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JACC REVIEW TOPIC OF THE WEEK

Mitral Valve Dysfunction in Patients With Annular Calcification

JACC Review Topic of the Week

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ABSTRACT

Mitral annular calcification (MAC) is a common clinical finding and is associated with adverse clinical outcomes, but the clinical impact of MAC-related mitral valve (MV) dysfunction remains underappreciated. Patients with MAC frequently have stenotic, regurgitant, or mixed valvular disease, and this valvular dysfunction is increasingly recognized to be independently associated with worse prognosis. MAC-related MV dysfunction is a distinct pathophysiologic entity, and importantly much of the diagnostic and therapeutic paradigm from published rheumatic MV disease research cannot be applied in this context, leaving important gaps in our knowledge. This review summarizes the current epidemiology, pathophysiology, diagnosis, and classification of MAC-related MV dysfunction and proposes both an integrative definition and an overarching approach to this important and increasingly recognized clinical condition.
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Mitral annular calcification (MAC), a common incidental finding in asymptomatic patients, is common in the aging population and is linked to poor cardiovascular outcomes.[1-4] Significant valvular dysfunction directly related to MAC occurs in a minority of patients, yet the importance of MAC-related mitral valve (MV) dysfunction is increasingly recognized, as this now represents the dominant etiology of MV stenosis in Western populations and is itself associated with worse prognosis.[5] However, data regarding MAC-related MV dysfunction are limited, and significant challenges exist in the diagnostic and therapeutic approach to these patients, ranging from limitations of conventional echocardiographic assessment to ongoing controversy regarding clinical benefit of surgical or percutaneous treatment options in this high-risk population.

In this review we aim to: 1) summarize the prevalence and pathophysiology of MAC-related MV dysfunction; 2) highlight strengths and limitations of contemporary diagnostic imaging tools in this patient population; and 3) provide an overview of the prognostic implications of MAC-related MV disease.

EPIDEMIOLOGY

MAC was first described pathologically more than a century ago, and reports since have progressively expanded the anatomical, functional, and prognostic understanding of this condition. Although initial diagnosis was by pathology, radiography, and ultimately fluoroscopy, starting in the 1970s echocardiographic features of MAC were recognized, allowing more widespread and easier detection and diagnosis. At present MAC is commonly diagnosed by either

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ABBREVIATIONS AND ACRONYMS

CT = computed tomography

HFpEF = heart failure with preserved ejection fraction

LV = left ventricular

LVOT = left ventricular outflow tract

MAC = mitral annular calcification

MR = mitral regurgitation

MS = mitral stenosis

MV = mitral valve

MVA = mitral valve area

TEE = transesophageal echocardiography

TMG = transmitral gradient

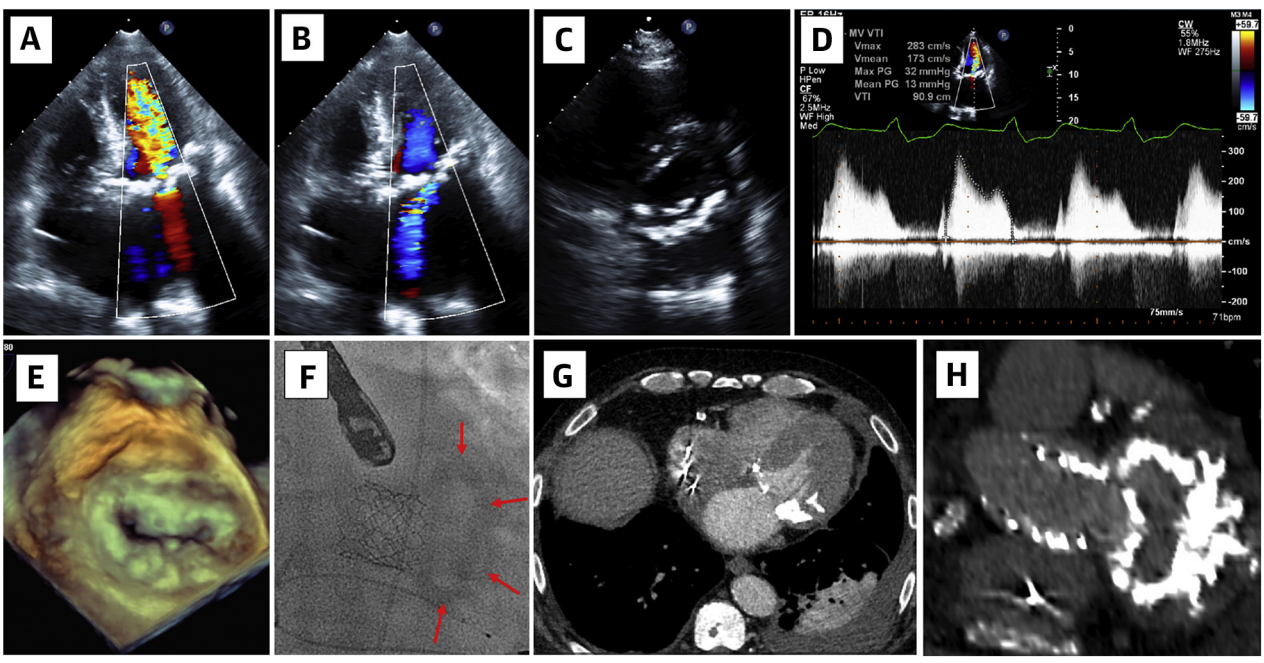
echocardiography or computed tomography (CT), and prevalence estimates typically range from 8% to 15% in the general population, up >40% or higher in studies of elderly individuals,[4] with considerable variation according to the specific population studied and the diagnostic modality used. MAC is more common in women, patients of advanced age, and those with chronic kidney disease and is associated with multiple cardiovascular risk factors,[3,4,6,7] likely because of shared pathophysiologic mechanisms with atherosclerosis. In addition, MAC is known to be associated with calcific aortic valve disease and with conditions that increase stress on the MV annulus, such as hypertension, left ventricular (LV) hypertrophy, and MV prolapse.[2,8]

HIGHLIGHTS

- MAC is increasingly prevalent in the elderly and associated with adverse outcomes.
- Percutaneous transcatheter mitral valve replacement (valve-in-MAC) is a promising intervention, but outcome benefit has not been established.
- Prospective studies are needed to establish criteria for assessment of MAC severity and clinical risk stratification, clarify indications for intervention, and compare management strategies.

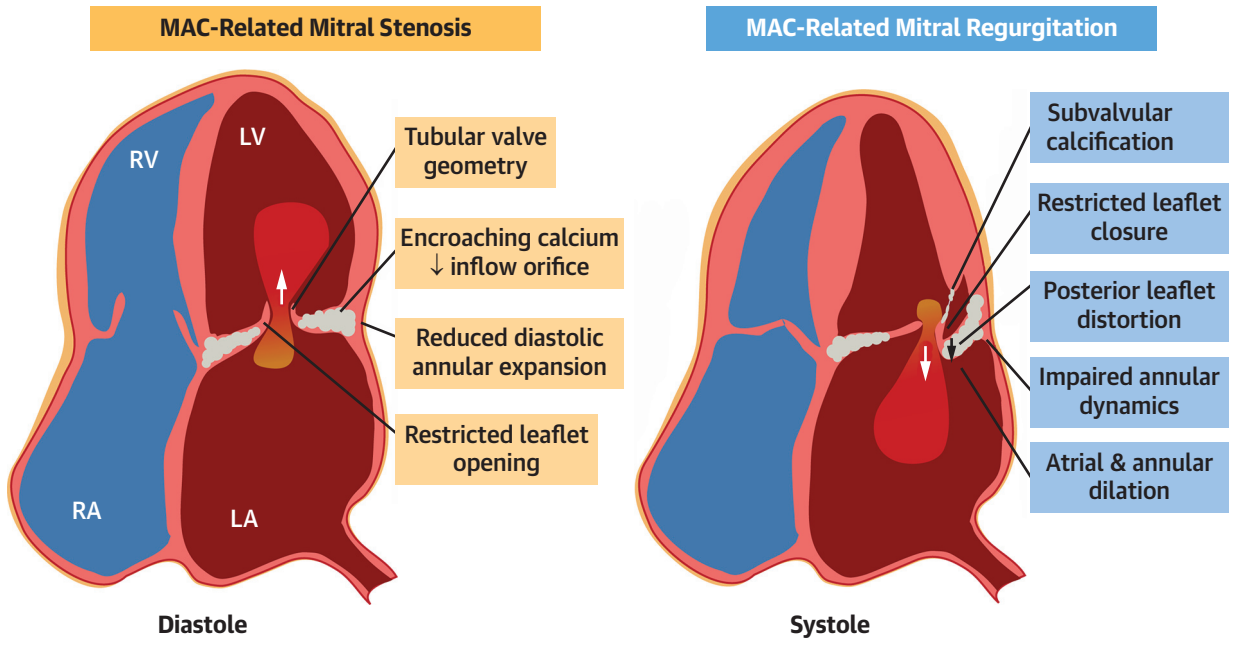
The prevalence of MAC-related MV dysfunction, however, is less well described, at least in part because of the absence of a clear and well-established definition of what constitutes "MAC-related MV dysfunction." In its simplest formulation, a pathologic elevation in the mean transmitral gradient (TMG) directly related to the presence of MAC can be regarded as a marker of valve dysfunction. This can be associated with mitral stenosis (MS), mitral regurgitation (MR), or both (mixed valve disease). In our assessment in patients with MAC, a cutoff value of 3 mm Hg was established, above which the TMG was pathologically elevated on the basis of nonlaminar, turbulent flow on color Doppler imaging.[5] In a large cohort of patients with MAC, such pathologic

FIGURE 1 Clinical Example of a Patient With MAC-Related Mitral Valve Dysfunction



Representative echocardiographic **(A to E)**, fluoroscopic **(F)**, and computed tomographic **(G and H)** images of a 75-year-old man with mitral annular calcification (MAC)–related mitral valve (MV) dysfunction. Key findings included bulky, circumferential MAC and mixed MV dysfunction with severe stenosis and moderate regurgitation.

FIGURE 2 Pathophysiology of Stenosis and Regurgitation in MAC-Related Mitral Valve Dysfunction



Key pathophysiologic features of stenotic and regurgitant physiology in mitral annular calcification (MAC)-related mitral valve dysfunction. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

elevation in gradient occurred in approximately 8%. This prevalence is in line with prior reports of MS in patients with MAC.[9] An alternative description to define MAC-related MV dysfunction includes any MS (assessed by mean TMG or MV area [MVA]) and/or moderate or greater MR in the presence of MAC, with a reported prevalence of 16% in a large cohort.[10]

Elevations in the TMG indicative of MV dysfunction have been reported in 0.2%-0.5% of unselected patients undergoing transthoracic echocardiography,[11] with MR the most common form of MV dysfunction. The prevalence of MAC-related MV dysfunction tends to be higher within selected populations. Prior chest radiation, for instance, is associated with clinically significant valvular dysfunction in 6%-15% of individuals.[11] Similarly, significant MAC-related MV dysfunction is particularly common among patients with aortic stenosis; in one cohort, almost 25% of patients with aortic stenosis had MVA <1.5 cm^2.[12] Rates of MV dysfunction are unsurprisingly higher in individuals with anatomically more severe MAC,[13] and patterns of MV dysfunction tend to be more evenly distributed in this group; in one surgical series, the dominant valvular lesion was MS in 33%, MR in 26%, and mixed in 31%.[14] An example of a patient with severe MAC and MV dysfunction is shown in **Figure 1**.

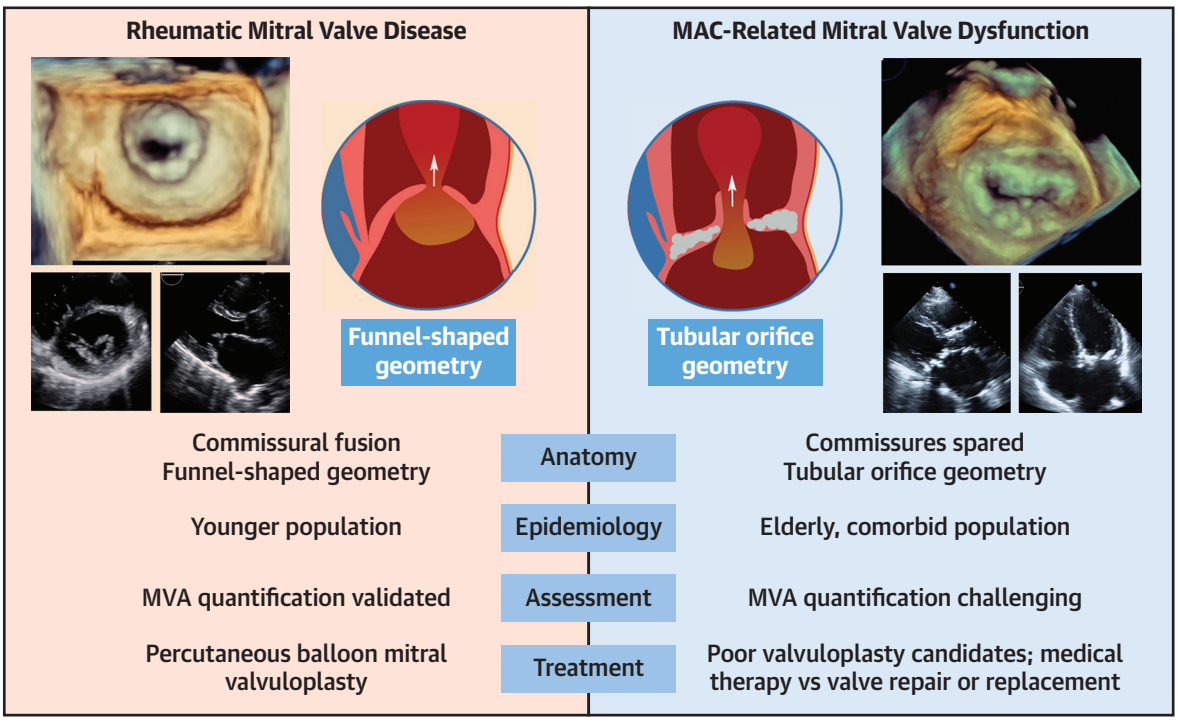
Data are limited on the natural progression of MAC-related MV dysfunction. Single-center series have documented an average TMG progression rate of 0.04 ± 0.0097 mm Hg/y, with highest progression (3 times the average rate) in patients with anatomically severe MAC and higher baseline gradients and only minimal progression in those with less severe calcification.[15] Similar findings have been seen in CT-based studies, in which the strongest predictor of MAC progression has been the baseline calcium burden.[7] Additional research is required to better define risk factors for progression of MV dysfunction, thereby establishing appropriate follow-up intervals and (potential) timing of intervention.

PATHOPHYSIOLOGY

Given the heterogeneity of both MAC itself and the associated MV dysfunction across individuals and populations, it is unsurprising that exact pathophysiologic mechanisms underlying the valvular dysfunction, and how they work synergistically to result in significant, often mixed valve disease, remain elusive.

MECHANISMS OF REGURGITATION IN MAC. MR in patients with MAC is often multifactorial (**Figure 2**). First, MAC may extend onto and directly involve

FIGURE 3 **Differences Between Rheumatic Disease and MAC-Related MV Dysfunction**



Key differences between rheumatic MV disease and MAC-related MV dysfunction. These are distinct disease processes with important differences from anatomy to treatment, and the diagnostic and therapeutic paradigm from rheumatic disease cannot be applied in MAC. MVA = mitral valve area; other abbreviations as in Figure 1.

leaflets, resulting in restricted leaflet motion and impaired coaptation. Second, extension of posterior MAC underneath the posterior leaflet may push the posterior leaflet toward the atrium, distorting valvular geometry and reducing the available surface for coaptation.[2] Third, extra-annular chordal calcification, especially toward the commissures, may cause leaflet restriction and further impair coaptation. Finally, the presence of calcium in the annulus can disrupt mitral annular dynamics. Under normal circumstances (ie, in the absence of significant annular calcium), the mitral annulus passively flexes along the commissural axis in conjunction with LV systolic contraction, deepening the saddle shape and resulting in a greater coaptation surface without leaflet distortion.[2,16] Normal annular motion also results in changes in annular area, which peaks during diastole and reaches a minimum shortly after left atrial contraction, and annular shape, which changes from elliptical to become more circular, both of which are believed to facilitate ventricular filling and minimize regurgitation.[2] Annular calcium, however, as well as calcium that extends into the basal LV myocardium, can impair these intricate processes, likely contributing to impaired coaptation.[8,16,17]

MECHANISMS OF STENOSIS IN MAC. Annular calcium itself can extend into and encroach upon the mitral orifice area, obstructing diastolic transmitral inflow, hence causing some degree of MS (Figure 2). This mechanism often takes the form of a "shelf" of calcium at the base of the mitral leaflets that displaces the leaflets into the valve orifice.[17] Calcium extension onto the leaflets, particularly the anterior mitral leaflet, further restricts leaflet motion, resulting in more severe stenotic physiology.[18] In this regard, the mechanism of inflow obstruction in MAC represents an important distinction from rheumatic MS (Figure 3). In the latter condition, commissural fusion results in a funnel-shaped valve maximally stenotic at the leaflet tips. In contrast, in MAC-related MV dysfunction, the level of obstruction is typically closer to the annular level, with leaflets forming more of a tubular shape.[17,19] Less commonly, in some cases leaflet encroachment can result in decreased leaflet

TABLE 1 Proposed Multiparametric Grading Systems of MAC Anatomical Severity

Eleid et al[21]			Xu et al[22]			
MAC Grade	Annulus	Extra-Annular Calcium	MAC Grade	Qualitative Echocardiographic Grading	Quantitative CT Grading	Special Features
Grade 1 (mild)	Focal noncontiguous calcification limited to <180° total annular circumference	None	Grade 1	<90° and noncontiguous	<1,000 Agatston units	None
			Grade 2	90°-<180°	1,000-<3,000 Agatston units	Calcification of subvalvular structures and leaflets by CT Involvement of one trigone
Grade 2 (moderate)	Dense continuous calcification limited to <270° total annular circumference	Posterior and/or anterior leaflet calcification may be present	Grade 3	180°-<270°	3,000-5,000 Agatston units	Extension into LVOT Mobile MAC Involvement of both trigones
Grade 3 (severe)	Dense continuous calcification extending past the commissures into anterior annulus or complete circumferential MAC (≥270° calcification arc)	Posterior and/or anterior leaflet calcification may be present Papillary muscle or ventricular myocardial calcification may be present	Grade 4	270° to circumferential	>5,000 Agatston units	Heavy extension into LVOT Infiltration into myocardium

CT = computed tomographic; LVOT = left ventricular outflow tract; MAC = mitral annular calcification.

excursion and a reduced opening angle, resulting in a level of obstruction slightly more apically displaced below the annular plane.[20]

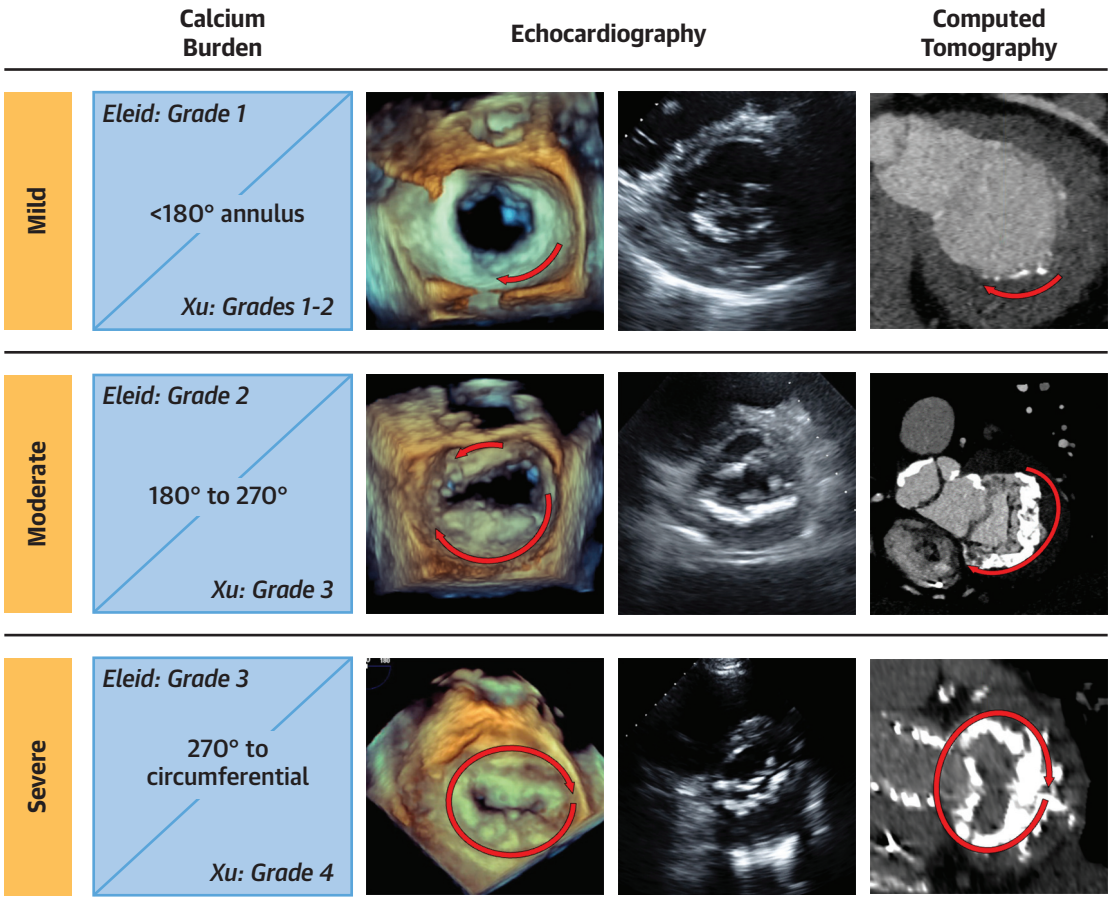
DIAGNOSTIC EVALUATION AND CHALLENGES

The diagnostic evaluation of MAC-related MV dysfunction centers on defining 2 key features: 1) the anatomical extent of the calcium; 2) the impact on valve function. Significant MAC is often noted incidentally on fluoroscopy as part of other cardiac procedures, but this modality provides only very limited diagnostic information and best serves as to prompt additional imaging. More comprehensive anatomical assessment can be performed using both echocardiography and CT, with the latter modality additionally allowing quantification of calcium burden using the Agatston score. CT provides a high degree of spatial resolution to definitively visualize the location and circumferential extent of the calcium, most typically done through the use of multiplanar reconstruction to create a short-axis view of the mitral annulus, in addition to determining the degree of calcium extension on the valve leaflets or into the subvalvular apparatus or the basal ventricular myocardium.[21] Two recent scoring systems have been proposed to standardize assessment of the anatomical burden of annular calcium (**Table 1, Figure 4**), one focused on a qualitative assessment of calcium extent[21] and the other additionally incorporating quantitative assessment with the Agatston score[22]; both also feature an assessment of the extent of extra-annular calcium. Notwithstanding some small differences, these 2 grading systems largely overlap, and there is no consensus as to optimal grading approach or definitions. A key limitation of this anatomical assessment, however, is the absence of information on the hemodynamic impact of the valvular lesion, and the prognostic implications of these different grading schema of MAC extent remain largely undefined, making this a key area of future research.

The role of other cross-sectional imaging modalities in the diagnostic evaluation of MAC remains limited. Dedicated positron emission tomographic protocols have been shown to image MAC disease activity (calcification and inflammation) and predict disease progression, although targeted therapies are not yet available.[23] Magnetic resonance imaging, in turn, is less well suited for imaging calcified structures and serves primarily as an adjunct assessment of MR severity.

A limited but important role for both CT and magnetic resonance imaging lies in the provision of anatomical evaluation and diagnostic clarity in cases of caseous MAC, which differs considerably from the other types of MAC. Caseous MAC refers to an inflammatory process with liquefactive necrosis of the annular calcium[21] and is of unclear etiology and uncertain clinical significance. It appears on echocardiography as a smooth and reflective outer rim that surrounds an echolucent necrotic core and can be confused with cardiac tumors, particularly when large and mass-like.[17] Caseous MAC is less often associated with significant valve dysfunction and can spontaneously regress or even disappear, presumably because of erosion or rupture of the shell with embolization of the necrotic core. In this setting, caseous MAC is thought to relate to an increased risk

FIGURE 4 **Imaging Grading of Mitral Annular Calcium**



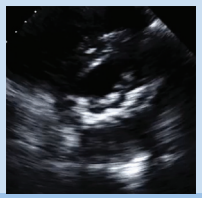
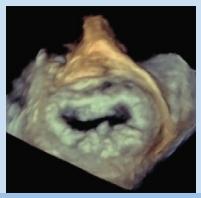
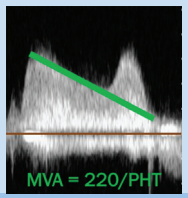
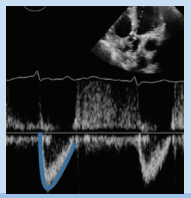
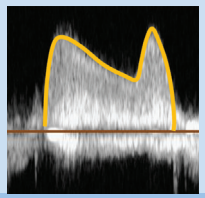
Two recent imaging grading systems have been proposed to standardize assessment of the anatomical burden of annular calcium.[21,22] Both scoring systems focus largely on the circumferential extent of calcium around the mitral annulus, in addition to including features such as the Agatston score and the degree of extra-annular calcium (not depicted).

for stroke. Both CT and magnetic resonance imaging can be helpful in establishing a correct diagnosis, avoiding overtreatment and/or unnecessary surgical referral.[22]

Despite significant challenges, echocardiography remains the preferred method for defining the degree and type of valvular dysfunction in patients with MAC. In patients with stenotic physiology, the echocardiographic severity assessment relies on the TMG and on calculation of MVA. However, unlike in rheumatic MS, most metrics for MVA calculation by echocardiography cannot be directly applied in significant MAC, because of imaging challenges (**Figure 5**), concomitant valvular abnormalities, and comorbid ventricular alterations.

Direct planimetry by 2-dimensional echocardiography, the gold standard for rheumatic MS, is not a reliable metric for MAC-related MV dysfunction. Because of the lack of commissural fusion, the limiting orifice in MAC is typically nonplanar and located closer to the calcified annular plane rather than at the leaflet tips (**Figure 3**). This area is difficult to visualize, particularly in patients with significant acoustic shadowing from anterior calcium. Three-dimensional echocardiography can overcome some of these limitations and is a promising technique for MVA evaluation in patients with MAC[19] but presents substantial difficulties for use in daily clinical care. The pressure half-time method, in turn, has limited validity in the setting of abnormal LV and left atrial compliance, tending to overestimate MVA in patients with decreased LV compliance,[24] which is common in an elderly MAC population. The proximal isovelocity surface area method for effective orifice area

FIGURE 5 **Challenges of Echocardiographic Assessment in MAC-Related MV Dysfunction**

	Mitral Valve Area (MVA)				Pressure Gradient
	2D Planimetry	3D Planimetry	Pressure Half-Time (PHT)	Continuity Equation	Mean Pressure Gradient
					
Description	Direct planimetry of the valve opening orifice	Planimetry of MVA from 3D dataset	Empiric calculation extrapolated from rheumatic MS	Calculates MVA based on MV flow and LVOT stroke volume	Mean pressure gradient using continuous wave doppler
Limitations	Poor image quality in presence of MAC	TTE images often inadequate, need for TEE	Overestimates MVA in case of decreased LA/LV compliance	Unreliable in moderate or more MR or AR, irregular rhythms	Flow dependent (heart rate and rhythm, high output states)
Challenges in MAC	Orifice nonplanar, not located at leaflet tips Shadowing due to calcium	Technically difficult Time consuming Acoustic shadowing	MAC population often LVH, AS, decreased compliance	MAC is typically "mixed" VHD, with often some degree of MR; AF common	Heart rate Impact of diastolic dysfunction

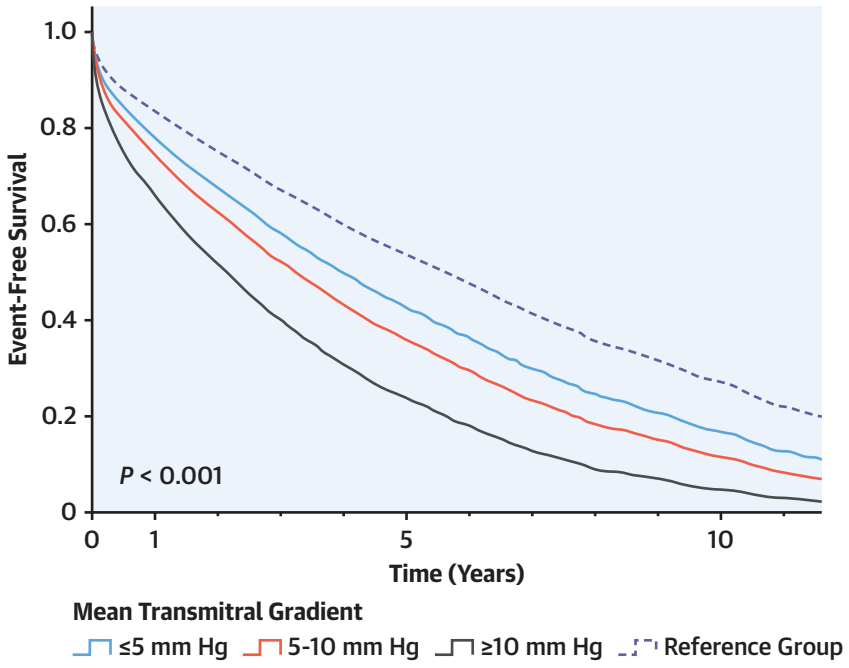
There are multiple important challenges of echocardiographic assessment of MAC-related MV dysfunction. Many metrics extrapolated from rheumatic disease have limitations in patients with significant MAC and associated comorbidities. The transmitral gradient is one metric that integrates the hemodynamic impact of both stenosis and regurgitation and has independent prognostic value in this population. 2D = 2-dimensional; 3D = 3-dimensional; AF = atrial fibrillation; AR = aortic regurgitation; AS = aortic stenosis; LVH = left ventricular hypertrophy; LVOT = left ventricular outflow tract; MR = mitral regurgitation; MS = mitral stenosis; TEE = transesophageal echocardiography; TTE = transthoracic echocardiographic; VHD = valvular heart disease; other abbreviation as in Figures 1, 2, and 3.

calculation, finally, also has limited applicability, because of the noncircular (crescent-like) inflow orifice in MAC and its inherent complexity and technical difficulty.[21] In light of these limitations, the continuity equation is probably the best technique to calculate the valve area in MAC, bearing in mind inaccuracy in patients with significant (moderate or greater) aortic or MR or with atrial fibrillation (given need to measure LV outflow tract [LVOT] and transmitral flow in different cardiac cycles).

With MR, in turn, metrics for severity assessment are similar to those used in other etiologies. The principal challenge here is acoustic shadowing from annular calcium, which can frequently limit visualization of the regurgitant jet. Clinicians should accordingly maintain a high index of suspicion for the possibility of underappreciated MR, including careful evaluation in transthoracic echocardiographic views less affected by acoustic shadowing. For this reason, transesophageal echocardiography (TEE) is appropriate if significant MR is suspected, and MR quantification is particularly encouraged if imaging is adequate.

Given the limitations and complexities of many diagnostic approaches and the elevated prevalence of mixed MV disease in MAC, we propose to not rely on one single echocardiographic measure of MVA but also focus upon the TMG as a metric that integrates the severity of MV dysfunction encompassing both regurgitation and stenosis. The TMG has powerful prognostic importance, independent of age, sex, and cardiovascular comorbidities, and additionally is easily acquired and does not require advanced expertise or processing capability.[5] Well-known limitations of the TMG include its flow dependency, being affected by changes in heart rate, cardiac output, and rheologic factors such as hematocrit or hemoglobin level. Nonetheless, the prognostic value of the

FIGURE 6 Outcome in MAC-Related MV Dysfunction



Outcomes in patients with MAC-related MV dysfunction are incrementally worse with increasing MV dysfunction as assessed by the mean transmitral gradient after adjusting for age and comorbidities. Adapted with permission from Bertrand et al.[5] Abbreviations as in Figure 1.

TMG is robust to these limitations,[5] although common sense dictates that extreme cases (eg, marked tachycardia, anemia, low-output heart failure) are not the best settings in which to perform this hemodynamic assessment. A "flow-corrected" or projected TMG was proposed by Kato et al[25] to help account for this limitation, which may yield a helpful metric in selected patients.

Finally, assessment of LV diastolic function and in particular the estimation of LV filling pressures is subject to limitations in patients with MAC, primarily because the annular calcium impairs annular velocity assessment by tissue Doppler imaging (e′).[26] These challenges in assessing diastolic filling in the setting of significant MAC point to a particularly salient point in this population, which is the difficulty of separating valve from ventricle in teasing out the driver of symptoms and disease mechanisms.[27] Among patients with elevated TMG, for instance, it is challenging to parse out to what extent the abnormality is driven by MV dysfunction itself rather than by ventricular relaxation abnormalities, a challenge particularly salient given the high prevalence of comorbid heart failure with preserved ejection fraction (HFpEF) among patients with MAC-related MV dysfunction. This has important implications on patient management, and additional mechanism-oriented research, ideally coupling echocardiographic with careful hemodynamic assessment, is required to better understand this important topic.

Integrating the diverse available forms of functional and anatomical imaging in the diagnostic evaluation and management of patients with MAC-related MV dysfunction is challenging and has been the focus of several excellent reviews.[17,21,22,28,29] Viewed broadly, the role of different imaging modalities relates primarily to the stage of patient care, from diagnosis to assessment of MV dysfunction to evaluation and planning for potential intervention. CT is highly sensitive for detection of MAC and, as noted earlier, provides optimal resolution of the anatomical extent of the calcium, but the importance of this information is limited until the patient is being evaluated for intervention because of symptomatic, severe MV dysfunction. Hemodynamic assessment by transthoracic echocardiography, in turn, is the cornerstone of severity determination, although an integrative approach is necessary given limitations to almost all echocardiographic metrics (Figure 5). In patients with exertional symptoms out of proportion

to the resting indexes of MV dysfunction, exercise echocardiography can be considered to evaluate the hemodynamic impact of the MAC-related MV dysfunction during exercise.[30] TEE serves a complementary role for severity assessment or clarification of mechanism, particularly in symptomatic patients in whom transthoracic echocardiographic imaging quality is limited by acoustic shadowing, which often impairs visualization of valve leaflets and complicates the quantification of regurgitant jets. TEE also plays a central role in the evaluation of candidacy for surgery or transcatheter procedures, as well as in periprocedural guidance.[29]

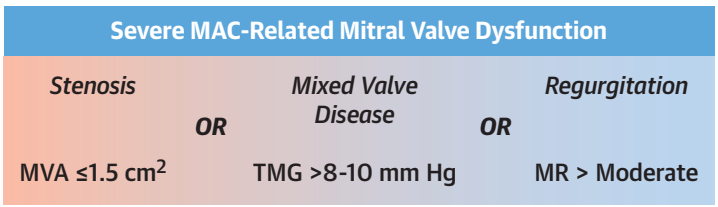
Finally, in patients with severely symptomatic MAC-related MV dysfunction, cardiac CT plays a crucial role in preintervention planning. CT is central in preoperative evaluation for patients deemed to be surgical candidates, whether for traditional repair or replacement or, more recently, open (direct) implantation of transcatheter valves in the mitral position. CT is similarly essential in defining anatomical eligibility for potential transcatheter procedures, including predicting risk for adverse outcomes during these procedures (eg, device embolization)[31] and calculating the "neo-LVOT," the minimal LVOT area that is expected after transcatheter valve deployment.[32] This "neo-LVOT" is a powerful predictor of the risk for postprocedural LVOT obstruction, a common and potentially catastrophic complication of valve-in-MAC procedures.[28,33]

MAC-RELATED MV DYSFUNCTION AND CLINICAL OUTCOMES

Until recently, data on clinical outcomes in patients with MAC-related MV dysfunction have been limited, at least in part because of the absence of broadly accepted diagnostic criteria. Overall, though, the adverse prognosis associated with MAC-related MV dysfunction is well established. In a cohort of patients with MAC and MS reported by Pasca et al,[13] survival rates at 1, 5, and 10 years were 78%, 47%, and 25% and were worse depending upon the severity of MV dysfunction. Similarly, a large cohort of individuals with stenotic, regurgitant, or mixed MV disease reported 1-, 5-, and 10-year survival rates of 75%, 40%, and 18%, with survival markedly impaired in the high-gradient (≥10 mm Hg) group (67% at 1 year, 25% at 5 years, and 11% at 10 years) (**Figure 6**).[5]

Within much of the spectrum of MAC-related MV dysfunction, additive MR on top of inflow obstruction appears to worsen outcome,[5,13] as does the presence of comorbid valve disease such as aortic stenosis and tricuspid regurgitation.[13] Among individuals with markedly elevated TMG (≥10 mm Hg), however, this impact appears to be attenuated, likely because of the already adverse hemodynamic impact of the gradient elevation and the very poor prognosis in this population.[5] Greater anatomical severity of the MAC itself, likely a marker for more advanced disease, has also been associated with more rapidly progressive valvular dysfunction[15] and worse prognosis.[3,6] Finally, elevated pulmonary artery pressures have been linked to worse outcomes controlling for the severity of MV dysfunction, with increased mortality with pulmonary pressures >50 mm Hg.[34]

FIGURE 7 Proposed Definition of Severe MAC-Related Mitral Valve Dysfunction

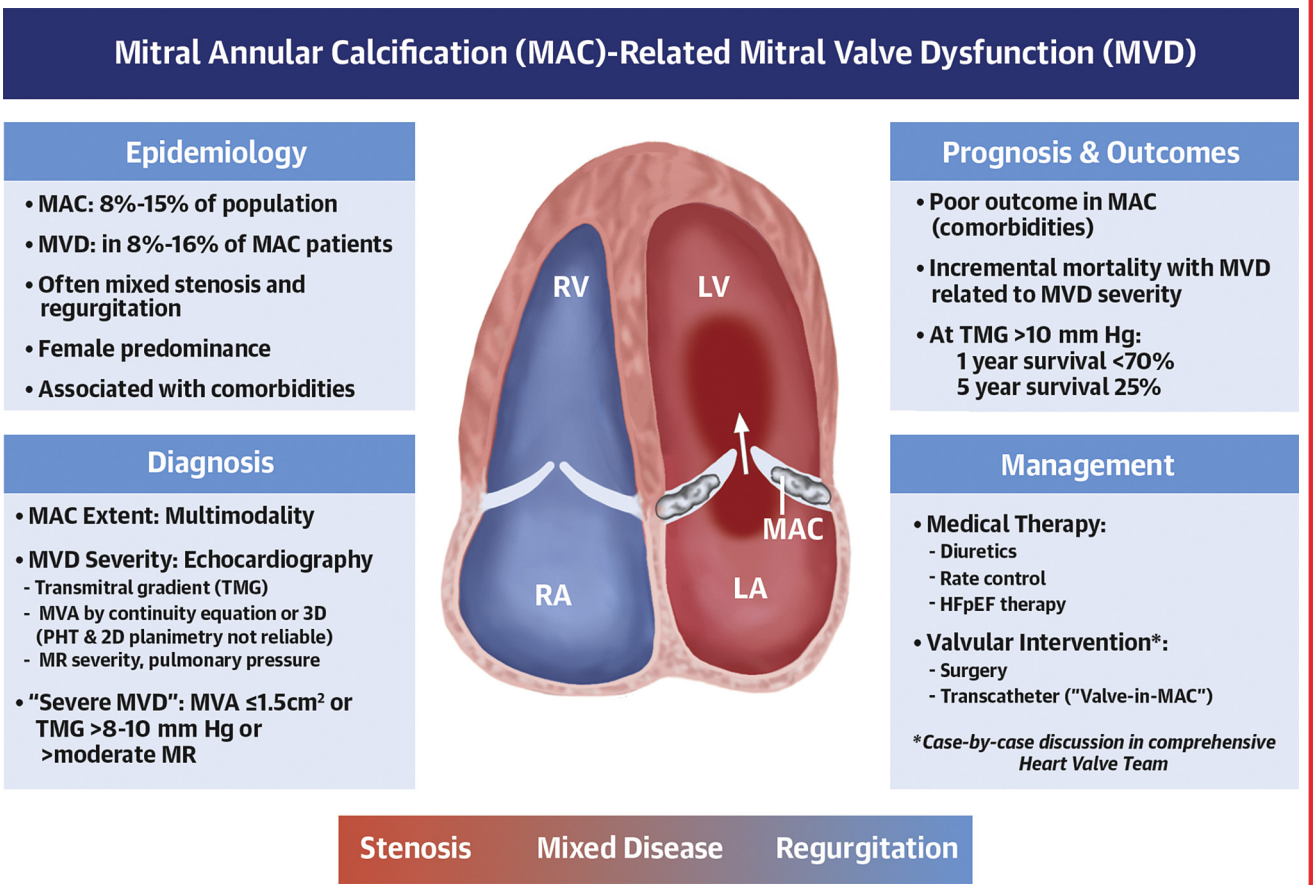


Proposed framework for defining "severe" mitral annular calcification (MAC)–related mitral valve dysfunction with the goal of integrating stenotic, regurgitant, and mixed valve disease. TMG = transmitral gradient. Other abbreviations as in **Figures 1, 3, and 5**.

At present, there are no broadly accepted criteria for defining severity of MAC-related MV dysfunction. On the basis of currently available outcome data[5,34] and the inclusion criteria in ongoing intervention studies (MITRAL II [Mitral Implantation of Transcatheter Valves]; NCT04408430), we propose a unifying definition of "severe" MAC-related MV dysfunction, integrating stenotic, regurgitant, or mixed disease, as MVA ≤1.5 cm² or more than moderate MR or TMG >8-10 mm Hg at a normal heart rate (**Figure 7**).

There are also well-established associations between MAC and stroke, but the extent to which these are causal or related to the MV dysfunction remains uncertain. Epidemiologic links between MAC and stroke have been described for many years,[6] with a potential pathophysiologic connection in terms of atherosclerosis but also an increased risk for atrial fibrillation in patients with MAC.[35] Degenerative changes of the MAC itself can also serve as a source of embolus. A link between the valve dysfunction and incident atrial fibrillation or stroke has not been established, although there is a plausible mechanism due to increased left atrial pressures.

CENTRAL ILLUSTRATION Cardinal Features of Mitral Annular Calcification-Related Mitral Valve Dysfunction



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Mitral valve (MV) dysfunction related to mitral annular calcification (MAC) encompasses a range of valvular pathology from stenosis to regurgitation to mixed valvular disease. Key features of MAC-related MV dysfunction including epidemiology, diagnostic approach, prognosis, and management are shown. 2D = 2-dimensional; 3D = 3-dimensional; HFpEF = heart failure with preserved ejection fraction; MAC = mitral annular calcification; MVA = mitral valve area; MVD = mitral valve dysfunction; PHT = pressure half-time; RA = right atrium; RV = right ventricle; Rx = medication; TMG = transmitral gradient; w/ = with.

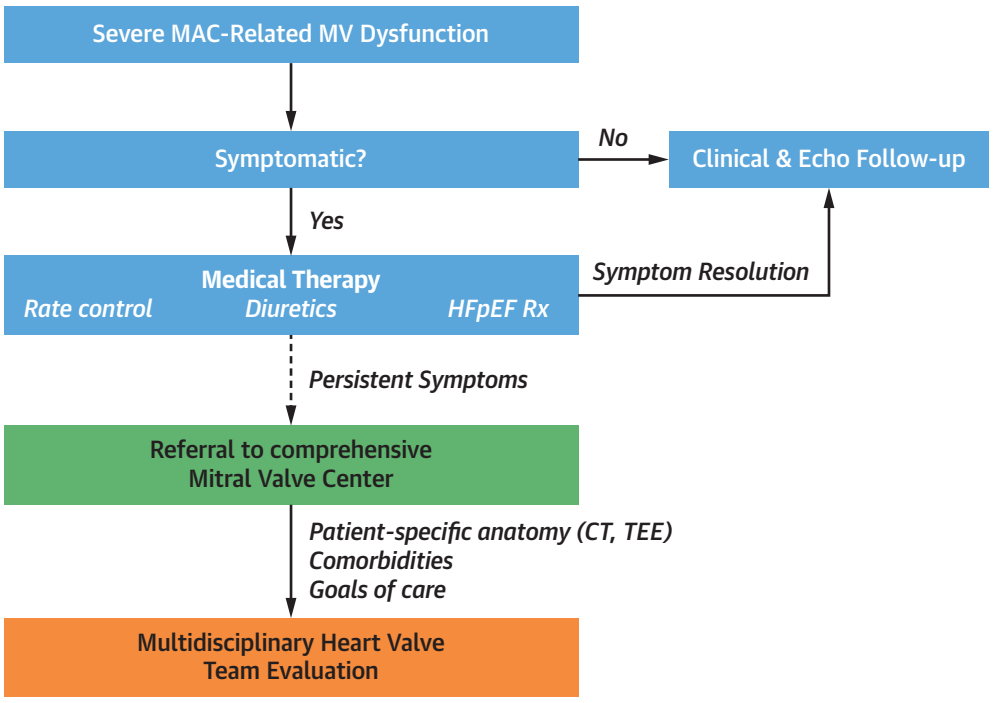
MANAGEMENT

The cornerstone of treatment of MAC-related MV dysfunction remains medical management with diuretic therapy and, if there is significant inflow obstruction, heart rate control with the goal of optimizing diastolic filling time (Central Illustration). Underlying HFpEF is common in this population, and therapies with established benefit in HFpEF should be considered.

Valvular interventions to directly address the valvular dysfunction, including surgery and transcatheter interventions such as valve-in-MAC and in limited circumstances edge-to-edge repair, are technically challenging and associated with a high degree of morbidity and mortality in this population.[33] Even after a successful procedure with significant reduction in transvalvular gradient, the mean left atrial pressure may remain elevated in the setting of poor left atrial and LV compliance, as is common in an elderly HFpEF population.[27] Therefore, only a subset of patients will benefit from valvular intervention, and this assessment is based on integration of patient-specific anatomical considerations, comorbidity burden, and patient goals of care and should be discussed on a case-by-case basis by the multidisciplinary heart valve team.[36]

In routine clinical practice, patients with MAC to consider for referral to a comprehensive valve center are those with severe symptoms refractory to medical

FIGURE 8 Management of MAC-Related MV Dysfunction



Proposed management approach for patients with MAC-related MV dysfunction. Decisions regarding surgical or percutaneous intervention are complex and should be undertaken in conjunction with a multidisciplinary heart valve team. CT = computed tomography; Echo = echocardiographic; HFpEF = heart failure with preserved ejection fraction; Rx = medication; other abbreviations as in Figures 1 and 5.

therapy, when symptoms are related to severe MAC-related valve dysfunction as based on an integrated clinical and imaging assessment (Figure 8). Detailed discussion of the full spectrum of procedural options for patients with MAC-related MV dysfunction is beyond the scope of this review, and the current state of both surgical[37] and percutaneous[38] approaches[37,39] as well as the wide range of emerging devices[40] have been summarized previously.

FUTURE DIRECTIONS

Decades of research has established that MAC is associated with significant cardiovascular comorbidity, while more recent efforts have expanded our understanding of the degree to which MAC-associated MV dysfunction is itself an important driver of adverse outcomes. Looking ahead, a key path of future research will be to better define which patients are likely to benefit from the emerging array of valvular interventions. This will require a greater ability to dissect the contribution of valvular dysfunction from the underlying comorbidity burden and ventricular abnormalities, as well as prospective randomized outcomes trials. The ongoing MITRAL II pivotal trial plans to recruit 110 patients at high operative risk with severely symptomatic MAC-related MV dysfunction (defined as severe MAC with MVA ≤1.5 cm^2 and/or more than moderate MR) for transseptal valve-in-MAC implantation. The trial is not randomized but will include a registry of 100 patients with untreated MAC managed conservatively. Along the same lines, an additional area of focus must be on evaluation of MAC-related MV dysfunction earlier in the disease course than most patients typically present to clinical attention presently. An improved understanding of prognostic markers and disease activity might allow more prompt diagnosis and, possibly, either modification of disease course or earlier intervention while the risk profile of doing so remains viable.

CONCLUSIONS

MAC-related MV dysfunction is increasing in prevalence as the population ages and is associated with worse prognosis on top of already significant morbidities. The diagnostic assessment of valve

dysfunction severity is often challenging because of mixed valvular pathology, in which case the pressure gradient can be useful for prognostication. Valvular interventions to address severe MAC-related MV dysfunction demand careful discussion by the multidisciplinary heart valve team, on the basis of dedicated anatomical imaging and patient goals of care. Further research is needed to establish metrics for risk stratification and evidence-based indications for intervention in this challenging population.

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