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SUPPLEMENTARY MATERIAL

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

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

Supplementary Table 1. Full search query.

SEARCH TERMS	SEARCH PERFORMED ON THE 2nd September 2024
WEB OF SCIENCE	(ALL=("transcatheter mitral valve repair") OR ALL=("percutaneous mitral valve repair") OR (ALL=("edge-to-edge") AND ALL=("mitral valve"))) AND (ALL=("heart failure"))
SCOPUS	(TITLE-ABS-KEY ("transcatheter mitral valve repair") OR KEY ("percutaneous mitral valve repair") OR TITLE-ABS-KEY ("edge-to-edge") AND TITLE-ABS-KEY ("mitral valve") AND TITLE-ABS-KEY ("heart failure"))
PUBMED	("transcatheter mitral valve repair"[All Fields] OR "percutaneous mitral valve repair"[All Fields] OR ("edge-to-edge"[All Fields] AND "mitral valve"[All Fields])) AND ("heart failure"[MeSH Terms] OR"heart failure"[All Fields])
COCHRANE CENTRAL	(("transcatheter mitral valve repair" OR "percutaneous mitral valve repair" OR ("edge-to-edge" AND "mitral valve")) AND ("heart failure")) (Word variations have been searched)

Supplementary Table 2. Assessment of risk of bias utilizing Cochrane risk of bias tool for randomized controlled trials.

	COAPT Trial	MITRA-FR Trial	RESHAPE-HF2 Trial
Random sequence generation (selection bias)	Low risk	Low risk	Low risk
Allocation concealment (selection bias)	Low risk	Low risk	Low risk
Blinding of participants and personnel (performance bias)	High risk	High risk	High risk
Blinding of outcome assessment (detection bias)	Low risk	Low risk	Low risk
Incomplete outcome data (attrition bias)	Low risk	Low risk	Low risk
Selective reporting (performance bias)	Low risk	Low risk	Low risk
Other bias	Low risk	Low risk	Low risk

Supplementary Table 3. Baseline characteristics of study population.

	COAPT Trial	MITRA-FR Trial	RESHAPE-HF2 Trial
Male – no./total no. (%)	393/614 (64.0)	227/304 (74.7)	406/505 (80.4)
Medical and surgical history – no./total no. (%)			
Hypertension	494/614 (80.5)	-	268/510 (52.5)
Diabetes	229/614 (37.3)	89/304 (29.3)	176/505 (34.9)
Previous MI	316/614 (51.5)	127/304 (41.8)	279/510 (54.7)
Previous PCI	283/614 (46.1)	135/303 (44.6)*	243/505 (48.1)
Previous CABG	247/614 (40.2)		133/505 (26.3)
ICM	373/614 (60.7)	180/303 (59.4)	324/505 (64.2)
History of AF or AFL	339/614 (55.2)	97/289 (33.6)	243/505 (48.1)
Previous stroke/TIA	105/614 (17.1)	-	59/505 (11.7)
History of COPD	143/614 (23.3)	-	71/505 (14.1)
HHF within previous year	351/614 (57.2)	118/304 (38.8)†	333/505 (65.9)
Therapy used at baseline – no./total no. (%)			
ACEI/ARB	391/614 (63.7)	224/304 (73.7)	376/505 (74.5)
ARNI	22/614 (3.6)	31/280 (11.1)	68/505 (13.5)
Beta-blocker	555/614 (90.4)	272/304 (89.5)	484/505 (95.8)
SGLT2i	-	-	46/505 (9.1)
Diuretic	547/614 (89.1)	300/304 (98.7)	482/505 (95.4)
MRA	308/614 (50.2)	166/303 (54.8)	415/505 (82.2)
Oral Anticoagulant	265/614 (43.2)	186/304 (61.2)	315/505 (62.4)
ICD	192/614 (31.3)	105/303 (34.7)	178/505 (35.2)
CRT	224/614 (36.5)	81/303 (26.7)‡	145/504 (28.8)
NYHA functional class I or II – no./total no. (%)	240/613 (39.2)	100/304 (32.9)	124/505 (24.6)
EROA, cm^2 - (n)	0.40±0.15 (591)§	0.31±0.10 (304)§	0.25±0.07 (505)§
<0.30 cm^2 – no./total no. (%)	0/604 (0.0)	157/304 (51.6)	319/478 (66.7)
Left ventricular end-diastolic volume, ml - (n)	192.7 ±71.1 (575)§	257.2±67.0 (304)§¥	202.7±70.0 (505)§

Continuous values are given as means ± standard deviations. ACEI: angiotensin converting enzyme inhibitor; AF: atrial fibrillation; AFL: atrial flutter; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitior; CABG: coronary-artery bypass graft; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronization therapy; EROA: effective regurgitant orifice area; HHF: hospitalization related to heart failure; ICD: implantable cardioverter defibrillator; ICM: ischemic cardiomyopathy; MI: myocardial infarction; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; SGLT2i: Sodium-glucose cotransporter 2 inhibitor; TIA: transient ischemic attack.

* Reported as coronary revascularization.

† At least two hospitalizations related to heart failure.

‡ Cardiac resynchronization therapy defibrillator.

§ Estimates of overall means and standard deviations using data from controlled group and intervention group reported separately.
Mean and/or standard deviations estimated from median and interquartile range.
Effective regurgitant orifice area less than 0.27 cm^2

¥ Converted from indexed value using a mean of body surface area of 1.9 m^2

Supplementary Table 4. Sensitivity analysis of six-minute walk test distance at 12 months of follow-up.

Study	Intervention Mean±SD | No.		Control Mean±SD | No.		Weight (%)	Mean Difference (95% CI), IV
COAPT Trial (2018)	-4.6±134.8	230	-57.6±152.5	237	36.5%	53.00 [26.91, 79.09]
MITRA-FR Trial (2018)	339±151	82	363±157	77	24.1%	-24.00 [-71.94, 23.94]
RESHAPE-HF2 Trial (2024)	34±105.9	188	5.1±97.6	164	39.4%	28.90 [7.63, 50.17]
			Total (95% CI)			**24.94 [-8.96, 58.84]**
	Test for overall effect using a random-effect model [DerSimonian—Laird]: Z = 1.44 (P = 0.15)					
	Heterogeneity: Tau^2 = 642.02; Chi^2 = 7.81, df = 2 (P = 0.02); I^2 = 74%					

Random-effects meta-analysis based on the DerSimonian and Laird method with data pooled from: COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial; MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial; and RESHAPE-HF2 (A Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation) trial. Sensitivity analysis that pooled the 12-month endpoint value for MITRA-FR, instead of the change from baseline (to avoid using estimated mean and standard deviation). COAPT and RESHAPE-HF2 effect values are in the form of change from baseline. The effect measure was mean difference and weighted using the generic inverse variance method. IV: inverse variance.