MITRAL REGURGITATION

Classification

Mechanisms of mitral regurgitation (MR) are classified as **primary** (organic or degenerative due to intrinsic valve lesions) or **functional or secondary** (mitral valve is structurally normal and disease results from valve deformation caused by ventricular or atrial remodeling).

Epidemiology

A trivial form of this valve disease is often seen in healthy people. Moderate or severe MR is the most frequent valve disease in general, and the second most common form of valvular heart disease (after AS) needing surgery.[1, 2] The prevalence of moderate or severe MR in the US general population is estimated 1.6%,[3] while the prevalence of mitral valve prolapse is approximately 2-3% and half of them have maximal leaflet thickness of at least 5 mm.[4] The prevalence of MR, both degenerative and secondary, increases with age.[5] In 2017, there were an estimated 18.1 million cases of degenerative mitral valve disease, and 35700 degenerative mitral valve disease deaths globally, with higher rates among women.[6] The prevalence of MVP is approximately 2% (150 million people globally). However, only 5% to 10% of affected individuals develop clinically significant degenerative MR with occurrence increased with increasing age.[7]

Aetiology

Primary MR may result from disorders of the valve leaflets or the mitral apparatus (chordae tendinae, papillary muscles, annulus). The main causes in the western world are degenerative disease (60–70% of cases), and ischaemic mitral regurgitation (20%) usually due to an inferior infarction involving the anterolateral and the posteromedial papillary muscle.[1] Degenerative disease is due to mitral valve prolapse and rarely due to annular calcification.[7] Exposure to fluoroquinolone antibiotics has also been associated with an increased risk of developing left-sided valvular regurgitation.[8]

Mitral valve prolapse, defined on echocardiography as systolic single-leaflet or bileaflet displacement >2 mm beyond the long-axis annular plane, with >5 mm leaflet thickening. Two main aetiologies of mitral valve prolapse (MVP) are described. ***Myxomatous MVP***, also known as Barlow's disease, that is characterized by excess tissue including chordal thickening/elongation, annular dilation and calcification with low probability of chordal rupture, and ***fibroelastic deficiency***, the most common form, that is characterized by chordal thinning, elongation, and/or high probability of rupture, with classic findings of prolapse and

MR of varying severity.[9] Fibroelastic deficiency typically affects older adults (>60 years) and is characterized by thin, translucent leaflets and chords with a thickened, redundant, prolapsing, or flail segment, usually P2, often with focal chordal rupture in an otherwise normal valve with minimal annular dilatation. Barlow disease characteristically affects younger adults (<60 years), and valves are severely dilated with bileaflet prolapse, thickened and redundant leaflets, and elongated chordae. In actual practice, degenerative MR valves often have features of both phenotypes.[7] MVP is the most common functional abnormality associated with degenerative mitral valve disease, resulting from both leaflet redundancy and chordal elongation with a prevalence of 2.4% in the general population.[10, 11] Although older studies suggested a higher prevalence of MVP among women, recent data indicate that the prevalence of MVP is similar between sexes.[4] LV fibrosis is more prevalent in MVP than non-MVP, suggesting a MVP-related cardiomyopathy.[12, 13] Mitral valve prolapse (MVP) can be familial or sporadic. Parental MVP is associated with increased prevalence of offspring MVP,[4] and multiple loci for ***autosomal dominant*** nonsyndromic mitral valve prolapse and a gene responsible for a rare ***X-linked*** form have been described.[14] The X-linked form is associated to a mutation in the **FLNA *gene*** and presents specific characteristics, beside classical features of MVP, with leaflet motion paradoxically restricted in diastole. It is associated with a substantial life-time risk of valve surgery, but MR is amenable to classical repair.[15] Less common causes are ***rheumatic disease*** (2-5% in western countries but the leading cause in developing countries), ***endocarditis*** (2-5%), ***cardiomyopathies, congenital anomalies, carcinoid disease, systemic lupus erythematosus (Liebman-Sacks), atrial fibrillation, and anorectic drugs.*** Amphetamine derivatives such as ***fenfluramine, phentermine and benfluorex*** may account for up to 7% with regurgitant valve disease in general.[16] Despite earlier reservations, ***fluroquinolone*** use is not associated with valvular regurgitation.[17] ***Acute MI*** (45% of acute MR cases), ***endocarditis*** (28%), chordal or papillary muscle rupture (26%) or disfunction due to ***ischemia, acute rheumatic carditis, myocarditis, Takotsubo cardiomyopathy, and prosthetic valve dysfunction*** may lead to **acute MR.**[18]
Secondary or functional MR may be due to left ventricular or left atrial dysfunction. It occurs in 11% to 59% of patients after a myocardial infarction and is present in >50% of patients with dilated cardiomyopathy. [19-21] The abnormal and dilated left ventricle causes papillary muscle displacement, which in turn results in leaflet tethering with associated annular dilation that prevents coaptation. The prognosis of these patients is worse than other kinds of MR, and the therapeutic approach is not established.
Atrial functional MR typically occurs in the context of AF and/or HFpEF. Isolated annular dilation, and atriogenic leaflet tethering are mechanical culprits.[22]

Pathophysiology and Natural History

Acute MR

In acute MR, the unprepared left atrium and left ventricle cannot accommodate the regurgitant volume which causes large v waves in the left atrium, and results in pulmonary congestion. Patients with chronic MR and preserved LV function may tolerate the marked increase in volume better, whereas patients with impaired ventricular function may quickly decompensate with acute worsening of MR.[1, 2]

Chronic MR

In chronic cases, the adaptive changes to volume overload include left ventricular (LV) dilatation and eccentric hypertrophy, and left atrial enlargement that allows accommodation of the regurgitant volume at a lower pressure. Regurgitant fractions <0.40 may be tolerated indefinitely. The LV ejection fraction (LVEF) in chronic MR is usually greater than normal because of the increase in preload and the afterload-reducing effect of ejection into the low-impedance left atrium. Thus, LV dysfunction in severe MR is defined as LVEF<=60% or an elevated end-systolic dimension (>40 mm by ACC/HA, and >45 mm by ESC). Advanced myocardial dysfunction may occur while LV ejection fraction appears normal. Ventricular dysfunction should be suspected when end-systolic dimensions are large, but is often masked by a large ejection volume and is revealed after surgical elimination of mitral regurgitation, with a postoperative average immediate LVEF drop of about 10%. In patients with primary mitral regurgitation, RV function impairment is frequent (30%), a predictor of postoperative cardiovascular survival, and depends weakly on pulmonary artery systolic pressure but mainly on left ventricular remodeling and septal function.[23] Thus, biventricular impairment is a powerful predictor of both cardiovascular and overall survival. In patients with significant primary MR and preserved LVEF, baseline RV systolic pressure ≥35 mm Hg is independently associated with reduced survival.[24] The risk of AF and heart failure increase with severity of MR. Patients with severe MR usually develop symptoms within the next 6 to 10 years and have an increased risk for sudden death. The rate of death from cardiovascular causes among asymptomatic patients with at least moderate mitral regurgitation or an LVEF < 50% exceeds 3% per year. Patients with severe MR and flail leaflets have an annual mortality of 6 to 7% and in 10 years 90% of them are dead or require MV operation.[25-27] MR severity, as well as RBBB, LVEF, and the presence of RV scar, are independent predictors of RVEF in patients with ischaemic cardiomyopathy.[28] Exercise-induced increase in secondary MR is associated with impaired exercise capacity and increased mortality.[19]

In patients with more than mild ***atrial functional MR***, left ventricular systolic function does not decline more than in patients without MR over time, but diastolic dysfunction may develop, resulting in heart failure with preserved ejection fraction as a

key determinant of mortality.[29]

Mitral Valve Prolapse

The prognosis of mitral valve prolapse has been considered benign in the absence of moderate to severe MR, LVEF<50% and thickened mitral leaflets (>5 mm) with survival similar to this of people without prolapse.[11, 30] The MIDA-Q score is strongly, independently, and incrementally associated with long-term survival after MVP diagnosis (from 97% with score 0 to 5% with score>=13) irrespective of presentation (Table 1).[31] Mitral leaflet thickness, as opposed to LV dysfunction and the presence of MR, has not been found an independent predictor of mortality.[4] Framingham data indicate that up to 25% of patients with MVP progress to significant MR over 3 to 16 years.[10] Infective endocarditis (100 cases per 100,000 patient-years of follow-up), spontaneous chordal rupture, and sudden death are higher in patients with a flail leaflet than in the general population. In the presence of flail leaflets the rate of infective endocarditis is 1.5% per year and that of sudden death 1.8% per year.[11] Fibrin emboli, as well as the increased incidence of mitral valve prolapse in Von Willebrand's disease and other coagulopathies, are responsible for visual symptoms with involvement of the ophthalmic or posterior cerebral circulation. MR of mitral valve prolapse that is purely mid-late systolic has more benign consequences and outcomes than holosystolic MR.[32] Sudden cardiac death may also occur especially in young athletes and women with arrhythmias and particular charcateristics.[33]

In approximately 2.4% of the general population ***mitral valve prolapse*** (MVP) can be detected.[30] In the majority of cases, MVP is isolated and not associated with other conditions. However, MVP can also be seen as part of other clinical syndromes such as connective tissue disorders (associated with an identifiable disorder such as connective tissue disease, e.g., Marfan syndrome and Ehlers-Danlos syndrome) and idiopathic dilated cardiomyopathy.[34] A familial pattern is seen in approximately 35-50% of cases of MVP, suggesting a heritable component in this condition.[35]

Mitral valve prolapse is associated with otherwise unexplained cardiac arrest with a reported annual incidence <1% in unselected individuals.[9] However, at autopsy, the prevalence of MVP among young patients with sudden arrhythmic death is reported between 4-7%.[9, 36] The diagnosis of ***arrhythmogenic MVP*** (Figure 1 and Table 1) requires the presence of MVP (with or without mitral annulus disjunction) combined with frequent (≥5% total PVC burden) or complex (NSVT, VT, VF) ventricular arrhythmias in the absence of any other well-defined arrhythmic substrate.[9] The most frequent sustained arrhythmia is VF.[37]

Arrhythmogenic MVP is a result of the increased mechanical stress placed on the subvalvular apparatus and surrounding myocardium by the prolapsing leaflets and elongated chordae, leading to CMR-detected localized myocardial fibrosis.[9, 38, 39] Patients who may experience sudden cardiac death are mostly females with bileaflet prolapse, ventricular

arrhythmias of LV origin (outflow tract alternating with papillary muscle/fascicular origin), and frequent ECG repolarization abnormalities on inferior leads. [33, 39-41] The perinatal period appears to impose increased risk of malignant ventricular arrhythmias in women with high-risk arrhythmic mitral valve prolapse.[42] Ventricular arrhythmias are more frequent in patients with replacement fibrosis, but are not associated with the grade of mitral regurgitation. [13, 43] However, mitral regurgitation and the 'Pickelhaube sign' (increased peak systolic lateral velocity of the mitral annulus >16m/s) are also predictors of ventricular arrhythmias.[41, 44] The presence of ventricular arrhythmias with RBBB morphology, suggesting the origin from the LV in patients with MVP and no mitral regurgitation, is the expression of more pronounced morphologic and mechanical mitral apparatus abnormalities as well as underlying myocardial tissue abnormality.[45]

A prominent ***mitral annulus disjunction (MAD)***, has also been associated with sudden cardiac death (Figure 2).[9, 46] The association among arrhythmic events and MAD has been shown to be independent of the presence of MVP, thus indicating that MAD itself may be an arrhythmogenic entity.[44] However, this did not translate to excess mortality.[47] MAD is a rather ubiquitous finding in the heart when the hinge of the mural leaflet is assessed within the overall atrioventricular junction, although not always in the same place.[48, 49] Thus, more studies are needed to prove and better define its arrhythmogenic potential. Sudden cardiac death and arrhytmias do occur in aasociation with MAD and MVP but they are not as common as to have an adequate number of events.

Presentation

Acute MR Patients who develop acute severe MR usually present with symptomatic heart failure because their ventricles are ill prepared to accept the sudden increase in volume load. Some patients may present solely with new-onset dyspnea, without evidence of impending cardiovascular collapse, and may be misdiagnosed.

Chronic MR The patient may be entirely asymptomatic, even during vigorous exercise, or present with dyspnea (Tables 2 and 3).

Physical Examination

Acute MR Physical examination of the precordium may be misleading, because a normal-sized left ventricle does not produce a hyperdynamic apical impulse.

The **systolic murmur** of MR may not be holosystolic and may even be absent.

A **third heart sound** or **early diastolic flow rumble** may be the only abnormal physical finding.

Chronic MR

Displaced apical impulse in severe MR

Soft S_1 and **widely split S_2**

Late-systolic murmur in MVP or papillary muscle dysfunction

Midsystolic click and perhaps **TR** in the presence of MVP

Holosystolic murmur in chordal rupture and flail leaflet. The radiation of the murmur follows the direction of the regurgitant jet. With a flail posterior leaflet, the murmur radiates anteriorly and may mimic aortic stenosis, whereas a murmur associated with a flail anterior leaflet radiates to the back.

A **diastolic rumble and S_3** may be present and do not necessarily indicate LV dysfunction.

Loud P_2 due to pulmonary venous hypertension indicates advanced disease.

Investigations

Chest Radiography. Cardiomegaly due to LV and left atrial enlargement may be seen in chronic MR. Kerley B lines and interstitial edema can be seen in acute MR or progressive LV failure. Predominant MS is suggested my mild cardiomegaly and significant changes in the lung fields. A unilateral pattern that is found in 2% of cases of pulmonary edema, usually of the right upper lobe, is always associated with severe functional or organic MR.[50] This entity should be differentiated from lobar pneumonia.

Electrocardiography. Left atrial enlargement and atrial fibrillation. Left ventricular enlargement in approximately 30% of patients, and RV hypertrophy in 15%. AF is associated with increased mortality.[51] An artificial intelligence–enabled electrocardiography (AI-ECG) algorithm has been validated for left ventricular diastolic function (LVDF) and filling pressure determination. In patients with significant MR, the grading of LVDF by AI-ECG has been found independently associated with all-cause mortality.[52]

Transthoracic echocardiography demonstrates the disruption of the MV but may underestimate lesion severity by inadequate imaging of the color flow jet.[53, 54] Thus, if there is normal or hyperdynamic systolic function of the left ventricle on a transthoracic echocardiogram in a patient with acute heart failure, the suspicion of severe MR should be raised. Quantitative assessment of regurgitation is feasible by quantitative Doppler based on mitral and aortic stroke volumes or flow convergence analysis with color flow imaging proximal to the regurgitant orifice (***proximal isovelocity surface area - PISA***) (Tables 4 and 5, and Figures 3 and 4). A jet height <=2mm effectively separates physiological backflow

from mild MR.[4] However, these indices should be always interpreted within the clinical context.[55] Measures of effective regurgitant orifice area (EROA) and regurgitant volume depend on LV size and LV-LA pressure gradient, and can be inaccurate in acute MR, particularly in the context of tachycardia. Assessment of mid- or late MR in the context of mitral leaflet prolapse may also be misleading because jet area and EROA by flow convergence appear similar to those of holosystolic MR. 3-D measurement of vena contracta area and regurgitant volume is superior to 2-D methods.[56] 3-D analysis of the annular shape has also been shown prognostically significant; flattening of the annular saddle (normal) shape is associated with progressive leaflet billowing and increased chordal rupture.[57] Use of multi-detector row computed tomography (MDCT) to reconstruct and measure by planimetry the narrowest part of the mitral regurgitant orifice area at systole, instead of using echo EROA, may be more accurate for calculation of regurgitant volume.[58] In asymptomatic primary MR, absence of left ventricular contractile reserve, that is better assessed using exercise-induced changes in LV myocardial longitudinal function rather than in LVEF, is independently associated with two-fold increase in risk of cardiac events. [59] Assessment of mitral annulus disjunction is shown in Figure 2. Atrial secondary MR should be also considered (Figure 5).

Transesophageal echocardiography can more accurately assess the color flow jet, and direct successful surgical repair, particularly in acute MR.

Exercise testing with or without Doppler assessment before and after exercise in symptomatic patients in whom there is a discrepancy between symptoms and resting measures of LV function and pulmonary artery pressure. It is very helpful in identifying patients who develop pulmonary hypertension (>60 mm Hg) with exercise. Impaired exercise capacity (age- and sex-matched predicted METS) can develop in the absence of significant overt symptoms and is associated with adverse long-term outcomes.[60]

Cardiac catheterisation is indicated when the noninvasive tests are inconclusive to resolve the severity of MR.

Coronary angiography is necessary before surgery in the hemodynamically stable patient over 40 years of age or with risk factors or clinical suspicion of coronary artery disease. LV angiography at the RAO projection allows visualization and quantification of the regurgitant jet but the method depends on the amount of contrast injected and the size of the LA.

Cardiac Magnetic Resonance provides accurate measurement of regurgitant flow and LV volumes and is an emerging modality of increasing significance.[61] Doppler-derived PISA has lower accuracy in the presence of noncircular effective regurgitant orifice area, eccentric, multiple, or late-systolic jets, and CMR is more accurate than echocardiography in assessing the severity of, especially primary, CMR.[62, 63] Some of these limitations can be reduced by

using contrast-enhanced or three-dimensional echocardiographic acquisitions. Four-dimensional flow (4D flow) CMR, particularly with gadolinium enhancement, is emerging as a valuable tool for the evaluation of MR.[61] While the presence of a flail leaflet and wall-impinging jet of mitral regurgitation (Coanda effect) on echocardiography are associated with higher regurgitant volumes and fractions, they are frequently not associated with severe MR as assessed by means of CMR.[64] Systolic curling, defined as a downward systolic motion of the posterior mitral ring, resulting in a curled appearance of the adjacent myocardium on cardiac imaging is correlated with ventricular arrhythmias.[45] It might be also useful for risk stratification of patients with mitral leaflet prolapse, ECG depolarization abnormalities on inferior or inferolateral leads, complex ventricular arrhythmias with right bundle-branch block morphology on 12-lead ECG Holter monitoring, and a history of presyncope or syncope.[39] CMR is essential for the risk stratification of patients with ventricular arrhythmias.[13]

Biomarkers such as B-natriuretic peptide are related to functional class but their value for risk stratification is limited.

Therapy

Acute MR

Medical therapy is aimed at stabilizing hemodynamics in preparation for surgical repair or MV replacement (usually with endocarditis). Nitroprusside in the normotensive patient and nitroprusside combined with dopamine in hypotension are administered. Aortic balloon counterpulsation that increases forward output and mean arterial pressure while diminishing regurgitant volume and LV filling pressure and can also be used. MV repair or replacement combined with CABG for papillary muscle rupture-induced MR can be now offered with a <10% mortality.[18] Surgical mortality for endocarditis-induced acute MR is 10-20%. The prognosis of patients with ischemic cardiogenic shock is inversely related to the degree of MR. Early intervention, surgical or through percutaneous mitral valve repair may mitigate the poor prognosis associated with conservative therapy in patients with post-MI MR.[65]

Chronic MR

Medical therapy

Medical therapy is aimed at reducing the afterload and pulmonary congestion with ACE/ARB and diuretics (Table 6). In asymptomatic and normotensive patients with normal LV function vasodilators are not indicated, since by decreasing LV size and mitral closing force they may increase mitral prolapse. Beta blockers in MR may increase LVEDD and were thought to be contraindicated but subsequent evidence indicated beneficial reverse remodeling especially in functional MR, but also in degenerative disease.[66] They are also recommended in patients

with MVP, no severe MR and palpitations. Aspiring (75-325 mg od) or warfarin in nonresponders is recommended for patients with MVP and TIAs.

In patients with stable heart failure and functional MR, the combination of sacubitril/valsartan is superior to valsartan alone.[67] Optimal medical therapy, including cardiac resynchronization where appropriate, is mandatory for patients with functional MR.

Surgical Therapy

Primary MR

Surgery is mainly recommended for ***symptomatic patients with severe MR***, and ***asymptomatic patients with severe MR and LV dysfunction (LVEF 30-60% and LVESD ≥40-45 mm)*** (Tables 7 and 8, and Figures 6 and 7). Surgery could be considered in the setting of serial imaging studies that reveal a progressive increase in LV size or decrease in LVEF. Mitral valve repair is recommended for asymptomatic patients with severe MR and well preserved LV function,[27, 68-70] although no randomized data exist to allow certain conclusions. Most retrospective studies support early repair, particularly in the context of primary MR,[71, 72] and before the establishment of pulmonary hypertension.[73] A watchful waiting approach, should probably be preferred if the likelihood of a high-quality repair is low, and in the presence of high surgical risk and/or low probability of a durable repair which is typically the case in very elderly patients with relevant co-morbidities and/or complex valve lesions.[69] Individual effective regurgitant orifice area (EROA) values may be useful for prognostic assessment, with increasing mortality, even in the presence of moderate degenerative MR, appearing with > EROA 20 mm^2, and especially, >30 mm^2.[74] In addition, in patients of the MIDA registry with MR due to flail mitral leaflet but without class I indication for surgery, early operation was associated with greater long-term survival and lower risk of heart failure compared to initial conservative management.[75] Thus, an approach of early identification and surgical referral should be always individualized and, perhaps, considered regardless of age.

MV repair is recommended over **MV replacement.** [76, 77] In ischemic MR, chordal-sparing replacement and repair have not been found different by means of survival and left ventricular reverse remodeling at 12 months (CTSN trial).[78] Operative mortality in an analysis of Medicare data, intraoperative mortality for patients who underwent repair was 3.9% compared with 8.9% for replacement.[79] However, reference centers with known expertise may offer > 95% likelihood of successful repair with a <1% mortality.[80] Calcified mitral annulus, rheumatic disease, and involvement of the anterior leaflet diminish the likelihood of repair. Surgical experience is a major determinant of success and long-term outcome of repair.[81] In experienced centers, reoperation after 10 years is necessary in 5% of patients with repaired posterior leaflet prolapse and 10% of those with anterior leaflet repair. MV repair for degenerative MR restores life span to normal except in patients with symptoms

at rest and impaired left ventricular function. Advanced age and complex mitral valve pathologies increases the risk of late recurrent MR.[82] but is not a contra-indication for surgery.[79] For **ring annuloplasty**, care is needed to take into account the mismatch of actual LV size relative to ring size, that is associated with increased risk of MR recurrence.[83] Pathoanatomically-directed surgical techniques for MR are discussed in detail in the 2017 ACC Expert Consensus on the Management of MR.[84] **Minimally invasive and robotic** surgical repair is now also feasible.[85, 86] The 1-year **permanent pacemaker** implantation rate is 4.5% after MV repair, and 10.5% after MV replacement. (Table 9).[87] The choice of a **mechanical or bioprosthetic** valve is discussed in detail in the relevant Chapter on Prosthetic Valves.

In patients with moderate TR or tricuspid annular dilation who are undergoing degenerative mitral repair, concomitant tricuspid annuloplasty may improve outcomes.[88] When repair is not feasible, chordal-sparing MV **replacement** with preservation of the subvalvar apparatus is preferred.

The benefit of addition of **tricuspid repair** at the time of mitral valve surgery is not established (see TR).[89] Compared to isolated MVR, adding tricuspid valve annuloplasty is associated with a higher risk of 90-day permanent pacemaker implantation that is associated with an increase in mortality, HFH, and endocarditis.[90]

The development of **AF** in a patient with degenerative MR identifies a subgroup at high risk of adverse outcomes that may be improved with valve repair surgery.[91] In patients with **persistent AF** who undergo mitral surgery, PV isolation or a Maze procedure provides a higher rate of freedom from AF (63 vs 29%), but the risk of implantation of a permanent pacemaker is also increased.[92] In the US, concomitant surgical ablation is performed in approximately 60% of patients with AF who undergo mitral valve operations.[93] Recommendations for the management of AF are provided in the relevant Chapter.

Secondary (functional) MR

Heart failure therapy is mandatory for both atrial and ventricular functional MR.[94] However, reverse LV remodeling alone is usually insufficient for ameliorating functional MR because annular dilatation, LV dilation and dysfunction, and insufficient leaflet growth also affect leaflet coaptation. Sodium-glucose cotransporter 2 inhibitors may be considered in this setting.[95]

The prognosis of patients with secondary (functional) MR is worse than other kinds of MR, and the role of surgery is controversial, [20, 21] without, so far, any conclusive evidence for any survival benefit.[96, 97] Although CABG may improve MR in some patients,[98] moderate ischemic mitral regurgitation does not reliably resolve,[99] and development of significant MR may be actually seen following isolated CABG.[100] Recently, an analysis of the STICH trial cohort suggested potentially improved survival when MV repair with an annuloplasty ring

was added to CABG in ischemic patients with LVEF<=35% and moderate to severe MR.[101] However, no effect on mortality with addition of annuloplasty has been seen in the three RCTs conducted so far. [102-104] In the most recent of them, in patients with moderate ischemic mitral regurgitation, the addition of mitral-valve repair to CABG did not even result in a higher degree of left ventricular reverse remodeling either at one,[104] or two-years follow-up.[105] Mitral valve repair provided a more durable correction of MR but was associated with an early hazard of increased neurologic and events and arrhythmias.[105] A retrospective analysis of the Duke Databank demonstrated that in patients with significant CAD and moderate or severe MR, CABG alone had the lowest risk of death, compared to CABG plus MV surgery or to medical therapy.[106] In another retrospective series from Duke in patients with moderate or significant MR and LVEF<=30%, MV surgery was associated with higher survival than no MV surgery, but, again, CABG was not inferior to CABG plus MV surgery.[107] Thus, the role of surgery is controversial, particularly when concomitant revascularization is not an option owing to significant operative mortality, high rates of recurrent MR, and absence of proven survival benefit.[108] Recommendations are provided in Figures 9-10, and Tables 10-12.

Undersized annuloplasty might offer a satisfactory result if performed before the onset of severe LV dilatation and in the absence of echocardiographic predictors of post-operative residual or recurrent MR.[108] Cardiac resynchronization therapy is a potential therapeutic option in heart failure patients with moderate-severe functional MR and high risk for surgery.[97, 109] Left bundle branch pacing also emerges as an alternative to biventricular pacing with excellent preliminary results.[110]

Interventional Therapy

Percutaneous techniques for MR such as edge-to-edge anterior and posterior leaflet attachment with a clip (MitraClip, PASCAL), transcatheter direct annuloplasty with an implant (Cardioband), and coronary sinus cinching (Carillon) and are also available (Tables 13and 14). [21, 111-113] The EVEREST II randomized controlled trial failed to show convincing benefits of the Mitraclip technique in comparison with surgical repair in all-comers with severe MR.[114] Subsequent analysis of the 1-year adjudicated outcomes of all patients with secondary MR in the EVEREST II, the prospective High-Risk Registry, and the REALISM Continued Access Registry, including both high-risk and non–high-risk patients, demonstrated reduction of MR severity, symptom improvement, and positive ventricular remodelling with the MitraClip procedure.[115] In the MITRA-RF randomized trial on patients with LVEF 15-40% and effective regurgitant orifice area >20 mm^2, percutaneous mitral valve repair with the Mitraclip device did not reduce the rate of death or hospitalization for heart failure at 1 year compared to medical therapy.[116] In the COAPT randomized trial on patients

with LVEF 20-50% and effective regurgitant orifice area (ERO) >30 mm^2, transcatheter mitral valve repair resulted in a lower rate of hospitalization for heart failure and lower all-cause mortality within 24 months of follow-up than medical therapy alone.[117] The proportion of patients with the relevant condition (heart failure and secondary mitral regurgitation) who actually got randomized was relatively low.[118] The recent COAPT-PAS registry has also provided promising results.[119] In patients undergoing mitral surgery for failed transcatheter edge-to-edge repair operative mortality was 10.6%, versus 2.8% in a subgroup analysis of elective patients with underlying degenerative disease in a report of the Society of Thoracic Surgeons in the US. The extremely low feasibility of subsequent mitral repair has major implications for patients with degenerative disease in lower-risk and younger age categories considered eligible for both transcatheter edge-to-edge repair and surgical mitral valve repair.[120] Transcatheter edge-to-edge repair may also be suitable for degenerative (primary) MT, especially in the case of an isolated middle scallop (P2) prolapse of the posterior leaflet, with more challenging anatomies associated with worse outcomes.[121] It may also be useful in inoperable patients with atrial functional MR.[122]

MitraClip is now FDA-approved for both primary and secondary MR. However, in primary mitral regurgitation early mortality with percutaneous intervention has been high (9%), and >50% of patients have been left with residual or recurrent >=2/4 MR at 1 year.[108] High one-year mortality (26%) has also been reported in patients with functional MR in the presence of severe TR.[123] Perhaps it is reasonable to consider MitraClip in patients with ERO>=30 mm^2 and without excess LV dilatation after intense medical therapy.[124, 125] New devices such as the PASCAL system are under study and provide similar results.[125, 126] Following transcatheter valve repair 1-6 months of dual antiplatelet therapy (aspirin plus clopidogrel) is recommended.[127]

Mitral valve implantation by means of transcatheter heart valves in failed bioprosthetic surgical valves (valve-in-valve [ViV]) and annuloplasty rings (valve-in-ring [ViR]) via a transapical or transseptal approach for severe MR or dysfunctional biological mitral prosthesis is also feasible, and several devices are under investigation.[128-130] Mitral ViV, in particular, has acceptable safety and clinical outcomes for failed bioprosthese in high-risk, [130-132] or even intermediate/ low-risk patients.[133] Anticoagulation is as for surgical replacement with an bioprostetic valve (3-6 month targeting an INR of 2.5).[127]

The optimal therapy of patients with **arrhythmic mitral valve prolapse** is not established. Beta blockers may be helpful, and ICD may be needed y indicated as secondary prevention in MVP patients experiencing out-of-hospital cardiac arrest, after the exclusion of other underlying reversible cardiac diseases. Catheter ablation targeting arrhythmia triggers may be useful in reducing ICD shocks.[134] Surgical mitral valve repair or replacement has

been demonstrated to reduce the burden of malignant arrhythmias, but data are rather scarse and controversial.[135]

Recommendations for patients with **mixed AS/MR valve disease** are presented in Chapter 19.

Non-cardiac Surgery

In asymptomatic patients with moderate or greater degrees of MR and normal LV systolic function with less than severe pulmonary hypertension (pulmonary artery systolic pressure <50 mmHg), elective noncardiac surgery can be performed.[136] In patients with severe secondary MR who remain symptomatic despite guideline-directed medical therapy (including CRT if indicated), valve intervention (transcatheter or surgical) should be also considered before NCS, in eligible patients with an acceptable procedural risk (Figure 9). If LV dysfunction is severe (EF <30%), non-cardiac surgery should only be performed if strictly necessary, after optimization of medical therapy for HF. Recommendations are also presented in Table 15.

Exercise

Recommendations for exercise and participation in sports are provided in Table 16.

Pregnancy

Significant MR (as well as TR, and combined valvular regurgitation) can be associated with increased risk of cardiac complications when high-risk features, such as left ventricular systolic function or pulmonary hypertension, are present.[137] In asymptomatic women with severe MR (Stage C1) and a valve suitable for repair who are considering pregnancy, the ACC/AHA 2020 GL on VHD recommend valve repair before pregnancy at a Comprehensive Valve Center but only after detailed discussion with the patient about the risks and benefits of the surgery and its effect on future pregnancies (IIb-C-EO.) Valve surgery during pregnancy is recommended in severe valve regurgitation and with NYHA class IV HF symptoms (Stage D) refractory to medical therapy (IIa-C-LD).[136] For general recommendations see Chapter on General Principles.

References

1. Enriquez-Sarano M, et al. Mitral regurgitation. *Lancet*. 2009;373:1382-94.
2. Nishimura RA, et al. Mitral valve disease--current management and future challenges. *Lancet*. 2016;387:1324-34.
3. Nkomo VT, et al. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005-11.
4. Delling FN and Vasan RS. Epidemiology and pathophysiology of mitral valve prolapse: new insights into disease progression, genetics, and molecular basis. *Circulation*. 2014;129:2158-70.
5. Kodaly SK and al. e. Valvular Heart Disease in Patients ≥80 Years of Age. *J Am Coll Cardiol*. 2018.
6. Yadgir S, et al. Global, Regional, and National Burden of Calcific Aortic Valve and Degenerative Mitral Valve Diseases, 1990-2017. *Circulation*. 2020;141:1670-1680.
7. Chikwe J, et al. Degenerative Mitral Regurgitation: From Prolapse to Precision Therapy. *Circulation*. 2026;154:2052-2063.
8. Etminan M and al. e. Oral Fluoroquinolones and Risk of Mitral and Aortic Regurgitation. *JACC*. 2019.
9. Sabbag A, et al. EHRA expert consensus statement on arrhythmic mitral valve prolapse and mitral annular disjunction complex in collaboration with the ESC Council on valvular heart disease and the European Association of Cardiovascular Imaging endorsed cby the Heart Rhythm Society, by the Asia Pacific Heart Rhythm Society, and by the Latin American Heart Rhythm Society. *Europace*. 2022;24:1981-2003.
10. Delling FN, et al. Evolution of Mitral Valve Prolapse: Insights From the Framingham Heart Study. *Circulation*. 2016;133:1688-95.
11. Foster E. Clinical practice. Mitral regurgitation due to degenerative mitral-valve disease. *N Engl J Med*. 2010;363:156-65.
12. Kitkungvan D, et al. Myocardial Fibrosis in Patients With Primary Mitral Regurgitation With and Without Prolapse. *J Am Coll Cardiol*. 2018;72:823-834.
13. Constant Dit Beaufils AL, et al. Replacement Myocardial Fibrosis in Patients with Mitral Valve Prolapse: Relation to Mitral Regurgitation, Ventricular Remodeling and Arrhythmia. *Circulation*. 2021.
14. Delling FN, et al. Familial clustering of mitral valve prolapse in the community. *Circulation*. 2015;131:263-8.
15. Le Tourneau T, et al. New insights into mitral valve dystrophy: a Filamin-A genotype-phenotype and outcome study. *Eur Heart J*. 2017.
16. Tribouilloy C, et al. Frequency of drug-induced valvular heart disease in patients previously exposd to benfluorex: a multicentre prospective study. *Eur Heart J*. 2013;34:3580-7.
17. Strange JE, et al. Oral fluoroquinolones and risk of aortic or mitral regurgitation: a nationwide nested case-control study. *Eur Heart J*. 2021.
18. Stout KK and Verrier ED. Acute valvular regurgitation. *Circulation*. 2009;119:3232-41.
19. Bertrand PB and al. e. Exercise Dynamics in Secondary Mitral Regurgitation Pathophysiology and Therapeutic Implications. *Circulation*. 2017;135:297-314.
20. Sannino A and al. e. Survival and Cardiovascular Outcomes of Patients With Secondary Mitral Regurgitation: A Systematic Review and Meta-analysis *JAMA Cardiology*. 2017.
21. Bartko PE, et al. Secondary valve regurgitation in patients with heart failure with preserved ejection fraction, heart failure with mid-range ejection fraction, and heart failure with reduced ejection fraction. *Eur Heart J*. 2020;41:2799-2810.

22. Farhan S, et al. Pathophysiology, Echocardiographic Diagnosis, and Treatment of Atrial Functional Mitral Regurgitation: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2022;80:2314-2330.
23. Le Tourneau T, et al. Right ventricular systolic function in organic mitral regurgitation: impact of biventricular impairment. *Circulation*. 2013;127:1597-608.
24. Mentias A, et al. Effect of Pulmonary Vascular Pressures on Long-Term Outcome in Patients With Primary Mitral Regurgitation. *J Am Coll Cardiol*. 2016;67:2952-61.
25. Avierinos JF, et al. Natural history of asymptomatic mitral valve prolapse in the community. *Circulation*. 2002;106:1355-61.
26. Enriquez-Sarano M, et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med*. 2005;352:875-83.
27. Rosenhek R, et al. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation*. 2006;113:2238-44.
28. Sabe MA, et al. Predictors and Prognostic Significance of Right Ventricular Ejection Fraction in Patients With Ischemic Cardiomyopathy. *Circulation*. 2016;134:656-65.
29. Naser JA, et al. The Natural History of Atrial Functional Mitral Regurgitation. *J Am Coll Cardiol*. 2024;83:1495-1507.
30. Freed LA, et al. Prevalence and clinical outcome of mitral-valve prolapse. *N Engl J Med*. 1999;341:1-7.
31. Essayagh B, et al. The MIDA-Q Mortality Risk Score: A Quantitative Prognostic Tool for the Mitral Valve Prolapse Spectrum. *Circulation*. 2023;147:798-811.
32. Topilsky Y, et al. Mitral valve prolapse with mid-late systolic mitral regurgitation: pitfalls of evaluation and clinical outcome compared with holosystolic regurgitation. *Circulation*. 2012;125:1643-51.
33. Miller MA and al. e. Arrhythmic Mitral Valve Prolapse. *JACC*. 2018.
34. Glesby MJ and Pyeritz RE. Association of mitral valve prolapse and systemic abnormalities of connective tissue. A phenotypic continuum. *JAMA*. 1989;262:523-8.
35. Levy S, et al. Genetic mechanisms underlying arrhythmogenic mitral valve prolapse: Current and future perspectives. *Heart Rhythm O2*. 2023;4:581-591.
36. Alqarawi W, et al. The Prevalence and Characteristics of Arrhythmic Mitral Valve Prolapse in Patients With Unexplained Cardiac Arrest. *JACC Clin Electrophysiol*. 2023;9:2494-2503.
37. Sabbag A, et al. Characterizing Sustained Arrhythmias in Patients With Arrhythmic Mitral Valve Prolapse: Insights From the SAVE-MVP collaboration. *JACC Clin Electrophysiol*. 2025.
38. Constant Dit Beaufils AL, et al. Replacement Myocardial Fibrosis in Patients With Mitral Valve Prolapse: Relation to Mitral Regurgitation, Ventricular Remodeling, and Arrhythmia. *Circulation*. 2021;143:1763-1774.
39. Basso C, et al. Arrhythmic Mitral Valve Prolapse and Sudden Cardiac Death. *Circulation*. 2015;132:556-66.
40. Sriram CS, et al. Malignant bileaflet mitral valve prolapse syndrome in patients with otherwise idiopathic out-of-hospital cardiac arrest. *J Am Coll Cardiol*. 2013;62:222-30.
41. Korovesis T, et al. Arrhythmogenic mitral valve prolapse. *Arrhythm Electrophysiol Rev*. 2021.
42. Sabbag A, et al. Mitral valve prolapse: arrhythmic risk during pregnancy and postpartum. *Eur Heart J*. 2024;45:1831-1839.
43. Han HC, et al. Systematic quantification of histologic ventricular fibrosis in isolated mitral valve prolapse and sudden cardiac death. *Heart Rhythm*. 2020.
44. Dejgaard LA, et al. The Mitral Annulus Disjunction Arrhythmic Syndrome. *J Am Coll Cardiol*. 2018;72:1600-1609.
45. Perazzolo Marra M and al. e. Determinants of Ventricular Arrhythmias in Mitral Valve Prolapse. *JACC EP*. 2024.
46. Asada S, et al. Prevalence, Characteristics, and Arrhythmogenic Substrate of Mitral Annular Disjunction Assessed by Cardiac Magnetic Resonance Imaging in Patients With Apparently Idiopathic Ventricular Arrhythmia. *J Arrhythm*. 2025;41:e70172.
47. Essayagh B, et al. The Mitral Annular Disjunction of Mitral Valve Prolapse: Presentation and Outcome. *JACC Cardiovasc Imaging*. 2021;14:2073-2087.
48. Anderson RH, et al. Anatomy of the mitral valve relative to controversies concerning the so-called annular disjunction. *Heart*. 2023;109:734-739.
49. Anderson RH, et al. Mitral annular disjunction: a ubiquitous finding with or without mitral valvar prolapse. *Heart*. 2024;110:463-465.
50. Attias D, et al. Prevalence, characteristics, and outcomes of patients presenting with cardiogenic unilateral pulmonary edema. *Circulation*. 2010;122:1109-15.
51. Grigioni F, et al. Atrial fibrillation complicating the course of degenerative mitral regurgitation: determinants and long-term outcome. *J Am Coll Cardiol*. 2002;40:84-92.
52. Tsaban G and al. e. Using Electrocardiogram to Assess Diastolic Function and Prognosis in Mitral Regurgitation. . *JACC* 2024;84 2278–2289.
53. Lancellotti P, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2013;14:611-44.
54. Zoghbi WA, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2017;30:303-371.

55. Grayburn PA, et al. Defining "severe" secondary mitral regurgitation: emphasizing an integrated approach. *J Am Coll Cardiol*. 2014;64:2792-801.
56. Grayburn PA, et al. Quantitation of mitral regurgitation. *Circulation*. 2012;126:2005-17.
57. Lee AP, et al. Quantitative analysis of mitral valve morphology in mitral valve prolapse with real-time 3-dimensional echocardiography: importance of annular saddle shape in the pathogenesis of mitral regurgitation. *Circulation*. 2013;127:832-41.
58. van Rosendael PJ, et al. Integrated imaging of echocardiography and computed tomography to grade mitral regurgitation severity in patients undergoing transcatheter aortic valve implantation. *Eur Heart J*. 2017.
59. Magne J, et al. Left ventricular contractile reserve in asymptomatic primary mitral regurgitation. *Eur Heart J*. 2014;35:1608-16.
60. Naji P, et al. Predictors of long-term outcomes in patients with significant myxomatous mitral regurgitation undergoing exercise echocardiography. *Circulation*. 2014;129:1310-9.
61. Garg P, et al. Cardiovascular magnetic resonance imaging in mitral valve disease. *Eur Heart J*. 2025;46:606-619.
62. Uretsky S, et al. Discordance between echocardiography and MRI in the assessment of mitral regurgitation severity: a prospective multicenter trial. *J Am Coll Cardiol*. 2015;65:1078-88.
63. Penicka M, et al. Prognostic Implications of Magnetic Resonance - Derived Quantification in Asymptomatic Patients with Organic Mitral Regurgitation: Comparison with Doppler Echocardiography-Derived Integrative Approach. *Circulation*. 2017.
64. Uretsky S and al. e. Characterization of Primary Mitral Regurgitation With Flail Leaflet and/or Wall-Impinging Flow. *JACC*. 2021.
65. Haberman D, et al. Conservative, surgical, and percutaneous treatment for mitral regurgitation shortly after acute myocardial infarction. *Eur Heart J*. 2022;43:641-650.
66. Ahmed MI, et al. A randomized controlled phase IIb trial of beta(1)-receptor blockade for chronic degenerative mitral regurgitation. *J Am Coll Cardiol*. 2012;60:833-8.
67. Kang DH, et al. Angiotensin Receptor Neprilysin Inhibitor for Functional Mitral Regurgitation. *Circulation*. 2019;139:1354-1365.
68. Gillam LD and Schwartz A. Primum non nocere: the case for watchful waiting in asymptomatic "severe" degenerative mitral regurgitation. *Circulation*. 2010;121:813-21; discussion 821.
69. De Bonis M and Bolling SF. Mitral valve surgery: wait and see vs. early operation. *Eur Heart J*. 2013;34:13-9.
70. Wigginton JG, et al. Part 9: Adult Advanced Life Support: 2025 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2025;152:S538-S577.
71. Enriquez-Sarano M and Sundt TM, 3rd. Early surgery is recommended for mitral regurgitation. *Circulation*. 2010;121:804-11; discussion 812.
72. Grigioni F, et al. Outcomes in mitral regurgitation due to flail leaflets a multicenter European study. *JACC Cardiovasc Imaging*. 2008;1:133-41.
73. Barbieri A, et al. Prognostic and therapeutic implications of pulmonary hypertension complicating degenerative mitral regurgitation due to flail leaflet: a multicenter long-term international study. *Eur Heart J*. 2011;32:751-9.
74. Antoine C, et al. Clinical Outcome of Degenerative Mitral Regurgitation: Critical Importance of Echocardiographic Quantitative Assessment in Routine Practice. *Circulation*. 2018.
75. Suri RM, et al. Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. *JAMA*. 2013;310:609-16.
76. Glower DD. Surgical approaches to mitral regurgitation. *J Am Coll Cardiol*. 2012;60:1315-22.
77. Lazam S, et al. Twenty-Year Outcome after Mitral Repair Versus Replacement for Severe Degenerative Mitral Regurgitation. Analysis of a Large, Prospective, Multicenter International Registry. *Circulation*. 2016.
78. Goldstein D, et al. Two-Year Outcomes of Surgical Treatment of Severe Ischemic Mitral Regurgitation. *N Engl J Med*. 2016;374:344-53.
79. Vassileva CM, et al. Long-term survival of patients undergoing mitral valve repair and replacement: a longitudinal analysis of Medicare fee-for-service beneficiaries. *Circulation*. 2013;127:1870-6.
80. Badhwar V, et al. Volume-Outcome Association of Mitral Valve Surgery in the United States. *JAMA Cardiol*. 2020;5:1092-1101.
81. Chikwe J and al. e. Relation of Mitral Valve Surgery Volume to Repair Rate, Durability, and Survival *J Am Coll Cardiol*. 2017;69:2 3 9 7 – 4 0 6.
82. David TE, et al. Late outcomes of mitral valve repair for mitral regurgitation due to degenerative disease. *Circulation*. 2013;127:1485-92.
83. Capoulade R, et al. Impact of Left Ventricular to Mitral Valve Ring Mismatch on Recurrent Ischemic Mitral Regurgitation After Ring Annuloplasty. *Circulation*. 2016;134:1247-1256.
84. O'Gara PT, et al. 2017 ACC Expert Consensus Decision Pathway on the Management of Mitral Regurgitation: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2017;70:2421-2449.
85. Suri RM, et al. Robotic Mitral Valve Repair for Simple and Complex Degenerative Disease: Midterm Clinical and Echocardiographic Quality Outcomes. *Circulation*. 2015;132:1961-8.
86. Pausch J, et al. Early outcome of endoscopic mitral valve surgery in elderly patients: a high-volume single center experience. *Front Cardiovasc Med*. 2023;10:1182752.

87. Moskowitz G and al. e. Incidence and Risk Factors for Permanent Pacemaker Implantation Following Mitral or Aortic Valve Surgery. *JACC*. 2019.
88. Chikwe J, et al. Impact of Concomitant Tricuspid Annuloplasty on Tricuspid Regurgitation, Right Ventricular Function, and Pulmonary Artery Hypertension After Repair of Mitral Valve Prolapse. *J Am Coll Cardiol*. 2015;65:1931-8.
89. Gammie JS, et al. Concomitant Tricuspid Repair in Patients with Degenerative Mitral Regurgitation. *N Engl J Med*. 2021.
90. Iribarne A and al. e. Permanent Pacemaker Implantation and Long-Term Outcomes of Patients Undergoing Concomitant Mitral and Tricuspid Valve Surgery. *JACC*. 2024.
91. Grigioni F and al. e. Long-Term Implications of Atrial Fibrillation in Patients With Degenerative Mitral Regurgitation. *JACC*. 2019.
92. Gillinov AM, et al. Surgical ablation of atrial fibrillation during mitral-valve surgery. *N Engl J Med*. 2015;372:1399-409.
93. Ad N, et al. Left-Sided Surgical Ablation for Patients With Atrial Fibrillation Who Are Undergoing Concomitant Cardiac Surgical Procedures. *Ann Thorac Surg*. 2017;103:58-65.
94. Milwidsky A, et al. Medical Therapy for Functional Mitral Regurgitation. *Circ Heart Fail*. 2022;15:e009689.
95. Kang DH, et al. Ertugliflozin for Functional Mitral Regurgitation Associated With Heart Failure: EFFORT Trial. *Circulation*. 2024;149:1865-1874.
96. Baumgartner H and al. e. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017.
97. O'Gara PT and Mack MJ. Secondary Mitral Regurgitation. *N Engl J Med*. 2020;383:1458-1467.
98. Penicka M, et al. Predictors of improvement of unrepaired moderate ischemic mitral regurgitation in patients undergoing elective isolated coronary artery bypass graft surgery. *Circulation*. 2009;120:1474-81.
99. Lam BK, et al. Importance of moderate ischemic mitral regurgitation. *Ann Thorac Surg*. 2005;79:462-70; discussion 462-70.
100. Campwala SZ, et al. Mitral regurgitation progression following isolated coronary artery bypass surgery: frequency, risk factors, and potential prevention strategies. *Eur J Cardiothorac Surg*. 2006;29:348-53.
101. Deja MA, et al. Influence of mitral regurgitation repair on survival in the surgical treatment for ischemic heart failure trial. *Circulation*. 2012;125:2639-48.
102. Chan KM, et al. Coronary artery bypass surgery with or without mitral valve annuloplasty in moderate functional ischemic mitral regurgitation: final results of the Randomized Ischemic Mitral Evaluation (RIME) Trial. *Circulation*. 2012;126:2502-10.
103. Fattouch K, et al. POINT: Efficacy of adding mitral valve restrictive annuloplasty to coronary artery bypass grafting in patients with moderate ischemic mitral valve regurgitation: a randomized trial. *J Thorac Cardiovasc Surg*. 2009;138:278-85.
104. Smith PK, et al. Surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med*. 2014;371:2178-88.
105. Michler RE, et al. Two-Year Outcomes of Surgical Treatment of Moderate Ischemic Mitral Regurgitation. *N Engl J Med*. 2016;374:1932-41.
106. Castleberry AW, et al. Surgical revascularization is associated with maximal survival in patients with ischemic mitral regurgitation: a 20-year experience. *Circulation*. 2014;129:2547-56.
107. Samad Z, et al. Management and outcomes in patients with moderate or severe functional mitral regurgitation and severe left ventricular dysfunction. *Eur Heart J*. 2015;36:2733-41.
108. De Bonis M, et al. Surgical and interventional management of mitral valve regurgitation: a position statement from the European Society of Cardiology Working Groups on Cardiovascular Surgery and Valvular Heart Disease. *Eur Heart J*. 2016;37:133-9.
109. van Bommel RJ, et al. Cardiac resynchronization therapy as a therapeutic option in patients with moderate-severe functional mitral regurgitation and high operative risk. *Circulation*. 2011;124:912-9.
110. Ponnusamy SS, et al. Response of functional mitral regurgitation in nonischemic cardiomyopathy to left bundle branch pacing. *Heart Rhythm*. 2022;19:737-745.
111. Chambers JB and al. e. Standards defining a 'Heart Valve Centre': ESC Working Group on Valvular Heart Disease and European Association for Cardiothoracic Surgery Viewpoint. *Eur Heart J*. 2017;38:2177–2183.
112. Prendergast BD, et al. Transcatheter heart valve interventions: where are we? Where are we going? *Eur Heart J*. 2019.
113. Metra M, et al. Evidence Generation and Implementation of Transcatheter Interventions for Atrioventricular Valvular Heart Disease in Heart Failure: Current Status and Future Directions. *Circulation*. 2025;151:1342-1363.
114. Feldman T, et al. Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. *J Am Coll Cardiol*. 2015;66:2844-54.
115. Ailawadi G, et al. One-Year Outcomes After MitraClip for Functional Mitral Regurgitation. *Circulation*. 2019;139:37-47.
116. Obadia JF, et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. *N Engl J Med*. 2018.
117. Stone GW, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *N Engl J Med*. 2018;379:2307-2318.

118. Pocock SJ and Collier TJ. Statistical Appraisal of 6 Recent Clinical Trials in Cardiology: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;73:2740-2755.
119. Goel K and al. e. Transcatheter Edge-to-Edge Repair in 5,000 Patients With Secondary Mitral Regurgitation: COAPT Post-Approval Study *JACC*
2023.
120. Chikwe J and al. e. Mitral Surgery after Transcatheter Edge-to-Edge Repair: Society of Thoracic Surgeons Database Analysis. *JACC*. 2021.
121. Ben-Shoshan J, et al. Predictors of Outcomes Following Transcatheter Edge-to-Edge Mitral Valve Repair. *JACC Cardiovasc Interv*. 2020;13:1733-1748.
122. Kaneko T, et al. Transcatheter edge-to-edge repair vs medical therapy in atrial functional mitral regurgitation: a propensity score-based comparison from the OCEAN-Mitral and REVEAL-AFMR registries. *Eur Heart J*. 2026;47:1304-1314.
123. Sorajja P and al. e. Outcomes With Transcatheter Mitral Valve Repair in the United States. An STS/ACC TVT Registry Report. *J Am Coll Cardiol*. 2017.
124. Enriquez-Sarano M, et al. Treatment of Functional Mitral Regurgitation. *Circulation*. 2019;139:2289-2291.
125. Coats AJS, et al. The management of secondary mitral regurgitation in patients with heart failure: a joint position statement from the Heart Failure Association (HFA), European Association of Cardiovascular Imaging (EACVI), European Heart Rhythm Association (EHRA), and European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC. *Eur Heart J*. 2021.
126. Lim DS, et al. Randomized Comparison of Transcatheter Edge-to-Edge Repair for Degenerative Mitral Regurgitation in Prohibitive Surgical Risk Patients. *JACC Cardiovasc Interv*. 2022.
127. Calabrò P and al. e. Antithrombotic Therapy in Patients Undergoing Transcatheter Interventions for Structural Heart Disease. *Circulation*. 2021;144:1323–1343.
128. Guerrero M, et al. Thirty-Day Outcomes of Transcatheter Mitral Valve Replacement for Degenerated Mitral Bioprostheses (Valve-in-Valve), Failed Surgical Rings (Valve-in-Ring), and Native Valve With Severe Mitral Annular Calcification (Valve-in-Mitral Annular Calcification) in the United States: Data From the Society of Thoracic Surgeons/American College of Cardiology/Transcatheter Valve Therapy Registry. *Circ Cardiovasc Interv*. 2020;13:e008425.
129. Urena M and al. e. Current Indications for Transcatheter Mitral Valve Replacement Using Transcatheter Aortic Valves. Valve-in-Valve, Valve-in-Ring, and Valve-in-Mitral Annulus Calcification. *Circulation*. 2021.
130. Russo G, et al. Transcatheter Mitral Valve Implantation: Current Status and Future Perspectives. *Circ Cardiovasc Interv*. 2021;14:e010628.
131. Simonato M, et al. Transcatheter Mitral Valve Replacement After Surgical Repair or Replacement: Comprehensive Midterm Evaluation of Valve-in-Valve and Valve-in-Ring Implantation From the VIVID Registry. *Circulation*. 2021;143:104-116.
132. Alperi A and al. e. Current Status and Future Prospects of Transcatheter Mitral Valve Replacement: JACC State-of-the-Art Review. *JACC*. 2021.
133. Goel K, et al. Contemporary Outcomes and Trends for the Transseptal Mitral Valve-in-Valve Procedure Using Balloon Expandable Transcatheter Valves in the United States. *Circulation*. 2024;150:1493-1504.
134. Syed FF, et al. Sites of Successful Ventricular Fibrillation Ablation in Bileaflet Mitral Valve Prolapse Syndrome. *Circ Arrhythm Electrophysiol*. 2016;9.
135. Basso C, et al. Mitral Valve Prolapse, Ventricular Arrhythmias, and Sudden Death. *Circulation*. 2019;140:952-964.
136. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease. *JACC*. 2020.
137. Pfaller B and al. e. Risk Associated With Valvular Regurgitation During Pregnancy. *JACC*. 2021.