Percutaneous Mitral-Valve Intervention for Secondary Mitral Regurgitation: Data From Real-Life

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Abstract: Many questions were raised due to the divergent results between cardiovascular outcomes assessment of the MitraClip percutaneous therapy for heart failure patients with functional mitral regurgitation (COAPT) and multicenter study of percutaneous mitral valve Repair MitraClip device in patients with severe secondary mitral regurgitation (MITRA-FR) trials on the use of percutaneous mitral valve repair for secondary mitral regurgitation. This paper examined pooled patients' characteristics and outcomes from real-life experience compared with those in the 2 landmark trials. A comprehensive search identified eligible studies published in 2020 and 2021. Mean difference and odds ratio (OR) were used to compare continuous and categorical data. Thirty-three studies included more than 9200 patients. Patients in landmark trials were younger than in real-life, less likely to present with severe heart failure symptoms ([COAPT: OR 0.25; 95% CI: 0.21, 0.31]; [MITRA-

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FR: OR 0.32; 95% CI: 0.23, 0.45]) or severe mitral regurgitation grade (COAPT only: OR 0.57; 95% CI: 0.45, 0.71) with larger left ventricular end diastolic volume. Procedure success (OR 1.94; 95% CI: 1.10, 3.40) was more frequent with lower all-cause mortality (OR 0.73; 95% CI: 0.54, 0.99) in COAPT. Real-life patients experienced more favorable procedural and clinical outcomes compared with MITRA-FR patients. Real-life data on percutaneous mitral valve repair in secondary mitral regurgitation showed important variations in patient selection and procedural outcomes. Rates of death and heart failure hospitalization in observational studies were lower than MITRA-FR but higher than COAPT trial. (Curr Probl Cardiol 2023;48:101889.)

Introduction

Valvular heart diseases are a crucial public health problem. Mitral valve regurgitation (MR) is the second most common valvular disease,[1] with an overall prevalence of 2% in the general population. In the United States, there are more than 5 million cases having secondary MR (SMR), which is a predictor of mortality and a factor of poor prognosis.[2-4] A study showed that 49% of patients with severe mitral regurgitation (MR) have been denied surgery. Percutaneous or transcatheter edge-to-edge repair of the mitral valve using MitraClip (Abbott Vascular, Santa Clara, California) has surfaced as a therapeutic option for secondary or functional MR,[3] to decrease MR severity through the approximation of anterior and posterior leaflets of the valve.[4]

In 2018, MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) then COAPT (cardiovascular outcomes assessment of the MitraClip percutaneous therapy for heart failure patients with functional mitral regurgitation) trials were published. Both trials examined the efficacy and safety of MitraClip use in moderate-to-severe or severe SMR compared with optimal medical therapy.[5,6] MITRA-FR trial (n = 304) demonstrated that MitraClip reduced the severity of SMR safely without a difference in the rate of primary outcome (ie, death or unplanned heart failure hospitalization) at 1-year follow-up.[5] Whereas COAPT trial (n = 614) found significant reduction in the rates of primary (ie, hospitalization for heart failure) and all 10 secondary endpoints, including death, after 2 years.[6] The conflicting

findings have brought into question the differences and similarities between the 2 trials.

While randomized controlled trials are considered the cornerstone for an evidence-based practice, there is often a limitation in their generalizability due to their controlled conditions and strict eligibility criteria. Thus, real-world evidence provides an important complementary source of information that has been recently acknowledged by regulatory bodies.[7] Real-world evidence can also be integral to recognize and characterize the patients who underwent percutaneous mitral valve repair. Herein, this systematic review and meta-analysis examined the characteristics and outcomes of patients with SMR from the observational studies who underwent percutaneous valve repair in comparison with those in the MITRA-FR and COAPT trials.

Methods

This systematic review and meta-analysis were performed in agreement with Cochrane handbook for systematic reviews, preferred reporting items for systematic reviews and meta-analyses statement, and meta-analysis of observational studies in epidemiology checklist. The protocol was registered in the international prospective register of systematic reviews (PROSPERO 2022 CRD42022343331).

Eligibility and Search Strategy

A comprehensive systematic search using MEDLINE, Embase and Centrale was conducted by 2 independent authors to identify the observational studies published in 2020 and 2021 and enrolled adult patients with secondary or functional MR who underwent MitraClip intervention. The search terms were broad and included: "MitraClip," "MitraClip AND 'mitral valve'," "transcatheter mitral valve repair," "percutaneous mitral valve repair," and "edge-to-edge" AND "mitral valve". The references' lists of the included studies and relevant systematic reviews were searched manually for additional publications. Corresponding authors were contacted to solicit unpublished or additional details as appropriate. The search strategy is detailed in Table S1. The percutaneous or transcatheter mitral valve intervention for SMR using MitraClip device was the intervention group regardless of the comparator type or its presence. Studies were excluded if recruited 10 or less patients, published in non-English language, investigated devices other than MitraClip. Other exclusion criteria included MR of primary or mixed etiology, specific patient

population (eg, fibroelastic deficiency), or specific clinical setting (eg, postmyocardial infarction or cardiogenic shock). For the studies from the same registries or centers with similar or overlapping recruitment periods, the one with larger sample size was included.

Study Selection and Data Extraction

The search records were initially screened at abstract level. Following the elimination of duplicates and ineligible publications, relevant abstracts were retrieved in full text. For the included studies, data were extracted for study and patient characteristics, medical or device therapy at baseline, pre- and postprocedure echocardiographic features, and outcomes. Clinical outcomes (ie, death, rehospitalization and major adverse cardiovascular events [MACE]) were the main outcomes of interest. The main procedural outcome was procedural success defined as MR grade $\leq$2+.

Bias Assessment

The risk of bias in non-randomized studies of interventions (ROBINS-I) tool was used to evaluate the methodological quality of the included studies. The tool has 7 domains, and the level of bias is assigned as no information, low, moderate, serious, or critical risk.[8]

Statistical Analysis

Patient variables from observational studies were compared with those in randomized studies using a random-effects model for each variable. Mean difference (MD) and odds ratio (OR), with 95% confidence intervals (95% CI), were used to compare continuous and categorical data, respectively. R software was used for noncomparative pooling of variables, and RevMan software was used for the comparative meta-analysis. Significant statistical heterogeneity was indicated by Q statistic *P*-value less than 0.1 or by I^2 more than 50%.

Results

Search Result

Detailed literature search strategy is presented in Table S1 and Figure S1. Fifty-nine records retrieved in full text were published in 2020 (n = 27) and 2021 (n = 32). Thirty-three studies were included in the

analysis after eliminating 6 studies that recruited special patient population and 20 trials with a potential of having duplicate population that is, same registry or center with overlapping recruitment periods (Table S2). The characteristics and outcomes of individual studies including those with overlapping population are presented along with the included studies in Tables S3-S7. Seventeen corresponding authors were emailed to request additional data or clarification, only 4 responded.

Study Characteristics

The 33 studies recruited approximately 9200 patients between 2008 and 2020 in different countries, with vast majority from Europe. All studies reported characteristics and outcomes of patients with SMR who underwent MitraClip implantation, of which 12 interventional studies compared MitraClip intervention with medical therapy or surgical intervention and the remaining without comparison arms.

Patient Characteristics

The mean age was 74.47 $\pm$ 0.66 and 67.6% of patients were men. The prevalence of diabetes, hypertension and atrial fibrillation was 31.7%, 70.8%, and 56.1%, respectively. The proportion of patients with ischemic etiology (54.4%) was higher than that of those with nonischemic MR (40.0%). Most patients were symptomatic at presentation (86.8%; ie, New York Heart Association [NYHA] class III/IV), and more patients had MR grade 4+ (71.3%) than grade 3+ (33.6%). The pooled variables of included studies are shown in Tables 1 – 3, Tables S8 – S9, and Figures S2 – S6.

COAPT vs Real-Life. Patients in COAPT were younger (MD -2.70; 95% CI: -4.03, -1.37, $P < 0.0001$) with higher body mass index (MD 0.76; 95% CI: 0.11, 1.41, $P = 0.02$) and more likely to have cardiac history (OR 2.49; 95% CI: 1.96, 3.15, $P < 0.00001$) and MR of ischemic etiology (OR 1.29; 95% CI: 1.01, 1.65, $P = 0.04$). Furthermore, they were more likely to have history of hypertension (OR 1.90; 95% CI: 1.43, 2.54, $P < 0.0001$), stroke (OR 1.87; 95% CI: 1.38, 2.53, $P < 0.0001$), and renal impairment (OR 1.53; 95% CI: 1.18, 1.97, $P = 0.001$). They were less likely to present with more severe symptoms, that is, NYHA III/IV (OR 0.25; 95% CI: 0.21, 0.31, $P < 0.00001$) but with significantly higher natriuretic peptides levels. COAPT patients were more likely to be on betablocker therapy (OR 2.87; 95% CI: 1.93, 4.28, $P < 0.00001$) and to

undergo cardiac device implantation (OR 2.57; 95% CI: 2.01, 3.28, $P < 0.00001$). They were less likely to present with severe MR grade (OR 0.57; 95% CI: 0.45, 0.71, $P < 0.00001$) but with lower left ventricular ejection fraction (LVEF) (MD -2.56; 95% CI: -3.59, -1.53, $P < 0.00001$) and larger left ventricular end-diastolic volume (LVEDV) (MD 35.19; 95% CI: 27.39-42.99, $P < 0.00001$) (Tables 1-2, Table S8, Figure S7).

MITRA-FR vs Real-Life. MITRA-FR patients were younger (MD -4.30; 95% CI: -5.91, -2.69, $P < 0.00001$) with more males were enrolled (OR 1.72; 95%CI: 1.16, 2.55, $P = 0.007$). They were less likely to have atrial fibrillation (OR 0.42; 95% CI: 0.29, 0.59, $P < 0.00001$), renal impairment (OR 0.10; 95% CI: 0.07, 0.16, $P < 0.00001$) and NYHA III/IV class symptoms upon presentation (OR 0.32; 95% CI: 0.23, 0.45, $P < 0.00001$). However, natriuretic peptides levels were significantly higher. MITRA-FR patients were more likely to be on renin-angiotensin-aldosterone system inhibitors (OR 1.88; 95% CI: 1.23, 2.86, $P = 0.003$), beta-blocker therapy (OR 2.10; 95% CI: 1.28, 3.45, $P = 0.003$), and to undergo cardiac device implantation (OR 1.97; 95% CI: 1.42, 2.75, $P < 0.00001$). In addition, their LVEDV was significantly larger (MD 98.79; 95% CI: 87.49, 110.09, $P < 0.00001$)](Tables 1-2, Table S8, Figure S8).

Procedural and Clinical Outcomes

COAPT vs Real-Life. Procedural success was more frequent among COAPT patients (OR 1.94; 95% CI: 1.10, 3.40, $P = 0.02$), without a difference in the number of clips implanted per procedure. At 12-month follow-up, they maintained significant procedural success (OR 6.13; 95% CI: 3.33, 11.28, $P < 0.00001$) with better symptomatic relief (NYHA I/II: OR 1.91; 95% CI: 1.43, 2.56, $P < 0.00001$) and lower all-cause mortality (OR 0.73; 95% CI: 0.54, 0.99, $P = 0.04$) (Table 3, Table S9, Figure S7).

MITRA-FR vs Real-Life. Immediate procedural success was less frequent among MITRA-FR patients (MR 1+: OR 0.47; 95% CI: 0.33, 0.67, $P < 0.0001$; MR2+: OR 0.56; 95% CI: 0.36, 0.89, $P = 0.01$) but more patients had symptomatic improvement (NYHA I/II: OR 1.56; 95% CI: 1.04, 2.33, $P = 0.03$). Although MITRA-FR patients were less likely to die due to cardiovascular causes (OR 0.28; 95% CI: 0.17, 0.47, $P < 0.00001$), they experienced worse outcomes including composite of death or hospitalization for heart failure (OR 1.87; 95% CI: 1.31, 2.66, $P = 0.0005$),

TABLE 1. Patient baseline characteristics

Variable	Total reporting studies, relative to all observational studies; n (%)	Pooled variables (real-life)	COAPT trial (mean ± SD or %) (population size)	COAPT vs pooled variable (MD/OR; 95% CI)	MITRA-FR trial (mean ± SD or %) (population size)	MITRA-FR vs pooled variable (MD/OR; 95% CI)
Age (y)	33/33 (100%)	74.4 ± 0.66 (73.1, 75.7); Q = 11.7, $P = 0.99$	71.7 ± 11.8 (n = 302)	-2.70 (-4.03, -1.37), $P < 0.0001$	70.1 ± 10.1 (n = 152)	-4.30 (-5.91, -2.69), $P < 0.00001$
Male	33/33 (100%)	67.6% (65.2, 70.0); $I^2 = 77\%$, $P < 0.01$	201/302 (66.6%)	0.91 (0.72, 1.16), $P = 0.47$	120/152 (78.9%)	1.72 (1.16, 2.55), $P = 0.007$
BMI (kg/m^2)	19/33 (57.6%)	26.24 ± 0.28; Q = 14.81, $P = 0.97$	27.0 ± 5.8 (n = 302)	0.76 (0.11, 1.41), $P = 0.02$	-	-
Hypertension	22/33 (66.7%)	70.8% (68.8, 74.5); $I^2 = 88\%$, $P < 0.01$	243/302 (80.5%)	1.90 (1.43, 2.54), $P < 0.0001$	-	-
Cardiac surgery	24/33 (72.7%)	21.8% (18.6, 25.3); I^2=87%, $P < 0.01$	121/302 (40.1%)	2.49 (1.96, 3.15), $P < 0.00001$	-	-
Ischemic etiology	12/33 (36.4%)	54.4% (45.3, 63.4); $I^2 = 95\%$, $P < 0.01$	184/302 (60.9%)	1.29 (1.01, 1.65), $P = 0.04$	95/152 (62.5%)	1.38 (0.98, 1.93), $P = 0.06$
Atrial fibrillation	27/33 (81.8%)	56.1% (51.2, 61.3); $I^2 = 93\%$, $P < 0.01$	173/302 (57.3%)	1.06 (0.84, 1.33), $P = 0.64$	49/142 (34.5%)	0.42 (0.29, 0.59), $P < 0.00001$
Stroke	13/33 (39.4%)	11.5% (8.6, 14.9); $I^2 = 88\%$, $P < 0.01$	56/302 (18.5%)	1.87 (1.38, 2.53), $P < 0.0001$	-	-
COPD	19/33 (57.6%)	49.9% (45.1, 54.7); $I^2 = 84\%$, $P < 0.01$	71/302 (23.5%)	0.31 (0.24, 0.41), $P < 0.00001$	-	-
Renal insufficiency	14/33 (42.4%)	58.4% (50.9, 65.7); $I^2 = 97\%$, $P < 0.01$	214/299 (71.6%)	1.53 (1.18, 1.97), $P = 0.001$	22/152 (14.5%)	0.10 (0.07, 0.16), $P < 0.00001$
GFR (mL/min)	12/33 (36.4%)	46.8 ± 2.22; Q = 4.28, $P = 0.99$	50.9 ± 28.5 (n = 302)	4.10 (0.89, 7.31), $P = 0.01$	48.8 ± 19.7 (n = 152)	2.00 (-1.13, 5.13), $P = 0.21$
BNP (pg/mL or ng/L)	5/33 (15.1%)	627 ± 0.24; Q = 6.79, $P = 0.23$	1014.8 ± 1086 (n = 302)	387.80 (265.32, 510.28), $P < 0.00001$	765 (417, 1281) (n = 152)	138.00 (103.66, 172.34), $P < 0.00001$
NT-proBNP (pg/mL or ng/L)	17/33 (51.5%)	2284.88 ± 205.45; Q = 30.47, $P = 0.20$	5174.3 ± 6566.6 (n = 302)	2889.40 (2148.78, 3630.02), $P < 0.00001$	3407 (1948, 6790) (n = 152)	1122.10 (921.56, 1322.64), $P < 0.00001$
NYHA II	20/33 (60.6%)	13.8% (9.8, 18.4); $I^2 = 92\%$, $P < 0.01$	129/302 (42.7%)	4.09 (3.23, 5.18), $P < 0.00001$	56/152 (36.8%)	3.20 (2.29, 4.48), $P < 0.00001$
NYHA III	20/33 (60.6%)	64.5% (59.6, 69.3); I^2=89%, $P < 0.01$	154/302 (51.0%)	0.61 (0.48, 0.76), $P < 0.0001$	82/152 (53.9%)	0.68 (0.49, 0.94), $P = 0.02$
NYHA IV	21/33 (63.6%)	23.1% (18.5, 28.0); $I^2 = 89\%$, $P < 001$	18/302 (6.0%)	0.23 (0.14, 0.37), $P < 0.00001$	14/152 (9.2%)	0.37 (0.21, 0.63), $P = 0.0004$
NYHA III/IV	24/33 (72.7%)	86.8% (82.7, 90.4); $I^2 = 93\%$, $P < 0.01$	172/302 (57.0%)	0.25 (0.20, 0.31), $P < 0.00001$	96/152 (63.1%)	0.32 (0.23, 0.45), $P < 0.00001$
High risk	1/33 (3.03%)	100% (93.8, 100); I^2 = N/A	205/299 (68.6%)	0.02 (0.00, 0.30), $P = 0.005$	-	-
STS risk score (%)	12/33 (36.7%)	5.22 ± 0.46; Q = 20.45, $P < 0.05$	7.8 ± 5 (n = 302)	3.26 (2.70, 3.82),n $P < 0.00001$	-	-
ACEI/ARB/ARNI	9/33 (27.3%)	71.3% (57.6, 83.3); $I^2 = 99\%$, $P < 0.01$	217/302 (71.9%)	1.04 (0.80, 1.34), $P = 0.79$	125/152 (82.2%)	1.88 (1.23, 2.86), $P = 0.003$
Beta-blocker	19/33 (57.6%)	82.6% (78.6, 86.3); $I^2 = 92\%$, $P < 0.01$	275/302 (91.1%)	2.87 (1.93, 4.28), $P < 0.00001$	134/152 (88.2)	2.10 (1.28, 3.45), $P = 0.003$

(*continued on next page*)

TABLE 1. (*continued*)

Variable	Total reporting studies, relative to all observational studies; n (%)	Pooled variables (real-life)	COAPT trial (mean ± SD or %) (population size)	COAPT vs pooled variable (MD/OR; 95% CI)	MITRA-FR trial (mean ± SD or %) (population size)	MITRA-FR vs pooled variable (MD/OR; 95% CI)
OAC	4/33 (12.1%)	43.3% (23.1, 64.8); $I^2 = 89\%$, $P < 0.01$	140/302 (46.4%)	1.24 (0.95, 1.62), $P = 0.12$	93/152 (61.2%)	2.26 (1.58, 3.23), $P < 0.00001$
CRT/CRT-D	18/33 (54.5%)	24.0 (18.6, 29.8); $I^2 = 94\%$, $P < 0.01$	115/302 (38.1%)	1.94 (1.53, 2.47), $P < 0.00001$	46/151 (30.5%)	1.38 (0.97, 1.97), $P = 0.07$
Any cardiac device	24/33 (72.7%)	43.0% (34.5, 51.8); $I^2 = 97\%$, $P < 0.01$	206/302 (68.1%)	2.57 (2.01, 3.28), $P < 0.00001$	94/151 (62.3%)	1.97 (1.42, 2.75), $P < 0.00001$

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB; angiotensin receptor blockers; ARNI, Angiotensin receptor and neprilysin inhibitors; BMI, body mass index; BNP, B-type natriuretic peptide; COAPT, cardiovascular outcomes assessment of the MitraClip percutaneous therapy; COPD, chronic obstructive pulmonary disease; CRT; Cardiac resynchronization therapy; CRT-D; Cardiac resynchronization therapy-defibrillator; GFR, glomerular filtration rate; MD, mean difference; MITRA-FR, multicentre study of percutaneous mitral valve repair MitraClip device in patients with severe secondary mitral regurgitation; NT-pro-BNP, N-terminal pro−B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; OAC, oral anticoagulant; SD, standard deviation; STS, Society of Thoracic Surgeons.

TABLE 2. Baseline echocardiographic measurements

Variable	Total reporting studies; n (%)	Pooled variable	COAPT trial	COAPT vs Pooled variable (MD/OR)	MITRA-FR trial	MITRA-FR vs Pooled variable (MD/OR)
MR grade 3+	20/33 (60.6%)	33.6% (24.7, 43.0); $I^2 = 98\%$, $P < 0.01$	148/302 (49.0%)	1.91 (1.52, 2.41), $P < 0.00001$	46/123 (37.4%)	1.19 (0.82, 1.72), $P = 0.36$
MR grade 4+	23/33 (69.7%)	71.3% (59.9, 81.5); $I^2 = 98\%$, $P < 0.01$	154/302 (51.0%)	0.57 (0.45, 0.71), $P < 0.00001$	76/123 (61.8%)	0.88 (0.61, 1.27), $P = 0.50$
EROA cm^2	18/33 (54.5%)	0.33 ± 0.1; Q = 12.86, $P = 0.96$	0.41 ± 0.15	0.08 (0.06, 0.10), $P < 0.00001$	0.31 ± 0.1	-0.02 (-0.04, -0.00), $P = 0.01$
LVESD (cm)	15/33 (45.4%)	5.47 ± 0.11; Q = 45.94, $P = 0.0045$	5.3 ± 0.9	-0.17 (-0.27, -0.07), $P = 0.001$	-	-
LVEDD (cm)	22/33 (66.7%)	6.09 ± 0.06; Q = 39.84, $P = 0.16$	6.2 ± 0.7	0.11 (0.03, 0.19), $P = 0.006$	-	-
LVESV (mL)	17/33 (51.5%)	115.87 ± 6.0; Q = 17.16, $P = 0.92$	135.5 ± 56.1	19.63 (13.30, 25.96), $P < 0.00001$	-	-
LVEDV (mL)	22/33 (66.7%)	159.21 ± 3.38; Q = 26.07, $P = 0.76$	194.4 ± 69.2	35.19 (27.39, 42.99), $P < 0.00001$	258.8 ± 71.1*	98.79 (87.49, 110.09), $P < 0.00001$
LVEF (%)	32/33 (96.9%)	33.86 ± 0.68; Q = 48.15, $P = 0.30$	31.3 ± 9.1	-2.56 (-3.59, -1.53), $P < 0.00001$	33.3 ± 6.5	-0.56 (-1.59, 0.47), $P = 0.29$
LVEF (reduced; ≤30%)	4/33 (12.1%)	37.7% (24.9, 51.3); $I^2 = 97\%$, $P < 0.01$	231/281 (82.2%) (≤40%)	6.86 (4.99, 9.43), $P < 0.00001$	-	-

Abbreviations: COAPT, cardiovascular outcomes assessment of the MitraClip percutaneous therapy; EROA, effective regurgitant orifice area; LVEDD, left ventricular end-diastolic dimension/diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume; MD, mean difference; MR, mitral regurgitation; MITRA-FR, multicenter study of percutaneous mitral valve repair MitraClip device in patients with severe secondary mitral regurgitation; OR, odds ratio.
*136.2 ± 37.4 mL/m^2 converted to ml using 1.9 m^2.

TABLE 3. Procedural and clinical outcomes

Variable	Total reporting studies; n (%)	Pooled variable	COAPT trial	COAPT vs Pooled variable (OR)	MITRA-FR trial	MITRA-FR vs Pooled variable (OR)
Procedural outcomes (Post procedure or at discharge)						
MR grade 1+ or ≤1+	15/33 (45.4%)	62.1% (55.7, 68.2); $I^2 = 91\%$, $P < 0.01$	214/260 (82.3%)	2.78 (2.01, 3.84), $P < 0.00001$	54/123 (43.75%)	0.47 (0.33, 0.67), $P < 0.0001$
MR grade 2+	14/33 (42.4%)	29.0% (24.9, 33.4); $I^2 = 88\%$, $P < 0.01$	33/260 (12.7%)	0.35 (0.25, 0.51), $P < 0.00001$	23/123 (18.75%)	0.56 (0.36, 0.89), $P = 0.01$
MR grade ≤2+	18/33 (54.5%)	89.2% (84.6, 93.1); $I^2 = 95\%$, $P < 0.01$	247/260 (95.0%)	1.94 (1.10, 3.40), $P = 0.02$	115/123 (93.5%)	1.47 (0.71, 3.02), $P = 0.30$
MR grade ≥3+	15/33 (45.4%)	11.3% (7.4, 15.9); I^2=93%, $P < 0.01$	13/260 (5.0%)	0.52 (0.29, 0.91), $P = 0.02$	8/123 (6.25%)	0.68 (0.33, 1.41), $P = 0.30$
MR grade 3+	14/33 (42.4%)	8.3% (4.8, 12.5); $I^2 = 92\%$, $P < 0.01$	9/260 (3.5%)	0.48 (0.24, 0.94), $P = 0.03$	-	-
MR grade 4+	13/33 (39.4%)	2.9% (1.5, 4.7); $I^2 = 81\%$, $P < 0.01$	4/260 (1.5%)	0.66 (0.24, 1.79), $P = 041$	-	-
Clinical outcomes						
Hospital for HF within 12 mo	7/33 (21.2%)	26.9% (21.0, 33.3); $I^2 = 83\%$, $P < 0.01$	-	-	74/152 (48.7%)	2.58 (1.83, 3.63), $P < 0.00001$
All-cause mortality within 12 mo	9/33 (27.3%)	22.5% (17.0, 28.6); $I^2 = 86\%$, $P < 0.01$	57/302 (19.1%)	0.73 (0.54, 0.99), $P = 0.04$	37/152 (24.3%)	1.01 (0.69, 1.48), $P = 0.96$
CV death at 12 mo	2/33 (6.1%)	43.2% (0.9, 94.1); $I^2 = 98\%$, $P < 0.01$	-	-	33/152 (21.7%)	0.28 (0.17, 0.47), $P < 0.00001$
Death or hospitalization for HF within 12 mo	3/33 (9.1%)	38.3% (26.1, 51.4); I^2=91%, $P < 0.01$	-	-	83/152 (54.6%)	1.87 (1.31, 2.66), $P = 0.0005$
MACE at 12 mo	3/33 (xx%)	17.3% (1.5, 44.3); $I^2 = 99\%$, $P < 0.01$	-	-	86/152 (56.6%)	5.38 (3.76, 7.70), $P < 0.00001$
NYHA I/II at 12 mo	12/33 (xx%)	72.1% (62.2, 80.9); $I^2 = 99\%$, $P < 0.01$	171/237 (72.2%)	1.91 (1.43, 2.56), $P < 0.00001$	76/112 (67.8%)	1.56 (1.04, 2.33), $P = 0.03$
MR grade ≤2+ at 12 mo	13/33 (xx%)	81.3% (75.8, 86.2); $I^2 = 95\%$, $P < 0.01$	199/210 (94.8%)	6.13 (3.33, 11.28), $P < 0.00001$	79/97 (81.4%) (Paired data)	1.49 (0.89, 2.49), $P = 0.13$

Abbreviations: COAPT, cardiovascular outcomes assessment of the MitraClip percutaneous therapy; CV, cardiovascular; HF, heart failure; MACE, major adverse cardiovascular events; MITRA-FR, multicentre study of percutaneous mitral valve repair MitraClip device in patients with severe secondary mitral regurgitation; MR, mitral regurgitation; NYHA, New York Heart Association; OR, odds ratio.

hospitalization for heart failure (OR 2.58; 95% CI: 1.83, 3.63, $P < 0.00001$), and MACE (OR 5.38; 95% CI: 3.76, 7.70, $P < 0.00001$) at 12 months (Table 3, Table S9, Figure S8).

Risk of Bias

The overall risk of bias assessment was critical for all-cause mortality and MR grade ≤2+ at 12 months, and serious for the following outcomes: all-cause mortality within 24 months, hospitalization for heart failure at 12 and 24 months, composite of death or hospitalization for heart failure within 12 or 24 months (Tables S10.1-S10.9).

Discussion

This systematic review explored the similarities and differences of patient characteristics and outcomes between published observational and landmark studies. In comparison with COAPT and MITRA-FR trials, patients in real-life were older, more likely to present with more severe symptoms and MR grade, having smaller LVEDV, and less likely to undergo cardiac device implantation. In addition, procedural success was less frequent and less likely to be maintained at 12-month follow-up when compared with COAPT, which may have contributed to lower 12-month survival in the real-life experience. Whereas real-life patients were less likely to have heart failure hospitalization or death, or experience MACE at 12 months when compared with MITRA-FR patients. To the best of our knowledge this is the first meta-analysis to conduct a comparison between pooled data from observational and landmark studies in patients with SMR who underwent MitraClip intervention.

The answer to the questions about the different results between COAPT and MITRA-FR trials seems to be multifaceted and may be attributed to differences in several aspects such as methodology, MR severity, ventricular remodeling, and optimization of medical therapy. The inclusion and exclusion criteria of both trials were divergent, for example, COAPT patients were more selective hence their recruitment was slow and prolonged (Table S11). MITRA-FR sample size was smaller and type II error cannot be ruled out.[2] It is unclear whether different geographical regions of both studies have affected the results. The primary efficacy endpoints and their statistical analyses were different between the 2 trials, and the longer follow-up in COAPT may have allowed capturing more events.[9]

MITRA-FR trial applied different MR severity criteria (ie, effective regurgitant orifice area [EROA] $\geq$ 0.20 cm^2 and/or regurgitant volume $\geq$30mL) from COAPT (ie, EROA $\geq$ 0.30 cm^2 and/or regurgitant volume $\geq$ 45mL). COAPT patients had more severe MR (EROA: 0.41 $\pm$ 0.15 cm^2) than those in MITRA-FR (EROA: 0.31 $\pm$ 0.01 cm^2), which is comparable to present pooled EROA of 0.33 $\pm$ 1.0 cm^2. However, MITRA-FR patients had more severe left ventricular (LV) disease evidenced by larger LVEDV than that for COAPT (258.8 $\pm$ 71.1 vs 194.4 $\pm$ 69.2 mL, respectively) or the present real-life patients (159.21 $\pm$ 3.38 mL). Severe LV dilation and LV dysfunction were correlated with recurrent MR, reverse remodeling, and unfavorable outcomes after surgical intervention for ischemic MR,[3] thus, possible better clinical outcomes in COAPT. The difference in LVEDV was possibly attributed to the exclusion of patients with very severe LV dilation in COAPTT trial unlike MITRA-FR which did not impose any limits.[2,3] LVEF criteria in COAPT ranged from 20% to 50%, whereas in the MITRA-FR ranged from 15% to 40%. without a big difference between mean values (31.3 $\pm$ 9.1% vs 33.3 $\pm$ 6.5%) and our pooled results (33.86 $\pm$ 0.68%).

To put the findings of this meta-analysis in the context of large observational reports published before 2020, earlier studies and registries included patients regardless of their MR etiology. Patients with SMR usually accounted for more than 70% of the population.[10,11] Further analysis from these registries on patients with SMR alone,[12,13] along with that from the endovascular valve edge-to-edge repair program[14] and a study of a relatively large sample size[15] are listed and compared with this paper's pooled data in Table 4. The endovascular valve edge-to-edge repair program[14] recruited less males (59.1%) and patients with MR grade 4+ (22.7%), who had better LVEF (43%) and symptoms relief at 12-month follow-up (NYHA I/II: 83.0%). Whereas Kitamura and colleagues recruited more symptomatic patients (NYHA III/IV: 92.5%) and reported higher mortality rate (42.1%).[15]

Limitations

The first limitation of this paper is the observational aspect of real-life data that creates bias and confounding.[16] The included studies varied in size with only 1 study recruited more than 1000 patients and 5 enrolled more than 500 participants each. Most of the reports came from Europe which may limit results generalizability and comparison with studies from other regions. Only few studies reported clinical outcomes with various follow-up durations without consistent reporting of heart failure

TABLE 4. Reports on patients with secondary mitral regurgitation

Variable	EVEREST program[14]	ACCESS-EU (Phase I)[12]	TCVT registry[13]	Kitamura et al[15]	Kaddoura et al (pooled variables)
Recruitment period	August 2005 to December 2013	October 2008 to April 2011	January 2011 to December 2012	September 2009 to June 2016	1999 to September 2020
Recruitment duration (y)	8	2.5	2	7	0.5-19
Country	North America	Europe	Europe (8 countries)	Germany	Europe (majority)
Number of sites	37	14	25	2	1-40
Sample size	616	393	452	575	~ 9,900
Age (y)	73.3 ± 10.5 (616)	73.0 ± 8.9 (n = 393)	72.8 ± 9.8 (n = 452)	1. 74.0 ± 9.0 (n = 310)§ 2. 73.0 ± 9.7 (n = 222)§	74.37 ± 0.66
Male	59.1 (364/616)	267/393 (68.0%)	306/452 (68.0%)	367/532 (69.0%)	67.6% (65.3-69.9)
NYHA III/IV	495/615 (80.5%)	331/393 (84.2%)	400/452 (88.5%)	454/491 (92.5%)	86.2% (82.1-89.9)
MR 3+	355/616 (58.1%)	155/393 (40.0%)	29/203 (14.3%)*	232/575 (40.3%)	35.7% (25.6-43.1)
MR 4+	139/616 (22.7%)	232/393 (59.0%)	172/203 (84.7%)†	284/575 (49.4%)	70.0% (58.7-80.2)
LVEDV (mL)	162.2 ± 52.8 (558)	-	1. 173.9 ± 74.1 (n = 106)§ 2. 168.8 ± 101.7 (n = 145)§	-	159.21 ± 3.38
LVEF (%)	43.2 ± 11.7 (558)	-	1. 35.5 ± 12.0 (n = 106)§ 2. 38.4 ± 14.7 (n = 145)§	1. 3.14 ± 1.2 (31.4 ± 12.0) (n = 299)§2. 3.32 ± 1.49 (33.2 ± 14.9) (n = 217)§	33.86 ± 0.68
Outcomes					
MR ≤ 2+ at 12 mo	349/413 (84.5%) At 12 months	-	192/271 (70.8%)	-	81.3% (75.8-86.2)
NYHA I/II at 12 mo	511/616 (83.0%)	-	120/203 (59.1%)‡	-	72.1% (62.2-80.9)
Hospitalization for HF at 12 mo	-		95/370 (25.8%)	-	26.9% (21.0-33.3)
All-cause death at 12 mo	138/616 (22.4%)	67/393 (17.0%)	55/370 (15.0%)	224/532 (42.1%)	22.5% (17.0-28.6)
CV death at 12 mo	-	37/393 (9.4%)	-	-	43.2% (0.9-94.1)

Abbreviations: ACCESS-EU, ACCESS-Europe, a two-phase observational study of the MitraClip system in Europe; CV, cardiovascular; EROA, effective regurgitant orifice area; EVEREST, endovascular valve edge-to-edge repair; HF, heart failure; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; TCVT, transcatheter valve treatment sentinel pilot registry.

*Study used term "moderate."

†Study used term "severe."

‡Study used term "No/mild."

§Comparison groups in the study.

medication use. The quality of the included studies was low with critical or serious risk of bias, in addition to high heterogeneity among them. As such, results and conclusion of this analysis should be interpreted with caution. More well-designed randomized studies are needed to delineate the optimal criteria in selecting patients who will benefit from the transcatheter approach. The RESHAPE-HF2 (a clinical evaluation of the safety and effectiveness of the MitraClip system in the treatment of clinically significant functional mitral regurgitation) trial, is a registered ongoing randomized trial (NCT02444338) aims to investigate the efficacy of MitraClip implantation on top of medical therapy in comparison with medical therapy alone. The study will recruit 650 symptomatic heart failure patients, with LVEF of 15% to 45% and moderate-to-severe or severe SMR and EROA $\geq$ 0.30 cm^2, that is, COAPT criteria for MR severity.

Conclusion

Real-life data on percutaneous mitral valve repair in SMR showed important variations in patient selection and procedural outcomes especially when compared with COAPT trial. Rates of death and heart failure hospitalization in observational studies were lower than in MITRA-FR but higher than in COAPT trial at 1-year follow-up.

Declaration of Competing Interest

We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere. All authors have read and approved the manuscript and all authors have no conflict of interest to declare in relation to this paper.

Ethics Approval and Consent to Participate

Not applicable.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2023.101889.

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez SM. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;368 (9540):1005–11.
2. Barros-Gomes S, Tarasoutchi F, Rodrigues ACT, et al. Percutaneous treatment of secondary mitral regurgitation by MitraClip: Mitra-FR vs. COAPT. *Arq Bras Cardiol* 2021;116(5):1011–8.
3. Atianzar K, Zhang M, Newhart Z, Gafoor S. Why did COAPT win while MITRA-FR failed? Defining the appropriate patient population for MitraClip. *Interv Cardiol* 2019;14(1):45–7.
4. Pibarot P, Delgado V, Bax JJ. MITRA-FR vs. COAPT: lessons from two trials with diametrically opposed results. *Eur Heart J Cardiovasc Imaging* 2019;20(6):620–4.
5. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018;379(24):2297–306.
6. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;379(24):2307–18.
7. Nazha B, Yang JC, Owonikoko TK. Benefits and limitations of real-world evidence: lessons from *EGFR* mutation-positive non-small-cell lung cancer. *Future Oncol* 2021;17(8):965–77.
8. Sterne JAC, Higgins JPT, Elbers RG, et al. ROBINS-I. Risk of bias in non-randomized studies of interventions (ROBINS-I): detailed guidance. Available from. Risk of bias tools - ROBINS-I detailed guidance (2016) Accessed June 2022.
9. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT Trials. *JACC Cardiovasc Imaging* 2019;12(2):353–62.
10. Maisano F, Franzen O, Baldus S, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. *J Am Coll Cardiol* 2013;62(12):1052–61.
11. Nickenig G, Estevez-Loureiro R, Franzen O, et al. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 Pilot European Sentinel Registry. *J Am Coll Cardiol* 2014;64(9):875–84.
12. Schäfer U, Maisano F, Butter C, et al. Impact of Preprocedural left Ventricular ejection fraction on 1-year outcomes after MitraClip implantation (from the ACCESS-EU Phase I, a prospective, multicenter, nonrandomized postapproval study of the MitraClip therapy in Europe). *Am J Cardiol* 2016;118(6):873–80.
13. Pighi M, Estevez-Loureiro R, Maisano F, et al. Immediate and 12-month outcomes of ischemic versus nonischemic functional mitral regurgitation in patients treated with MitraClip (from the 2011 to 2012 pilot sentinel registry of percutaneous edge-to-edge mitral valve repair of the European Society of Cardiology). *Am J Cardiol* 2017;119 (4):630–7.
14. Ailawadi G, Lim DS, Mack MJ, et al. One-year outcomes after MitraClip for functional mitral regurgitation. *Circulation* 2019;139(1):37–47.

15. Kitamura M, Kaneko H, Schlüter M, et al. Predictors of mortality in ischaemic versus non-ischaemic functional mitral regurgitation after successful transcatheter mitral valve repair using MitraClip: results from two high-volume centres. *Clin Res Cardiol* 2019;108(3):264–72.
16. Wang MT, Bolland MJ, Grey A. Reporting of limitations of observational research. *JAMA Intern Med* 2015;175(9):1571–2.