Current Cardiology Reports (2019) 21: 139
https://doi.org/10.1007/s11886-019-1221-x

MYOCARDIAL DISEASE (A ABBATE AND G SINAGRA, SECTION EDITORS)

Treatment of Functional Mitral Regurgitation in Heart Failure

Enrico Fabris[1] · Antonio De Luca[1] · Giancarlo Vitrella[1] · Davide Stolfo[1] · Marco Masè[1] · Renata Korcova[1] · Marco Merlo[1] · Serena Rakar[1] · Arnoud W. J. van't Hof[2,3] · Elvin Kedhi[4] · Andrea Perkan[1] · Gianfranco Sinagra[1]

Published online: 16 November 2019

Abstract

Purpose of Review To analyze the current state of the art of functional mitral regurgitation (FMR) treatment.

Recent Findings The first-line treatment of severe FMR consists of guideline medical therapy (GMT) and resynchronization therapy when indicated; the impact of new medical therapies like sacubitril/valsartan needs further assessment. Valvular intervention may be considered in FMR symptomatic patients despite GMT, and can be performed surgically or percutaneously. MitraClip is a safe percutaneous procedure associated with symptoms improvement. Recently, the COAPT trial showed superior outcomes for MitraClip versus GMT contrasting the MITRA-FR trial which showed no benefit of MitraClip compared with GMT. These results should be interpreted as complementary rather than opposite.

Summary The COAPT trial provided a "proof of concept" that percutaneous treatment of severe FMR in patients without too advanced left ventricular disease translates into a prognostic benefit. Careful patient selection will play a critical role in defining the clinical niche for successful interventions.

Keywords Functional mitral regurgitation · Mitral valve repair · Transcatheter interventions · MitraClip · Heart failure · Heart team

Introduction

Functional mitral regurgitation (FMR) is a frequent finding in patients with heart failure (HF) and left ventricular (LV) systolic dysfunction. In ischemic and non-ischemic LV adverse remodeling, the integrity of the mitral valve (MV) is preserved and FMR is caused by annular dilatation and leaflet tethering linked to papillary-muscle displacement. Treatment of FMR is based on the treatment of the LV pathology and guidelines support first-line treatment with medical therapy and cardiac

This article is part of the Topical Collection on *Myocardial Disease*

✉ Enrico Fabris
enrico.fabris@hotmail.it

Antonio De Luca
deluca.antonio.md@gmail.com

Giancarlo Vitrella
giancarlo.vitrella@gmail.com

Davide Stolfo
davide.stolfo@gmail.com

Marco Masè
marco91ts@gmail.com

Renata Korcova
r_korcova@yahoo.it

Marco Merlo
marco.merlo79@gmail.com

Serena Rakar
serenarakar@hotmail.com

Arnoud W. J. van't Hof
arnoud.vant.hof@mumc.nl

Elvin Kedhi
ekedhi@me.com

Andrea Perkan
aa.perkan@gmail.com

Gianfranco Sinagra
gianfranco.sinagra@asuits.sanita.fvg.it

[1] Cardiovascular Department, University of Trieste, Via Valdoni 7, 34129 Trieste, Italy

[2] Department of Cardiology, Maastricht University Medical Center, Maastricht, the Netherlands

[3] Department of Cardiology, Zuyderland Medical Center, Heerlen, the Netherlands

[4] AZ Sint-Jan Brugge, Bruges, Belgium

re-synchronization therapy (CRT) (when indicated) [1]. However in persisting symptomatic patients with severe FMR, surgery may be considered although the level of evidence is low given the uncertain benefit [1]. Indeed, isolated surgical treatment has failed to demonstrate long-term outcome benefits unless the LV is treated as well (e.g., coronary revascularization) [1]. An integrative approach for diagnosis and management is central to optimal patient care. Indeed, while surgical mitral repair remains the gold standard for low-risk patients with degenerative mitral regurgitation, the advent of transcatheter therapy repair is becoming an emerging therapy in high-risk patients with FMR, expanding the indications for MV repair, and extending interventional treatments to older and sicker population. This review aims to report an updated overview on FMR and his treatment.

Prevalence and Mechanisms of FMR

FMR is a common finding in patients with myocardial dysfunction, with a prevalence of moderate to severe FMR ranging from 6 to 29% in patients with chronic HF [2, 3]. FMR is associated with poor outcomes with an almost two-fold increased risk of all-cause and cardiac mortality and hospitalization due to HF in patients with ischemic or idiopathic cardiomyopathies [4]. However, it remains debated whether FMR is a central driving force of poor prognosis or rather a bystander, reflecting the severity of ventricular disease [4, 5].

FMR is characterized by an anatomically normal MV apparatus and results from an unfavorable global or regional LV remodeling from non-ischemic and ischemic causes. Indeed, (1) reduced closing forces due to ventricular dysfunction along with annular dilatation and flattening, (2) leaflet tethering secondary to papillary-muscle displacement, and (3) degree of papillary muscle desynchrony result in incomplete MV closure. In addition, increased left atrial pressure can contribute to valve tenting. Chronic volume overload induces further LV remodeling in a vicious cycle at the base of the progression of the disease [6, 7].

FMR can occur in up to half of patients after myocardial infarction (MI) [7]. In this case, particularly after a transmural posterior MI, regional LV remodeling and dysfunction can determine apical-posterolateral displacement of the posterior papillary muscle, resulting in reduced mobility of the posterior leaflet and consequent malcoaptation [8].

More recently, atrial FMR has been described as a result of atrial enlargement and annular dilatation, most often in patients with history of persistent/chronic atrial fibrillation [9].

The onset or worsening of FMR may also follow pacemaker implantation [10, 11]. Right ventricular apical pacing causes an abnormal LV activation, leading to papillary muscle desynchrony and delayed reduction of mitral annular size that physiologically occurs in early systole. Moreover, loss of atrioventricular synchrony during ventricular pacing may contribute to worsening of FMR.

Finally, FMR may be caused by systolic anterior motion (SAM) of the MV in patients with hypertrophic cardiomyopathy and can contribute to dynamic obstruction of LV outflow tract. The anterior displacement of papillary muscles resulting in an anterior position of coaptation plane, and elongation of leaflets and chordae tendineae constitutes a favorable anatomical substrate for SAM of the MV. Moreover, SAM is associated with a variable degree of MR, particularly when the posterior leaflet is not long or mobile enough to move anteriorly with the anterior leaflet, resulting in poor coaptation [12].

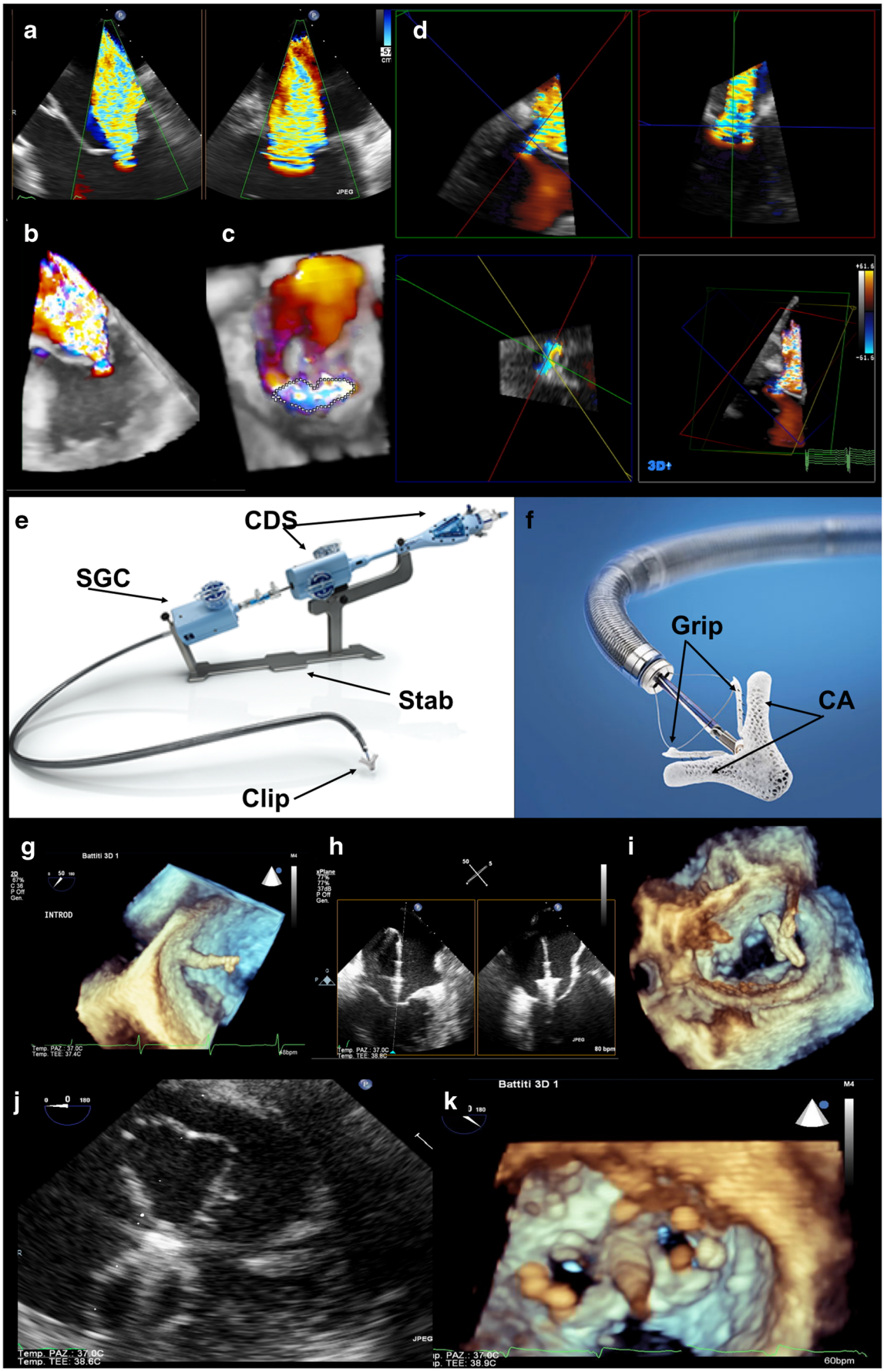
Fig. 1 **a**–**d** Study of the mitral regurgitation (MR) severity at transesophageal echocardiography: **a** *X*-plane color-Doppler oriented to MR jet, severe MR is evident. **b**–**d** 3D color Doppler for the quantification of 3D-vena contracta area (3D-VCA). **e**–**f** MitraClip device: **e** Vision of the device. **f** Magnification of the clip. **g**–**i** Intraprocedural transesophageal echocardiography during MitraClip procedure: **g** Trans-septal puncture. **h**, **i** *X*-plane and 3D volume rendering views during device orientation. **j**–**k** Intraprocedural transesophageal echocardiography after MitraClip deployment, with creation of double orifice anatomy: **j** Transgastric short-axis view. **k** 3D volume rendering of mitral valve viewed from the left ventricle. CA, clip arms; CDS, clip delivery system; Grip, grippers; SGC, steerable guide catheter; Stab, stabilizer

Evaluation of Functional Mitral Regurgitation Severity (2D and 3D Echocardiography)

Transthoracic echocardiography (TTE) is the first-line imaging modality for the morphological and functional evaluation of the MV and allows quantification of LV volumes and function, detection of wall motion abnormalities as well as identification of hemodynamic consequences of MR, such as elevated pulmonary artery pressure and right ventricular dysfunction [13]. Transesophageal echocardiography (TEE) ensures a thorough evaluation of the MV apparatus to clarify the mechanism of MR, and may be helpful for planning surgical or interventional MV repair [14].

Recommendations from international societies suggest a multiparametric approach for the evaluation of the severity of MR [15, 16]. Vena contracta width (VCw), measured at the narrowest point of the regurgitant jet, is a semi-quantitative method for the evaluation of MR. A VCw $<$ 3 mm indicates mild MR, whereas VCw $\geq$ 7 mm indicates severe MR. Intermediate values need a quantitative method due to the overlap between MR grades [15, 16].

The flow convergence method is the most recommended quantitative approach. It estimates the effective regurgitant orifice area (EROA) from the radius of proximal isovelocity surface area (PISA) and peak velocity of MR jet. The same method allows the determination of the regurgitant volume (RVol). PISA method has several limitations, mainly due to the assumption of hemispheric symmetry of velocity distribution proximal


a
b
c
d
3D+
e
CDS
SGC
Stab
Clip
f
Grip
CA
g
Battiti 3D 1
INTROD
h
i
j
k
Battiti 3D 1
60bpm

to a circular regurgitant lesion. However, in FMR, the regurgitant orifice has an ellipsoidal shape. Moreover, the PISA radius and the regurgitant orifice dynamically change during the cardiac cycle, with early and late systolic peaks and mid-systolic decrease, leading to a potential underestimation of disease severity [15, 16]. The introduction of 3D color Doppler echocardiography permits the direct measurement of vena contracta area by using a multiplanar reconstruction approach, avoiding geometrical assumptions and allowing more accurate quantification of MR [17] (Fig. 1).

Diverging definitions regarding the severity criteria for FMR are provided by guidelines [15, 16]. Whereas EACVI recommendations define severe FMR to an EROA ≥ 20 mm^2 and RVol ≥ 30 ml, ASE guidelines use a higher threshold (EROA ≥ 40 mm^2, RVol ≥ 60 ml). These discrepancies are mainly attributable to evidence of worse prognosis for patients affected by FMR and EROA ≥ 20 mm^2, but exposes to the risk of overtreatment [16]. Recently, Bartko et al. [18•] proposed a unifying concept for the quantitative assessment of FMR, based on the evaluation of EROA, RVol, and regurgitant fraction (RFrac). In their study, the authors proposed a risk-based algorithm. Thresholds reflecting high-risk were EROA ≥ 30 mm^2 and RVol ≥ 45 ml. In the intermediate-risk subset (EROA 20–29 mm^2, RVol 30–44 ml), a RFrac ≥ 50% emerged as a valuable tool for further risk discrimination. Indeed, a RFrac ≥ 50% suggests a hemodynamically significant FMR and re-stratifies patients in the high-risk subset.

Finally, the pathophysiological relationship between EROA and LV end-diastolic volume and function should not be forgotten. The new conceptual framework proposed by Grayburn et al. [19•] introduces the concept of proportionate and disproportionate FMR to determine whether or not the estimated degree of MR is expected on the basis of LV dilatation (Fig. 2).

Medical Therapy and Timing of Intervention

FMR is not a primary disease of the valve; therefore, reestablishing the competency of the MV is not curative. Guideline-directed medical therapy (GDMT), favoring LV reverse remodeling (LVRR), can improve the degree of FMR and is the first-line treatment for chronic HF patients who also have FMR. Diuretics, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and aldosterone antagonist, are recommended for all patients with HF and reduced ejection fraction HFrEF and NYHA class ≥II and should be the first step in the treatment of HF patients with FMR [20]. In patients with dilated cardiomyopathy receiving optimal medical treatment, early improvement of FMR is frequent (53%) and is a favorable independent prognostic factor [21]. Recently, the PRIME trial, a small double-blind randomized controlled trial, although too small to show any clinical benefits, showed a reduction in echo-derived EROA in sacubitril/valsartan compared with valsartan alone in patients with HFrEF and chronic FMR [22].

The severity of FMR is dynamic and is significantly influenced by ventricular loading conditions. Medical optimization can decrease mitral regurgitation (MR), pulmonary congestion, fluid overload, and myocardial ischemia, and is an essential step before deciding on intervention. Thus, options for MV intervention should be evaluated when symptoms persist after optimization of GDMT and CRT (if indicated). CRT is indicated in patients with LV ejection fraction (LVEF) ≤ 35%,

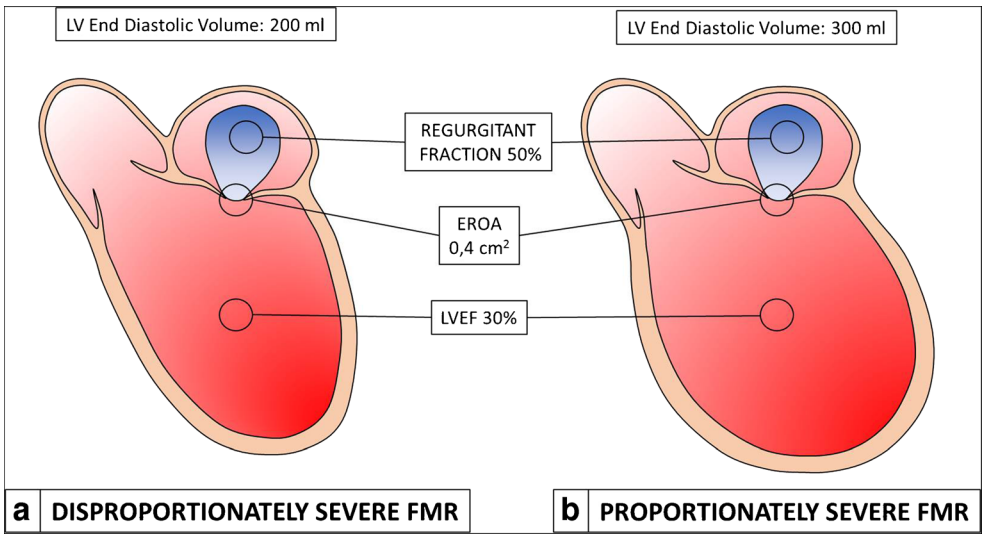


Fig. 2 Disproportionately and proportionately severe functional mitral regurgitation (FMR) with respect to left ventricular end-diastolic volume and ejection fraction (LVEF). As proposed by Grayburn et al. [19•], in less remodeled left ventricles (**a**), a severe FMR is unexpected and therefore disproportionate to the degree of LV dilatation. In such cases, mitral valve repair should be considered as a therapeutic target. By contrast, in advanced remodeled left ventricles (**b**), the same degree of FMR is expected if related to LV dilatation. These patients seem not to benefit from transcatheter mitral valve repair compared with medically treated subjects

HF symptoms (NYHA class II–IV) despite maximum GDMT, and a wide QRS (≥ 150 ms with left bundle branch block (LBBB)). Class of recommendation and level of evidence vary according to QRS morphology and duration (lower strength of recommendations when QRS duration is 130–150 ms, especially if not associated with LBBB) [20]. The role of CRT in reducing FMR in patients with LV dysfunction, increased QRS duration, and both NYHA class I/II and III/IV, has been showed (at mid-term follow-up of 6 months) [21]. Whether the improvement in FMR after CRT results in superior survival [23], the absence of MR improvement is a significant independent predictor of both all-cause and cardiovascular mortality [24]. Three echocardiographic features showed independent association with amelioration of significant MR after CRT: anteroseptal to posterior wall radial strain dyssynchrony > 200 ms, lack of severe LV dilatation (end-systolic dimension index < 29 mm/m [2]), and lack of scar at papillary muscle insertion sites [25]. Moreover, echocardiographic evaluation of acute hemodynamic response to CRT is helpful to early identification of the favorable FMR evolution [26].

Isolated surgery of severe FMR carries significant operative mortality, has high rates of recurrent mitral regurgitation, and lacks a proven survival benefit [27, 28]. Only patients undergoing coronary artery bypass grafting (CABG) with associated severe FMR have a strong indication to MV surgery (in particular patients with LVEF > 30%) [1]. In other cases, although severe FMR is associated to a worse prognosis, there is no conclusive evidence that correcting it improves survival. Thus, indications for isolated surgery in FMR are particularly restrictive [1]. The optimal surgical approach remains controversial. While MV repair with an undersized complete ring to restore leaflet coaptation and valve competence is the preferred technique [1], valve replacement should be considered in patients with echocardiographic risk factors for residual or recurrent mitral regurgitation [15].

In a recent randomized controlled trial, valve-sparing MV replacement resulted in similar LVRR and equivalent 2-year mortality, but the rate of recurrence of moderate or severe MR was significantly higher with mitral-valve repair, resulting in more HF–related adverse events and cardiovascular admissions [29].

Moreover, in patients with moderate FMR that are scheduled to undergo CABG, indication for MV surgery remains controversial. The addition of mitral-valve repair did not lead to significant differences in LVRR at 2 years and did not significantly improve survival or reduce overall adverse events or readmissions and was associated to increased rate of perioperative complications [29].

Percutaneous edge-to-edge repair for FMR is a low-risk option that may fulfill a major unmet need. Despite its reduced efficacy in reducing MR compared with surgery [30], it can improve symptoms, functional capacity, and quality of life and may induce LVRR [31]. Moreover, percutaneous edge-to-edge repair recently showed to be able to lower the rate of hospitalization for heart failure and all-cause mortality within 24 months of follow-up compared with guideline-directed optimal medical therapy alone [32••]. Edge-to-edge MV repair with the MitraClip system (Abbott Vascular, Santa Clara, CA, USA) is the most widely used device [33] with more than 70,000 procedures already performed worldwide.

MitraClip Device

The MitraClip System (Abbott Vascular, Santa Clara, CA) consists of a steerable guide catheter (SGC) and the clip delivery system (CDS). The SGC has a tapered dilator to advance it into the femoral vein and left atrium (LA) following transeptal puncture. The CDS comprises a steerable sleeve handle, the delivery catheter handle, and the clip itself, with its grippers and arms (Fig. 1).

MitraClip Procedure and Echocardiographic Guidance During Intervention

The MitraClip procedure is performed under general anesthesia, primarily to avoid discomfort to the patient, particularly in the context of extended periods of TEE evaluation. TEE is of paramount importance for the guidance of MitraClip procedure, for the assessment of the result and for the detection of complications. The combination of two-dimensional, bi-plane (also called *X*-plane) and three-dimensional views provides a comprehensive image of cardiac structures, as well as delivery catheters, wires, and device. Percutaneous femoral venous access is obtained. Transeptal puncture is performed in the optimal site (superiorly and posteriorly in the interatrial septum, 3.5 cm above the mitral annular plane) under TEE guidance (Fig. 1) (bicaval, short-axis at the base, and 4-chamber views), and the 24F SGC is advanced over the guide wire into the left atrium. After SGC fixation to a stabilizer, the CDS is advanced into the left atrium through the SGC, and the CDS is steered towards the mitral valvular commissure. In these phases, TEE should be used to avoid potential complications, such as left atrial appendage perforation and left atrial wall injury. Once an ideal position—over the zone where the MR jet is greatest—is confirmed (intercommissural and 3-chamber cross-plane view for medial-lateral and anterior-posterior position), the clip is orientated perpendicularly to the commissure (3D en-face view) and advanced through the valve (Fig. 1). The DC handle is retracted slowly to grasp both leaflets in the device. Once leaflet capture is confirmed, the grippers are pushed down and the clip is closed, thus creating a double orifice MV anatomy simulating the Alfieri surgical technique (Fig. 1). The clip is released after reduction in MR, adequate tissue grasping, and absence of significant stenosis

(mean residual gradient < 6 mmHg) are confirmed by TEE. Otherwise, the clip can be repositioned or retrieved into the SGC and removed from the body. Additional clips may be deployed in case of significant residual MR after the first clip; in most cases, a maximum of two MitraClip devices are required (in COAPT trial [32••], a mean of 1.7 ± 0.7 clips per patient, range 1 to 4, was implanted). When a satisfactory result is achieved, the system is removed from the femoral access site, and the presence of residual MR as well as size and direction of shunting of the residual iatrogenic atrial septal defect are evaluated.

The MitraClip procedure is generally safe and well tolerated. Aside from the risks associated with general anesthesia, those specific to the procedure include the following: vascular access site complications, new onset atrial fibrillation, left atrial perforation with cardiac tamponade, rupture of mitral leaflet, clip entanglement and disruption of subvalvular apparatus, clip detachment and embolization, and endocarditis. The complication rate is overall low and decreases with increasing operator and institutional experience [29, 34].

Evidence from Multicenter Registries

Between 2013 and 2015, 4 observational studies (ACCESS-EU [31], the Pilot Sentinel [34], the GRASP-IT [35], and the TRAMI [36]) provided evidence on "real-world" experience with MitraClip in Europe (Table 1). Overall, the "real-world" experience highlighted that patients undergoing MitraClip implantation were usually old (mean age > 70 years) and highly symptomatic (NYHA III/IV in about 85% of individuals). All 4 registries included patients with both primary and FMR but the latter consisting of at least 70% of the cases. The assessment of MR severity was different depending on the echocardiographic protocol adopted (both mild, moderate, severe, and 1+, 2+, 3+, 4+ scales were used). Percutaneous "edge-to-edge" repair had excellent efficacy in reducing MR with high procedural success, accompanied by scarce safety issues, proving low operator dependency of this technique when performed in high-trained centers. Long-term outcomes were fairly homogeneous in showing improvement of symptoms and quality of life.

Evidence from Randomized Studies

The Endovascular Valve Edge-to-Edge Repair Study (EVEREST II) trial was the first randomized study assessing efficacy and safety of percutaneous MV repair. Even though only 27% of the enrolled patients were affected by FMR, the trial showed similar efficacy and superior safety of the percutaneous procedure when compared with surgical approach, at the cost of higher rates of MV dysfunction at 1-year follow-up [37]. In 2018, MITRA-FR [38••] and COAPT [32••] trials addressed the role of percutaneous MV repair in symptomatic (NYHA II-IV) patients with severe FMR despite GDMT. Although giving discordant results, they inspired vibrant debate in the cardiological community leading to new theories and better insights in the role of FMR in HF.

COAPT vs MITRA-FR Trials

Both COAPT [32••] and MITRA-FR [38••] trials randomized patients to MitraClip plus GDMT or GDMT alone. The industry-sponsored COAPT randomized study showed that transcatheter MV repair resulted in a lower rate of hospitalization for heart failure and lower all-cause mortality within 24 months of follow-up than GDMT alone [32••]. These results were contrasting with those from the MITRA-FR, which showed no benefit of MitraClip compared with GDMT [38••].

A possible explanation for these different outcomes was that there were differences in baseline valvular and ventricular characteristics between the patient populations of the two trials. Patients in the COAPT trial patients had more severe MR and smaller LV volume, whereas MITRA-FR patients had a lesser degree of MR and more dilated LV, suggesting that the MITRA-FR population was more severe (Table 2). Moreover, the selection criteria with at least one HF hospitalization within the previous year were present in MITRA-FR; however, hospitalization for HF within previous 1 year in COAPT population was 57%.

The potential differences in baseline medical therapy in MITRA-FR and COAPT may suggest a potential confounding bias (patients in the control group of COAPT had significantly less renin-angiotensin-system blockade prescription than patients in the intervention group) although this difference is unlikely to explain by itself the difference on HF events. Probably, COAPT trial has better isolated the true incremental impact of reducing MR in patients without severe LV dilation [39].

Recently, authors [40] have proposed that FMR patients represent a heterogeneous group, mainly consisting of 2 subsets: patients in whom FMR is explained by the leaflet tethering and annular dilatation produced by marked enlargement of the LV cavity (proportionate MR), and patients in whom LV enlargement alone is not responsible for the severity of MR (disproportionate MR). When FMR severity is proportionate to LV dilatation (such as in MITRA-FR), patients benefit from treatments aimed at LVRR but may not respond to interventions directly aimed at reducing the MR. Conversely, patients with disproportionate MR (such as in COAPT) may benefit from treatments aimed at directly restoring leaflet coaptation through mechanical means [40]. However, whether treatment decisions based on this new construct translate to real and meaningful clinical benefits for the patients is still unproven [39].

Table 1 Observational multicenter studies with MitraClip

	Access-EU	Sentinel Pilot	Grasp-IT	TRAMI
Site	Europe	Europe	Italy	Germany
Years of enrollment	2008–2012	2011–2012	2008–2013	2010–2013
No. of patients (% males)	567 (64)	628 (63)	304 (64)	749 (61)
Age (years)	74 (SD ± 10)	74 (SD ± 9.7)	72 (SD ± 10)	76 (IQR = 71–81)
NYHA III/IV (%)	85	85	80	89
Log. EuroSCORE (%)	23 (SD ± 18.3)	20.4 (SD ± 16.7)	6 (IQR 3–11)*	20 (12–31)
Functional MR (%)	77	72	79	71
LVEF at baseline	LVEF ≤ 0.40 (53%)	43% (SD ± 0.16)	37% (SD ± 0.14)	LVEF < 0.30 (34%) LVEF 0.30–0.50 (35%)
Severity of MR at baseline	3/4+ in 98%	Severe in 86%	4+ in 70%	Severe in 94%
Severity of MR at discharge	3/4+ in 8.8%	Severe in 1.8%	3/4+ in 8.3%	Severe in 2.3%
Severity of MR at Follow up	3/4+ in 21.1%	Severe in 6%	–	–
In-hospital mortality (%)	–	2.9	–	2.4
Mortality at 30 days (%)	3.4	3.0	3.4	4.5
Mortality at 1 year (%)	17.3	15.3	20.8	20.3

*EuroSCORE II

Predictors of Procedural Success

Immediate post-procedural results after MitraClip are generally reported as satisfactory with > 95% rates of acute-procedural MR correction [32••, 38••]. However, in real word, the rate of recurrence of MR > 2+ at 1-year follow-up has been reported > 20% [31]. Larger ventricular dimensions, more compromised LV function, higher level of natriuretic hormones, right ventricular impairment, advanced functional status, and renal failure predict worse prognosis in MitraClip recipients [41]. These features, however, identify patients with more advanced underlying HF rather to represent useful markers of durable results after intervention.

In large-scale registries, procedural failure was the only variable associated with the risk of MR recurrence and the magnitude of residual MR correlated with 1-year survival [36, 42, 43]. Small retrospective studies explored the anatomical characteristics of the mitral apparatus identifying the diameter of the mitral annulus and the restricted motion of the posterior leaflet as potential markers of increased risk of MR recurrence [44, 45]. Moreover, LV contractile reserve, assessed by speckle tracking dobutamine stress echocardiography, could improve the selection of best candidates for the percutaneous correction of FMR [46].

In the MITRA-FR [38••] and COAPT [32••] trials, 17% and 5%, respectively, of patients had recurrent residual FMR ≥ 2+ at 1 year. The opposite results of the COAPT and MITRA-FR have shed the light on the definition of the patient with the higher probability of gaining benefit from the procedure and the lower risk of early failure in order to improve prognosis and avoid futility.

Reverse Remodeling After MitraClip, a Dream Come True?

LVRR in HF patients exerts a favorable impact on prognosis and is considered a main target of medical therapy [47]. The correction of FMR offers a theoretical basis to further promote the regression of the maladaptive remodeling due to longstanding LV volume overload. Moreover, the hemodynamic stabilization of less stable patients could aid the gradual uptitration of HF medications. Nevertheless, available data on LVRR after MitraClip are discordant [34, 48–50]. In both degenerative and FMR, reduction in LV end-diastolic volume (LVEDV) has been associated with the degree of residual MR at 12 months. The reduction of LV volumes at end-diastole and at end-systole, and LA volumes demonstrated LVRR when MR severity was reduced to either 1+ or 2+ by MitraClip therapy [51]. Oppositely, other studies failed to demonstrate significant changes in LV dimensions and function. A possible explanation is the more advanced disease of these patients. Indeed, in about 200 patients from three Italian hospitals, markers of less advanced disease as freedom from HF hospitalizations and LV end-diastolic diameter < 75 mm were the predictors of LVRR [52]. LVRR was associated with lower adjusted risk of all-cause mortality and HF hospitalizations but with only a trend towards the reduction of cardiovascular mortality [52]. Finally, in the COAPT trial, only a trivial reduction in LV end-diastolic volume was observed in the treated arm; however, the control group experienced a mean 17-ml increase in LV end-diastolic volume [32••]. Therefore, the timing of intervention may be considered a potential

Table 2 MITRA-FR and COAPT trials

	MITRA-FR	COAPT
Centers	37 (France)	78 (North America)
Duration (months)	40	57
Eligibility criteria		
NYHA	II–IV	II–IV
LVEF (%)	15–40	20–50
LVESD (mm)	–	< 70
EROA (mm^2)	> 20	> 30
Regurgitant volume (ml)	> 30	> 45
HF hospitalization and BNP	At least 1 hospitalization within 1 year	○ At least 1 hospitalization within 1 year and/or ○ BNP > 300 pg/ml NTproBNP > 1500 pg/ml
Eligibility committee	Local	Central
Population characteristics		
No. of patients (males %)	304 (74)	614 (64)
Age (years)	70	72
NYHA III/IV (%)	67	60.4
EROA (mm^2)	31 ± 10	40.5 ± 15
LVEDVi (ml/m^2)	135 ± 35	101 ± 34
ACEi, ARB, ARNI (%)	84.7	67.1
Beta-blockers (%)	89.5	90.3
MRA (%)	54.8	50.1
Diuretics (%)	98.6	89.1
Outcomes		
Acute MR ≥ 3+ (%)	9	5
MR ≥ 3+ at 1 year (%)	17	5
Mortality at 1 year (MitraClip + GDMT vs GDMT, %)	24.3 vs 22.4	18.8 vs 23.2
Mortality/HF hospitalization at 1 year (MitraClip + GDMT vs GDMT, %)	55 vs 51	34 vs 47

crucial aspect. Indeed, earlier intervention may prevent irreversible LV dysfunction due to longstanding LV volume overload.

Other Devices for Percutaneous Repair: Transcatheter Annuloplasty Technique

Technologies that restore the shape of the MV annulus (annuloplasty technique) have emerged and are at different stages of investigation as a potential catheter-based solution for patients with FMR.

The CARILLON Mitral Contour System (Cardiac Dimensions, Inc., Kirkland, WA, USA) is the second CE-marked catheter-based device to address purely functional MR. The device uses the coronary sinus to achieve indirect annuloplasty. The nitinol-based device that has a proximal and distal anchor is placed into the coronary sinus to reduce its diameter and allows approximation of the MV leaflets. The indirect modality of action and the variability of the location of the coronary sinus are the main reservations related to this approach. Even though reduction of MR and inverse LV remodeling have been showed [53], indication and selection criteria for suitable patients, the expected complications, and the long-term results with regard to survival and quality of life still remain unclear [53].

The Cardioband MV Reconstruction System (Edwards Lifesciences, Irvine, CA, USA) is a transcatheter direct annuloplasty implant that closely reproduces surgical ring implantation and annulus plication. The adjustable Dacron band is delivered through a transeptal access and implanted on the atrial side of the mitral annulus. The study that led to the CE

approval of the device showed a reasonable performance and safety at 1 year with most patients having moderate or less MR and significant functional improvements [22].

Finally, the Mitralign device (Mitralign Inc., Tewksbury, MA) mimics a surgical suture annuloplasty; it is performed using a retrograde arterial approach. The device attempts to achieve annular size reduction by placing paired couples of annular pledgeted sutures from the ventricle to atrial side of the mitral annulus. This treatment showed to initiate LV reverse remodeling and to provide clinical improvement during 6 months after treatment [54].

So far, only the MitraClip device has undergone extensive human investigation, and the reproducibility of results and the real effectiveness of the other devices still remain to be demonstrated [33]. The complex anatomy of the MV and mitral apparatus and the interplay of the valve with the LV are the main components causing the difficulties in developing and evaluating new mitral devices.

Decision Making and Importance of a Multidisciplinary Heart Team Approach

Managing care for patients with complex cardiovascular disease has changed substantially over the last decade. Patients are older, have more complex cardiovascular disease, and have a greater number of comorbidities. The decision between treatment of MR (catheter-based or surgical), ventricular assist devices, heart transplantation, and continued conservative therapy should be made by the Heart Team after careful individual evaluation of the patient in order to select the best candidates for a particular treatment, avoiding futility.

If interventional therapy is considered, a multidisciplinary team involving HF specialists, interventionalists, imaging experts, and cardiac surgeons should be involved in patient evaluation and decision making [55,56]. A team may better interpret examination results and specific conditions and may combine local therapeutic capability while avoiding professional bias that may come from a single subspecialist's point of view. Indeed heart team may also elevate the cognitive interchange that occurs among the specialties. Establishing formats for interaction by the Heart Team is essential. In some institutions, there will the development of a structural heart disease center to facilitate the process [57]. The heart team should focus on patient evaluation, selection, education, with intensive efforts at discussion of the risk/benefit ratio, and alternative strategies of care [58]. Indeed, the central goal of patient-centric care requires that the patient and family be sufficiently educated about the alternatives available so that their expectations can be met as fully as possible.

Conclusions

The essential, first-line, treatment of severe FMR consists of GMT, and CRT when indicated. In persisting symptomatic patient with severe FMR despite optimized medical therapy, the benefit of valve interventions is uncertain especially because is not always clear whether FMR plays a leading role in heart failure progression or rather represent a mere marker of severity. FMR correction can be performed surgically or percutaneously with the MitraClip procedure as the most widely used device. Recently, COAPT [32••] and MITRA-FR [38••] trials have given discordant results; however, the two trials should be interpreted as complementary rather than opposite.

The MITRA-FR trial enrolled patients who had FMR that was proportionate to the degree of left ventricle dilatation, whereas the patients enrolled in the COAPT trial, compared with MITRA-FR, had an higher EROA but LV volumes that were smaller, indicative of disproportionate MR [19•].

The COAPT [32••] trial showed that MitraClip procedure resulted in a lower rate of hospitalization for HF and lower mortality within 24 months of follow-up than medical therapy alone and may be considered a "proof of concept" that the treatment of severe FMR in patients without too advanced ventricular disease translate into a prognostic benefit.

Careful patient selection with the Heart Team approach will play a critical role in defining the clinical niche for successful transcatheter interventions, because the selection of good candidates for these therapies remains still a clinical challenge.

Compliance with Ethical Standards

Conflict of Interest Enrico Fabris, Antonio De Luca, Giancarlo Vitrella, Davide Stolfo, Marco Masè, Renata Korcova, Marco Merlo, Serena Rakar, Elvin Kedhi and Andrea Perkan declare that they have no conflict of interest.

Arnoud WJ van't Hof reports grants from Medtronic and Abbott, and personal fees from AstraZeneca.

Gianfranco Sinagra reports personal fees from Novartis, Vifor pharma, Boston, Bayer, AstraZeneca, and Dompè.

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.

References

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

1. 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.
2. Rossi A, Dini FL, Faggiano P, Agricola E, Cicoira M, Frattini S, et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy.

Heart. 2011;97(20):1675–80. https://doi.org/10.1136/hrt.2011.225789.
3. Varadarajan P, Sharma S, Heywood JT, Pai RG. High prevalence of clinically silent severe mitral regurgitation in patients with heart failure: role for echocardiography. J Am Soc Echocardiogr. 2006;19(12):1458–61. https://doi.org/10.1016/j.echo.2006.06.009.
4. Sannino A, Smith RL, Schiattarella GG, Trimarco B, Esposito G, Grayburn PA. Survival and cardiovascular outcomes of patients with secondary mitral regurgitation. JAMA Cardiol. 2017;2(10):1130–9. https://doi.org/10.1001/jamacardio.2017.2976.
5. Goliasch G, Bartko PE, Pavo N, Neuhold S, Wurm R, Mascherbauer J, et al. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. Eur Heart J. 2018;39(1):39–46. https://doi.org/10.1093/eurheartj/ehx402.
6. Inciardi RM, Rossi A, Benfari G, Cicoira M. Fill in the gaps of secondary mitral regurgitation: a continuum challenge from pathophysiology to prognosis. Curr Heart Fail Rep. 2018;15(2):106–15. https://doi.org/10.1007/s11897-018-0379-7.
7. Nappi F, Avatar Singh SS, Santana O, Mihos CG. Functional mitral regurgitation: an overview for surgical management framework. J Thorac Dis. 2018;10(7):4540–55. https://doi.org/10.21037/jtd.2018.07.07.
8. Piérard LA, Carabello BA. Ischaemic mitral regurgitation: pathophysiology, outcomes and the conundrum of treatment. Eur Heart J. 2010;31(24):2996–3005. https://doi.org/10.1093/eurheartj/ehq411.
9. Liang JJ, Silvestry FE. Mechanistic insights into mitral regurgitation due to atrial fibrillation: "atrial functional mitral regurgitation". Trends Cardiovasc Med. 2016;26(8):681–9. https://doi.org/10.1016/j.tcm.2016.04.012.
10. Mark JB, Chetham PM. Ventricular pacing can induce hemodynamically significant mitral valve regurgitation. Anesthesiology. 1991;74(2):375–7 http://www.ncbi.nlm.nih.gov/pubmed/1990916. Accessed May 19, 2019.
11. Wong DTL, Leong DP, Khurana S, Puri R, Tayeb H, Sanders P. Severe mitral regurgitation due to right ventricular apical pacing. Case Reports. 2010;2010(oct29 1):bcr1220092524. https://doi.org/10.1136/bcr.12.2009.2524.
12. Sherrid MV, Balaram S, Kim B, Axel L, Swistel DG. The mitral valve in obstructive hypertrophic cardiomyopathy: a test in context. J Am Coll Cardiol. 2016;67(15):1846–58. https://doi.org/10.1016/j.jacc.2016.01.071.
13. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1–39.e14. https://doi.org/10.1016/j.echo.2014.10.003.
14. Wunderlich NC, Beigel R, Ho SY, Nietlispach F, Cheng R, Agricola E, et al. Imaging for mitral interventions: methods and efficacy. JACC Cardiovasc Imaging. 2018;11(6):872–901. https://doi.org/10.1016/j.jcmg.2018.02.024.
15. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, 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(7):611–44. https://doi.org/10.1093/ehjci/jet105.
16. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, 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(4):303–71. https://doi.org/10.1016/j.echo.2017.01.007.
17. Goebel B, Heck R, Hamadanchi A, Otto S, Doenst T, Jung C, et al. Vena contracta area for severity grading in functional and degenerative mitral regurgitation: a transoesophageal 3D colour Doppler analysis in 500 patients. Eur Heart J Cardiovasc Imaging. 2018;19(6):639–46. https://doi.org/10.1093/ehjci/jex056.
18.• Bartko PE, Arfsten H, Heitzinger G, Pavo N, Toma A, Strunk G, et al. A unifying concept for the quantitative assessment of secondary mitral regurgitation. J Am Coll Cardiol. 2019;73(20):2506–17. https://doi.org/10.1016/j.jacc.2019.02.075 **This article provides further insights regarding the evaluation of the severity of mitral regurgitation**.
19.• Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. JACC Cardiovasc Imaging. 2019;12(2):353–62. https://doi.org/10.1016/j.jcmg.2018.11.006 **This article introduces the concept of proportionate and disproportionate functional mitral regurgitation**.
20. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016;37(27):2129–200. https://doi.org/10.1093/eurheartj/ehw128.
21. St John Sutton MG, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation. 2003;107(15):1985–90. https://doi.org/10.1161/01.CIR.0000065226.24159.E9.
22. Kang D-H, Park S-J, Shin S-H, Hong GR, Lee S, Kim MS, et al. Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation. Circulation. 2019;139(11):1354–65. https://doi.org/10.1161/CIRCULATIONAHA.118.037077.
23. van Bommel RJ, Marsan NA, Delgado V, Borleffs CJW, van Rijnsoever EPM, Schalij MJ, et al. Cardiac resynchronization therapy as a therapeutic option in patients with moderate-severe functional mitral regurgitation and high operative risk. Circulation. 2011;124(8):912–9. https://doi.org/10.1161/CIRCULATIONAHA.110.009803.
24. Cipriani M, Lunati M, Landolina M, Proclemer A, Boriani G, Ricci RP, et al. Prognostic implications of mitral regurgitation in patients after cardiac resynchronization therapy. Eur J Heart Fail. 2016;18(8):1060–8. https://doi.org/10.1002/ejhf.569.
25. Onishi T, Onishi T, Marek JJ, Ahmed M, Haberman SC, Oyenuga O, et al. Mechanistic features associated with improvement in mitral regurgitation after cardiac resynchronization therapy and their relation to long-term patient outcome. Circ Heart Fail. 2013;6(4):685–93. https://doi.org/10.1161/CIRCHEARTFAILURE.112.000112.
26. Stolfo D, Tonet E, Barbati G, et al. Acute hemodynamic response to cardiac resynchronization in dilated cardiomyopathy: effect on late mitral regurgitation. Pacing Clin Electrophysiol. 2015;38(11):1287–96. https://doi.org/10.1111/pace.12731.
27. Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. J Am Coll Cardiol. 2005;45(3):381–7. https://doi.org/10.1016/j.jacc.2004.09.073.
28. Mihaljevic T, Lam B-K, Rajeswaran J, Takagaki M, Lauer MS, Gillinov AM, et al. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. J Am Coll Cardiol. 2007;49(22):2191–201. https://doi.org/10.1016/j.jacc.2007.02.043.
29. Panaich SS, Arora S, Badheka A, Kumar V, Maor E, Raphael C, et al. Procedural trends, outcomes, and readmission rates pre-and post-FDA approval for MitraClip from the National Readmission Database (2013-14). Catheter Cardiovasc Interv. 2018;91(6):1171–81. https://doi.org/10.1002/ccd.27366.
30. Mauri L, Foster E, Glower DD, Apruzzese P, Massaro JM, Herrmann HC, et al. 4-year results of a randomized controlled trial

of percutaneous repair versus surgery for mitral regurgitation. J Am Coll Cardiol. 2013;62(4):317–28. https://doi.org/10.1016/j.jacc.2013.04.030.

31. Maisano F, Franzen O, Baldus S, Schäfer U, Hausleiter J, Butter C, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. J Am Coll Cardiol. 2013;62(12):1052–61. https://doi.org/10.1016/j.jacc.2013.02.094.

32.•• Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med. 2018;379(24):2307–18. https://doi.org/10.1056/NEJMoa1806640 **This is an important large randomized trial that showed superior outcomes for Mitraclip compared with medical therapy in patients with functional mitral regurgitation**.

33. Barbanti M, Immè S, Grasso C. Transcatheter mitral valve repair: a brief review. EuroIntervention. 2015;11(Suppl W(W)):W42–4. https://doi.org/10.4244/EIJV11SWA10.

34. Nickenig G, Estevez-Loureiro R, Franzen O, Tamburino C, Vanderheyden M, Lüscher TF, et al. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 pilot European Sentinel Registry. J Am Coll Cardiol. 2014;64(9):875–84. https://doi.org/10.1016/j.jacc.2014.06.1166.

35. Capodanno D, Adamo M, Barbanti M, Giannini C, Laudisa ML, Cannata S, et al. Predictors of clinical outcomes after edge-to-edge percutaneous mitral valve repair. Am Heart J. 2015;170(1):187–95. https://doi.org/10.1016/j.ahj.2015.04.010.

36. Puls M, Lubos E, Boekstegers P, von Bardeleben RS, Ouarrak T, Butter C, et al. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry. Eur Heart J. 2016;37(8):703–12. https://doi.org/10.1093/eurheartj/ehv627.

37. Feldman T, Foster E, Glower D, Kar S. Percutaneous repair or surgery for mitral regurgitation. New Engl J Med. 2011;364(15):2187–98. https://doi.org/10.1056/NEJMoa1011205.

38.•• Obadia J-F, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med. 2018;379(24):2297–306. https://doi.org/10.1056/NEJMoa1805374 **The first large randomized trial comparing MitraClip treatment versus medical therapy in patients with functional mitral regurgitation**.

39. Batchelor W, Starling RC, Stone GW. Secondary mitral regurgitation: is it time for a paradigm shift in treatment? JACC Heart Fail. 2019;7(6):522–6. https://doi.org/10.1016/j.jchf.2019.04.003.

40. Packer M, Grayburn PA. Contrasting effects of pharmacological, procedural and surgical interventions on proportionate and disproportionate functional mitral regurgitation in chronic heart failure. Circulation. 2019;CIRCULATIONAHA.119.039612. https://doi.org/10.1161/CIRCULATIONAHA.119.039612.

41. Senni M, Adamo M, Metra M, Alfieri O, Vahanian A. Treatment of functional mitral regurgitation in chronic heart failure: can we get a "proof of concept" from the MITRA-FR and COAPT trials? Eur J Heart Fail. 2019;2019:ejhf.1491. https://doi.org/10.1002/ejhf.1491.

42. Whitlow PL, Feldman T, Pedersen WR, Lim DS, Kipperman R, Smalling R, et al. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (endovascular valve edge-to-edge repair) high risk study. J Am Coll Cardiol. 2012;59(2):130–9. https://doi.org/10.1016/j.jacc.2011.08.067.

43. Sürder D, Pedrazzini G, Gaemperli O, Biaggi P, Felix C, Rufibach K, et al. Predictors for efficacy of percutaneous mitral valve repair using the MitraClip system: the results of the MitraSwiss registry. Heart. 2013;99(14):1034–40. https://doi.org/10.1136/heartjnl-2012-303105.

44. Stolfo D, De Luca A, Morea G, et al. Predicting device failure after percutaneous repair of functional mitral regurgitation in advanced heart failure: implications for patient selection. Int J Cardiol. 2018;257:182–7. https://doi.org/10.1016/j.ijcard.2018.01.009.

45. Taramasso M, Denti P, Latib A, Guidotti A, Buzzatti N, Pozzoli A, et al. Clinical and anatomical predictors of MitraClip therapy failure for functional mitral regurgitation: single central clip strategy in asymmetric tethering. Int J Cardiol. 2015;186:286–8. https://doi.org/10.1016/j.ijcard.2015.03.236.

46. De Luca A, Stolfo D, Korcova R, et al. Prognostic value of global longitudinal strain-based left ventricular contractile reserve in candidates for percutaneous correction of functional mitral regurgitation: implications for patient selection. J Am Soc Echocardiogr. in press.

47. Merlo M, Pyxaras SA, Pinamonti B, Barbati G, Di Lenarda A, Sinagra G. Prevalence and prognostic significance of left ventricular reverse remodeling in dilated cardiomyopathy receiving tailored medical treatment. J Am Coll Cardiol. 2011;57(13):1468–76. https://doi.org/10.1016/j.jacc.2010.11.030.

48. Pleger ST, Schulz-Schönhagen M, Geis N, Mereles D, Chorianopoulos E, Antaredja M, et al. One year clinical efficacy and reverse cardiac remodelling in patients with severe mitral regurgitation and reduced ejection fraction after MitraClip implantation. Eur J Heart Fail. 2013;15(8):919–27. https://doi.org/10.1093/eurjhf/hft046.

49. Taramasso M, Maisano F, Latib A, Denti P, Buzzatti N, Cioni M, et al. Clinical outcomes of MitraClip for the treatment of functional mitral regurgitation. EuroIntervention. 2014;10(6):746–52. https://doi.org/10.4244/EIJV10I6A128.

50. Berardini A, Biagini E, Saia F, Stolfo D, Previtali M, Grigioni F, et al. Percutaneous mitral valve repair: the last chance for symptoms improvement in advanced refractory chronic heart failure? Int J Cardiol. 2017;228:191–7. https://doi.org/10.1016/j.ijcard.2016.11.241.

51. Grayburn PA, Foster E, Sangli C, Weissman NJ, Massaro J, Glower DG, et al. Relationship between the magnitude of reduction in mitral regurgitation severity and left ventricular and left atrial reverse remodeling after MitraClip therapy. Circulation. 2013;128(15):1667–74. https://doi.org/10.1161/CIRCULATIONAHA.112.001039.

52. Adamo M, Godino C, Giannini C, Scotti A, Liga R, Curello S, et al. Left ventricular reverse remodelling predicts long-term outcomes in patients with functional mitral regurgitation undergoing MitraClip therapy: results from a multicentre registry. Eur J Heart Fail. 2019;21(2):196–204. https://doi.org/10.1002/ejhf.1343.

53. Bail DHL. Treatment of functional mitral regurgitation by percutaneous annuloplasty using the Carillon Mitral Contour System-currently available data state. J Interv Cardiol. 2017;30(2):156–62. https://doi.org/10.1111/joic.12370.

54. Nickenig G, Schueler R, Dager A, Martinez Clark P, Abizaid A, Siminiak T, et al. Treatment of chronic functional mitral valve regurgitation with a percutaneous annuloplasty system. J Am Coll Cardiol. 2016;67(25):2927–36. https://doi.org/10.1016/j.jacc.2016.03.591.

55. Seferovic PM, Ponikowski P, Anker SD, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019;2019:ejhf.1531. https://doi.org/10.1002/ejhf.1531.

56. Sinagra G, Fabris E, Tavazzi L. The evolution of cardiology: changes, future challenges and opportunities. Futur Cardiol. 2017;13(2):161–71. https://doi.org/10.2217/fca-2016-0050.
57. Chambers JB, Lloyd G, Rimington HM, et al. The case for a specialist multidisciplinary valve clinic. J Heart Valve Dis. 2012;21(1):1–4 http://www.ncbi.nlm.nih.gov/pubmed/22474734. Accessed July 5, 2019.
58. Holmes DR, Rich JB, Zoghbi WA, Mack MJ. The heart team of cardiovascular care. J Am Coll Cardiol. 2013;61(9):903–7. https://doi.org/10.1016/j.jacc.2012.08.1034.