Meta-Analysis of Relation Between Left Ventricular Dysfunction and Outcomes After Transcatheter Mitral Edge-to-Edge Repair

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Randomized controlled trials (RCTs) and observational studies provided conflicting results regarding the role of left ventricular (LV) function on outcomes after transcatheter edge-to-edge repair (TEER). The study aimed to provide a comprehensive assessment of the interplay between severe LV dysfunction and TEER outcomes. Multiple electronic databases, including PubMed, EMBASE, Scopus, Web of Science, and CENTRAL, were searched to identify studies on TEER for secondary mitral regurgitation reporting outcomes stratified for LV ejection fraction <30% and ≥30%. The prespecified primary end points were the composite of all-cause death or heart failure (HF) hospitalization and New York Heart Association (NYHA) class III/IV. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by random-effects models. Multiple sensitivity analyses accounting for baseline characteristics and study design were applied. A total of 6 studies (1,957 patients) with 1 year or 2 years of follow-up were available. Severe LV dysfunction was associated with an increased risk of death or HF hospitalization (OR 1.71, 95% CI 1.14 to 2.57). Conversely, comparable rates of NYHA class III/IV (OR 1.06, 95% CI 0.82 to 1.38) or secondary end points (reinterventions, recurrence of significant secondary mitral regurgitation) were found regardless of the baseline LV function. Subgroup meta-analysis found no difference in the composite primary end point between patients with LV ejection fraction <30% and ≥30% enrolled in RCTs. In conclusion, TEER seems to be associated with higher mortality or HF hospitalization rates in patients with severe LV dysfunction. However, RCTs found no differences between groups. No impact of LV function was found on the risk of NYHA class III/IV or other clinical outcomes. **(Am J Cardiol 2022;175:88−96)**

Introduction

Although left ventricular (LV) ejection fraction (LVEF) is a known predictor of adverse outcomes after cardiac and noncardiac surgery, randomized controlled trials (RCTs) showed no impact of LV dysfunction on transcatheter edge-to-edge repair (TEER) outcomes.[1−5] Whether this finding can be validated in the real world, where strict selection criteria cannot always be applied, needs to be quantitatively assessed.[6] A more profound understanding of this interplay can ultimately improve the assessment of patient profile and proper timing to benefit the most from TEER. In this background, we performed a comprehensive meta-analysis to provide a quantitative assessment of evidence regarding the safety and efficacy of MitraClip (Abbott Vascular, California) implantation according to baseline LV dysfunction in patients with heart failure (HF) and secondary mitral regurgitation (SMR).

Methods

This meta-analysis is registered in PROSPERO (International prospective register of systematic reviews; CRD42020219951) and was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and the Meta-analysis Of Observational Studies in Epidemiology group (Supplementary Method 1).[7,8] Randomized trials and observational studies on TEER with MitraClip in patients with SMR were evaluated for inclusion in this meta-analysis. Studies were considered eligible if they satisfied all the following prespecified criteria: (1) they reported clinical data after TEER with the MitraClip device; (2) the reported outcomes were stratified for severely reduced and nonseverely reduced LVEF (i.e., LVEF <30% and LVEF ≥30%); (3) they included at least 50 patients; (4) there were no overlapping populations; (5) there was a minimum 12-month follow-up time. No publication date or publication status restrictions were applied.

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A systematic search of the literature was performed in PubMed, EMBASE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials from database inception up to the final search date of November 15, 2020. In addition, the reference lists of previous systematic reviews and included articles were screened to find further potentially relevant studies (backward snowballing). The search strings are available in Supplementary Method 2. Two reviewers (AS, MM) independently searched the electronic bibliographic databases. After removing duplicates, the title and abstract were screened to exclude nonrelevant studies; subsequently, the full text of the remaining results was retrieved for further appraisal. Discrepancies were discussed and resolved with a senior reviewer (CG). A dedicated electronic database was used for data extraction and included: sample size, baseline characteristics of patients, follow-up time, and outcome measures. Missing data were provided by the corresponding authors (MiZüBr) and by Abbott (ACCESS-EU) where available. Two independent reviewers (AS, MM) performed the study-level qualitative assessment of the risk of bias for randomized trials and observational studies.[9,10] All studies included had appropriate ethical oversight and approval.

The prespecified coprimary end points were as follows: (1) the composite of all-cause death or HF hospitalization; (2) a New York Heart Association (NYHA) functional class III or IV at follow-up. Secondary end points were all-cause death, HF hospitalization, mitral valve re-intervention (surgical or percutaneous), and mitral regurgitation (MR) grade >2+.

A random-effects model using the "empirical Bayes" (Paule-Mandel) estimator was applied.[11] Study-level and pooled estimates were reported as odds ratios (ORs) and 95% confidence intervals (CIs). If available, collecting the numbers of actual observations at follow-up was preferred over the whole sample size, avoiding assumptions about any participants for whom the outcome was not measured.[12] Baseline characteristics were also presented as pooled weighted means or incidences and 95% CIs. Whenever applicable, mean ± SD was calculated from the reported median and interquartile range according to Wan et al.[13] Statistical heterogeneity was assessed using the Cochran Q statistic and I^2 values. I^2 values of <25%, 25% to 50%, or >50% were indicative of low, moderate, or high heterogeneity, respectively.[14] Publication bias and small study effect were assessed by visual inspection of funnel plots and using Begg's test. The potential interaction between study design (RCTs vs observational studies) and treatment effect was investigated with subgroup analyses for the primary end points. For this purpose, a random-effects meta-regression analysis with the Hartung-Knapp-Sidik-Jonkman adjustment was performed.[15] Meta-regressions were performed to evaluate the potential impact of several characteristics (year of publication, estimated risk of bias, age, systolic pulmonary artery pressure, LV end-diastolic diameter, SMR grade, NYHA class, the prevalence of male patients, diabetes mellitus, atrial fibrillation, hypertension, and ischemic SMR) on the outcomes of interest at follow-up. A leave-one-out sensitivity analysis was conducted to show how each study might affect the overall estimate. Further sensitivity analyses included the calculation of ORs with 95% CIs using a fixed-effects model with the Mantel-Haenszel method and the calculation of risk ratios with 95% CIs with both fixed-effects and random-effects models. To account for heterogeneity in follow-up, we calculated the incidence rate ratios using patients/year and a mixed-effects Poisson regression model with random study effects. Statistical significance was set at $p < 0.05$ (2-sided). All analyses were performed with R Software Version 4.0.2 (R Foundation, for Statistical Computing, Vienna, Austria) packages meta and metafor.

Results

Search strategy results and study selection process are illustrated in Figure 1 and Supplementary Method 2. A total of 2 RCTs and 4 observational studies were found to be eligible for inclusion in our meta-analysis. The main features of included studies are listed in Supplementary Table 1, Table 1. The follow-up duration was 2 years for the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) RCT,[4] for the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) RCT,[16] and the MiZüBr (Milan-Zürich-Brescia) registry,[17] whereas the ACCESS-EU (A Two-Phase Observational Study of the MitraClip® System in Europe),[18] Pascual et al,[19] and the TRAMI (transcatheter mitral valve interventions) registry[20] reported 1-year outcomes. A total of 1,957 patients with SMR who underwent TEER with the MitraClip device were analyzed. Of them, 433 patients were enrolled in RCTs, whereas 1,524 patients were included in observational studies. The baseline characteristics of the study populations are listed in Table 2. The mean age was 72 (71-74) years, and most (73% [68-77]) were male. Almost all patients had a moderate-to-severe or severe SMR, whose etiology was ischemic in 2/3 (64% [55-71]). The proportion of patients with NYHA class III/IV was lower in RCTs compared with observational studies. The risk of bias was assessed for every RCT and observational study as listed in Supplementary Tables 2 and 3, respectively. Included studies were equally distributed between the low and moderate risk of bias, with no domain having a high risk of bias. Visual inspection of funnel plots and the Begg and Mazumdar rank correlation tests indicated the absence of significant publication bias and small study effects for all the outcomes, Supplementary Figure 1.

The presence of severe LV dysfunction was associated with an increased risk of all-cause death or HF hospitalization (OR 1.71, 95% CI 1.14 to 2.57), with a moderate degree of heterogeneity (I^2 46%). Conversely, the proportion of NYHA class III/IV did not differ regardless of the degree of LV function (OR 1.06, 95% CI 0.82 to 1.38), with heterogeneity that was not detectable (I^2 0%), Figure 2. Secondary end points are illustrated in Figure 3. As well as the primary composite end point, the occurrence of its components, all-cause death (OR 1.84, 95% CI 1.22 to 2.79, I^2 60%), and HF hospitalization (OR 1.83, 95% CI 1.40 to 2.38, I^2 0), was increased in the group with LVEF <30%. Conversely, no differences were found in the rates of recurrent MR grade >2+ (OR 0.94, 95% CI 0.61 to 1.45, I^2 23%)

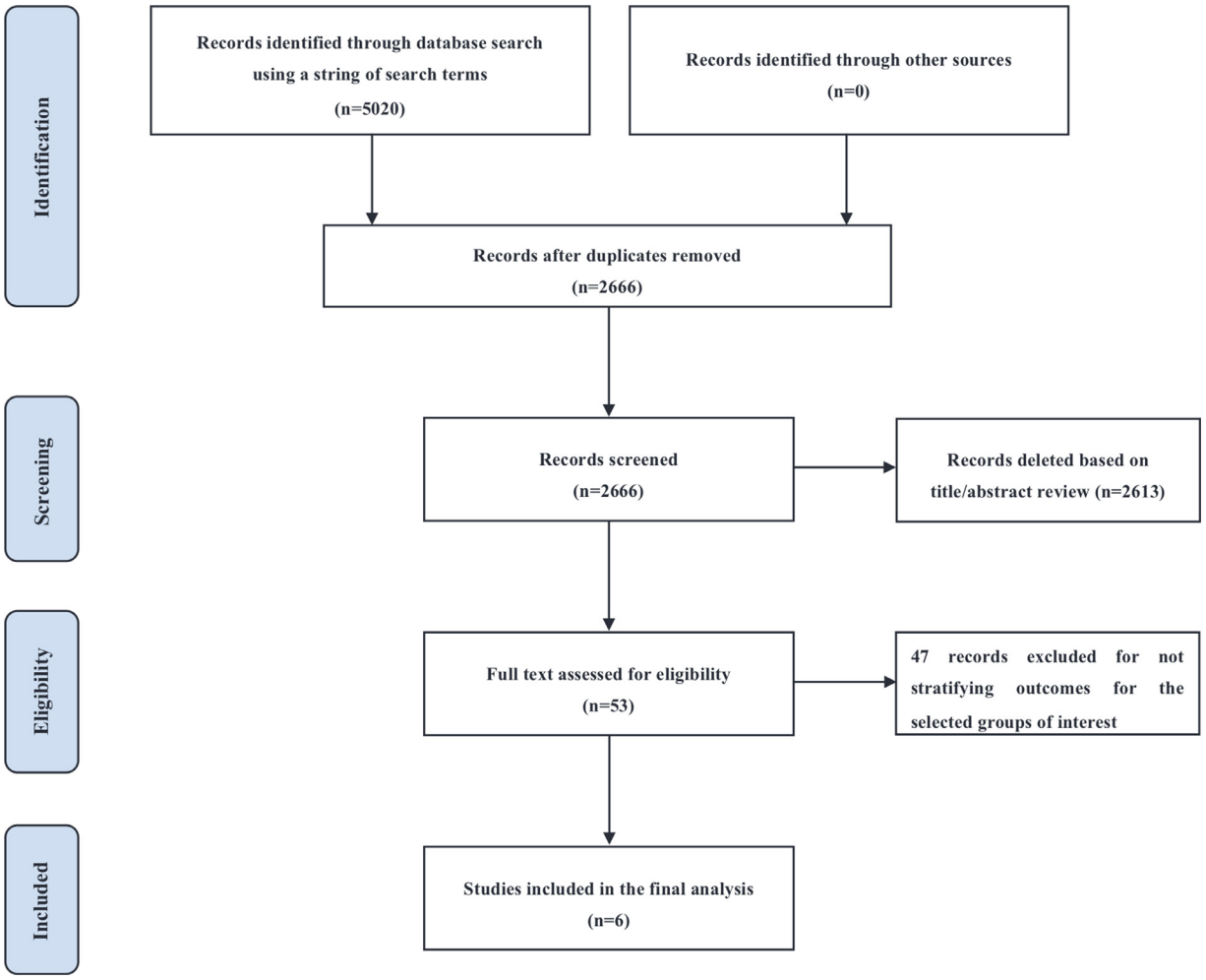

Figure 1. Flow chart of the study selection progress.

and mitral valve reinterventions (OR 0.54, 95% CI 0.24 to 1.21, I^2 0).

A subgroup analysis of the primary composite end point stratifying for the study design (i.e., RCT vs observational studies) showed findings consistent with the primary analysis in the observational group (OR 2.42, 95% CI 1.60 to 3.68, I^2 0), whereas no differences in the rates of outcome were observed in RCTs (OR 1.23, 95% CI 0.82 to 1.84, I^2 0), Figure 4. Indeed, meta-regression analysis detected a significant impact of study design and baseline NYHA class III/IV, which was most represented in observational studies, on treatment effect, explaining all the estimated heterogeneity (β −0.681 [CI −1.126 to −0.235] and β 0.029 [CI 0.001 to 0.057], respectively), Supplementary Table 4. Additional meta-regression analysis found no significant interactions between baseline clinical and echocardiographic characteristics, year of publication, and risk of bias with treatment effect (Supplementary Figure 2, Supplementary Table 4).

Table 1
Key features of 6 multicenter studies

Study	Year of publication	Study design	N of patients			Follow-up (months)
			Overall	LVEF <30%	LVEF ≥30%	
ACCESS-EU [18]	2016	Observational	388	172	216	12
MiZüBr [17]	2018	Observational	302	151	151	24
TRAMI [20]	2018	Observational	546	208	338	12
COAPT [4]	2018	RCT	281*	121†	140†	24
MITRA-FR [5]	2019	RCT	152	37	115	24
Pascual et al [19]	2020	Observational	288	144	144	12

* Data on ejection fraction were available for 281/302 patients.
† Patients available at 24-month follow-up.
LVEF = left ventricular ejection fraction; RCT = randomized controlled trial.

Table 2
Baseline characteristics of included patients

Study	Age (years)	Male	Diabetes	Hypertension	Atrial fibrillation	NYHA III/IV	Ischemic etiology	sPAP (mmHg)	LVEDD (mm)	MR ≥3	N. of clips implanted per patient
ACCESS-EU [18]	73±9	68%	34%	76%	63%	85%	42%	43±14	64±13	100%	1.5±0.6
MiZüBr [17]	72±10	76%	32%	67%	47%	78%	68%	46±15	67±10	100%	1.8±0.7
TRAMI [20]	75±7	62%	31%	79%	45%	89%	76%	44±16	61±11	96%	1.4±0.6
COAPT [4]	72±12	67%	35%	80%	57%	57%	61%	44±13	62±7	100%	1.7±0.7
MITRA-FR [5]	70±10	79%	33%	-	34%	63%	62%	-	69±8	100%	-
Pascual et al [19]	72±10	79%	33%	79%	57%	88%	65%	-	-	100%	1.5±0.6
Pooled estimates: mean/incidence (95% CI)	72 (71-74)	73% (68-77)	33% (31-36)	76% (70-82)	52% (44-60)	80% (70-87)	64% (55-71)	44 (43-45)	65 (62-67)	100% (97-100)	1.6 (1.4-1.7)

CI = confidence interval; LVEDD = left ventricular end-diastolic diameter; MR = mitral regurgitation; NYHA = New York Heart Association; sPAP = systolic pulmonary artery pressure.

Results obtained with the calculation of OR using a fixed-effects model and risk ratio with both fixed-effects and random-effects were consistent with the primary analysis for every investigated outcome, Supplementary Figures 3 and 4. Leave-one-out and cumulative meta-analyses were used to attest to and confirm the significant impact of observational studies on heterogeneity and composite primary end point, Supplementary Figure 5. When accounting for different follow-up times using the incidence rate ratio (patients/year), we found no differences with the primary analysis for every explored outcome, Supplementary Figure 6.

Discussion

The present meta-analysis investigated the impact of LV dysfunction on clinical outcomes after TEER for SMR. The main findings of this study can be summarized as follows:

1 The risk of death or HF hospitalization and its individual components was higher in patients with severe LV dysfunction (LVEF <30%);
2 No differences were detected in terms of functional status (NYHA class III/IV), recurrence of significant MR (>2+), and need for further mitral valve interventions;
3 When accounting for the RCT design, baseline LV function had no significant impact on the composite primary end point rates.

The presence of SMR has been historically found to be associated with increased mortality regardless of the degree of LV dysfunction.[21] Even patients with less severe HF exhibit a greater risk of death when affected by moderate-to-severe or severe SMR.[22] In patients with severe coronary artery disease and significant SMR, surgical mitral valve repair does not confer a survival benefit when added to coronary bypass artery grafting.[23] Further studies, including only patients with severe LV dysfunction who underwent isolated surgical mitral valve repair for SMR or combined with surgical coronary revascularization, reported conflicting results.[24,25] Therefore, given the absence of a clear independent prognostic benefit and the substantial risk of complications, mitral valve surgery for SMR is not frequently performed.[24,26,27] Almost half of the symptomatic patients presenting with severe SMR are denied surgery and an impaired LV function is one of the most advocated reasons.[28]

The advent of TEER therapies has provided a less invasive solution to the unmet need for SMR reduction. TEER with the MitraClip is the most commonly performed procedure, with a large body of literature supporting its results in terms of SMR reduction and clinical outcomes. Nevertheless, whether preoperative LV dysfunction may impact patient outcomes after TEER has been poorly investigated. Contrasting results regarding the prognostic role of LV dysfunction are evident based on the study design. The RCTs on TEER have found no differences when stratifying patients for their baseline LV function.[4,5] Conversely, pooled results from 4 observational studies show an association between the occurrence of the previously mentioned end points and severe LV dysfunction.[17–20] These discrepancies deserve an appropriate interpretation and need to be

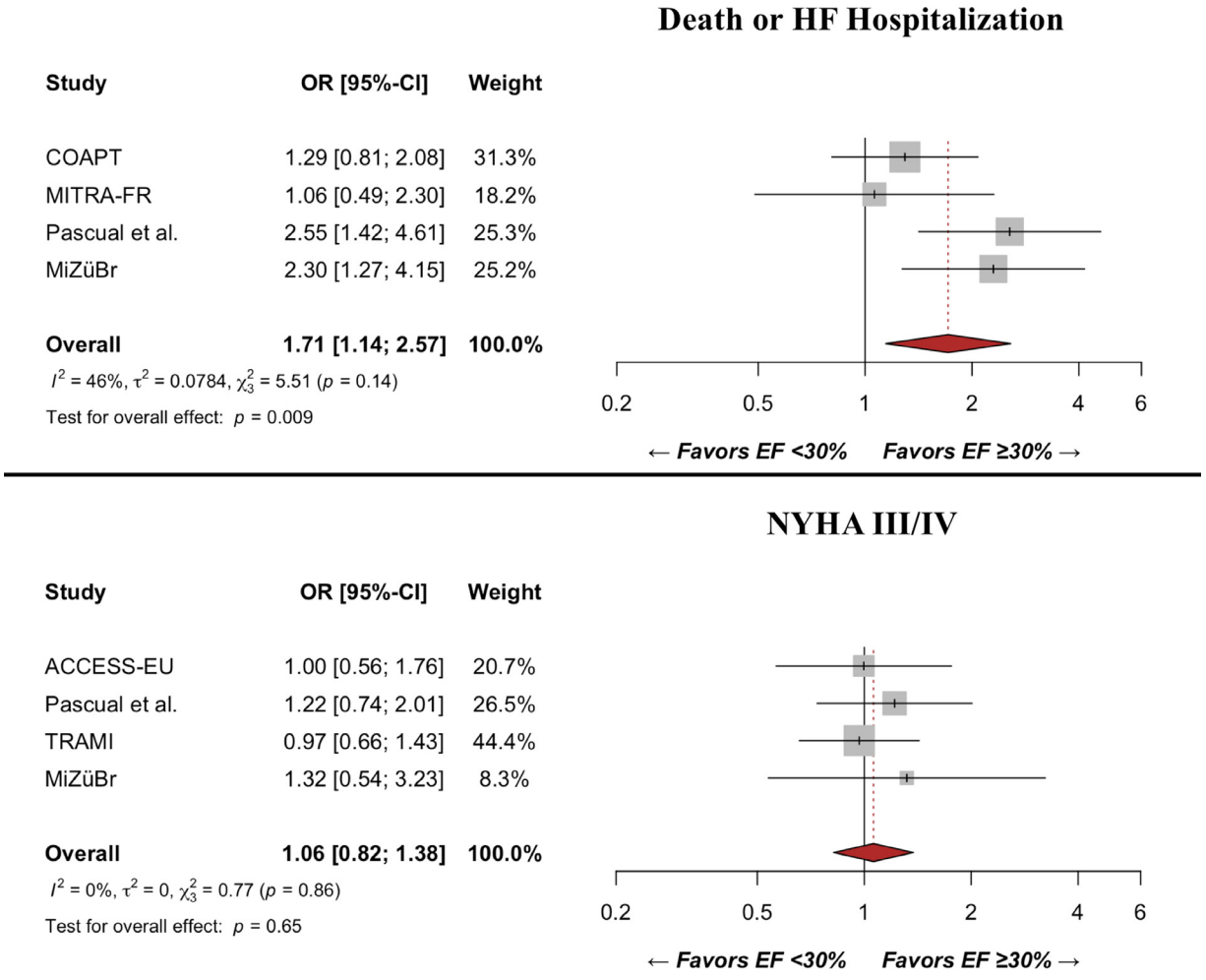

Figure 2. Primary end points. Forest plots of primary end points assessed with random-effects models. EF = ejection fraction.

reconciled to avoid prognostic and therapeutic uncertainties. LV dysfunction, identified as severely depressed LVEF (i.e., <30%), is a well-known independent predictor of poor operative outcomes after cardiac and noncardiac surgery.[1–3] Therefore, guideline recommendations strongly recommend early intervention before LV dysfunction occurs.[29] It is surprising that the RCTs found no impact of LVEF on outcomes in patients who underwent TEER. This

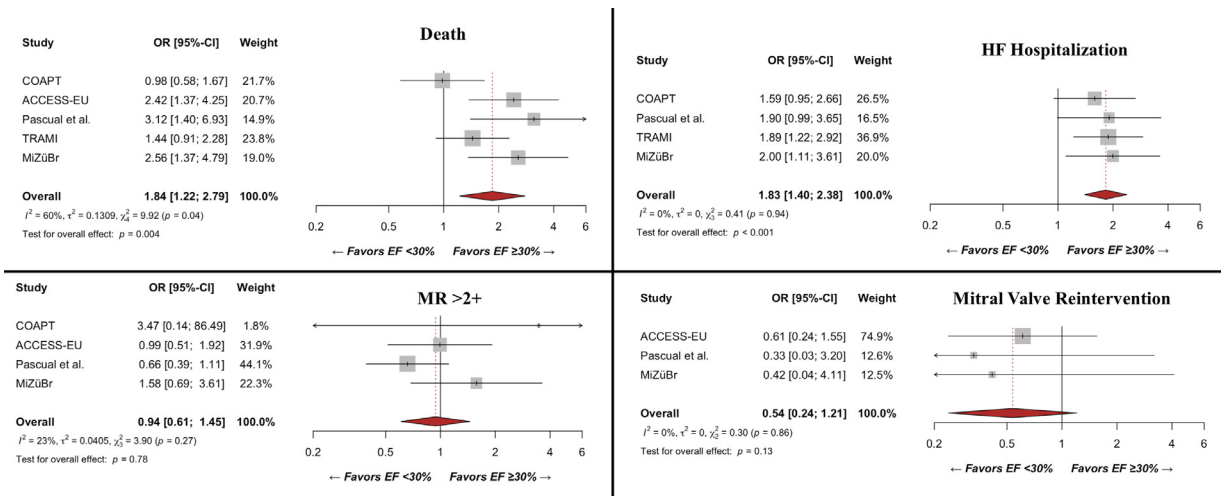

Figure 3. Secondary end points. Forest plots of secondary end points assessed with random-effects models. EF = ejection fraction.

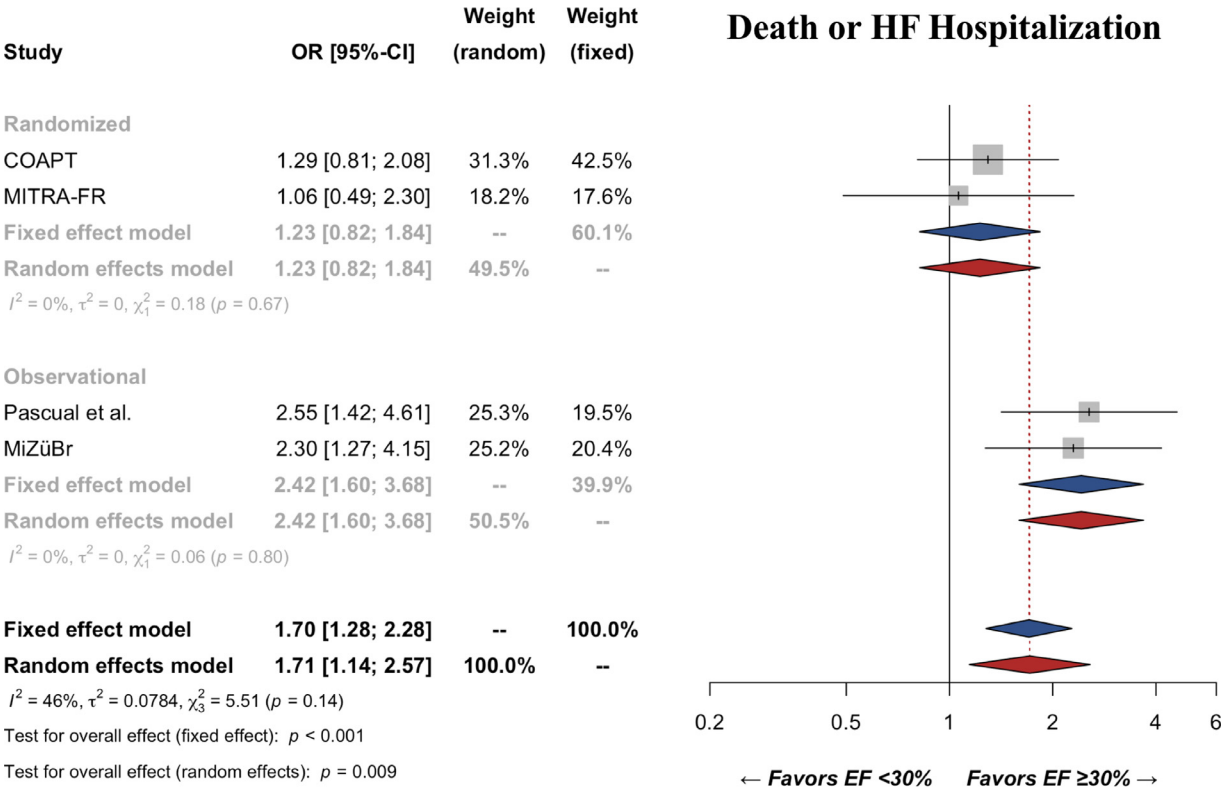

Figure 4. Subgroup meta-analysis for study design. Forest plot of subgroup meta-analysis investigating the impact of study design on the composite primary end point assessed with fixed-effects and random-effects models. EF = ejection fraction.

controversy may arise from differences in the enrolling criteria of the studied populations. Although RCTs have included only patients with LVEF of 15% to 40%[5] or 20% to 50%,[4] observational studies have not applied such an entry criterion, including also patients with midrange LVEF (40% to 49%) and preserved LVEF (>50%), Figure 5. Amputating the tail values of the LVEF distribution in selected patients of RCTs (striped areas; Figure 5) may have nullified the prognostic effect of LV function. Treating patients with less impaired or preserved LV function may have resulted in better outcomes for the group with LVEF >30% of observational studies. Beyond better LV function alone, valvular disease in this group may have had a different underlying etiology, such as atrial MR caused by annular dilatation because of atrial fibrillation (atrial functional MR) or HF with preserved LVEF. Indeed, atrial functional MR is associated with significantly better outcomes than ventricular functional (secondary) MR after both surgical and transcatheter procedures.[30,31] Moreover, unlike RCTs, observational studies might have included TEER procedures in extremely frail patients with very low LVEF (i.e., <15% to 20%) in the context of a compassionate strategy or with the aim of bridging therapy whenever a prognostic benefit could not be expected.[32] This may have further widened the gap between patients with and without severe LV dysfunction in the observational studies, thus highlighting the prognostic role of LV dysfunction. Even when a prognostic benefit is uncertain, patients with advanced HF can greatly benefit from TEER for the following reasons: hemodynamic stabilization, symptomatic relief, normalization of pulmonary arterial pressures, and reduction in HF hospitalizations.[33]

The persistent symptomatic improvements and long-lasting results, represented by NYHA functional class status and residual SMR, were not affected by baseline LV function. Similarly, the numbers of re-interventions on the mitral valve were not significantly different between the 2 studied groups (LVEF <30% and LVEF ≥30%). Although severe LV dysfunction makes patients less appropriate surgical candidates, this seems not to be influential in those who underwent TEER.

The results of the present meta-analysis have to be interpreted, acknowledging the following limitations. This is a study-level meta-analysis, and its findings are average treatment effects. Since a patient-level analysis was unfeasible, we could not evaluate the distribution and effect of baseline characteristics in the studied groups (LVEF <30% and LVEF ≥30%) or the LVEF as a continuous variable. Including RCTs and observational studies that may differ in patient selection criteria and medical therapy optimization, has resulted in expected heterogeneity and conflicting results for the composite of all-cause death or HF hospitalization. Nevertheless, the cost of increasing heterogeneity by including observational studies is offset by having a "real life" view of TEER performance that helps design future studies (e.g., to investigate patients with extremely impaired LV function or having HF with preserved LVEF and/or atrial functional MR). Meta-regression analyses of the tested variables on effect estimates have a limited number of studies and should be considered hypothesis-

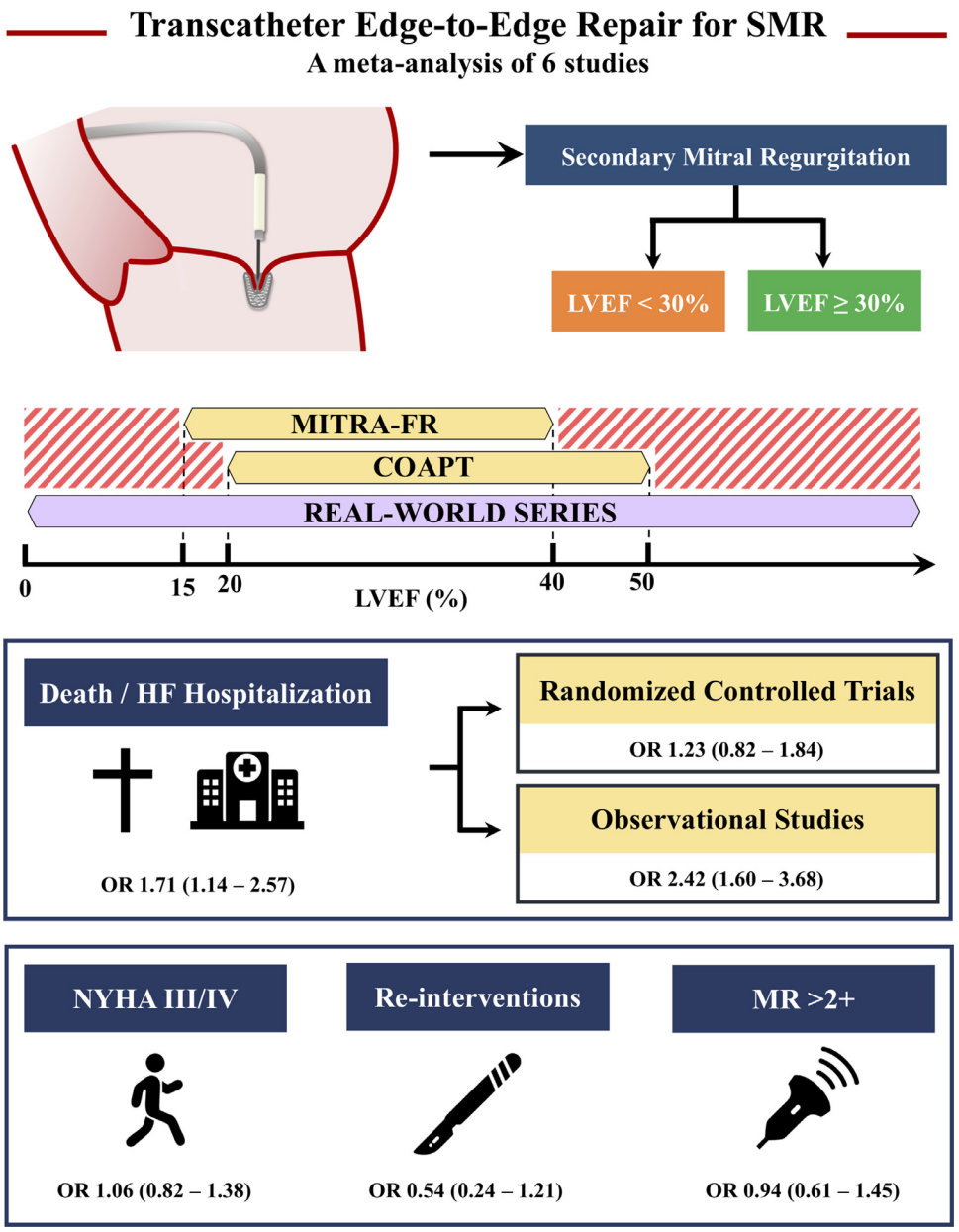

Figure 5. Central Figure: the included studies investigated the outcomes of transcatheter edge-to-edge repair with the MitraClip in patients with LVEF <30% versus ≥30%. The distributions of LVEF in the study populations show some differences: whereas the observational studies included the full range of LVEF values, the RCTs excluded those <15% to 20% and >40% to 50% *(striped areas)*. The ORs and CIs of the analyzed outcomes are reported under the central figure.

generating. Considering the hemodynamics of severe SMR with its afterload-reducing effect, it is reasonable to understand how this mechanism translates into an underestimation of the LV systolic dysfunction using only LVEF.[34] However, this measure is the most easily obtainable and widely used to stratify patients with SMR in previous surgical and transcatheter studies.

In conclusion, our study suggests that TEER with MitraClip could be more effective in reducing all-cause death or HF hospitalization in patients without severe LV dysfunction. In RCTs, baseline LV function had no impact on the primary composite end point. No differences were found in terms of NYHA class status, recurrence of significant SMR, and reoperations on the mitral valve.

Disclosures

The authors have no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.03.059.

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