## Title
Current methods to assess mitral annular calcification and its risk factors



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## Authors
Birudaraju, Divya
Cherukuri, Lavanya
Pranesh, Shruthi
et al.

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**Title: Current Methods to assess severity of Mitral annular calcification**

**Authors:** Divya Birudaraju, MD[1]; Lavanya Cherukuri, MD[1]; Shruthi Pranesh, MD[2]; Matthew J. Budoff, MD[1]

**Authors Affiliation:**

1. Division of Cardiology, Lundquist Institute for Biomedical Innovation at Harbor-UCLA, Torrance, California
2. Division of Cardiology, Penn State Holy Spirit Hospital. Harrisburg, Pennsylvania.

# Cover Letter

Dear Editors,

On behalf of my co-authors, I wish to submit an article entitled “Current Methods to assess severity of Mitral annular calcification”. All the authors contributed substantially to this original work and have read and approved the article. All authors who have participated in the report agree with its content. None of the article contents are under consideration for publication in any other journal or have been published in any other journal.

There are no conflicts of interests to disclose.

Thank you for your consideration and please see the attached.

We hope to hear from you soon.

Address all correspondence including requests for reprints to:

**Matthew J Budoff, MD, FACC, FAHA**
Lundquist Institute for Biomedical Innovation at Harbor-UCLA
1124 W. Carson Street, RB2
Torrance, CA 90502, USA
Tel (310) 222-4107
Fax (310) 787-0448
Email: mbudoff@lundquist.org

**Abstract:**

Mitral annulus calcification (MAC) is a chronic, non-inflammatory, degenerative mechanism of the fibrous base of the mitral valve. While MAC was originally thought to be an age-related degenerative process, there is evidence that other mechanisms, such as atherosclerosis and abnormal calcium phosphorus metabolism, also contribute to the development of MAC.

**Areas covered:** This paper summarizes, existing perception of clinically valid definition of MAC and the pathophysiological processes that lead to the development of MAC and the diagnostic implications of this disease entity.

**Expert commentary:** Minimal evidence exists on the natural history and progression of MAC. Characterization of MAC progression and identification of predisposing risk factors can help to validate hypotheses. MAC is most commonly asymptomatic and incidental finding. Echocardiography is the primary imaging modality for identification and characterization of MAC and associated mitral valve (MV) disease. For patients with an indication for MV surgery, computed tomography (CT) is a complementary imaging modality for MAC. MAC is generally recognized by its characteristic density, location, and shape on echocardiography and CT, unusual variants are sometimes confused with other lesions.

**Key words:** Mitral annulus calcification (MAC), Chronic Kidney disease (CKD), Echocardiography, Computed Tomography (CT).

## Introduction:

Mitral valve is the most common site of calcification after the coronary arteries [1] and mitral annulus calcification (MAC) is an age-related degenerative process of mitral annulus fibrotic ring [2]. The most complex of the cardiac valves is the mitral valve [3], and the pathophysiological mechanism of MAC is controversial. The most popular theory is the progressive degeneration of the annulus during life [4], with thickening and disorientation of the collagen fibers, decreased mucopolysaccharides and progressive accumulation of fatty tissues [5]. MAC involves the deposition of calcium and lipids in the mitral valve fibrous tissue supporting structure which includes mitral annulus, chordae tendineae, papillary muscles and left ventricular free wall [6]. Previous studies have shown that MAC independently correlates with aortic and mitral valve dysfunction, heart failure, stroke, carotid stenosis, coronary artery disease (CAD), atrial fibrillation (AF), cardiovascular mortality, and overall mortality [7,8]. Individuals with MAC are at high risk of cardiovascular events, thromboembolic events, pacemaker implantation and valve replacement [8].

## Anatomy of mitral valve

The mitral valve has two leaflets: the anterior leaflet, parallel to the aorto-mitral curtain; and the posterior leaflet. Both leaflets are bound to the dynamic mitral ring at their basal ends, while several chordae tendineae

arise from the ventricular surfaces and are distally attached to the papillary muscles [9]. The two leaflets of mitral valve are slightly different in shape and referred to as anterior and posterior leaflets by clinicians. While neither definition is anatomically accurate, the terms aortic and mural leaflets are preferred [10]. Mural (posterior) leaflets are narrow and has indentations, extending two-thirds around the left atrioventricular junction. Sometimes indentations are called clefts. These do not usually extend all the way through leaflet to annulus, if the extension is seen through annulus, it is considered to be associated with the pathological regurgitation process [11]. Carpentier's nomenclature describes the, most lateral segment as P1, which lies adjacent to anterolateral commissure, P2 is central and can significantly vary in size, and most medial is P3 segment, which lies adjacent to posteromedial commissure [12]. The aortic (semilunar anterior) leaflet is divided into three regions as A1, A2, and A3, corresponding to adjacent regions of the mural leaflet.

Although the basal-to-margin lengths and the length of the basal attachments of each mitral leaflet are very different, the surface area of each leaflet is almost the same. The posterior leaflet has a real bundle of fibrous tissue (annulus) separating the left atrium myocardium from the left ventricle myocardium [4]. The mitral annulus divides the left atrium from the left ventricle (LV). The annulus which demarcates the leaflet hinge line is oval shape being larger than antero-posterior diameter though A2 and P2. It is not rigid, fibrous but pliable, changing shape during cardiac cycle [10]. It has a complex shape of a saddle, separated into the anterior and posterior parts. The anterior annulus crosses the left and right fibrous trigones and is anatomically coupled to the aortic annulus. The posterior annulus occupies the majority of the annular perimeter and consists of a discontinuous fibrous tissue rim that is occasionally disrupted by fat [13]. MAC most commonly seen in posterior annulus [4]. Anatomical changes of mitral valve leads to mitral stenosis (MS) and mitral regurgitation (MR) [14].

## Diagnostic Imaging Modalities of MAC:

MAC appearance varies differently on various imaging modalities, calcific demarcation of mitral annulus may be shown in chest x-ray [15].On fluoroscopy, MAC may be shown as radiopaque structure during coronary angiography in the atrioventricular groove[22], but it's not accurate modality to assess MAC [3]**.** Echocardiography (Echo) and cardiac computed tomography (CT) are feasible non-invasive imaging modalities to determine the MAC. Echocardiography is less sensitive and has a limited capability to differentiate between calcification and fibrosis. In contrast, CT detects calcification of heart valves along with extra cardiac structures and is quantified by the agatston method. The largest differences in prevalence of MAC between the MESA and other population-based studies might be attributed to age of study population and diagnostic modalities used. The evidence-based studies to detect the prevalence of MAC using either cardiac CT or Echo were summarized in Table 1.

### Echocardiography

Echo is the best modality to demonstrate MAC, as it appears in the shape of the letters J, C, U or O(posterior mitral ring) [15]. The calcification of mitral valve usually starts around the posterior leaflet of valve appearing as "J" or "C" and with involvement of anterior leaflet the "C" closes forming an "O". MAC can be identified as an echo-dense band beneath the posterior mitral leaflet by M-mode Echo, with motion paralleling that of the free ventricular wall [6]. The 2-dimensional echo technique reveals more clearly the position of the MAC at the angle between the posterior LV wall and the posterior mitral leaflet [16]. The Framingham heart study performed between 1979 and 1981, 2-dimensional (2-D) M-mode echocardiograms were obtained through a parasternal window for all the participants and MAC was identified after assessing three cardiac cycles as an echo dense band throughout the systole and diastole [17]. The Cardiovascular Health Study, MAC was

assessed by a robust  structure located at the junction of the atrioventricular groove and posterior mitral leaflet [18]. Anterior leaflet calcification with restricted mobility occurs in MS [19]. Assessment of mitral annulus should be systematic. MAC (focal vs. circumferential) better accomplished on short-axis mitral valve (parasternal short-axis at the base of TTE or short-axis mitral valve from gastro-esophageal junction) echocardiography. If the images of short-axis are indisponible, inspection of mitral annulus by rotating the apical imagery plane (TTE) or mid-esophageal windows (TEE) allows for evaluation [14].

MAC is rarely associated with calcific MS and left ventricle inflow obstruction. The mitral valve area (MVA) and mitral valve gradient should be examined if calcific MS is suspected on Echo. The inflow obstruction results in a funnel-shaped valve at the leaflet tips due to commissural fusion in individuals with MS due to rheumatic valve disease. Whereas, the mitral valve appears as a tunnel shaped orifice at the mitral annulus sparing the leaflet tips distinguishes the calcific MS due to MAC from rheumatic mitral disease. The continuous wave of spectral doppler obtained from apical or mid-esophageal views provides the hemodynamic changes of left ventricle inflow obstruction. However, to determine the best imaging view for measuring the mitral valve pressure gradients, color doppler imaging is recommended which also evaluates the severity of associated MR. The mitral valve gradients are elevated with increased transvalvular flow and highly dependent on the heart rate, duration of diastolic filling (mitral “E” wave), cardiac output, severity of associated MR and degree of inflow obstruction. The accuracy of the early mitral inflow velocity to mitral annular early diastolic velocity (E/e) ratio is affected by the presence of MAC. The mitral e wave is reduced with a significant MAC.  Whereas, “E” is increased with MR, elevated inflow gradient and decreased left ventricular compliance. Such a pressure gradient is not the best marker to determine the severity of MS and is also dependent on MVA.  Several methods of Echo modalities were proposed to assess the MVA

such as continuity equation, pressure half-time, planimetry using 2-D Echo and real-time 3-dimensional Echo. However, all those have limitations as previously published [14,20,21]. Doppler Echo and 3-dimensional Echo measurements are more accurate and reliable in assessing the MVA. Chu et al. [22] compared the different Echo methods estimating the MVA in patients with calcified MS. The pressure half-time overestimates MVA compared to continuity equation but 3-dimensional Echo measurements correlated well with continuity equation. If TTE measurements are inadequate to assess the severity of MS, then TEE is recommended and is also feasible in the majority of the patients. TTE have limited quantification of MR due to acoustic shadowing of structures posterior to mitral annulus calcification. Additionally, the transducer of TEE is closer to LA and is helpful to better visualize the extent of MR. TTE and TEE are useful adjunctive methods to determine MS, whereas TEE is excellent for detection of MR.

Computed tomography

CT is a robust non-invasive method for direct visualization of coronary and valvular calcifications. The high CT spatial resolution detects the calcification with high accuracy compared to other imaging modalities [23–25]. Misalignments and motion artifacts effects the diagnostic performance of CT in patients with elevated heart rates, arrhythmia and conduction abnormalities [26]. The autogating capability of new generation CT provides the images of diastolic phase for low heart rates and both systolic and diastolic phases for high heart rates. The recent advancements in software and scanner technology acquires the excellent quality of images with spatial temporal resolution, excellent endocardial border, high contrast to noise ratio and software-based motion correction. Additionally, CT’s iterative reconstruction ability reduces the image noise and effective radiation dose without affecting the diagnostic accuracy.

MAC is discovered incidentally on CT imaging [27]  The CT is used to assess the exact location and extent of the MAC. The circumferential annular calcification thickness (mm) is best viewed using multiplanar reformatting to establish a short-axis view. Maximum MAC score is 10 and grading is derived from i) annulus thickness (<5 mm = 1 point, 5 to 9.99 mm = 2 points, ≥10 mm = 3 points) ii) extension of annular calcification (<180° = 1 point, 180° to 270° = 2, ≥ 270°=3) iii) involvement of one or both mitral leaflets (none=0, anterior leaflet =1, posterior leaflet = 2) and iv) trigone calcification ( none = 0, anterolateral = 1, posteromedial = 1) (add an image for calcification of mitral leaflets ) [27–29]. The severity of MAC is determined based on grade points as mild ≤ 3, moderate = 4 to 6 and severe ≥ 7. CT is particularly useful for the identification of caseous mitral annulus calcification, which can be mistaken for intracardiac tumor, but is more likely to be due to MAC liquefaction. Caseous calcification typically occurs on the CT as a uniform hyperdense mass along the mitral annulus surrounded by thick calcifications [30]. The different imaging characteristics of these entities may make a distinction between MAC and the caseous MAC. When these calcifications liquefy and become caseous, they have a more ovoid, mass-like appearance than non-caseous MAC. Whereas MAC often mimics the mass, caseous MAC are more focal, and can be included in differential diagnostic considerations of intracardiac mass [31].

Both contrast and non-contrast CT can evaluate the extent of MAC. However, contrast CT aids the clinician to determine the calcification of mitral valve leaflet (anterior or posterior), sub valvular apparatus involvement, or myocardial calcification extension. Additionally, contrast CT images enable the evaluation of other anatomical cardiac structures (coronary arteries and aorta), peri coronary fat attenuation index, cardiac volumes, ejection fraction, wall motion and intracardiac thrombus without additional imaging [32]. However, it is not possible to obtain the trans mitral gradients and associated MR with CT.

**Table 2: Key studies: prevalence of mitral annular calcification on echocardiography and cardiac computed tomography**

| Study | Objective | Imaging modality | n | Age, years (mean ± SD) | Prevalence of MAC, n (%) | Results |
|---|---|---|---|---|---|---|
| Weissler-Snir et al. [33] | Characteristics of patients aged < 50years with MAC and assessed its association with CVD risk factors compared to patients aged > 50years | Echo | 56 | 44.2 ± 6.9 | 56 | The young patients (age < 50years) with MAC<br>● Predominantly male (71%vs36%, p<0.001) with history of smoking (39% vs 22%, p=0.003)<br>● 52% have CKD with creatinine clearance <60 ml/min and 24% of these underwent renal transplantation.<br>● 41% died (3 had CKD, 5 severe AS, 1 familial hyperlipidemia treated with plasmapheresis, and 1 malignancy) with a mean age of 46years during median follow-up of 7years<br>Older patients (age >50years) with Mac<br>● Significantly hypertensive (84%) and dyslipidemia (64%) with CAD (65%) |
| The Framingham Heart Study [17] | Incidence of cardiovascular morbidity and mortality among the individuals with MAC | Echo | 1197 | 73 ± 7.3 | 169 (14) | Reported 307 cardiovascular events and 621 deaths. MAC was significantly increased risk of<br>● Incident CVD events (HR = 1.5; 95% CI: 1.1- 2.0; p < 0.05)<br>● CVD deaths (HR = 1.6; 95% CI: 1.1- 2.3; p < 0.05)<br>● All-cause mortality (HR = 1.3; 95% CI: 1.04 - 1.6; p < 0.05)<br>The risk of incident CVD, CVD death, and all-cause mortality increase by ≈10% for every 1-mm increase in MAC. |
| Cardiovascular Health Study [34,35] | Inflammatory, lipid, and mineral metabolism markers association with cardiac valve calcification | Echo | 3585 | 72 ± 5 | 1432 (41) | MAC showed<br>● Positive association with FGF-23 (RR = 1.040; 95% CI: 1.004–1.078; p = 0.03)<br>● Negatively association with fetuin-A (RR = 0.949; 95% CI: 0.911–0.98; p = 0.01) |

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| Movahed et al. [36] | Correlation between MAC and cardiac abnormalities. | Echo | 24380 ECHOs | 68 ± 5 | 1494 (6.1) | MAC was significantly associated with<br>● Mitral regurgitation (OR = 2.0, 95% CI: 1.6-2.6, p < 0.0001)<br>● Tricuspid regurgitation (OR = 3.8, 95% CI :2.9-4.8, p < 0.0001)<br>● Aortic stenosis (OR = 1.4, 95% CI:1.08-1.9, p = 0.01)<br>● Left atrial enlargement (OR=1.3, 95% CI: 1.06 - 1.7; P = 0.02)<br>● Left ventricular hypertrophy (OR = 1.9, 95% CI: 1.5 -2.4, p < 0.0001)<br>● Reversed E/A ratio (OR = 1.7, 95% CI: 1.4 -2.2, p < 0.0001)<br>● Age > 50 (OR = 4.8, 95% CI: 3.5 - 6.4, p < 0.0001)<br>No significant correlation was reported with AR or MS. |
| Nair et al. [37] | Incidence of conduction defects in patients with MAC was studied | Echo | 104 | 70 ± 9 | 104 | ● Significantly increased rate of conduction defects such as atrial fibrillation or atrioventricular block in patients with MAC(12% diabetics, 31% with CAD, 24% HTN). |
| Hunold et al. [38] | Prevalence, diagnostic and therapeutic consequences of accidental findings in patients who underwent electron-beam tomography of heart for coronary artery calcium | CT/ Echo | 1812 | 61 ± 10 | 11 (0.6) | ● Accidental cardiac valve abnormalities were found in 17% (n=317) of study population.<br>● Mild MS/MR was observed in 30 patients referred to TTE out of 131(7.2%) patients who have mitral valve calcification. However, no therapeutic interventions were provided to those patients.<br>● Investigators did not assess the severity of calcification. |
| Mahnken et al. [27] | Prevalence and clinical significance of incidental mitral valve calcification on MDCT compared to | CT/ Echo | 390 | 62.4 ± 12.2 | 33 (8.5) | ● No evidence of MS on ECHO but revealed minor calcifications of the mitral valve leaflets on MDCT in 3 patients (0.8%)<br>● Patients with MAC were significantly older than those without calcification (70.6 ± 8.3 vs 61.5 ± 12.2 years p< 0.0001) |

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| | echocardiography | | | | | ● Significant correlation was reported between the degree of MDCT mitral valve calcification and the severity of mitral valve disease determined by ECHO (no sclerosis vs mitral sclerosis vs mitral stenosis; $p < 0.0001$)<br>● Good agreement was observed between the MAC on MDCT and MS detected on ECHO ($k = 0.498$) |
| Willmann et al. [28] | Impact of ECG gated MDCT image quality in diagnosing mitral valve abnormalities | CT/Echo | 20 | - | 9 (45) | ● 95-100% agreement was achieved by MDCT compared with ECHO<br>● MDCT is feasible to detect valvular abnormalities such as mitral valve leaflets thickening, presence of MAC, and valvular leaflets calcification. |
| Allison et al. [39] | Association between vascular atherosclerotic calcification and aortic or mitral annular calcification | CT | 1242 | 70.5 ± 9.4 | 99 (8) | ● MAC is significantly associated with calcification of abdominal aorta (OR=5.1, P=0.01) and thoracic aorta (OR=1.4 P=0.02) |
| Takami et al. [40] | Prevalence of MAC in patients undergoing aortic valve replacement | CT | 106 | 72 ± 8 | 56 (53) | ● Most commonly observed in dialysis-dependent elder populations with tricuspid aortic valve stenosis.<br>● No adverse effect on survival after aortic valve replacement for at least within 2years |
| Abramowitz et al. [41] | Prevalence of MAC and its clinical significance in patients with severe aortic stenosis evaluated for transcatheter aortic valve replacement (TAVR) | CT | 761 | 83.0 ± 8.5 | 375 (49.3) | ● MAC severity was evaluated: 3.4% were with mild MAC, 9.5% with moderate MAC, and 9.5% were with severe MAC.<br>● Third day mortality and major complications<br>● Severe MAC was reported as a strong predictor of all-cause mortality ( HR = 1.95, 95% CI: 1.24-3.07, P = 0.00),; cardiovascular mortality ( HR = 2.35, 95% CI: 1.19-4.66; P = |

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| | | | | | | 0.01) and a new permanent pacemaker implantation (OR= 2.83, 95% CI: 1.08-7.47; P = 0.03) following TAVR |
| Toufan et al. [8] | Incidental finding of mitral valve calcification on CT and the presence and severity of mitral valve disease on ECHO. | CT | 50 | 69.5 ± 8.64 | 32 (64) | ● CT well differentiated the location of calcification between mitral valve leaflet and mitral valve annulus and is consistent with the previous studies [27] [28].<br>● MAC is predominantly detected on posterior annulus (48%) followed by posterior leaflet (18%) and anterior annulus (16%).<br>● MAC did not show any correlation with MS. However, all patients with MS had mitral valve leaflet calcification with or without mitral annular calcification. |
| Elmariah et al. [42] | History and risk factors that predict incidental MAC and its progression in MESA cohort | CT | 5895 | 62 ± 10 | 534 (9) | Incidental MAC: strongly predicted by age (OR = 2.25 per 10years, 95% CI: 1.97-2.58, p < 0.0001), female gender, Caucasians, body mass index, diabetes, hypertension, hyperlipidemia, serum cholesterol, smoking and IL-6.<br>Accelerated MAC progression: strongly predicted by baseline MAC score (□=0.89 per 10 AU, 95% CI: 0.86-0.92, p<0.0001) followed by ethnicity (p=0.01), smoking(p=0.0008) and diabetes (p=0.03). |
| Penn Diabetes Heart Study [43] | Risk factors associated with the presence and extent of MAC in type 2 diabetes mellitus patients without cardiovascular disease or chronic kidney disease | CT | 1753 | 66 | 212 (12) | ● In a multivariable logistic regression: type 2 diabetic patients, the presence and extent of MAC was significantly correlated with age, female gender, Caucasian race, duration of diabetes and presence of any CAC. These results were consistent with Elmariah et al. [42] |

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| CRIC study [44] | Prevalence and relationship of MAC in adults with chronic kidney disease | CT | 2070 | 64.7±7.7 | 331 (16) | MAC is more prevalent in<br>● Aged<br>● Caucasian race<br>● Decreased GFR<br>● Elevated phosphate |

## Risk factors and cardiac abnormalities associated with MAC:

MAC is a multifactorial condition and main risk factors include females, advanced age, CKD, MS, altered hemodynamic stress, atherosclerosis, and cardiovascular risk factors.

*Age and Gender:*

Age and gender are non-modifiable risk factors of cardiovascular disease. Risk factors such as hypertension, diabetes, smoking, obesity and inflammation may have led to age-related structural and functional changes in the cardiovascular system [45]. Weissler-Snir et al. [33] reported that the older (>50 years) patients with MAC were significantly hypertensive (84%) and dyslipidemia (64%) with CAD (65%). The overall MAC prevalence was reported as 9% in patients with mean age 62 ± 10years (53% women) in the Multi-Ethnic Study of Atherosclerosis (MESA) (Elmariah et al. 2013). Previous studies have demonstrated that prevalence of MAC significantly increases with age and age is considered as a strong predictor of MAC (OR = 2.25 per 10years, 95% CI: 1.97-2.58, $p < 0.0001$) [42]. The Northern Manhattan Study enrolled 1955 subjects without prior myocardial infarction or ischemic stroke, MAC was noted in 27% of the study population with mean age 68years. Echocardiographic MAC prevalence was 14% and 42% in two studies enrolling the older study population of age 70 and 76 years respectively [17,18] . Mahnke et al. [27] reported that individuals with MAC were significantly older than those without calcification (70.6 ± 8.3 vs 61.5 ± 12.2 years $p< 0.0001$). The most recent study has shown the higher prevalence of MAC among elderly women (median age 81years) compared to men (85% vs

73%; p<0.001)[46]. The association between MAC and aging is proven by the fact that it is present in 90years of adults at the time of autopsy (17% men and 43% women) [47]. Not only prevalence but also the severity of MAC increases with age [36,48].

Female gender are at high risk of developing MAC (p<0.01) [23]. The Framingham study reported that women were more than twice as likely to have sub mitral (annular) calcification than men [49]. Adler et al. [50] enrolled 165 patients with MAC who underwent cardiac catheterization and around 61% were found to be women (p = 0.03). The exposure of women to endogenous estrogens during the reproductive age regulates the various metabolic factors such as lipids, inflammatory markers and coagulant system has been assumed to delay the onset of atherosclerotic disease and various cardiovascular diseases [51]. Conversely, the data regarding the characteristics of young patients (<50years) with MAC enrolled 56 patients with a significant male study population (71% vs 36%, p<0.001). Furthermore, the prevalence is similar among both women and men as observed in Atherosclerosis Risk in Communities study and the Cardiovascular Health Study [39,48,52].

*Ethnicity:*

Ethnic variability is a strong predictor of incident MAC (p=0.01). MAC prevalence was predominant in Caucasians (12%), followed by Hispanics (10%). However, Kanjanauthai et al. [23] reported that Caucasians and Hispanics did not show any significant difference in association with MAC. Additionally, African Americans (7%) demonstrated to have lower incidence of MAC followed by Chinese (5%). Elmariah et al. [42] observed that ethnicity black (β = −13.97; 95% CI: −26.36 to −1.59; P=0.03) and Hispanic (β= −15.24; 95% CI: −28.26 to −2.22; P=0.02) slows the progression rate of MAC. Furthermore, A cross-sectional study has observed that African American and Hispanic races were protective against MAC in chronic renal

insufficiency patients [44]. Previous studies have reported that racial differences were not only found in MAC but also in other valvular calcifications and presence of coronary artery calcium [53,54].

*Conduction abnormalities and Atrial Fibrillation*

In 1908, Bonninger first identified MAC as being associated with a complete heart block [55]. In 1910, Dewitzky provided detailed pathological descriptions of 36 cases and demonstrated a close resemblance to an aortic valve related process described by Monckeberg in 1904 [56]. In 1935, Yater and Cornell had demonstrated the extension of the mitral calcified mass to the Bundle of His leading to the heart block histopathologic ally [57]. Calcification of mitral valve annulus fibrosis was usually observed in older people at autopsy and was believed to be a sequel to rheumatic heart disease [56,58]. However, there was often no indication of a prior illness; MAC is now commonly known as the final stage of the inflammatory process.

MAC is associated with high Incidence of conduction abnormalities (bundle branch block and atrioventricular blocks) and atrial fibrillation (AF) because of the close location of atrioventricular nodes and bundle of His to the cardiac fibrous skeleton. Lev and Lenegre proposed that the age-related degenerative mitral annulus process may be associated with or accompanied by a sclerodegenerative process within the conduction system [59,60]. The precise mechanism is unknown and the diffuse conduction system disease can disrupt inter- and intra-atrial conduction, contributing to the development of AF [61].The Framingham study reported 12 fold high risk of AF in subjects with sub mitral calcium compared to those without it (20 of 162, 12% vs 53 of 5,532, 1%) [49]. Nair et al. [37] enrolled 104 patients (mean age 70±9 years; 55 women) with echocardiographic evidence of MAC and evaluated the incidence of conduction defects determined by ECG. 70% were found to have conduction defects and concluded that the presence of a slower ventricular response in these patients may be attributed to the

involvement of atrioventricular node and/or bundle of His by annular calcification. The probability of MAC-related conduction defects is similar between calcification affecting either the posterior or the anterior and posterior mitral annulus only. MESA study reported that 4.6% out of 9% of participants with MAC developed AF over a median follow-up of 8.5years (HR = 1.9, 95% CI: 1.5-2.5). By applying MAC to the Framingham Heart Study and CHARGE AF risk scores for AF, the investigators observed that the improved C-statistics from 0.769 to 0.776 (P = 0.03) and 0.788 to 0.792 (P = 0.08), respectively [62].

AF is the most common arrhythmia and its prevalence significantly increases with age from 0.5-1% to 8% after 80years of age. Left atrial enlargement is the key predictor for the association between AF and MAC as described by Strong Heart Study [63]. Volume and pressure overload leading to left atrial enlargement can cause mitral regurgitation [64], resulting in an increased risk of AF [65]. Incidence of AF varies between 5.4% to 47.1% in patients with MAC. MAC was also associated with a high incidence of atrial fibrillation (HR=1.6; 95% CI: 1.1-2.2) in a multivariable-adjusted analysis and this association was attenuated by further adjustment for left atrial size (HR=1.4; 95% CI: 0.9–2.0) [66]. The pooled analysis from 13 studies demonstrated a significant elevated risk of AF in MAC patients (OR = 2.34; 95% CI: 1.91-2.85; P=.000) [7]. The pooled analysis from Li et al. assessed the association between MAC and major adverse cardiovascular events (MACEs) among 2418 patients with AF and MAC. During a median follow-up of 1.3years, 353 patients reported MACEs and demonstrated a statistically significant higher risk of MACEs among AF patients with MAC (OR = 2.34; 95% CI: 1.24- 4.41; *P* = .009). MAC was reported as an independent predictor of recurrent AF after cryoablation [67]. In addition, arterial stiffness and inflammation in the presence of MAC could enhance the likelihood of AF [68]. AF patients with MAC were at greater risk for cerebrovascular and cardiovascular events [7]. Current rhythm control strategies suggest that clinicians should take

appropriate measures to prevent AF and to reduce the adverse outcomes with AF [7].

*Valvular abnormalities:*

MAC was significantly associated with valvular abnormalities such as MR, tricuspid regurgitation (TR) and aortic stenosis (AS), but not MS or aortic regurgitation (AR). Hunold et al. [38] analyzed 1812 patients who underwent electron-beam tomographic scans for evaluation of coronary artery calcium and reported 17% of accidental heart valve calcifications. Calcified mitral valve annulus becomes dense and rigid, interfering with the closure of the valve leaflet that causes MR [36]. The main components of the pathophysiological MR process are decreased forward stroke volume; left atrium enlargement to accommodate the elevated LAV and pressure; and elevated left ventricular systolic ejection fraction. Absence of left atrial dilation in individuals with MR increases the pulmonary arterial pressure resulting in pulmonary edema and TR [69]. The association between MAC and TR can be explained by a rise in pulmonary arterial pressure secondary to MR or AS.

There is a conflicting data between the association of MAC and MS. The development of MS in MAC individuals may have been due to decreased normal annular dilatation during diastole with impaired anterior mitral leaflet mobility which contributes to left ventricle inflow obstruction. Movva et al. [70] assessed the association of MAC with MS/MR among 75 hemodialysis patients (mean age = 60 ± 14 years; 60% men). MR (81%) is more prevalent compared to MS (28%). Labovitz et al. [71] evaluated the 51 patients who had an echocardiographic evidence of MAC and 8% of the study population had significant MS with mitral valve area < 2cm2. Aronow et al. [72] have found that 10% of 293 patients with MAC on echocardiogram have MS murmur. On the other hand, few studies did not show any significant correlation between the presence of MAC and MS [8,36]. All the MS patients

were found to have mitral valve leaflet calcification with or without mitral annular calcification. So, the prevalence of MS varies based on MAC extension to leaflets.

Movahed et al. [36] observed MAC in 15% of patients with AS, compared to 6% without AS (p =0.01). Mitral and aortic valve calcifications share the same pathophysiological mechanism as vascular atherosclerosis by basement membrane disruption, macrophages and T-lymphocytes infiltration, and lipid deposition. Aortic stenosis and hypertension raise left ventricular pressures, increase mitral valve stress and facilitate irregular movement of the valve which enhances degenerative process and aid in premature calcification [2]. Elmariah et al. [73] demonstrated the strong correlation between left ventricular hypertrophy and the prevalence, severity and incidence of MAC. Statin therapy has been shown to reduce the progression of moderate to severe AS and this might be attributed to statin anti-inflammatory properties rather its lipid-lowering effects [74]. For inoperable or high-risk surgical patients with severe AS, transcatheter aortic valve replacement (TAVR) is a treatment of choice [75]. However, the recent advancements of cardiac CT determine the need for TAVR in patients with severe AS and MAC is frequently an incidental finding in these CT examinations [76]. Furthermore, the severity of MAC was reported as a strong predictor of all-cause mortality (p=0.01), cardiovascular mortality (P = 0.01) and new permanent pacemaker implantation following TAVR (OR= 2.83, 95% CI: 1.08-7.47; P = 0.03) [41].

*Atherosclerosis*

Atherosclerosis is a complex histopathological process. The arterial branch points (left main coronary artery and distal abdominal aorta) and vascular regions are more likely to develop atherosclerosis due to altered shear stress or enhanced blood flow turbulence. Similarly, the location of mitral and aortic valve attachment to annulus is also the location of turbulent blood flow and

are at high risk of developing atherosclerosis [39]. Previous studies have demonstrated the histopathological similarities between vascular atherosclerosis and the degenerative changes of cardiac valves [77,78]. Allison et al. [39] evaluated the calcium extension in 1242 asymptomatic patients by electron-beam computed tomography and 8% had MAC. The calcification of abdominal aorta had the highest likelihood for the presence of MAC (OR=5.1, P=0.01) whereas, in a separate regression analysis thoracic aorta calcification was significantly associated with MAC (OR=1.4 P=0.02). MAC also demonstrated a significant association with carotid artery stenosis [50,79]. Furthermore, the persistent inflammatory disorders and cardiovascular risk factors increase the risk of atherosclerosis and MAC.

Systemic inflammation plays a vital role in the pathogenesis and progression of atherosclerosis and MAC. Inflammation is a major consequence of renin angiotensin system (RAS) imbalance and oxidative stress that contributes to vascular remodeling and endothelial dysfunction [80,81]. As a consequence of this remodeling, the activation of Angiotensin II receptor increases the production of cell adhesion causing monocyte aggregation which transforms into macrophages and later to the foam cells. This mechanism is demonstrated by a pathological study showing the collection of foam cells in the coronary artery endothelium, the ventricular surface of posterior mitral valve leaflet, and on the aortic surface of aortic valve cusps identified in the adult study population. Cytokines and pro-inflammatory markers (Interleukins, CRP) are secreted by foam cells, resulting in the disturbance of intima media elasticity, with migration of smooth muscle cells to the sub-endothelial space transforming into fibrocytary or myofibrocytary cells. Furthermore, the experimental study inducing systemic arterial atherosclerosis in rabbits observed the deposition of fatty plaques in areas of high intramural tension (aortic surface of the aortic valve cusps and ventricular surface of the posterior mitral leaflet), which evolves and degenerates into calcific deposits, accelerating the process of atherosclerosis

[82]. This data suggests the MAC as a predictor of systemic atherosclerosis and may serve as a marker for subclinical atherosclerosis. In addition to the above mechanisms, the immune system has recently been illustrated in pathogenesis of atherosclerosis as a result of activated lymphocytes and immunoglobulins [83,84]. Association of the MAC and atherosclerosis were well established in a study which demonstrated a relationship between MAC and the existence of b2-Glycoprotein I antibodies (b2GpI) [15]. Furthermore, absence of MAC is a strong indicator to rule out obstructive coronary artery disease in women but not in men [85].

MAC identifies CAD with a sensitivity and specificity of 60% and 56%, respectively, and with negative and positive predictive values of 52% and 64%, respectively [86]. A stronger indicator was found to be the absence of MAC for absence of CAD relative to all traditional risk factors except for the absence of diabetes mellitus. Benjamin et al. [66] have shown an increased incidence of CAD among individuals with MAC compared to the control group (28.8% vs 17.4%; p =0.006). Adler et al. [50] reported echocardiographic evidence of MAC as a marker for high prevalence (89% vs 75%, p = 0.001) and severity of CAD (3-vessel disease: 45% vs 24%, p = 0.001; left main coronary artery: 13% vs 5%, p=0.009). Similarly, Atar et al. demonstrated that MAC (n= 6207/ 17735; 35%) as an independent predictor of severe obstructive CAD (88% *v*s 68%, p = 0.0004) with 92% of positive predictive value. Individuals with MAC have found to have significant left main coronary artery stenosis (14% v 4%, p = 0.009) and triple vessel CAD (54% v 33%, p = 0.002). The MESA study observed an increase in the probability of MAC was 9%,19% and 15% with an increase in the CAC scores of 1 to 99, 100 to 399, and ≥400, respectively (p<0.0001) [87]. The prevalence ratio of MAC in those with mild CAC (1 to 99) after controlling for demographics and other risk factors was 2.13 (95 percent CI: 1.69-2.69) but increased to 7.57 (95 percent CI 5.95-9.62) for CAC >400. This correlation, however, weakened but persisted after age, sex, and other typical cardiovascular risk factors were

modified, indicating that the presence of MAC is an indicator of atherosclerotic burden. The presence of MAC was associated with an increased prevalence of >70% of coronary artery stenosis (80% vs 62%) in study with a population of 2465 patients (mean age = 69 ± 13 years; 1028 women) who underwent coronary angiography for suspected coronary artery disease [88]. Three vessel disease was reported to be more common with severe MAC (47%) and in those with mild to moderate MAC (35%) than with no MAC (30%).

*Stroke*

The MAC score represents the functional and structural features of the MAC, as measured by echocardiography, which can contribute to the risk of stroke. MAC score obtained based on MAC mobility, echo dense mass with central echolucencies indicating caseous necrosis in peri annular region (23 vs. 7%, $p<0.001$) and functional mitral stenosis (12 vs. 7%, $p = 0.042$) showed significant association with stroke [89]. The Cardiovascular Health Study demonstrated that calcification of the left-sided cardiac valve or annulus is associated with 33% higher risk of occult MRI-defined cerebral infarction (RR=1.24, 95% CI:1.05-1.47) [35]. In left-sided calcified structures, the formation of microthrombi can involve turbulent mitral or aortic blood flow, followed by fragmentation of red cells and the release of adenosine diphosphate and thromboplastin, resulting in microthrombus formation and non-calcific embolism. Since patients can remain asymptomatic, cerebral thromboembolism from calcified heart valves is more likely underestimated and the severity of symptoms often depends on the size of the emboli. Additionally, MAC and stroke correlation may be due to AF and complex aortic atherosclerosis. In order to prevent atrial fibrillation in patients with MAC, clinicians should take close attention to the extent of complex aortic atherosclerosis and the degree of calcification [90]. Whereas, Benjamin et al. [66] found the significant association between presence of MAC and stroke (RR=2.10, 95% CI: 1.24-3.57, p=0.006) in subjects without known history of

AF or CAD or heart failure. Each millimeter rise in thickness of the MAC from M mode echocardiography increases the relative risk of stroke by 1.27 for men (95% CI: 1.06-1.52, p = 0.009) and 1.19 for women (95% CI: 1.06-1.34, P = 0.003). Kizer et al. [91] followed 2723 American Indians who had no clinical history of cardiovascular disease and reported 19 incidence of strokes in MAC patients over a median follow-up of 7years. After adjusting for age and gender, the investigators observed that individuals with MAC have a significant high rate of stroke (RR=3.12, 95% CI: 1.77-5.25) and not for aortic valve sclerosis (RR=1.15, 95% CI: 0.45-2.49). Karas et al. [92] has found that proximal complex aortic atheroma acts as a direct marker for enhanced risk of stroke which is associated with MAC (adjusted OR= 2.74; 95 percent CI: 1.22-6.16), but they did not identify whether MAC was an independent risk factor for stroke. De Marco et al. [93] and Herskovitz et al. [94] demonstrated MAC as a strong independent predictor of ischemic stroke. MAC existence and severity can predict stroke and the identification of MAC provides valuable information about the prognosis relative to traditional risk factors of stroke. Treating these MAC patients with antithrombotic therapy reduces the risk of thromboembolic stroke. Patients with MAC were 1.7 times more likely to experience thromboembolic strokes than those without MAC, in the absence of anti-thrombotic therapy [95].

*Chronic kidney disease*

Patients with renal disease are at high risk of calcium accumulation in coronary arteries and heart valves due to inflammatory, hormonal and electrolyte dysregulation [96]. Inflammation is one of the early step in the pathogenesis of atherosclerosis and vascular calcification due to imbalance between the pro- and anti-inflammatory markers such as IL-1, IL-6, CRP, TNF-α and fetuin-A (a multifunctional glycoprotein that inhibits dystrophic calcification). Wang et al. [97] reported that serum fetuin-A is inversely associated with cardiac valve calcification (p=0.002). The main contributing factor to MAC is abnormal calcium-phosphorus metabolism especially in

chronic kidney disease (CKD) patients [3] and previous studies have shown an association between the MAC and abnormal calcium metabolism [15,98–100]. Roberts et.al [100] reported an analysis of 18 necropsy patients examining the effect of chronic hypercalcemia on the heart and demonstrated that chronic hypercalcemia is associated with accelerated deposition of calcium in the cardiac annulus and valve cusps, in the media and intima of the coronary arteries and in the individual myocardial fibers. Thus, chronic hypercalcemia in Roberts' theory can be a risk factor for calcium deposition in the mitral annulus, myocardial and coronary arteries. Maher et al. [101] followed 87 hemodialysis patients over a mean of 7.5years and reported that premature MAC is frequent in dialysis patients which might be due to abnormal calcium and phosphate metabolism. Similarly, the excess amount of phosphate accumulates in the tunica media or intimal layer and activates the genes that transform vascular smooth muscle cells and pericytes to osteoblast-like cells which promotes calcification. The extreme bone loss due to postmenopausal osteoporosis and hypovitaminosis D might cause ectopic calcium deposits in elderly women. Calcium sensing receptors present in endothelium, vascular smooth muscle cells and cardiomyocytes have cardioprotective properties by suppressing the parathyroid hormone produced secondary to hypovitaminosis D. However, these receptors expression is reduced in CKD patients and thereby increasing the risk of calcification. The upregulated fibroblast growth factor 23 (FGF23) in CKD patients promotes vascular calcification and is proposed as an independent predictor of the severity of coronary stenosis and the number of stenotic vessels. The Cardiovascular Health Study demonstrated that FGF-23 was significantly associated with MAC with a relative risk (RR) of 1.040 (95% CI: 1.004-1.078) whereas fetuin A was negatively associated with an RR of 0.989 (95% CI 0.911-0.989). MAC was found in more than 26% of patients with chronic kidney disease [15,98]. Jesri et al. [102] enrolled 41 patients with documented MAC on echocardiography and 60% had CKD (GFR<60 ml/min/1.73m$^2$) with a relative

risk of 1.8 compared to controls. Significant worse renal function is associated with MAC, measured by creatinine and glomerular filtration rate ($p < 0.001$). Previous studies have shown the higher prevalence of MAC in end stage renal disease (ESRD) patients who are receiving renal transplant therapy [103–106]. ESRD individuals with MAC are significantly associated with increased mortality ($p = 0.04$, log rank test) and severe CAD ($p \leq 0.001$) compared to those without [107]. Furthermore, Alamir et al. [44] reported that multiple other risk factors might play a significant role with MAC in the general population but these may not play a vital role in patients with CKD.

**Conclusion:** Risk factors for MAC in patients with myxomatous degeneration and severe MR include older age, female gender, severe renal dysfunction and larger preoperative left atrial size. Nevertheless, favorable early and late results can be achieved with mitral valve repair in this population. In conclusion, morphological and functional characteristics of MAC had incremental value in association with cardiovascular events, thromboembolic events, stroke, and conduction abnormalities over traditional risk factors.

**Expert commentary:**

The normal mitral valve controls the flow of blood from the left atrium to the left ventricle without a substantial regurgitation during systole and forward gradient during diastole. Proper functioning requires not just normal functioning of leaflets, but also structured coordination of leaflets with the annulus, chordae tendineae, and the papillary muscles (PMs). Despite its frequency, the clinical importance of MAC is grossly underestimated. Indeed, MAC is associated with an increased risk of cardiovascular diseases, mitral valve disease, arrhythmia, and mortality, but its pathophysiology is not well known. Diagnostic modalities CT and echocardiography to examine the pathology of MAC and to elucidate the factors associated with its prevalence, disease activity and disease progression. Patients with MAC (34%) had increased inflammatory and calcifying activity through positron emission

tomography imaging in the mitral annulus. In addition, calcification activity was most closely correlated with computed tomography-MAC calcium score, inflammation, female sex, and renal dysfunction. Similarly, MAC progression on repeat computed tomography scans after 2 years was closely correlated with baseline MAC, with the fastest rate of progression in those with high baseline computed tomography-MAC scores and the highest calcification frequency. By comparison, typical cardiovascular risk factors and calcification activity in bone or remote atherosclerotic areas have not been correlated with disease activity or progression. This indicates that MAC is defined by a vicious cycle of calcium, injury and inflammation. Further large randomized trials are required to support the targeted MAC therapeutic strategies for breaking this vicious cycle of calcification.

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