Curr Treat Options Cardio Med (2019) 21: 19
DOI 10.1007/s11936-019-0723-6

Mitral Annular Calcification and Calcific Mitral Stenosis: Therapeutic Challenges and Considerations

Philippe B. Bertrand, MD, PhD[1]
Christos G. Mihos, DO[2]
Evin Yucel, MD[1,*]

Address
[*,1]Cardiac Ultrasound Laboratory, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St, Yawkey 5E, Boston, MA, 02114, USA
Email: eyucel@partners.org
[2]Echocardiography Laboratory, Columbia University Division of Cardiology, Mount Sinai Heart Institute, Miami Beach, FL, USA

Published online: 30 March 2019

This article is part of the Topical Collection on *Valvular Heart Disease*

Keywords Mitral annular calcification · Calcific mitral stenosis · Degenerative mitral stenosis · TMVR · Mitral valve surgery

Abstract

Purpose of review Mitral annular calcification (MAC) and associated calcific mitral stenosis (MS) are frequent in the aging population, although optimal management remains debated and outcomes are poor. This article summarizes challenges in the diagnosis and therapy of calcific MS, the indications for valve intervention, procedural concerns, and emerging treatment options.
Recent findings Surgical mitral valve replacement is the procedure of choice in symptomatic patients at acceptable surgical risk, with transcatheter mitral valve replacement (TMVR) being evaluated in clinical trials as an alternative for patients at prohibitive surgical risk. Significant challenges exist with the currently available technology and outcomes have been suboptimal. Optimizing the patient-selection process by using multimodality imaging tools has proven to be essential.
Summary MAC and calcific MS is an increasingly prevalent, challenging issue with poor outcomes. While surgical valve replacement can be performed in patients with acceptable surgical risk, TMVR can be considered for patients at higher risk. Clinical trials are underway to optimize outcomes. Dedicated device designs and techniques to minimize risk of left ventricular outflow tract obstruction, paravalvular leakage, and device embolization are to be awaited.

Introduction

Mitral annular calcification (MAC) is a chronic, degenerative process originating at the level of the posterior fibrous mitral annulus that can be associated with—and less frequently is the primary cause of—significant mitral valve (MV) dysfunction [1••, 2]. The estimated prevalence of MAC ranges from 8 to 15% in the general population. MAC is more common in women, in advanced age, chronic kidney disease, and it is associated with multiple cardiovascular risk factors [3–8]. In fact, the pathophysiologic mechanisms of MAC share similarities with the pathogenesis of atherosclerosis [9–11]. Prior chest irradiation is another specific cause of annular calcification, which more commonly involves the anterior mitral annulus and aortic-mitral intervalvular fibrosa [12, 13]. 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 hypertrophy, and MV prolapse [14]. As such, the prevalence of MAC in people ≥ 65 years of age is over 40% [15]. In aortic stenosis patients referred for transcatheter aortic valve replacement (TAVR), MAC is reported in up to 50% of the cases. "Severe" (circumferential) MAC, causing severe mitral stenosis (MS), is present in up to 24% of TAVR patients [16, 17].

While commonly an asymptomatic and incidental finding, MAC is a marker of poor cardiovascular status and outcome [3, 15, 18, 19]. Significant valvular stenosis directly caused by the calcification occurs in the minority of patients, although prevalence increases with increasing life expectancy [20•]. Pathologic elevations in the mean transmitral gradients have been reported in 0.2–0.5% of patients undergoing transthoracic echocardiography. The prevalence increases to 2.5% in patients > 90 years of age [21, 22] and to > 20% in younger hemodialysis outpatients [23]. Significant MS is reported in approximately 8% of patients with echocardiographic evidence of MAC [24], typically mixed with coexisting mitral regurgitation (MR) [25, 26]; however, one needs to account for the increased regurgitant volume leading to increased MS gradients. In addition, a growing proportion of elderly patients will present with significant MV disease in the presence of MAC, posing a challenge to conventional treatment modalities.

The optimal therapeutic strategy for patients with calcific MS remains complex and debated [20•, 27•]. First, indications for intervention are ill-defined in this typically elderly population with significant comorbidities. Second, conventional surgical and percutaneous interventions to repair or replace the MV in case of calcific disease are known to be associated with considerable complexities and risk. The purpose of this article is to provide an overview of the currently available treatment options for calcific MS, the indications for intervention, and the respective procedural concerns. Finally, emerging therapeutic interventions and potential improvements toward future clinical application will be discussed.

Diagnostic challenges in calcific mitral valve stenosis

International guideline recommendations for the treatment of MS must be applied cautiously in patients with calcific valve disease [28, 29]. Indeed, most of the recommendations are based on outcome data in rheumatic MS and should not be extrapolated to calcific valve dysfunction. Percutaneous balloon valvuloplasty is usually not an option in these patients who often have mixed mitral valve disease. Moreover, in contrast to patients with rheumatic MS, the valve commissures typically retain their pliability and mobility, rendering balloon valvuloplasty anatomically less indicated [1••, 4]. Sparing of the commissures also explains the relatively low rate of isolated severe hemodynamic stenosis in MAC patients when compared to rheumatic valve disease, with pathologic gradients only occurring once the anterior MV leaflet has become calcified and immobile [22]. In developed countries, the MS etiology and prevalence are shifting from rheumatic to calcific MV disease. According to recent studies, some degree of calcific MS may now account for 12 to 26% of all MS cases [20•]. In the Euro Heart Survey, when subdividing the age groups 50 to 70, 70 to 80, and > 80 years, calcific MS accounted for approximately 10–15%, 30%, and 60% of all MS cases, respectively [30, 31].

Decision-making in patients with calcific MV disease is based on a thorough echocardiographic evaluation and confirmation of stenosis severity. A mitral valve area (MVA) ≤ 1.5 cm^2 is now considered to be severe MS. This usually corresponds to a mean transmitral mean gradient of > 5 to 10 mmHg at a normal heart rate [28]. The echocardiographic assessment of calcific MS however is subject to several challenges [32••, 33, 34], as the "classic" echocardiographic techniques used for MVA evaluation (pressure half-time method, proximal isovelocity surface area, continuity equation, and mitral valve planimetry) lack validation in calcific MV disease. The pressure half-time method (MVA = 220/pressure half time), as first described by Liv Hatle in 1979 [35], is influenced by the compliance of the left ventricle and atrium. In patients with diastolic dysfunction related to decreased left ventricular compliance, as is frequently observed in an elderly population with MAC and associated risk factors, the pressure half-time method has been shown to significantly overestimate MVA and should thus be used cautiously [36]. The continuity equation for calculation of the effective orifice area is not valid in cases of significant concomitant mitral (or aortic) regurgitation, which is highly prevalent in degenerative calcific disease. Calcium-shadowing artifacts pose additional challenges to the assessment of concomitant MR severity, and transesophageal echocardiography may be indicated in some cases to accurately diagnose mixed valvular disease [37]. Similarly, direct two-dimensional MV planimetry to assess MVA, which is the gold standard in rheumatic MS patients, is difficult and unreliable in calcific MS because of the orifice geometry (absence of commissural fusion) and the presence of calcium. Direct planimetry using three-dimensional echocardiography and color flow Doppler has been proposed showing a good correlation with MVA by continuity equation; however, data are limited [38].

Treatment

Medical management

The prognosis of patients with calcific MS is generally poor. Pasca and colleagues [39•] retrospectively studied a cohort of 1004 patients with calcific MS, defined as severe MAC without commissural fusion and a mean transmitral diastolic gradient of > 2 mmHg. Over a mean follow-up period of 3.5 ± 2.8 years, there were 549 deaths, with 1-, 5-, and 10-year survival rates of 78%, 47%, and 25%, respectively. The 5-year calculated mortality rate of 53% was three times the calculated mortality rate of an age- and gender-matched group from the US general population. A possible protective effect of renin-angiotensin system blockers and statins was noted using propensity score analysis, although further validation is needed with prospective follow-up. Risk factors for increased mortality included older age, renal insufficiency, atrial fibrillation, and concomitant valvular lesions [39•].

In symptomatic patients with severe calcific MS, the cornerstone of therapy is medical management with heart rate control and optimization of volume status using diuretics [20•, 29, 40]. Beta blockers and calcium channel blockers are most commonly used to lower the heart rate and/or to rate-control coexisting atrial fibrillation with the aim to decrease transmitral flow and thus diastolic pressure gradients and symptoms. In patients with symptoms refractory to medical therapy, the decision of invasive valve intervention should be made on a case-by-case basis, weighing the considerable risks of intervention with the expected benefits.

Mitral valve surgery

Surgical MV replacement remains the intervention of choice to treat severe symptomatic calcific MS in patients with low or intermediate surgical risk [20•]. The presence of annular calcification introduces a number of technical challenges to the procedure and to the anchoring of the replacement prosthesis. Addressing the annular calcification causes a surgical dilemma between a "respect" strategy and a "resect" strategy [27•]. Mitral valve replacement while preserving the calcium bar ("respect") is associated with increased risk of significant paravalvular leakage, injury to the left circumflex coronary artery or conduction system, and the use of smaller sized valve prostheses prone to prosthesis-patient mismatch. Debridement of the calcified tissue ("resect") allows for better valve seating, larger valve sizing, and lower risk of paravalvular leakage [41, 42]. However, this technique comes with the risk of weakening the annulus and increasing the risk of catastrophic atrioventricular groove disruption [43]. Several methods have been proposed for dedicated annular debridement and reconstruction to avoid this complication with good technical results and outcome [44, 45], but longer cardiopulmonary bypass times and technical expertise are implicated [27•, 46].

In patients with MAC presenting predominantly with MR, depending on the extent of leaflet calcification, MV repair could be achievable. In 1996, Professor Carpentier described his surgical methods for annular debridement and reconstruction demonstrating feasibility and durable technical success with mainly MV repair [44]. More recently, long-term outcome data from the Leiden group are confirmative that MV repair for calcific MV disease is feasible and safe in MAC patients when performing dedicated annular decalcification and reconstruction [47]. Even in an elderly population aged > 70 years, outcomes of repair remain superior to replacement as shown in a recent analysis from the STS Adult Cardiac Surgery Database [48].

Transcatheter mitral valve replacement

A growing number of elderly patients with severe MAC are at high or prohibitive surgical risk. Transcatheter mitral valve replacement (TMVR) for the treatment of severely calcified MVs has therefore gained attention, in similarity with TAVR for calcific aortic stenosis [49]. Despite the conceptual similarities, i.e., deploying a stented bioprosthesis into a surrounding bulk of calcium, the elliptical, saddle-shaped mitral valve annulus and MV annular dynamics pose significant challenges to percutaneous MV replacement/implantation [50]. Major concerns for TMVR have been the anchoring of the prosthesis, obstruction of the left ventricular outflow tract (LVOT) by the displaced anterior mitral leaflet, and occurrence of significant paravalvular leakage, typically at the level of the commissures [21, 51].

Two multicenter registries of the initial real-world experience with TMVR in MAC patients provide insights into the current challenges. The TMVR in MAC Global Registry included 116 patients in 51 centers worldwide who underwent TMVR with compassionate use of balloon-expandable transcatheter heart valves (98% Edwards-SAPIEN valves; Edwards Lifesciences, Irving, CA, USA) between September 2012 and March 2017 [52, 53••]. Mean age was 73 ± 12 years, 68% were female, and surgical risk was very high with a mean Society of Thoracic Surgeons (STS) score of 15.3 ± 11.6%. Procedural success was achieved in 77% of patients, with 15% of patients needing a second valve implantation due to either migration or severe regurgitation. LVOT obstruction with hemodynamic compromise occurred in 13 patients (11.2%) and was ultimately fatal in 11 (9.4%). Thirty-day and 1-year all-cause mortality was 25% and 53.7%, respectively. On multivariable Cox regression analysis, LVOT obstruction was found to be an independent predictor of mortality at 30 days (HR 3.16, 95% CI 1.19 to 8.36; $p = 0.02$) and at 1 year (HR 3.56; 95% CI 1.81 to 7.01; $p < 0.001$).

The TMVR multicenter registry included a subgroup of 58 valve-in-MAC patients (81% Edwards-SAPIEN valve; 15.5% Lotus valve, Boston Scientific, Marlborough, MA, USA; 3.4% Direct Flow valve, Direct Flow Medical, Santa Rosa, CA, USA) in 40 European and American centers after November 2015 [54•]. Mean age was 75 ± 11 years, 71% were female, and the mean STS score was 10.1 ± 6.9%. Technical success rate was only 62%, with LVOT obstruction (defined as increment in mean LVOT gradient ≥ 10 mmHg from baseline) occurring in almost 40% of patients. Thirty-day and 1-year all-cause mortality was 34.5% and 62.8%, respectively, with postprocedural moderate or greater MR identified as an independent predictor of worse outcome.

These registry data are consistent in highlighting the contemporary limitations and challenges of TMVR in MAC. Nevertheless, there are reassuring signals in these registries indicating that the procedural learning curve is steep and the outcomes are improving with increasing experience. In the TMVR in MAC Global Registry, there was a trend toward lower 30-day mortality in the second half of patients treated (31% vs. 19%; $p = 0.07$). Moreover, 4 patients (7.6%) needed conversion to surgery in the first half of the experience (7.6%) versus no need for conversion to surgery in the second half ($p = 0.04$). A prospective feasibility trial for TMVR (MITRAL trial, NCT02370511) has recruited a subgroup of 30 patients with MAC for either transseptal or transatrial TMVR. Preliminary results presented at TCT in 2017 showed a 30-day mortality of less than 20%, with the best outcomes observed in the transseptal group.

Evolving strategies and considerations

The initial experience with balloon-expandable TMVR in MAC has demonstrated important limitations of the currently available technology. Several strategies and solutions are emerging to overcome the respective challenges and to improve outcome of TMVR in MAC (Table 1).

Advanced *multimodality imaging with computer-assisted planning and simulation* is emerging as an essential step in the pre-procedural work-up and selection of TMVR patients [21, 55]. Cardiac computed tomography (CT) allows accurate detection and characterization of the extent of MAC, evaluation of the mitral annulus and valve area, and assessment of anatomic suitability for different

Table 1. Remaining challenges and potential solutions for transcatheter valve interventions in calcific mitral stenosis

Challenge	Potential solutions	Ongoing trial
LVOT obstruction	Dedicated pre-procedural planning Anterior leaflet resection Hybrid approach Septal ablation	LAMPOON, NCT03015194 SITRAL, NCT02830204
Device embolization	Dedicated device designs Hybrid approach	SITRAL, NCT02830204
Paravalvular leakage	Pre-procedural planning and simulation Dedicated device designs	
Valve thrombosis	Standardized anticoagulation schemes Prospective vigilance and reporting	

devices [56–59]. Post-processing tools and software to "virtually" overlay prosthetic valves of various sizes in the MV position allow estimation of the expected "neo-LVOT" [60, 61] (Fig. 1). Wang and colleagues showed validity of this prediction technique by demonstrating that a predicted neo-LVOT surface area of ≤ 189.4 mm^2 has a 100% sensitivity and 96.8% specificity for predicting TMVR-induced LVOT obstruction (defined as an increase of > 10 mmHg LVOT gradient post-TMVR) [62]. These CT techniques offer significant improvement

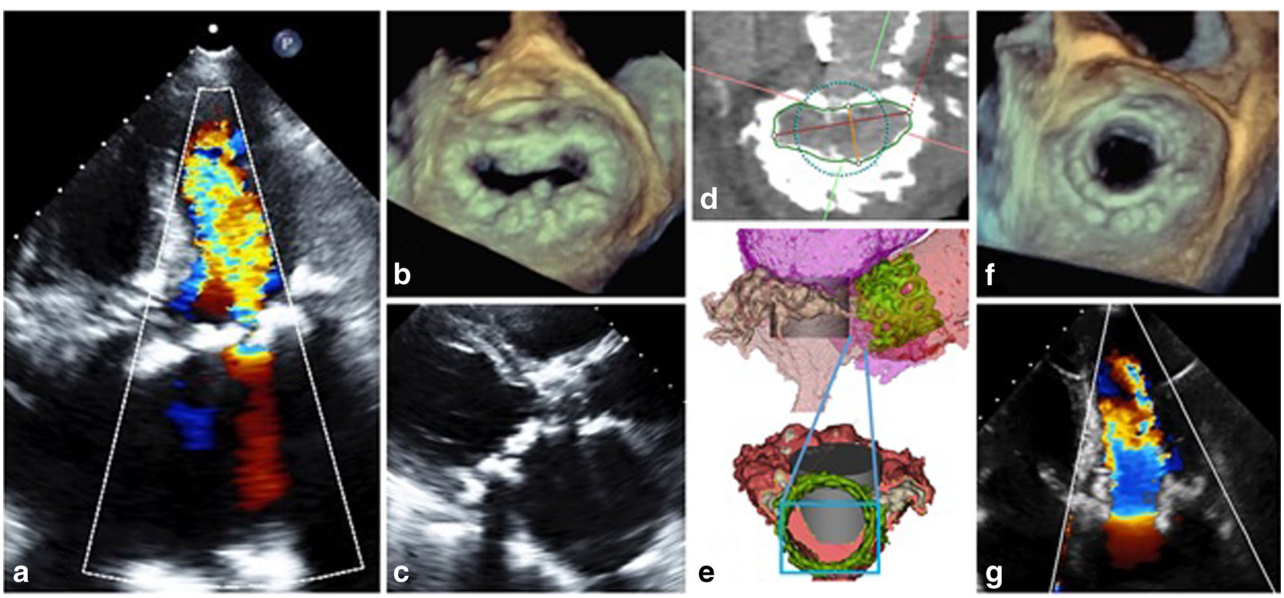

Fig. 1. Clinical example of a patient with severe calcific mitral valve disease treated with transcatheter valve-in-MAC after dedicated image-based planning. Apical four-chamber TTE view (**a**) and parasternal long-axis view (**c**) demonstrating severe annular calcium extending into the leaflets and importantly into the anterior leaflet causing significant mitral stenosis by color Doppler. Three-dimensional TEE imaging (**b**) confirms severe circumferential MAC while preserving the commissures, in contrast to the classic rheumatic pattern. Computer tomography is used for pre-procedural anatomic assessment and virtual overlay of a 29-mm SAPIEN 3 (Edwards Lifesciences, Irvine, CA) device (**d**), calculating the predicted neo-LVOT in three-dimensional reconstruction (Mimics software, Materialise NV, Belgium) (**e**). Post-procedural imaging (**f**, **g**) confirms adequate device seating, unrestricted transmitral inflow, no evidence of LVOT obstruction, and absence of paravalvular leakage.

to the pre-procedural TMVR evaluation and are gradually becoming essential in the work-up. Further advances to this technique can be obtained by using computer modeling tools that actually simulate device deployment (instead of merely overlaying an undeformed device geometry), thereby accounting for device-native heart tissue interaction and the displacement of the calcified MV leaflets, as demonstrated by De Jaegere et al. [63]. The latter tools have the potential to predict occurrence of post-procedural paravalvular leakage as well [64] and could be integrated in the real-time procedural imaging [65]. Finally, another option for assessing device-tissue interaction for pre-procedural planning and simulation of TMVR deployment is by the use of three-dimensional printing techniques based on patient-specific anatomic reconstruction [66, 67].

In patients at highest risk of LVOT obstruction, a novel transcatheter approach with *intentional laceration of the anterior mitral leaflet* has been proposed to prevent LVOT obstruction post-TMVR [68]. This technique creates a longitudinal split/slit of the middle scallop (A2) of the anterior MV leaflet, immediately before TMVR. As a result, chordal attachments displace the split anterior mitral leaflet away from the LVOT after the cylindrical prosthesis is implanted which allows blood to flow unobstructed across the prosthesis stent struts. The first in-human experience included one patient with severe MAC predicted to have life-threatening LVOT obstruction after TMVR, in which successful leaflet laceration was performed [69]. The technical safety and outcomes of anterior MV leaflet laceration are currently being studied in the prospective LAMPOON trial (NCT03015194).

Another approach to prevent or treat TMVR-related LVOT obstruction is *transcoronary alcohol septal ablation* in patients with unfavorable septal anatomy for TMVR. This technique can be used as a bailout during the TMVR procedure [70, 71], although preferably it is performed 4 to 6 weeks before TMVR in patients at high predicted risk of obstruction to allow for basal septal tissue necrosis/remodeling to take place. Drawbacks of this technique include sacrificing myocardium and risk of conduction system injury and subsequent pacemaker dependence. Moreover, this technique is unsuitable in patients with a thin interventricular septum.

A *hybrid surgical approach* is being investigated after initial reports of transatrial "direct vision" deployment of a percutaneous balloon-expandable SAPIEN (Edwards Lifesciences, Irvine, CA) valve prosthesis in severe MAC patients [72–74]. This hybrid approach overcomes some of the surgical issues encountered with valve suturing in the calcium and device undersizing. It allows for resection of the anterior leaflet before deploying the valve prosthesis, alleviating the risk of LVOT obstruction. Furthermore, device seating and anchoring can be assessed prior to release, as well as risk of significant paravalvular leakage. The major drawback however is the need for thoracotomy and cardiopulmonary bypass in patients already believed to be at high risk for cardiac surgery. This approach is being investigated within the prospective SITRAL trial (Surgical Implantation of TRAnscatheter vaLve in Native Mitral Annular Calcification, NCT02830204).

Dedicated mitral valve devices are expected to further improve the TMVR technique as compared to the currently implanted cylindrical prostheses designed for aortic valve procedures [75–77]. However, patients with severe MAC and calcific MS have typically been excluded in the initial experience of these dedicated MV devices. Current evidence with newer devices in MAC patients is therefore limited to case reports [78].

Finally, *anticoagulation regimens* after TMVR deserve consideration. Reports of subclinical device thrombosis in TAVR valves [79] have increased vigilance, not in the least for bioprosthetic valves in the mitral position. Quick et al. reported a hemodynamically significant valve thrombosis following valve-in-valve TMVR occurring 3 months after being discharged on dual antiplatelet therapy regimen [80]. Capretti et al. found an incidence of 3 valve thromboses in a total of 70 TMVR procedures. In two of the patients, the thrombosis occurred after discontinuation of oral anticoagulation following a 3-month post-procedural regimen of oral anticoagulation and aspirin [81]. Longer-term anticoagulant therapy may therefore be necessary in combination with antiplatelet therapy.

Conclusions and future perspectives

MAC and calcific MS is an increasingly prevalent clinical conundrum in the current era, as the optimal management remains challenging with overall poor outcomes. Surgical MV replacement is the procedure of choice in symptomatic patients with acceptable surgical risk. TMVR is being evaluated as an alternative for those patients at prohibitive surgical risk. Important challenges exist with the currently available technologies, and outcomes have been suboptimal. Optimizing the patient-selection process by using multimodality imaging tools is essential. Studies evaluating different techniques to minimize the risk of LVOT obstruction, paravalvular leakage, and device embolization are currently under investigation.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Abramowitz Y, Jilaihawi H, Chakravarty T, Mack MJ, Makkar RR. Mitral annulus calcification. J Am Coll Cardiol. 2015;66(17):1934–41. https://doi.org/10.1016/j.jacc.2015.08.872.
This is a great overview article on mitral annular calcification.

2. Silbiger JJ. Anatomy, mechanics, and pathophysiology of the mitral annulus. Am Heart J. 2012;164(2):163–76. https://doi.org/10.1016/j.ahj.2012.05.014.

3. Fox CS, Vasan RS, Parise H, Levy D, O'Donnell CJ, D'Agostino RB, et al. Mitral annular calcification

predicts cardiovascular morbidity and mortality. Circulation. 2003;107(11):1492–6. https://doi.org/10.1161/01.cir.0000058168.26163.bc.
4. Nestico PF, Depace NL, Morganroth J, Kotler MN, Ross J. Mitral annular calcification: clinical, pathophysiology, and echocardiographic review. Am Heart J. 1984;107(5 Pt 1):989–96.
5. Kanjanauthai S, Nasir K, Katz R, Rivera JJ, Takasu J, Blumenthal RS, et al. Relationships of mitral annular calcification to cardiovascular risk factors: the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis. 2010;213(2):558–62. https://doi.org/10.1016/j.atherosclerosis.2010.08.072.
6. Fox CS, Larson MG, Vasan RS, Guo CY, Parise H, Levy D, et al. Cross-sectional association of kidney function with valvular and annular calcification: the Framingham heart study. J Am Soc Nephrol. 2006;17(2):521–7. https://doi.org/10.1681/ASN.2005060627.
7. Elmariah S, Budoff MJ, Delaney JA, Hamirani Y, Eng J, Fuster V, et al. Risk factors associated with the incidence and progression of mitral annulus calcification: the multi-ethnic study of atherosclerosis. Am Heart J. 2013;166(5):904–12. https://doi.org/10.1016/j.ahj.2013.08.015.
8. Abd Alamir M, Radulescu V, Goyfman M, Mohler ER 3rd, Gao YL, Budoff MJ, et al. Prevalence and correlates of mitral annular calcification in adults with chronic kidney disease: results from CRIC study. Atherosclerosis. 2015;242(1):117–22. https://doi.org/10.1016/j.atherosclerosis.2015.07.013.
9. Adler Y, Fink N, Spector D, Wiser I, Sagie A. Mitral annulus calcification–a window to diffuse atherosclerosis of the vascular system. Atherosclerosis. 2001;155(1):1–8.
10. Allison MA, Cheung P, Criqui MH, Langer RD, Wright CM. Mitral and aortic annular calcification are highly associated with systemic calcified atherosclerosis. Circulation. 2006;113(6):861–6. https://doi.org/10.1161/CIRCULATIONAHA.105.552844.
11. Hamirani YS, Nasir K, Blumenthal RS, Takasu J, Shavelle D, Kronmal R, et al. Relation of mitral annular calcium and coronary calcium (from the Multi-Ethnic Study of Atherosclerosis [MESA]). Am J Cardiol. 2011;107(9):1291–4. https://doi.org/10.1016/j.amjcard.2011.01.005.
12. Heidenreich PA, Hancock SL, Lee BK, Mariscal CS, Schnittger I. Asymptomatic cardiac disease following mediastinal irradiation. J Am Coll Cardiol. 2003;42(4):743–9. https://doi.org/10.1016/s0735-1097(03)00759-9.
13. Adabag AS, Dykoski R, Ward H, Anand IS. Critical stenosis of aortic and mitral valves after mediastinal irradiation. Catheter Cardiovasc Interv. 2004;63(2):247–50. https://doi.org/10.1002/ccd.20158.
14. Elmariah S, Delaney JA, Bluemke DA, Budoff MJ, O'Brien KD, Fuster V, et al. Associations of LV hypertrophy with prevalent and incident valve calcification: Multi-Ethnic Study of Atherosclerosis. J Am Coll Cardiol Img. 2012;5(8):781–8. https://doi.org/10.1016/j.jcmg.2011.12.025.
15. Barasch E, Gottdiener JS, Larsen EK, Chaves PH, Newman AB, Manolio TA. Clinical significance of calcification of the fibrous skeleton of the heart and aortosclerosis in community dwelling elderly. The Cardiovascular Health Study (CHS). Am Heart J. 2006;151(1):39–47. https://doi.org/10.1016/j.ahj.2005.03.052.
16. Mejean S, Bouvier E, Bataille V, Seknadji P, Fourchy D, Tabet JY, et al. Mitral annular calcium and mitral stenosis determined by multidetector computed tomography in patients referred for aortic stenosis. Am J Cardiol. 2016;118(8):1251–7. https://doi.org/10.1016/j.amjcard.2016.07.044.
17. Ancona MB, Giannini F, Mangieri A, Regazzoli D, Jabbour RJ, Tanaka A, et al. Impact of mitral annular calcium on outcomes after transcatheter aortic valve implantation. Am J Cardiol. 2017;120(12):2233–40. https://doi.org/10.1016/j.amjcard.2017.09.006.
18. Fulkerson PK, Beaver BM, Auseon JC, Graber HL. Calcification of the mitral annulus: etiology, clinical associations, complications and therapy. Am J Med. 1979;66(6):967–77.
19. Kohsaka S, Jin Z, Rundek T, Boden-Albala B, Homma S, Sacco RL, et al. Impact of mitral annular calcification on cardiovascular events in a multiethnic community: the Northern Manhattan Study. J Am Coll Cardiol Img. 2008;1(5):617–23. https://doi.org/10.1016/j.jcmg.2008.07.006.
20.• Sud K, Agarwal S, Parashar A, Raza MQ, Patel K, Min D, et al. Degenerative mitral stenosis: unmet need for percutaneous interventions. Circulation. 2016;133(16):1594–604. https://doi.org/10.1161/CIRCULATIONAHA.115.020185.
A recent overview of percutaneous interventions.
21. Eleid MF, Foley TA, Said SM, Pislaru SV, Rihal CS. Severe mitral annular calcification: multimodality imaging for therapeutic strategies and interventions. J Am Coll Cardiol Img. 2016;9(11):1318–37. https://doi.org/10.1016/j.jcmg.2016.09.001.
22. Muddassir SM, Pressman GS. Mitral annular calcification as a cause of mitral valve gradients. Int J Cardiol. 2007;123(1):58–62. https://doi.org/10.1016/j.ijcard.2006.11.142.
23. Movva R, Murthy K, Romero-Corral A, Seetha Rammohan HR, Fumo P, Pressman GS. Calcification of the mitral valve and annulus: systematic evaluation of effects on valve anatomy and function. J Am Soc Echocardiogr. 2013;26(10):1135–42. https://doi.org/10.1016/j.echo.2013.06.014.
24. Labovitz AJ, Nelson JG, Windhorst DM, Kennedy HL, Williams GA. Frequency of mitral valve dysfunction from mitral anular calcium as detected by Doppler echocardiography. Am J Cardiol. 1985;55(1):133–7.
25. Movahed MR, Saito Y, Ahmadi-Kashani M, Ebrahimi R. Mitral annulus calcification is associated with valvular and cardiac structural abnormalities. Cardiovasc Ultrasound. 2007;5:14. https://doi.org/10.1186/1476-7120-5-14.

26. Akram MR, Chan T, McAuliffe S, Chenzbraun A. Non-rheumatic annular mitral stenosis: prevalence and characteristics. Eur J Echocardiogr. 2009;10(1):103–5. https://doi.org/10.1093/ejechocard/jen179.
27.• Bedeir K, Kaneko T, Aranki S. Current and evolving strategies in the management of severe mitral annular calcification. J Thorac Cardiovasc Surg. 2018. https://doi.org/10.1016/j.jtcvs.2018.05.099.
This is an article that focuses on the surgical strategies to treat mitral annular calcification.
28. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22):e57–185. https://doi.org/10.1016/j.jacc.2014.02.536.
29. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739–91. https://doi.org/10.1093/eurheartj/ehx391.
30. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. Eur Heart J. 2003;24(13):1231–43.
31. Iung B, Baron G, Tornos P, Gohlke-Barwolf C, Butchart EG, Vahanian A. Valvular heart disease in the community: a European experience. Curr Probl Cardiol. 2007;32(11):609–61. https://doi.org/10.1016/j.cpcardiol.2007.07.002.
32.•• Oktay AA, Gilliland YE, Lavie CJ, Ramee SJ, Parrino PE, Bates M, et al. Echocardiographic assessment of degenerative mitral stenosis: a diagnostic challenge of an emerging cardiac disease. Curr Probl Cardiol. 2017;42(3):71–100. https://doi.org/10.1016/j.cpcardiol.2017.01.002.
This article focuses on the echocardiographic challenges in diagnosing degenerative mitral stenosis.
33. Payvandi LA, Rigolin VH. Calcific mitral stenosis. Cardiol Clin. 2013;31(2):193–202. https://doi.org/10.1016/j.ccl.2013.03.007.
34. Silbiger JJ. Pitfalls in the echocardiographic evaluation of mitral annular size, shape, and dynamics in patients with mitral annular calcification. J Am Soc Echocardiogr. 2015;28(10):1255–6. https://doi.org/10.1016/j.echo.2015.06.012.
35. Hatle L, Angelsen B, Tromsdal A. Noninvasive assessment of atrioventricular pressure half-time by Doppler ultrasound. Circulation. 1979;60(5):1096–104.
36. Karp K, Teien D, Bjerle P, Eriksson P. Reassessment of valve area determinations in mitral stenosis by the pressure half-time method: impact of left ventricular stiffness and peak diastolic pressure difference. J Am Coll Cardiol. 1989;13(3):594–9.
37. Bertrand PB, Levine RA, Isselbacher EM, Vandervoort PM. Fact or artifact in two-dimensional echocardiography: avoiding misdiagnosis and missed diagnosis. J Am Soc Echocardiogr. 2016;29:381–91. https://doi.org/10.1016/j.echo.2016.01.009.
38. Chu JW, Levine RA, Chua S, Poh KK, Morris E, Hua L, et al. Assessing mitral valve area and orifice geometry in calcific mitral stenosis: a new solution by real-time three-dimensional echocardiography. J Am Soc Echocardiogr. 2008;21(9):1006–9. https://doi.org/10.1016/j.echo.2008.05.010.
39.• Pasca I, Dang P, Tyagi G, Pai RG. Survival in patients with degenerative mitral stenosis: results from a large retrospective cohort study. J Am Soc Echocardiogr. 2016;29(5):461–9. https://doi.org/10.1016/j.echo.2015.12.012.
The authors report on outcome of patients with significant mitral annular calcification who are managed conservatively.
40. Banovic M, DaCosta M. Degenerative mitral stenosis: from pathophysiology to challenging interventional treatment. Curr Probl Cardiol. 2018;44:10–35. https://doi.org/10.1016/j.cpcardiol.2018.03.004.
41. Genoni M, Franzen D, Vogt P, Seifert B, Jenni R, Kunzli A, et al. Paravalvular leakage after mitral valve replacement: improved long-term survival with aggressive surgery? Eur J Cardiothorac Surg. 2000;17(1):14–9.
42. Okada Y. Surgical management of mitral annular calcification. Gen Thorac Cardiovasc Surg. 2013;61(11):619–25. https://doi.org/10.1007/s11748-013-0207-7.
43. Deniz H, Sokullu O, Sanioglu S, Sargin M, Ozay B, Ayoglu U, et al. Risk factors for posterior ventricular rupture after mitral valve replacement: results of 2560 patients. Eur J Cardiothorac Surg. 2008;34(4):780–4. https://doi.org/10.1016/j.ejcts.2008.06.009.
44. Carpentier AF, Pellerin M, Fuzellier JF, Relland JY. Extensive calcification of the mitral valve annulus: pathology and surgical management. J Thorac Cardiovasc Surg. 1996;111(4):718–29 discussion 29-30.
45. Uchimuro T, Fukui T, Shimizu A, Takanashi S. Mitral valve surgery in patients with severe mitral annular calcification. Ann Thorac Surg. 2016;101(3):889–95. https://doi.org/10.1016/j.athoracsur.2015.08.071.
46. Feindel CM, Tufail Z, David TE, Ivanov J, Armstrong S. Mitral valve surgery in patients with extensive calcification of the mitral annulus. J Thorac Cardiovasc Surg. 2003;126(3):777–82.
47. Tomsic A, Hiemstra YL, van Brakel TJ, Versteegh MIM, Marsan NA, Klautz RJM, et al. Outcomes of valve repair for degenerative disease in patients with mitral annular calcification. Ann Thorac Surg. 2018. https://doi.org/10.1016/j.athoracsur.2018.08.017.
48. Hendrix RJ, Bello RA, Flahive JM, Kakouros N, Aurigemma GP, Keaney JF, et al. Mitral valve repair vs replacement in elderly with degenerative disease: analysis of the STS Adult Cardiac Surgery Database. Ann Thorac Surg. 2018. https://doi.org/10.1016/j.athoracsur.2018.09.018.

49. Himbert D, Bouleti C, Iung B, Nejjari M, Brochet E, Depoix JP, et al. Transcatheter valve replacement in patients with severe mitral valve disease and annular calcification. J Am Coll Cardiol. 2014;64(23):2557–8. https://doi.org/10.1016/j.jacc.2014.09.047.
50. Van Mieghem NM, Piazza N, Anderson RH, Tzikas A, Nieman K, De Laat LE, et al. Anatomy of the mitral valvular complex and its implications for transcatheter interventions for mitral regurgitation. J Am Coll Cardiol. 2010;56(8):617–26. https://doi.org/10.1016/j.jacc.2010.04.030.
51. Regueiro A, Granada JF, Dagenais F, Rodes-Cabau J. Transcatheter mitral valve replacement: insights from early clinical experience and future challenges. J Am Coll Cardiol. 2017;69(17):2175–92. https://doi.org/10.1016/j.jacc.2017.02.045.
52. Guerrero M, Dvir D, Himbert D, Urena M, Eleid M, Wang DD, et al. Transcatheter mitral valve replacement in native mitral valve disease with severe mitral annular calcification: results from the first multicenter global registry. JACC Cardiovasc Interv. 2016;9(13):1361–71. https://doi.org/10.1016/j.jcin.2016.04.022.
53.•• Guerrero M, Urena M, Himbert D, Wang DD, Eleid M, Kodali S, et al. 1-year outcomes of transcatheter mitral valve replacement in patients with severe mitral annular calcification. J Am Coll Cardiol. 2018;71(17):1841–53. https://doi.org/10.1016/j.jacc.2018.02.054.
This article reports on the 1-year outcomes of transcatheter mitral valve replacement (valve-in-MAC strategy).
54.• Yoon SH, Whisenant BK, Bleiziffer S, Delgado V, Dhoble A, Schofer N, et al. Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification. Eur Heart J. 2018. https://doi.org/10.1093/eurheartj/ehy590.
This article reports on outcomes after TMVR in patients who have failed bioprosthesis or significant MAC.
55. Khalique OK, Hahn RT. Multimodality imaging in transcatheter mitral interventions: buzzword or modern age toolbox? Circ Cardiovasc Imaging. 2016;9(6). https://doi.org/10.1161/CIRCIMAGING.116.005071.
56. Blanke P, Dvir D, Cheung A, Ye J, Levine RA, Precious B, et al. A simplified D-shaped model of the mitral annulus to facilitate CT-based sizing before transcatheter mitral valve implantation. J Cardiovasc Comput Tomogr. 2014;8(6):459–67. https://doi.org/10.1016/j.jcct.2014.09.009.
57. Blanke P, Dvir D, Cheung A, Levine RA, Thompson C, Webb JG, et al. Mitral annular evaluation with CT in the context of transcatheter mitral valve replacement. J Am Coll Cardiol Img. 2015;8(5):612–5. https://doi.org/10.1016/j.jcmg.2014.07.028.
58. Murphy DJ, Ge Y, Don CW, Keraliya A, Aghayev A, Morgan R, et al. Use of cardiac computerized tomography to predict neo-left ventricular outflow tract obstruction before transcatheter mitral valve replacement. J Am Heart Assoc. 2017;6(11). https://doi.org/10.1161/JAHA.117.007353.
59. Newland JA, Tamuno P, Pasupati S, Davis M, El-Gamel A, Devlin G, et al. Emerging role of MDCT in planning complex structural transcatheter intervention. J Am Coll Cardiol Img. 2014;7(6):627–31. https://doi.org/10.1016/j.jcmg.2014.04.006.
60. Blanke P, Naoum C, Dvir D, Bapat V, Ong K, Muller D, et al. Predicting LVOT obstruction in transcatheter mitral valve implantation: concept of the neo-LVOT. J Am Coll Cardiol Img. 2017;10(4):482–5. https://doi.org/10.1016/j.jcmg.2016.01.005.
61. Wang DD, Eng M, Greenbaum A, Myers E, Forbes M, Pantelic M, et al. Predicting LVOT obstruction after TMVR. J Am Coll Cardiol Img. 2016;9(11):1349–52. https://doi.org/10.1016/j.jcmg.2016.01.017.
62. Wang DD, Eng MH, Greenbaum AB, Myers E, Forbes M, Karabon P, et al. Validating a prediction modeling tool for left ventricular outflow tract (LVOT) obstruction after transcatheter mitral valve replacement (TMVR). Catheter Cardiovasc Interv. 2018;92(2):379–87. https://doi.org/10.1002/ccd.27447.
63. de Jaegere P, Rajani R, Prendergast B, Van Mieghem NM. Patient-specific computer modeling for the planning of transcatheter mitral valve replacement. J Am Coll Cardiol. 2018;72(8):956–8. https://doi.org/10.1016/j.jacc.2018.05.064.
64. Karady J, Ntalas I, Prendergast B, Blauth C, Niederer S, Maurovich-Horvat P, et al. Transcatheter mitral valve replacement in mitral annulus calcification - "the art of computer simulation". J Cardiovasc Comput Tomogr. 2018;12(2):153–7. https://doi.org/10.1016/j.jcct.2017.12.007.
65. Serban R, Redwood S, Prendergast B, Rajani R. Real-time image integration for transcatheter mitral valve replacement in mitral annular calcification. J Thorac Cardiovasc Surg. 2018. https://doi.org/10.1016/j.jtcvs.2018.09.029.
66. Vukicevic M, Mosadegh B, Min JK, Little SH. Cardiac 3D printing and its future directions. J Am Coll Cardiol Img. 2017;10(2):171–84. https://doi.org/10.1016/j.jcmg.2016.12.001.
67. Izzo RL, O'Hara RP, Iyer V, Hansen R, Meess KM, Nagesh SVS, et al. 3D printed cardiac phantom for procedural planning of a transcatheter native mitral valve replacement. Proc SPIE Int Soc Opt Eng. 2016;9789. https://doi.org/10.1117/12.2216952.
68. Khan JM, Rogers T, Schenke WH, Mazal JR, Faranesh AZ, Greenbaum AB, et al. Intentional laceration of the anterior mitral valve leaflet to prevent left ventricular outflow tract obstruction during transcatheter mitral valve replacement: pre-clinical findings. JACC Cardiovasc Interv. 2016;9(17):1835–43. https://doi.org/10.1016/j.jcin.2016.06.020.
69. Babaliaros VC, Greenbaum AB, Khan JM, Rogers T, Wang DD, Eng MH, et al. Intentional percutaneous laceration of the anterior mitral leaflet to prevent outflow obstruction during transcatheter mitral valve replacement: first-in-human experience. JACC Cardiovasc Interv. 2017;10(8):798–809. https://doi.org/10.1016/j.jcin.2017.01.035.

70. Deharo P, Urena M, Himbert D, Brochet E, Rouleau F, Pinaud F, et al. Bail-out alcohol septal ablation for left ventricular outflow tract obstruction after transcatheter mitral valve replacement. JACC Cardiovasc Interv. 2016;9(8):e73–e6. https://doi.org/10.1016/j.jcin.2016.01.010.
71. Guerrero M, Wang DD, Himbert D, Urena M, Pursnani A, Kaddissi G, et al. Short-term results of alcohol septal ablation as a bail-out strategy to treat severe left ventricular outflow tract obstruction after transcatheter mitral valve replacement in patients with severe mitral annular calcification. Catheter Cardiovasc Interv. 2017;90(7):1220–6. https://doi.org/10.1002/ccd.26975.
72. Lee R, Fukuhara S, George I, Borger MA. Mitral valve replacement with a transcatheter valve in the setting of severe mitral annular calcification. J Thorac Cardiovasc Surg. 2016;151(3):e47–e9. https://doi.org/10.1016/j.jtcvs.2015.10.040.
73. Murashita T, Suri RM, Daly RC. Sapien XT transcatheter mitral valve replacement under direct vision in the setting of significant mitral annular calcification. Ann Thorac Surg. 2016;101(3):1171–4. https://doi.org/10.1016/j.athoracsur.2015.05.048.
74. Russell HM, Guerrero ME, Salinger MH, Manzuk MA, Pursnani AK, Wang D, et al. Open atrial transcatheter mitral valve replacement in patients with mitral annular calcification. J Am Coll Cardiol. 2018;72(13):1437–48. https://doi.org/10.1016/j.jacc.2018.07.033.
75. Badhwar V, Thourani VH, Ailawadi G, Mack M. Transcatheter mitral valve therapy: the event horizon. J Thorac Cardiovasc Surg. 2016;152(2):330–6. https://doi.org/10.1016/j.jtcvs.2016.03.049.
76. Ferrari E, Dvir D, Guerrero M. Transcatheter mitral valve replacement in degenerated calcified native mitral valves: is the currently available technology suitable? Eur J Cardiothorac Surg. 2016;50(3):391–5. https://doi.org/10.1093/ejcts/ezw188.
77. Partida RA, Elmariah S. Transcatheter mitral valve interventions: current therapies and future directions. Curr Treat Options Cardiovasc Med. 2017;19(5):32. https://doi.org/10.1007/s11936-017-0538-2.
78. Sorajja P, Gossl M, Bae R, Tindell L, Lesser JR, Askew J, et al. Severe mitral annular calcification: first experience with transcatheter therapy using a dedicated mitral prosthesis. JACC Cardiovasc Interv. 2017;10(11):1178–9. https://doi.org/10.1016/j.jcin.2017.03.026.
79. Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofoed KF, De Backer O, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. N Engl J Med. 2015;373(21):2015–24. https://doi.org/10.1056/NEJMoa1509233.
80. Quick S, Speiser U, Strasser RH, Ibrahim K. First bioprosthesis thrombosis after transcatheter mitral valve-in-valve implantation: diagnosis and treatment. J Am Coll Cardiol. 2014;63(18):e49. https://doi.org/10.1016/j.jacc.2013.11.067.
81. Capretti G, Urena M, Himbert D, Brochet E, Goublaire C, Verdonk C, et al. Valve thrombosis after transcatheter mitral valve replacement. J Am Coll Cardiol. 2016;68(16):1814–5. https://doi.org/10.1016/j.jacc.2016.07.757.