Technische Universität München
Fakultät für Medizin

# Long-term outcome after mitral valve repair using chordal replacement

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Vollständiger Abdruck der von der Fakultät für Medizin der Technischen Universität München

zur Erlangung einer

Doktorin der Medizin (Dr. med.)

genehmigten Dissertation.

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Die Dissertation wurde am 21.11.2022 bei der Technischen Universität München eingereicht

und durch die Fakultät für Medizin am 18.04.2023 angenommen.

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**Abbreviations**

| | |
|---|---|
| AML | anterior mitral leaflet |
| AF | Atrial fibrillation |
| AS | aortic stenosis |
| BL | bileaflet |
| CWD | Continuous wave doppler |
| CI | Confidence interval |
| DMR | degenerative mitral regurgitation |
| EACTS | European Association for Cardiothoracic Surgery |
| ePTFE | expanded polytetrafluoroethylene |
| EROA | Effective regurgitant orifice area |
| ESC | European Society of Cardiology |
| HR | Hazard ratio |
| LA | left atrium |
| LV | left ventricle |
| LVEF | Left ventricular ejection fraction |
| LVESD | Left ventricular end-systolic diameter |
| MR | mitral regurgitation |
| MV | mitral valve |
| MVR | Mitral valve repair |
| NYHA | New York Heart Association |
| PISA | proximal isovelocity surface area |
| PML | posterior mitral leaflet |
| RF | Regurgitant fraction |
| RV | right ventricle |
| RVol | Regurgitant Volume |

| | |
|---|---|
| SAM | Systolic anterior motion |
| sPAP | Systolic pulmonary artery pressure |
| SV | Stroke volume |
| TEE | transesophageal echocardiography |
| TEER | Transcatheter edge-to-edge repair |
| TTE | transthoracic echocardiography |
| VC | vena contracta |
| VHD | valvular heart disease |

**Abstract**

Objective: The long-term results of mitral valve repair using “non-resection” techniques, such as annuloplasty and chordal replacement, for degenerative mitral valve regurgitation were investigated.

Methods: All consecutive patients with degenerative mitral regurgitation, who underwent mitral valve repair with chordal replacement between 2003 and 2010 in the German Heart Centre Munich, were reviewed. Endpoints of this retrospective study were survival, cumulative incidence of reoperation on the mitral valve and cumulative incidence of recurrent more than moderate mitral regurgitation. The median follow-up was 10.86 years with a range of 0.01 to 15.86 years.

Results: A total of 346 patients were evaluated. The median follow-up period was 10.86 (0.01 – 15.86) years. The 30-day mortality rate was 0.56% (2/346), whereas the 5-year survival was 92.97 ± 1.41%. At 5 years, cumulative incidence of recurrent mitral regurgitation was 6.87 ± 1.57%, and cumulative incidence of reoperation on the mitral valve was 3.69 ± 1.05%. Survival at 10 years was 83.35 ± 2.15%. At 10 years, cumulative incidence of recurrent mitral regurgitation was 13.31 ± 2.22%, and cumulative incidence of reoperation was 7.84 ± 1.55%. Cox regression analysis identified age, diabetes mellitus, and reduced left ventricular ejection fraction <55% as independent risk factors for death. Left ventricular ejection fraction <55% was revealed as independent risk factor for significant recurrent mitral regurgitation.

Conclusions: This study demonstrated excellent long-term outcomes with low incidence of reoperation after mitral valve repair using chordal replacement. Our findings emphasized the importance of early intervention in severe degenerative mitral regurgitation, especially in patients with reduced left ventricular ejection fraction.

**Zusammenfassung**

Hintergrund: Es wurden die Langzeit-Ergebnisse nach Mitralklappenplastik mit ausschließlich Chordae-Ersatz und Anuloplastie zur Behandlung der degenerativen Mitralklappeninsuffizienz untersucht.

Methodik: Alle Patienten, die im Zeitraum von 2003 bis 2010 im Deutschen Herzzentrum München eine Mitralklappenplastik mit Chordae-Ersatz aufgrund einer degenerativen Mitralklappeninsuffizienz erhalten haben, wurden analysiert. Die Studienziele dieser retrospektiven Analyse waren das Überleben, die kumulative Inzidenz einer erneuten signifikanten Mitralklappeninsuffizienz und die kumulative Inzidenz einer Reoperation.

Ergebnisse: Insgesamt wurden 346 Patienten analysiert. Das mittlere Follow-Up betrug 10.86 Jahre (0.01 – 15.86 Jahre). Die 30-Tage Letalität liegt bei 0.56% (2/346). Das 5-Jahres Überleben liegt bei 92.97 ± 1.41%. Nach 5 Jahren lag die kumulative Inzidenz der erneuten signifikanten Mitralklappeninsuffizienz bei 6.87 ± 1.57% und die kumulative Inzidenz der Reoperation bei 3.69 ± 1.05%. Das 10-Jahres Überleben lag bei 83.35 ± 2.15%. Nach 10 Jahren lag die kumulative Inzidenz der erneuten signifikanten Mitralklappeninsuffizienz bei 13.31 ± 2.22% und die kumulative Inzidenz der Reoperation bei 7.84 ± 1.55%. Unabhängige Risikofaktoren für Tod waren Alter, Diabetes mellitus und eine reduzierte linksventrikuläre Pumpfunktion <55%. Zudem war eine reduzierte linksventrikuläre Pumpfunktion <55% ein unabhängiger Risikofaktor für eine erneute signifikante Mitralklappeninsuffizienz.

Diskussion: Die Mitralklappenplastik mit Chordae-Ersatz ist mit exzellenten Langzeit-Ergebnissen assoziiert, vor allem mit einer niedrigen Inzidenz für Reoperation. Die Ergebnisse dieser Arbeit bekräftigen außerdem die frühzeitige operative Behandlung der degenerativen Mitralklappeninsuffizienz, insbesondere bei Patienten mit reduzierter linksventrikulärer Funktion.

## Publications

Results of the present work were previously published in:

Lang M, Vitanova K, Voss B, Feirer N, Rheude T, Krane M, Günther T, Lange R. Beyond the 10-year horizon: Mitral valve repair solely with chordal replacement and annuloplasty. Ann Thorac Surg. 2022 Jun 8:S0003-4975(22)00803-7. doi: 10.1016/j.athoracsur.2022.05.036. Epub ahead of print. PMID: 35690138. (Lang, Vitanova et al. 2022)

## Background

### *Mitral valve regurgitation*

Mitral valve regurgitation (MR) is the second most common valvular heart disease (VHD) requiring treatment following aortic stenosis (AS) in Europe. The prevalence of MR rises with age and lies at over 10% in the population over 75 years. Its overall prevalence lies at 1-2%. (Iung, Baron et al. 2003, Nkomo, Gardin et al. 2006) Since life expectancy of the general population in Europe is already high and tends to further increase, safe and standardized treatment of MR is of high importance. (Nickenig, Mohr et al. 2013)

### *Etiology*

MR can be classified as primary MR and secondary MR: Primary MR, i.e. degenerative (DMR) or structural MR, is caused by degenerative changes of the mitral leaflets, elongation or rupture of chordae tendineae or papillary muscle, flail leaflet, severe retraction or large perforation. (Figure 1) In secondary MR, i.e. functional or non-structural MR, the mitral valve (MV) itself and its parts are not primarily diseased. Pathologic changes of the left ventricle (LV) or left

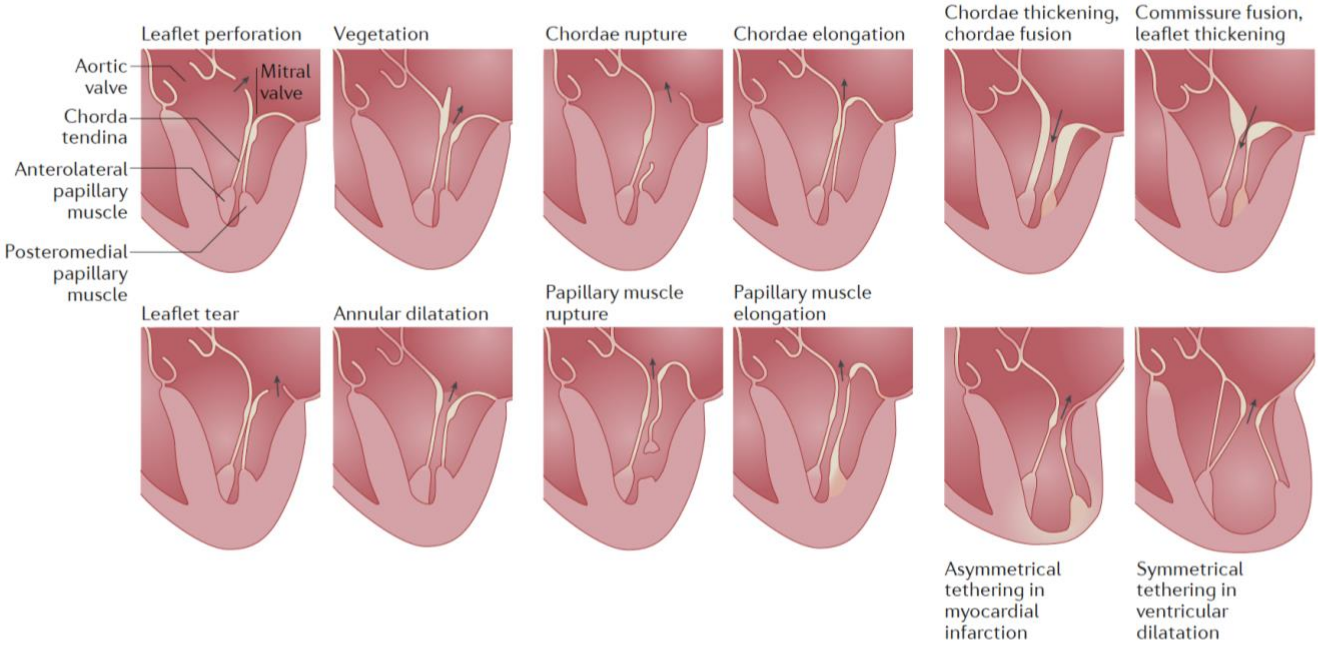



*Figure 1. Etiology of Mitral Regurgitation*. (Del Forno, De Bonis et al. 2020)

atrium (LA), for example ischemic or dilatative cardiomyopathy, are causing a distortion of the MV apparatus leading to insufficient MV closure. (Figure 1)

### *Pathophysiology*

The leaflets of the MV close in early systole as soon as LV pressure reaches and exceeds LA pressure. The papillary muscles and chordae tendineae provide tension on the leaflets and cause closure of the leaflets during contraction of the LV in systole. If sufficient closure of the MV is not obtained, blood will flow back into the LA as regurgitant volume. This volume overload and eventually also pressure overload is causing the LA to dilate. Increasing pressure and volume of the LA is impeding drainage of the pulmonary veins and blood is further regurgitating into the pulmonal system, ultimately leading to pulmonary congestion. As a result, reactive pulmonal hypertension is developing. Pulmonal hypertension is increasing right ventricular (RV) load, which can further cause RV insufficiency. In addition, the LV must increase its stroke volume to maintain an adequate cardiac output, as a sufficient part of LV volume is lost as regurgitant volume. This volume overload can lead to eccentric hypertrophy and dilatation of the LV and further cause LV insufficiency.

### *Symptoms*

Many patients remain asymptomatic over a long period of time. Chronic MR can be compensated by various adapting mechanisms such as LA dilatation and LV hypertrophy. However, as soon as LV dysfunction commences, symptoms will become apparent, which include palpitations, dyspnea, orthopnea, and fatigue. Symptoms of RV dysfunction include venous stasis, peripheral edema and congestive hepatopathy. In acute MR patients may develop pulmonal edema and cardiac shock.

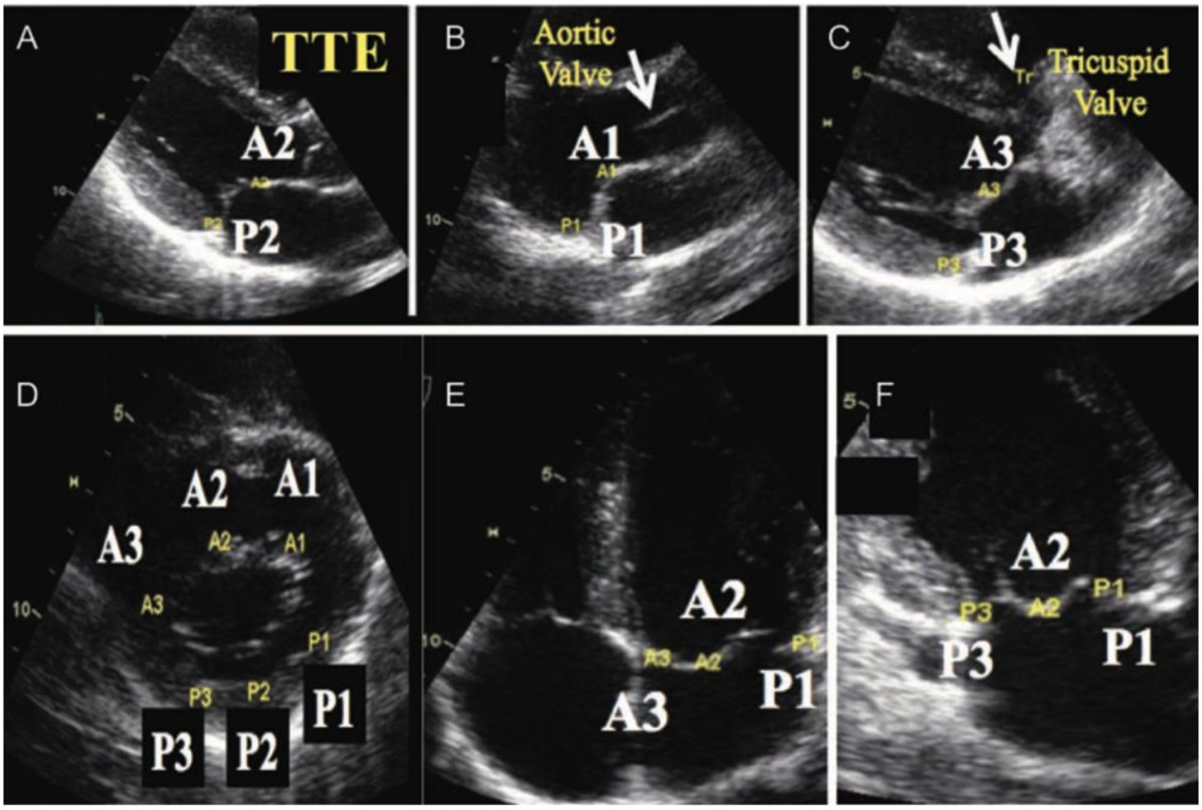



Figure 2. Analysis of the mitral valve in two-dimensional transthoracic echocardiography (TTE). A1-3 describe the scallops of the anterior leaflet; P1-3 describe the scallops of the posterior leaflet. (Lancellotti, Tribouilloy et al. 2013)

*Evaluation*

The most important tools to assess MV morphology are two-dimensional transthoracic echocardiography (TTE) and two-dimensional transesophageal echocardiography (TEE). Two-dimensional TTE and TEE allow the assessment of all six scallops and the regurgitant jet, which may identify the prolapsing segment (Figure 2). It also gives information about the existence of calcification and the extent of other anatomic variations, which are essential for planning of the optimal treatment. When available, three-dimensional imaging allows a more comprehensive description of the mitral pathology (Figure 3). This especially applies to involvement of the anterior mitral leaflet (AML) and commissural alterations. The three-dimensional view of the MV is identical to the surgeon's intraoperative view of the valve and hence is important for preoperative planning. (Lancellotti, Tribouilloy et al. 2013) Echocardiography provides multiple parameters and measurements to evaluate MR pathology, which are used to describe MR severity. Color flow mapping is most commonly

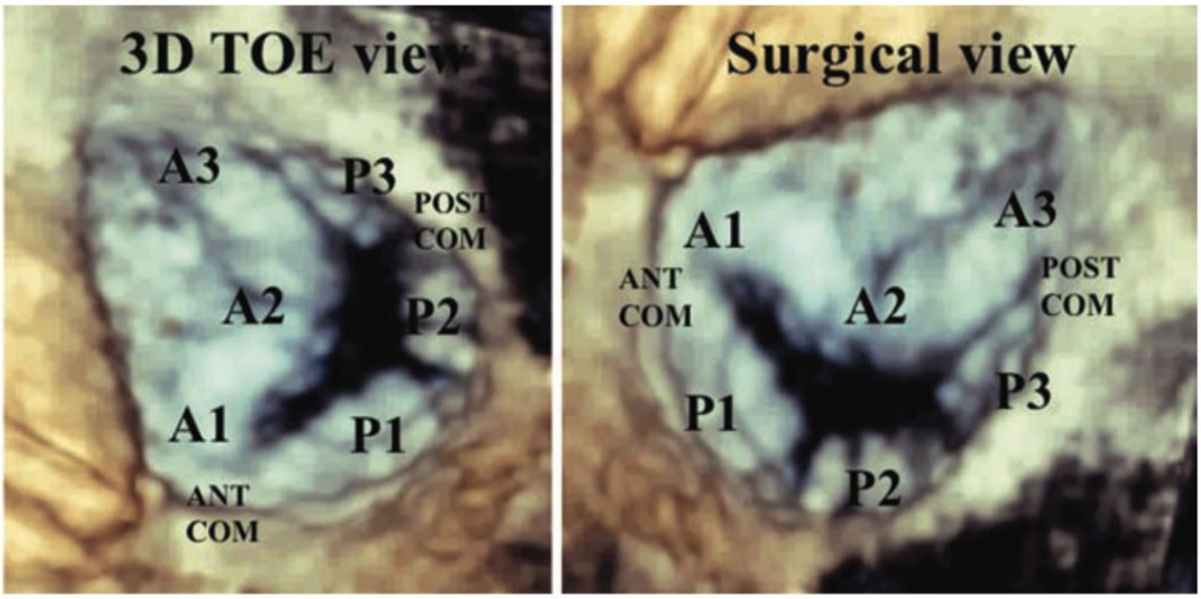



Figure 3. Three-dimensional transesophageal echocardiography (TEE) of the mitral valve. The left image shows standard TEE view. The right image shows the surgical view of the mitral valve. A1-3, scallops of the anterior leaflet. Ant com, anterior commissure. P1-3, scallops of the posterior leaflet. Post com, posterior commissure. (Lancellotti, Tribouilloy et al. 2013)

used to assess MR severity. (Chaliki, Nishimura et al. 1998) However, often this method is not precise enough, as the color flow display depends on numerous technical and hemodynamic factors. Thus, a bigger jet into the LA does not necessarily imply severity of MR. (McCully, Enriquez-Sarano et al. 1994) Still a large eccentric jet reaching the posterior wall of the LA is a strong indicator for severe MR, nonetheless color flow imaging can be misleading and is prone to errors. It should hence be used to detect MR and should then initiate further investigation. (Lancellotti, Tribouilloy et al. 2013) Another parameter for assessment of MR severity is vena contracta (VC) width. The VC is the narrowest portion of the regurgitant flow and therefore approximates the regurgitant orifice. (Tribouilloy, Shen et al. 1992) It has been shown, that VC width correlates with regurgitant volume and is able to distinguish severe from mild MR. (Hall, Brickner et al. 1997) VC width of > 7mm represents severe MR and VC width < 3mm means mild MR. (Lancellotti, Tribouilloy et al. 2013) VC relies on the assumption that orifice area is circular, which however is not always the case. Especially in secondary MR the orifice area is proven to be more elliptic than circular, also in primary MR a circular orifice area cannot be assumed. (Kahlert, Plicht et al. 2008) Also VC width tends to underestimate MR severity if there are multiple regurgitant jets. (Zoghbi, Adams et al. 2017) Considering this, VC width is not exact enough since distinction of more than just severe and mild MR is desired. Hence, when VC width is 3-7mm, which suggests severe MR, further investigation by a more quantitative method is necessary. (Lancellotti, Tribouilloy et al. 2013) The flow convergence method, i.e. proximal isovelocity surface area (PISA) method, is the most reliable method for determination of MR severity in common clinical practice. For calculation of flow convergence precise measurement of the parameters is indispensable. Errors are common especially with eccentric jets and even with experienced readers, hence PISA should always be seen in relation to other echocardiographic measures. Another method is continuous wave doppler (CWD) measurement, which provides information about MR velocity, thus hemodynamic consequences of MR. MR velocity is dependent on LV and LA pressure and hence allows to draw conclusions whether MR is hemodynamically relevant. For example, a low MR velocity suggests low blood pressure or increased LA pressure. Usually, maximum MR velocity is 4-6m/sec. Additionally, the density and contour of velocity profile allow further interpretation: jet contour allows conclusions about LA pressure and jet density suggests MR severity. (Zoghbi, Adams et al. 2017) LA and LV volumes are important additional indicators of MR severity and its hemodynamic relevance. Significant MR causes, as described above, volume overload on the LV, which leads to LV dilatation and further LV dysfunction. Another consequence of chronic significant MR is LA dilatation. Both are important factors in determining the need for surgical intervention. As well is effective regurgitant orifice area (EROA), which is strongly associated with increased mortality if elevated. In 2018, Antoine et al. demonstrated excess mortality in patients with DMR and an EROA >=20mm$^2$ as compared to the general population, which further increased with rising EROA levels. (Antoine, Benfari et al. 2018)

### *Grading of MR severity*

Multiple parameters are included in assessment of MR severity (Figure 4). It is important to keep in mind not only the amount of MR itself, but also its hemodynamic consequences. For example, patients with chronic severe MR have established compensatory mechanisms and

| | MR severity[*] | | | |
|---|---|---|---|---|
| | Mild | Moderate | | Severe |
| **Structural** | | | | |
| MV morphology | **None or mild leaflet abnormality** (e.g., mild thickening, calcifications or prolapse, mild tenting) | Moderate leaflet abnormality or moderate tenting | | **Severe valve lesions** (primary: flail leaflet, ruptured papillary muscle, severe retraction, large perforation; secondary: severe tenting, poor leaflet coaptation) |
| LV and LA size[†] | Usually normal | Normal or mild dilated | | Dilated[‡] |
| **Qualitative Doppler** | | | | |
| Color flow jet area[§] | **Small, central, narrow, often brief** | Variable | | Large central jet (>50% of LA) or eccentric wall-impinging jet of variable size |
| Flow convergence[‖] | **Not visible, transient or small** | Intermediate in size and duration | | **Large throughout systole** |
| CWD jet | Faint/partial/parabolic | Dense but partial or parabolic | | Holosystolic/dense/**triangular** |
| **Semiquantitative** | | | | |
| VCW (cm) | <0.3 | Intermediate | | ≥0.7 (>0.8 for biplane)[¶] |
| Pulmonary vein flow[#] | **Systolic dominance** (may be blunted in LV dysfunction or AF) | Normal or systolic blunting[#] | | Minimal to no systolic flow/ **systolic flow reversal** |
| Mitral inflow[**] | **A-wave dominant** | Variable | | E-wave dominant (>1.2 m/sec) |
| **Quantitative[††,‡‡]** | | | | |
| EROA, 2D PISA ($cm^2$) | <0.20 | 0.20-0.29 | 0.30-0.39 | ≥0.40 (may be lower in secondary MR with elliptical ROA) |
| RVol (mL) | <30 | 30-44 | 45-59[††] | ≥ 60 (may be lower in low flow conditions) |
| RF (%) | < 30 | 30-39 | 40-49 | ≥50 |

*ROA*, Regurgitant orifice area.
Bolded qualitative and semiquantitative signs are considered specific for their MR grade.
*All parameters have limitations, and an integrated approach must be used that weighs the strength of each echocardiographic measurement. All signs and measures should be interpreted in an individualized manner that accounts for body size, sex, and all other patient characteristics.
†This pertains mostly to patients with primary MR.
‡LV and LA can be within the "normal" range for patients with acute severe MR or with chronic severe MR who have small body size, particularly women, or with small LV size preceding the occurrence of MR.
§With Nyquist limit 50-70 cm/sec.
‖Small flow convergence is usually <0.3 cm, and large is ≥ 1 cm at a Nyquist limit of 30-40 cm/sec.
¶For average between apical two- and four-chamber views.
#Influenced by many other factors (LV diastolic function, atrial fibrillation, LA pressure).
**Most valid in patients >50 years old and is influenced by other causes of elevated LA pressure.
††Discrepancies among EROA, RF, and RVol may arise in the setting of low or high flow states.
‡‡Quantitative parameters can help subclassify the moderate regurgitation group.

Figure 4. Grading the severity of chronic MR by echocardiography. AF, atrial fibrillation; CWD, continuous wave doppler; EROA, effective regurgitant orifice area; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; MV, mitral valve; RF, regurgitant fraction; VCW, vena contracta width. (Zoghbi, Adams et al. 2017)

developed a dilated and compliant LA and hence remain asymptomatic. Whereas patients with acute MR, who do not have certain compensatory mechanisms and whose LA is of a normal size and function, acutely develop severe symptoms. (Zoghbi, Adams et al. 2017) The algorithm for grading of MR severity is shown in Figure 5. There are specific signs and measurements obtained by Doppler echocardiography including color flow jet area, VC width, PISA radius, mitral inflow, CWD and size of LA and LV, which distinguish mild from severe MR. If MR is defined as mild or severe by 4 or more of those criteria, no further examination is necessary. However, if those signs are inconclusive further measurements are necessary, including EROA, regurgitant volume (RVol) and regurgitant fraction (RF), which is the percentage of regurgitant volume as compared to stroke volume (SV). Severe and moderate MR might have overlapping characteristics, which make allocation to either one of them difficult. Hence, a further subclassification of MR into 4 grades is reasonable. In conclusion, grading of MR is simple if multiple measurements yield congruent results. However, in many cases measurements are contradictory and a more integrative approach using numerous parameters and signs is required. In those cases subclassification into 4 grades is helpful (Figure 5). (Zoghbi, Adams et al. 2017)

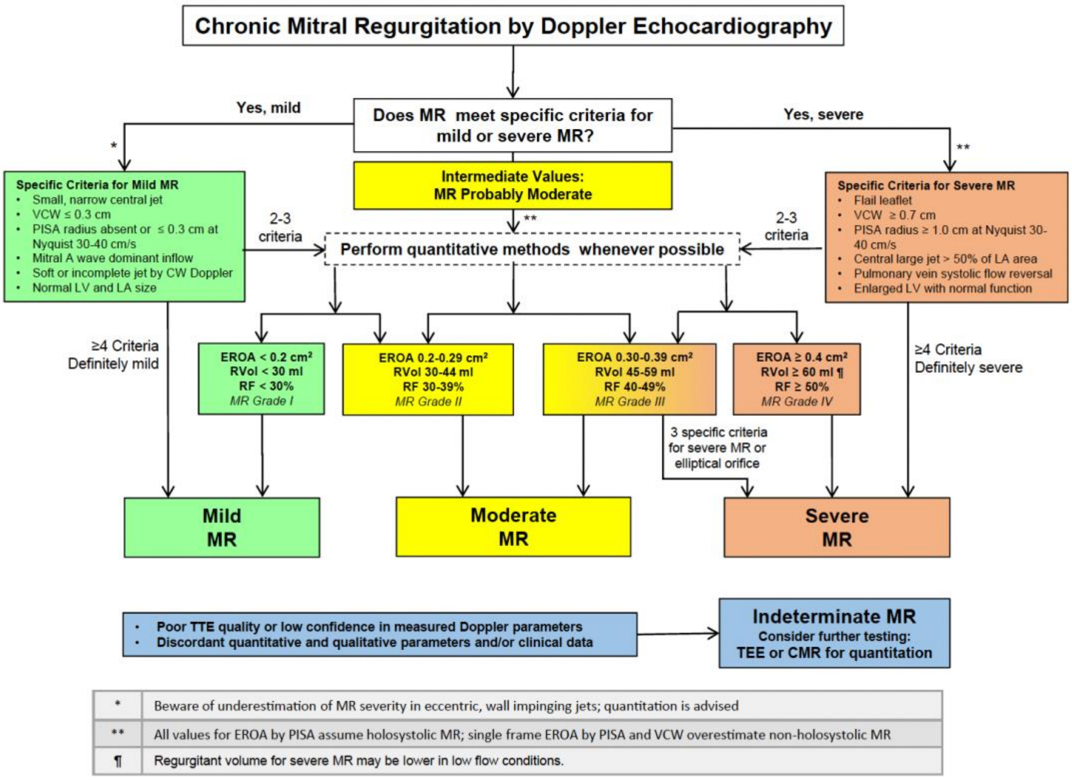



Figure 5. Algorithm for the integration of multiple parameters of MR severity. CMR, cardiovascular magnetic resonance; EROA, effective regurgitant orifice area; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; RF, regurgitant fraction; RVol, regurgitant volume; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; VCW, vena contracta width. (Zoghbi, Adams et al. 2017)

### *Indication*

Treatment for DMR is mainly surgical. Medical therapy may be necessary in patients with heart failure in consequence to MR and should follow current heart failure guidelines. However, for patients with DMR and preserved cardiac function no medical therapy is recommended. Indication for surgery should always be discussed in a specialized Heart Team. According to

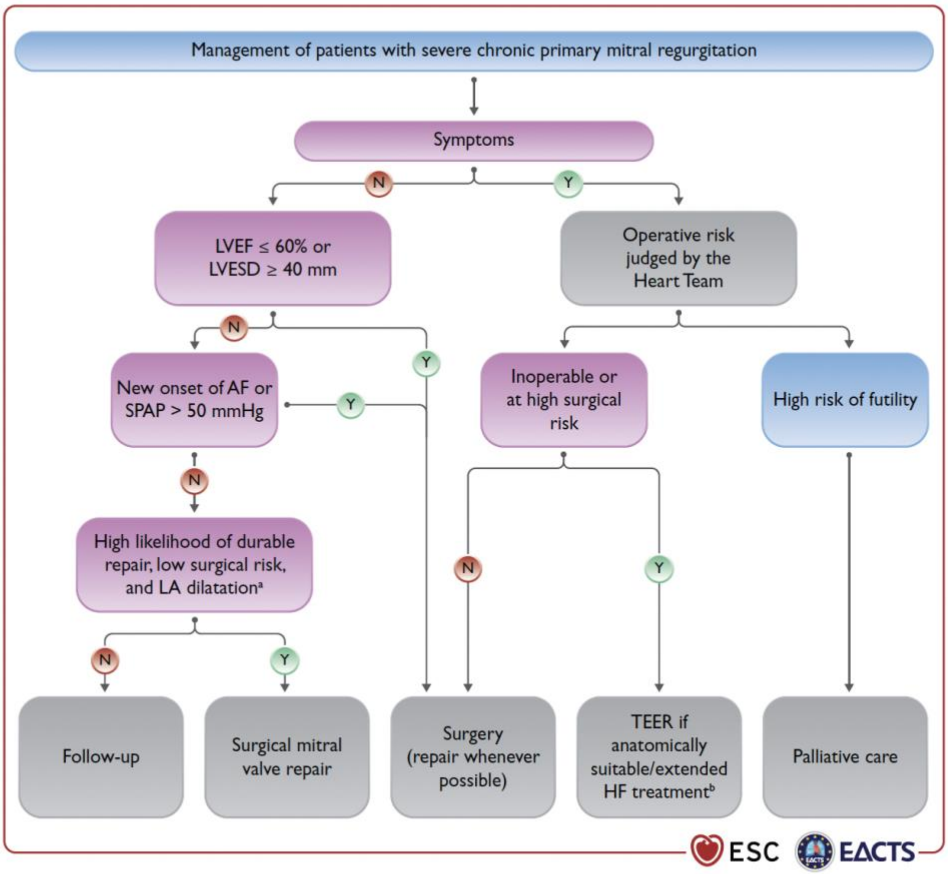



Figure 6. Management of patients with severe MR. AF, atrial fibrillation; HF, heart failure; LA, left atrium; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; SPAP, systolic pulmonary arterial pressure; TEER, transcatheter edge-to-egde-repair. [a]LA dilatation: volume index > 60mL/$m^2$ or diameter >55mm at sinus rhythm. [b]Extended heart failure treatment includes the following: CRT, ventricular assist devices, heart transplantation. (Vahanian, Beyersdorf et al. 2021)

the European Society of Cardiology (ESC) / European Association for Cardiothoracic Surgery (EACTS) Guidelines for the management of valvular heart disease published in 2021, symptomatic patients with severe DMR and low surgical risk are recommended surgery. Asymptomatic patients with severe DMR are recommended surgery if LV dysfunction becomes apparent, i.e. reduction of left ventricular ejection fraction (LVEF) < 60% and/or left ventricular end-systolic diameter (LVESD) ≥ 40mm. Surgery is also recommended in asymptomatic patients with severe DMR and atrial fibrillation (AF) and/or pulmonary hypertension (systolic pulmonary artery pressure >50mmHg) as consequence to MR, even if LV function is preserved. If surgical risk is low, surgery can be considered in patients with significant LA dilatation resulting from severe DMR (Figure 6). (Vahanian, Beyersdorf et al. 2021) Impaired LV function, LA dilatation, AF and pulmonary hypertension have been identified as predictors of worse outcomes in several studies. (Tribouilloy, Grigioni et al. 2009, Suri, Vanoverschelde et al. 2013) Hence, those criteria must be considered when discussing indication for surgery. Symptomatic patients with severe DMR and high surgical risk should be considered for transcatheter edge-to-edge repair.

*Mitral valve repair*

Mitral valve repair (MVR) is the procedure of choice for treatment of DMR, especially when performed in an experienced repair center. Several studies have shown the superiority of MVR to MV replacement especially regarding survival and LV function. (David, Uden et al. 1983, Jokinen, Hippeläinen et al. 2007, Gillinov, Blackstone et al. 2008) In the 1980s, Alain Carpentier revolutionized MVR by publishing a paper descibing reproducable methods of repair while explaining the main principles of underlying pathophysiology. (Carpentier 1983)

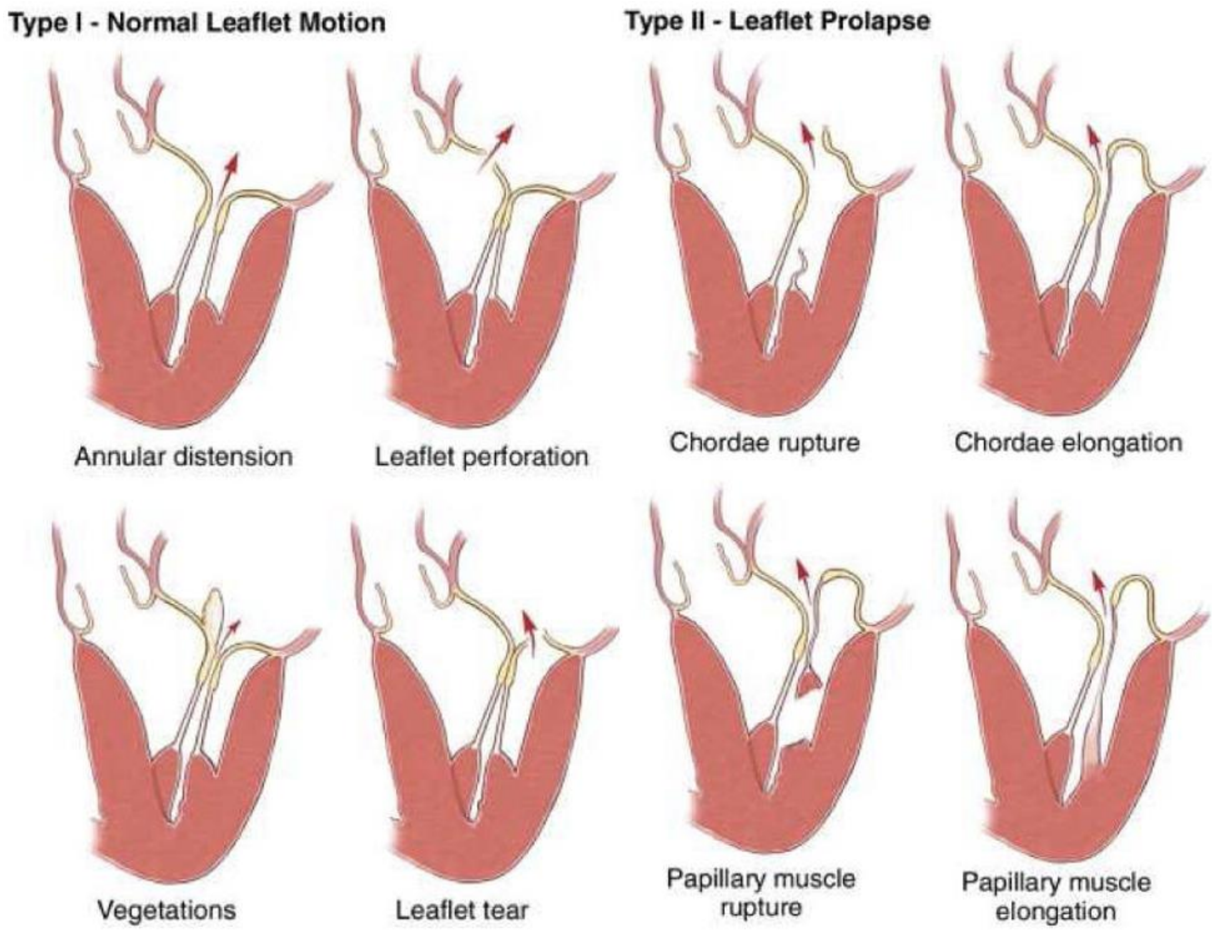



Figure 7. Mitral Regurgitation Type I and II as described by Alain Carpentier. (Alain Carpentier 2010)

His work standardized MVR and increased the success rate of MVR immensely over the

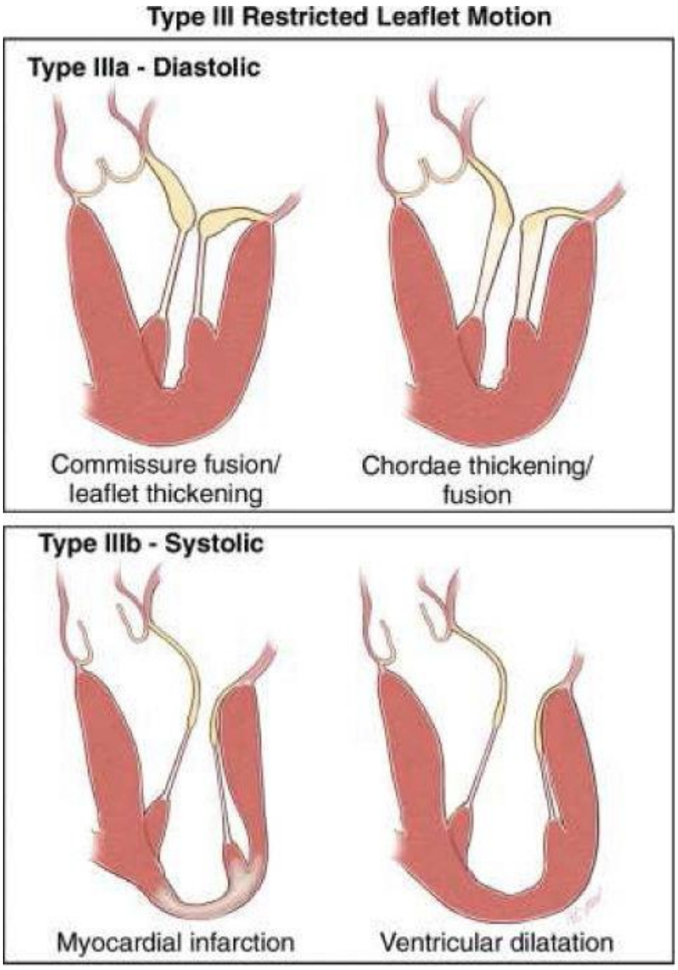


Figure 8. Mitral Regurgiation Type IIIa and IIIb as described by Alain Carpentier. (Alain Carpentier 2010)

following years. Carpentier and his collegues simplified classification of valve pathology by concentrating on function rather than lesion, as there are only two functional aberrations: leaflet prolapse and leaflet restriction. Leaflet prolapse is apparent when the free margin of the leaflet stays above the plane of the MV annulus during systole. Conversely, leaflet restiction is present when motion of the leaflet is limited and hence impairing MV opening during diastole. This simplified approach enables classification of MR into three groups: MR type I is usually caused by annular dilatation and leaflet perforation, leaflet motion is not impaired. (Figure 7) MR type II is defined by leaflet prolapse, which is caused by chordae elongation or rupture and even ruptur of papillary muscles. (Figure 7) MR type III presents as leaflet restriction. MR type IIIa describes restricted leaflet motion during diastole, which can be caused by calcification, commissural fusion, leaflet thickening, as well as chordal fusion and thickening. (Figure 8) Restricted leaflet motion during systole is classified as MR type IIIb and is associated with ventricular dyskinesia and dilatation as a result of cardiomyopathy, i.e. ischemic cardiomyopathy. (Figure 8) (Carpentier 1983) The techniques of repair described by Alain Carpentier are based on three main principles, which are stabilization of the annulus, preservation of physiologic leaflet motion and enabling of a large surface of coaptation. Stabilization of the MV annulus is ought to improve size and shape of the MV orifice to prevent stenosis and allow physiological leaflet closure. It is performed using either a prosthetic ring or a band. The appropriate size of annuloplasty is chosen according to the size of the AML using a preformed sizer. The ring is then implanted using mattress sutures minding a steady space interval in between the sutures. Annuloplasty is performed in almost all cases of MVR, even if annular dilatation is not evident, to prevent dilatation in the future. (Carpentier 1983) Carpentiers' approach to mural leaflet prolapse is rectangular resection. Rectangular resection aims to excise the prolapsing portion of the leaflet. Usually, as the name states, a quadrangular portion from the free margin to the annulus is resected. Leaflet continuity is then reinstated by suture of the free margins of the leaflet and annular plication. (Figure 9) In some cases triangular resection is performed, which is mainly used to shorten the free margin of the leaflet and not primarily to resect prolapsing leaflet tissue. (Carpentier 1983) Prolapse of the AML is challenging to repair. Alain Carpentier states to have experienced setbacks when applying resection techniques to the AML, especially when chordal rupture is existing. Hence, he and his colleagues developed other methods focusing on chordal manipulation that led to improved results: Transposition of strong mural chordae, which are opposing the prolapsing portion, by detaching them from the leaflet and

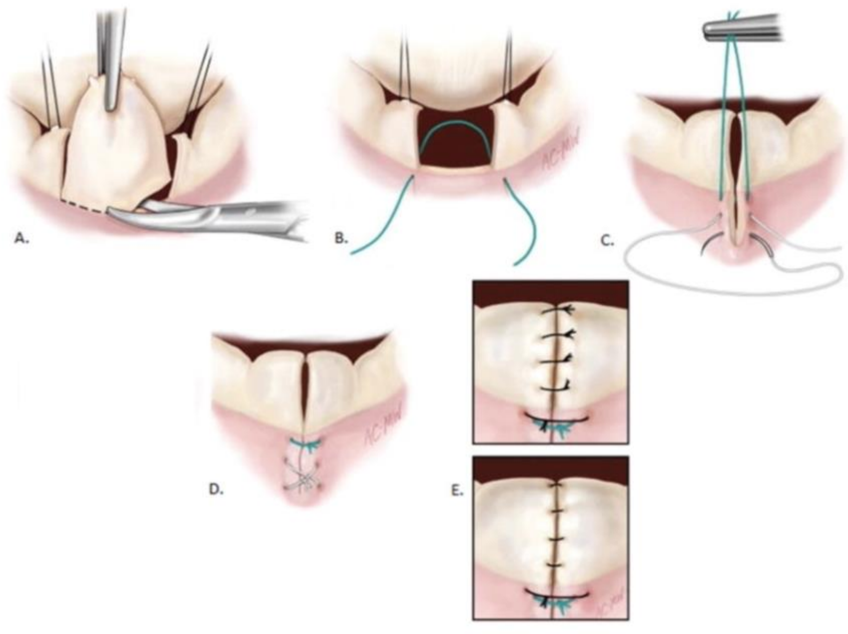



Figure 9. Quadrangular Resection as described by Carpentier. A. Quadrangular portion of prolapsed P2 leaflet is excised. B. An interrupted mattress suture is placed through the annulus at the limits of the resected area. C. A figure-of-eight suture is placed through the annulus to plicate the annulus. D. Completed annular plication.
E. Interrupted sutures are placed to reapproximate the resected leaflet edges, with knots inverted or everted. (Alain Carpentier 2010)

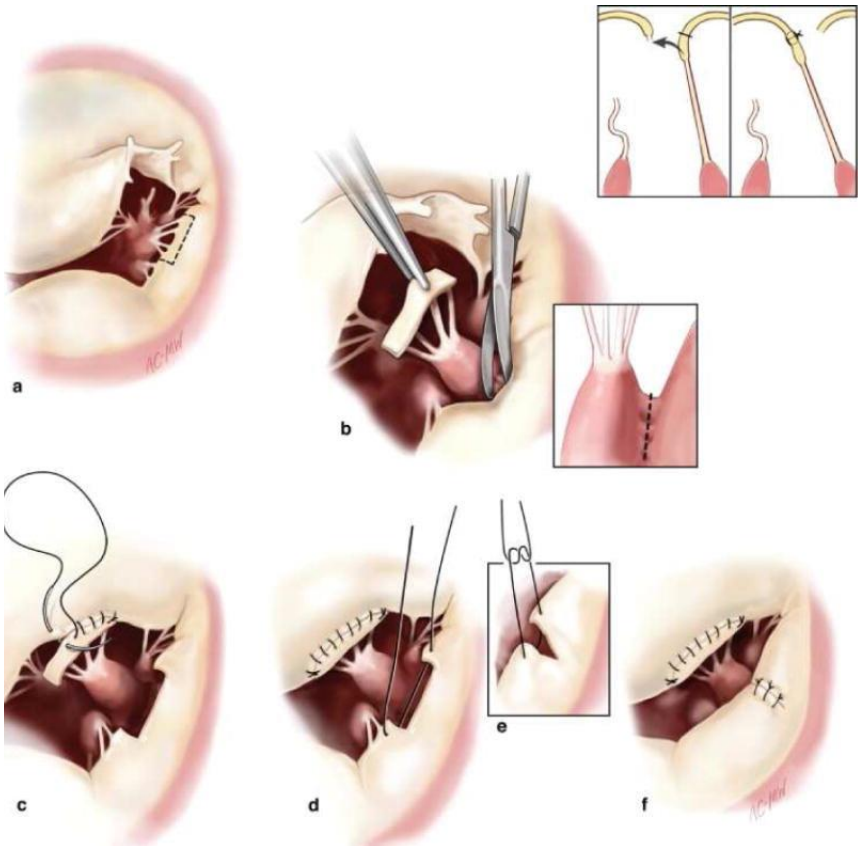



Figure 10. Transposition of chordae tendineae. A. Posterior leaflet adjacent to the area of prolapsed leaflet is identified.B. Posterior leaflet tissue is mobilized with attached chordae, with mobilization of papillary muscle as necessary. C. Reattachment of posterior chordae to prolapsed anterior leaflet. D, E. Reapproximation of posterior leaflet edges. F. Completed chordal transposition. (Alain Carpentier 2010)

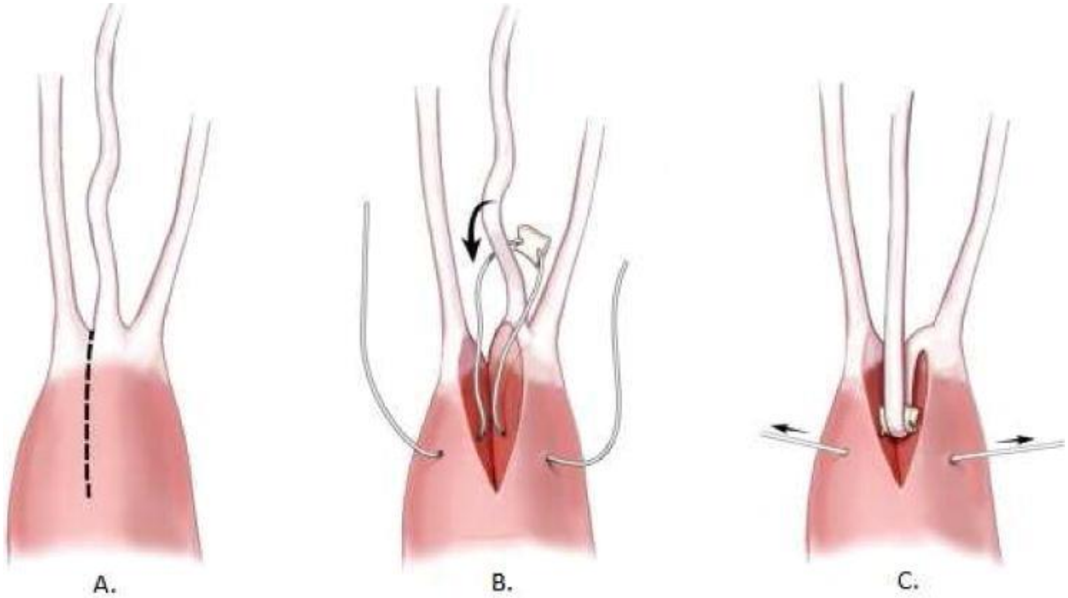



Figure 11. **Chordal shortening. A.** Papillary muscle is divided. **B.** Pledgeted suture is passed around excess chord. **C.** Pledgeted suture around excess chord is invaginated into divided papillary muscle, which is subsequently reapproximated. (Alain Carpentier 2010)

attaching them to the free margin of the AML (Figure 10); Shortening of elongated chordae by folding the excess length of the chordae into the papillary muscle (Figure 11); Fixation of the free leaflet  margin on secondary chordae when there are strong secondary chordae near the prolapsing portion available. (Carpentier 1983) Leaflet restriction is treated by correcting the underlying causes, according to Carpentier. Commissurotomy is performed where usually a commissure is expected and incision commences about 6mm from the annulus towards the MV orifice. Chordal thickening, which is often responsible for leaflet thickening, is treated by removal of those mostly secondary chordae. Importantly, chordae on the margin of the leaflet must remain as they avert prolapse. However, if those marginal chordae are thickened and subsequently cause restriction, they ought be fenestrated. (Carpentier 1983) For a long time, those methods established by Carpentier and his colleagues were considered gold standard and until today those methods are performed regularly. However, especially Carpentiers' techniques on chordal transposition and shortening are difficult and hence did not always involve promissing results. (Smedira, Selman et al. 1996)

*Chordal replacement*

Chordal replacement offers a different approach to chordal rupture or elongation and has been a topic of interest since the first MVR have been performed. However, before Vetter and collegues successfully established expanded polytetrafluoroethylene (ePTFE) sutures for chordal replacement in an animal model in 1986, experiments were performed with other materials. In the 1960s, case reports and small clinical series were published on chordal replacement with different types of sutures, including silk and mersilene. (JANUARY, FISHER et al. 1962, Kay and Egerton 1963, MENGES, ANKENEY et al. 1964, SANDERS, SCANNELL et al. 1965) Results were not promising as some of those patients died during surgery or needed early reoperation for technical failures. In addition, follow-up data on surviving patients was limited. At the same time, experimental and clinical research with pericardial tissue as replacement for chordae tendineae yielded more auspicious early results. (Frater 1964, Frater, Berghuis et al. 1965) Nevertheless, after a few years the pericardium showed extensive fibrosis and calcification,

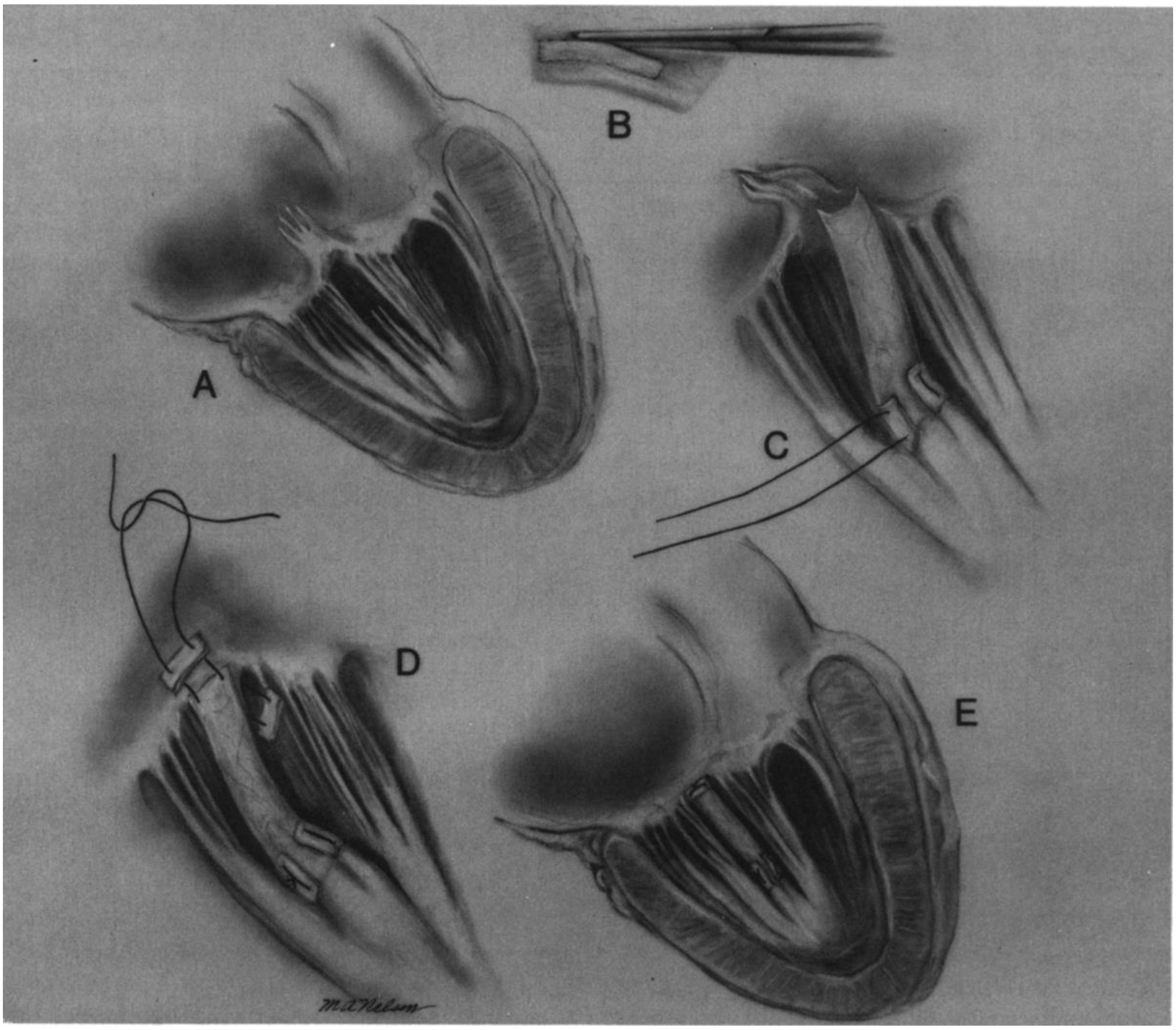



Figure 12. Chordal replacement with autologous pericardium as described by Rittenhouse et al. (Rittenhouse, Davis et al. 1978)

which again led to failure of repair. In the 1980s, chordal replacement with pericardium was reassesed after experiments with autologous pericardium showed excellent early results (Figure 12). (Rittenhouse, Davis et al. 1978) This time, Frater and collegues treated xenograft pericardium with gluturaldehyde to improve longevity. (Frater, Gabbay et al. 1983, Gabbay, Bortolotti et al. 1984) Narrow stripes of both autologous and gluturaldehyde-treated xenograft pericardium were sutured to the AML or posterior mitral leaflet (PML) and papillary muscles. Although initial healing was good in both specimen, in long term calcification and stiffening was observed in all cases. (Frater, Gabbay et al. 1983, Gabbay, Bortolotti et al. 1984) All of those studies made clear that, although the concept of chordal replacement is reproducible and versatile, long-lasting material is needed for this technique to be successful. Vetter and his collegues took an interest in ePTFE sutures as it was discovered that arterial grafts made of GoreTex were covered by endothelious tissue on the first 1-2 mm. It was shown that fibroblasts attach to intermodal spaces in the structure of ePTFE. This inspired Vetter et al. to test ePTFE sutures as neochords in sheep: it was demonstrated, that neochords of ePTFE sutures were covered with fibrous and endothelial tissue within a few months after implantation. (Vetter 1985) First experiments were performed with 2-0 and 3-0 ePTFE sutures, but those impaired chordal flexibility. Thereafter, Zussa et al. published promising data using 5-0 ePTFE sutures as neochords in an experimental and clinical setting and demonstrated preserved chordal flexibility, while maintaining host coverage of the sutures (Figure 13). (Zussa, Frater et al.

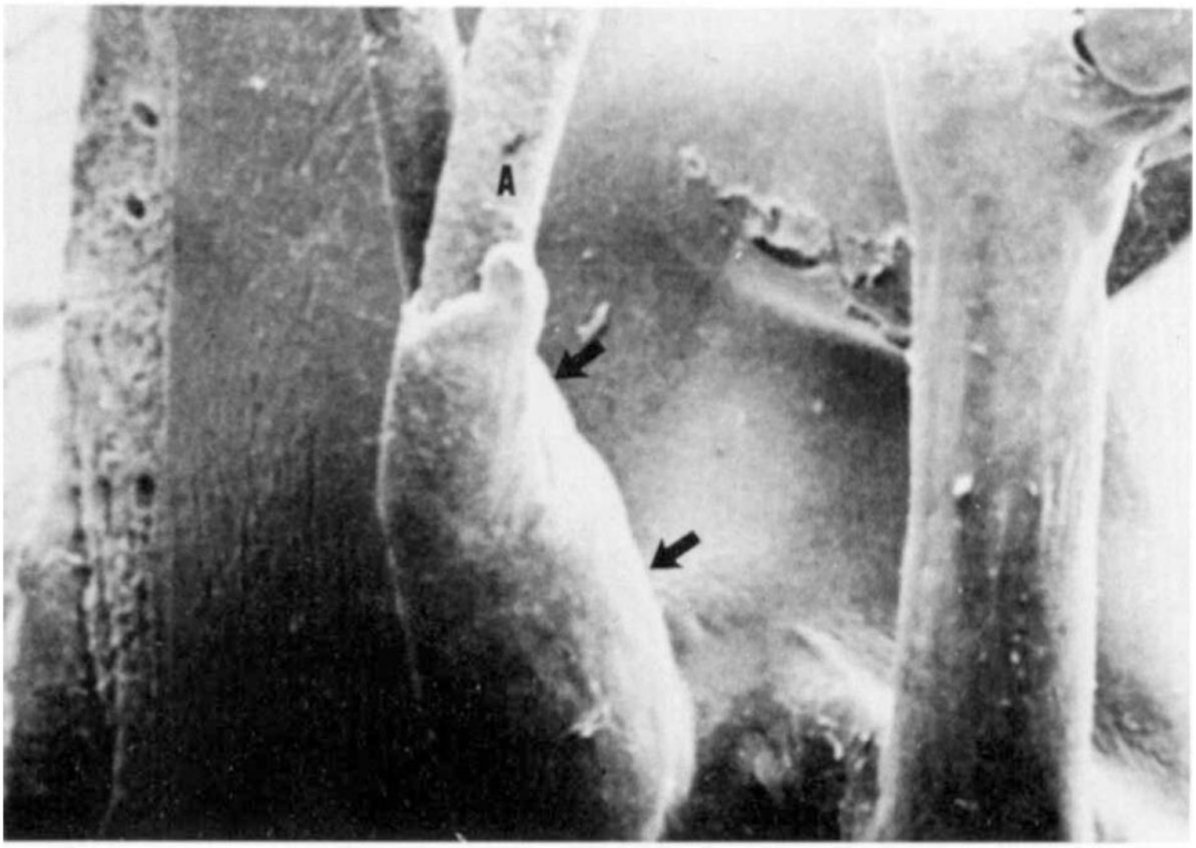



Figure 13. ePTFE chordae (A) partially covered by growing fibrous tissue (arrows) in an animal model. (Zussa, Frater et al. 1990)

1990) Those results were reinforced by an experimental study published by Revuelta et al., which demonstrated complete coverage of ePTFE sutures with collagen tissue resembling that of native chordae tendineae without any sign of calcification. (Revuelta, Garcia-Rinaldi et al.

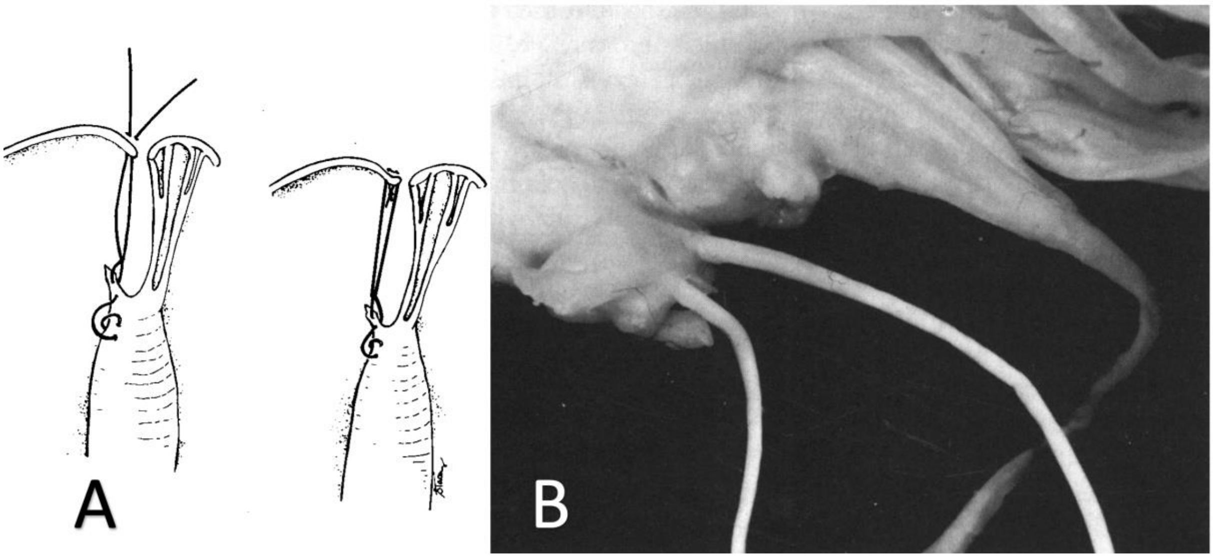


Figure 14. A. Graph of chordal replacement using 5-0 ePTFE sutures. B. Photograph of two ePTFE sutures as compared to one native chord 9 month postoperatively. (David, Bos et al. 1991)

1989) Inspired by those findings, clinical studies were performed and the technique was applied to patients with DMR and subsequently to patients with rheumatic disease. In 1989, Tirone David published a study on MVR using chordal replacement with ePTFE sutures in 22 patients, who could not be treated with regular methods. (DAVID 1989) He demonstrated excellent early results with 18 patients showing no sign of residual MR, 3 patients with mild MR and 1 patients with moderate MR over a mean follow-up period of 17 months (Figure 14). Another work by David et al. involving a slightly larger patient cohort showed similar short-term results and noted that chordal replacement might be easier applied than conventional methods of chordal transfer and shortening. (David, Bos et al. 1991) In 1998, David et al. published the outcome of MVR with and without chordal replacement in a cohort of 324 patients with a mean follow-up of 3 ± 2.5 years (ranging from 0.5 – 13 years). (David, Omran et al. 1998) In this study, patients with AML and bileaflet (BL) prolapse mostly received chordal replacement and patients with posterior mitral leaflet (PML) prolapse were treated with other repair techniques, especially leaflet resection. Through this study, it could be demonstrated that neochordal replacement increases the probability of MVR. In addition, chordal replacement did not rise the risk of complications and was associated with excellent results as compared to other MVR techniques.

*Different Surgical techniques using Chordal Replacement*

Chordal replacement with ePTFE sutures is performed by passing a two-armed 4-0 suture through the fibrous part of the papillary muscle. Then both arms are individually passed through the free margin of the leaflet about 4 – 5 mm apart. After determination of the correct length of the leaflet by distending the ventricle with saline solution via the MV with a bulb syringe, the ends of both arms are tied on the atrial surface of the leaflet on a hemostatic clip or a pledget. (Zussa, Frater et al. 1990) Usually multiple neochords are placed, depending on the individual pathology. Moreover, stabilization of the MV annulus is crucial for successful MVR and is achieved by annuloplasty with a ring or a band. (Gillinov, Tantiwongkosri et al. 2009) When David et al. first performed chordal replacement, they used 5-0 ePTFE sutures and tied the two ends on the ventricular side after passing each arm twice through the free margin of the mitral leaflet. (Figure 15) (David, Bos et al. 1991, David, Omran et al. 1998) Neochords were placed at areas where the native chord was attached. In addition, most patients in David's publication also received ring annuloplasty. (David, Omran et al. 1998) The main challenge of chordal replacement is to determine the correct length of neochords and maintaining the correct length without sliding the knot. Numerous surgeons have addressed this issue in their research and over the recent years different approaches were developed to cope with it. In 2000, von Oppell and collegues have introduced "premeasured" ePTFE loops: The correct length is measured with a measuring devise, e.g. a ruler, and loops are formed in the premeasured length by tying a knot over a

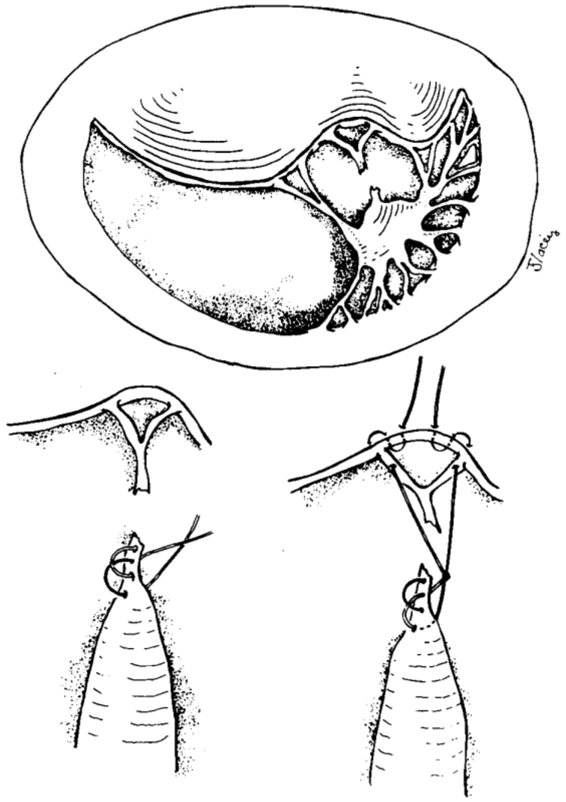


Figure 15. Replacement of chordae tendineae by passing each arm twice through the free margin of the mitral leaflet. (David, Bos et al. 1991)

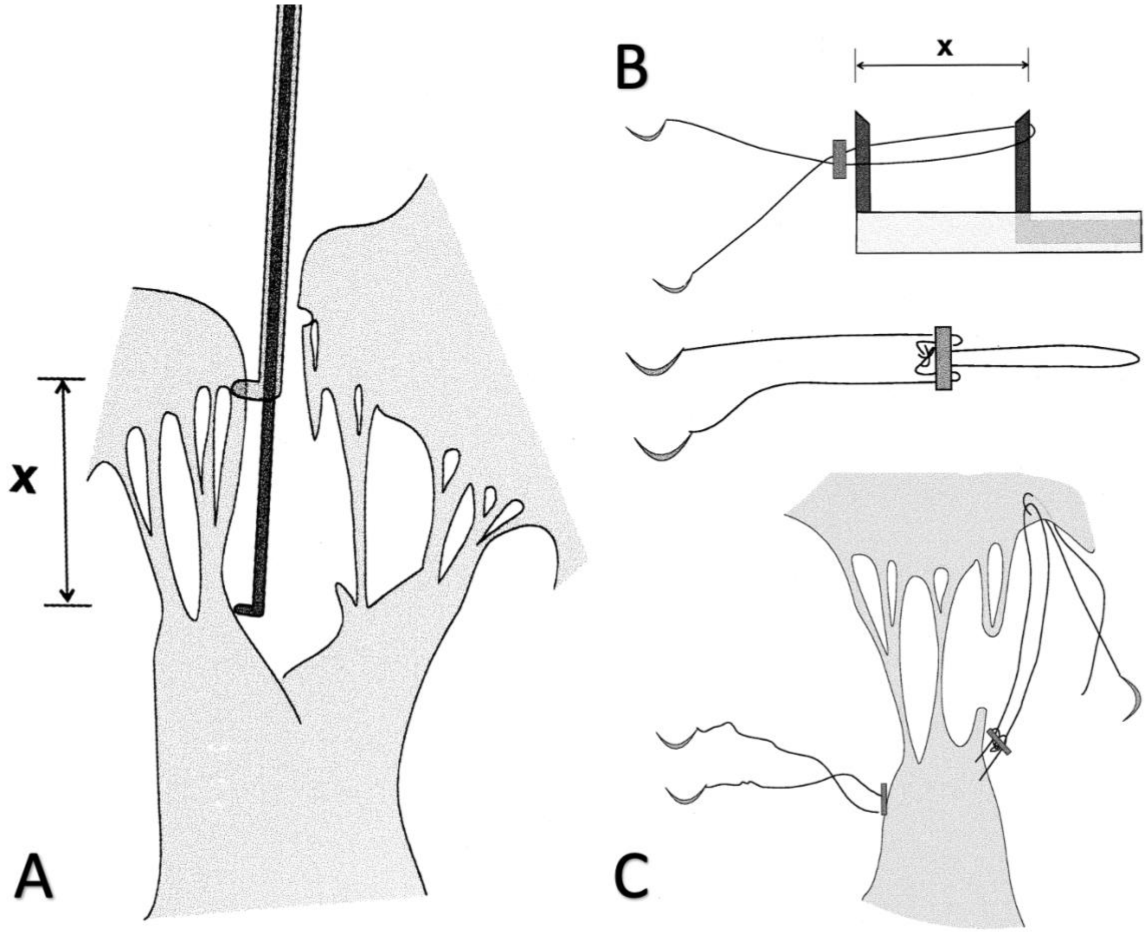



Figure 16. Premeasured ePTFE loops as described by Oppell et al. in 2000. A. The correct length is measured with a ruler. B. Loops are formed in the premeasured length by tying a knot over a pledget. C. The loop is fixed on the papillary muscle and attached to the leaflet using another ePTFE suture. (von Oppell and Mohr 2000)

Figure 17. Three chordal loops using one ePTFE suture, the loop-technique. (Gillinov and Banbury 2007)

small and flat pledget. (von Oppell and Mohr 2000) The suture is then fixed on the papillary muscle using the pledget as secure platform and a second ePTFE suture is used to attach the chordal loop on the mitral leaflet (Figure 16). Gillinov et al. adopted the “loop-technique”: a caliper was used for measurement of chordal length and up to 4 chordal loops were built per suture and pledget (Figure 17). (Gillinov and Banbury 2007) In 2008, Chan et al. proposed another method by securing the correct length with a rubber-protected artery forceps and then tying the knots on it. The correct length is marked on the ePTFE suture with a sterile pen and is determined by matching chordae length to those of the nonprolapsing leaflet. (Chan, Chiu et al. 2008) At the same time, Smith and collegues performed chordal replacement by building chordal loops as described by von Oppell and Mohr (von Oppell and Mohr 2000) but securing them with a U-clip device made from nitinol. (Smith and Stein 2008) In 2006, Rankin et al. introduced another method of length adjustment: both arms of the ePTFE suture were tied on the atrial side with a single slip-knot, which was then locked with a clip and valve competence was tested with saline solution. The slip-knot allows adjustment of chordal length during testing of MV competence. Once the correct length is found 8 more knots are tied on the clip to secure the knot, then the clip is removed. (Figure 18) (Rankin, Orozco et al. 2006)

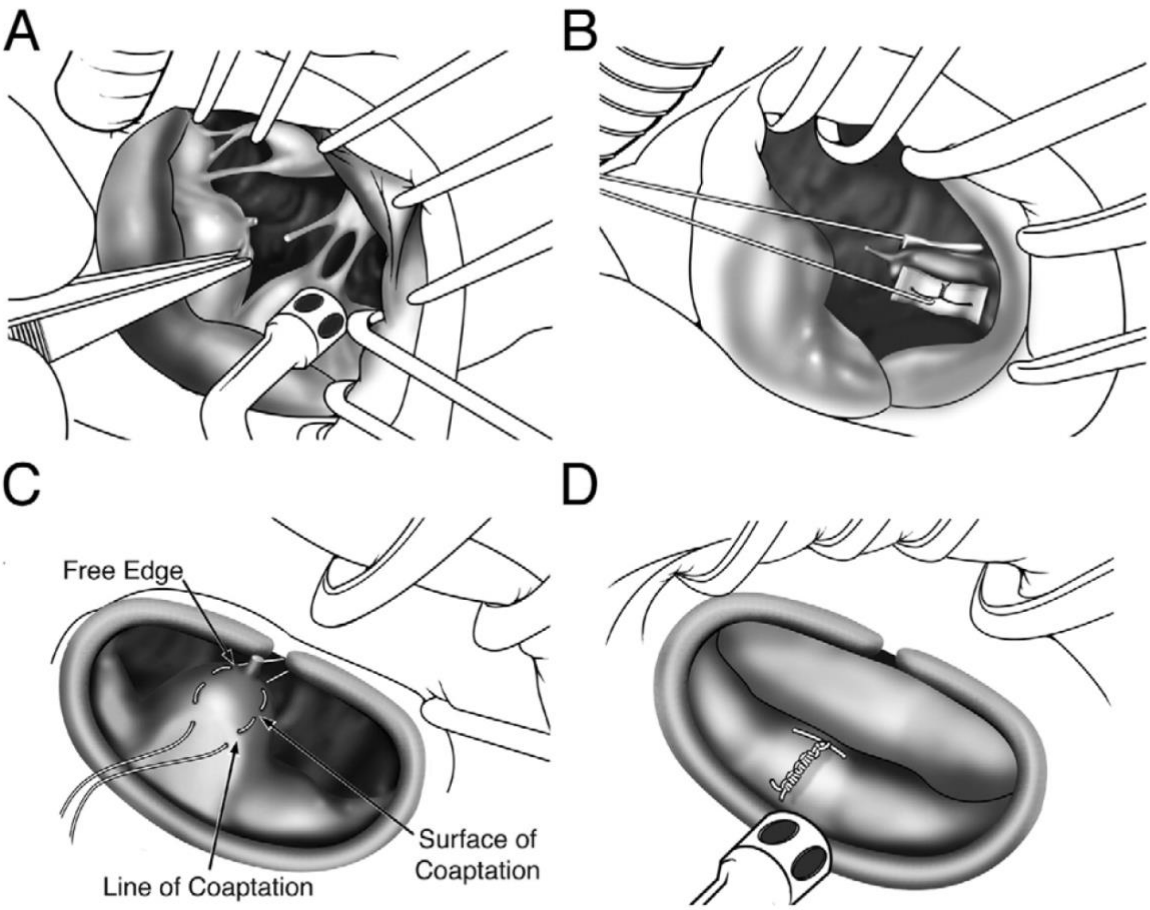



Figure 18. Chordal replacement as described by Rankin et al. in 2006. A. The prolapsing segment is identified. B. The ePTFE suture is passed through the papillary muscle. C. Both arms of the ePTFE suture are passed through the leaflet at the point of maximal prolapse. D. After the correct length is determined, 8 more knots are made to secure the knot. (Rankin, Orozco et al. 2006)

*Recent developments in MVR and objectives of this study*

There is persisting controversy regarding the optimal technique for MVR, i.e. either to resect pathologic leaflet tissue or to preserve leaflet tissue using neochords. In 2008, Falk et al. published a prospective study comparing chordal replacement with resection techniques in patients with prolapse of the PML. (Falk, Seeburger et al. 2008) No significant difference could be demonstrated in between both groups in terms of perioperative complications, rate of reoperation, transmitral pressure gradients and MV orifice area. Moreover, a previous study of our group which compared chordal replacement with quadrangular resection in patients with PML prolapse could not show any difference in survival, recurrent MR and reoperation. (Lange, Guenther et al. 2010) Due to overall excellent outcomes in several studies and the possibility of combination to other repair techniques, chordal replacement has been widely adopted and is performed regularly. In recent years several studies were performed demonstrating excellent mid- and long-term outcomes of MVR using chordal replacement for DMR. (Salvador, Mirone et al. 2008, Tabata, Kasegawa et al. 2014, Hata, Fujita et al. 2015, David, David et al. 2020) In all those studies a significant number of patients received chordal replacement combined with resection techniques. In 2014, Castillo et al. published a study of 188 patients with AML and BL prolapse, who received MVR with various techniques including chordal replacement in 43.5%. (Castillo, Anyanwu et al. 2014) They describe a "lesion-based surgical approach" including all kinds of repair techniques chosen according to each individual case of DMR, which enabled a 99.5% repair rate. This reinforces the idea to concentrate on the optimal repair for each individual case of DMR while working with all repair techniques available, and to less concentrate on proofing the superiority of any repair technique as all cases of DMR are unique. However, long-term data on MVR using solely chordal replacement remains inadequate still. Only one study, published by David et al. in 2013, investigates long-term outcomes after MVR solely with neochordal replacement and annuloplasty. (David, Armstrong et al. 2013) In the present study, we examined long-term results up to 10 years after MVR using chordal replacement and ring annuloplasty for DMR at the German Heart Center Munich.

## Methods

This study was conducted according to the ethical standards of the Declaration of Helsinki. Informed consent was waived. The Research Ethics Committee of the Technical University of Munich approved the study protocol (number 498/20 S). Between 2003 and 2010, 346 patients underwent MVR with neochordal replacement and annuloplasty for DMR at the German Heart Center, Munich. All patients who underwent any concomitant cardiac procedures, except maze procedure, patients with congenital heart disease, and previous mitral valve surgery were excluded. Based on the prolapse localization, the patients were divided into three groups: prolapse of the AML, prolapse of the PML, and BL prolapse. Patients' data were retrospectively identified from the clinical database of the center. All medical reports, including operative protocols and inpatient and outpatient notes, were reviewed. The degree of MR was assessed during preoperative echocardiographic evaluation. MR severity was classified as none/trivial (0), mild (I), moderate (II), moderate-to-severe (III), or severe (IV). (Zoghbi, Adams et al. 2017) Follow-up data included current symptoms, echocardiographic data, and need for reoperation on the MV. Clinical and early postoperative echocardiographic data were collected from our local database and analyzed retrospectively. Late echocardiographic data were collected from the referring cardiologists. All patients were contacted via mail and invited to complete a questionnaire. A sample of the questionnaire can be found in the appendix. Survival data for each patient were systematically cross-referenced by telephone, referring cardiologists, and international databases. Follow-up was completed for 93% (322/346) of patients. The endpoints of this study were long-term survival, cumulative incidence of significant recurrent MR, and cumulative incidence from MV reoperation.

### *Operative technique*

MVR was performed via median sternotomy or anterolateral thoracotomy. Cardiopulmonary bypass was established at systemic hypothermia of 32°C, cannulation techniques depended on the method of thoracotomy, and cardioplegia was administered using crystalloid solution.

All patient included in this study were treated solely by chordal replacement and annuloplasty. For chordal replacement, a 4-0 ePTFE suture without pledgets was passed twice through the fibrous portion of either the anterior or the posterior papillary muscle. Both ends were individually passed through the free margin of the prolapsing leaflet from the left ventricle to the atrium. The suitable length of the neochords was determined during distension of the left ventricle with saline solution. The ideal length of the neochords was secured with a clip and then tied on the left atrial side. Intraoperative TEE was used routinely in all patients to evaluate the operative outcome. If more severe forms of residual MR above mild were observed, the outcome was improved during a second cardiopulmonary bypass run.

*Statistical Analysis*

Continuous variables were expressed as mean ± standard deviation, except stated otherwise. All data were analyzed using IBM SPSS version 25 (IBM Corp., Armonk, NY, USA) and NCSS Data Analysis Software (NCSS, LLC, Kaysville, Utah). Patient survival was estimated using Kaplan-Meier analysis, whereas significance was assessed using the log-rank test. A competing risk analysis was performed using Cox-Mantel logrank test for survival. The cumulative incidence of significant recurrent MR and reoperation was calculated, and the statistical significance was defined using Gray's test. Patients with recurrent significant MR and reoperation due to endocarditis were excluded from calculation of cumulative incidence. Cox regression analysis was used to identify potential risk factors associated with recurrent MR, reoperation, and mortality. The variables included age, sex, atrial fibrillation, preoperative New York Heart Association (NYHA) class, preoperative LVEF <55%, associated diseases (arterial hypertension, diabetes mellitus, hyperlipidemia), location of prolapse, presence of Morbus Barlow, endocarditis, and aortic clamping time. All significant variables in univariate analysis were included in a multivariate model. Annuloplasty rings and bands were compared using Kaplan-Meier estimation of survival and calculation of cumulative incidence of reoperation. The hazard ratios (HR) and 95% confidence intervals (CI) were estimated. P-values <0.05 were considered statistically significant.

Table 1. Patients' baseline data

| | |
|---|---|
| Age (years) | 59.28 ± 12.32 |
| Male sex | 249 (72) |
| Height (cm) | 176.55 ± 36.16 |
| Weight (kg) | 77.56 ± 11.93 |
| Atrial fibrillation | 79 (22.83) |
| Associated diseases | |
| Hypertension | 183 (55.89) |
| Diabetes mellitus | 11 (3.17) |
| Hyperlipidemia | 49 (14.16) |
| Peripheral arterial disease | 4 (1.16) |
| Previous stroke | 11 (2.89) |
| Previous myocardial infarction | 4 (1.16) |
| Infective endocarditis | 15 (4.34) |
| Degree of MR | |
| MR II | 36 (11.01) |
| MR III | 234 (71.56) |
| MR IV | 57 (17.43) |
| NYHA functional class | |
| Class II | 21 (6.27) |
| Class III | 300 (89.55) |
| Class IV | 14 (4.18) |
| LVEF < 55% | 26 (9.06) |

Numbers are presented as n (%), except stated otherwise. LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association

Table 2. Operative data

| | |
|---|---|
| Morbus Barlow | 48 (13.87) |
| Surgical approach | |
| Anterolateral thoracotomy | 251 (72.54) |
| Median sternotomy | 95 (27.46) |
| Localization of leaflet prolapse | |
| AML | 30 (8.67) |
| PML | 266 (76.88) |
| BL | 50 (14.45) |
| Localization of chordae rupture | |
| AML | 12 (4.58) |
| PML | 240 (91.60) |
| BL | 10 (3.82) |
| Elongation of chordae | 158 (45.66) |
| Annuloplasty | |
| none | 1 (0.29) |
| Medtronic Galloway Future Band | 308 (89.02) |
| Medtronic Galloway Future Ring | 35 (10.12) |
| Carpentier Edwards Physio Ring | 1 (0.29) |
| Medtronic Profile 3D Ring | 1 (0.29) |
| Maze procedure | 20 (5.78) |
| Aortic cross clamping time (min) | 81.77 ± 22.69 |
| Extracorporal circulation time (min) | 114.20 ± 32.54 |

Numbers are presented as n (%), except stated otherwise. AML, anterior mitral leaflet; BL, bileaflet; PML, posterior mitral leaflet

## Results

### *Patient Data*

From 2003 to 2010, 807 patients underwent isolated MVR at the German Heart Center, Munich. A total of 346 (42.87%) patients underwent MVR solely with chordal replacement and annuloplasty. The mean age of the patients was 59.28 years (range: 26.85–86.48 years) and 249 (71.97%) patients were males. The clinical characteristics of patients and operative data are summarized in Tables 1 and 2. At surgery, most patients presented symptomatic, as assessed by NYHA functional class. However, the left ventricular ejection fraction was mostly preserved. The mean LVEF was 67.55 ± 13.71%. MR III was most common (Figure 19). Rupture and elongation of native chords was observed in 75.43% and 45.66% of patients, respectively. In all patients, MVR was performed by artificial chordal replacement and annuloplasty using a ring or band. The number of neochords used ranged from 1 – 7 with a median of 3 chords. Most commonly 2 and 3 neochords were implanted in 37.57% and 34.97% of cases, respectively. Only 7.22%, 13.58% and 4.34% of patients received 1, 4 and 5 neochords each. Six and 7 neochords were applied in only 2.02% and 0.29% of cases (Figure 20). All patients received annuloplasty, except for one patient with extensive annular calcification. In 89.02% of cases, annuloplasty was performed using a band (Table 2). The sizes of implanted annuloplasty ring or band were 26–38 (Figure 21). Ring sizes 32 and 34

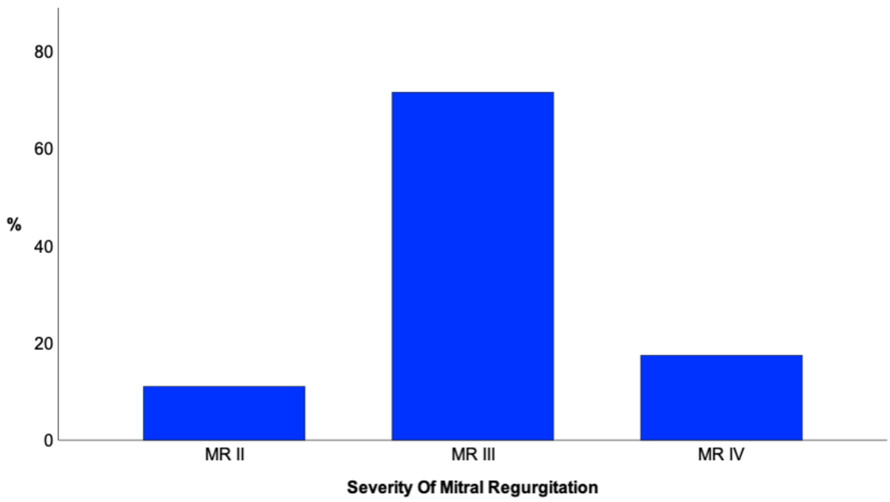



Figure 19. Preoperative ratio of degenerative mitral regurgitation severity. DMR, degenerative mitral regurgitation.

were most used in 24.06% and 23.48% each. Ring sizes 30, 36 and 38 were less often used in 19.42%, 15.94% and 10.72% respectively. With 6.09% and 0.29% ring sizes 28 and 26 were least often used. The perioperative complications are summarized in Table 3. Systolic anterior motion (SAM) occurred in 10 patients; in 8 patients, SAM resolved with increasing intravascular volume and decreasing positive inotrope medication. The other 2 patients needed re-repair during a second cardiopulmonary bypass run.

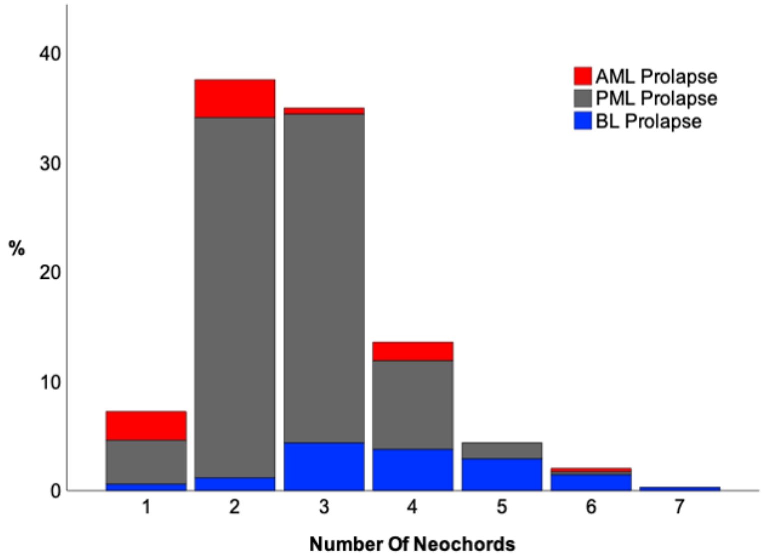



Figure 20. Percentage of Neochords used according to localization of leaflet prolapse. AML, anterior mitral leaflet; BL, bileaflet; PML, posterior mitral leaflet.

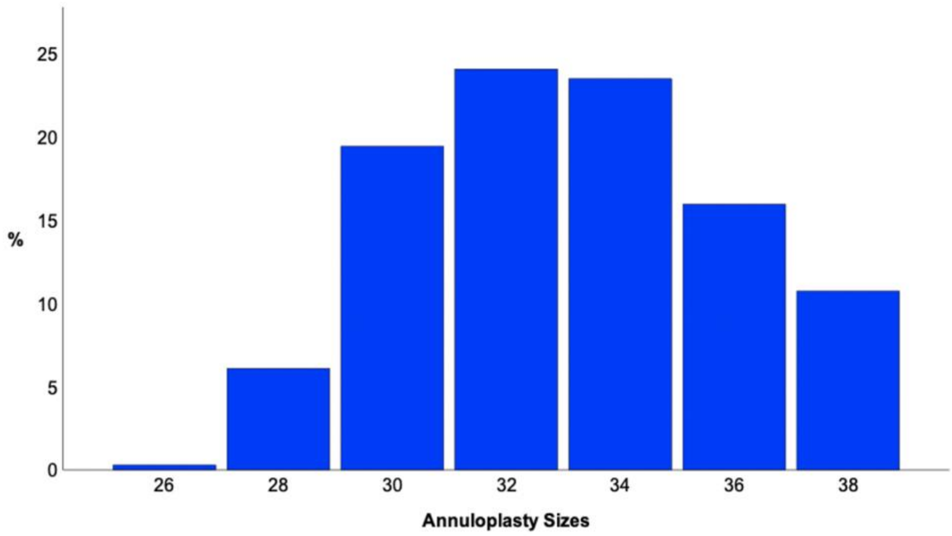



Figure 21. Sizes of annuloplasty in percent.

Table 3. Perioperative complications

| | |
|---|---|
| Systolic anterior motion | 10 (2.89) |
| Rethoracotomy | 5 (1.45) |
| Implantation of pacemaker | 3 (0.87) |
| Myocardial infarction | 3 (0.87) |
| Pericardiotomy | 3 (0.87) |
| Acute kidney failure | 2 (0.58) |
| Apoplexy | 1 (0.29) |
| Mesenteric ischemia | 1 (0.29) |
| Atrioventricular rupture | 1 (0.29) |
| Abdominal bleeding | 1 (0.29) |
| Intracranial bleeding | 1 (0.29) |

Numbers are presented as n (%)

*Survival*

The median follow-up period was 10.86 years (0.01 – 15.86 years). The median echocardiography follow-up period was 8.40 years (0.00 – 15.60 years). Two early deaths were recorded; both deaths were related to low cardiac output syndrome. Additionally, 56 late deaths occurred. Kaplan-Meier estimated survival rates at 1, 5, and 10 years were 97.65 ± 0.82%, 92.97 ± 1.41%, and 83.35 ± 2.15%, respectively (Figure 22). Patients with AML prolapse had survival rates of 100%, 92.98 ± 4.79%, and 71.97 ± 9.11% at 1, 5, and 10 years, respectively. Survival rates of patients with PML prolapse were 97.71 ± 0.92%, 93.67 ± 1.53%, and 85.24 ± 2.32% at 1, 5, and 10 years, respectively. Patients with BL prolapse had survival rates of 95.96 ± 2.80%, 89.26 ± 4.55%, and 79.84 ± 6.04% at 1, 5, and 10 years, respectively. No significant difference was observed among the groups ($P$ = 0.36; AML vs. PML, $P$ = 0.16; AML vs. BL, $P$ = 0.50; PML vs. BL, $P$ = 0.58) (Figure 23). Findings of the Cox-Mantel logrank test are summarized in Table 4. Multivariate cox regression analysis identified age (HR, 1.122;

95% CI, 1.081 – 1.163; *P* < 0.001), LVEF <55% (HR, 2.446; 95% CI, 1.138 – 5.257; *P* = 0.022), and diabetes mellitus (HR, 2.761; 95% CI, 1.044 – 7.305; *P* = 0.041) as independent risk factors for death (Table 5).

Table 4. Competing risk analysis for survival: Cox-Mantel Logrank Test

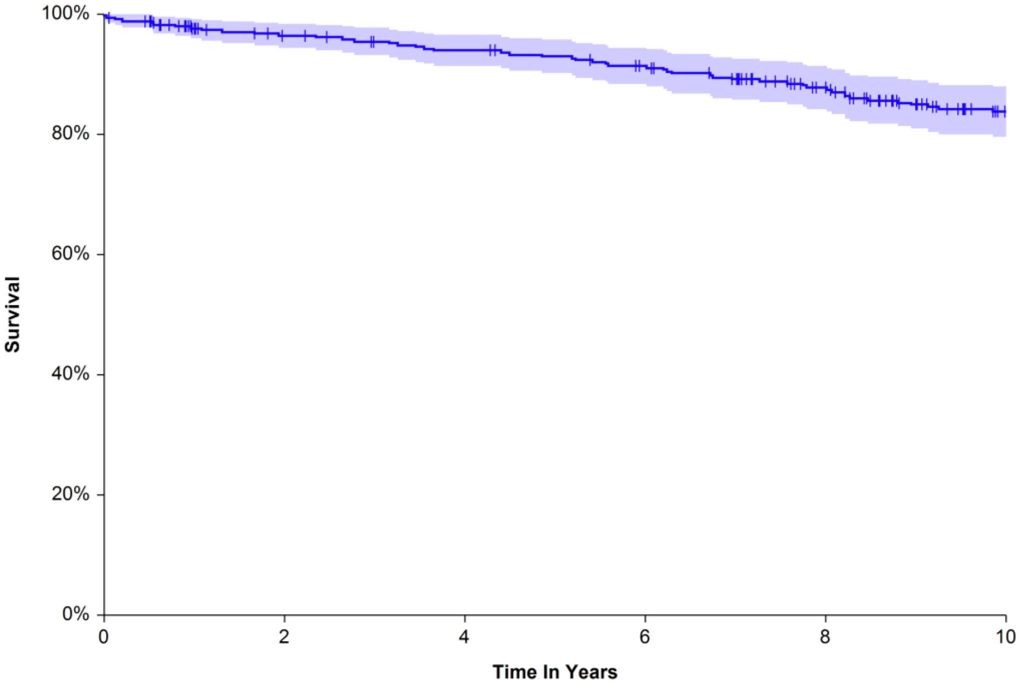
| Group Ratio | Hazard Ratio | Lower 95% CI for HR | Upper 95% CI for HR | P-value |
|---|---|---|---|---|
| AML/PML | 1.71 | 0.68 | 4.30 | 0.1608 |
| AML/BL | 1.38 | 0.52 | 3.67 | 0.5015 |
| PML/AML | 0.59 | 0.23 | 1.47 | 0.1608 |
| PML/BL | 0.82 | 0.38 | 1.77 | 0.5793 |
| BL/AML | 0.72 | 0.27 | 1.91 | 0.5015 |
| BL/PML | 1.23 | 0.57 | 2.65 | 0.5793 |

AML, anterior mitral leaflet; BL, bileaflet; CI, confidence interval; HR, hazard ratio; PML, posterior mitral leaflet

Table 5. Predictors of mortality as identified by cox regression analysis

| Parameter | HR | 95% CI | p-value |
|---|---|---|---|
| Age | 1.122 | 1.081 – 1.163 | < .001 |
| LVEF | 2.446 | 1.138 – 5.257 | 0.022 |
| Diabetes mellitus | 2.761 | 1.044 – 7.305 | 0.041 |

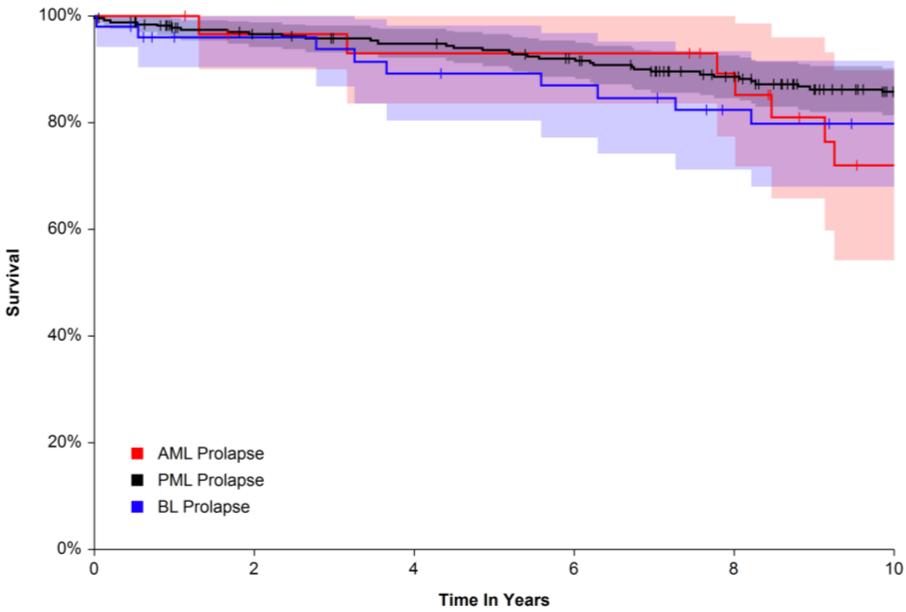
CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction




Number At Risk

| | | | | | |
|---|---|---|---|---|---|
| 346 | 311 | 299 | 286 | 254 | 206 |

Figure 22. Overall Survival.




Number At Risk

| | | | | | | |
|---|---|---|---|---|---|---|
| AML Prolapse | 30 | 27 | 26 | 26 | 23 | 15 |
| PML Prolapse | 266 | 241 | 233 | 222 | 198 | 161 |
| BL Prolapse | 50 | 43 | 40 | 38 | 33 | 30 |

Figure 23. Survival according to leaflet prolapse. AML, anterior mitral leaflet; BL, bileaflet; PML, posterior mitral leaflet.

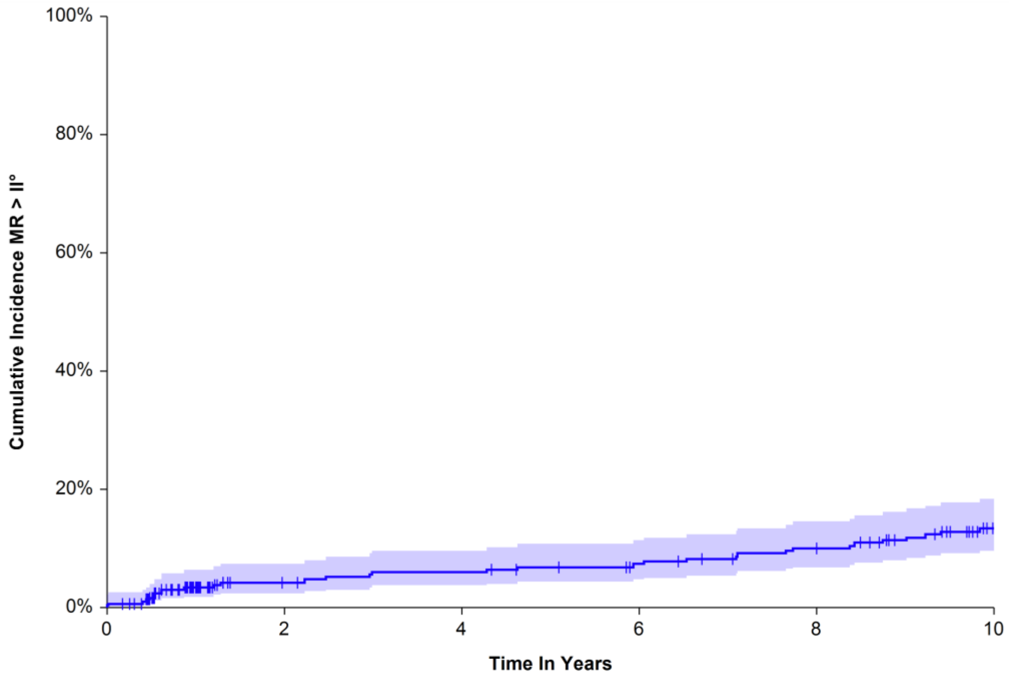
*Recurrent MR >II°*

Significant recurrent MR occurred in 48 patients during follow-up. Seven of these patients were diagnosed with infective endocarditis. Cox regression analysis revealed LVEF <55% prior to operation as the only predictor of significant recurrent MR (HR, 3.255; 95% CI, 1.235 – 8.579; p = 0.017). Overall, the cumulative incidence of recurrent MR >II° was 3.44 ± 1.07% (95% CI, 1.87 – 6.34) at 1 year, 6.87 ± 1.57% (95% CI, 4.38 – 10.76) at 5 years, and 13.31 ± 2.22% (95% CI, 9.61 – 18.45) at 10 years (Figure 24 and Table 6). The cumulative incidence of recurrent MR in patients with AML prolapse were 4.23 ± 4.14% (95% CI, 0.62 – 28.79), 4.23 ± 4.14% (95% CI, 0.62 – 28.79), and 27.13 ± 10.38% (95% CI, 12.82 – 57.41) at 1, 5, and 10 years, respectively. In patients with PML prolapse, recurrent MR occurred with cumulative incidence of 3.14 ± 1.17% (95% CI, 1.51 – 6.52), 7.68 ± 1.92% (95% CI, 4.70 – 12.55), and 13.09 ± 2.52% (95% CI, 8.98 – 19.07) at 1, 5, and 10 years, respectively. In comparison, patients with BL prolapse had cumulative incidence of recurrent MR of 4.55 ± 3.15% (95% CI, 1.18 – 17.65) at 1 year, 4.55 ± 3.15% (95% CI, 1.18 – 17.65) at 5 years, and 7.48 ± 4.19% (95% CI, 2.49 – 22.45) at 10 years. No significant difference among the groups was observed (*P* = 0.41; AML vs. PML, *P* = 0.42; AML vs. BL, *P* = 0.18; PML vs. BL, *P* = 0.33) (Figure 25).

Table 6. Competing risk analysis - Cumulative Incidence of recurrent significant MR

| Time | Cumulative Incidence of Recurrent MR | Lower 95% CI for Cum. Inc. | Upper 95% CI for Cum. Inc. | Std. Error of Cum. Inc. |
|---|---|---|---|---|
| 1 year | 0,0344 | 0,0187 | 0,0634 | 0,0107 |
| 5 years | 0,0687 | 0,0438 | 0,1076 | 0,0157 |
| 10 years | 0,1331 | 0,0961 | 0,1845 | 0,0222 |

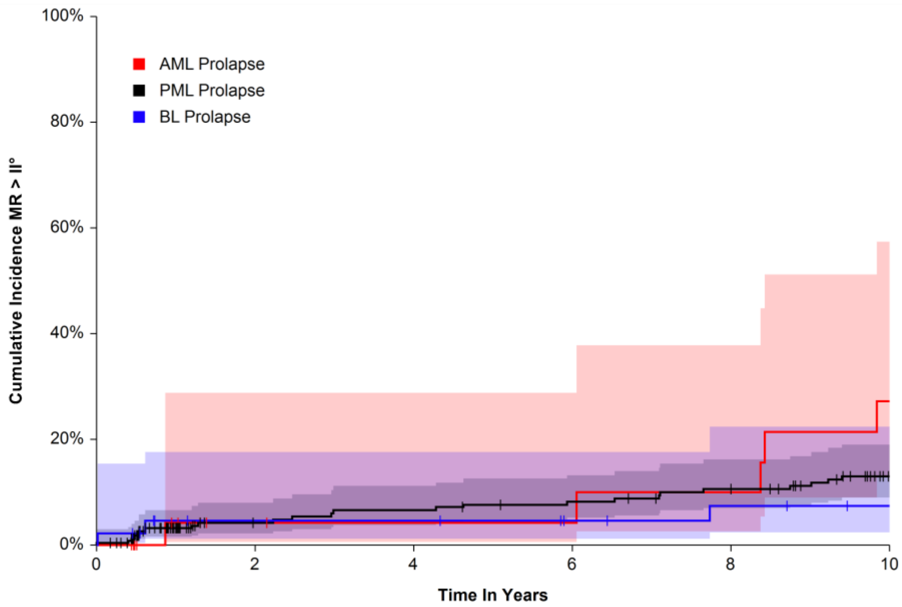
p = 0.41 (Gray’s test). CI, confidence interval; MR, mitral regurgitation




Number At Risk

| | | | | | |
|---|---|---|---|---|---|
| 310 | 190 | 183 | 173 | 158 | 130 |

Figure 24. Cumulative incidence of recurrent mitral regurgitation. MR, mitral regurgitation




Number At Risk

| | | | | | | |
|---|---|---|---|---|---|---|
| AML Prolapse | 29 | 14 | 12 | 12 | 10 | 7 |
| PML Prolapse | 236 | 145 | 140 | 133 | 123 | 102 |
| BL Prolapse | 45 | 31 | 31 | 28 | 25 | 21 |

Figure 25. Cumulative Incidence of recurrent mitral regurgitation according to leaflet prolapse AML, anterior mitral leaflet; BL, bileaflet; MR, mitral regurgitation; PML, posterior mitral leaflet

*Reoperation*

Reoperation on the MV was performed in 38 (10.98%) patients after a median period of 7.07 years (range: 0.00 – 14.13 years). Two patients underwent reoperation within 1 week after surgery, and 4 patients underwent reoperation within 1 year after surgery. Reason for reoperation was significant recurrent MR in 29 cases and endocarditis in 7 cases. In 4 cases avulsion of neochords was observed, of those 2 presented with acute endocarditis. In 4 cases central ruptures of neochords occurred, one of those presented with acute endocarditis. In 10 cases re-repair of the MV was possible and in 25 cases MV replacement was performed. One patient received a mitral clip. In 2 cases the cause and method of reoperation is unknown. Reasons and methods for reoperation are summarized in table 7.
Ten patients with significant recurrent MR did not undergo reoperation. 4 patients present with progression of MV degeneration: 3 with re-prolapse of the posterior leaflet; 1 with extensive calcification of the mitral valve. All of those were recommended reoperation but have not yet been scheduled for reoperation at latest follow-up. Cox regression analysis could not reveal any independent risk factors for reoperation on the MV. In total, the cumulative incidence of reoperation was 1.80 ± 0.73% (95% CI, 0.81 – 3.98), 3.69 ± 1.05% (95% CI, 2.12 – 6.43), and 7.84 ± 1.55% (95% CI, 5.33 – 11.54) at 1, 5, and 10 years, respectively (Figure 26 and Table 8). In patients with AML prolapse, the cumulative incidence of reoperation on the MV was 0% and 16.04 ± 7.42% (95% CI, 6.48 – 39.70) at 5 and 10 years, respectively. In patients with PML prolapse, the cumulative incidence was 1.57 ± 0.78% (95% CI, 0.60 – 4.16), 4.04 ± 1.25% (95% CI, 2.20 – 4.71), and 7.16 ± 1.68% (95% CI, 4.52 – 11.34) at 1, 5, and 10 years, respectively. Whereas in patients with BL prolapse, the cumulative incidence of reoperation was 4.09 ± 2.83% (95% CI, 1.05 – 15.89), 4.09 ± 2.83% (95% CI, 1.05 – 15.89), and 6.47 ± 3.63% (95% CI, 2.16 – 19.40) at 1, 5, and 10 years, respectively. No significant difference among the three groups was observed ($P$ = 0.75; AML vs. PML, $P$ = 0.50; AML vs. BL, and $P$ = 0.48; PML vs. BL $P$ = 0.84) (Figure 27).

Table 7. Reoperation

| **Reason for Reoperation** | |
|---|---|
| Recurrent MR | 29 (76.32) |
| Endocarditis | 7 (18.42) |
| Rupture of neochords | 4 (10.53) |
| With endocarditis | 1/4 (25) |
| Avulsion of neochords | 4 (10.52) |
| With endocarditis | 2/4 (50) |
| **Method of Reoperation** | |
| MV re-repair | 10 (26.32) |
| MV replacement | 25 (65.79) |
| Method unknown | 2 (5.26) |

Numbers are presented as n (%). MR, mitral regurgitation; MV, mitral valve

Table 8. Competing risk analysis - Cumulative Incidence of Reoperation

| Time | Cumulative Incidence of Reoperation | Lower 95% CI for Cum. Inc. | Upper 95% CI for Cum. Inc. | Std. Error of Cum. Inc. |
|---|---|---|---|---|
| 1 year | 0,0180 | 0,0081 | 0,0398 | 0,0073 |
| 5 years | 0,0369 | 0,0212 | 0,0643 | 0,0105 |
| 10 years | 0,0784 | 0,0533 | 0,1154 | 0,0155 |

p = 0.75 (Gray's test). CI, confidence interval

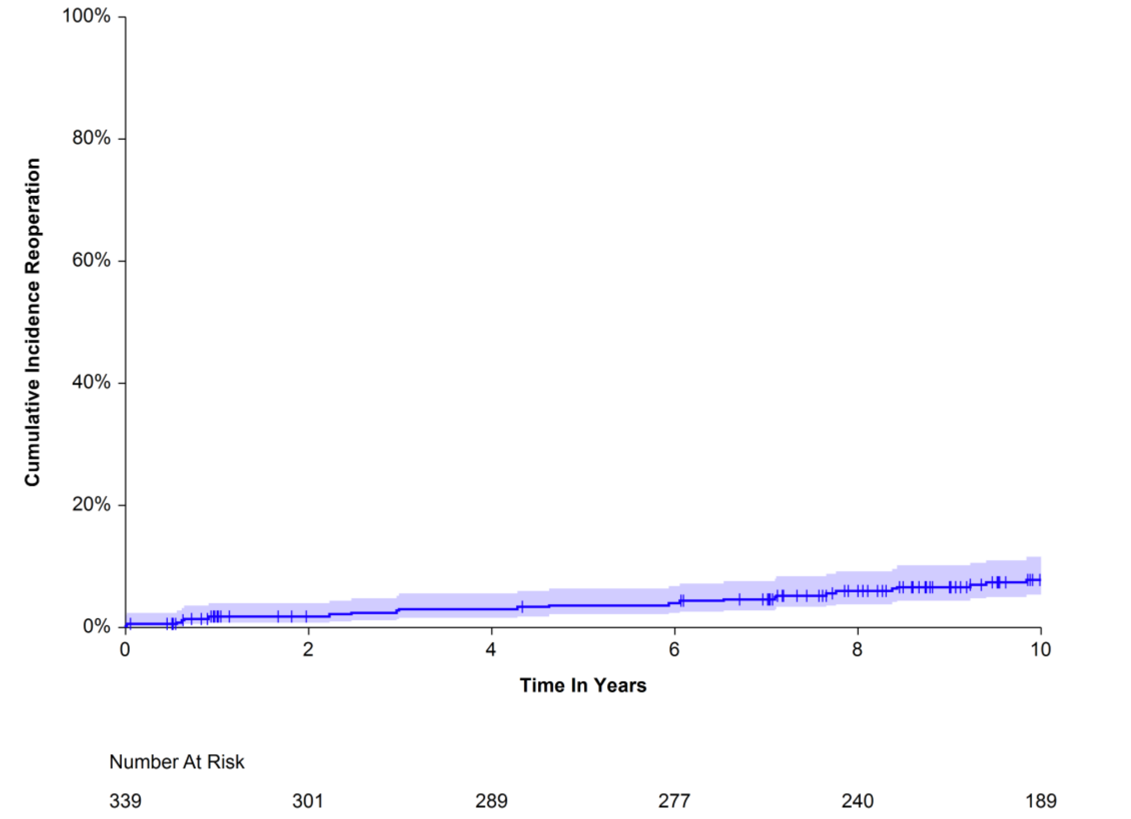



Figure 26. Cumulative incidence of reoperation on the mitral valve

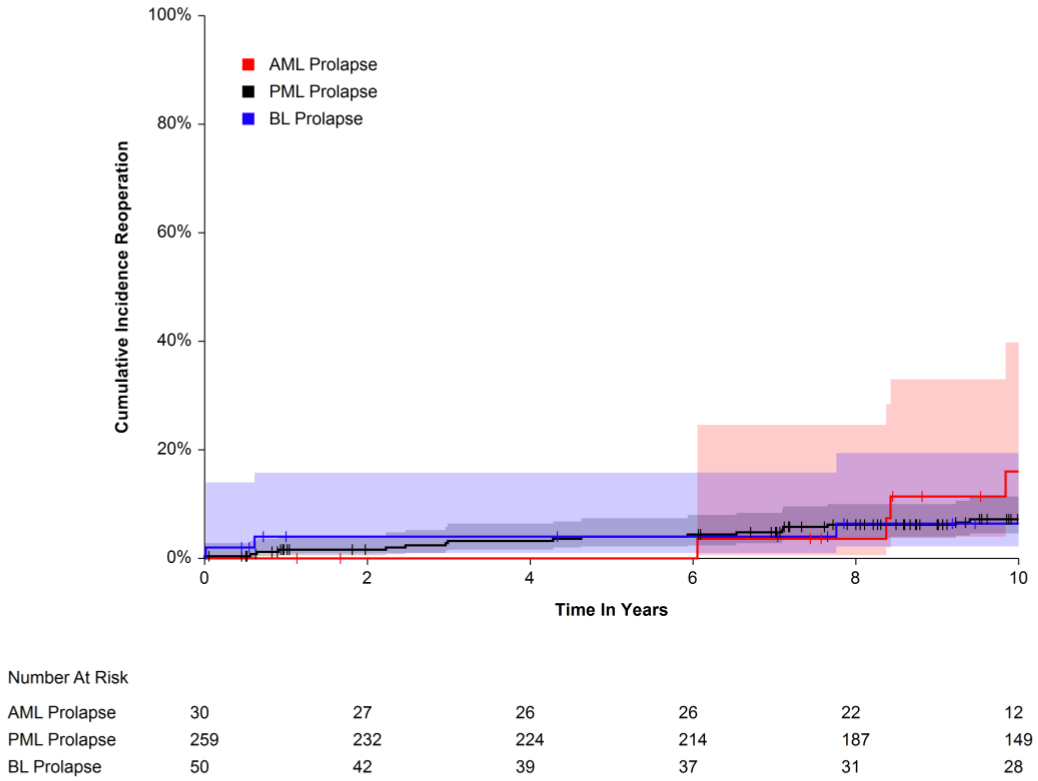
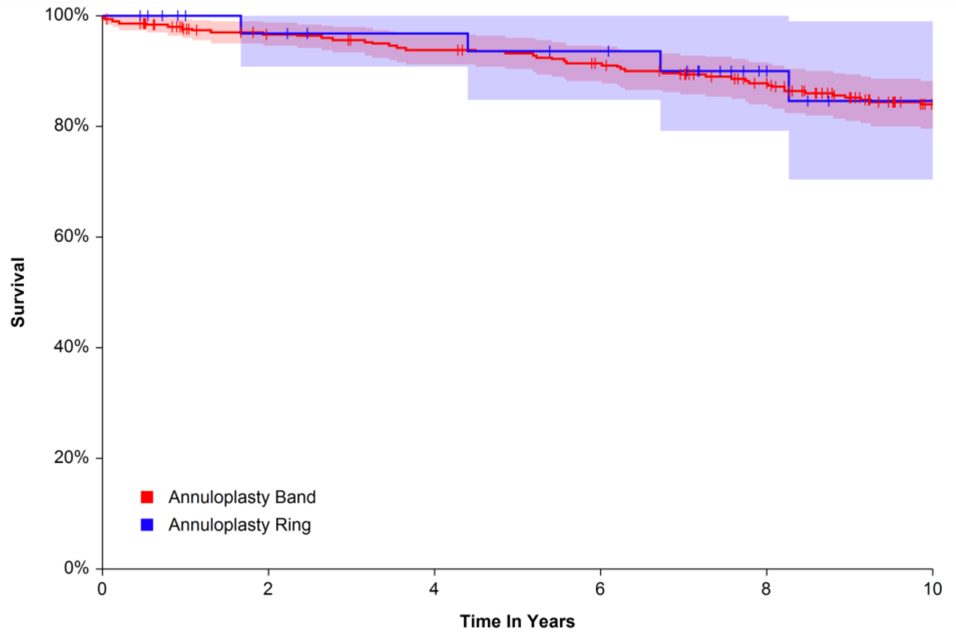



Figure 27. Cumulative incidence of reoperation on the mitral valve according to leaflet prolapse. AML, anterior mitral leaflet; BL, bileaflet; PML, posterior mitral leaflet

*Annuloplasty*

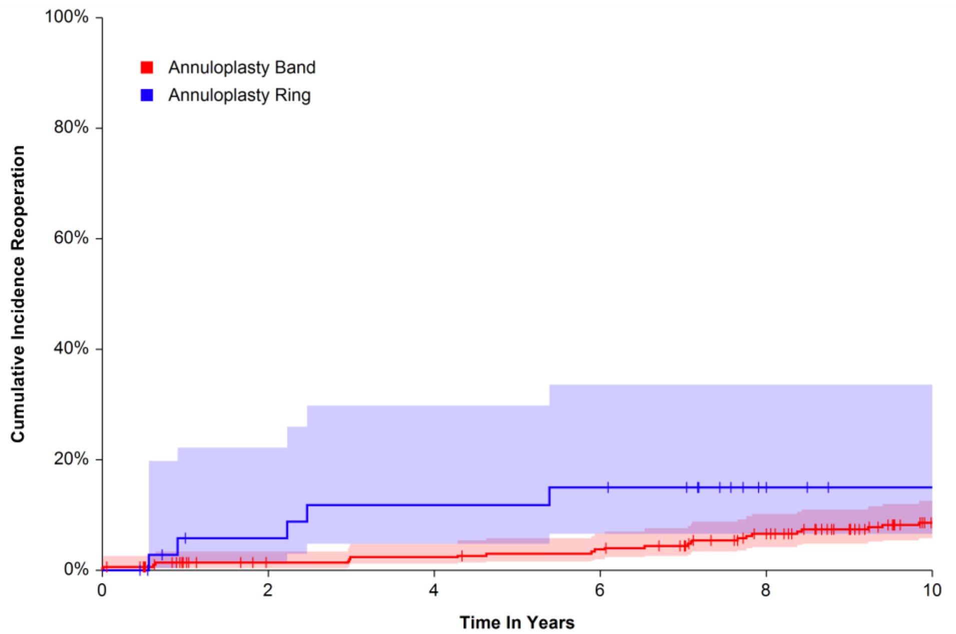
In 89.02% (n = 308) cases annuloplasty was performed using a band. Only 10.69% (n = 37) of patients received a ring. We performed a comparison in survival and cumulative incidence of reoperation between annuloplasty rings and bands, although one must keep in mind the highly varying group sizes and potential bias that inheres. Patients with annuloplasty bands had a survival rate of 97.70 ± 0.86% at 1 year, 93.20 ± 1.47% at 5 years and 83.48 ± 2.24% at 10 years. Patients with an annuloplasty ring had a survival rate of 100% at 1 year, 93.53 ± 4.43% at 5 years and 84.65 ± 7.31% at 10 years. There is no significant difference among those groups (P = 0.73). (Figure 28) Cumulative Incidence of reoperation for patients with an annuloplasty band was 1.31 ± 0.65% (95% CI, 0.50 – 3.47) at 1 year, 3.03 ± 1.00% (95% CI, 1.59 – 5.77) at 5 years and 8.54 ± 1.67% (95% CI, 5.82 – 12.54) at 10 years. Cumulative incidence of reoperation for patients with an annuloplasty ring was 5.80 ± 3.98% (95% CI, 1.51 – 22.28), 11.88 ± 5.58% (95% CI, 4.73 – 29.84) and 14.92 ± 6.16% (95% CI, 6.64 – 33.52) at 1, 5 and 10 years respectively. There is no significant difference among those groups (P = 0.07). (Figure 29)




Number At Risk

| | | | | | | |
|---|---|---|---|---|---|---|
| Annuloplasty Band | 308 | 280 | 270 | 259 | 237 | 192 |
| Annuloplasty Ring | 37 | 31 | 29 | 27 | 17 | 14 |

Figure 28. Survival according to annuloplasty ring and band.




Number At Risk

| | | | | | | |
|---|---|---|---|---|---|---|
| Annuloplasty Band | 308 | 278 | 267 | 255 | 225 | 177 |
| Annuloplasty Ring | 37 | 30 | 28 | 26 | 17 | 14 |

Figure 29. Cumulative Incidence of reoperation according to annuloplasty ring and band.

## Discussion

This study provides long-term outcomes after MVR using chordal replacement with a median follow up of 10.86 years in a cohort of patients, which is low risk in terms of comorbidities, age and ventricular function, hence representable when compared to the average patient with DMR that receives surgery. We could demonstrate an excellent long-term survival of 83.35% at 10 years. Additionally, we could prove the durability of chordal replacement regardless of underlying localization of leaflet prolapse. Most importantly, we showed a low cumulative incidence of reoperation on the MV of 7.84% at 10 years.

Persisting controversy regarding the optimal technique for MVR exists, and long-term data on chordal replacement remain inadequate. There are short- and mid-term studies comparing chordal replacement with resection techniques, which could not provide evidence of the superiority of any of these methods in terms of survival and recurrent MR. (Falk, Seeburger et al. 2008, Lange, Guenther et al. 2010, Lawrie, Earle et al. 2011) A meta-analysis by Mazine *et al.*, which included one randomized controlled trial and seven observational studies, demonstrated that chordal replacement might correlate with reduced risk of reoperation and improved postprocedural LVEF, as compared to leaflet resection. (Mazine, Verma et al. 2018) In 2008, Falk *et al.* published a randomized controlled trial including 126 patients, who either received neochordal replacement or leaflet resection. (Falk, Seeburger et al. 2008) Chordal replacement was associated with a significantly larger surface of coaptation than leaflet resection, which suggests more durable repair. In 2010 our group published a comparison of chordal replacement and leaflet resection in a cohort of 397 patients with PML prolapse. We have proven, that chordal replacement allows the implantation of significantly larger annuloplasty rings, which permits preservation of physiologic leaflet mobility. (Lange, Guenther et al. 2010) Consequently, chordal replacement with annuloplasty was found to facilitate the three main principles of MVR, as described by Alain Carpentier in 1983. (Carpentier 1983) These principles include stabilization of the annulus, maintenance of physiologic leaflet motion, and creation of a large surface of coaptation.

*Survival*

Long-term survival was high with 83.35% at 10 years. This finding is comparable to that of David et al. published in 2013, which had a survival rate of 85.7% at 10 years. This study included 606 patients, who received MVR using chordal replacement for treatment of DMR. (David, Armstrong et al. 2013) We identified age, diabetes mellitus, and LVEF as independent risk factors for survival by cox regression analysis. In comparison, in 2019 David *et al.* published data on 746 patients who underwent chordal replacement combined with resection techniques for DMR. In that study, survival was dependent on age, hypertension, and reduced LVEF. (David, David et al. 2020) Considering this, it must be kept in mind that LVEF of <55% might be underestimated in patients with severe MR. When the MV is competent again postoperatively, a reduced LVEF may become even more obvious. These findings confirm the importance of early intervention in symptomatic patients with severe MR. The current 2021 Guidelines for the management of valvular heart disease (Vahanian, Beyersdorf et al. 2021) recommend surgical repair in patients with DMR and reduced LVEF ≤60% despite being asymptomatic. (Figure 6)

*Reoperation on the MV*

Cumulative incidence of reoperation after MVR with chordal replacement was 7.84% at 10 years. This finding is in accordance with a study by David *et al.*, which included 606 patients receiving MVR using chordal replacement. They reported a freedom from reoperation of 94.7% at 10 years. (David, Armstrong et al. 2013) However, the reoperation rate on the MV does not necessarily reflect the functional status of the valve in patients who have not undergone reoperation. We observed a difference in cumulative incidence of recurrent MR and reoperation on the MV. Cumulative incidence of recurrent MR and reoperation on the MV at 10 years were 13.31% and 7.84% respectively. When comparing the individual groups this difference is even more apparent: especially in patients with AML and PML prolapse the numbers differ. This difference might be due to patients with advanced age and concomitant comorbidities, who were no longer eligible for surgery. In addition, some patients might be asymptomatic and/or refuse reoperation. This emphasizes that the rate of reoperation does not necessarily imply the rate of significant recurrent MR.

### *Repair Failures*

With 38 patients receiving reoperation the question arises whether those would have profited from other repair techniques. In 27 cases the cause for reoperation was valve-related, such as increased leaflet thickening, leaflet prolapse, rupture of chordae tendineae, endocarditis and leaflet restriction. Resection techniques have been promoted superior as they claim to resect pathologic tissue. However, degenerative disease is complex and resection techniques have not been proven to attenuate disease progression. In 9 cases the cause for reoperation was procedure-related such as rupture of neochords, elongation of neochords and suture dehiscence. Precise and accurate application of chordal replacement, especially placement and length of neochords, is crucial to their success. The same applies to any repair methods including resection techniques.

### *Prolapse of the AML*

Although there was no significant difference in between the groups, patients with prolapse of the AML had worse outcomes in all three endpoints of this study. Cumulative incidence of recurrent MR after 10 years lies at 13.31%. The cumulative incidence of recurrent MR for patients after AML prolapse supersedes both other groups shortly after 8 years and lies at 27.13% after 10 years. In contrast, in patients with PML or bileaflet prolapse the cumulative incidence of recurrent MR is 13.09% and 7.48% at 10 years respectively. This observation is not entirely new. In 2014 Tabata *et al.* analysed 700 patients, who received MVR for MR. (Tabata, Kasegawa et al. 2014) All patients were treated with neochordal replacement, however 67.5% additionally received leaflet resection for MVR. They reported that patients with AML prolapse had a significantly lower freedom from recurrent MR at 10 years of 63.5% than patients with BL and PML prolapse, with rates of 83.6% and 81.1%, respectively. In 2013

David *et al.* observed a significantly higher risk of reoperation in patients with AML prolapse than in patients with PML and BL prolapse. (David, Armstrong et al. 2013) In our study, we observed a remarkable, although not significant, difference in survival. In patients with AML prolapse survival was 71.97% at 10 years, whereas in patients with PML and BL prolapse survival rates were 85.24% and 79.84% at 10 years, respectively. Some studies suggest that patients with AML prolapse present with further advanced degenerative disease and more severe comorbidities. (David, Ivanov et al. 2005, Suri, Schaff et al. 2006) In this study, the proportion of patients with AML prolapse was low. Therefore, further studies with higher numbers of cases are needed.

*Morbus Barlow*

This study included 48 patients with Morbus Barlow. Morbus Barlow is a malformation of the MV apparatus, which is associated with myxomatous and excessive MV leaflets. Leaflets “billow” into the LA and are diffusely thickened and calcified, which further increases over time. MV annulus is mostly dilated, and often abnormal annular motion is observed. The big, thickened and in general massively altered leaflets of the Barlow valve are challenging to repair and bear a high risk for repair failure. Nevertheless, Morbus Barlow was not identified as an independent predictor of recurrent MR and reoperation on the MV. The main reason for the excellent outcome of patients with Morbus Barlow after repair with chordal replacement might be the possibility to implant larger annuloplasty rings. (Lange, Guenther et al. 2010) Large annuloplasty rings have been proven to be of advantage in patients with excess leaflet tissue and annular dilatation, as is the case in Morbus Barlow. (Adams, Anyanwu et al. 2006) In addition, since MVR was performed on the surgeon’s discretion, those 48 patients might be highly selected. Morbus Barlow varies highly among patients, and therefore might require a combination of repair techniques according to disease severity and progression to ensure optimal treatment for all patients. (Barlow, Ali-Ghosh et al. 2021)

### *Progress in MVR technique*

As mentioned above, at our center the main principle of MVR is to comply to Carpentier's triad (Carpentier 1983) while avoiding resection techniques. Over time substantial progress could be observed. The most important development was the implementation of annuloplasty rings over annuloplasty bands as we could observe improved annulus stabilization. In this study we could not identify a significant difference between rings or bands, however the compared groups vary greatly in size hence results may be biased. Another study performed by our team analyzed 378 patients, who received MV annuloplasty using a ring with a large antero-posterior diameter. (Sideris, Burri et al. 2022) By that, the incidence of postprocedural SAM was reduced to zero. This finding suggests the superiority of annuloplasty rings with a large anterior-posterior diameter in patients who are at risk for SAM. Additionally, annuloplasty sutures are placed before analyzing the MV for improved view of the MV. For sizing a standardized sizer is used, whereas the surgeon orientates on the size of the anterior mitral leaflet and not on the native mitral annulus diameter.

### *Alternatives for high-risk patients*

For patients with severe, symptomatic MR and high operative risk minimal-invasive treatment options exist. The edge-to-edge technique, also called the 'Alfieri stitch', is a method to reduce MR by suturing the prolapsing scallop of the AML to the opposite edge of the PML. (Alfieri and Maisano 1999) This technique was enhanced to a transcatheter edge-to-edge repair (TEER), which connects both leaflets using a mechanical tool that is inserted through the atrial septum. (Feldman, Wasserman et al. 2005) TEER has been proven to be a safe method for patients with severe DMR, who are considered inoperable. (Feldman, Foster et al. 2011, Feldman, Kar et al. 2015, Sorajja, Vemulapalli et al. 2017) However, percutaneous MVR is less effective in reduction of MR as compared to conventional MVR. (Buzzatti, Van Hemelrijck et al. 2019) Hence, TEER only holds a IIb recommendation for treatment of DMR in the current guidelines on treatment of valvular heart disease: TEER must be considered beneficial in each individual case, specific echocardiographic criteria for qualification must be met and patients must be considered at high surgical risk by the Heart Team. (Vahanian, Beyersdorf et al. 2021) Most importantly, the main regurgitant jet must origin from the middle scallops of the AML or PML. (Mauri, Garg et al. 2010) The extent of coaptation gap, the leaflet size and length, and a large flail gap affect the success of TEER and must be considered beforehand. (Chakravarty, Makar et al. 2020) However, TEER is more commonly used in inoperable patients with severe functional MR and persisting, symptomatic heart failure despite optimized guideline-directed medication. Two randomized controlled trials, MITRA-FR and COAPT, have demonstrated that TEER is a safe method in high-risk patients with functional MR and symptomatic heart failure. (Stone, Lindenfeld et al. 2018, Iung, Armoiry et al. 2019) Nevertheless, the MITRA-FR trial could not report any significant difference in terms of survival and hospitalization among patients treated with TEER and patients treated with guideline-directed medication only at 12 and 24 months of follow-up. (Iung, Armoiry et al. 2019) In contrast, the COAPT trial observed a lower rate of hospitalization and mortality in patients treated with TEER additional to optimized medical therapy at 24 months of follow-up. (Stone, Lindenfeld et al. 2018) Therefore, the current 2021 ESC/EACTS Guidelines for the management of valvular heart disease recommend TEER only in patients with heart failure and severe functional MR, who remain symptomatic despite optimized medical therapy. Patients with less severe functional MR and/or highly restricted LVEF <15% are not recommended intervention. (Vahanian, Beyersdorf et al. 2021) Other promising minimal-invasive treatment options, such as transapical valve implantation, are currently investigated, but further data are needed.

*Limitations*

This study is a retrospective, observational study with all the limitations that inheres. Follow-up echocardiography was performed by numerous cardiologists, and we relied on their expertise for interpretation of the results. No standardized protocol for echocardiography was used. Although follow-up visits with cardiologists were strongly recommended in each case, symptomatic patients might be more likely to receive follow-up than asymptomatic ones. Additionally, surgery was performed by a small team of surgeons in a single, highly specialized center, thus results might not be generalizable.

## Conclusion

This study was performed to provide further information on long-term outcomes after MVR using solely chordal replacement with ePTFE sutures combined with annuloplasty, and hence further strengthen the common use of this technique in MVR.

This study showed that chordal replacement and annuloplasty is associated with excellent long-term results regardless of localization of leaflet prolapse, especially low cumulative incidence of reoperation. In addition, reduced LVEF at operation as independent risk factor for death and recurrent mitral regurgitation emphasizes the importance of early intervention in severe degenerative mitral regurgitation.

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## Danksagung

Ich möchte an dieser Stelle meinen Dank den Personen aussprechen, die mich im Rahmen dieser Dissertation begleitet und unterstützt haben.

Mein größter Dank geht an meine Betreuerin PD Dr. med. Keti Vitanova für ihre unermüdliche Geduld und konstante Unterstützung. Sie hatte immer ein offenes Ohr für jegliche Probleme, die im Laufe der Arbeit aufgekommen sind, und hatte immer eine Lösung parat. Zudem war sie immer für mich erreichbar - trotz Arbeit, Urlaub oder Mutterschutz - wofür ich unglaublich dankbar bin.

Außerdem möchte ich Prof. Dr. Rüdiger Lange danken, der dieses Projekt vorgeschlagen hatte und mich in der Ausführung und Korrektur unterstützt hatte. Seine konstruktive Kritik und hilfreichen Kommentare haben diese Dissertation und auch die Publikation des Projekts positiv beeinflusst und geprägt.

Weiters möchte ich Dr. med. Thomas Günther großen Dank für die gute Zusammenarbeit aussprechen. Ohne seine Hilfe wäre dieses Projekt nicht möglich gewesen.

Ich möchte mich auch bei meinem Mentor PD Dr. med. Tobias Rheude bedanken, der schnell und zuverlässig alle meine Anfragen und Bitten beantwortet hat. Außerdem möchte ich mich für seine schnellen Korrekturen und hilfreichen Kommentare bedanken, die den kardiologischen Standpunkt vertreten haben.

Zuletzt muss ich mich noch bei Dr. med. Nina Feirer für die gute Zusammenarbeit und den konstruktiven Austausch bedanken.

## Appendix

*Questionnaire*

Herr/Frau
Nachname Vorname
Straße, Hausnummer
PLZ-Ort

Sehr geehrte/r Herr/Frau Nachname,

Sie sind am »Operationsdatum« im Deutschen Herzzentrum München an der Mitralklappe operiert worden.
Obgleich dieser Eingriff bereits einige Zeit zurück liegt, möchten wir Sie heute erneut kontaktieren und uns nach Ihrem Befinden erkundigen.

Als Universitätskrankenhaus ist es uns wichtig, die Behandlung unserer Patienten stetig weiter zu entwickeln und zu verbessern.
Wir möchten die optimale Behandlungsstrategie für jeden einzelnen Patienten finden, um so möglichst genau auf die Bedürfnisse unserer Patienten eingehen zu können.

Aus diesem Grund und zur Sicherung unserer Qualität führen wir regelmäßig anonymisierte Studien durch, in welchen wir den Gesundheitszustand unserer Patienten über einen langen Zeitraum beobachten.

**Ihre persönlichen Daten werden selbstverständlich nicht weitergegeben.**

Sie finden im Anschluss einige Fragen zu Ihrem postoperativen Verlauf.

Bitte beachten Sie, dass die Fragen standardisiert sind und nicht mit Ihrem persönlichen Fall in Verbindung stehen.

Wir bedanken uns herzlich für Ihre Mithilfe und die Beantwortung der Fragen.

Bei Rückfragen erreichen Sie mich wie folgt:

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Tel.: 089 1218 2966
Fax: 089 1218 4113
Zu Händen Frau Lang

Herzlichen Dank und freundliche Grüße

Miriam Lang
Assistenzärztin der Klinik

PD Dr. med. Keti Vitanova
Oberärztin der Klinik

Herr/Frau <u>Nachname Vorname</u>
<u>Straße, Hausnummer</u>
<u>PLZ-Ort</u>

Hatten Sie nach dem Eingriff an der Mitralklappe eine weitere Operation am Herzen?
Falls **JA**, <u>welche</u> war das? <u>Wann</u> und <u>wo</u> wurde die Operation durchgeführt?

Ist bei Ihnen nach dem Eingriff ein Schlaganfall aufgetreten?
Falls **JA**, erläutern Sie bitte kurz welche Symptome bei Ihnen aufgetreten sind und ob Sie aktuell noch Symptome haben.

Hatten Sie nach dem Eingriff Atemnot, Beinödeme und/oder einen Leistungsknick?
Falls **JA**, erläutern Sie bitte kurz wann und in welchem Ausmaß diese Symptome aufgetreten sind.

Haben Sie manchmal Herzrasen oder Herzstolpern?
Falls **JA**, wie häufig und schwer treten diese Symptome auf?

Ist bei Ihnen ein Vorhofflimmern bekannt?
Falls **JA**, seit wann?

Sind Sie regelmäßig beim niedergelassenen Kardiologen in Behandlung?
Falls **JA**, haben Sie aktuelle Befunde? Wie heißt Ihr Kardiologe?

Nehmen Sie blutverdünnende Medikamente ein? Falls eine regelmäßige Messung des Quick-Wertes/ des INR-Wertes notwendig ist, führen Sie diese selbst durch?

## Einverständniserklärung des Patienten zur Übermittlung von Befunden

## - § 73 Abs. 1 b SGB V

Name:

Vorname:

Geburtsdatum:

Ich bin damit einverstanden, dass das Deutsche Herzzentrum Befunde von mir einholt, die beispielsweise einem Facharzt, dem Hausarzt, einem behandelnden Krankenhaus oder einem anderen Leistungserbringer, bei dem ich in Behandlung bin, vorliegen.

Die betreffenden Personen sind verpflichtet, diese Informationen an das deutsche Herzzentrum weiterzuleiten.

Ich bin damit einverstanden, dass meine Daten vom Deutschen Herzzentrum für wissenschaftliche Zwecke genutzt und nicht an Dritte weiter gegeben werden.

Dass ich diese Einverständniserklärung jederzeit ganz oder teilweise widerrufen kann, ist mir bekannt.

______________________________

Ort Datum

______________________________

Unterschrift des Patienten