trial heterogeneity was moderate (I^2=53.5%; p=0.117), and after

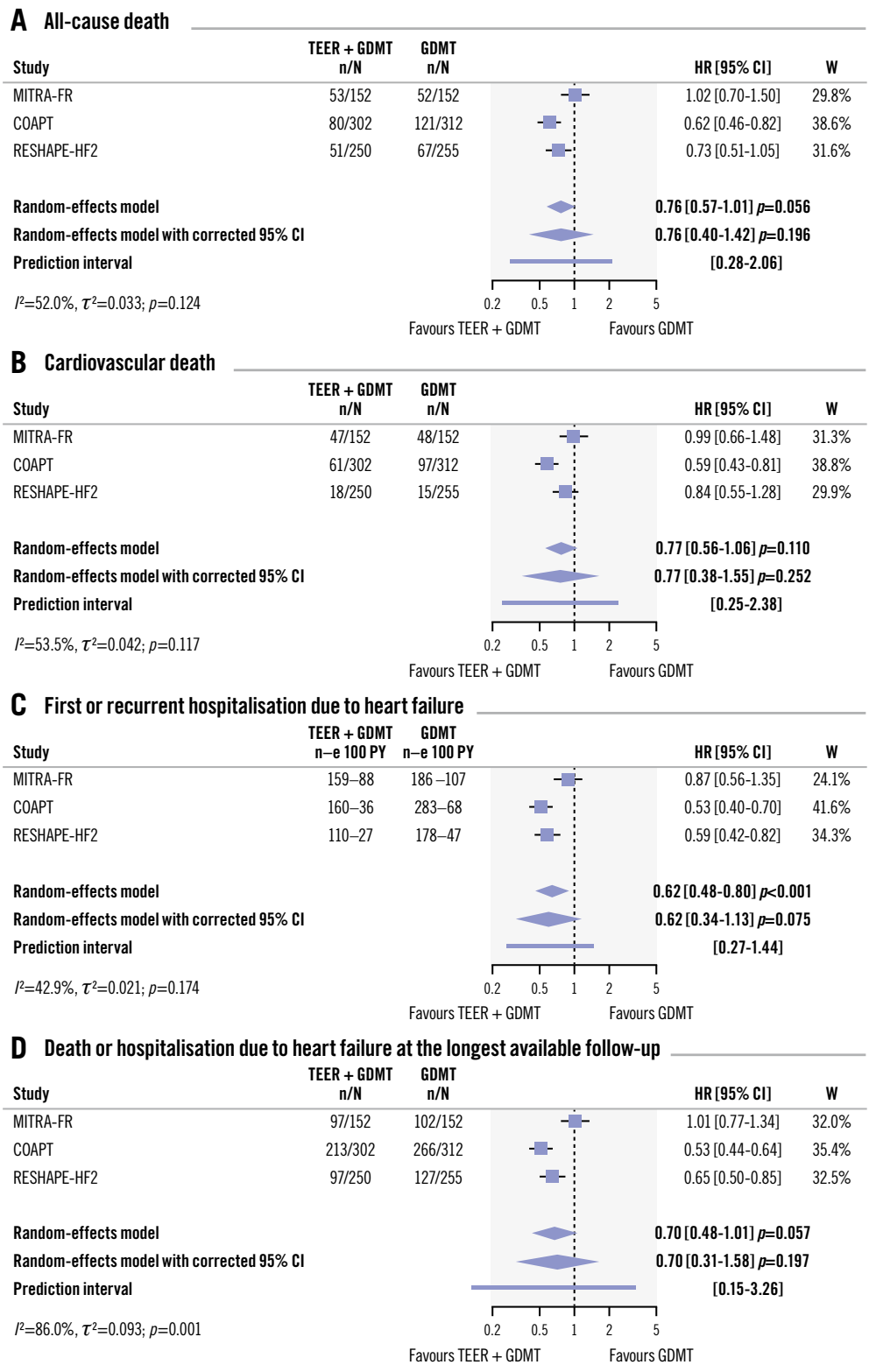
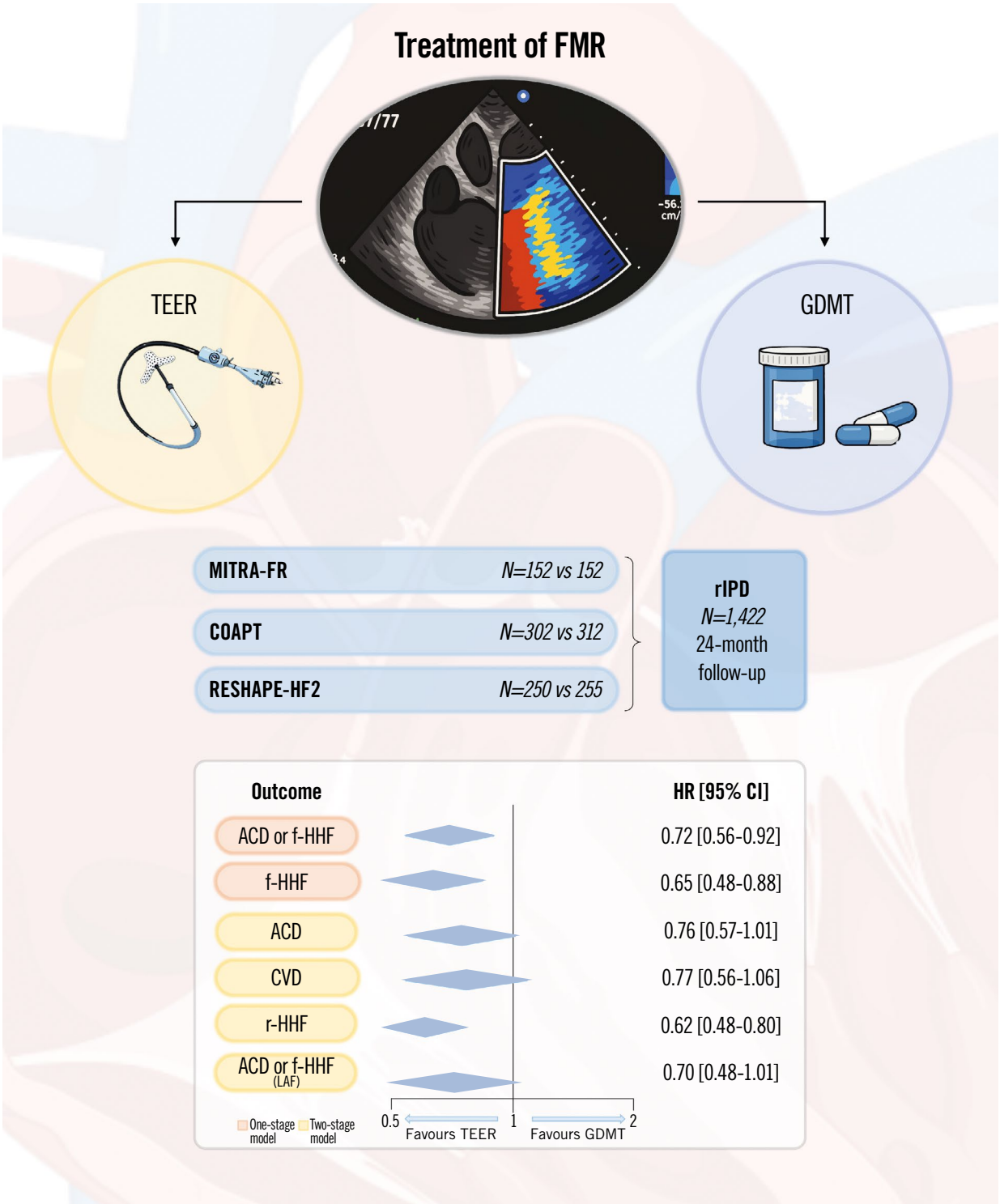


Figure 3. *All-cause death and cardiovascular death between TEER plus GDMT and GDMT alone. CI: confidence interval; GDMT: guideline-directed medical therapy; HR: hazard ratio; TEER: transcatheter edge-to-edge repair; W: weight*

excluding MITRA-FR, a significant reduction was observed associated to cardiovascular death with TEER plus GDMT compared with GDMT alone (HR 0.68, 95% CI: 0.49-0.96; p=0.029) **(Supplementary Figure 3)**.

Accounting for both first and recurrent hospitalisations due to heart failure, the results remained consistent with the time-to-first event analysis, using the standard analysis (HR 0.62, 95% CI: 0.48-0.80; p<0.001). However, after correcting the

Randomised trials and pooled effects of TEER plus GDMT versus GDMT alone for moderate-to-severe FMR.



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ACD: all-cause death; CI: confidence interval; CVD: cardiovascular death; f-HHF: first hospitalisation due to heart failure; FMR: functional mitral regurgitation; GDMT: guideline-directed medical therapy; HR: hazard ratio; LAF: longest available follow-up; r-HHF: first or recurrent hospitalisation for heart failure; rIPD: reconstructed individual patient data; TEER: transcatheter edge-to-edge repair

95% CI, the difference was no longer statistically significant (HR 0.62, 95% CI: 0.34-1.13; p=0.075) **(Figure 3)**. In line with the other outcomes, between-trial heterogeneity was essentially attributable to MITRA-FR, and both the COAPT and RESHAPE-HF2 trials were required to reach a significant difference between treatment groups **(Supplementary Figure 3)**. Considering the maximum available follow-up of the COAPT trial (5 years), the results marginally failed to remain statistically significant (HR 0.70, 95% CI: 0.48-1.01; p=0.057) **(Figure 3)**.

Discussion

This meta-analysis integrates data from the COAPT, MITRA-FR, and RESHAPE-HF2 trials, offering a comprehensive and up-to-date evaluation of mitral valve TEER performed in patients with symptomatic moderate-to-severe FMR[6,11-15]. By pooling the entire evidence from randomised clinical trials accrued thus far, the reconstructed time-to-event individual patient data one-stage analysis demonstrated that TEER plus GDMT is more effective than GDMT alone in reducing a composite of death or first hospitalisation due to heart failure as well as the individual outcome of first hospitalisation due to heart failure **(Central illustration)**. However, while the two-stage analysis for first hospitalisation due to heart failure was consistent with the one-stage analysis, the two-stage analysis for death or first hospitalisation due to heart failure was not associated with a significant difference between treatment groups. In addition, substantial between-trial heterogeneity between treatment groups was observed, and consequently, the conservatively corrected 95% CIs and the prediction intervals denoted significant residual uncertainty, highlighting the need for more data[7].

MITRA-FR was the first randomised trial comparing TEER plus GDMT with GDMT alone for the treatment of FMR[11]. In this trial, the primary composite endpoint of 1-year all-cause death or hospitalisation for heart failure and the individual endpoints of all-cause death and hospitalisation due to heart failure did not support a prognostic improvement after invasive treatment, though TEER was not associated with safety concerns[11]. The contrasting conclusions of COAPT renewed enthusiasm for TEER as an intervention to improve the prognosis of patients with symptomatic moderate-to-severe FMR who are deemed unsuitable for surgery, likely saving this therapeutic option from oblivion[12]. In the COAPT trial, the primary endpoint of hospitalisation due to heart failure at 2-year follow-up was significantly lower in patients assigned to TEER plus GDMT than in those assigned to GDMT alone, with annualised incidences of 35.8% per patient-years and 67.9% per patient-years, respectively[12].

Reconciling the conclusions between the MITRA-FR and COAPT trials is challenging. Beyond some observed differences in baseline characteristics and comorbidity burden, the selection of patients to be included in the trial and the management of heart failure before and after TEER may have played a role in the dissimilar conclusions of the two trials. In the COAPT trial, FMR severity was assessed by a core laboratory, and an independent multidisciplinary committee, including heart failure specialists, verified the eligibility of inclusion of each patient based on whether heart failure treatments at the maximum tolerated dose were employed without tangible clinical improvements and excluded a reduction in mitral regurgitation severity during the intensified run-in phase. In the MITRA-FR trial, less standardised procedures may have led to a more liberal selection of patients. Against this background, some differences in the medications used before TEER between MITRA-FR and COAPT may indicate higher heterogeneity in the stage of FMR disease, though they cannot be directly and definitively linked with diverging outcomes. In this context, a different proportion of patients on cardiac resynchronisation therapy may also have had an influence. Regarding patient selection, it is fundamental to recognise that, on equal terms of baseline left ventricular ejection fraction and ischaemic aetiology, some echocardiographic inclusion criteria in MITRA-FR led to a less restrictive inclusion of patients compared with COAPT. Specifically, patients enrolled in the MITRA-FR trial showed larger left ventricular end-diastolic volumes and lower effective regurgitant orifice areas compared with those enrolled in the COAPT trial. These findings provided the groundwork for the hypothesis that patients enrolled in the MITRA-FR trial more frequently had proportionate FMR, while those enrolled in the COAPT trial more frequently had disproportionate FMR[16]. Specifically, in some patients with FMR, the effective orifice area is proportionate to the degree of left ventricular dilatation, allowing for a more effective response to medications that reduce left ventricular end-diastolic volume[16]. In contrast, in some patients with FMR, the effective orifice area is disproportionately higher than the degree of left ventricular end-diastolic volume, implying a narrower margin for treatment with medications and higher benefits of interventions on the valve[16]. While useful to reconcile COAPT and MITRA-FR, this framework has not been robustly validated in retrospective TEER cohorts and should be regarded as hypothesis-generating[17,18].

These differences likely supported selection at a different stage in the natural history of FMR, and long-term follow-up results were consistent with these considerations[19,20]. Although procedural efficacy in the two trials was high, exceeding 90%, regardless of the treatment by TEER plus GDMT or GDMT alone, patients in the MITRA-FR trial at 2-year follow-up exhibited a lower rate of NYHA Class ≤II, larger left ventricular end-diastolic volumes, and less durable FMR grade ≤2 reduction compared with those in the COAPT trial[16]. The variability of GDMT monitoring and adherence after TEER further complicates the interpretation of outcomes. In COAPT, more stringent GDMT assessment protocols were mandated, including functional and laboratory examinations[12]. In MITRA-FR, less rigorous monitoring raises questions about the extent of GDMT optimisation and possible therapeutic differences between treatment groups[11].

The recent publication of the early terminated RESHAPE-HF2 trial results has mitigated the uncertainty surrounding TEER efficacy. In this trial, 24-month cardiovascular death or hospitalisation due to heart failure was significantly lower in patients assigned to TEER plus GDMT than in those assigned to GDMT alone, with annualised incidences of 37.0% per patient-years and 58.9% per patient-years, respectively[6]. Despite significant challenges, including an accrual lasting approximately 8 years, the predominant recruitment from two countries (Greece and Poland), accounting for nearly 80% of patients, and changes in GDMT for heart failure during the

trial, RESHAPE demonstrated consistent long-term clinical benefits of TEER across outcomes. Specifically, first-time and recurrent event analyses of hospitalisation due to heart failure and the mean change in Kansas City Cardiomyopathy Questionnaire - Overall Summary score supported the significant improvements associated with TEER. These results were consistent with the sustained improvements in exercise capacity and quality of life previously observed in the COAPT trial[12].

While the COAPT trial showed a significant reduction in all-cause death, the RESHAPE-HF2 trial did not confirm this conclusion[6,12]. In the present meta-analysis, the lack of significant differences between TEER plus GDMT and GDMT alone in terms of all-cause death and cardiovascular death may indicate that TEER benefits primarily involve symptoms and quality of life. Nevertheless, it should also be acknowledged that numerical trends towards significant reductions in all-cause and, to a lesser extent, cardiovascular death may be a function of insufficient statistical power for these individual outcomes. These findings underscore the need for more data to provide definitive conclusions[6].

Recently, another meta-analysis of randomised trials explored the comparison of TEER plus GDMT versus GDMT alone in patients with significant FMR[7]. In the present study, we used different methods compared with the meta-analysis by Anker and colleagues. In particular, unlike the previous meta-analysis, we used one-stage analyses based on reconstructed time-to-event individual patient data and frailty models. In addition, slight differences in two-stage random-effects meta-analyses may be attributed to different parametrisation[7]. In our study, the 95% CIs of summary estimates computed by frailty models were narrower than those of two-stage analyses – and therefore than those of standard random-effects analyses in the meta-analysis by Anker and colleagues – because the one-stage analysis generally is more convenient in terms of statistical power. However, beyond these statistical differences, our findings are broadly consistent with the meta-analysis by Anker and colleagues, and the main distinction lies in the critical interpretation of the substantial between-trial heterogeneity[7]. Notably, even in the meta-analysis by Anker and colleagues, none of the summary estimates obtained using random-effects models with conservative 95% CI adjustment via the Hartung-Knapp method reached statistical significance. Despite this, the authors concluded that the results were sufficiently consistent and presented adjusted 95% CIs as merely "broader", even though they were no longer supportive of a significant difference[7].

Finally, the MATTERHORN trial has recently demonstrated not only the non-inferiority of TEER compared with surgical mitral valve repair or replacement in high-risk patients but also its superiority in terms of major procedural complications and hospital length of stay[21]. Notably, in this trial, symptom relief after TEER remained stable at 1-year follow-up, with no significant differences compared with surgical mitral valve repair or replacement[21]. These findings have been endorsed by contemporary guidelines, which recommend TEER to reduce heart failure hospitalisations and improve quality of life in symptomatic ventricular FMR receiving optimised GDMT (Class I, Level of Evidence A)[22]. Longer-term data from MATTERHORN and similar trials will be crucial for assessing the durability of TEER compared with surgery, thereby consolidating its role as a sustainable alternative to surgery in high-risk patients who meet guideline indications[21,23,24].

Limitations

The results of this meta-analysis should be interpreted considering the following limitations. First, this meta-analysis was based on study-level and reconstructed time-to-event data, implying limited flexibility and dependency on original reporting. Nevertheless, the randomised design ensured a negligible influence of individual patient associations on the outcomes between groups, and all trials showed overall high methodological quality and an acceptable extent of reported data. Second, the composite primary endpoint of RESHAPE-HF2 included cardiovascular death instead of all-cause death[6] for the one-stage analysis. Third, between-trial heterogeneity was high, likely implying some differences in the selection of patients. Access to individual patient data may provide more insights into this assumption and possible causal associations. Fourth, GDMT may have varied across trials, changes in the guidelines during the prolonged course of trials may have influenced GDMT, and more recently approved medications for heart failure were available only to the last patients enrolled in the RESHAPE-HF2 trial[6]. Fifth, the long recruitment periods across trials likely reveal accurate screening and selection of patients, posing some considerations about the generalisability of results. Finally, only one TEER system was employed across trials, and the results may not apply to other devices. Additionally, although new transcatheter therapies for FMR, including annuloplasty and valve replacement techniques, may offer alternative options to or complement TEER, strategies involving a combination of interventions or a bioprosthetic valve still warrant randomised trials[18].

Conclusions

In patients with FMR, TEER plus GDMT is associated with a significant reduction in death or hospitalisation due to heart failure and hospitalisation due to heart failure compared with GDMT alone. However, the observation of high between-trial heterogeneity translated into non-significant between-group differences in these outcomes when employing more conservative methods. Although a clear numerical trend favouring TEER plus GDMT was observed, all-cause death and cardiovascular death did not significantly differ between treatment groups. The exclusion of MITRA-FR was instrumental in eliciting improved survival in the TEER plus GDMT group compared with the GDMT-alone group. Whether these findings reflect differences in patient selection warrants clarification by further research.

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Guest Editor

This paper was guest edited by Franz-Josef Neumann, MD, PhD; *Department of Cardiology and Angiology, University*

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Conflict of interest statement

D. Capodanno declares speaker fees or honoraria from Daiichi Sankyo, Sanofi, and Terumo. The other authors have no relevant conflicts of interest to declare related to the topic of this manuscript. The Guest Editor reports consultancy fees from Novartis and Meril Life Sciences; and speaker honoraria from Meril Life Sciences.

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Supplementary data

Supplementary Appendix 1. List of included trials.
Supplementary Table 1. PRISMA checklist.
Supplementary Table 2. Search strategy for each database.
Supplementary Table 3. Outcome definitions.
Supplementary Table 4. Inclusion and exclusion criteria in the included trials.
Supplementary Figure 1. Flow diagram and data extraction.
Supplementary Figure 2. Risk-of-bias assessment.
Supplementary Figure 3. Leave-one-out analyses.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-25-00737

Supplementary data

Supplementary Appendix 1. List of included trials.

Mitra-FR[11,22]

Jean-François Obadia, David Messika-Zeitoun, Guillaume Leurent, Bernard Iung, Guillaume Bonnet, Nicolas Piriou, Thierry Lefèvre, Christophe Piot, Frédéric Rouleau, Didier Carrié, Mohammed Nejjari, Patrick Ohlmann, Florence Leclercq, Christophe Saint Etienne, Emmanuel Teiger, Lionel Leroux, Nicole Karam, Nicolas Michel, Martine Gilard, Erwan Donal, Jean-Noël Trochu, Bertrand Cormier, Xavier Armoiry, Florent Boutitie, Delphine Maucort-Boulch, Cécile Barnel, Géraldine Samson, Patrice Guerin, Alec Vahanian, and Nathan Mewton.
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Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation: Outcomes at 2 Years[22].
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COAPT[12,23]

Gregg W. Stone, JoAnn Lindenfeld, William T. Abraham, Saibal Kar, Scott Lim, Jacob M. Mishell, Brian Whisenant, Paul A. Grayburn, Michael Rinaldi, Samir R. Kapadia, Vivek Rajagopal, Ian J. Sarembock, Andreas Brieke, Steven O. Marx, M.D., David J. Cohen, Neil J. Weissman, Michael J. Mack.
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DOI: 10.1056/NEJMoa2300213.

RESHAPE-HF2[6,24]

Stefan D. Anker, Tim Friede, Ralph-Stephan von Bardeleben, Javed Butler, Muhammad-Shahzeb Khan, Monika Diek, Jutta Heinrich, Martin Geyer, Marius Placzek, Roberto Ferrari, William T. Abraham, Ottavio Alfieri, Angelo Auricchio, Antoni Bayes-Genis, John G.F. Cleland, Gerasimos Filippatos, Finn Gustafsson, Wilhelm Haverkamp, Malte Kelm, Karl-Heinz Kuck, Ulf Landmesser, Aldo P. Maggioni, Marco Metra, Vlasis Ninios, Mark C. Petrie, Tienush Rassaf, Frank Ruschitzka, Ulrich Schäfer, P. Christian Schulze, Konstantinos Spargias, Alec Vahanian, Jose Luis Zamorano, Andreas Zeiher, Mahir Karakas, Friedrich Koehler, Mitja Lainscak, Alper Öner, Nikolaos Mezilis, Efstratios K. Theofilogiannakos, Ilias Ninios, Michael Chrissoheris, Panagiota Kourkoveli, Konstantinos Papadopoulos, Grzegorz Smolka, Wojciech Wojakowski, Krzysztof Reczuch, Fausto J. Pinto, Łukasz Wiewiórka, Zbigniew Kalarus, Marianna Adamo, Evelyn Santiago-Vacas, Tobias F. Ruf, Michael Gross, Joern Tongers, Gerd Hasenfuss, Wolfgang Schillinger, Piotr Ponikowski.
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Hospitalization of Symptomatic Patients With Heart Failure and Moderate to Severe Functional Mitral Regurgitation Treated With MitraClip: Insights From RESHAPE-HF2[24]. Journal of American College of Cardiology 2024;84:2347-2363.
DOI: 10.1016/j.jacc.2024.08.027.

Supplementary Table 1. PRISMA checklist.

Section and Topic	Item #	Checklist item	Page
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2-3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2-4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	2-3, Table S4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Table S2, Figure S1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	2-4, Table S2, Figure S1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Figure S1
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	2-4, S8, Figure S1
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	2-4, Table S4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	2-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	2-4, Figure S3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	2-5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	2-5, Figure S1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	2-5, Figure S1
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	2-5, Figure S1,
	13d	Describe any methods used to synthesize results and provide	2-5

Section and Topic	Item #	Checklist item	Page
		a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	2-5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	2-5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	2-5, Figure S3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	2-5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure S1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	2-5, S3-4
Study characteristics	17	Cite each included study and present its characteristics.	6, S3-4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure S3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	7-8, Figure 1, Figure 2, Figure 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	6, Figure S3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	7-8, Figure 1, Figure 2, Figure 3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	7-8, Figure 1, Figure 2, Figure 3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	7-8, Figure 1, Figure 2, Figure 3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	7-8, Figure 1, Figure 2, Figure 3, Figure S3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	7-8, Figure 1, Figure 2, Figure 3
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9-12
	23b	Discuss any limitations of the evidence included in the review.	12
	23c	Discuss any limitations of the review processes used.	12
	23d	Discuss implications of the results for practice, policy, and future research.	9-13
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2-3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2-3

Section and Topic	Item #	Checklist item	Page
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	2-3
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	1
Competing interests	26	Declare any competing interests of review authors.	1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Figure S3

Supplementary Table 2. Search strategy for each database.

Database	Search string	Numbers of results
MEDLINE through PubMed	("Mitral Valve"[Title/Abstract] AND ("Insufficiency"[Title/Abstract] OR "Regurgitation"[Title/Abstract]) AND "Repair"[Title/Abstract] AND "Randomized Controlled Trial"[Publication Type])	144
Scopus	TITLE-ABS(Mitral) AND TITLE-ABS(Insufficiency OR Regurgitation) AND TITLE-ABS(Repair) AND TITLE-ABS(Random*)	477
Web of Science	(TI=(Mitral) OR AB=(Mitral)) AND ((TI=(Insufficiency) OR AB=(Insufficiency)) OR (TI=(Regurgitation) OR AB=(Regurgitation))) AND (TI=(Repair) OR AB=(Repair)) AND (TI=(Random*) OR AB=(Random*))	412
Embase through Ovid	(Mitral.ti. or Mitral.ab.) and (Insufficiency.ti. or Insufficiency.ab. or (Regurgitation.ti. or Regurgitation.ab.)) and (Repair.ti. or Repair.ab.) and (Random*.ti. or Random*.ab.)	794

Supplementary Table 3. Outcome definitions.

	Mitra-FR	COAPT	RESHAPE-HF2
All-cause death	Any death	Any death meeting or not meeting the definitions of cardiovascular death (e.g., death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma).	NR
Cardiovascular death	Cardiovascular mortality was defined as death occurring with any of the following contributing conditions: • heart failure • myocardial infarction • thromboembolism or hemorrhagic stroke • heart arrhythmia and conduction system disturbance • cardiovascular infection, sepsis, endocarditis • tamponade • sudden, unexpected death • other cardiovascular device or intervention failure • death of unknown cause (adjudicated as cardiovascular)	Defined by the VARC 1 as any one of the following: • Any death due to proximate cardiac cause (e.g. MI, cardiac tamponade, worsening heart failure), or • Unwitnessed death and death of unknown cause, or • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure, or • Death caused by non-coronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease	Cardiovascular death is defined by the Valve Academic Research Consortium (VARC)76 as any one of the following: • Any death due to proximate cardiac cause (e.g. MI, cardiac tamponade, worsening heart failure) • Unwitnessed death and death of unknown cause • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • Death caused by non-coronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease
Hospitalization due heart failure	The definition for unplanned heart failure hospitalization requires: 1) hospitalization for worsening heart failure for >24 h; and 2) administration of intravenous or mechanical heart failure therapies, especially loop diuretics; or 3) heart failure symptoms/signs. The diagnosis of heart failure is on the basis of at least two of these items: 1) symptoms of worsening heart failure such as increased dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue and/or history of weight gain;	Defined as an event that meets the following criteria: A) Requires hospitalization with treatment in any inpatient unit or ward in the hospital for at least 24 hours, including emergency department stay; B) Subject has clinical signs and/or symptoms of heart failure, including new or worsening dyspnea, orthopnea, paroxysmal nocturnal dyspnea, increasing fatigue, worsening functional capacity or activity intolerance, or signs and/or symptoms of volume overload; C) Results in intravenous (e.g., diuretic or vasoactive therapy) or invasive (e.g., ultrafiltration, IABP, mechanical assistance) treatment for heart failure. For the purpose of the Clinical Investigational Plan,	Defined as an event that meets the following criteria: A) Any presentation at a hospital or urgent treatment center requiring completion of the hospital admission procedures or equivalent and/or at least an overnight stay or until death of the patient, or B) An unplanned treatment given in an outpatient setting in which an IV diuretic and/or IV vasodilator and/or IV inotrope is administered, and Presence of all the following criteria: 1a) New or increased symptoms of heart failure (e.g., shortness of breath/dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea,

	2) physical examination evidence of worsening heart failure such as neck vein distention, pulmonary rales, ascites or pedal edema, and/or hypotension or signs of worsening end-organ perfusion; and/or 3) diagnostic evidence of worsening heart failure such as radiographic pulmonary congestion, natriuretic peptide levels greater than the upper limit of normal.	overnight stays at nursing home facilities, physical rehab or extended care facilities, including hospice, do not meet the Clinical Investigational Plan definition of hospitalization. All hospitalizations, including the index hospitalization for the MitraClip procedure, if complicated by acute worsening heart failure that would have prompted an admission to hospital for heart failure, and requires intravenous or invasive treatment and hospitalization is extended by 24 hours, as defined above, will also be considered a heart failure hospitalization. Elective heart failure "tune-ups" that occur following the MitraClip procedure and prolong hospitalization will not count as a heart failure hospitalization. D) Subject arrives in emergency department with clinical presentation meeting the criteria of heart failure but dies in the emergency department before hospital admission. Patients admitted for an LVAD or heart transplant will also be considered to have had a heart failure hospitalization.	fatigue/reduced exercise tolerance, pulmonary edema, jugular venous distension (JVD), rales, S3, hepatojugular reflux, altered hemodynamics, peripheral edema, cardiomegaly) 2a) New or increasing signs of heart failure including signs of fluid retention (e.g., pulmonary rales, elevated JVD, peripheral edema, increased weight), or objective evidence of heart failure (e.g., pulmonary edema/congestion in chest X ray, elevated natriuretic peptide) 3b) Change in heart failure therapy defined as initiation of intravenous diuretics and/or vasodilators and/or inotropes (excluding cardiac glycosides) or mechanical ventilation or mechanical support (intra-aortic balloon pump ventricular assist device), or 1b) Patient is hospitalized as a result of another cause but associated with worsening heart failure at the time of admission

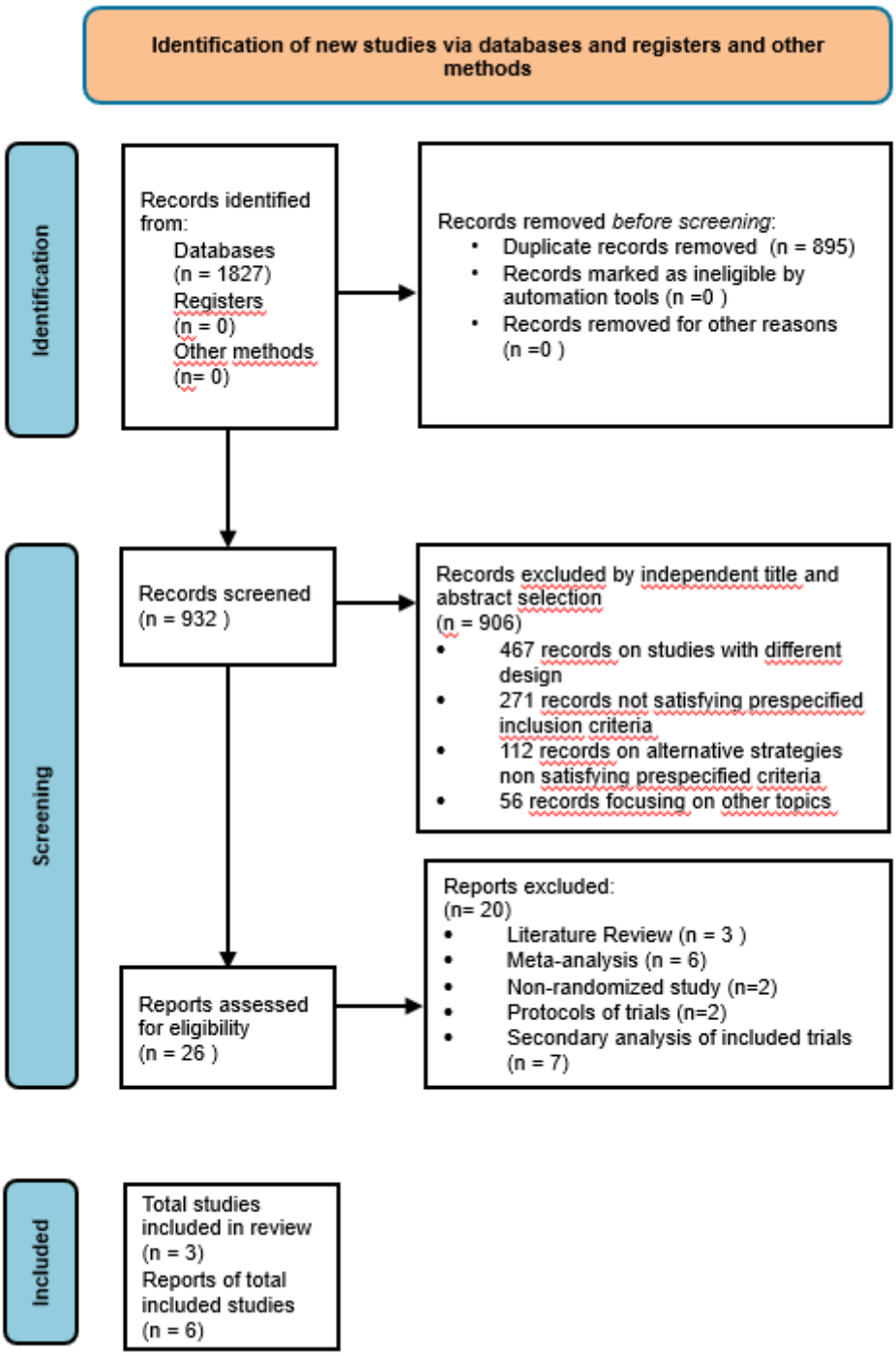
ED, emergency department; HF, heart failure; IABP, intra-aortic balloon pump; IV, intravenous; LVAD, left ventricular assist device; MI, myocardial infarction; PCI, percutaneous coronary intervention; VARC, Valve Academic Research Consortium.

Supplementary Table 4. Inclusion and exclusion criteria in the included trials.

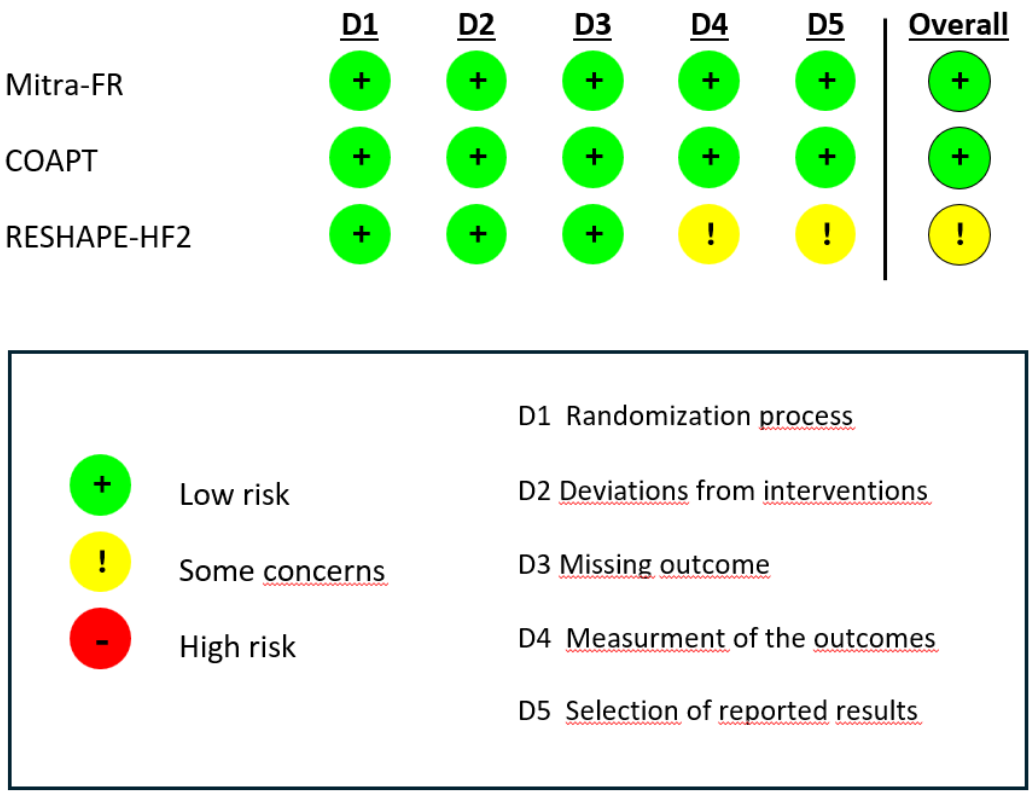
	Mitra-FR	COAPT	RESHAPE-HF2
Inclusion Criteria	• Age >18; • Severe secondary MR (regurgitant volume >30 mL/beat • EROA >20 mm²); • NYHA Class ≥ II; ≥ 1 • HF hospitalization < 12 mo; • LVEF between 15% and 40%; OMT for HF; • Not eligible for MV surgery: • Willingness to participate (signed informed consent); • Affiliation to a health insurance system	•Age ≥ 18; •Symptomatic secondary MR (3+ or 4+) from ischemic/non-ischemic cardiomyopathy; •OMT for CAD, LV dysfunction, MR, HF; •NYHA II, III or ambulatory IV; • ≥ 1 HF hospitalization < 12 mo or corrected BNP ≥ 300/NT-proBNP ≥ 1500; •Not eligible for MV surgery; •LVEF 20–50%, LVESD ≤70 mm; •Non-commissural jet feasible for MitraClip; • CK-MB < ULN; • Feasible transseptal & femoral access; •Written informed consent.	• Age 18–90; • Clinically significant FMR (3+ or 4+) confirmed by core lab < 90 days; • On OMT w/ stable doses (except diuretics) during the last 2 weeks; • Symptomatic (NYHA ≥ II) < 30 days before randomization; • ≥ 1 HF hospitalization < 12 mo or BNP ≥ 300 pg/mL or NT-proBNP≥ 1000 pg/mL after OMT; • Symptomatic CHF (NYHA ≥ II) w/ LVEF 20–50%; • 6MWT feasible (unless NYHA IV); • Written informed consent provided and commitment to follow-up
Exclusion Criteria	• Eligible for MV surgery; Primary MR; MI or CABG < 3 months; • CRT < 3 months; Cardioversion < 3 months; • TAVI < 3 months; • Need for any CV surgery (including transplant list); • PCI < 1 month; • Previous surgical MV repair; • RRT; • Active infection needing antibiotics; • Severe hepatic insufficiency; • Stroke < 3 months; • Life expectancy <12 months; • Uncontrolled arterial hypertension; • Hypersensitivity to nitinol; • Participation in another trial; • Pregnancy; • No health insurance; • Under legal protection (guardianship/curatorship); Any Corelab assessment outside predefined parameters; Anatomically not suitable for MitraClip (per Abbott proctor)	•Untreated significant CAD needing revascularization; • CABG/PCI/TAVR <30 days; •Aortic/tricuspid disease needing intervention; • COPD requiring O2 or chronic steroids); •Stroke <30 days; •Severe carotid stenosis (>70%) or carotid surgery <30 days; •ACC/AHA stage D HF; Estimated PASP >70 mmHg; •Restrictive/HOCM/pericardial/infiltrative cardiomyopathy; •Hemodynamic instability w/ SBP<90 mmHg or shock (inotropes or mechanical support); •RV failure w/ right-sided HF; CRT <30 days; •MV orifice <4.0 cm²; Leaflet anatomy unsuitable for MitraClip; •Need for emergent or urgent surgery; •Planned cardiac surgery <12 mo; •Life expectancy <12 mo; Modified Rankin ≥ 4; •Status 1 or prior heart transplant; •Prior MV surgery/prosthesis; •Intracardiac mass/thrombus/vegetation; •Active endocarditis/rheumatic disease;	• MR primarily due to degenerative disease; • Status 1 heart transplant or prior HTx; • New HF drug class introduced in past 2 weeks; • ACS, TIA, or stroke < 90 days; • Any PCI, CV surgery, or AF ablation < 90 days; • Implant/revision of a rhythm device < 90 days; • Need for CV surgery; MV surgery is the preferred option; • RRT; • Uncontrolled HTN (BP >180/105) or hypotension (BP <90 systolic); • Unstable angina or significant uncorrected valvular/other CV disease; • 6MWT >475 m; MVA <3.0 cm² (or borderline per criteria); • Leaflet anatomy unsuitable for MitraClip; • IVC filter or ipsilateral DVT present; • Contraindication to transseptal catheterization/TEE; • Intracardiac mass, thrombus, or vegetation detected; • Active endocarditis or RHD; • Severe AS/AR or other structural heart disease (except DCM) causing HF, or

		• Active infection needing antibiotics; • TEE contraindicated/high risk; • Hypersensitivity to required meds; • Pregnancy or planned <12 mo; • Ongoing investigational study; • Vulnerable population or no informed consent	hemodynamic instability requiring support; • Active infection requiring antibiotics; • Known hypersensitivity/contraindication to procedural meds; • Severe RV failure or severe TR; • History of bleeding diathesis or refusal of blood transfusion; • Pregnancy or planned pregnancy < 12 months; • Life expectancy <12 months; • Participation in another investigational study; • Belonging to a vulnerable population preventing proper consent

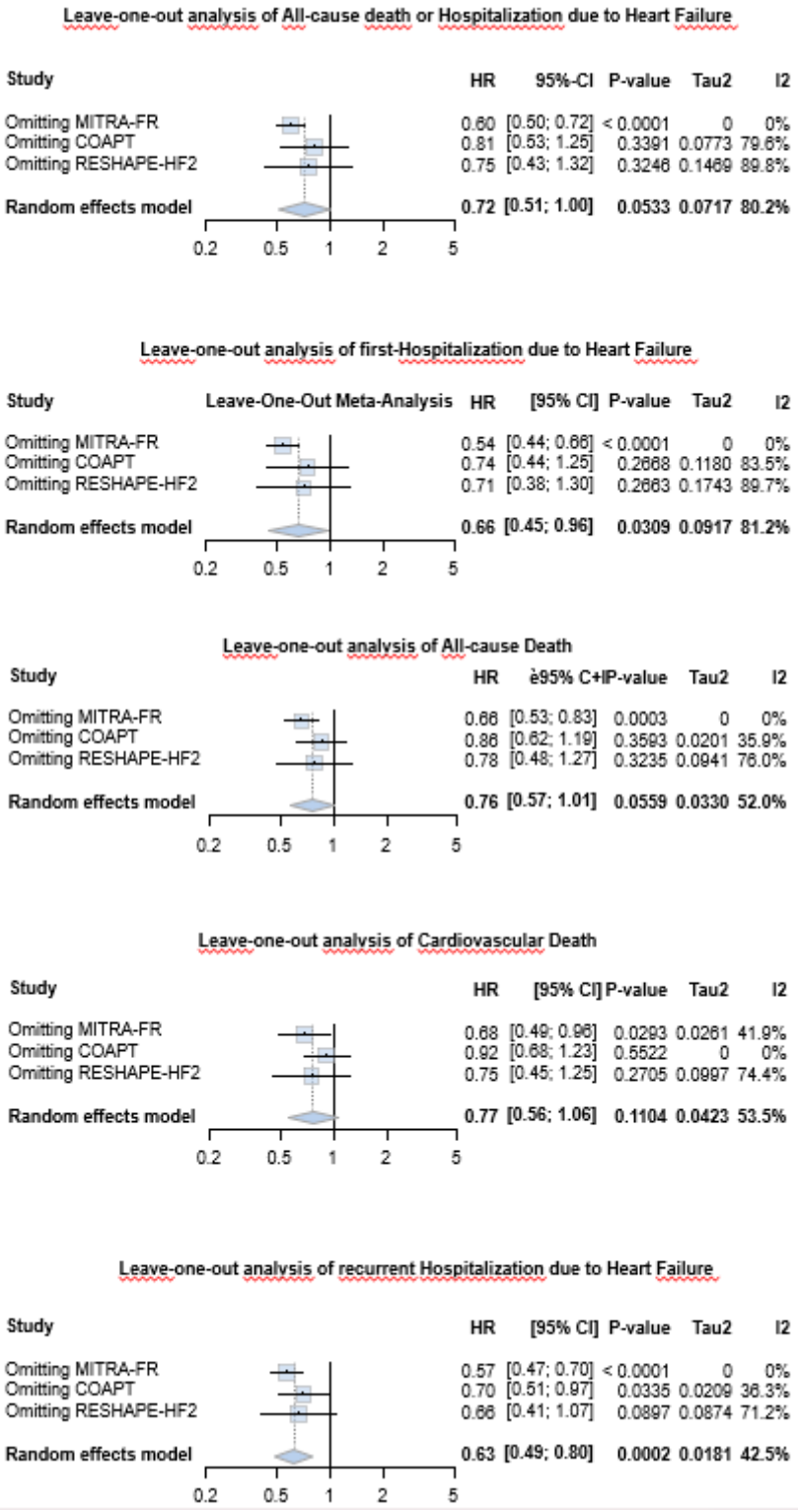
ACS, acute coronary syndrome; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CK-MB, creatine kinase-MB isoenzyme; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DCM, dilated cardiomyopathy; DVT, deep vein thrombosis; HF, heart failure; HOCM, hypertrophic obstructive cardiomyopathy; HTN, hypertension; HTx, heart transplantation; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation; MV, mitral valve; MVA, mitral valve area; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; RHD, rheumatic heart disease; RRT, renal replacement therapy; RV, right ventricle; SBP, systolic blood pressure; TAVI, transcatheter aortic valve implantation; TAVR, transcatheter aortic valve replacement; TEE, transesophageal echocardiography; TIA, transient ischemic attack; TR, tricuspid regurgitation; ULN, upper limit of normal; 6MWT, 6-minute walk test.



Supplementary Figure 1. Flow diagram and data extraction.



Supplementary Figure 2. Risk-of-bias assessment.



Supplementary Figure 3. Leave-one-out analyses.