Structural Heart 8 (2024) 100284

Articles and Issues Available at ScienceDirect

Structural Heart

journal homepage: www.structuralheartjournal.org

Original Research

Mitral Regurgitation "Proportionality" in Functional Mitral Regurgitation and Outcomes After Mitral Valve Transcatheter Edge-to-Edge Repair: A Systematic Review and Meta-Analysis

Avalon Moonen, BSc (Med), MBBS [a], Jacob Cao, BSc, MSc, MClinTRes, MBBS [a,b], David S. Celermajer, MBBS, MSc, PhD, DSc [a,c,d], Martin K.C. Ng, BSc (Med), MBBS, PhD [a,c,d,*]

[a] Faculty of Medicine, University of Sydney, Sydney, NSW, Australia
[b] Department of Cardiology, St Vincent's Hospital, Sydney, NSW, Australia
[c] Department of Cardiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia
[d] Heart Research Institute, Sydney, NSW, Australia

ARTICLE INFO

Article history:
Submitted 31 August 2023
Revised 2 January 2024
Accepted 29 January 2024
Available online 15 March 2024

Keywords:
MitraClip
Mitral regurgitation
Proportionate MR
TEER

ABSTRACT

Background: Certain patients with functional mitral regurgitation survive longer with fewer heart failure hospitalizations after undergoing transcatheter edge-to-edge repair (TEER); however, clinical markers identifying who will benefit have not been established. The 'proportionality' of mitral regurgitation (MR) severity compared to left ventricular size has been hypothesized to predict clinical outcome.

Methods: We sought to combine existing studies to compare outcomes between 'proportionate' MR and 'disproportionate' MR in patients undergoing TEER. PubMed and Medline were searched from January 2018 until May 2023. Data was extracted and synthesized by 2 independent authors using random effects models with risk ratios (RRs) for binary outcomes. The primary outcome was a combined endpoint of all-cause mortality or heart failure hospitalization (ACM/HFH). Other outcomes of interest included ACM and residual >2+ MR after TEER.

Results: Six trials with a total of 1594 patients (mean age 71 years, 66% male) were included, which assessed MR proportionality using either a ratio of estimated regurgitant orifice area to left ventricular end-diastolic volume (EROA:LVEDV) or regurgitant fraction. Seven hundred and five (mean age 70 years, 75% male) were classified as proportionate MR, and 889 (mean age 72 years, 60% male) had disproportionate MR. There was no significant association between MR proportionality (by EROA:LVEDV) and ACM (RR 0.79, 95% confidence interval [CI] 0.44-1.42). Proportionality did not significantly associate with ACM/HFH, though there were divergent effect signals when proportionality was measured by EROA:LVEDV (RR 0.80, 95% CI 0.45-1.44) or regurgitant fraction (RR 1.48, 95% CI 0.53-4.11). Disproportionate MR showed a greater association with residual MR > 2+ post-TEER that did not meet statistical significance (RR 1.86, 95% CI 0.77-4.49).

Conclusions: In patients undergoing TEER for functional mitral regurgitation, MR proportionality was not significantly associated with ACM/HFH, all-cause mortality, or residual MR.

ABBREVIATIONS

EROA, estimated regurgitant orifice area; FMR, functional mitral regurgitation; HFH, heart failure hospitalization; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; MR, mitral regurgitation; RF, regurgitant fraction; TEER, transcatheter edge-to-edge repair.

Introduction

As the field of transcatheter valvular intervention has evolved and technical proficiency has advanced, so too has the spectrum of potentially treatable patients and conditions, to the point where almost all heart valve pathologies can feasibly be treated via transcatheter techniques. In the face of an increasing burden of valvular heart disease and relatively unrestrained by earlier anatomical or technical limitations,[1] it is critical

* Address correspondence to: Martin K.C. Ng, BSc (Med), MBBS, PhD, Department of Cardiology, Royal Prince Alfred Hospital, Camperdown, New South Wales 2050.
E-mail address: martin.ng@sydney.edu.au (M.K.C. Ng).

https://doi.org/10.1016/j.shj.2024.100284

that structural heart interventions are targeted at those who will derive benefit.

In 2018, 2 major randomized controlled trials of mitral transcatheter edge-to-edge repair (TEER) in patients with functional mitral regurgitation (FMR) and symptomatic heart failure were published.[2,3] These reported divergent results for apparently similar populations. Various explanations for this have been put forward. The proportionality theory proposes that the relative severity ('proportionality') between mitral regurgitation (MR) and left ventricular (LV) dilatation/remodeling differentiates response to TEER; MR was deemed 'proportionate' if MR severity (measured by effective regurgitant orifice area [EROA]) was at or below that expected for the LV dilatation (measured by end diastolic volume) and deemed 'disproportionate' if the MR was above that expected from the LV volume.[4]

Several studies have attempted to test this theory and reported conflicting results. Here we present a systematic review of the literature and meta-analysis of results to assess whether or not FMR proportionality is associated with response to TEER.

Methods

Adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines,[5] we performed a systematic search of the PubMed and Medline databases from January 2018 to May 2023 to identify all studies assessing MR proportionality in adult patients undergoing mitral TEER for FMR. Figure 1 shows the flowchart of study identification and screening. After identifying relevant publications using a comprehensive search strategy, 2 reviewers (A.M. and J.C.) independently screened study abstracts using prespecified inclusion criteria. Studies were considered if they satisfied the following criteria:

- Population: adults with more than moderate (2+) MR undergoing mitral TEER
- Exposure: baseline proportionate mitral regurgitation (p-MR) using any measure of MR proportionality
- Comparison: baseline disproportionate mitral regurgitation (d-MR), using any measure of MR proportionality
- Outcome: the primary outcome was a combined endpoint of all-cause mortality or heart failure hospitalization (ACM/HFH) at 12 months; secondary outcomes included all-cause mortality at 24 months and residual MR > 2+

Statistical Analysis

Selected studies were meta-analyzed using a random-effects model ($I^2 \geq 50\%$). p-MR was compared to d-MR, and binary outcomes were presented using risk ratios (RRs) with 95% confidence intervals (95% CIs). Data were analyzed using SPSS version 24.0 (IBM Corp, Armonk, New York) and Cochrane RevMan[6] was used to generate Forrest plots.

Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses search flowchart is shown in Figure 1. The search identified 1434 studies, of which 14 met criteria to proceed to full-text screening. Six trials with a total of 1594 patients (mean age 71 years, 66% male) were included, which assessed MR proportionality using either a ratio of estimated regurgitant orifice area to left ventricular end-diastolic volume (EROA:LVEDV) or regurgitant fraction (RF). Seven hundred and five (44%) patients (mean age 70 years, 75% male) were classified as p-MR and 889 (56%) patients (mean age 72 years, 60% male) as d-MR. In all studies, mitral TEER was performed with the MitraClip device. The mean follow-up duration was 20 ± 5 months, and all studies reported outcomes at a minimum of 12 months follow-up. Table 1 summarizes the key features of the included studies, and Table 2 compares the two groups at baseline. The overall quality of observational studies was "high," according to the Newcastle-Ottawa Scale.

As shown in Figure 2, there was no significant association of MR proportionality by EROA:LVEDV with all-cause mortality (RR 0.79, 95% CI 0.44-1.42). MR proportionality by RF was associated with a 3.5-fold risk of

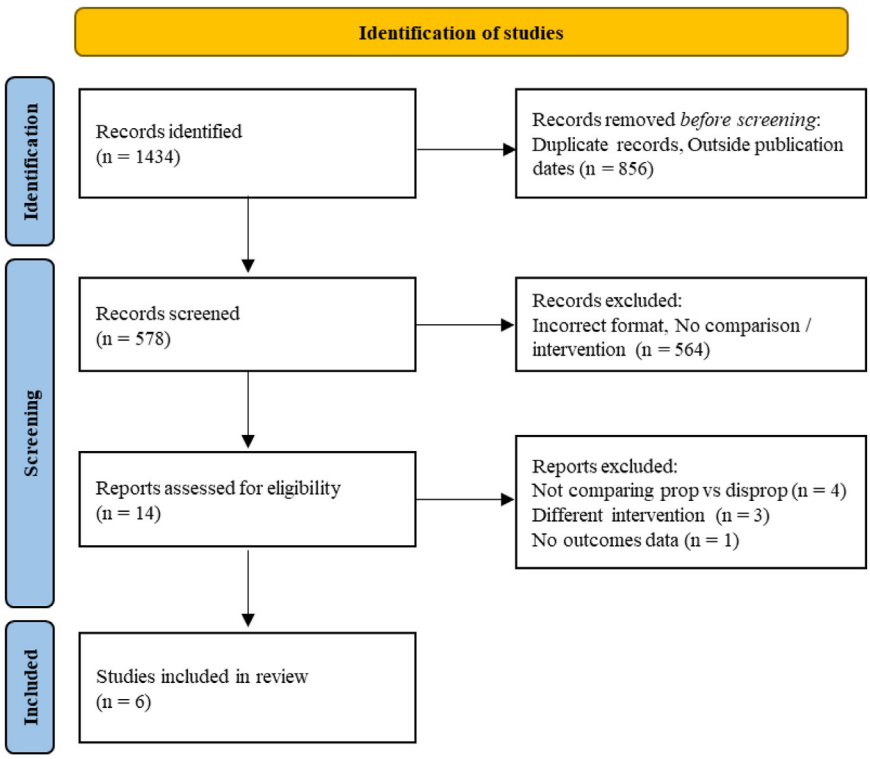

Figure 1. Flowchart of process of study identification and systematic review.

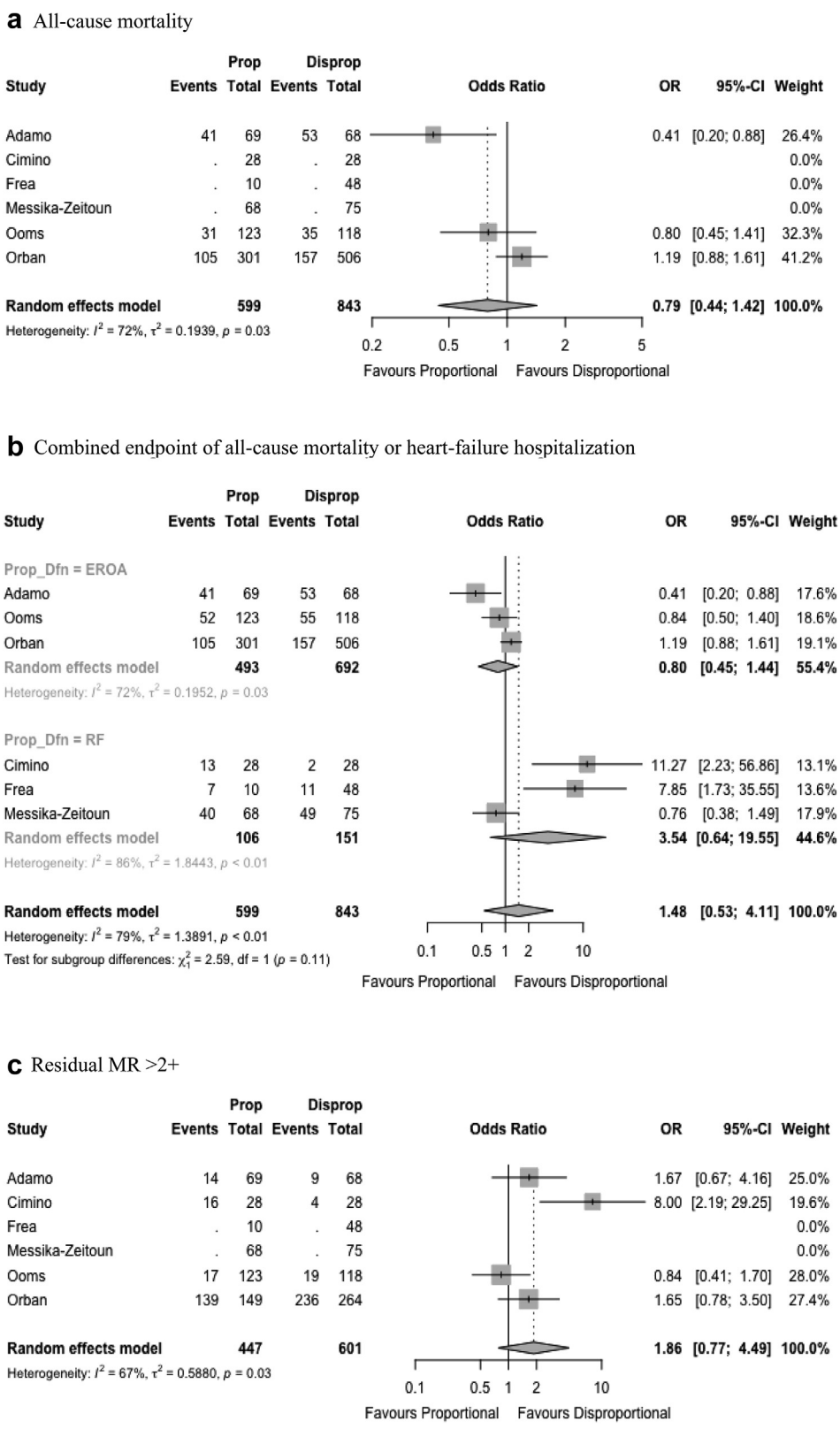

Figure 2. Proportionate vs disproportionate mitral regurgitation outcomes post- transcatheter edge-to-edge repair for functional mitral regurgitation. Squares represent individual studies, with the size proportional to the weight in the meta-analysis. Horizontal lines and widths of diamonds show 95% CIs. (a) All-cause mortality. (b) Combined endpoint of all-cause mortality or heart-failure hospitalization. (c) Residual mitral regurgitation >2+.
Abbreviations: CI, confidence interval; EROA, effective regurgitant orifice area; MR, mitral regurgitation; OR, odds ratio; RF, regurgitant fraction.

all-cause mortality in d-MR vs p-MR, though with wide CIs (RR 3.5, 95% CI 0.54-19.5).

Proportionality did not significantly associate with ACM/HFH, though there were divergent overall effect signals when proportionality was measured by EROA:LVEDV (RR 0.80, 95% CI 0.45-1.44) or RF (RR 1.48, 95% CI 0.53-4.11), with wide CIs.

d-MR showed a stronger association with residual MR >2+ post-TEER, with a 1.86-fold risk of significant residual MR post-TEER for d-

Table 1
Characteristics of the included studies

First author	Year published	Study site	Recruitment	Design	Inclusion	Exclusion	Criteria for d-MR	Follow-up duration
Adamo[7]	2020	Italy, Switzerland	December 2008-May 2016	Retrospective, observational, cohort	3+/4+ FMR undergoing TEER	DMR, incomplete baseline echo data	EROA/LVEDV ratio >1.4 (median)	24
Cimino[8]	2022	Italy	Not specified	Prospective, observational, cohort	(1) severe FMR (2) LVEF <45% (3) high risk (4) NYHA III-IV despite OMT (5) high-quality echo windows	(1) DMR (2) unsuitable for MitraClip (3) low life expectancy	RF >50%	12
Frea[9]	2021	Italy	June 2016-June 2018	Retrospective, observational, cohort	(1) severe FMR (2) LVEF ≤235% (3) NYHA IV	DMR, contraindication to TEE, HF due to specific cardiomyopathies Post-TEER >2+ MR or MG ≥4mmHg	RF >50%	12
Messika-Zeitoun[10]	2021	France	Dec 2013-Mar 2017	Prospective, observational, cohort	(1) severe FMR (EROA >20mm^2 or RVol >30 mL) (2) LVEF 15%-40% (3) NYHA II-IV despite OMT		RF >50% EROA/EDV >0.15	24
Ooms[11]	2022	Netherlands, Belgium	2011-2019	Retrospective, observational, cohort	(1) 3+/4+ FMR (2) HFrEF despite OMT (3) TEER feasible	Previous MVr/MVR, HTx, untreated CAD, LVEF >55%, other structural dz, sBP >180	EROA/LVEDV ratio >0.13 (median) RVol/LVEDV ratio ≥0.20 (median)	24
Orban[12]	2021	Europe	Nov 2008-Jan 2019	Retrospective, observational, cohort	(1) severe FMR treated with TEER	Not specified	d-MR: EROA/LVEDV ratio ≥0.165p-MR: EROA/LVEDV ratio <0.115	22

Notes. All TEER procedures were performed with MitraClip.
Abbreviations: CAD, coronary artery disease; DMR, degenerative mitral regurgitation; EDV, end diastolic volume; EROA, estimated regurgitant orifice area; FMR, functional mitral regurgitation; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HTX, heart translpant; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MG, mean gradient; MR, mitral regurgitation; MVr, mitral valve repair; MVR, mitral valve replacement; OMT, optimal medical therapy; RF, regurgitant fraction; RVol, regurgitant volume; sBP, systolic blood pressure; TEER, transcatheter edge-to-edge repair; TEE, transesophageal echocardiography.

Table 2
Pooled characteristics of d-MR and p-MR subgroups

Variable	Proportionate MR (n = 705)	Disproportionate MR (n = 889)
Age (y)	70 ± 3	72 ± 3
Sex (male)	397 (75%)	459 (60%)
HTN	333 (64%)	447 (62%)
CKD	242 (54%)	409 (63%)
Stroke	53 (11%)	57 (8%)
AF	285 (54%)	492 (64%)
IHD	294 (56%)	355 (49%)
NYHA III/IV	486 (92%)	679 (88%)
LVEF (%)	28 ± 3	32 ± 4
LAV (mL)	62 ± 29	60 ± 28
MR 4+	214 (43%)	371 (54%)
LVEDV (mL)	244 ± 24	175 ± 38
LVESV (mL)	165 ± 8	105 ± 17
EROA (cm^2)	0.3 ± 0.1	0.4 ± 0.1
EROA/LVEDV (cm^2/mL)	1.0 ± 0.2	2.5 ± 0.4
RV/LVEDV (mL/mL)	0.13 ± 0.02	0.32 ± 0.05
RVol (mL)	32 ± 5	51 ± 3
TR >2+	34 (28%)	56 (47%)
TR PG (mmHg)	41 ± 4	41 ± 5

Notes. Mean ± standard deviation or number (percentage).
Abbreviations: AF, atrial fibrillation; CKD, chronic kidney disease; EROA, estimated regurgitant orifice area; HTN, hypertension; IHD, ischemic heart disease; LAV, left atrial volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association; RV, right ventricle; RVol, regurgitant volume; TR, tricuspid regurgitation; PG, peak gradient.

MR vs p-MR, though this ranged from a 23% lower risk to a 4.5-fold risk (RR 1.86, 95% CI 0.77-4.49).

Discussion

Our analysis shows that differentiating proportionate and disproportionate FMR in patients undergoing mitral TEER was not significantly associated with all-cause mortality and heart failure hospitalizations, all-cause mortality alone, or >2+ residual MR.

The 2 proportionality measurements of RF and EROA:LVEDV produced divergent associations with outcomes, with a trend toward increased ACM/HFH that was disproportionate when RF was used and a more neutral result when EROA:LVEDV was used. This may result from the inherent physiological issues that limit the reliability of using quantitative measurements of regurgitation severity in FMR,[13,14] and require additional clinical investigation to define whether d-MR to LV size as determined by RF/LVEDV is better able to predict TEER responders in FMR.

There is no agreed approach to assessing proportionality in FMR; included studies used either EROA:LVEDV or RF, though one study evaluated 11 different proportionality measures.[10] In the subset of FMR patients in which quantitative assessment can be reliably made, numerous dynamic factors (cardiac output, increased LV dimensions, chamber compliance, preload, and afterload) affect the EROA and regurgitant volume. FMR severity may also be quantitatively assessed by RF,[15,16] which integrates cardiac output and considers LV remodeling. Due to the volume-dependent nature of MR, these measurements are best evaluated as a series of measurements over time in medically optimized and euvolemic patients rather than a single measurement being used diagnostically.

There has been no previous systematic review and meta-analysis evaluating the MR proportionality hypothesis in patients with FMR undergoing TEER, though this hypothesis has certainly generated substantial discussion.

The physiologic association between MR severity and LV size is conceptually important in approaching FMR[17]; however, whether this identifies suitable and durable TEER responders remains unsubstantiated. This meta-analysis does not support the proposal that a greater

relative degree of FMR (disproportionate FMR) in relation to LV dimensions consistently identifies patients more likely to benefit from intervention.

Prospective RCTs evaluating the impact of MR:LV proportionality on outcomes in patients undergoing TEER for FMR are needed to resolve this hypothesis, potentially integrating advanced imaging techniques such as 3D echocardiography or cardiac magnetic resonance imaging. Ideally, the judgment of proportionality should integrate both quantitative and qualitative measures of FMR severity, as well as various criteria to describe the bidirectional relationship of MR severity and LV geometry. LV dysfunction in FMR may be the most important factor influencing mortality and HFH and potentially explains the inconclusive results of TEER interventions in FMR. We note there have been no published studies investigating LV contractile reserve as assessed by stress imaging in predicting responders to TEER in FMR and suggest this as a potential future research direction. Finally, clinical studies to date have largely focused on survival and hospitalization endpoints, neglecting in our opinion, the most clinically important outcome of valvular intervention—the impact on the patient's symptoms and physical function. Improvements in NYHA functional class, 6MWD, and quality of life are important patient-centered clinical outcomes and should be routinely assessed in studies of TEER in FMR.

Limitations

Published studies on this topic have predominantly been observational and retrospective; however, RCTs are required to reduce bias. The wide CIs in this meta-analysis were likely due to small sample size and heterogeneity. Larger cohort sizes using consistent methods for defining proportionality would address this.

The ongoing MATTERHORN and RESHAPE-HF2 RCTs evaluating TEER vs surgery or guideline-directed medical therapy, respectively, may help identify responders and refine TEER selection algorithms.

Conclusions

In patients undergoing TEER for FMR, MR proportionality was not significantly associated with ACM/HFH, all-cause mortality, or residual MR.

ORCIDs

Avalon Moonen https://orcid.org/0000-0002-0039-3911

Ethics Statement

This research adheres to the relevant ethical guidelines for research on human subjects. PROSPERO ID: CRD42022330456.

Funding

The authors have no funding to report.

Disclosure Statement

The authors report no conflict of interest.

References

1 Khatib D, Neuburger PJ, Pan S, Rong LQ. Transcatheter mitral valve interventions for mitral regurgitation: a review of mitral annuloplasty, valve replacement, and chordal repair devices. *J Cardiothorac Vasc Anesth*. 2022;36(10):3887-3903.
2 Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379(24):2307-2318.
3 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):2297-2306.
4 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):353-362.
5 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
6 *Review Manager (RevMan) Web*. The Cochrane Collaboration; 2020. Accessed February 25, 2024. https://revman.cochrane.org
7 Adamo M, Cani DS, Gavazzoni M, et al. Impact of disproportionate secondary mitral regurgitation in patients undergoing edge-to-edge percutaneous mitral valve repair. *EuroIntervention*. 2020;16(5):413-420.
8 Cimino S, Agati L, Filomena D, et al. 3D echo characterization of proportionate and disproportionate functional mitral regurgitation before and after percutaneous mitral valve repair. *J Clin Med*. 2022;11(3):645.
9 Frea S, Pidello S, Boretto P, et al. Disproportionate functional mitral regurgitation predicts a favourable response after MitraClip implant in patients with advanced heart failure. Real-world evidence of a new conceptual framework. *Int J Cardiol*. 2021;323:208-212.
10 Messika-Zeitoun D, Bernard I, Armoiry X, et al. Impact of mitral regurgitation severity and left ventricular remodeling on outcome after MitraClip implantation: results from the Mitra-FR trial. *JACC Cardiovasc Imaging*. 2021;14(4):742-752.
11 Ooms JF, Bouwmeester S, Debonnaire P, et al. Transcatheter edge-to-edge repair in proportionate versus disproportionate functional mitral regurgitation. *J Am Soc Echocardiogr*. 2022;35(1):105-115.e8.
12 Orban M, Karam N, Lubos E, et al. Impact of proportionality of secondary mitral regurgitation on outcome after transcatheter mitral valve repair. *JACC Cardiovasc Imaging*. 2021;14(4):715-725.
13 Hagendorff A, Knebel F, Helfen A, et al. Disproportionate mitral regurgitation: another myth? A critical appraisal of echocardiographic assessment of functional mitral regurgitation. *Int J Cardiovasc Imaging*. 2021;37(1):183-196.
14 Hahn RT. Disproportionate emphasis on proportionate mitral regurgitation-are there better measures of regurgitant severity? *JAMA Cardiology*. 2020;5(4):377-379.
15 Grayburn PA, Carabello B, Hung J, et al. Defining "severe" secondary mitral regurgitation: emphasizing an integrated approach. *J Am Coll Cardiol*. 2014;64(25):2792-2801.
16 Kamoen V, Calle S, De Buyzere M, Timmermans F. Proportionate or disproportionate secondary mitral regurgitation: how to untangle the Gordian Knot? *Heart*. 2020;106(22):1719-1725.
17 Bernard J, Ternacle J, Hadjadj S, et al. Reappraisal of the regurgitation severity vs left ventricular dilation conceptual framework for the management of secondary mitral regurgitation. *Can J Cardiol*. 2022;38(11):1775-1778.