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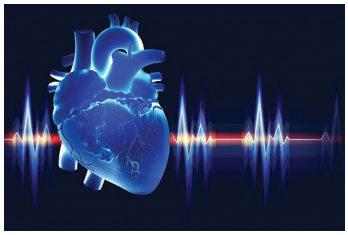
(MSc in Heart Failure - Cardio-oncology - Cardiac Rehabilitation)



Μεταπτυχιακή Διπλωματική Εργασία

«Η θέση του MitraClip σε ασθενείς με χρόνια Καρδιακή Ανεπάρκεια»

υπό

Ταβουλάρη Δημητρίου

Ιατρός

Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διπλώματος Μεταπτυχιακών Σπουδών

«Καρδιακή ανεπάρκεια – Καρδιο-ογκολογία – Καρδιαγγειακή αποκατάσταση»

Λάρισα, Ιανουάριος 2024

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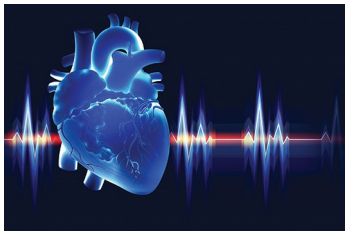

The role of MitraClip in patients with chronic Heart Failure

«Βεβαιώνω ότι η παρούσα διπλωματική εργασία είναι αποτέλεσμα δικής μου δουλειάς και δεν αποτελεί προϊόν αντιγραφής. Στις δημοσιευμένες ή μη δημοσιευμένες πηγές έχω χρησιμοποιήσει εισαγωγικά και όπου απαιτείται έχω παραθέσει τις πηγές τους στο τμήμα της βιβλιογραφίας».

Υπογραφή:

ΤΑΒΟΥΛΑΡΗΣ ΔΗΜΗΤΡΙΟΣ

Πανεπιστήμιο Θεσσαλίας, Σχολή Επιστημών Υγείας, Τμήμα Ιατρικής, 2024

ΔΙΕΥΘΥΝΤΗΣ ΤΟΥ ΠΡΟΓΡΑΜΜΑΤΟΣ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

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2. Ανυφαντάκης Ζαχαρίας Αλέξανδρος, Επιμελητής Α' Καρδιολογίας, Πανεπιστημιακό Νοσοκομείο Λάρισας
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Τσαρούχας Κωνσταντίνος, Επιμελητής Α' Καρδιολογίας, Πανεπιστημιακό Νοσοκομείο Λάρισας

Τίτλος εργασίας στα αγγλικά: The role of MitraClip in patients with chronic Heart Failure

Ευχαριστίες

Αρχικά θα ήθελα να εκφράσω την ευγνωμοσύνη μου στον Καθηγητή κ. Αθανασίου Αθανάσιο που διενήργησε ως Επιβλέπων Καθηγητής στην εκπόνηση της παρούσας διπλωματικής εργασίας. Η καθοδήγησή του υπήρξε καθοριστική κατά την διάρκεια της συγγραφής της, ενώ χωρίς τα επικοδομητικά του σχόλια και τον χρόνο που αφιέρωσε δεν θα ήταν εφικτή η ολοκλήρωσή της.

Επίσης ο ρόλος του κ. Ανυφαντάκη ως συμβούλου αποτέλεσε καταλυτικό παράγοντα με την πολύτιμη βοήθειά του στην περάτωση της εργασίας.

Θα ήταν παράλειψή μου να μην ευχαριστήσω την Καρδιολογική Κλινική του Πανεπιστημιακού Γενικού Νοσοκομείου Λάρισας, μαζί με τον Διευθυντή κ. Σκουλαρίγκη Ιωάννη, τον καθηγητή κ. Τρυποσκιάδη Φίλιππο, τον καθηγητή κ. Γιαμούζη Γρηγόριο, τον κ. Ξανθοπόπουλο Ανδρέα, καθώς και τον κ. Παπαμιχάλη Μιχαήλ οι οποίοι κατά την διάρκεια των φοιτητικών μου χρόνων, με έφεραν σε επαφή με το αντικείμενο της Καρδιολογίας και η συνεργασία μου μαζί τους μου επέτρεψε να διευρύνω τους ορίζοντές μου.

Ένα θερμό ευχαριστώ στην κ. Σίμου Ανθή, γραμματεία της Καρδιολογικής Κλινικής και του Μεταπτυχιακού Προγράμματος Σπουδών για την συνεχή αρωγή της.

Κλείνοντας, ευχαριστώ την οικογένειά μου και την Κατερίνα, χωρίς την υποστήριξη και την υπομονή των οποίων, δεν θα ήταν εφικτή η ολοκλήρωση αυτής της εργασίας.

Ταβουλάρης Δημήτριος

Περίληψη

Η Καρδιακή Ανεπάρκεια είναι ένα κλινικό σύνδρομο το οποίο επηρεάζει περισσότερους από 64 εκατομμύρια ανθρώπους παγκοσμίως, έχοντας μεγάλο αρνητικό αντίκτυπο στην επιβίωσή τους, την ποίοτητα ζωής τους και το υγειονομικό κόστος. Οι βαλβιδοπάθειες αποτελούν μία αρκετά συχνή αιτιολογία της Καρδιακής Ανεπάρκειας, με κυριότερη αιτία την μυξωματώδη εκφύλιση της μιτροειδούς βαλβίδας, η επίπτωση της οποίας αυξάνεται με την ηλικία. Αυτή η σχέση δύναται και να αναστραφεί, καθώς οι μισοί περίπου ασθενείς με Καρδιακή Ανεπάρκεια αναπτύσσουν βαλβιδική νόσο, με την μορφή της ανεπάρκειας μιτροειδούς. Η ανεπάρκεια της μιτροειδούς βαλβίδας ταξινομείται περαιτέρω βάσει αιτιολογίας σε πρωτοπαθή και δευτεροπαθή. Ανεξαρτήτως όμως αιτιολογίας, η παρουσία μετρίου ή σοβαρού βαθμού ανεπάρκειας μιτροειδούς σχετίζεται με φτωχή πρόγνωση, αυξάνοντας τη συννοσηρότητα και τη θνησιμότητα. Ακόμη και η παρουσία ηπίου βαθμού δευτεροπαθούς ανεπάρκειας μιτροειδούς προμηνύει αρνητική έκβαση. Το MitraClip αποτελεί μία διαδερμική, διακαθετηριακή μέθοδο επιδιόρθωσης της μιτροειδούς βαλβίδας, εμπνευσμένη από την double orifice technique. Η αποτελεσματικότητά της είναι ήδη αποδεδειγμένη σε ανεγχείρητους ασθενείς με πρωτοπαθή Ανεπάρκεια Μιτροειδούς, καθώς αποτρέπει την μόνιμη δυσλειτουργία της αριστερής κοιλίας ή αναστέλλει την επιδείνωση της ήδη εγκατεστημένης Καρδιακής Ανεπάρκειας. Αντιθέτως, ο ρόλος του MitraClip σε ασθενείς με χρόνια Καρδιακή Ανεπάρκεια και επακόλουθη δευτεροπαθή Ανεπάρκεια Μιτροειδούς, οι οποίοι δύνανται να προσκομίσουν ευεργετικό αποτέλεσμα, παραμένει αμφιλεγόμενος. Αυτό οφείλεται στα αντιφατικά αποτελέσματα των μέχρι τωρα δημοσιοποιημένων τυχαιοποιημένων κλινικών μελέτων.

Λέξεις - κλειδιά: MitraClip, Καρδιακή Ανεπάρκεια, Πρωτοπαθής Ανεπάρκεια Μιτροειδούς, Δευτεροπαθής Ανεπάρκεια Μιτροειδούς, Transcatheter Edge-to-Edge Repair

Abstract

Heart Failure is a clinical syndrome affecting more than 64 million persons globally, imposing a great burden on patients' survival, quality of life, functional capacity and healthcare costs. Valvular Heart Disease constitutes a fairly common aetiology of Heart Failure, with the prevailing culprit being myxomatous degeneration of the Mitral valve, whose prevalence increases with age. This relationship can also be inverted, since approximately half of Heart Failure patients develop Mitral valve disease, in the form of Mitral valve Regurgitation. Mitral valve regurgitation can be further classified according to aetiology into Primary and Secondary. Irrespective of aetiology the presence of moderate or severe Mitral Regurgitation confers a poor prognosis, increasing morbidity and mortality. Even the presence of mild secondary Mitral Regurgitation portends a poor prognosis. The MitraClip system is a percutaneous transcatheter Mitral valve repair approach, modelled after the double orifice technique. Its efficacy has been proven in inoperable patients with Primary Mitral Regurgitation preventing permanent Left Ventricle dysfunction and Heart Failure deterioration. However, the role of MitraClip in patients with chronic Heart Failure and subsequent secondary Mitral Regurgitation, in whom it may prove beneficial, remains controversial, due to the conflicting results of the so far published randomized controlled trials.

Key words: MitraClip, Heart Failure, Primary Mitral Regurgitation, Secondary Mitral Regurgitation, Transcatheter Edge-to-Edge Repair

Table of contents

Introduction

Heart Failure (HF) is defined as a clinical syndrome with signs and/or symptoms caused by a functional and/or structural cardiac abnormality and further corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion.**[1]** It is a multi-faceted syndrome with prevalence rates between 1% and 3% of the general adult population in developed countries, accompanied by significant mortality at 1 and 5 years, being 15%-30% and 50%-75% respectively. The prevalence is expected to increase due to population ageing, better diagnostic tools and more effective life-prolonging treatment in HF patients. Valvular Heart Disease (VHD) constitutes the primary aetiology in 8% to 11% in this population. Meanwhile, 21% of HF with reduced ejection fraction (HFrEF) and HF with mildly reduced ejection fraction (HFmrEF) and 28% of HF with preserved ejection fraction (HFpEF) patients are burdened by VHD.**[2]**

Valve disease (VD) affected 2.5% of the US 2000 population, with mitral regurgitation (MR) being the prevailing cause, with a prevalence of 1.7%. The frequency of MR increases with advancing age (0.5%-1.0% at 18-64 years, 6.4% at 65-74 years and 9.3% at ≥ 75 years).**[3]** Meanwhile, MR is the second most common VD in Europe, following aortic stenosis.**[4]** The clinical course of VD is not always benign, since affected patients present a higher adjusted mortality risk ratio than the general population.**[3]** MR being a relatively common cause of HF, aside from increased morbidity and mortality, leads to deterioration of functional capacity (FC), quality of life (QoL) and increased healthcare costs.**[2]** Furthermore, a significant percentage of patients is denied surgical intervention, due to high surgical risk **[4]** or unproven survival benefit in secondary MR (SMR), accompanied by significant perioperative risk and high rates of recurrent regurgitation.**[5]** Thus, a transcatheter edge-to-edge repair (TEER) was developed **[6]**, mimicking the Alfieri technique **[7]**, the MitraClip system (fig.1), as an alternative treatment to patients with high surgical risk or contraindications. It's efficacy and safety has been proven in primary MR (PMR) in the EVEREST II clinical trial**[9]**, whereas in SMR the data remain conflicting due to discordant results of the two published clinical trials MITRA-FR**[10]** and COAPT.**[11]**

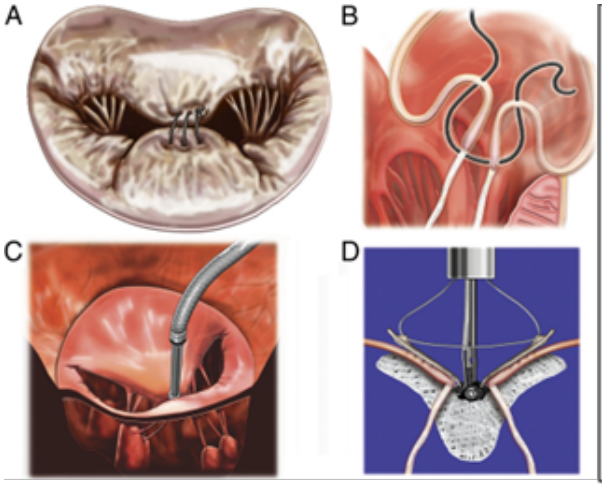

Figure 1: Surgical Edge-to-Edge Technique Versus MitraClip; A) Double orifice technique. B) The sutures engage the free edge of the facing leaflets. C) The MitraClip is implanted in the A2-P2 region, similarly to the surgical technique. D)The free edges of the leaflets are engaged between the clip arms and the grippers. Ref.[8]

Pathophysiology

The mitral valve (MV), anatomically, consists of the mitral annulus (MA), a saddle-shaped structure interconnecting the left atrium (LA) and the left ventricle (LV), the anterior and posterior leaflets, the LV wall, from which the anterolateral and posteromedial papillary muscles (PM) protrude, and the chordae tendineae.**[12]** The anterior leaflet is trapezoidal shaped, occupying 1/3 of the MA, while the narrower posterior leaflet, crescent-shaped, has a scalloped appearance, occupying the remainder 2/3 of the MA.**[13]** The scallops divided by clefts are labelled as P1, P2 and P3 starting from lateral to medial, and correspond to the A1, A2 and A3 portions of the anterior leaflet, despite the latter being anatomically undivided.**[13,14]** The chordae tendineae originate from the PM heads, insert into both leaflets, and are characterized as primary and secondary, depending on the site of their attachment, the leaflet free edge or ventricular surface respectively.**[12,13]** Tertiary chordae arise from the LV wall or it's trabeculations and insert only into the posterior leaflet.**[14]** The anatomic integrity of the valve apparatus is vital to its function, enabling unimpeded blood flow into the LV during diastole, proper leaflet coaptation in prevention of retrograde flow during systole and the formation of the left ventricular outflow tract (LVOT).**[13]** During the cardiac cycle the MV is not a passive bystander**[15]**, but a complex interplay of its components is required to prevent mitral prolapse or systolic anterior motion (SAM), by keeping the leaflets inside the LV and beneath LVOT.**[12]** During LV systole, the MA contracts, reducing its area, facilitating leaflet coaptation and reducing stress**[16].** Meanwhile the

PM-chordal apparatus provides constant circumferential support to the MV, evening out the stress distribution, preventing prolapse.**[13]** The latter is achieved owing to the location of origin of the PM, the apical and middle thirds of the LV, allowing them to exert a vertical force through the chordae tendineae, ensuring proper leaflet coaptation during systole, despite the imposed LV end-systolic (LVES) pressure.**[17]**

Imbalance of systolic leaflet tethering and LV contractile closing forces or impaired leaflet size leads to improper apposition of the leaflets and consequently MR.**[18]** Thus, there is retrograde blood flow [regurgitant volume (RVol)] into the LA, through a regurgitant lesion [effective regurgitant orifice (ERO)], driven by the transvalvular pressure gradient between the LV and LA. RVol flows back into the LV, the following diastolic period of the cardiac cycle, causing volume overload of both LA and LV.**[19]** MR can be classified according to aetiology into PMR, resulting from an intrinsic disease of the MV**[20]**, and into SMR or functional MR (FMR), due to alterations in a structurally normal valvular apparatus secondary to LV or LA disease.**[21]** Irrespective of the aetiologic classification, MR can be further classified based on functionality, with the Carpentier classification: type I is characterized by normal leaflet motion, accompanied by dilated MA or leaflet perforation, type II by excessive leaflet motion and type III by systolic and diastolic restricted leaflet motion (type IIIa) or systolic (type IIIb).**[22]**

Primary Mitral Regurgitation

The prevailing aetiology of PMR in developed countries is mitral valve prolapse (MVP) (Carpentier type II), due to myxomatous degeneration (DMR)**[4,23]**, affecting 2.4% of the general population.**[24]** MVP is defined as systolic superior displacement of one or both leaflets and one or multiple scallops, into the LA ≥ 2mm.**[24,25]** Primary MVP has been associated with two main phenotypes, Barlow's disease and fibroelastic deficiency (FED). Barlow's disease or diffuse myxomatous degeneration (DMD) presents with thickening of both leaflets, which are redundant with excessive tissue, MA dilation and thickened elongated chordae tendineae.**[26]** Patients affected are usually at their fifth decade of life. FED typically presents with a prolapsed or flail posterior

segment (usually P2), which is thickened and redundant, whereas the rest of the MV is thin and almost lucid.**[25]** The thin, friable chords, in many cases lead to their rupture and consequently a flail leaflet. Patients affected are usually at their sixth to seventh decade of life.**[26]** In DMR early systolic anteroposterior contraction of the MA is attenuated, resulting in a decreased saddle shape accentuation and thus larger mitral annulus area in end-systole, further inhibiting proper leaflet coaptation. This phenomenon is more profound in Barlow's disease than in FED.**[25]** MVP can, rarely, be secondary to connective tissue diseases such as Marfan or Ehlers Danlos syndrome type IV or Osteogenesis Imperfecta.**[23]**

Other causes of PMR, based on functional classification, are leaflet perforation and cleft leaflets (Carpentier type I). Rheumatic heart disease (RHD), mitral annulus calcification (MAC), radiation induced, drug induced, inflammatory diseases and connective tissue disorders are classified as Carpentier type IIIa. RHD is the leading cause of PMR in developing countries.**[23,27]** MAC is a degenerative process of the MA with a prevalence of 8-15%. It is independently associated with age, and accumulating evidence support the association with CKD and common pathogenesis with atherosclerosis. This process seems to further deteriorate with comorbidities that increase MV stress. Furthermore, MAC is related to higher risk of cardiovascular (CV) disease, MV disease, arrhythmias and worse surgical and transcatheter intervention outcomes.**[28]** According to the Euro Heart Survey on Valvular Heart Disease in 3.5% of patients with MR the primary aetiology was infective endocarditis (IE).**[4]** IE or trauma, causing flail leaflet, and myocardial infarction (MI), causing PM rupture, present as acute severe MR accompanied with high mortality, requiring emergency surgery.**[26]**

In acute severe MR, there is acute volume overload. The normal size and compliance of LA**[19]** and LV**[29]** lead to increased peak systolic wall stress, compared to chronic volume overload.**[30]** The retrograde flow to the low pressure LA, leads to an increase in LA pressure, which is transmitted to the pulmonary circulation, causing pulmonary venous hypertension (PH) and congestion. Another contributor to this phenomenon is the preload-dependent increase in LV stiffness.**[19,29,30]**

If the onset of MR is not as sudden, cardiac output and forward stroke volume is maintained. At this stage, the main compensatory mechanisms are the increased myocardial contractility, due to favourable loading conditions (via the Frank-Starling mechanism), and the decreased afterload, due to the regurgitant flow to the low impedance LA.**[26,29]** As the disease progresses the chronic compensated state begins. The chronic volume overload and increased end-diastolic wall stress lead to LV chamber remodelling and enlargement. Myocardial elongation, addition of new sarcomeres in series and concomitant remodelling of the extramyocardial matrix, allowing for slippage of myocardial cells, gradually enable eccentric hypertrophy.**[30]** End-systolic wall stress is normal. This increase in end-diastolic volume, results in increased total stroke volume and normal or increased EF.**[29]** LA remodelling is, also, observed, with increased LA compliance and volume, maintaining normal on near normal LA pressure.**[31]**

In MVP the degree of MR increases over time, although the progression varies. Due to the eccentric hypertrophy of the LV, the PM are displaced, tethering the MV leaflets. Thus, MR degree exacerbates depending on the progression of the lesions or of the MA dilation. This disease progression further aggravates LV and LA dilation and remodelling.**[32-34]**

This vicious cycle, gradually, signals the transition to the chronic decompensated stage of MR. LV dilates further, becoming unable to compensate, due to decreased contractile function. Continued spherical mid to apical LV remodelling leads to higher LV end-systolic volume and higher afterload.**[35]** All these factors contribute to progressive LV systolic dysfunction. This detrimental transition to irreversible LV dysfunction may be insidious, because favourable loading conditions preserve the EF within normal range.**[31]** The onset of symptoms may be further delayed due to sedentary lifestyle.**[36]** Patients with irreversible LV dysfunction and HF have a worse survival and surgical prognosis. This is the reason that ESC and ACC/AHA guidelines recommend surgical repair in asymptomatic patients with LVEF $\leq$ 60% and/or LV end-systolic dimension (LVESD) $\geq$ 40mm.**[5,37]**

Prognosis

Chronic MR has a variable clinical course. Presence of severe MR, in medically managed, patients is associated with 6.3% yearly mortality, compared to expected rates, whereas presence of moderate MR, is associated with about 3% of yearly mortality rates in the same population.**[38,39]** Meanwhile, mild MR had similar 5-year survival to the general population. The majority of patients (84%) with severe MR, defined as ERO area $\geq 40mm^2$, were dead or required late surgery at five years. Thus, surgery seems to be unavoidable.**[40]** Surgical intervention is the only treatment that reduces mortality and prevents HF.**[39]** Primary independent predictors of death, CV morbidity and MVP related events (HF, mitral surgery, endocarditis and death related to MVP) are the presence of moderate to severe degree of MR and EF <50%. Slight MR, Flail leaflet, age >50 years, atrial fibrillation (AF) and LA diameter ≥40mm constitute secondary risk factors, associated with CV morbidity.**[38,41]** The presence of symptoms predicts worse prognosis depending on severity. NYHA III and IV patients had 34% yearly mortality, while NYHA I and II patients had 4.1%.**[38]** Sudden death is commensurate to the severity of symptoms in medically managed MR, due to flail leaflet, with prevalence being 1%-7.8% (NYHA I to NYHAIII and IV). Higher incidence is observed in patients with AF and reduced systolic function.**[42]** Baseline RSVP >35mmHg confers worse prognosis in severe MR.**[43]**

Secondary Mitral Regurgitation

Approximately, a little over half (56.2%) of HF patients are burdened with FMR. Moderate or higher MR grade is present in 29.8% of FMR patients.**[44]** FMR is secondary to LV disease, due to local or global LV remodelling.**[21]** The primary aetiology for LV remodelling can either be ischemic cardiomyopathy (ICM) (Carpentier type IIIb) or non-ischemic dilated cardiomyopathy (DCM) (Carpentier type I).**[45]** LV presents a significant increment in both volume and sphericity index. These alterations along with global LV dysfunction are more pronounced in DCM versus ICM.**[46]** Mechanistical corollaries, secondary to LV remodelling contributing to FMR are

various degrees of PM displacement, MA dilation and flattening and LV dysfunction.**[47]**

PM displacement, results in MV leaflet tethering and MV tenting. Leaflet tenting inhibits normal coaptation during systole, allowing for apposition limited to leaflet tips.**[48]** In DCM, due to increased sphericity, there is a symmetrical PM displacement with increased interpapillary distance, leading to a single, predominant, central MR jet. Contrary, in ICM, regional wall motion abnormalities confer an asymmetrical PM displacement, leading to an eccentric posterior MR jet.**[46,48]** ICM following inferior myocardial infarction (MI) has a higher incidence of FMR burden, than an anterior MI, despite milder grades of LV remodelling and dysfunction. This is attributable to more substantial posteromedial PM displacement, resulting in greater tethering distance and thus MV tenting.**[49]** Alongside MV tenting, MA loss of contraction is the second major determinant of MR degree.**[50]** The latter is in part due to MA dilation and flattening, rendering it inefficient in reducing MV stress, during systole.**[45,51]** LV systolic dysfunction and consequently reduced closing forces antagonistic to leaflet tethering, is exacerbating FMR further.**[45]**

Another potential primary cause of FMR is Left Bundle Branch Block (LBBB), since in about one third of patients with CRT implantation, MR was significantly reduced from moderate or severe to non-significant.**[52]** The inducing mechanisms are the dyssynchrony of PM and LV contraction and further LV remodelling. LBBB impairs the normally earlier PM contraction to the LV, ensuring proper MV leaflet apposition to prevent regurgitation.**[17]** Simultaneously, the early systolic transvalvular pressure gradient is reduced, secondary to LBBB derived LV remodelling, further exacerbating FMR as described above.**[52,53]**

Increased imposed tethering stress on MV leaflets can lead them to adaptation through cellular changes and mesenchymal differentiation.**[54]** MV leaflet area and thickness is increased compared to healthy hearts, while leaflet coaptation is reduced. Leaflet adaptation is similar, independent of aetiology and global or local remodelling.**[55]** Higher degrees of FMR were associated with lower leaflet to annular ratio, despite non-significant differences in leaflet area increment. Consequently, more severe FMR is present in patients with insufficient leaflet adaptation to stress, due to PM tethering and LV alterations.**[56]**

Another phenotype of FMR, atrial FMR (Carpentier type I), can be distinguished secondary to longstanding persistent AF causing LA enlargement. LA dilation in FMR patients, contrary to MVP, has been associated with MA dilation. Thus, FMR is caused due to increased MA dilation and flattening, secondary to LA dilation derived from chronic persistent AF.**[57,58]** Figure 2 summarizes all possible mechanisms of SMR.

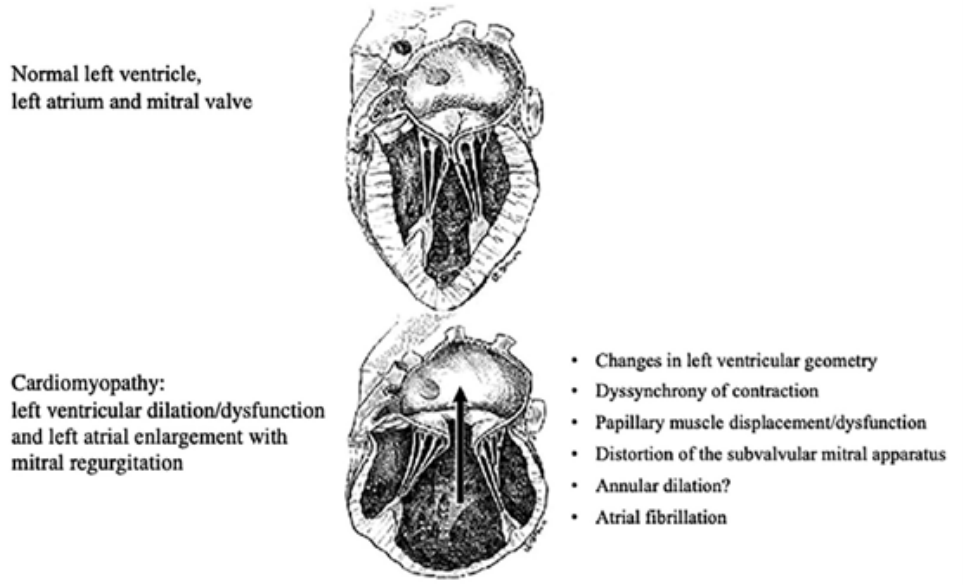

Figure 2: Mechanisms of SMR in ischemic and non-ischemic cardiomyopathy, Ref. [59]

Prognosis

FMR's contributing role to HF prognosis has been debated with various studies providing conflicting results. It is unclear whether FMR has a more active, potentially treatable role in the clinical course of the disease, due to chronic volume overload, or whether it constitutes a severity assessment marker of LV dysfunction.**[60]** Prevalence of severe FMR increases with worsening LV function. Patients burdened by baseline severe grade FMR have a worse long-term prognosis with reduced survival and increased major adverse cardiovascular events (MACE) [defined as CV death, HF hospitalizations (HFH) and HF heart transplant (HTx)].**[60-62]** Even the presence of mild grade FMR portends a worse prognosis.**[62]** Goliasch et al. identified a potentially interventionally treatable phenotype. Severe FMR patients with NYHA class II-III, moderate LV dysfunction and NT-proBNP (between 871 and 2360pg/mL) displayed a

worse outcome.**[61]** Another study showed that follow-up assessment of MR severity might have a more impactful predictive role. At follow-up patients with unchanged severe FMR, or deterioration to severe FMR, despite guideline-directed medical therapy (GDMT) were at higher risk for death and MACE (defined as a composite of all-cause death, HF Htx, HFH or malignant arrythmias). Moreover, they presented worse long-term adverse cardiac remodelling. In contrast, longstanding sustained non-severe FMR or improvement from severe to non-severe, was associated with better outcomes and attenuation of LV remodelling progression, suggesting FMR's active contribution. FMR was improved in 40% of patients on GDMT, properly titrated diuresis and salt and fluid restriction intake.**[63]**

There was not a significant mortality association with severe grade FMR in NYHA class IV patients with larger sized LVs, larger sized LAs, severe tricuspid regurgitation (TR) and LVEF ≤30%.**[61,62]** This observation can, probably, be attributed to declining severe FMR significance compared to extensive LV impairment.**[62]**

LBBB presence was significantly associated with decreased responsiveness to GDMT, whereas CRT implantation has been shown to significantly reduce FMR grade in one third of patients.**[52]**

The prevalence of atrial FMR is 4-8%, increasing up to 28% in patients with longstanding AF of over 10 years. Patients have been shown to have a worse prognosis, when they are burdened with concomitant atria functional TR. Due to population ageing, the prevalence will presumably rise, potentially creating a major health problem. There is an absence of specific treatment strategies studied.**[57]**

Imaging – Diagnosis and Severity Assessment

Transthoracic Echocardiography (TTE) is the first-line imaging technique used in diagnosis and assessment of MR. In case of MR detection by TTE, a cascade of multiple echocardiographic parameters is used in order to elucidate MV anatomy, MR aetiology, mechanism and severity. An integration of multiple qualitative, semi-quantitative and quantitative Doppler echocardiographic parameters is necessary, since every single one has specific limitations and probability of correct MR assessment

increases when there is concordance between them. Aetiology and mechanism of MR should not be considered identical, because a single cause may induce MR by different mechanisms. The distinction between PMR and SMR should always be made clear. PMR, most commonly caused by MVP can be diagnosed at the parasternal long-axis window as a systolic displacement of the mitral leaflets into the LA of at least 2mm. Conversely, in SMR, MV leaflet malcoaptation, tethering and restricted mobility, due to PMs outward displacement, along with MA dilation are observed. When the detected degree of MR is greater than mild, a quantitative estimation of MR should be attempted. During assessment of chronic MR, a variety of hemodynamic factors should be taken into consideration, that lead to false estimation of MR severity, thus impacting therapeutic approach. MR is dynamic in nature and there is a temporal variation of ERO during systole. Consequently, timing of regurgitation should be assessed when estimating MR grade. MR severity is further dependent on loading conditions. Blood pressure should always be measured, during MR grade assessment, since a decrement in loading conditions or contractility translates into underestimation of MR severity. Moreover, variable cardiac cycle lengths or rapid ventricular response in patients with AF may impair proper MR grading. Lastly, in atrioventricular conduction abnormalities with a prolonged PR interval, LA systolic contraction leads to ineffective valve coaptation and consequently into diastolic MR fluctuation.

The first Doppler method of MR grade evaluation is Colour Flow Doppler, which consists of the regurgitant jet area, the Vena contracta (VC) and the flow convergence parameters. Jet area is a first-line Doppler parameter for MR screening. However, it is less reliable for MR grading due to being dependent on MR jet orientation, with MR underestimation in eccentric jets and MR overestimation in SMR, where the regurgitant orifice geometry is usually elliptical. VC is the calculated jet area, leaving the regurgitant orifice, thus an index of ERO area (EROA). It is a semi-quantitative Doppler parameter, able to be calculated both at central and eccentric jets, with values <3mm indicating mild MR and >7mm indicating severe MR. The values in-between should not be used for MR assessment and a different method should be preferred. A significant limitation regarding this method is the presence of multiple jets and a non-circular orifice geometry, such as the often-observed elliptical regurgitant orifice in SMR, leading to MR severity underestimation. The flow convergence method is used both qualitatively and quantitatively, with its accuracy being more reliable in isolated central

MR jets and circular orifices than the opposite. Qualitatively, a large flow convergence indicates the presence of severe MR, whereas quantitatively it is used for the measurement of the proximal isovelocity surface area (PISA) radius. PISA radius is used to calculate EROA and RVol. The temporal ERO variations in MR may lead to errors in PISA calculation. Its calculation is based on a circular orifice assumption, thus it may possibly underestimate MR severity in SMR. Furthermore, PISA is calculated instantaneously, decreasing its reliability in non-holosystolic MR patients, with MR grade overestimation in late-systolic PMR and underestimation in biphasic FMR. RVol is the preferred MR grading assessment parameter in these patients. In case multiple MR jets are present, PISA should be applied to all of them.

Another echocardiographic parameter is the Continuous Wave Doppler (CWD). Measured MR velocity provides useful information for the hemodynamic status of the patient, with low MR peak velocity ~4m/s being indicative of hemodynamic compromise, such as low blood pressure or increased LA pressure. The contour and density signal of CWD are qualitative parameters of MR severity. Further assessment of the hemodynamic status is feasible with the TR jet assessment and pulmonary arterial systolic pressure (PASP) estimation.

The Pulsed Doppler method may be used to determine stroke volume at the LVOT and MV to further calculate RVol and regurgitant fraction (RF). LV volumes may be underestimated with the use of 2D echocardiographic techniques, thus 3D echocardiographic methods may be used or ultrasound contrast for more accurate LV endocardial border identification. Evaluation of LV diastolic function is also useful in MR. E-wave of mitral inflow is usually increased due to dominant early filling in severe MR. However, mitral inflow in SMR is less reliable, since E-wave dominance could also be attributed to elevated filling pressures. The presence of RHD or MAC may impact E-wave velocity. Instead, LA contraction (A-wave) dominance should exclude severe MR. These parameters are more reliable patients with impaired myocardial relaxation or older than 50 years of age. Moreover, the identification of systolic flow reversal in more than one pulmonary vein, is characteristic of severe grade MR. A blunted pulmonary vein flow pattern may be present in concomitant AF or increased LA pressure, possibly diminishing its value in FMR. Operators should measure pulmonary venous flow pattern in more than one vein and be able to differentiate it from MR jet contamination.

LV and LA volumes and function should be estimated at baseline, in to order to plan the therapeutic approach and evaluate the outcome. Longstanding severe MR almost certainly contributes to LA and LV enlargement, thus the presence of normal range values should question the diagnosis. Exercise testing may be helpful in patients with a sedentary lifestyle or equivocal clinical findings. Failure to increase LVEF, EROA increment ≥13mm ^{2} or PA pressure elevation ≥60mmHg during exercise, have been associated with adverse outcomes.

In case MR severity assessment with TTE is inconclusive transoesophageal echocardiography (TEE) is used, since it portraits more accurately the underlying mechanism, aetiology and severity of MR. However, during TEE, reduced loading conditions, due to sedation, should be taken into account for MR grading, along with a possible underestimation of systolic output. TEE is further, used in assessing eligibility and planning surgical or interventional therapeutic approach. CMR is an alternative imaging method, in case echocardiographic data are inadequate or discrepancies exist in comparison to patient's symptoms.**[64,65]** According to the ESC/EACTS guidelines the echocardiographic criteria determining the presence of severe MR (table 1), are identical in both PMR and SMR.**[5]** Concordance, also, exists between the ESC/EACTS and ACC/AHA guidelines regarding the criteria defining severe MR.**[5,37]**

Table 1[5]	PMR	SMR
Qualitative		
MV morphology	Flail leaflet, ruptured papillary muscle, severe retraction, large perforation	Normal leaflets but with severe tenting, poor leaflet coaptation
Colour Flow jet area	Large central jet (>50% of LA) or eccentric wall impinging jet of variable size	Large central jet (>50% of LA) or eccentric wall impinging jet of variable size
Flow convergence	Large throughout systole	Large throughout systole
CWD jet	Holosystolic/dense/triangular	Holosystolic/dense/triangular
Semi-quantitative		
VC width (mm)	≥7 (≥8 mm for biplane)	≥7 (≥8 mm for biplane)
Pulmonary Vein Flow	Systolic flow reversal	Systolic flow reversal
Mitral Inflow	E-wave dominant (>1.2 m/s)	E-wave dominant (>1.2 m/s)
TVI mitral/TVI aortic	>1.4	>1.4
Quantitative		
EROA (mm^2)	≥40 mm2	≥40 mm2 (may be ≥30 mm2 if elliptical regurgitant orifice area)
RVol (ml/beat)	≥60 mL	≥60 mL (may be ≥45 mL if low flow conditions)
RF (%)	≥50%	≥50%
Structural		
LV	Dilated (ESD ≥40 mm)	Dilated
LA	Dilated (diameter ≥55 mm or volume≥60 mL/m2)	Dilated

MitraClip Procedure and Optimal MV Morphology

The MitraClip device is a percutaneous transcatheter MV repair approach, modelled after the Alfieri Edge-to-Edge technique.[**7]** The MitraClip is an implant mounted on a clip delivery system (CDS). It consists of 2 arms. Each arm's length and width is 9mm and 4mm respectively, whereas on the inner portion of the device, the presence of two

adjacent grippers ensures proper leaflet capture during arm closure. The implant is made out of cobalt/chromium and it is further covered by a polyester fabric, enhancing tissue healing. Opening and closure of the MitraClip arms is adjusted by the CDS handle. Patients undergo the procedure under general anaesthesia. TEE and fluoroscopic guidance, during the procedure, are key for proper clip positioning and efficacy. Firstly, transeptal puncture is performed, via a femoral venous approach. The puncture site is preferably oriented mid-superiorly and posteriorly of the fossa ovalis in order to facilitate maneuvering of the CDS. Puncture sites are determined by the MR jet orientation and aetiology, with lower sites being necessary for lateral MR jets and FMR aetiology, whereas higher sites are required for medial MR jets and DMR aetiology. Heparin is administered after the puncture. Following the transeptal puncture, the guide catheter is delivered at the atrial septum with a tapered dilator. The guide catheter is tri-axially steerable, enabling anteroposterior and medial-lateral movements with a proximal diameter of 24F and a distal of 22F. The CDS is then inserted through the guide catheter into the LA. Under continuous TEE and fluoroscopic guidance, the MitraClip device is positioned inside the MR jet. Opening of the arms at a span of 60° and perpendicular positioning to the leaflet coaptation line, follows. Next, the clip is cautiously inserted into the LV, the arms are fully opened, position is reverified and a slight retraction of the clip is performed in order to grasp both leaflets. Lowering of the grippers and clip closure, secures the leaflet approximation. Residual MR, adequate grasping of both MV leaflets and presence of MS is then assessed via TEE. The clip may be reopened and repositioned to achieve procedural success. Upon satisfactory results the clip is released (fig.3). Otherwise, a second or more clips may be necessary, after medial repositioning of the first, for residual MR elimination. Various anatomical factors, such as leaflet thickness, may influence the required number of clips implanted in up to 40% of cases. After the MitraClip is released, the CDS and the guide catheter are withdrawn. After withdrawal, possible peri-interventional complications and the atrial septal defect should be evaluated, in case of a clinically significant shunt, followed by haemostasis at the femoral venous puncture site.**[8,66-69]**

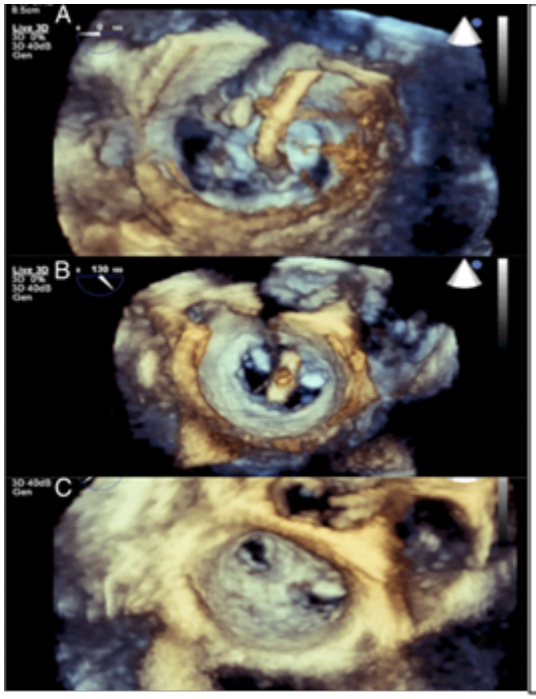

Figure 3: 3D Echocardiography to Guide the MitraClip Implant Procedure; (A) The MitraClip delivery system is positioned in the left atrium across the septum and directed toward the mitral valve, along the long axis of the heart and perpendicular to the annular plane. (B) The clip arms are opened and oriented perpendicularly to the line of coaptation. (C) The clip has been implanted, and a double orifice valve is obtained. 3D = 3-dimensional. Ref. [8]

Optimal anatomic criteria for MitraClip procedural success have been defined as a cental A2-P2 MR jet, MV orifice area >4cm ^{2} , mobile posterior leaflet ≥10mm and absence of calcifications. Moreover, in DMR flail width <15mm and flail gap <10mm are preferred. Meanwhile, in FMR coaptation depth <11mm and normal leaflet mobility are considered optimal.**[9,67]**

Published results from the Transcatheter Valve Therapy registry supports that procedural success, procedural time and lower incidence of complications are greater with increasing institutional and operator experience. Improvement is reported after about 50 implantation procedures and continues up to about 200 cases.**[70]**

In 'real world' practice not all patients are eligible for MitraClip implantation according to the above-described anatomic criteria. Thus, some MV morphology variations were further classified as conditionally suitable. Possible acceptable MV morphology for clip implantation includes an MR jet in A1-P1 or A3-P3 (as long as chordal entanglement is avoided), MV orifice area 3-4cm ^{2} , mobile length of the posterior leaflet 7-10mm, mild calcifications away from grasping area, flail width >15mm, if larger annulus capacity allows for >1 clips, coaptation depth ≥11mm and Carpentier type IIIb leaflet motion. More complicated anatomy, however, should be tackled in more experienced institutions.**[67]**

Newer iterations of the original MitraClip device have been designed to address different MV morphologic variations. In 2018 the XTR clip was introduced with longer arms and grippers, 12mm each, in order to facilitate grasping.**[71]** The MitraClip G4 iteration (NT/NTW and XT/XTW) offers 4 different sizes, 2 different arm lengths (9mm or 12mm) and 2 different arm widths (4mm or 6mm), allowing the proper clip selection depending on MV anatomical variation. Moreover, independent leaflet grasping ability is possible, along with real-time LA pressure monitoring during the procedure.**[72]**. None of the newer devices, however, have been associated with a decrement in the necessary number of clips implanted for procedural success.**[71,72]**

Observational studies – Outcomes and Clinical Predictors

Registry data show that in 'real world' practice the majority of patients undergoing MitraClip implantation are elderly, high surgical risk and burdened by FMR. A variety of published registries report high acute and long-term procedural success, alongside NYHA class improvement and low in-hospital mortality.**[73-77]** Additionally, improvements in QoL and 6-minute walk distance (6MWD) have been observed.**[76,77]** Moreover, reverse LV remodelling with reduction in LV dimensions was, also, reported after TEER among DMR and FMR patients and in non-responders to CRT implantation.**[77,78]**

Different baseline predictors, associated with detrimental effect after TEER procedure, have been identified from various studies. Adverse outcome predictors are divided into pre-procedural clinical and echocardiographic characteristics. Such outcomes are defined as device failure, residual or recurrent MR and increased mortality. The clinical predictors are consisted of NYHA class, AF, previous valve intervention, renal dysfunction and surgical risk scores. Additionally, the pre-procedural echocardiographic presence of restricted leaflet motion, LVESV >110ml, LVEDV >216ml, PH with PASP >50mmHg, RV dysfunction or severe TR is associated with worse TEER outcomes. Taking into consideration the criteria above during TEER candidate selection, may be prove beneficial in risk-stratification and in optimal result achievement.**[79]**

Meta-analytical studies

A multitude of meta-analytical studies of observational and randomised controlled trial studies, have been conducted, in an attempt to illuminate the efficacy and safety of TEER procedure among the different MR aetiologies, alongside a comparison to GDMT or surgical approaches.

A few meta-analytical studies comparing MitraClip implantation in combination with GDMT to GDMT alone have been published, all yielding similar results. The study population of these meta-analyses consisted mainly of high risk FMR patients in whom TEER was beneficial, with statistically significant improvement of survival and HFH readmissions reduction, after pooled analysis.**[80,81,82]** In one of them there was a non-significant trend for HFH readmissions reduction.**[82]** Furthermore, high acute procedural success was observed, with low percentages (12%) of residual MR grade >2+ post clip implantation.**[80]** The mortality reduction benefit of TEER remained statistically significant and became even more robust over a longer follow-up period, with a same trend regarding HFHs.**[81]**

Another meta-analysis evaluating TEER efficacy between ischemic and non-ischemic MR, provided non-significant differences in a primary composite endpoint of all-cause mortality and HFHs, and secondary endpoints of HFHs, NYHA class and MV re-intervention rates. However, a statistically significant increment of all-cause deaths was noted in ischemic MR aetiology post TEER. When accounting for the follow-up length differences among the included studies the rates of the primary endpoint and its individual components were significantly more frequent in ischemic MR patients.**[83]**

In a pooled analysis of FMR patients undergoing MitraClip implantation comparing the baseline characteristic and outcomes, MR grade ≤2+ was present at 92.76% at discharge and 83.36% at a median 12-month follow-up. Moreover, at a median 12-month follow-up significant improvement in NYHA class, LV reverse remodelling, LVEF increment and SPAP reduction were observed, compared to baseline. AF emerged as a clinical predictor of decreased survival and reduced LV reverse remodelling at a median 12-month follow-up, a result not confirmed during the 2-year follow-up, possibly due to a lower number of included studies. The higher mortality rates in this meta-analysis

(18.47% at 1-year and 31.08% at 2-year follow-up) than the EVEREST II trial were attributed to a higher risk population inclusion.**[84]**

Survival rates, residual MR grade ≤2+ and device complications at 1-year follow-up after TEER procedure were similar between patients with DMR and FMR. DMR patients, however, presented higher MV reoperation rates, whereas FMR patients had more frequent HFH readmission rates. Both of these differences can be possibly attributed to the higher risk profile of FMR patients, presenting with more comorbidities, greater LV remodelling and worse systolic LV function. According to the authors of this meta-analysis FMR patients underwent TEER due to less clear surgical indications, whereas DMR patients underwent TEER, driven mainly by comorbidities rendering them at high or prohibitive surgical risk.**[85]**

A few meta-analytical studies comparing MitraClip implantation to surgical approach underlined the higher risk profile of patients undergoing TEER. Similar mid-term and long-term survival outcomes are however reported in both study arms, supporting the efficacy of TEER approach.**[86.87]** Despite the shorter hospitalization length of the TEER arm**[86]**, higher rates of MR recurrence and MV reoperation are observed, rendering MitraClip implantation less efficacious and durable than surgery, possibly due to the lack of concomitant annuloplasty.**[86,87]** TEER provides a greater safety profile than surgical techniques, albeit intervention in patients with unlikely benefit should be avoided.**[86]**

Clinical trials

EVEREST II

The Endovascular Edge-to-Edge Repair Study (EVEREST) II was the first clinical trial studying the efficacy and safety of the MitraClip device. It was a multicenter, randomized, unblinded, controlled trial comparing Mitraclip implantation to surgical intervention. The study population consisted of 279 patients with moderate-to-severe or severe (grade 3+ or 4+) MR. Inclusion criteria were defined to be: 1) moderate-to-

severe or severe MR 2) presence of symptoms along with LVEF >25% and LV end-systolic diameter (LVESD) ≤55mm 3) absence of symptoms along with either LVEF ≥25% to ≤60%, LVESD ≥40mm to ≤55mm, new onset of AF or PH and 4) MR jet origin from A2 to P2 scallop malcoaptation. All patients had to be eligible for surgical intervention. DMR was the primary aetiology in 73% of patients, whereas the rest had FMR. The participants were randomized in a 2 to 1 ratio to either TEER procedure (184 patients) or surgical intervention (95 patients). The primary efficacy endpoint was defined as a composite of freedom from all-cause death, surgical intervention for MV dysfunction and moderate-to-severe or severe MR at 12 months. The safety endpoint was defined as the proportion of patients with major adverse events (MAE) at 30 days (table 2).**[9,88]**

Table 2[9,88]: MAE as a composite of:	
All-cause death	Deep-wound infection
MI	Ventilation for > 48 hours
Surgical reoperation after failed MV surgery	Gastrointestinal complication in need of surgery
Non-elective CV surgery due to adverse effects	New-onset AF
Stroke	Septicaemia
Renal failure	Transfusion of ≥2 blood units

1 MitraClip device was implanted in 90 patients and 2 devices in 68 patients.**[89]** MV surgery consisted of multiple surgical techniques. Surgical intervention was superior to TEER, regarding the primary efficacy endpoint (73% vs 55%, P=0.007) and inferior, regarding the primary safety endpoint (48% vs 15%, P<0.001). At 12 months, the rates of death were 6% in both randomized groups (P=1.00). Similarly, at 12 months, the rates of moderate-to-severe or severe MR (grade 3+ or 4+) were 21% for TEER and 20% for MV surgery (P=1.00). The difference in the primary efficacy endpoint was driven by the greater need for reoperation in the TEER group vs the surgical control group (20% vs 2.2%, P<0.001). The reason for reoperation was insufficient MR reduction post implantation (3 patients), before hospital discharge (5 patients), due to unsuccessful device implantation (17 patients), single leaflet device attachment (SLDA)

(9 patients) and presence of symptoms (3 patients). No device embolization or substantial mitral stenosis (MS), post MitraClip implantation, were observed. Non-significant differences were observed regarding the primary efficacy endpoint, among patients who underwent reoperation and the surgical control group (67% vs 73%, P=0.42). Although, the former group had greater rates of MAE (34%) than the TEER group. The higher rates of MAE in the control group were mainly driven by the increased need of blood transfusion and there was not a significant difference between groups after exclusion of those patients (5% vs 10%, P=0.23%, TEER vs MV surgery).**[9]** However, red blood cell transfusion can impact patient prognosis.**[90]** Furthermore, at 12 month follow up, compared to baseline, there was significant reduction in LV end-diastolic and end-systolic volumes (LVEDV, LVESV) and LVEF in both study groups, though the reduction in the control group was greater. Significant improvement was also noted in QoL and NYHA functional class in both groups. QoL improvement was durable in the 12 months in the TEER group, whereas a decrement was observed in the control group, attributed to the invasiveness of the operations. At the 2-year mark the rates of the primary efficacy endpoint were still significantly different (52% vs 66%, P=0.04, TEER vs MV surgery). The rates of death were 11% vs 11%, of reoperation for MV dysfunction 22% vs 4% and moderate-to-severe or severe MR 20% vs 22%.**[9]**

In the EVEREST II trial protocol, the statistical analysis was planned based on the assumption of MitraClip being less efficient but safer than surgical MR correction. It was calculated that a study population of 279 patients (186 in the TEER arm and 93 in the surgery arm) would provide 80% power to detect, in the per-protocol analysis, non-inferiority of the device by a prespecified margin of -31% at a 0.05 significance level, accounting for an estimated 9% patient loss at 12-month follow-up. At the same time, this study population provided more than 80% power to detect a 6% safety superiority of MitraClip in the per-protocol analysis and a 2% safety superiority in the intention-to-treat analysis. The final study population in the TEER arm was marginally less than the prespecified, however at 12-month follow-up more patients, than those accounted as lost to follow-up, participated, thus minimizing the chance of a type II error.**[9,88]**

In a subgroup analysis of the EVEREST II trial, not prespecified in the original study design and thus exploratory, MV surgical intervention was not superior in patients older than 70 years and in FMR patients compared to DMR.[**9]**

The 4-year results of the EVEREST II trial showed a durable result of the MitraClip implantation procedure. The primary efficacy endpoint was 39.8% vs 53.4% (TEER vs MV surgery) with the rates of all-cause death, reoperation for MV dysfunction and presence of moderate-to-severe or severe MR (grade 3+ or 4+) being 17.4% vs 17.8% (P=0.914), 24.8% vs 5.5% (P<0.001) and 21.7% vs 24.7 (P=0.745) respectively. Interestingly, patients in need of reoperation due to insufficient MR reduction post TEER procedure, did so within the first 6 months of initial MitraClip implantation. After the 1-year mark few patients in both groups required reoperation (3 in TEER vs 2 in MV surgery). Meanwhile, non-inferiority of TEER was sustained for FMR patients. 1 patient (0.6%) in the TEER group presented with mitral stenosis in the 4-year follow-up. LV dimensions reduction, improvement of QoL and NYHA class remained durable in both study arms.**[89]**

Similarly, in the published 5-year results of the EVEREST II trial, the primary efficacy endpoint remained significant (44.2% vs 64.3%, P=0.01, TEER vs MV surgery). Between the studied groups (TEER vs MV surgery), the rate of death, reoperation for MV dysfunction and presence of moderate-to-severe or severe MR were 20.8% vs 26.8% (P=0.4), 27.9% vs 8.9% (P=0.003) and 12.3% vs 1.8% (P=0.02) respectively. From 6 month to 5-year follow-up, the rates of reoperation in both cohorts did not differ significantly. TEER procedure had comparable durable effects to MV surgery in patients older than 70 years, patients with FMR or LVEF <60%. LV dimensions reduction, improvement of QoL and NYHA class remained significant in both groups compared to baseline. Despite inferiority of TEER in MR reduction and greater residual MR, freedom from all-cause death did not differ between the study arms, same with LV remodelling. The latter was attributed to a possible attenuation of MA dilation due to MitraClip implantation and consequently preservation of LV geometry. Reduction of MR deterioration and LV dimensions were observed in the TEER arm, despite the absence of a concomitant annuloplasty ring implantation, as shown by NYHA class improvement in addition to LV remodelling.**[91]**

MITRA-FR

The Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) trial was a multicenter, randomized, unblinded, controlled trial comparing the addition of TEER procedure to GDMT vs GDMT alone. Inclusion criteria were the presence of severe FMR, characterized as EROA >20mm ^{2} or RVol >30ml/beat, LVEF 15%-40%, NYHA class ≥II, GDMT and at least one HFH on the last 12 months. FMR grading was based on echocardiographic criteria of the 2012 ESC guidelines. Patients eligible for MV surgical intervention were excluded from the study. 152 patients were randomized to TEER plus GDMT group and 152 patients were randomized to GDMT alone group (controls). Mean EROA of the TEER group was 31±10 mm ^{2} . Total final study population post-randomisation was 304 patients. The primary efficacy endpoint was defined to be a composite consisting of all-cause death or unplanned HFH at a 12-month follow-up. Meanwhile, CV death, freedom from MACE (death, stroke, MI or unplanned HFH), along with each component of the primary endpoint were the secondary endpoints of the trial. Medical therapy was prescribed and titrated in each individual patient according to current guidelines at the time. There were no baseline differences in medical treatment, among the studied population, though no further data were reported by the 12-month follow-up. Overall, 138 successful TEER procedures were observed with 1 MitraClip implantation in 63 patients, 2 clips in 62 patients and three or more clips in 13 patients. In 8 patients, in the TEER group, no implantation was attempted and in 6 patients, implantation was unsuccessful. Residual MR of grade ≤2+ was achieved post TEER in 91.9% of patients. In the intention to treat analysis no significant differences were observed either in the primary efficacy or each individual secondary endpoint between the trial arms. Regarding the primary endpoint results in the TEER plus GDMT vs GDMT alone group, were 54.6% vs 51.3%, P=0.53. Similarly, the secondary endpoints results were 24.3% vs 22.4% for all-cause death, 48.7% vs 47.4% for unplanned HFH, 21.7% vs 20.4% for CV death and 56.6% vs 51.3% for MACE, none reaching statistical significance. However, frequency of stroke (ischemic or haemorrhagic), severe haemorrhage and renal replacement therapy was higher in the TEER group. The per-protocol analysis of follow-up data presented similar results. No further results regarding LV dimensions, durability of MR reduction, NYHA class, 6MWD brain-natriuretic peptide levels and

QoL could be extrapolated, although they were prespecified in the original study design as secondary outcomes at 1-year follow-up. It was attributed to the presence of substantial selection bias, due to a wide range of missing data at 12-month follow-up, despite 99% of patients participating in it. Based on an analysis on imputed data for NYHA functional class, at 12 months, both arms presented improvement compared to baseline, but no difference between them was observed.**[10]**

According to the MITRA-FR protocol a sample size of 288 patients was considered sufficient to provide 80% power, at a two-sided alpha level of 0.05, in order to detect a 17% decrement of the primary efficacy endpoint in the TEER group, taking into account a 10% patient attrition. Enrolled subjects further exceeded the prespecified study population. A possible explanation to the neutrality of the trial outcome could be that the study did not have enough power to detect a smaller endpoint difference, although no such trend was observed.**[10]**

MITRA-FR investigators conducted a 24-month follow-up to match the follow-up period of COAPT trial, though further core lab analysis was not included. Despite the extended follow-up period the results remained neutral, with no significant differences in outcomes in either primary efficacy or secondary endpoints. In the TEER vs control group, the primary endpoint was 63.8% vs 67.1%, whereas rates for all-cause death, unplanned HFH, CV death and MACE were 34.9% vs 34.2%, 55.9% vs 61.8%, 20.5% vs 21.1% and 66.4% vs 65.4% respectively. The low number of adverse effects, post MitraClip implantation, provides evidence for the safety of the procedure. Consistent outcomes resulted in the per-protocol analysis. There was a tendency for a decrement in HFH rate from 12 to 24 months, failing to reach statistical significance. In the TEER group vs GDMT alone group the rate of HFH hospitalizations was 88.3 per 100 patient-years vs 106.9 per 100 patient-years (Hazzard ratio (HR) 0.87, 95% Confidence Interval (CI) 0.56-1.35).**[92]**

Based on the latter observation, a landmark analysis of the MITRA-FR trial was published in 2022, in 140 patients that did not reach the primary endpoint by the 12-month mark. These patients were relatively healthier than the ones that reached the primary endpoint, presenting with lower NYHA class, lower risk scores, fewer comorbidities, less MR degree and better LV function. According to the results, patients treated with MitraClip implantation in addition to GDMT, had lower, almost half,

though not significant, annual HFH rates from 12 to 24 months. The results should be interpreted as hypothesis-generating due to the nature of landmark analyses.**[93]**

COAPT

The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients (COAPT) trial was a multicenter, randomized, unblinded, controlled trial studying the outcomes of TEER addition to maximum tolerated GDMT in symptomatic HF patients with moderate-to-severe or severe FMR. Inclusion criteria were defined as presence of symptoms in moderate-to-severe or severe FMR (grade 3+ or 4+) patients (NYHA class II-IV ambulatory), with LVEF 20%-50%, with preceded guideline directed treatment of coronary artery disease, HF, LV dysfunction and MR. LVES dimension (LVESd) had to be smaller than 70mm. Participants had to have a minimum of one HFH in the prior year and/or corrected BNP ≥300pg/ml or corrected NT-proBNP ≥1500pg/ml. Non-commissural MR jet and a favourable MR implantation anatomy were deemed necessary. Moreover, maximum tolerated GDMT was firstly evaluated and titrated by a local heart team during screening process and further validated by a central eligibility committee. In contrast, subjects burdened with chronic obstructive pulmonary disease (COPD) in need of continuous oxygen supply or estimated PASP >70mmHg, were excluded from the study. MV surgery eligibility, also excluded patients from participating.**[11,94]** The final study population consisted of 614 patients randomized in a 1 to 1 ratio in either the intervention group (TEER plus GDMT) (302 patients) or the control group (GDMT alone) (312 patients). In the TEER group mean EROA was 41±15mm ^{2} . According to the trial protocol primary efficacy was specified as the accumulated HFHs at 24 months, whereas primary safety as freedom from TEER related complications (table 3) at 1 year.

Table 3[11]: Intervention related complications
SLDA
Clip embolization
MS requiring surgery
Endocarditis requiring CV surgery
Any complication requiring CV surgery
Left ventricular assist device (LVAD) implantation
Heart transplantation (HTx)

Further secondary endpoints were prespecified: 1) MR grade ≤2+ at 12 months, 2) all-cause deaths at 12 and 24 months, 3) all-cause hospitalizations at 24 months, 4) QoL changes at 12 months, 5) 6MWD changes at 12 months, 6) NYHA changes at 12 months, 7) LVEDV changes at 12 months and 8) a composite of all-cause mortality, stroke, MI or CV surgery for TEER complications at 30 days. Procedural success was achieved in 98% (287) of 293 patients in whom TEER was attempted, with 1 device implantation in 106 patients, 2 in 157 patients, 3 in 23 patients and 4 in 1 patient. MR grade reduction ≤2+ was achieved in 247 patients. 2 cases with SLDA and 1 device embolization were observed at 12 months. At 24 months MitraClip implantation (vs control group), significantly reduced the primary efficacy outcome rates per patient-year (35.8% vs 67.9%, P<.001, number needed to treat (NNT) 3.1). The primary safety endpoint was 96.6%, higher than the prespecified rate of 88%, deemed acceptable at study design. Significant outcome improvements were also observed in every prespecified secondary endpoint. Between the trial arms (intervention vs control groups) all-cause death at 24-months was significantly reduced with MitraClip implantation (29.1% vs 46.1%, P<0.001, NNT 3.9), driven by HF related causes. Similar results were observed for all-cause hospitalizations at 24 months. The beneficial effects on mortality were observed more than 12 months after MitraClip implantation, whereas the HFH reduction was notable during the first month. MR grade ≤2+ at 1 year follow-up was present in 94.8% of the intervention group vs 46.9% of the control group. Furthermore, statistically significant improvements were noted in QoL, NYHA class and FC of

patients in the intervention group. Very mild reverse remodelling was achieved with TEER and LVEDV at 12 months was significantly less severe post TEER procedure. Contrary, patients on GDMT had higher rates of LVAD implantation or HF HTx. The beneficial effects of TEER procedure were independent of age, HF aetiology, surgical risk, FMR severity and LV dimensions and function at baseline.**[11]**

In the COAPT trial protocol it was prespecified that a sample size of 610 participants were necessary for an approximate 80% power at a one-sided alpha level 0.05 for the primary efficacy endpoint and 305 device group participants would provide >95% power for the primary safety endpoint, both accounting a 7.5% withdrawal attrition at 12 months. For the same withdrawal rate at 12 months, the same sample size provided an approximate 80% power to detect a 10% difference in all-cause mortality at 24-months. The study population consisted of 614 patients (302 at the intervention arm and 312 at the control arm), thus marginally fulfilling the required sample size to minimize type II errors. The rest of the secondary endpoints for the participating study population had an estimated power of 80% to over 95%.**[94]** The principal results remained consistent after imputation for the missing data at follow-up.**[11]**

Different analyses on outcome data of the COAPT trial have specified various baseline predictors (table 4) of worse prognosis in patients with moderate-to-severe or severe FMR, despite maximally tolerated GDMT.

Table 4:[95-102] Baseline predictors of worse prognosis	
AF	Right ventricle (RV) dysfunction as assessed by RV-pulmonary artery uncoupling (PA)
Worse renal dysfunction	TR ≥ moderate grade
Type II diabetes	Higher NYHA class
Lower serum albumin level	6MWD <240m

MitraClip implantation benefits were significantly consistent, independently of these poor outcome baseline predictors.**[95-102]** Device implantation in patients with longstanding AF was associated with lower stroke rates.**[95]** History of COPD confers a worse prognosis and TEER procedure significantly improved HFH rates and health

status.**[103]** In a post hoc analysis of the COAPT trial outcomes, TEER was the strongest predictor of therapeutic response at 1 year. Other independent baseline predictors were lower serum creatinine and QoL scores measured by the KCCQ.**[104]** Moreover, an increment of ≥10 points in KSSQ-overal summary score in the first month, predicted a 14% lower mortality or HFH risk, possibly allowing for early identification of non-responders to beneficial outcomes.**[105]** Similarly, an increase in baseline LV global longitudinal strain at 6 months was associated with significant improvement in clinical outcome, regardless of treatment arm.**[106]**

At 36-month follow-up the durability of beneficial effects and the safety of TEER, in the intervention group, were further validated. Rates of the primary efficacy and safety endpoint were 35.5% vs 68.8% per patient-year, P<0.0001, NNT 3.0 (intervention vs control group) and 91.3% respectively. All-cause mortality was 42.8% vs 55.5%, P=0.001, NNT 7.9 (intervention vs control group). The NNT for the composite of all-cause death or HFH was 3.4 at 36 months, in comparison to the NNT 4.5 at 24 months. Thus, beneficial outcomes after MitraClip procedure proved durable and greater with time. The rest of secondary endpoints maintained statistical significance. Moreover, durable effects were also observed in MR grade, QoL and 6MWD improvements. Crossover to TEER treatment from the GDMT alone group, showed a tendency of improved outcomes, though it was susceptible to potential survivorship bias. Lastly, at 3 years, the progression of LV disease requiring LVAD implantation or HTx was 7.4% at the TEER group vs 11.4% at controls.**[107]**

Transcatheter Edge-to-Edge Repair – Current Status and Future Perspectives

2021 ESC/EACTS guidelines for management of VHD recommend that TEER may be considered for DMR in high surgical risk patients presenting symptoms, with favourable MitraClip implantation anatomy, in whom implantation is not considered futile [Class IIb, level of evidence (LoE) B]. Intervention in FMR patients depends on the presence of concomitant coronary artery disease (CAD) or other heart disease requiring treatment. In the presence of such comorbidities, TEER should be considered

in high surgical risk patients, after treatment of primary disease with percutaneous coronary intervention and/ or transcatheter aortic valve implantation (Class IIa, LoE C). In the absence of comorbidities TEER should be considered in high surgical risk symptomatic patients, fulfilling COAPT criteria (Class IIa, LoE B). In patients not fulfilling COAPT criteria, TEER may be considered after careful evaluation for LVAD implantation or HTx eligibility (Class IIb, LoE C).**[5]**

2020 ACC/AHA guidelines for management of VHD recommend that TEER can be beneficial in DMR NYHA III or IV patients, not eligible for surgery, with favourable device implantation anatomy and life expectancy ≥1 year (Class 2a, LoE B-NR). In persistently symptomatic patients (NYHA II-IV) with severe FMR due to LV systolic dysfunction, fulfilling the COAPT criteria, TEER may be beneficial (Class 2a, LoE B-R).**[37]**

The participants of the EVEREST II trial were predominantly burdened by moderate-to-severe or severe DMR (73% of the population study). According to the results of the EVEREST II trial, TEER was inferior to MV surgery regarding MR grade reduction, although it presented a superior safety profile.**[9]** The long-term efficacy and safety results of Mitraclip implantation were durable but still remained inferior and superior to MV surgery respectively. LV dimensions reduction and improvement of QoL and NYHA class, achieved with device implantation, in comparison to baseline, remained statistically significant during longer follow-up. Though, they were still inferior to surgical intervention.**[91]** Thus, MV surgery is the default intervention for treatment of DMR patients who are symptomatic (Class I, LoE B) or asymptomatic with either signs of LV dysfunction (defined by LVESD ≥40mm and/or LVEF ≤60%) (Class I, LoE B) or preserved LV function and AF or PH secondary to MR (Class IIa, LoE B). MV repair over replacement is the choice of surgical intervention in DMR patients, due to better survival when durable results are expected.**(5)** MR has been shown to be the prevailing VHD in the US and the second most common in Europe, further increasing with age.**[3,4]** The results of the Euro Heart Survey on VHD showed that 31.8% of patients with severe single valve disease were deemed inoperable. More than half (55.3%) were burdened with at least one non-cardiac comorbidity, such as old age (27.6%), COPD (13.6%), renal dysfunction (6.1%) and short life expectancy (19.3%), rendering them at high or prohibitive surgical risk.**[4]** TEER offers a rather effective and safe alternative treatment intervention in these inoperable patients with beneficial mortality and MR

reduction outcomes, preventing the establishment of permanent LV dysfunction and HF or attenuating its progression.**[5]**

SMR, most commonly, is a corollary of LV disease. Isolated MV surgical intervention does not confer a better prognosis, despite improvement of symptoms and QoL, since this approach does not offer treatment for the primary aetiology of the disease. MV replacement combined with chordal sparing is preferred over MV repair, due to lower incidence of recurrent MR and thus lower rates of HFH. MV surgery is recommended in severe FMR patients undergoing coronary artery bypass grafting (CABG) or other cardiac surgery. The results for moderate degree FMR remain controversial. In patients with AF burdened with atrial FMR, MV repair with ring annuloplasty may be a beneficial treatment with low operative risk.**[5,37]** On the contrary, in the COAPT trial, it has been shown that TEER efficiently reduces MR grade alongside with mortality and accumulated rates of HFH in inoperable patients with moderate-to-severe or severe FMR despite maximal GDMT, who fulfil specific criteria.**[11]**

However, the exact range of patient selection who may benefit from such a procedure still eludes us. That is due to the discordant results of the MITRA-FR and COAPT trials. In the attempt to reconcile the two trials, their differences must be elucidated. The discrepancies amount to differences in the inclusion of the study population, GDMT titration and procedural outcomes. First, the echocardiographic criteria of MR definition differed in each study, with MITRA-FR using an EROA >20mm ^{2} as the inclusion cut-off, whereas EROA ≥30mm ^{2} was used in COAPT. In addition, in COAPT, LVESd ≥70mm, severe PH and RV dysfunction were defined as exclusion criteria. No such restrictions were defined in MITRA-FR. Consequently, different patient populations were included in these trials. MITRA-FR-eligible patients presented with less severe MR grade (mean EROA 31±10mm ^{2}) and greater LV dimensions (mean LVEDV 135 ml/m ^{2}). Conversely, COAPT-eligible patients had more severe FMR (mean EROA 41±15mm ^{2}) and smaller LV dimensions (mean LVEDV 101 ml/m ^{2}). Second, in the run-in phase of COAPT, GDMT was titrated to maximum tolerated doses before randomization, by a heart failure specialist and was further evaluated by a central selection committee. Instead, in MITRA-FR GDMT was stipulated only by a local heart team. Moreover, in COAPT GDMT titration was reported in follow-up, but not in MITRA-FR. Significantly higher beta-blocker dose was reported in the COAPT intervention arm, suggesting that MitraClip implantation enabled further GDMT

optimization. Thus, more rigorous medical titration can be presumed in COAPT. Third, although acute procedural success was similar in both trials 92% vs 95% (MITRA-FR vs COAPT), residual FMR grade ≥2+ at 12-months follow-up was 17% vs 5%. The difference in echocardiographic criteria used and the increased difficulty of MR grading post MitraClip implantation must be taken into account when comparing procedural success. The difference in procedural efficacy could be partly attributed to lower rates of >1 clip implantation in MITRA-FR. Increased peri-procedural complication rates were reported in MITRA-FR. In COAPT, participants had less advanced LV disease and more severe FMR grades, GDMT treatment intensification and procedural success were presumably greater. Meanwhile, MITRA-FR participants appeared to be at a later stage of LV disease with lower FMR grades. Furthermore, during the screening period of the COAPT trial 61% of the enrolled population was not considered eligible, due to stricter inclusion criteria, vs 32% in MITRA-FR. Lastly, the difference in sample sizes between the two trials may have lead to MITRA-FR not having enough power to detect a smaller difference in outcomes. Taking all of the above into consideration, the conflicting results might be explained.**[108-111]**

MITRA-FR participants had an EROA that was roughly 30% smaller and LV volumes that were approximately 30% greater than the COAPT population study. In an attempt to reconcile the conflicting results of the two trials, Grayburn et al. proposed a new conceptual framework of proportionate and disproportionate SMR. Proportionate SMR refers to an EROA that is expected for a given degree of LV dilation, thus SMR should respond to medical and device therapy aimed at LV dysfunction. In contrast, disproportionate SMR refers to an EROA greater than the expected for a given LV volume, thus affecting the disease course and being a potential target for MV intervention. According to this concept, the discordant trial results are a consequence of patient enrolment. The majority of MITRA-FR participants had proportionate FMR, whereas the COAPT participants had more frequently disproportionate FMR, resulting in better outcomes in the latter.**[112]** A post-hoc analysis of the COAPT trial divided the COAPT study population into two groups, MITRA-FR-like patients and remaining COAPT patients. TEER procedure in MITRA-FR-like patients vs GDMT failed to produce significant benefit at 24-month all-cause mortality or HFHs, in contrast to the remaining COAPT patients. Both subgroups showed significant improvement in QoL at 1 year, whereas only the MITRA-FR-like group presented statistically significant

improvement at 6MWD at 1 year. Consequently, the proportional FMR concept failed to be robustly associated with MitraClip implantation outcome prediction. A similarly attenuated relation resulted from a 24-month analysis of six COAPT patients subgroups.**[113]** Moreover, a post-hoc analysis of the MITRA-FR trial reported no difference in outcomes between COAPT-like MITRA-FR participants vs non-COAPT-like. Also, no significant outcome difference in COAPT-like patients between treatment arms was observed.**[114]**

On the other hand, Gaasch et al. proposed that RVol is a better pathophysiological descriptor of FMR than EROA. They performed a volumetric study, showing that the RVol/LVEDV ratio was similar in COAPT vs MITRA-FR (0.15 vs 0.18), suggesting that in both trials the LV dilation was disproportionate to MR. Thus, concluding that the difference in outcomes should not be explained by an EROA/LVEDV analysis. It should be noted that presumed data for RVol and RF were used in the COAPT arm.**[115]** RVol/LVEDV ratio ≥0.2 in SMR has been shown to portend significantly decreased mortality after MV intervention, compared to RVol/LEVDV ratio <0.2. The inverse relationship, although not significant, has been observed with GDMT alone.**[116]** Therefore, FMR patients with RVol/LVEDV ratio ≥0.2 may have a beneficial outcome, though none of the two trials included such patient populations.**[115]** Greater clarity of echocardiographic data will prove helpful in an analysis of the two trials, not based on assumptions, elucidating prognostic factors for better outcomes.**[117]**

Bartko et al. advocated the use of RF ≥50% as a predictive tool for therapeutic decisions. In a risk stratification study based on EROA and RVol, in intermediate risk patients, with EROA ranging from 20 to 29mm ^{2} and RVol of 30 to 44 ml/beat, the presence of RF ≥50% was associated with worse outcomes, contrary to a RF <50%, thus suggesting a possibly beneficial MV intervention in this cohort.**[118]** Since no unifying theory has been validated at this time, European and American guidelines have adopted the COAPT criteria regarding TEER patient eligibility.**[5,37]**

In surgical repair of DMR, a concomitant annuloplasty of the MA with a prosthetic ring, provides improved leaflet coaptation and deters further MA dilation, thus increasing repair durability and preventing MR recurrence. In a retrospective study of DMR patients that underwent MV repair, mostly due to MAC, long-term results were suboptimal. At 12-year follow-up freedom from reoperation and MR grade ≥3+ were

51.3±7.75 % and 43±7.6% respectively. Of note, at ≤4-year follow-up patients without concomitant MAC presented greater freedom from the endpoints above than those with MAC, although at longer follow-up this difference became non-significant. Moreover, MR grade >1+ at discharge emerged as the sole predictive factor of these endpoints above.**[119]** In another comparative study, MV repair without annuloplasty had greater short and long-term postoperative MR degree than repair with concomitant annuloplasty, though freedom from reoperation and from death were similar after propensity-score matching.**[120]** Consequently, the lack of concomitant annuloplasty during TEER procedure may impair its long-term durability due to greater residual MR and omission of annular remodelling. However, these results are based on studies focused on DMR patients, thus they should not be extrapolated in FMR.**[119]** On the contrary, COAPT patients with MitraClip implantation presented less residual MR at 24-month follow-up compared to ischemic FMR patients with a downsized annuloplasty ring with similar MR severity in a previous trial.**[11]**

Although exploratory, results from the MitraBridge registry support the possibility of MitraClip implantation as a bridge strategy to HTx. The study population was stratified into three groups: 1) waiting HTx list, but unlikely to receive a suitable organ, 2) bridge to decision group that presented with clinical worsening and 3) bridge to candidacy group due to comorbidities increasing surgical risk or other reasons. 119 patients underwent the procedure with a high procedural success and 0% 30-day mortality. Beneficial outcomes, defined as the freedom from all-cause death, urgent HTx, LVAD implantation or first HFH, were 64% at 1-year follow-up. The yearly rates of freedom from HFH were 67%. All-cause mortality at 12 months was 4.5%, in contrast to the reported 13% yearly mortality, by the Eurotransplant waiting list in 2019. Furthermore, 15.5% of the participants became eligible for transplant and 23.5% had no longer HTx indication, due to clinical improvement. Interestingly the baseline characteristics in 80% of the participants, would exclude them from device implantation according to the COAPT criteria. The study population shared similar characteristics to the MITRA-FR patients, but were significantly younger, possibly explaining the positive results. The result should be regarded as hypothesis-generating and further studies are required to explore this treatment option**[121]**

In various small case series, the use of MitraClip has been proposed as an alternative intervention in patients with obstructive hypertrophic cardiomyopathy. Specifically, in

small series in prohibitive surgical risk patients, unable to undergo septal reduction therapy, TEER has been performed, reducing SAM and septal conduct. Thus, LVOT was reduced.**[122]** The results have been encouraging, achieving reduction of MR, resolution of SAM and LVOT improvement.**[123,124]** However, these data are limited and further clinical trials are needed to validate this hypothesis.

Chronic HF patients are often burdened by decrement in psychological and cognitive status, leading to a decline in QoL. In a pre-post-interventional controlled trial in 40 patients with end-stage HF with concomitant severe MR, psychological and cognitive function was assessed before and after MitraClip implantation. At 6 weeks after TEER significant improvement, was reported, in psychological and cognitive outcomes. Greater baseline impairment in HF patients was associated with greater derived benefit. Thus, TEER should not be withheld from patients with severely impaired cognitive function. Future longer-term studies are warranted to study these effects.**[125]**

Conclusion

The MitraClip system has been an innovative alternative treatment intervention for MR patients in high or prohibitive surgical risk, providing durable effective MR reduction, along with a high safety profile. In patients with DMR, TEER has been proven successful in altering the disease course, although it is less effective than surgery. Thus, MitraClip implantation presents an alternative MV intervention in inoperable DMR patients, averting permanent LV dysfunction and HF or halting further LV remodelling and HF deterioration (fig.4).

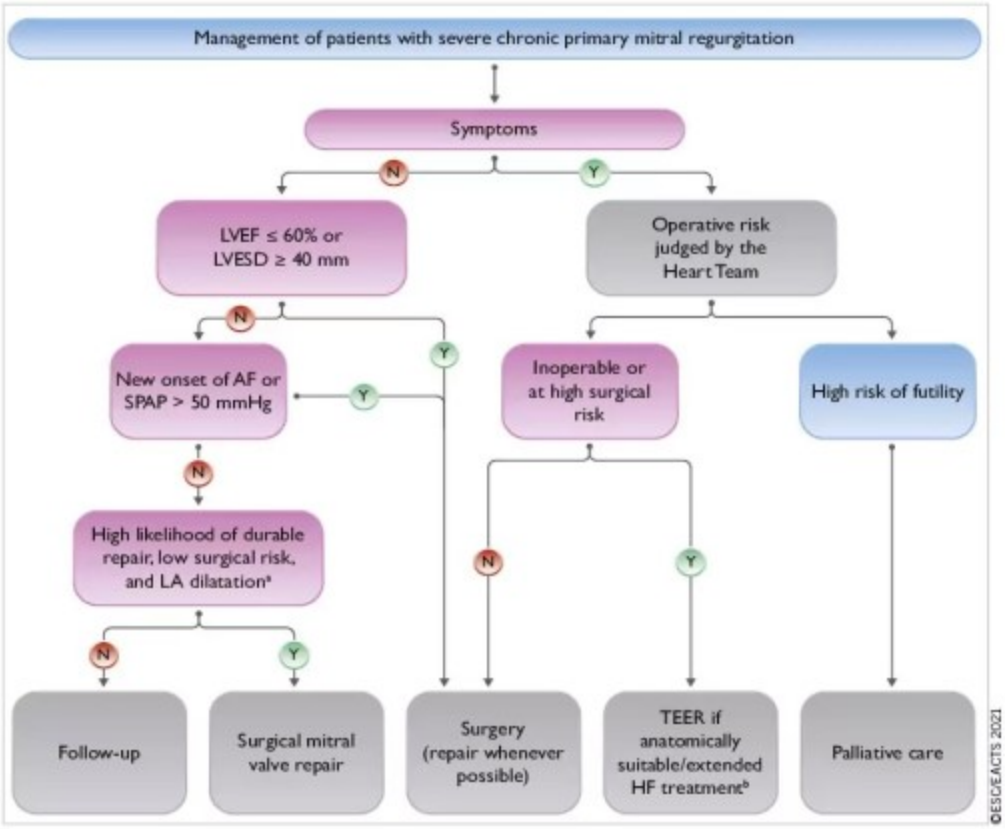

Figure 4: Management of patients with severe chronic primary mitral regurgitation. Ref.[5]

FMR treatment (fig.5) remains complex and necessary treatment interventions should be performed, prior to TEER. GDMT initiation with optimized titration and further treatment of CV comorbidities, such as revascularization, provide a robust foundation to achieve favourable outcomes. Additionally, CRT implantation in patients presenting indications, is mandatory prior to any MV intervention. MR echocardiographic quantification should be performed after clinical stabilization due to implementation of the above therapeutic approach, since MR is dependent on hemodynamic conditions.**[126]** Only then should a patient be thoroughly evaluated by a cardiac multidisciplinary team for TEER candidacy. However, despite various attempts, the fact remains that defining the cohort of FMR patients able to derive beneficial outcome has been controversial. At present, patient selection is based on COAPT criteria. In this subgroup of patients TEER substantially improves survival, reduces HFHs and ameliorates QoL and FC. However, due to the strict exclusion criteria, only a small portion of the ever-increasing number of HF patients with FMR seem candidates to the

proven benefit of MitraClip implantation. Careful, early evaluation of these patients should be performed, before HF advances, rendering TEER efficacy inadequate. In non-eligible patients according to COAPT criteria, TEER improves NYHA class and QoL. Thus, patient-preference, treatment targets and risk-stratification may be considered for MitraClip implantation. Further studies are required in order to expand the range of optimal TEER candidate selection, concomitantly with echocardiographic and clinical parameters with outcome predictive value. Data from the ongoing trials RESHAPE-HF2 and MATTERHORN may contribute to identification of more candidates deriving beneficial MitraClip implantation outcome. Finally, experimental transcatheter MV interventions in addition to TEER may improve patient prognosis.

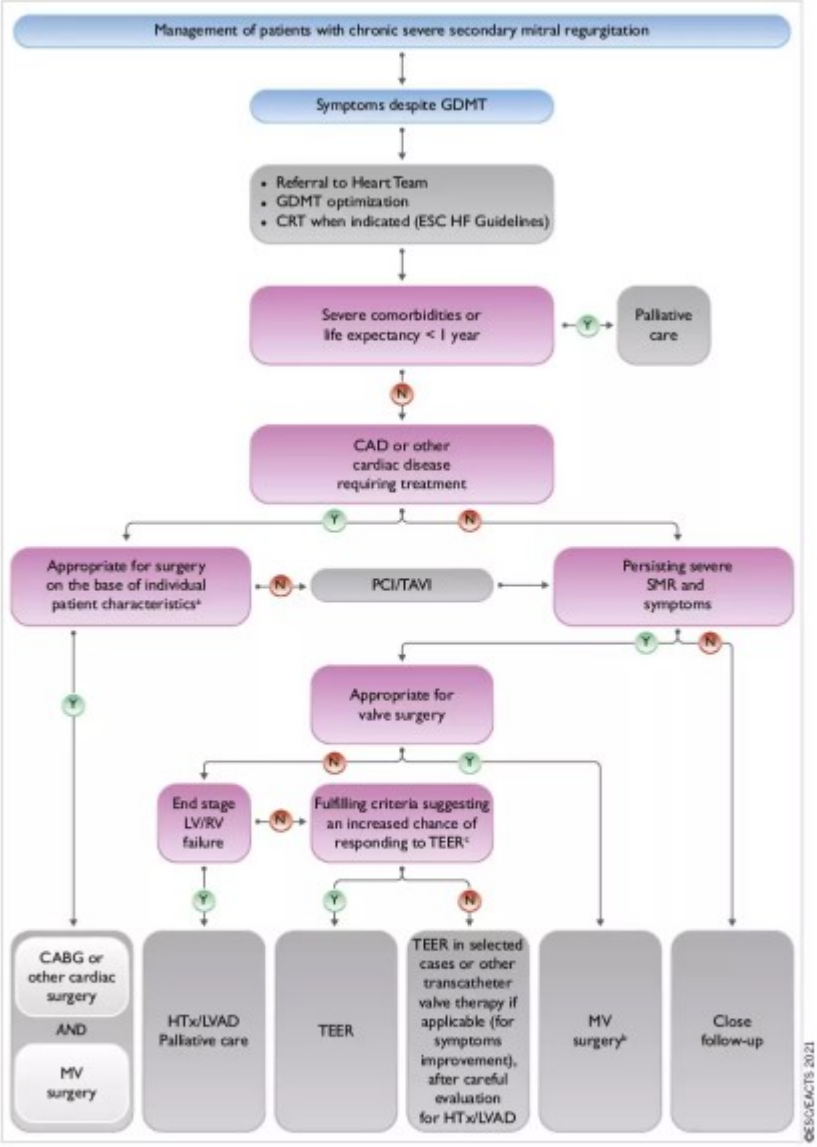

Figure 5: Management of patients with chronic severe secondary mitral regurgitation. Ref.[5]

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Τελευταία σελίδα

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