Mitral Annular Calcification:
A Comprehensive Systematic Review

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BACKGROUND

- Mitral annular calcification (MAC) is a chronic, degenerative process involving calcium deposition in the fibrous skeleton of the mitral valve annulus.
- Affects approximately 15% of the general population, with prevalence escalating significantly with age, chronic kidney disease (CKD), and metabolic disorders.
- Once considered benign, MAC is now recognized as an independent predictor of cardiovascular morbidity and mortality, associated with mitral valve dysfunction, conduction abnormalities, thromboembolism, and sudden cardiac death.
- Despite its clinical significance, comprehensive management guidelines remain limited, underscoring the need for this systematic synthesis.

METHODS

- **Design:** Systematic review following PRISMA 2020 guidelines
- **Databases:** PubMed, EMBASE, Cochrane Library, and Web of Science
- **Search Query:** ("Mitral Annular Calcification" OR "MAC") AND ("Epidemiology" OR "Pathogenesis" OR "Diagnostic Imaging" OR "Therapeutics")
- **Studies included:** 62 studies (2000–2024), including 12 large-scale trials
- **Inclusion:** Human subjects; MAC confirmed by echocardiography, CT, or MRI; cohort studies (n≥100) or RCTs
- **Exclusion:** Case reports, editorials, reviews; animal or in vitro studies
- **Quality assessment:** Newcastle-Ottawa Scale (observational studies) and Cochrane tool (RCTs)
- **Analysis:** Random-effects meta-analysis; heterogeneity assessed via I^2 statistic (I^2>50% = substantial)

PRISMA 2020 SELECTION FLOW

4,218 identified → 2,891 screened → 124 full-text → 62 included

EPIDEMIOLOGY

15.4%	43.7%	31.2%	1.6×
General Population	Age >80 Years	CKD Patients	Female Prevalence

EPIDEMIOLOGY: PREVALENCE & RISK (META-ANALYSIS)

FACTOR	PREVALENCE	OR (95% CI)
Age <60 yrs	3.5%	1.0 (Reference)
Age 60–80 yrs	18.7%	3.2 (2.6–3.9)
Age >80 yrs	43.7%	4.2 (3.1–5.7)
Female Sex	18.2%	1.6 (1.4–1.9)
CKD	31.2%	2.3 (1.9–2.8)

PATHOPHYSIOLOGY — MOLECULAR MECHANISMS

- **Endothelial Injury:** Hemodynamic stress activates TGF-β, promoting fibroblast-to-osteoblast differentiation and initiating the calcification cascade
- **Inflammation:** Elevated CRP (>3 mg/L) and IL-6 (>5 pg/mL) strongly correlate with MAC severity (r≈0.62, p<0.001)
- **Calcification Pathway:** ENPP1/ABCC6 mutations accelerate hydroxyapatite deposition; matrix Gla protein (MGP) deficiency impairs calcification inhibition
- **Genetics:** GWAS identifies susceptibility loci linked to lipid metabolism (APOE), calcium handling (TRPV1), and inflammation (IL-6)
- **Non-modifiable risk factors:** Age (HR 1.08/year), female sex (HR 1.6), elevated lippprotein(a) (HR 1.32 per SD) — from the MESA study
- **Modifiable risk factors:** Calcium-phosphate product >55 mg^2/dL^2, LDL >130 mg/dL, proinflammatory states

RISK FACTOR	HR (95% CI)	STUDY
Age (per 10 years)	2.14 (1.81–2.53)	MESA
Female Sex	1.60 (1.24–2.07)	MESA
CKD	2.31 (1.89–2.76)	FHS
Elevated Lp(a) (per SD)	1.32 (1.10–1.58)	MESA
High CanP Product (>55 mg^2/dL^2)	1.58 (1.27–1.96)	CKD Cohort
LDL >130 mg/dL	1.43 (1.15–1.78)	Multi-ethnic

DIAGNOSIS & IMAGING MODALITIES

Echocardiography (TTE) — First-line:
MAC appears as a dense echogenic band with posterior acoustic shadowing at the base of the posterior mitral leaflet. Sensitivity 87.5%, Specificity 93.2%. Three-dimensional echo improves annular sizing accuracy.

Computed Tomography (CT) — Gold Standard:
Enables precise quantification using the Agatston score. Each 100-unit increase carries HR 1.09 for mortality. Essential for pre-procedural TMVR planning and neo-LVOT assessment. Sensitivity 99.2%, Specificity 98.7%.

Cardiac MRI:
Distinguishes MAC from caseous necrosis and other mimics. Accuracy 91.7%, Specificity 95.3%. Particularly useful for soft-tissue characterization.

PET (^{18}F-Sodium Fluoride):
Detects metabolically active, early-stage calcification before structural changes are visible. Sensitivity 74%, Specificity 81%. Emerging role in risk stratification.

MODALITY	SENSITIVITY (%)	SPECIFICITY (%)
TTE	87.5	93.2
CT	99.2	98.7
MRI	91.7	95.3
PET	74.0	81.0

DIAGNOSTIC PERFORMANCE AT A GLANCE

TTE	CT	MRI	PET
Sens 87.5% Spec 93.2%	Sens 99.2% Spec 98.7%	Sens 91.7% Spec 95.3%	Sens 74.0% Spec 81.0%

- CT remains the preferred modality for pre-procedural planning.
- TTE is the recommended first-line screening tool given its wide availability, low cost, and good diagnostic performance.
- MRI and PET play complementary roles in complex or atypical cases.
- Serial echocardiographic surveillance is recommended for high-risk groups every 1–2 years to monitor MAC progression and detect valvular dysfunction early.

MEDICAL MANAGEMENT

- **Lipid-lowering (Statins):** High-intensity statin therapy slows MAC progression (5.1% vs. 6.7% annual volume increase, p=0.03). PCSK9 inhibitors show promise for lipoprotein(a) reduction.
- **Anti-inflammatory (Colchicine):** 0.5–0.6 mg/day reduces progression in high hsCRP patients (RRR 12%); currently under evaluation in dedicated MAC trials.
- **Antithrombotic therapy:** DOACs demonstrate efficacy comparable to warfarin with lower bleeding risk (HR 0.68). Anticoagulation recommmedie for mobile or ulcerated MAC with thromboembolic risk.
- **SNF472 (Emerging):** Novel hydroxyapatite crystal growth inhibitor showing 55% reduction vs. placebo (p=0.02) in hemodialysis patients with vascular calcification.
- **Mineral metabolism:** Control of calcium-phosphate product and phosphate binders critical in CKD patients to limit progression.

SURGICAL MANAGEMENT

- **Valve Repair:** Achieves 87% freedom from reoperation at 5 years; preferred when feasible to preserve native anatomy and avoid prosthesis-related complications.
- **Valve Replacement:** Complete decalcification achieves superior hemodynamic outcomes debridement (Prosthesis (76%), but annulus groove disruption and ventricular rupture.
- **Butterfly Technique:** Annular reconstruction approach that significantly reduces paravalvular leak rates (4.1% vs. 11.7%, p=0.02), particularly suited for intermediate-risk patients with circumferential MAC.

TRANSCATHETER APPROACHES (TMVR)

- **Technical success rate:** 72.2% overall
- **30-day mortality:** 10.8%; 1-year mortality: 25.3%
- **Complications:** LVOT obstruction (9.3%), paravalvular leak (12.7%), device embolization (3.1%)
- **Valve-in-MAC:** Higher LVOT obstruction risk (HR 2.26) but better paravalvular leak outcomes compared to valve-in-ring
- **Patient selection:** Critical evaluation of MAC distribution and predicted neo-LVOT area essential for procedural success
- **Dedicated devices** and techniques are rapidly evolving to improve outcomes

FUTURE DIRECTIONS

- **Molecular Targets:** Inhibition of ENPP1, modulation of Wnt/β-catenin, and matrix Gla protein (MGP) augmentation
- **Imaging Innovations:** AI-enhanced CT quantification and PET imaging for early detection and risk stratification
- **Trials:** Ongoing RCTs evaluating SNF472, colchicine, and intensive lipid-lowering strategies
- **Integration:** Combining multi-omics, advanced imaging, and clinical analytics for personalized MAC management
- **Goal:** Prevention, aarly detection, and tailored therapy to reduce MAC-related morbidity and mortality

CONCLUSION

Mitral annular calcification is a prevalent and multifaceted condition with significant clinical implications. Advances in understanding its pathophysiology, improving diagnostic accuracy, and developing innovative therapeutic strategies are essential to optimde patient outcomes. A multidsicipilnary, individualized approach remains the cornerstone of effective MAC management.