



# Early and mid-term outcomes of mitral annular calcification and transcatheter mitral therapy: a systematic review

Yosuke Sakurai<sup>1</sup>, Ashton McDonald<sup>2</sup>, Tsuyoshi Kaneko<sup>1</sup>

<sup>1</sup>Division of Cardiothoracic Surgery, Department of Surgery, Washington University in St. Louis, St. Louis, MO, USA; <sup>2</sup>Department of Surgery, Marshall University Joan Edwards School of Medicine, Huntington, WV, USA

Correspondence to: Tsuyoshi Kaneko, MD. Division of Cardiothoracic Surgery, Department of Surgery, Washington University in St. Louis, 660 S Euclid Ave., St. Louis, MO 63110, USA. Email: Kaneko@wustl.edu.

**Background:** Mitral annular calcification (MAC) poses technical and clinical challenges in patients undergoing mitral valve intervention. Patients with severe MAC were excluded from major previous randomized controlled trials evaluating mitral therapies. Consequently, outcomes following mitral transcatheter edge-to-edge repair (M-TEER) in this population remain controversial.

**Methods:** MEDLINE and EMBASE were searched through June 2025 to identify studies reporting outcomes after M-TEER in patients with MAC. This systematic review assessed the difference in MAC grading and M-TEER eligibility across studies. The definition of procedural success was documented to highlight inconsistencies. The primary endpoint was all-cause mortality during follow-up. Secondary endpoints included procedural success, heart failure rehospitalization, mitral valve reintervention, residual mitral regurgitation (MR), and mean mitral gradient.

**Results:** Six studies met inclusion criteria, including 2,808 patients undergoing M-TEER, of whom 363 (12.9%) had moderate-to-severe MAC. Most studies defined procedural success as MR reduction to grade  $\leq 2$ , though only one incorporated a mean transmitral gradient  $< 5$  mmHg. MR reduction to  $\leq 2$  rates were comparable between patients with none-mild MAC and moderate-severe MAC. However, device success (MR reduction  $\leq 2$  and mean gradient  $< 5$  mmHg) was significantly lower in MAC patients (56.1% versus 81.3%). Post-procedural mitral valve gradient  $> 5$  mmHg occurred in 18.5–48.3% of MAC cases. Two studies reported increased all-cause mortality in patients with moderate-severe MAC during follow-up, with a mean follow-up of 20.4 months. Residual MR and reintervention rates were generally similar between groups, though mitral valve gradients tended to be higher in MAC patients.

**Conclusions:** M-TEER is feasible in well-selected patients with moderate-to-severe MAC; however, elevated post-procedural gradients remain a concern and may impact long-term outcomes. The absence of standardized eligibility criteria for M-TEER and consistent MAC quantification limits optimal patient selection. Comparative studies with surgical repair/replacement and transcatheter mitral valve replacement are critically needed to define optimal therapy.

**Keywords:** Transcatheter edge-to-edge repair; mitral annular calcification (MAC); transcatheter mitral valve replacement (TMVR)



Submitted Aug 27, 2025. Accepted for publication Nov 14, 2025. Published online Nov 29, 2025.

doi: 10.21037/acs-2025-mac-0128

View this article at: <https://dx.doi.org/10.21037/acs-2025-mac-0128>

## Introduction

Patients with mitral annular calcification (MAC) and mitral regurgitation (MR) represent a challenging population to treat, and MAC has been associated with worse outcomes

following surgical mitral valve repair (1). Although patients with severe MAC have been excluded in previous randomized controlled trials (2), mitral transcatheter edge-to-edge repair (M-TEER) has been increasingly utilized in

patients with MAC, as they are often considered high-risk for surgical repair or replacement. Earlier studies supported the feasibility of M-TEER in carefully selected patients with severe MR (3).

However, previous studies included both functional mitral regurgitation and degenerative mitral regurgitation (FMR and DMR) and were often limited to consecutive patients undergoing M-TEER for severe MR with MAC. Eligibility criteria for M-TEER were inconsistently reported, and outcomes in patients who were declined M-TEER and treated medically were not reported. Patient selection likely influenced the reported clinical outcome following M-TEER. Furthermore, variability existed in the definition of MAC severity and procedural success. Differences in study design, such as comparing different MAC severities (e.g., none-mild MAC versus moderate-severe MAC, or no MAC versus any degree of MAC), have contributed to the heterogeneity in the findings. Due to these differences in eligibility criteria and definitions of moderate-severe MAC, the reported prevalence of moderate-to-severe MAC among patients undergoing M-TEER has varied widely, from 7% to 38% (4,5). Furthermore, follow-up durations were limited up to 1 to 2 years, and long-term outcomes remain scarce. Lastly, comparative studies between surgical repair/replacement, transcatheter mitral valve replacement (TMVR), and M-TEER are limited.

We therefore conducted a systematic review to identify gaps in the literature focused on patients undergoing M-TEER. We highlight differences in patient eligibility across studies, the variability in MAC severity quantification, and the limited data on long-term outcomes.

## Methods

The study protocol was prospectively registered with PROSPERO. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement standards (6). Ethical approval was not required for this study, as it was a systematic review.

All studies investigating outcomes following M-TEER in patients with MAC were identified through MEDLINE and EMBASE. Databases were searched through June 2025 using web-based search engines. Search terms included “mitral transcatheter edge-to-edge repair”, “mitral annular calcification”. We defined the PECO criteria as follows for the database search. P: patients with either DMR or FMR. E: M-TEER in patients with MAC. C: M-TEER in patients

without MAC. O: procedural success, residual MR, all-cause mortality, heart failure rehospitalization during follow-up. We included studies regardless of MR etiology (DMR or FMR), and the proportion of DMR was documented to characterize each study.

Relevant studies were identified by manually searching secondary sources, including references of initially identified articles, reviews, and commentaries. Two independent and blinded authors reviewed the search results separately to select articles. To avoid overlapping samples, country, institution, and enrolment year were reviewed. Study quality was assessed using the Risk of Bias in Non-Randomized Studies of Interventions tool (ROBINS-I) (7).

The primary endpoint was all-cause mortality during follow-up. The secondary endpoint was heart failure rehospitalization, reintervention, and procedural success, residual MR, and mitral valve pressure gradient. To summarize the key baseline characteristics, meta-analyses of proportions or means were performed. A random-effects model was chosen to account for between-study heterogeneity. For studies reporting medians with interquartile ranges, values were converted to estimated means and standard deviations using the methods described by Wan *et al.* (8). Analyses were conducted in R version 4.1.2 with the “meta” package (R Foundation for Statistical Computing, Vienna, Austria).

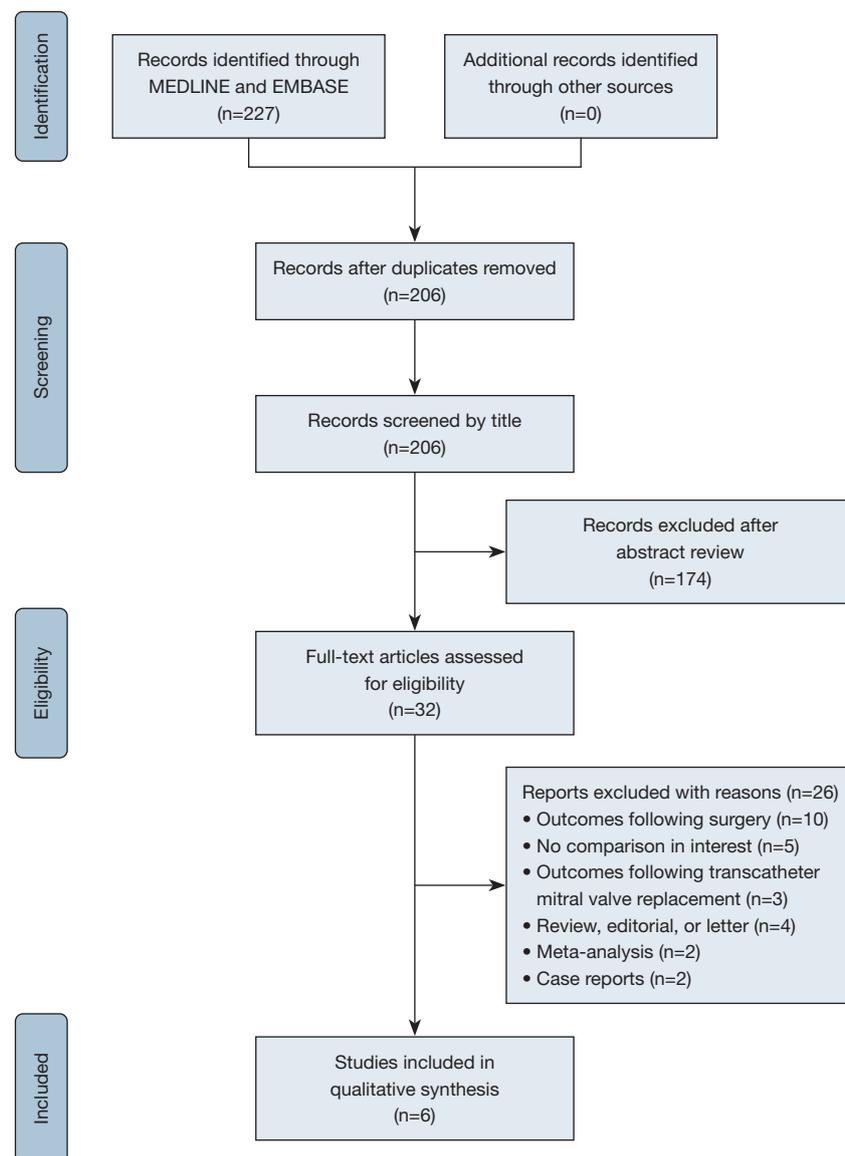
## Results

### Study selection

A systematic search yielded 227 studies. Of those, 32 articles were considered relevant for the meta-analysis. Following full-text review, 6 articles published from 2016 to 2024 met the inclusion criteria (*Figure 1*). A total of 2,808 patients underwent M-TEER. Of those, 2,446 patients had none-mild MAC, and 363 patients had moderate-severe MAC (12.9%).

### Study characteristics

The study profile and patient characteristics are summarized in *Table 1*. Study periods ranged from 2009 to 2022. The definition of MAC grading and eligibility for M-TEER in each study is shown in *Table 2*. Most studies defined MAC grades based on calcium distribution in the total annular circumference. Mild  $\leq 120^\circ$ , moderate  $< 240^\circ$ , and severe



**Figure 1** Workflow for selecting eligible papers according to PRISMA criteria. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

>240°. One study quantified the severity of MAC based on the following computed tomography (CT) findings: annulus calcium thickness, distribution of calcium in the annulus circumference, involvement of the fibrous trigones, and involvement of the mitral leaflets. Patient eligibility for M-TEER varied across studies (*Table 2*), and anatomical suitability was assessed in each institution. Patients were deemed to be high-risk for surgical mitral valve repair or replacement. The common exclusion criteria were baseline

mean mitral gradient >5 mmHg, mitral valve area (MVA) <3.5 or 4.0 cm<sup>2</sup>.

Patients with moderate-severe MAC were older compared with those with none-mild MAC (80.3 *vs.* 76.3 years) and more often female (56.3% *vs.* 42.2%). DMR was more frequent in the moderate-severe group (51.9% *vs.* 40.7%). The mean Society of Thoracic Surgeons (STS) score was higher in the moderate-severe group (8.5% *vs.* 6.3%). Left ventricular ejection fraction was greater in

**Table 1** Study design and prevalence of moderate-to-severe MAC across studies

Author	Year	Degenerative MR (%)	Control	Comparison	Number of patients			Prevalence of moderate to severe MAC (%)
					Total	None to mild MAC	Moderate to severe MAC	
Cheng (9)	2016	Not reported	None or mild MAC	Moderate to severe MAC	173	145	28	16.2
Fernández-Peregrina (5)	2022	39.3	None or mild MAC	Moderate to severe MAC	852	791	61	7.2
Taha Hatab (10)	2023	41.8	None or mild MAC	Moderate to severe MAC	280	249	31	11.1
Shechter (11)	2024	52.5	None or mild MAC	Moderate to severe MAC	968	867	101	10.4
Mustafa (4)	2024	57.0	None or mild MAC	Moderate to severe MAC	260	160	100	38.5
Tanaka (12)	2024	68.3	No MAC	Mild to severe MAC	275	234	41	14.9

MAC, mitral annular calcification; MR, mitral regurgitation.

**Table 2** MAC grading criteria and eligibility for M-TEER by study

Author	Year	MAC grading	Eligibility for M-TEER
Cheng (9)	2016	MAC was quantified as mild, moderate, or severe upon involvement of $\leq 120^\circ$ , $< 240^\circ$ , or $> 240^\circ$ of the annular circumferences	Not reported
Fernández-Peregrina (5)	2022	MAC was quantified as mild, moderate, or severe upon involvement of $\leq 120^\circ$ , $< 240^\circ$ , or $> 240^\circ$ of the annular circumferences or severe in case of a thickness $> 4$ mm	Leaflet calcification, short ( $< 7$ mm) or thick leaflets ( $> 5$ mm) or had a preprocedural mean gradient $> 5$ mmHg or a MVA $< 4$ cm <sup>2</sup> were declined for percutaneous repair
Taha Hatab (10)	2023	MAC was determined based on the calcium distribution on the annular apparatus: mild: focal noncontiguous calcification limited to $< 180^\circ$ of the annular circumference, moderate: continuous calcification $180^\circ$ to $< 270^\circ$ , and severe: continuous calcification $\geq 270^\circ$	Feasible anatomy
Shechter (11)	2024	MAC was quantified as mild, moderate, or severe upon involvement of $\leq 120^\circ$ , $< 240^\circ$ , or $> 240^\circ$ of the annular circumferences. Moderate-severe MAC was also defined by protrusion into the left ventricle	Not reported
Mustafa (4)	2024	MAC was quantified as mild, moderate, or severe upon involvement of $\leq 120^\circ$ , $< 240^\circ$ , or $> 240^\circ$ of the annular circumferences	Mean transmitral gradient $> 5$ mmHg, MVA $< 3.5$ cm <sup>2</sup> , and unsuitable leaflet morphology were excluded
Tanaka (12)	2024	MAC score was calculated based on the following CT findings: average annulus calcium thickness, distribution in the annulus circumference, fibrous trigones involvement, and mitral leaflet involvement	Patients with a pre-procedural mean transmitral gradient of $> 5$ mmHg or a prior history of mitral valve interventions were excluded from the present analysis

CT, computed tomography; MAC, mitral annular calcification; M-TEER, mitral transcatheter edge-to-edge repair; MVA, mitral valve area.

patients with moderate-severe MAC (55.0% vs. 48.0%), whereas the MVA was smaller (4.6 vs. 5.3 cm<sup>2</sup>) and the mean mitral gradient higher (2.8 vs. 2.2 mmHg). A summary of baseline characteristics is presented in *Tables 3,4*.

The risk of bias is summarized in *Figure 2*, showing that all included studies were considered to have a low to moderate risk of bias.

### Short-term outcomes

Five out of six studies defined procedural success as MR grade reduction to 2 or less. Procedural success rate ranged from 91.4% to 100% in the moderate-severe MAC group, and 92.6% to 97.1% in the none-mild MAC group. One study reported functional procedural success rate, which is defined as the successful implantation of the TEER devices with residual MR  $\leq 2$  and mean transmitral gradient  $< 5$  mmHg upon discharge. In this study, patients with moderate-severe MAC had a significantly lower functional procedural success rate of 56.1% compared to 81.3% in patients without MAC (12) (*Table 5*). Immediate residual MR and mean transmitral gradient are shown in *Table 6*. Although patients with moderate-severe MAC achieved similar MR grades, the mean transmitral gradient tended to be higher in the MAC group. The proportion of mean transmitral gradient  $> 5$  mmHg ranged from 18.5% to 48.3%.

### Outcomes during follow-up

Reported outcomes during follow-up are presented in *Table 7*. Two of six studies reported significantly worse all-cause mortality during follow-up in patients with moderate-severe MAC. Follow-up duration ranged from 12 to 29 months, with a weighted mean follow-up of 20.4 months. Three studies reported heart failure rehospitalization, and none of the results were statistically significant. Similarly, there was no significant difference in reintervention.

Echocardiographic outcomes during follow-up are shown in *Table 8*. Only one study reported a significantly worse residual MR grade 3 or 4 at 1 year, while the other five studies reported comparable residual MR at 1 year. In contrast, mean mitral valve gradients at 1 year were higher in the moderate-severe MAC group in most studies.

## Discussion

This systematic review analyzing the outcomes on M-TEER

in MAC patients highlighted several key findings. First, M-TEER is feasible to reduce MR in well-selected patients with MAC, although procedural success was mostly defined by MR reduction to moderate or less. Second, large number of patients had post-procedural mitral valve gradient  $> 5$  mmHg. Lastly, long-term outcomes were worse with moderate-severe MAC patients undergoing M-TEER. Our findings suggest that although M-TEER is feasible in well-selected patients with moderate-to-severe MAC, increased gradient and poor long-term survival indicates the need for alternative strategy in this high-risk cohort.

Despite limited data, this transcatheter approach appears to have a role in selected patients with MAC. MAC is a known independent predictor of mortality due to its association with multiple comorbidities. Historically, many patients with severe MAC left untreated due to high surgical risks and limited transcatheter options, and the natural history of untreated MAC is poor, with a 1-year survival rate of 72% (13,14). While the surgical approach remains the gold standard for patients at appropriate risks, MAC presents substantial anatomical and technical complexity during surgery, such as increased risks for atrioventricular groove disruption or circumflex artery injury, that contribute to elevated operative mortality (1). MAC is considered one of the most challenging pathologies to manage in cardiac surgery, prompting growing interest in transcatheter options including M-TEER.

One of the key procedural challenges with M-TEER in patients with MAC is the frequent development of elevated mitral valve gradient, as they may attenuate the benefit of MR reduction. Although the acceptable gradient threshold is not clearly defined, higher gradients appear to be associated with worse clinical outcomes during follow-up, particularly in patients with DMR (11,15). Several studies described the exclusion criteria for M-TEER based on a baseline mean mitral gradient  $> 5$  mmHg or MVA  $< 4.0$  cm<sup>2</sup> (4,5). Careful pre-procedural assessment is critical to identify patients at risk of excessive gradient after M-TEER. Long-term outcome data remain limited, and moderate-severe MAC may be associated with worse all-cause mortality during follow-up (10,12) Furthermore, reintervention rates may underestimate actual clinical failure, as many patients with severe MAC are poor candidates for further intervention due to frailty or comorbidities (16). Notably, subsequent surgery following failed M-TEER is associated with worse clinical outcomes and a low likelihood of valve repair (17,18).

**Table 3** Patient demographics and clinical characteristics stratified by MAC severity

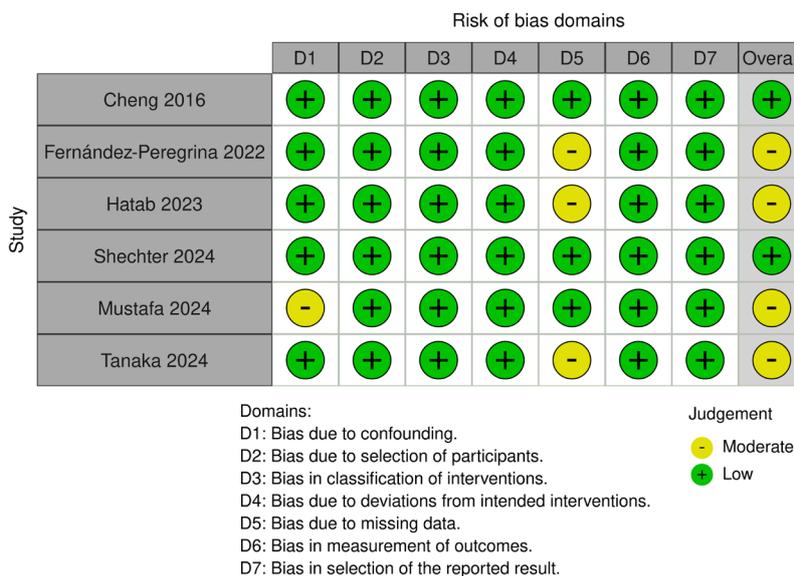
Author	Year	Study periods	Group	No. of patients	Age (years)	Female (%)	DM (%)	CAD (%)	Stroke (%)	AF (%)	Degenerative MR (%)	STS score (%)	EuroSCORE (%)	MVA (cm <sup>2</sup> )	TMPG (mmHg)	LVEF (%)	LVDd (cm)	LVDs (cm)
Cheng (9)	2016	2009–2014	None-mild MAC	145	75.7	37.2	27.6	52.4	NA	66.9	NA	10.1	NA	NA	1.8	51.5	5.46	3.97
			Moderate-severe MAC	28	84.2	60.7	21.4	64.3	NA	71.4	NA	13.2	NA	NA	2.2	61.6	4.92	3.33
Fernández-Peregrina (5)	2022	2012	None-mild MAC	791	72.8	34.0	44.2	52.7	9.9	58.2	30.1	3.0	4.9	5.3	1.7	40.4	6.08	4.49
			Moderate-severe MAC	61	78.3	55.7	39.3	42.6	9.8	63.9	39.3	4.0	5.6	4.9	2.3	52.5	5.31	3.49
Taha Hatab (10)	2023	2014–2022	None-mild MAC	249	76.4	41.0	24.1	35.3	10.0	60.7	54.3	4.8	NA	5.4	NA	51.2	5.30	3.80
			Moderate-severe MAC	31	79.0	61.3	51.6	51.6	29.0	45.2	41.8	9.1	NA	4	NA	52.8	4.90	3.20
Shechter (11)	2024	2013–2021	None-mild MAC	867	78.0	44.9	25.8	42.4	13.1	52.2	42.0	5.4	NA	5.5	3.0	50.0	5.30	3.90
			Moderate-severe MAC	101	83.0	52.5	34.0	49.5	15.8	63.4	52.5	6.8	NA	4.5	3.0	59.0	5.00	3.30
Mustafa (4)	2024	2018–2022	None-mild MAC	160	79.1	46.9	31.9	18.8	8.1	54.4	50.0	8.0	NA	5.0	3.2	48.1	5.40	4.10
			Moderate-severe MAC	100	77.9	56.0	28.0	17.7	8.1	50.0	57.0	9.1	NA	5.0	4.3	48.9	5.30	3.90
Tanaka (12)	2024	2013–2021	No MAC	160	76.5	51.9	21.9	51.2	7.5	83.8	29.4	NA	4.0	NA	1.5	49.8	NA	NA
			Mild MAC	74	79.5	50.0	32.4	54.1	6.8	81.1	44.6	NA	5.3	NA	1.6	54.4	NA	NA
			Moderate-severe MAC	41	81.3	61.0	24.4	53.7	12.2	68.3	68.3	NA	6.3	NA	2.0	60.0	NA	NA

AF, atrial fibrillation; CAD, coronary artery disease; DM, diabetes mellitus; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVDd, left ventricular end-diastolic diameter; LVD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; MAC, mitral annular calcification; MR, mitral regurgitation; MVA, mitral valve area; STS, Society of Thoracic Surgeons; TMPG, transmitral pressure gradient.

**Table 4** Summary of baseline characteristics stratified by MAC severity

Group	Age (years)	Female (%)	CAD (%)	Degenerative MR (%)	STS score (%)	MVA (cm <sup>2</sup> )	TMPG (mmHg)	LVEF (%)
None-mild MAC	76.3 [74.5–77.9]	42.2 [37.0–47.6]	41.5 [30.6–53.2]	40.7 [31.2–51.0]	6.3 [4.1–8.6]	5.3 [5.1–5.4]	2.2 [1.5–2.9]	48.0 [44.6–51.3]
Moderate-severe MAC	80.3 [78.4–82.1]	56.3 [51.1–61.3]	44.8 [30.8–59.6]	51.9 [42.5–61.3]	8.5 [5.8–11.2]	4.6 [4.2–5.1]	2.8 [1.9–3.6]	55.0 [51.2–58.9]

Data are presented as median [95% CI]. CAD, coronary artery disease; CI, confidence interval; LVEF, left ventricular ejection fraction; MAC, mitral annular calcification; MR, mitral regurgitation; MVA, mitral valve area; STS, Society of Thoracic Surgeons; TMPG, transmitral pressure gradient.



**Figure 2** The ROBINS-I. Green circles indicate a low risk of bias, yellow circles indicate a moderate risk of bias. ROBINS-I, Risk of Bias in Non-Randomized Studies of Interventions tool.

**Table 5** Procedural success definitions and rates in none-mild versus moderate-severe MAC groups

Author	Year	None to mild MAC, % (n/N)	Moderate to severe MAC, % (n/N)	Procedural success definition
Cheng (9)	2016	96.6 (140/145)	100.0 (28/28)	MR grade reduction to 2 or less
Fernández-Peregrina (5)	2022	94.9 (751/791)	91.8 (56/61)	MR grade reduction to 2 or less
Taha Hatab (10)	2023	92.6 (231/249)	91.4 (28/31)	MR grade reduction to 2 or less
Shechter (11)	2024	96.5 (837/867)	93.1 (94/101)	MR grade reduction to 2 or less
Mustafa (4)	2024	89.3 (143/160)	90.0 (90/100)	MR grade reduction to 2 or less
Tanaka (12)	2024	78.2 (183/234)	56.1 (23/41)	MR grade reduction to 2 or less and mean transmitral gradient <5 mmHg

MAC, mitral annular calcification; MR, mitral regurgitation.

**Table 6** Post-procedural mitral valve gradient and proportion with transmitral gradient >5 mmHg

Author	Year	Gradient (mmHg)		Gradient >5 mmHg (%)	
		None-mild MAC	Moderate-severe MAC	None-mild MAC	Moderate-severe MAC
Cheng (9)	2016	3.5±1.7	4.4±2.0	Not reported	Not reported
Fernández-Peregrina (5)	2022	3.0±1.3	3.6±1.3	5.0	18.5
Taha Hatab (10)	2023	4.0±1.8	5.5±2.1	20.4	48.3
Shechter (11)	2024	3.0 [2–4]	4.0 [3–5]	19.4	34.3
Mustafa (4)	2024	3.4±2.4	4.3±2.2	Not reported	Not reported
Tanaka (12)	2024	3.5±1.6	3.9±1.7	7.5	19.1

Values are expressed as mean ± SD or median [IQR]. IQR, interquartile range; MAC, mitral annular calcification; SD, standard deviation.

**Table 7** Clinical outcomes during follow-up after M-TEER

Author	Year	Follow-up duration (months)	All-cause mortality	HF rehospitalization	Reintervention
Cheng (9)	2016	29.2	HR 1.12 (95% CI: 0.55–2.28), P=0.753	Not reported	Not reported
Fernández-Peregrina (5)	2022	14.9	HR 2.0 (95% CI: 0.9–4.3), P=0.070	HR 1.5 (95% CI: 0.8–3.0), P=0.210	Not reported
Taha Hatab (10)	2023	23.1	HR 1.98 (95% CI: 1.27–3.10), P=0.002	21.7% (none-mild MAC) versus 12.9% (moderate-severe MAC), P=0.250	2.8% (none-mild MAC) versus 6.5% (moderate-severe MAC), P=0.260
Shechter (11)	2024	24.0	HR 1.18 (95% CI: 0.72–1.93), P=0.519	HR 1.27 (95% CI: 0.82–1.96), P=0.287	HR 1.74 (95% CI: 0.79–3.83), P=0.173
Mustafa (4)	2024	12.0	9.4% (none-mild MAC) versus 14% (moderate-severe MAC), P=0.249	Not reported	1.8% (none-mild MAC) versus 0% (moderate-severe MAC)
Tanaka (12)	2024	24.0	HR 2.52 (95% CI: 1.36–4.67), P=0.003	Not reported	1.1% (none-mild MAC) versus 2.1% (moderate-severe MAC), P=1.00

CI, confidence interval; HF, heart failure; HR, hazard ratio; MAC, mitral annular calcification; M-TEER, mitral transcatheter edge-to-edge repair.

**Table 8** Transthoracic echocardiography follow-up findings at 12 months after M-TEER

Author	Year	Echocardiography timing (months)	Residual MR grade 3 or 4 (%)		Gradient >5 mmHg (%)		Gradient (mmHg)	
			None-mild MAC	Moderate-severe MAC	None-mild MAC	Moderate-severe MAC	None-mild MAC	Moderate-severe MAC
Cheng (9)	2016	12	9.2	6.2	Not reported	Not reported	3.5±1.8	4.5±2.1
Fernández-Peregrina (5)	2022	12	20.5	9.4	Not reported	Not reported	3.6±1.7	4.6±2.1
Taha Hatab (10)	2023	12	6.8	11.1	Not reported	Not reported	4.2±2.2	5.0±2.2
Shechter (11)	2024	12	5.9	15.0	33.2	47.4	4 [3–5]	4 [3–6]
Mustafa (4)	2024	12	7.5	22.1	Not reported	Not reported	4.0±2.0	5.3±3.1
Tanaka (12)	2024	12	9.6	5.6	1.1	5.6 (P=0.14)	Not reported	Not reported

Values are expressed as mean ± SD or median [IQR]. IQR, interquartile range; MAC, mitral annular calcification; MR, mitral regurgitation; M-TEER, mitral transcatheter edge-to-edge repair; SD, standard deviation.

Moreover, the definition and quantification of MAC grade varied across studies. MAC was quantified by visual assessment on transthoracic echocardiography and classified as mild, moderate, or severe based on annular involvement of <120°, 120°–240°, or >240°, respectively.

However, this differs from more recent publications, which define mild as involving <180° of annulus (1,19,20). A recent consensus document recommends incorporating calcium thickness and leaflet/trigone involvement, although these factors were not consistently included (1).

Additionally, preoperative cardiac CT is recommended to assess detailed anatomical features when TMVR is being considered (19,21). While the cardiac CT-derived MAC score was developed primarily to estimate the feasibility of TMVR and associated procedural risks, it may also be useful for M-TEER candidates, as higher MAC scores and greater calcium volume were associated with lower rates of functional procedural success of M-TEER (12).

Lastly, we identified a gap in comparative studies evaluating alternative treatment modalities, such as conventional surgical repair or replacement, hybrid transatrial valve-in-MAC procedure, and transapical or transseptal TMVR. This lack of comparison stems from the fact that M-TEER has primarily been indicated in patients with high/prohibitive surgical risks, and most TMVR devices are at the clinical trial phase, limiting the availability of comparable populations. However, with the advancement of transcatheter treatment, it is expected that some borderline surgical risk patients will undergo M-TEER or TMVR. In fact, the overall mean STS score in this study was 5.3%, and one study reported an STS score of 3%, suggesting that some patients undergoing M-TEER may fall into a lower surgical risk category. Although the STS score alone does not fully capture the risks of intervention in patients with severe MAC, our findings indicate a potential opportunity for comparative studies in the future.

Among alternative options, outcomes following the hybrid transatrial valve-in-MAC procedure have been reported. This approach is used for patients with acceptable surgical risks but unfavorable anatomical features for conventional replacement. This technique allows direct deployment of balloon-expandable transcatheter valve, with potential adjunctive procedures, such as the use of pledgets or felts to prevent paravalvular leak, or anterior leaflet resection or septal myectomy to reduce left ventricular outflow (LVOT) obstruction. A recent multicenter registry reported a 30-day mortality of 9%, which is more favorable than the 21.4% reported in the MITRAL study's valve-in-MAC cohort (22,23). For patients with higher surgical risks and unsuitable anatomy for M-TEER, TMVR using dedicated mitral valve devices may be considered. TMVR device includes the transapical Tendyne valve (Abbott), which has recently received the U.S. Food and Drug Administration approval for use in patients with

MAC. Prior studies with Tendyne valve reported a 30-day mortality of 5–10% in patients with MAC (24,25). Other TMVR devices include Intrepid (Medtronic Inc.) and Sapien M3 (Edwards Lifesciences), both utilizing a transfemoral transseptal approach. A recent study showed promising technical success even in patients with MAC (26). Similarly, AltaValve system (4C Medical Technologies) has reported a high technical success rates in this population (27).

As transcatheter treatment continues to evolve, comparative studies are needed in patients with borderline surgical risks. Furthermore, rigorous anatomical screening is crucial for selecting effective interventions. In particular, comparative evaluation may be clinically meaningful in patients with borderline anatomical risks of mitral stenosis following M-TEER or LVOT obstruction following TMVR. Several ongoing trials now include patients with MAC (*Table 9*). However, it is important to note that the MAC cohort in these trials is single-arm, lacking a direct comparison.

### Study limitations

There are several limitations in this systematic review. All included studies were observational, with heterogeneity in MAC definitions, MR etiology, and follow-up duration. Additionally, a meta-analysis was not performed due to the limited number of new studies published since the most recent meta-analysis. Despite these limitations, our findings emphasize the need for standardized MAC assessment, clear eligibility criteria for M-TEER, and dedicated comparative trials to optimize treatment strategies for this complex patient population.

### Conclusions

M-TEER is a feasible option for reducing MR in well-selected patients with moderate-severe MAC. However, elevated post-procedural mitral gradients remain a concern. The absence of standardized eligibility criteria for M-TEER and consistent MAC quantification limits optimal patient selection. Comparative studies with surgical repair/replacement and TMVR, along with long-term follow-up, are critically needed to define optimal therapy and improve outcomes for this high-risk population.

**Table 9** Ongoing trials including patients with MAC undergoing transcatheter mitral valve replacement

Trial name	Device	Approach	Sponsor	NCT ID	Primary trial design	MAC cohort	Eligibility	Primary endpoint
SUMMIT	Tendyne	Transapical	Abbott	NCT03433274	TMVR (Tendyne) versus M-TEER (MitraClip)	Single-arm	Symptomatic, moderate-to-severe or severe mitral regurgitation or for patients with symptomatic mitral valve disease due to severe MAC	Death or HF at 1 year
ENCIRCLE	Sapien M3	Transseptal	Edwards Lifesciences	NCT04153292	Single-arm	Single-arm	Symptomatic, at least 3+ mitral regurgitation for whom commercially available surgical or transcatheter treatment options are deemed unsuitable	Death or HF at 1 year
APOLLO	Intrepid	Transseptal	Medtronic	NCT03242642	Single-arm	Single-arm	Subject is unsuitable for treatment with approved transcatheter repair or conventional mitral valve intervention	Death at 1 year for MAC cohort
AltaValve Pivotal Trial	AltaValve	Transapical or transseptal	4C Medical Technologies	NCT03997305	Single-arm	Single-arm	Symptomatic, severe mitral regurgitation. Subjects are at high risk for open-heart surgery	Cardiac death, stroke, or mitral valve related repeated intervention at 30-day

HF, heart failure; MAC, mitral annular calcification; M-TEER, mitral transcatheter edge-to-edge repair; NCT ID, National Clinical Trial identification number; TMVR, transcatheter mitral valve replacement.

## Acknowledgments

None.

## Footnote

*Funding:* None.

*Conflicts of Interest:* T.K. has received consulting fees from Edwards Lifesciences, Medtronic, 4C Medical, CardioMech, Cook Medical, and has been a speaker for Abbott and Baylis. The other authors have no conflicts of interest to declare.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

1. El-Eshmawi A, Halas M, Bethea BT, et al. The American Association for Thoracic Surgery (AATS) 2025 Expert Consensus Document: Surgical management of mitral annular calcification. *J Thorac Cardiovasc Surg* 2025;170:502-22.
2. Feldman T, Kar S, Elmariah S, et al. Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. *J Am Coll Cardiol* 2015;66:2844-54.
3. Ahmad S, Yousaf A, Ghumman GM, et al. Outcomes of transcatheter aortic valve replacement in patients with mitral annular calcification and concomitant mitral valve dysfunction: A systematic review and meta-analysis. *Cardiovasc Revasc Med* 2024;61:99-109.
4. Mustafa A, Basman C, Cinelli MP, et al. Contemporary experience of mitral transcatheter edge-to-edge repair technology in patients with mitral annular calcification. *Catheter Cardiovasc Interv* 2024;103:618-25.
5. Fernández-Peregrina E, Pascual I, Freixa X, et al. Transcatheter edge-to-edge mitral valve repair in patients with mitral annulus calcification. *EuroIntervention* 2022;17:1300-9.
6. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.
7. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
8. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135.
9. Cheng R, Tat E, Siegel RJ, et al. Mitral annular calcification is not associated with decreased procedural success, durability of repair, or left ventricular remodelling in percutaneous edge-to-edge repair of mitral regurgitation. *EuroIntervention* 2016;12:1176-84.
10. Hatab T, Bou Chaaya RG, Zaid S, et al. Feasibility and Outcomes of Mitral Transcatheter Edge-To-Edge Repair in Patients With Variable Degrees of Mitral Annular Calcification. *J Am Heart Assoc* 2023;12:e031118.
11. Shechter A, Lee M, Kaewkes D, et al. Implications of Mitral Annular Calcification on Outcomes Following Mitral Transcatheter Edge-to-Edge Repair. *Circ Cardiovasc Interv* 2024;17:e013424.
12. Tanaka T, Sugiura A, Schulz M, et al. Cardiac computed tomography-based assessment of mitral annular calcification in patients undergoing mitral transcatheter edge-to-edge repair. *J Cardiovasc Comput Tomogr* 2024;18:26-32.
13. Fox CS, Vasan RS, Parise H, et al. Mitral annular calcification predicts cardiovascular morbidity and mortality: the Framingham Heart Study. *Circulation* 2003;107:1492-6.
14. Kato N, Padang R, Scott CG, et al. The Natural History of Severe Calcific Mitral Stenosis. *J Am Coll Cardiol* 2020;75:3048-57.
15. Makkar RR, Chikwe J, Chakravarty T, et al. Transcatheter Mitral Valve Repair for Degenerative Mitral Regurgitation. *JAMA* 2023;329:1778-88.
16. Chehab O, Roberts-Thomson R, Bivona A, et al. Management of Patients With Severe Mitral Annular Calcification: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2022;80:722-38.
17. Zaid S, Avvedimento M, Vitanova K, et al. Impact of Mitral Regurgitation Etiology on Mitral Surgery After Transcatheter Edge-to-Edge Repair: From the CUTTING-EDGE Registry. *JACC Cardiovasc Interv*

- 2023;16:1176-88.
18. Chikwe J, O'Gara P, Fremes S, et al. Mitral Surgery After Transcatheter Edge-to-Edge Repair: Society of Thoracic Surgeons Database Analysis. *J Am Coll Cardiol* 2021;78:1-9.
  19. Guerrero ME, Grayburn P, Smith RL 2nd, et al. Diagnosis, Classification, and Management Strategies for Mitral Annular Calcification: A Heart Valve Collaboratory Position Statement. *JACC Cardiovasc Interv* 2023;16:2195-210.
  20. Eleid MF, Foley TA, Said SM, et al. Severe Mitral Annular Calcification: Multimodality Imaging for Therapeutic Strategies and Interventions. *JACC Cardiovasc Imaging* 2016;9:1318-37.
  21. Xu B, Kocyigit D, Wang TKM, et al. Mitral annular calcification and valvular dysfunction: multimodality imaging evaluation, grading, and management. *Eur Heart J Cardiovasc Imaging* 2022;23:e111-22.
  22. Guerrero M, Wang DD, Eleid MF, et al. Prospective Study of TMVR Using Balloon-Expandable Aortic Transcatheter Valves in MAC: MITRAL Trial 1-Year Outcomes. *JACC Cardiovasc Interv* 2021;14:830-45.
  23. Fatehi Hassanabad A, Rabbani M, Tam DY, et al. Direct Implantation of Transcatheter Valve in Mitral Annular Calcification: A Multicenter Study. *Ann Thorac Surg* 2025;119:129-36.
  24. Hell MM, Wild MG, Baldus S, et al. Transapical Mitral Valve Replacement: 1-Year Results of the Real-World Tendyne European Experience Registry. *JACC Cardiovasc Interv* 2024;17:648-61.
  25. Gössl M, Thourani V, Babaliaros V, et al. Early outcomes of transcatheter mitral valve replacement with the Tendyne system in severe mitral annular calcification. *EuroIntervention* 2022;17:1523-31.
  26. Coisne A, Ludwig S, Scotti A, et al. Outcomes Following Transcatheter Mitral Valve Replacement Using Dedicated Devices in Patients With Mitral Annular Calcification. *JACC Cardiovasc Interv* 2024;17:2141-53.
  27. Génèreux P, Wróbel K, Rinaldi MJ, et al. AltaValve Atrial Fixation System for the Treatment of Severe Mitral Regurgitation and Mitral Annular Calcification. *Struct Heart* 2024;8:100294.

**Cite this article as:** Sakurai Y, McDonald A, Kaneko T. Early and mid-term outcomes of mitral annular calcification and transcatheter mitral therapy: a systematic review. *Ann Cardiothorac Surg* 2025;14(6):395-406. doi: 10.21037/acs-2025-mac-0128