Personalised surgical treatment of functional mitral regurgitation

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Chapter 1

General introduction

Background

Mitral regurgitation (MR) can be classified as either organic or functional. Organic MR – also known as primary MR – is caused by structural or degenerative abnormalities of the mitral valve leaflets, annulus, chordae tendinae or papillary muscles. In functional MR, on the other hand, the mitral valve is structurally normal and becomes insufficient due to a combination of annular dilatation, increased mitral leaflet tethering and decreased closing forces, as a consequence of regional or global left ventricular (LV) remodelling.[1] As such, it is also referred to as secondary MR. Based on aetiology of LV remodelling, functional MR can be classified as either ischaemic or non-ischaemic.

MR is the most common valvular heart disease in high-income countries. The estimated prevalence of moderate to severe MR is 1.7% in the overall population, markedly increasing to 9.3% in patients of 75 years and older.[2] Functional MR represents approximately 30-56% of patients with significant MR and is – regardless of aetiology – associated with adverse clinical outcome.[3, 4] Consequently, functional MR carries a substantial burden of disease, which is – given its association with increasing age, and the rising age of the European population – likely to increase.[5-7]

Over the past decades, tremendous advances have been made in the medical and device therapy of functional MR and many different surgical and percutaneous interventions have been introduced. However, functional MR comprises a very heterogeneous disease and the optimal surgical treatment strategy for patients with functional MR is still a topic of debate.

In this thesis the surgical treatment of patients with functional MR – with undersized or restrictive mitral annuloplasty as the mainstay – is investigated. In particular, long-term clinical and echocardiographic outcomes after surgery and preoperative identification of patients likely to benefit from each treatment strategy are explored, in order to personalise the surgical approach and optimise outcomes for each patient.

Anatomy and function of the mitral valve

The mitral valve – also known as the left atrioventricular valve – is a complex apparatus, comprised of the (saddle-shaped) mitral annulus, anterior and posterior mitral valve leaflets, subvalvular apparatus (consisting of the chordae tendinae and the anterolateral and posteromedial papillary muscles), and adjacent LV wall. This complex anatomical structure is finely tuned to actively facilitate the dynamic process of mitral valve opening – enabling unrestricted inflow of blood from the left atrium (LA) to the LV – during diastole, and mitral valve closing – preventing the passage of blood from the LV back into the LA – during systole.

The mitral valve opens at the beginning of diastole, when LV pressure decreases and becomes lower than LA pressure, resulting in a blood flow down the pressure gradient. Mitral valve closure involves several forces acting on the mitral valve. Mitral valve closure starts at the end of diastole and beginning of systole, with a decrease in mitral valve orifice area due to anterior movement of the aortic root, contraction of the atrial fibres encircling the posterior annulus and contraction of the LV base.[8, 9] The decreased mitral valve orifice area moves the anterior and posterior mitral leaflet together and enables the first phase of mitral valve closure. Further coaptation of the mitral valve leaflets is facilitated by contraction of the LV during systole. On the one hand, LV contraction causes inward movement of the LV wall and papillary muscles, thereby relieving traction on the chordae tendinae and mitral valve leaflets, resulting in decreased tethering forces. On the other hand, LV contraction increases LV pressure resulting in increased closing forces acting on the mitral valve. Together, the balance of decreased tethering and increased closing forces results in adequate mitral leaflet closure during systole, while preventing prolapse of the mitral valve leaflets into the LA. Disruption in any of the forces acting on the mitral valve may disturb this delicate balance and result in MR.[1, 10]

Pathophysiology of functional mitral regurgitation

Definition and pathophysiologic mechanisms

Functional MR can be defined as a disease condition in which the mitral valve becomes insufficient as a consequence of LV remodelling, whereas the valve itself is – at least macroscopically – normal. Consequently, functional MR should be distinguished from organic MR – MR caused by structural or degenerative alterations of the mitral valve – in the coincidental presence of LV disease. Furthermore, papillary muscle rupture due to an acute myocardial infarction can result in acute ischaemic MR requiring urgent cardiac surgery.[11] However, such acute MR represents a different subset of disease and is not discussed in this thesis.

Left ventricular remodelling is a term used to describe genome expression, molecular, cellular and interstitial changes in response to myocardial injury, manifested clinically as changes in LV size, geometry and function.[12] Depending on the aetiology of LV remodelling, functional MR can be defined as either ischaemic or non-ischaemic. Ischaemic MR results from regional or global ischaemia, myocardial infarction, or both. MR in non-ischaemic cardiomyopathy has a multifactorial aetiology, in which toxic damage (e.g. alcohol, cocaine), immune mediated and inflammatory damage, infiltration (e.g. malignancy, hemochromatosis), metabolic (hormonal and nutritional) derangements and genetic abnormalities may play a role.[13]

Functional MR develops when LV remodelling results in incomplete mitral leaflet closure due to a combination of mitral annular alterations, increased tethering forces and decreased closing forces.[1] In the past, development of functional MR was primarily attributed to mitral annular alterations (mitral annular dilatation, flattening of its saddle shape and loss of systolic annular contraction).[9, 14, 15] However, a study by Otsuji et al.,[16] demonstrated that patients with isolated mitral annular dilatation due to lone atrial fibrillation did not develop moderate or severe functional MR, whereas patients with LV dilatation and dysfunction, who had comparable annular sizes but greater tethering lengths, did frequently develop important MR. These data suggest that isolated mitral annular enlargement is insufficient to cause significant MR and that development of MR depends on an altered force balance on the mitral leaflets due to LV dilatation and dysfunction.[16] Increased mitral leaflet tethering forces are characterised by restriction of the mitral valve leaflets into the LV cavity, thereby preventing adequate mitral leaflet coaptation. Mitral leaflet tethering proved to be determined by outward (apical, posterior and lateral) displacement of the papillary muscles, which in turn was found to be associated with altered LV geometry.[17, 18] Several in vitro and animal studies suggested that local rather than global LV geometrical alterations are the primary determinant of increased mitral leaflet tethering.[19-21] In a clinical study, Yiu and co-workers indeed demonstrated that local LV remodelling is the primary determinant of mitral leaflet tenting and effective regurgitant orifice area (EROA) – independent of global LV remodelling.[17] Decreased closing forces due to reduced LV contractility and LV dyssynchrony, were found to contribute to the development of functional MR as well. However, an experimental study showed that outward papillary muscle displacement (tethering forces) with maintained LV pressures (closing forces) leads to MR, whereas a pharmacological reduction of LV contraction to a left ventricular ejection fraction (LVEF) < 20% without concomitant LV dilatation does not.[19] These findings were confirmed by clinical studies.[15, 17] Nowadays, functional MR is generally assumed to be primarily related to increased mitral leaflet tenting. However, concomitant mitral annular alterations and decreased closing forces do augment the effects of mitral leaflet tethering and further increase the severity of functional MR.[16]

The complex pathophysiological mechanism and forces involved in functional MR, explain why it comprises such a dynamic and heterogeneous disease. Severity of MR may vary with changing loading conditions and during exercise[22], as will be discussed later. Even during a cardiac cycle, severity of MR was found to vary, with a typical decrease in EROA at midsystole – at the time of peak LV closing forces.[23] Furthermore, the degree of LV dysfunction can highly vary among patients developing functional MR.[17] In patients with non-ischaemic cardiomyopathy, MR develops when considerable LV remodelling has taken place and is therefore always accompanied by heart failure. Ischaemic MR may develop in the same way when diffuse ischaemia or extensive infarction leads to global LV remodelling. However, more frequently ischaemic MR results from local LV remodelling, following local myocardial infarction or ischaemia. In this situation LVEF can be relatively preserved and symptoms of heart failure may not yet have become manifest. The location of a myocardial infarction therefore plays an important role in the development of ischaemic MR. For example, patients with an inferior myocardial infarction generally have more papillary muscle displacement and consequently more tethering and a higher severity of MR, compared to patients with an anterior infarction, even though an anterior infarction results in more global LV remodelling with higher LV volumes and lower LVEF.[24, 25]

The mitral valve and left ventricle

In functional MR, the LV suffers from both the intrinsic myocardial disease and from the volume overload that ensues with MR. The (sub)cellular rearrangements in response to this myocardial injury, result in repair of myocardial injury and scar formation, which may – to some extent – be considered beneficial. Initially, this remodelling process is associated with maintained or improved cardiac output, but at the expense of significantly increased LV volumes. Over time, when LV remodelling continues, these changes become pathological. Left ventricular size (end-systolic volume) progressively increases, resulting in a decline in LVEF and altered geometry (resulting in a more spherical rather than elliptical LV). Furthermore, progressive ventricular dilation leads to increased LV wall stress, which may precipitate the energy imbalance and increase myocardial oxygen demand – which in ischaemic cardiomyopathy is already limited – leading to even more LV dilatation and contractile dysfunction.[12, 26] Consequently, functional MR results in a vicious cycle of progressive LV remodelling and worsening of MR (**Figure 1**), in which it is difficult to distinguish the ventricular and valvular component. Due to this vicious cycle, functional MR is found to be associated with an increased risk of heart failure and adverse prognosis, as will be discussed in more detail later.

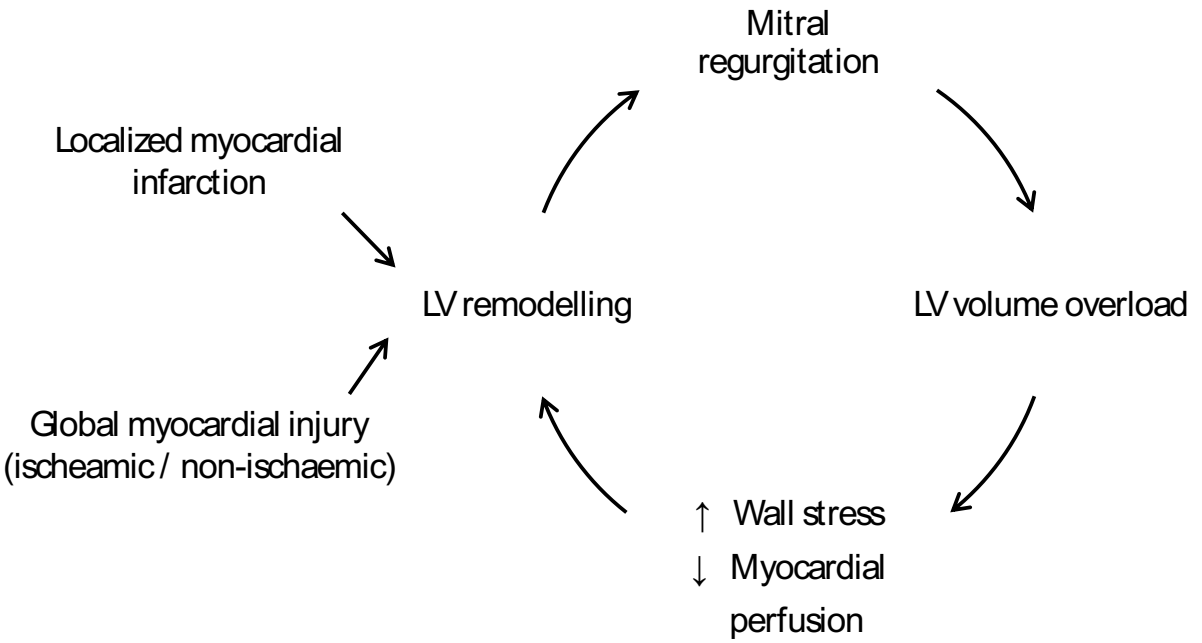

Figure 1. Vicious cycle of functional mitral regurgitation.

Many treatment options have been proposed to break the vicious cycle that ensues with functional MR. Their common aim is twofold: to restore mitral valve competence and initiate sustained LV reverse remodelling in order to improve clinical outcome. Left ventricular reverse remodelling, is a term used to describe an LV which is no longer in the circle of ongoing LV dilation and contractile dysfunction, but on a way back to a normal LV size, geometry and function. As in LV remodelling, the exact cellular and structural pathways of LV reverse remodelling are not fully elucidated. A decrease in LV size (volume or diameter) or improvement in LV function (LVEF) is often used as a clinical surrogate measure of reverse remodelling. Presence of LV reverse remodelling is associated with improved clinical outcome.[12, 27, 28]

Prevalence and clinical impact of functional mitral regurgitation

The exact epidemiology of functional MR is difficult to determine. Clinical assessment is imprecise since patients with functional MR are often asymptomatic and severity of symptoms (e.g. dyspnoea, fatigue) may be related to the underlying ventricular disease as well.[11] Furthermore, detection of a cardiac murmur lacks sensitivity and specificity, and the intensity of a murmur weakly correlates with the degree of MR, due to the decreased LV systolic function and atrial compliance.[11, 29-31] Consequently, the prevalence of functional MR can only be established by systematic echocardiographic assessment in a representative population. Available data regarding the prevalence and clinical impact of functional MR in the general population, following a myocardial infarction and in patients with heart failure will be discussed.

Mitral regurgitation in the general population

Data regarding the prevalence of (functional) MR in the general population is limited and the epidemiology of valvular heart disease has changed substantially over the past decades.[5]

In a population-based study investigating the prevalence of moderate to severe left-sided valvular heart disease by echocardiography in 11,911 patients in the United States, MR was the most commonly diagnosed valvular heart disease, with an overall prevalence of 1.7% and increasing with age to 9.3% in patients ≥75 years of age.[2] However, this study did not distinguish between different pathophysiological mechanisms of MR.[2]

In a community-based study in Olmsted county, isolated moderate or severe MR was diagnosed by echocardiography in 1,294 community residents.[32] The prevalence of MR in the overall adult population was 0.59% and increased with age. Secondary MR accounted for 56% of patients with MR. The 5- and 10-year survival rates of patients with secondary MR were 46% and 23% respectively, which was significantly lower than expected for the general county population of same sex and age (HR 2.7 [2.5 – 3.0], p <0.001).[32]

Finally, in a study including 63,463 patients referred for an echocardiogram in 19 European hospitals, moderate or severe MR was observed in 3,309 patients (5.2%).[3] Within this subgroup, 30% of patients had functional MR. Aetiology of functional MR was ischaemic in 51%, non-ischaemic in 32% of patients and unknown in 17%.[3]

Functional mitral regurgitation after myocardial infarction

Over the past decennia, the frequency and prognostic impact of functional MR after a myocardial infarction has been investigated in many studies. In the earliest reports, the prevalence of angiographically assessed functional MR ranged from 1.6 – 19%.[11] Currently, echocardiography is the recommended technique for assessment of MR, since it provides more adequate information on aetiology and severity of the regurgitation. An overview of studies reporting on the frequency of functional MR assessed by echocardiography, including >100 patients and published from the year 2000 onwards, is presented in Table 1. Reports regarding post-hoc analysis of randomised controlled trials (RCTs) and case-series are not discussed, since these studies are subject to selection and referral bias.

The reported prevalences of moderate to severe (or ≥ grade 2) functional MR after a myocardial infarction range from 6 – 37% (Table 1). This variation can be explained by the heterogeneity of the different reports. Study design was a cohort study in most reports,[33-38] whereas Bursi and co-workers were the first to perform a community-based study.[29] Furthermore, study populations are heterogeneous due to the fact that the definition of myocardial infarction has

changed over time and because some studies only included patients after a first myocardial infarction,[29, 36, 39] while others also included patients with a history of prior myocardial infarction or coronary artery disease.[33-35, 37, 38] The moment of imaging differed considerably between studies as well, with some performing an echocardiography within a few days to a week after myocardial infarction[33-38, 40-43] and others in the chronic phase.[29, 39] Finally, the method of quantification of the severity of MR varied between studies, with most reports using qualitative measurements (maximum regurgitant jet area)[29, 33-35, 38, 40, 43], whereas only a few reports used quantitative measurements (EROA, regurgitant volume [RVol]).[36, 37, 39, 42]

Survival 5 years after an acute myocardial infarction in patients with moderate to severe MR ranged from 67 – 37% (Table 1). In the study by Bursi et al.,[29] patients with moderate to severe MR had a 5-year survival of 40%, which was comparable to the 5-year survival rate of 38% in patients with MR in the study by Grigioni and colleagues.[39] In a report by Mentias and colleagues,[42] 4,005 patients underwent an echocardiography within 3 days following primary percutaneous coronary intervention for a STEMI. In this study, a graded association between severity of MR and survival was observed, with a 5-year survival of 84% in patients without MR, 77% in patients with grade 1 MR, 64% in patients with grade 2 MR, 46% in patients with grade 3 MR and 37% in patients with grade 4 MR.

The clinical impact of functional MR after a myocardial infarction was studied in many of the abovementioned reports (Table 1). An independent association between MR and increased all-cause mortality was observed in many reports, with hazard ratios for moderate to severe MR ranging from 1.7 to 5.0 (Table 1).[29, 33-35, 37-40, 42, 44] Even the presence of mild MR was found to be associated with adverse survival in several reports.[34, 35, 42] Grigioni et al. were the first to demonstrate that an EROA ≥20 mm^2 and RVol ≥30 mL are independently associated with mortality, which led to adjustment of the definition of severe functional MR in the guidelines, as will be discussed later.[39] Furthermore, an increased risk of heart failure was observed in patients with significant MR in several studies.[29, 33, 34, 36, 38, 40]

Presence of MR was found to be associated with clinical parameters such as increasing age,[29, 33-35, 37, 38, 40, 42-44] female gender,[29, 33, 34, 38, 40-42, 44] previous myocardial infarction,[33, 35, 38] diabetes,[33, 34, 38, 40] hypertension,[33, 35, 40] atrial fibrillation,[36] lower body mass index (BMI),[42] anaemia[42] and smoking.[33, 40, 42] Interestingly, studies regarding the association between MR and the location of myocardial infarction are conflicting. Although some reported that MR was associated with inferior[38, 42, 43] myocardial infarction, others observed no difference.[29, 35, 37, 40] The extent of myocardial infarction – assessed by Creatine Kinase[29] or Troponin I levels[34] – was not significantly associated with MR, and neither was the presence of STEMI compared to non-STEMI.[34] Echocardiographic parameters such as larger LV volumes[29, 44] and diameters,[34, 36, 40]

larger LA volume,[42] lower LVEF[29, 33, 36-38, 40-43], greater wall motion score index[29, 35, 36], higher sphericity[41] and higher RV pressure[29, 42] were associated with presence of MR. The association between MR and these echocardiographic parameters underlines the close relation between the mitral valve and LV, showing more (severe) MR in patients with more advanced LV remodelling. Finally, a longer door-to-balloon-time was found to be associated with the presence of MR as well[41, 42], indicating the need for rapid revascularization.

Functional mitral regurgitation in ischaemic or non-ischaemic heart failure

The epidemiology of functional MR in patients with heart failure has been described in many reports as well. An overview of the studies in which MR is assessed by echocardiography in a study population of >100 patients and published starting from the year 2000, is presented in Table 2.

The prevalence of moderate to severe (or ≥ grade 2) functional MR in patients with heart failure ranges from 20 – 60% (Table 2). As in the reports on the frequency of MR after a myocardial infarction, this wide variety can be explained by differences in study design, study population and the moment and method of echocardiographic assessment. Study design was cross-sectional in one report[31] and a cohort study in the other reports. Differences in study population are mainly due to variation in the definition of heart failure. Some studies simply state that patients with congestive heart failure were included without providing a further definition,[31, 45, 46] while others define heart failure by severity of LV dysfunction (LVEF <50%[47-49], ≤40%[50-52] or ≤35%[53-55]) or symptoms (New York Heart Association (NYHA) classification III/IV).[55] Except for one study including patients with non-ischaemic cardiomyopathy,[48] all studies included both patients with ischaemic and non-ischaemic heart failure. Of these reports, only two performed separate analysis for both aetiologies.[46, 55] Furthermore, severity of MR was either assessed using qualitative[49, 50, 52, 53] or quantitative parameters.[31, 45-48, 51, 54, 55] Finally, in only a few reports, patients received optimal guideline-directed medical therapy at time of inclusion.[47-49, 51]

Due to the abovementioned differences and due to variation in follow-up duration, survival rates of different reports are not comparable. The survival rates of each report are described in Table 2. Presence of moderate to severe MR was independently associated with all-cause mortality (HR 1.6 – 4.5) in many,[45, 46, 48-51, 53] but not in all reports.[47, 52, 54, 55] Moreover, moderate to severe MR was found to be related to heart failure hospitalizations or worsening heart failure symptoms in three reports,[47, 48, 54] whereas another study did not observe such a relation.[50]

Bursi and co-workers[49] performed a study in 469 patients with LVEF < 50% due to ischaemic (36%) or non-ischaemic (54%) cardiomyopathy, and observed absence of MR in 5%, grade 1

MR in 32%, grade 2 MR in 19%, grade 3 MR in 30% and grade 4 MR in 14% of patients. At 5 years follow-up, survival free of HTx was 83% in patients with no or grade 1 MR, 64% in patients with grade 2 MR, 59% in patients with grade 3 MR and 47% in patients with grade 4 MR. In this study, a worsening degree of functional MR was associated with a progressively increased risk of death or HTx (grade 3 MR: HR 2.0 [1.4– 3.0], grade 4 MR: HR 2.6 [1.6 – 4.1]), regardless of the aetiology of MR.

As mentioned, separate assessment of patients with ischaemic and non-ischaemic cardiomyopathy was performed in only two reports.[46, 55] Rossi et al.[46] included 1256 patients with chronic heart failure of which 27% had no MR, 49% had mild to moderate MR and 24% severe MR. Severe functional MR was a strong independent predictor for survival in both patients with ischaemic (HR 2.0 [1.4 – 2.7], p<0.001) and non-ischaemic (HR 1.9 [1.3 – 2.9], p = 0.002) cardiomyopathy. In patients with ischaemic cardiomyopathy, 5-year survival was 60% for patients with mild to moderate MR versus 23% in patients with severe MR; in patients with non-ischaemic cardiomyopathy, 5-year survival was 50% and 27%, respectively.

The presence of MR proved to be associated with clinical variables such as age,[46, 53, 54], worse NYHA functional class,[45, 46, 49, 51] and AF[51, 54], but also with echocardiographic characteristics namely lower LVEF[46, 47, 49, 51, 53, 54, 56]larger LV volumes,[45, 49, 50] LV diameters,[46, 53, 54, 56] and LA size,[45, 49, 53, 54, 56] degree of TR,[53, 56] and higher sPAP.[45, 56] These finding again demonstrate that an increasing MR prevalence is associated with increasing heart failure severity. However, Bursi and co-workers assessed the clinical impact of MR within different stages of heart failure and demonstrated that functional MR was an independent predictor of mortality in patients with NYHA class I-II, whereas in patients with NYHA class III-IV, MR was no longer a significant predictor of HTx-free survival after adjustment for confounders.[49] Similar findings were reported by Goliasch and co-workers[51] In this study, including 576 patients with heart failure (LVEF < 40%) receiving optimal medical therapy, 47% of patients had no or mild MR, 32% moderate MR and 21% severe MR. Increasing MR severity was independently associated with increasing mortality. However, after stratification for heart failure symptoms, severe MR was significantly associated with mortality in patients with NYHA class II (adjusted HR 2.2 [1.1 – 4.4], p = 0.03) and III (adjusted HR 1.8 [1.2 – 2.8], p = 0.008) but not in patients with NYHA class I (p = 0.73) or IV (p = 0.71). Furthermore, severe MR was associated with survival in patients with reduced LV function (LVEF 30-40%; adjusted HR 2.4 [1.4 – 4.2], p = 0.002), but not in patients with severely reduced LV function (LVEF < 30%; HR 1.3 [0.95 – 1.8], p = 0.10). The same applied for LV size (≤ moderately dilated LV; adjusted HR 2.0 [1.4 – 2.9], p <0.001 vs severely dilated LV: adjusted HR 1.4 [0.9 – 2.2], p = 0.11) and NT-proBNP levels (an association between severe MR and patients within the 2nd quartile of NT-proBNP (adjusted HR 2.2 [1.2 – 3.9], p = 0.009) but not within the 1st and 4th quartile). These results again reflect the complex interaction

between mitral valve and LV. Although MR seems to have a significant impact on clinical outcomes in patients with moderate degrees of heart failure, LV dysfunction rather than presence of MR seems to determine outcomes in patients with severe heart failure. This may also explain why some reports did not observe an independent association between functional MR and all-cause mortality and should be taken into account when considering surgical or percutaneous interventions to treat functional MR.

Overall, we can conclude that functional MR is a common phenomenon with an estimated prevalence of 6 – 37% following a myocardial infarction and 20 – 60% in patients with ischaemic or non-ischaemic heart failure. The prevalence of functional MR is higher in patients who are older, more often female and with a more advanced stage of LV remodelling. Presence of MR was found to have a graded and independent association with all-cause mortality and heart failure, which is already present in patients with only mild MR. However, in patients with severe heart failure outcomes seem primarily related to LV dysfunction rather than presence of MR.

Table 1. Prevalence and clinical impact of functional mitral regurgitation in patients after a myocardial infarction.

Study	n	Study population	TTE	Assessment	FU	LVEF	Prevalence of MR	Survival	HR and remarks
Abate 2016[44]	1599	STEMI treated with PCI + OMT	12 m	VCW, PISA	50 m	47±9%	30% grade 1 5% grade 2 3% grade 3	1 and 4 year: 98%, 93% no MR 93%, 86% with MR	MR ≥grade 2 independently associated with all-cause mortality (HR 1.7 [1.0-2.7]).
Aronson 2006[33]	1190	Acute MI survivors	2 [1-3] d	Max reg jet area	24 m	45%	40% mild 5.6% moderate 0.6% severe	3.3 years: 85% mild MR 67% moderate/severe MR	Moderate/severe MR independently associated with all-cause mortality (HR 2.0 [1.2-3.4]) and HF (HR 3.6 [2.0-6.4]).
Barra 2012[34]	796	Acute MI (45% STEMI, 54% non-STEMI)	<1 w	Max reg jet area	24 m		55% none 30% mild 12% moderate 3% severe	2 years: 88% no MR 78% mild MR 62% moderate MR 61% severe MR	MR severity (each increment) independently associated with all-cause mortality (HR 1.4 [1.0-2.0]). No difference between STEMI/non-STEMI.
Bursi 2005[29]	757	First acute MI	<30 d	Max reg jet area	4.7 y	46±14%	50% none 38% mild 12% moderate/severe	5 years: 72% no MR 62% mild MR 40% moderate/severe MR	Moderate/severe MR independently associated with all-cause mortality (HR 1.5 [1.1-2.0]) and HF (HR 3.4 [1.7– 6.8]).
Feinberg 2000[35]	417	Acute MI	< 48 h	Max reg jet area	1 y		65% none 29% mild 6% moderate/severe	1 year: 95% no MR 88% mild MR 76% moderate/severe MR	MR independently associated with 1-year mortality (HR 2.3 [1.0–5.2] for mild MR and HR 2.9 [1.0–8.5] for moderate/severe MR).
Grigioni 2001[39]	303	Q-wave MI	>16 d	RVol, EROA	5 y	33±13%	N/A	5 years: 61% without MR 38% with MR	MR independently associated with all-cause mortality (HR 1.9 [1.2-2.9]). ERO≥ 20mm2 and RVol ≥30ml independently associated with mortality. Study population: 194 patients with IMR matched to 109 without IMR
Lopez-Perez 2014[40]	1036	STEMI treated by primary PCI	< discharge	Max reg jet area	2.8 y	54%	45% none 44% mild 9% moderate	3 years FU: ± 98% no MR ± 97% mild MR	Moderate/severe MR independently associated with all-

							3% severe	± 95% moderate MR ± 80% severe MR	cause mortality (HR 3.1[1.3–7.2]) and HF (HR 3.3 [1.2–9.4]).
MacHaalany 2014[41]	174	STEMI treated by PCI	<1–3 d	Max reg jet area, VCW	366 d	46±12%	55% none 34% mild 11% moderate/severe	N/A	Moderate/severe MR independently associated with 1-year MACE (HR 2.6 [1.1 – 5.5]).
Mentias 2017[42]	4005	STEMI treated by primary PCI	<3 d	RVol, VCW, EROA, max reg jet area	5.9 y	45%	80% none 11% grade 1 6.5% grade 2 2.3% grade 3 0.7% grade 4	5 years: 84% no MR 77% grade 1 MR 64% grade 2 MR 46% grade 3 MR 37% grade 4 MR	MR independently associated with all-cause mortality (HR 1.3 for grade 1 MR, 1.7 for grade 2 MR, 2.4 for grade 3 MR and 2.5 for grade 4 MR).
Nunez-Gil 2013[36]	237	First non-STEACS and NYHA I-II	2 [1 – 3] d	EROA	7.0 y	56±15%	60% none 30% grade 1 6% grade 2 2.5% grade 3 1.3% grade 4	N/A	MR (per degree) independently associated with HF (HR 1.7 [1.1–2.6]) and MACE (HR 1.5 [1.2–1.9]).
Perez de Isla 2006[37]	300	First non-STEACS	<1 w	EROA	426 d	55%	63% grade 1 20% grade 2 14% grade 3 3% grade 4		MR independently associated with all-cause mortality (HR 5.0 [1.0–24]).
Persson 2010 [38]	725	ACS (STEMI n=343, non-STEMI n=256, unstable angina pectoris n=126)	<5 d	Color and continuous wave doppler	98 m		88% none/grade 1 12% ≥ grade 2	5 and 10 years: ±82%, ±75 no/grade 1 MR ±51%, ±30% ≥grade 2 MR	MR independently associated with all-cause mortality (HR 1.5 [1.1–2.2]) and HF (HR 2.1 [1.3 – 3.4]).
Uddin 2012[43]	888	STEMI treated by primary PCI	<72 h	Max reg jet area	3.1 y	48%	53% none/trace 36% mild 11% moderate/severe	5 years: 87% no/trace MR 82% mild MR 67% moderate/severe	After adjustment for age, moderate/severe MR not associated with survival (HR 1.3 [0.7 – 2.2]).

ACS = acute coronary syndrome, FU = follow-up, EROA = effective orifice area, HR = hazard ratio, LVSD = left ventricular systolic dysfunction, MI = myocardial infarction, MR = mitral regurgitation, NYHA = New York Heart Association, OMT = optimal medical therapy, PCI = percutaneous coronary intervention, STEACS = ST-elevation acute coronary syndrome, STEMI = ST-elevation myocardial infarction, TTE = transthoracic echocardiography, RVol = regurgitant volume, VCW = vena contracta width

Table 2. Prevalence and clinical impact of functional mitral regurgitation in patients with heart failure.

Study	n	Study population	Assessment	FU	LVEF	Prevalence of MR	Aetiology	Survival	HR and remarks
Agricola 2009[47]	404	≥ mild MR and HF (LVEF < 50%) receiving OMT	EROA, VCW	3.3 y	34±11%	41% mild 48% moderate 11% severe	77% IMR 24% NIMR	4 years: 64% mild MR 50% moderate MR 49% severe MR	Compared to mild MR, moderate/severe MR independently associated with cardiac mortality (HR 2.7 [1.2-6.1] and HF (HR 3.2 [1.9 – 5.2]), but not all-cause mortality.
Agricola 2011[48]	198	HF (LVEF < 50%), normal coronary vessels, receiving OMT	EROA, VCW	37 m	33±9%	35% none 32% mild 17% moderate 24% severe	100% NIMR	6 years: 72% no MR 63% mild MR 46% moderate MR 36% severe MR	Moderate/severe MR independently associated with all-cause mortality (HR 2.1 [1.2-3.6]) and HF (HR 2.1 [1-4.5]).
Bruch 2007[45]	370	Congestive HF	VCW, EROA, RVol, max reg jet area	790 d	31±10%	10% none 65% mild/moderate 25% severe	56% IMR 44% NIMR	4 years, event-free survival: 81% no, mild or moderate MR 51% severe MR	Severe MR independently associated with all-cause mortality (HR 2.4 [1.4–4.1]).
Bursi 2010[49]	469	Congestive HF (LVEF < 50%) receiving OMT	Max reg jet area	5 y	30%	5% none 32% grade 1 19% grade 2 30% grade 3 14% grade 4	36% IMR 64% NIMR	5 years, HTx-free survival: 83% no/grade 1 MR 64% grade 2 MR 59% grade 3 MR 47% grade 4 MR	MR independently associated with event-free survival: MR grade 2 HR 1.3 [0.8–2.1], grade 3 (HR 2.0 [1.4– 3.0], grade 4 (HR 2.6 [1.6 – 4.1]).
Cioffi 2005[50]	175	HF (LVEF < 40%) and age >70 y	Max reg jet area	12 m	29%	80% no/mild MR 20% moderate /severe	51% IMR 49% NIMR	1 year: 90% no or mild MR 51% moderate or severe MR	Moderate/severe MR independently associated with all-cause mortality (HR 4.5 [1.5–13.0]). No association MR and HF readmissions.
Goliasch 2018[51]	576	HF (LVEF < 40%) receiving OMT	VCW, EROA	62 m	27%	47% no/mild MR 32% moderate 21% severe	39% IMR 61% NIMR	N/A	Severe MR independently associated with all-cause mortality (HR 1.6 [1.2-2.1]).
Koelling 2002[53]	1436	HF (LVEF ≤ 35%)	Max reg jet area	369 d	20±5%	30% moderate 19% severe	59% IMR 41% NIMR	3 years: 57% mild MR 50% moderate MR 35% severe MR	Severe MR independently associated with all-cause mortality (HR 1.9 [1.4– 2.4]).

Mowakeaa 2018[42]	615	HF (LVEF ≤ 35%)	VCW, EROA, RVol, max reg jet area	2.9 y	27%	29% none 31% mild 40% moderate/severe	65% IMR 26% NIMR 4% mixed 5% unknown	3 years: ±82% no MR ±68% mild MR ±60% moderate or severe MR	MR associated with all-cause mortality (mild MR: HR 1.6; moderate/severe MR: HR 2.6), but not after adjustment for covariates. MR independently associated with HF hospitalizations (mild MR HR 1.7, moderate/severe HR 2.2).
Patel 2004[55]	558	HF (LVEF ≤ 35% and NYHA III/IV)	EROA, RVol, max reg jet area	5 y	21±7%	10% none 51% mild/moderate 22% moderate 17% moderate/severe	54% IMR 46% NIMR	5 years: 25% for IMR 54% for NIMR	MR not independently associated with all-cause mortality (moderate/severe MR HR 0.99 [0.8–1.3]).
Robbins 2003[52]	221	Congestive HF (LVEF ≤ 40%)	Max reg jet area	47 m	28±8%	59% moderate/severe (74% in-hospital patients, 45% outpatients)	Not specified	5 years: 81% none or mild MR 61% moderate or severe MR	MR not independently associated with all-cause mortality. Study population: 111 in-hospital patients, 110 outpatients.
Rossi 2011[46]	1256	Chronic HF	EROA, VCW, RVol	2.7 y	32±8%	27% none 49% mild/moderate 24% severe	61% IMR 39% NIMR	5 years: IMR: 60% mild-moderate MR 23% severe MR NIMR: 50% mild-moderate MR 27% severe MR (at 4 years)	Severe MR independently associated with all-cause mortality (HR 2.0 [1.5–2.6]; IMR HR 2.0 [1.4–2.7] and NIMR HR 1.9 [1.3–2.9]).
Varadarajan 2006[31]	370	Congestive HF	Max reg jet area, EROA, VCW	n/a	21±12%	5% none 44% grade 1 22% grade 2 15% grade 3 14% grade 4	39% IMR 61% NIMR	n/a	

FU = follow-up, EROA = effective orifice area, HF = heart failure, HR = hazard ratio, IMR = ischaemic mitral regurgitation, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, NIMR = non-ischaemic mitral regurgitation, NYHA = New York Heart Association, OMT = optimal medical therapy, TTE = transthoracic echocardiography, RVol = regurgitant volume, VCW = vena contracta width

Assessment of functional mitral regurgitation

Echocardiographic assessment of functional mitral regurgitation

Echocardiography is the recommended imaging technique for the assessment of functional MR.[57, 58] Two-dimensional transthoracic echocardiography (TTE) is usually the first-line imaging modality to assess the presence, severity and impact of functional MR. However, transoesophageal echocardiography can be performed if TTE is suboptimal or to obtain additional information on for example mitral valve geometry or eligibility for interventional/surgical procedures. A 3D echocardiography may provide an even more comprehensive evaluation of mitral valve morphology and is increasingly being used. Echocardiography also allows assessment of LV and LA geometry and function, right ventricular geometry and function, pulmonary artery pressure and function of the other valves.[59, 60]

Mitral valve morphology

Functional MR is characterised by restricted mitral leaflet closure during systole and can be classified as class IIIb according to Carpentier's classification (Table 3).[61] Restriction of the mitral leaflets can be symmetric (resulting in a central regurgitant jet) when restriction of both mitral leaflets results in incomplete coaptation, which is seen in patients with non-ischaemic cardiomyopathy and in patients with global ischaemia or after an anterior/inferior myocardial infarction. On the other hand, asymmetric restriction of the posterior mitral leaflet can be observed in patients with local LV remodelling after a posterior myocardial infarction, resulting in the so-called 'sea-gull sign' and an eccentric regurgitant jet.[59, 60]

Table 3. Carpentier's classification of mitral regurgitation.[61]

Type I	Normal leaflet motion
Type II	Excessive leaflet motion
Type III	Restrictive leaflet motion; restricted leaflet opening during diastole/systole (IIIa) or restricted leaflet closure during systole (IIIb)

Assessment of the severity of functional mitral regurgitation

Evaluation of the severity of MR should be performed pre-operatively. Since functional MR is dynamic and dependent on loading conditions, intra-operative assessment may lead to an underestimation of its severity due to decreased contractility and loading conditions caused by administration of general anaesthesia. [22, 60, 62, 63]

Severity of functional MR should be assessed by an integrative approach, using a combination of qualitative and quantitative parameters, as recommended by both the European and

American echocardiography societies.[59, 60] Qualitative findings include mitral valve morphology and visualization of the colour flow and continuous wave regurgitant jet. Semi-quantitative measures include vena contracta width, pulmonary vein flow and mitral inflow patterns. Finally, quantitative parameters of MR severity include EROA and RVol. Additional LV and LA dilation, and increased systolic pulmonary arterial pressure are supportive for severe functional MR. No single criterion is sufficient to establish the severity of MR.[59, 60]

The regurgitant colour flow jet area into the LA can provide information on the presence and direction of the jet and a semi-quantitative assessment of its severity. In general, a larger jet area represents more severe MR. However, the colour flow area of the regurgitant jet is dependent on many technical and haemodynamic factors (such as LA size and pressure) and is therefore not recommended to quantify the severity of MR.[59, 60]

The vena contracta is the narrowest area of the jet, just at or beyond the regurgitant orifice area, and is characterised by high velocities and laminar flow. The cross-sectional area of the vena contracta reflects the EROA – which is the narrowest area of actual flow – and can be used to quantify MR. The size of the vena contracta is independent of flow rate and driving pressure for a fixed orifice. However, if the EROA is dynamic, such as in functional MR, the vena contracta may vary with changing haemodynamics or during the cardiac cycle. Furthermore, the vena contracta area is based on the assumption that the regurgitant orifice is circular. Although the orifice is fairly circular in organic MR, it is usually crescent along the coaptation line of the mitral valve leaflets rather than circular in functional MR.[59, 60]

The flow convergence or proximal isovelocity surface area (PISA) is the most recommended approach to quantify the severity of MR. This method is derived from hydrodynamic principles, stating that as blood approaches a regurgitant orifice, its velocity increases and forms concentric shells of increasing velocity and decreasing surface area. The radius (r) of PISA is measured at mid-systole. Flow rate (Q) through the regurgitant orifice is than calculated as the hemisphere surface area multiplied by the aliasing velocity: $Q = 2\pi r^2 * V_{a.}$ The maximal EROA is assumed to occur at the time of peak regurgitant flow and peak regurgitant velocity (V_{pkreg}), and is consequently derived as: $EROA = (2\pi r^2 * V_a)/V_{pkreg.}$ The RVol can be estimated as the product of the estimated EROA and the velocity time integral (VTI) of the regurgitant jet: RVol = EROA * VTI. The PISA method provides a peak flow rate. EROA estimated by PISA is therefore the maximal EROA and may be slightly larger than EROA derived by other methods. Furthermore, the PISA method is based on the assumption that the velocity distribution proximal to the circular regurgitant orifice has a symmetric hemispheric shape. However, in functional MR, PISA may have an ellipsoid shape and two separate jets (one from the medial

and one from the lateral side of the coaptation line). In that case, the PISA method may underestimate severity of MR.[59, 60]

Pulsed wave Doppler can be used for the quantification of MR when the PISA and VC method are not accurate or applicable. Mitral regurgitant volume is then estimated by calculating the difference between total stroke volume and systemic stroke volume. However, this calculation is time-consuming and inaccurate in the presence of significant aortic regurgitation.

Defining the severity of functional mitral regurgitation

The guidelines' recommendations regarding the cut-off values to define severe functional MR have been changed several times.[57-60, 64, 65] Currently, the threshold for severe functional MR is defined as an EROA of ≥ 40 mm^2 and an RVol of ≥ 60 ml in the guidelines of the American College of Cardiology/American Heart Association[58] and American Society of Echocardiography[60], which is consistent with the threshold for severe organic MR. In the European guidelines,[57, 59] these cut-off values apply for organic MR as well. However, the guideline on the management of valvular heart disease of the European Society of Cardiology[57] states "In secondary mitral regurgitation, lower thresholds have been proposed to define severe mitral regurgitation compared with primary mitral regurgitation [20 mm^2 for EROA and 30 ml for RVol], owing to their association with prognosis.". The guideline of the European Association of Echocardiography[59] states "In functional ischaemic MR, an EROA ≥ 20 mm^2 or an RVol ≥ 30 ml identifies a subset of patients at an increased risk of cardiovascular events".

The threshold for identifying patients with severe functional MR remains a topic of debate.[66-68] The rationale for adjusting the threshold of severe functional MR is that the risk of total and cardiac mortality in patients with ischaemic MR with an EROA ≥ 20 mm^2 or an RVol ≥ 30ml were found to be high.[39, 48] Furthermore, quantifying the severity of functional MR is challenging compared to organic MR, as pointed out before. In functional MR, the reduced total LV forward stroke volume and crescent shaped regurgitant orifice may result in underestimation of RVol, EROA and vena contracta width. Consequently, a lower EROA cut-off may still quantify severe functional MR. However, those in favour of an EROA of ≥ 40 mm^2 and a RVol of ≥ 60 ml as threshold for severe functional MR argue that it is not clear whether the prognostic significance of an EROA ≥ 20 mm^2 is primarily due to the MR itself or to confounding factors such as age, LV status, the underlying heart disease and comorbidities. Furthermore, they argue that lowering the threshold to define severe functional MR, may also lower the threshold for (surgical) interventions, while RCTs have not yet proven a survival benefit for correction of MR.[68]

Further research is warranted to refine the severity criteria for functional MR. More accurate and reproducible measurements of vena contracta and EROA may be provided by 3D echocardiography, which is gaining more and more ground. In the meantime, it is important to keep in mind which definition of severe MR is used when interpreting results of studies on the treatment of functional MR.

Exercise echocardiography

Exercise echocardiography may be useful in evaluating patients with functional MR. Since functional MR comprises a dynamic phenomenon, exercise may unmask the presence of symptoms and an exercise induced increase in MR severity.[57, 60, 69] The preferred method to quantify severity of MR during exercise is EROA derived by PISA, although it may be technically challenging due to tachypnoea and tachycardia.[60, 69] The Doppler method is an alternative if the flow convergence region is inappropriate for PISA. The regurgitant jet is not reproducible and should not be used.[69]

Pathophysiologic mechanisms involved in an increase in MR severity during exercise are LV dilatation due to an increase in volume load, and LV dyssynchrony due to a rate-dependent conduction delay.[70, 71] Significant contractile reserve – in particular of the postero-basal segment – and/or a reduction in LV dyssynchrony, on the other hand, may decrease tethering forces and consequently reduce the severity of functional MR during exercise.[71, 72]

Functional MR severity was found to increase during exercise in over 75% of patients with heart failure, with both ischaemic and non-ischaemic aetiology.[70-74] Interestingly, predictors of increasing MR during exercise all proved to be related to (local) LV geometry – which in turn was related to papillary muscle displacement and mitral valve tenting.[72] These findings indicate that increased tethering forces are the primary mechanism for increased MR severity during exercise.

An exercise-induced increase in functional MR proved to be associated with poor exercise capacity.[73, 75] The mechanism for the association between dynamic MR and impaired exercise capacity was found to be the inability to increase forward stroke volume during exercise, and the fact that LA and pulmonary artery pressure increased excessively. Furthermore, a study by Lancellotti et al. showed that an increase in EROA of $\geq 13mm^2$ during exercise in patients with heart failure was observed in 30% of patients, and was associated with increased mortality and hospital readmissions for heart failure.[76, 77] Additionally, a resting EROA $\geq 20mm^2$ was associated with adverse clinical outcome as well – which supports the lower threshold of severe functional MR, as adopted in the European guidelines.[76]

Other imaging techniques

Cardiac magnetic resonance imaging (MRI) may provide additional information and can be considered when echocardiographic images are suboptimal or when there is a discrepancy between clinical symptoms and severity of MR by echocardiography. Cardiac MRI can provide highly accurate information on the mechanism and severity of MR. Since severity of MR is assessed by the difference between LV stroke volume and forward stroke volume, its evaluation does not rely upon the characteristics of the regurgitant jet. Furthermore, cardiac MRI is the golden standard for assessment of LV and LA volume and function and provides additional information on myocardial fibrosis (scar) and viability, which may have important implications for surgical intervention. When compared to echocardiography, disadvantages of cardiac MRI are its limited availability, higher costs, and uncertainty about safety in patients with metallic implants such as pacemakers and/or cardiac resynchronization/defibrillator devices.[60, 78]

Finally, multi-slice computed tomography may also provide a comprehensive assessment of mitral valve geometry and anatomy of the subvalvular apparatus. Furthermore, multi-slice computed tomography allows a detailed analysis of the papillary muscles and their relation with the adjacent LV wall. Such information may be of value to guide surgical procedures for functional MR, especially procedures addressing the subvalvular apparatus or LV geometry. A disadvantage of multi-slice computed tomography is the associated radiation exposure.[79]

Treatment of functional mitral regurgitation

The treatment of functional MR is included in many guidelines.[13, 57, 58, 65, 80-85] Optimal medical and device therapy are the cornerstone in the treatment of patients with functional MR. In patients with persisting MR and symptoms of heart failure despite optimal medical and device therapy, more invasive treatment options may be considered.[13, 57, 58, 65, 80-85] In line with the broad spectrum of disease and different aetiologies involved in functional MR, many interventions have been proposed, aiming at the mitral valve (mitral valve repair, mitral valve replacement or percutaneous interventions), the subvalvular apparatus (papillary muscle interventions), the LV (coronary artery bypass grafting (CABG), implantation of a CorCap cardiac support device (CSD) or left ventricular reconstruction [LVR]), or a combination thereof. In patients unlikely to benefit from these interventions, HTx or implantation of a left ventricular assist device (LVAD) may be considered.

The wide variety of treatment options reflect the fact that the optimal treatment strategy for patients with functional MR remains a topic of debate. Recommendations in the guidelines are not unequivocal and are based on many heterogeneous – predominantly observational – studies, whereas data from RCTs is scarce. The guidelines' recommendations on mitral valve interventions for the treatment of functional MR are summarised in Table 4.

This thesis will focus on the surgical treatment of functional MR, by mitral valve repair using an undersized or restrictive mitral annuloplasty ring. Mitral valve repair is always combined with optimal medical and device therapy, and for specific indications concomitant surgical procedures – such as CABG, LVR and implantation of a CSD – are performed. Alternative (surgical) interventions, such as subvalvular procedures, mitral valve replacement, percutaneous interventions and implantation of an LVAD, are beyond the scope of this thesis and will therefore only briefly be discussed in Chapter 2.

Optimal medical therapy

Optimal medical therapy – according to the guidelines for the treatment of heart failure – is the mainstay of therapy for patients with functional MR.[13, 57, 58, 83] Optimal medical therapy includes the administration of angiotensin converting enzyme (ACE) inhibitors (or angiotensin II receptor blockers [ARBs]/angiotensin receptor neprilysin inhibitors [ARNIs]), beta-blockers and mineralocorticoid/aldosterone receptor antagonists (MRAs). These drugs proved to reduce the risk of heart failure hospitalization and death in patients with heart failure and should be up-titrated to the maximum tolerated target dose. Furthermore, diuretics are recommended

in patients with signs and symptoms of congestion. In specific situations, other drugs such as digoxin, hydrazaline and isosorbide dinitrate can be considered.[13]

Potential mechanism of individual drugs on the treatment of functional MR

Data regarding the effect of individual heart failure drugs on the severity of functional MR are limited. We may however understand their potential effect by relating the pharmacological mechanism of each drug to the balance of forces involved in functional MR.

ACE inhibitors reduce the activity of the renin-angiotensin-aldosteron system by blocking the conversion of angiotensin I to angiotensin II and the breakdown of bradykinin. Consequently, they reduce ventricular pre- and afterload by inducing arterial and venous vasodilation, depressing sympathetic activity and promoting renal natriuretic and diuretic effects. Additionally, ACE inhibitors were found to inhibit cardiac remodelling. ARBs and ARNIs have similar effects. ARBs can be considered in patients not able to tolerate ACE inhibitors. ARNIs can be considered as a replacement for an ACE inhibitor in patients who remain symptomatic despite treatment with an ACE inhibitor, beta-blocker and MRA.[13]

Beta-blockers block the effects of (nor)epinephrine by binding to beta-adrenoreceptors and thereby reduce the deleterious effects of chronic sympathetic activation in patients with heart failure. Long-term administration of beta-blockers is associated with decreased pre- and afterload (by reducing peripheral vasoconstriction), improved myocardial contractility (due to restored beta-receptor responsiveness of the myocardium, reduced myocardial oxygen consumption and increased diastolic perfusion), and a lower heart rate and risk of arrhythmias. Finally, chronic administration of beta-blockade was found to have beneficial effects on LV remodelling.[86, 87]

MRAs inhibit the action of aldosterone. As such, these drugs have modest diuretic and natriuretic effects, resulting in a decrease in pre- and afterload. Furthermore, MRAs reduce the risk of LV remodelling, myocardial fibrosis and arrhythmias (due to decreased fibrosis and preservation of serum potassium levels).[88]

Diuretics increase excretion of sodium and water, thereby decreasing preload due to reduced blood volume and venous pressure. Long-term administration of diuretics may also reduce afterload by promoting systemic vasodilation.[89]

The impact of the abovementioned drugs on preload, afterload and LV remodelling, and consequently their potential effect on mitral leaflet tethering, closing forces and EROA, are summarised in Table 5. Preload reducing medication – such as diuretics – unload the LV and decrease LV volumes, which may result in reduced mitral leaflet tethering and consequently a

reduction in EROA. Furthermore, a decrease in preload may enhance closing forces, since LA pressure is reduced more than systolic LV pressure and since reduced LA overstretching may enhance LA contractility. A decrease in afterload – as caused by ACE inhibitors – can relieve mitral leaflet tethering by decreasing LV volumes and improving LV geometry. As a consequence of pre- and afterload reduction, LV wall stress and subsequently myocardial oxygen demand decrease which may improve myocardial contractility. Improved myocardial contractility may improve both closing forces (due to increased LV pressure) and tethering forces (due to improved geometry) acting on the mitral valve. Myocardial contractility may improve after long-term administration of beta-blockers as well. Finally, several drugs were found to reduce LV remodelling. Reverse remodelling may increase closing forces due to improved contractility and decrease tethering forces due to reduced LV dilation and improved LV geometry. Consequently, these drugs may reduce severity of functional MR by this mechanism as well.[70, 90]

Table 5. Potential effect of heart failure medication on the forces involved in functional MR.

	Preload	Afterload	LV remodelling	Closing force	Tethering force	EROA
ACEI	↓	↓↓	↓	=↑	↓	↓
BB	↓	↓	↓	=↑	↓	↓
MRA	↓	↓	↓	=↑	↓	↓
Diuretics	↓↓	=	=	↑	↓	↓↓

ACEI = angiotensin-converting enzyme inhibitor; BB = beta-blocker; EROA = effective regurgitant orifice area; MRA = mineralocorticoid receptor antagonist; MR = mitral regurgitation

Impact of optimal medical therapy on functional mitral regurgitation and outcomes

The impact of guideline-directed optimal medical therapy on functional MR has been investigated by Nasser and co-workers. In this study, the clinical management of 163 patients with heart failure (LVEF ≤ 40%) was standardised according to the heart failure guidelines and doses of heart failure medications were titrated to the maximally tolerated dose. At baseline, 31% of patients had severe functional MR. After optimization of medical therapy, 38% (19 of 50) of patients with severe functional MR evolved to non-severe MR, whereas 18% (21 of 113) of patients with non-severe MR evolved to severe MR. Patients with sustained severe functional MR or a deterioration to severe MR had increased LV end-diastolic volumes and significantly worse prognosis (MACE, mortality and hospitalizations for heart failure or VT/VF) compared to patients without severe functional MR or with improvement in MR.[91] Other studies also demonstrated that functional MR is still frequently observed in patients receiving optimal medical therapy, and that presence of functional MR despite optimal medical therapy is associated with adverse prognosis.[47-49, 51]

Recently, the Pharmacological Reduction of Functional Ischemic Mitral Regurgitation (PRIME) trial was conducted in South-Korea.[92] In this trial, 118 patients with heart failure and functional MR were randomised to receive valsartan (an ARB, n = 58) or sacubitril/valsartan (a novel complex of an ARB and an ARNI, n = 60). A significantly greater decrease in EROA was observed in the sacubitril/valsartan group (–0.058 cm^2 or –30%) compared to the valsartan group (–0.018cm^2 or –9%, p = 0.032). A significant decrease in MR (defined as absolute change in EROA >0.1 cm2 or a percentage change > 50%) was observed in 21 patients in the sacubitril/valsartan group versus 14 in the valsartan group; a significant increase in MR was only observed in 5 patients in the valsartan group. Furthermore, follow-up LV volumes were significantly smaller in the sacubitril/valsartan group. Although the beneficial effects of an ARNI in patients with heart failure and functional MR need to be confirmed in other, larger trials, these results are promising.

Cardiac resynchronization therapy

Cardiac resynchronization therapy (CRT) should be considered in symptomatic patients with functional MR, a reduced LVEF ≤ 35% and QRS duration ≥ 130ms, despite optimal medical therapy.[13]

Mechanism of CRT in the treatment of functional MR

Minimization of intraventricular and atrioventricular dyssynchrony by CRT may reduce the severity of functional MR by means of several mechanisms. First, CRT increases mitral closing forces by improving the efficiency of global LV contraction. These increased trans-mitral closing forces counterbalance the tethering forces involved in functional MR and consequently reduce EROA. Second, local synchronization may reduce mitral leaflet tethering forces due to improvement of the time delay between activation of the papillary muscles. Third, mitral annular geometry and function may be improved by coordination of the contraction of myocardial segments at the LV base. Fourth, atrioventricular synchronization may correct diastolic MR – if present – and consequently reduce LA pressure.[93]

CRT may affect functional MR both at short-term (immediately after CRT implantation) and long-term (weeks to months after CRT implantation). An immediate reduction of MR is predominantly due to improved contraction of the papillary muscle bearing LV segments, resulting in acute reduction of tethering forces. An immediate response to CRT results in an acute reduction of LV volume overload and contributes to LV reverse remodelling. Immediate reduction of MR was found to be an important determinant of a favourable response to CRT. The long-term reduction of functional MR is caused by LV reverse remodelling, which may

reduce both closing forces due to improved LV contractility and tethering forces due to a reduction in LV volumes and improvement in LV geometry. Consequently, the reduction of the volume overload that ensues with MR breaks the vicious cycle of LV wall stress and myocardial oxygen demand, which may further improve LV function and consequently MR.[93]

Impact of CRT on functional mitral regurgitation and outcomes

Several RCTs have investigated outcomes after CRT with optimal medical therapy as compared to optimal medical therapy alone in patients with heart failure and cardiac dyssynchrony. These trials demonstrated that CRT can reduce severity of functional MR and LV volumes, and improve symptoms, quality of life and survival.[94, 95]

The evolution of functional MR in patients undergoing CRT was studied by Cabrera-Bueno et al.[96] In this study, 76 patients with advanced dilated cardiomyopathy were included. At baseline 42% (32 of 76) of patients had significant MR (EROA > 20mm^2); in 34% (11 of 32) of these patients, MR had become insignificant 6 months after CRT, while seven (9%) patients developed significant MR. Persistence or development of functional MR after CRT was associated with a higher rate of clinical events (death, transplantation or readmission for heart failure), arrhythmic events and less reverse remodelling. Similar outcomes were described by van Bommel et al.[97], who demonstrated a significant reduction in MR (by ≥ 1 grade) 6 months after CRT in 49% (42 of 85) of patients with moderate-severe functional MR and high operative risk. Patients with an improvement in MR after CRT had better survival.

Coronary artery bypass grafting

Coronary artery revascularization directly addresses the underlying cause of ischaemic MR. Consequently, CABG forms a key element in the treatment of patients with ischaemic MR. The indications for CABG are described in the guidelines on myocardial revascularization.[80, 98]

Mechanism of CABG in the treatment of functional MR

The rationale behind CABG in the treatment of ischaemic MR is that revascularization may improve LV geometry and function, and consequently reduce papillary muscle displacement and mitral leaflet tethering forces. As such, there has been much debate on the question whether CABG alone would be sufficient in the treatment of patients with ischaemic MR, especially in patients with less than severe MR. Leaving the mitral valve untouched would also avoid the perioperative risks associated with a concomitant mitral valve procedure.

Impact of CABG on functional mitral regurgitation and outcomes

The impact of CABG on the severity of ischaemic MR has been studied in several observational studies,[99-101] but much information can also be obtained from the results of RCTs comparing CABG alone versus CABG with mitral valve repair for patients with moderate ischaemic MR.[102-104] In the RIME trial,[102] MR improved to no/mild in 50% of patients one year after CABG, whereas 47% of patients still had moderate MR and MR had worsened to moderate-severe in 3% of patients. One-year results of the CTSN trial demonstrated less than moderate MR in 59%, moderate MR in 26% and severe MR in 5% of patients after CABG. Outcomes of the RIME and CTSN trial will be discussed in detail in Chapter 2.

The clinical and echocardiographic impact of ischaemic MR in patients undergoing CABG alone was studied in several observational studies as well. A retrospective study by Fattouch et al.[101] evaluated 180 patients with coronary artery disease and moderate ischaemic MR who underwent CABG and 360 matched patients without ischaemic MR who also underwent CABG. Echocardiographic follow-up (mean 30 months) in 130 surviving patients with preoperative MR, demonstrated that MR had decreased to mild in 30%, remained moderate in 35% and had increased to severe in 35%. Patients without MR showed a significant reduction in LV diameters, whereas LV diameters increased in patients with residual MR. Additionally, 5-year survival was significantly worse in patients with preoperative ischaemic MR compared to patients without MR (74% versus 91%), as was freedom from cardiac-related events (62% versus 88%). Similar results were obtained by Grossi and colleagues, who demonstrated a graded relation between the degree of preoperative ischaemic MR and survival in 2242 patients undergoing CABG alone (5-year survival 86% in patients without MR, 84% in patients with mild MR and 70% in patients with moderate MR).[105]

These studies indicate that outcome after CABG alone is highly unpredictable with MR remaining unchanged or worse in 31-50% of patients undergoing CABG alone, and that presence of ischaemic MR is associated with ongoing LV remodelling and adverse clinical outcomes after CABG.

Table 4. Guidelines' recommendations for the interventional treatment of functional MR.

Guidelines of the European Society of Cardiology (ESC) and the European Association of Cardio-Thoracic Surgery (EACTS)			
Guideline	Recommendations	COR	LOE
CABG[80]	MV surgery is indicated in patients with severe secondary MR undergoing CABG and LVEF > 30%.	I	C
	MV surgery should be considered in symptomatic patients with severe secondary MR and LVEF < 30%, but with evidence of myocardial viability and an option for surgical revascularization.	IIa	C
Valvular heart disease [57]	Surgery is indicated in patients with severe secondary MR undergoing CABG and LVEF > 30%.	I	C
	Surgery should be considered in symptomatic patients with severe secondary MR, LVEF < 30% but with an option for revascularization and evidence of myocardial viability.	IIa	C
	When revascularization is not indicated, surgery may be considered in patients with severe secondary MR and LVEF >30% who remain symptomatic despite optimal medical management (including CRT if indicated) and have a low surgical risk.	IIb	C
	When revascularization is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary MR and LVEF >30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have a suitable valve morphology by echocardiography, avoiding futility.	IIb	C
	In patients with severe secondary MR and LVEF < 30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have no option for revascularization, the Heart Team may consider a percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a ventricular assist device or heart transplant according to individual patient characteristics.	IIb	C
Heart Failure[13]	Combined surgery of secondary MR and CABG should be considered in symptomatic patients with LV systolic dysfunction (LVEF < 30%), requiring coronary revascularization for angina recalcitrant to medical therapy.	IIa	C
	Isolated surgery of non-ischaemic MR in patients with severe functional MR and severe LV systolic dysfunction (LVEF < 30%) may be considered in selected patients in order to avoid or postpone transplantation.	IIb	C

Guidelines of the American Heart Association (AHA) and American College of Cardiology (ACC)			
Guideline	Recommendations	COR	LOE
CABG[81]	In patients undergoing CABG who have moderate ischemic MR not likely to resolve with revascularization, concomitant MV repair or replacement at time of CABG is reasonable.	IIa	B
	Patients undergoing CABG who have severe ischemic MR not likely to resolve with revascularization should have concomitant MV repair or replacement at the time of CABG.	I	B
Valvular heart disease[58, 65]	In patients with moderate ischemic MR undergoing CABG, the usefulness of mitral valve repair is uncertain.	IIb	B-R
	MV surgery is reasonable for patients with severe secondary MR who are undergoing CABG or AVR.	IIa	C
	It is reasonable to choose chordal-sparing MVR over downsized annuloplasty repair if operation is considered for severely symptomatic patients (NYHA III to IV) with severe ischemic MR and persistent symptoms despite GDMT for heart failure.	IIa	B-R
	MV repair or replacement may be considered for severely symptomatic patients (NYHA class III to IV) with severe secondary MR who have persistent symptoms despite optimal GDMT for heart failure.	IIb	B
Heart failure[82, 83]	Transcatheter mitral valve repair or mitral valve surgery for functional MR is of uncertain benefit and should only be considered after careful candidate selection and with a background of GDMT.	IIb	B
Guidelines of the American Association of Thoracic Surgery (AATS)			
Guideline	Recommendations	COR	LOE
Ischemic MV surgery[84]	In patients with moderate ischemic MR undergoing CABG, MV repair with and undersized complete rigid annuloplasty ring may be considered.	IIIb	B
	MV replacement is reasonable in patients with severe ischemic MR who remain symptomatic despite guideline directed medical and cardiac device therapy and who have a basal aneurysm/dyskinesis, significant leaflet tethering and/or severe LV dilatation (LVEDD >65mm).	IIa	B
	MV repair with an undersized complete rigid annuloplasty ring may be considered in patients with severe ischemic MR who remain symptomatic despite guideline directed medical and cardiac device therapy and who do not have a basal aneurysm/dyskinesis, significant leaflet tethering, or severe LV enlargement.	IIb	B

MR = mitral regurgitation, MV = mitral valve, CABG = coronary artery bypass grafting, COR = classification of recommendations, CRT = cardiac resynchronization therapy, GDMT = guideline directed medical therapy, LOE = level of evidence, LV = left ventricle, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction.

Restrictive mitral annuloplasty

History

Restrictive mitral annuloplasty (RMA) was first introduced by Bach and Bolling from the University of Michigan in 1994. In the first report on early outcomes after mitral annuloplasty, they demonstrated improved NYHA functional class, reduced LV volumes and increased LVEF in nine patients with end-stage cardiomyopathy (mean LVEF 15%).[106] In the next paper, reporting similar outcomes and a 1-year survival of 75% in 16 patients after mitral annuloplasty, Bolling first mentions the use of a ring undersized by "perhaps one size" (mean ring size 29).[107] In the discussion of a subsequent manuscript, Bolling states: "We started downsizing more and more. Now we are basically putting in the smallest rings that we can, and we have not seen mitral stenosis clinically in any patient."[108] These publications led to the introduction of RMA, which nowadays forms the mainstay of the surgical treatment of functional MR and is the subject of this thesis.

Rationale and surgical technique

The rationale behind mitral valve repair using an RMA ring is that it corrects mitral annular dilatation and enforces mitral leaflet coaptation, thereby abolishing MR. Furthermore, RMA reduces the size of the LV base, thereby re-establishing LV shape, lowering LV wall stress and initiating LV reverse remodelling.[108, 109] This mitral valve repair technique can be used in both patients with ischaemic and non-ischaemic MR.

Initially, RMA was performed using (semi-)flexible and incomplete mitral annuloplasty rings.[107] Nowadays, complete (semi-)rigid rings are generally recommended for the performance of RMA.[85] These (semi-)rigid rings may better reduce the septal-to-lateral dimension of the mitral annulus and a complete ring may also account for dilatation of the anterior mitral annulus. Indeed, a study comparing flexible rings with complete (semi-)rigid rings, observed less recurrent MR in patients who underwent RMA with a complete (semi-)rigid ring.[110]

In our hospital, RMA is performed by a structured approach. This approach consists of the implantation of a complete rigid or semi-rigid ring. The size of the ring is carefully determined by measuring the anterior leaflet height and then downsizing by 2 ring sizes (i.e. size 26 when measuring size 30). Mitral valve repair is considered successful in case of no or mild MR and a leaflet coaptation length of ≥ 8mm on intraoperative transoesophageal echocardiography. If these criteria are not met, further downsizing is performed. In patients with ischaemic MR, we always combine RMA with complete revascularization to address both the valvular and

ventricular component of functional MR. In patients with non-ischaemic MR, treatment of the intrinsic ventricular disease remains an uncovered area.

Results after RMA

Many observational studies on outcomes after RMA for ischaemic MR have been published. Several of these studies demonstrated that RMA results in durable correction of MR, reversal of LV remodelling and beneficial clinical outcomes,[111-113] whereas others could not confirm these beneficial outcomes.[114-116] Data regarding RMA for patients with non-ischaemic MR are limited, but improved NYHA functional class, better quality of life and LV reverse remodelling have been reported in these patients as well.[117, 118] Outcomes of observational studies are difficult to compare since they are highly heterogeneous due to differences in included patient populations, aetiology of MR, surgical technique, concomitant procedures and follow-up duration.

Over the last years, several RCTs on the surgical treatment of functional MR in the setting of ischaemic heart disease have been conducted. Three trials compared CABG alone versus CABG with concomitant mitral valve repair for moderate ischaemic MR[102-104, 119], whereas one trial compared mitral valve repair versus replacement for severe ischaemic MR.[120, 121] Although these trials were conducted to provide answers in the optimal surgical treatment of ischaemic MR, results regarding incidences of residual/recurrent MR, LV reverse remodelling and clinical outcome are not unequivocal and none of the trials was powered to detect a survival difference. Results of these trials will be discussed in Chapter 2.

RCTs comparing RMA versus optimal medical and device therapy for non-ischaemic MR have thus far not been conducted. However, much information regarding RMA for non-ischaemic MR can be obtained from the Acorn trial, which will be discussed in Chapter 2 as well.

Recurrent mitral regurgitation

Recurrence of MR after RMA was found to be associated with adverse outcome after RMA. Reported incidences of recurrent MR highly differ between studies. Although several studies demonstrated that RMA can ensure a durable correction of MR,[102, 111-113, 119] others report considerable incidences of MR recurrence.[114-116, 120, 121] When interpreting these studies, it is important to differentiate between residual and true recurrent MR. Residual MR is observed early after surgery and can partly be explained by the surgical technique – whether adequate downsizing is performed and whether absence of MR and a coaptation length of ≥8mm are confirmed on intra-operative echocardiography. Recurrent MR, on the other hand, was found to be associated with disease progression – ongoing LV remodelling – and may develop despite

a well-conducted mitral valve repair.[122] However, since in functional MR the mitral valve and LV are interrelated in a complex way, the causality between the two remains to be distinguished.

Many studies have focused on preoperative predictors for recurrent MR. Although several predictors – mainly reflecting mitral valve or LV configuration – have been identified, it remains difficult to identify individual patients most likely to benefit from mitral valve repair.

Functional mitral valve stenosis

A downsized mitral annuloplasty ring reduces mitral septal-to-lateral distance and also decreases mitral valve orifice area. Use of small, undersized mitral annuloplasty rings (ring size 24 and 26) has therefore raised concerns, in that extensive reduction of mitral annular dimension may obstruct antegrade mitral flow and may consequently induce a functional mitral valve stenosis.[123]

Since such a functional mitral stenosis may be even more pronounced during exercise, exercise echocardiography studies have been performed.[124-126] These studies demonstrated that functional mitral stenosis – when present after RMA – does not simply result from implantation of an undersized annuloplasty ring. Although the mitral orifice at annular level is fixed after implantation of a complete (semi-)rigid annuloplasty ring, the functional mitral valve area proved to be dynamic in response to exercise and was determined by the degree of diastolic anterior leaflet tethering.[124, 125]

Left ventricular reconstruction

According to the guidelines, LVR may be considered in selected heart failure patients, with intractable heart failure symptoms (NYHA III/IV), a large LV aneurysm, large thrombus formation, or ventricular arrhythmias.[80, 82] In our hospital, LVR is predominantly performed in patients with a post-infarction antero-septal LV aneurysm and refractory heart failure despite optimal medical and device therapy.

Rationale and surgical technique

The rationale behind LVR is that exclusion of the scar tissue will reduce LV volume (thereby reducing LV wall stress and improving the oxygen supply/demand relationship), reshape LV geometry (which realigns cardiac muscle fiber orientation) and consequently improve LV function. Left ventricular reconstruction is usually combined with myocardial revascularization, which may also enhance LV function.[127]

LVR is generally performed as described by Dor and colleagues.[128] After careful inspection of the transitional zone between scarred and non-scarred tissue, a shaping Fontan-stitch is placed at the transitional zone. The sizing and shaping of the residual ventricular cavity is performed using a shaping device filled to a volume of 55 ml/m^2 BSA, to avoid diastolic dysfunction by creating a too small LV cavity. After exclusion of the dyskinetic or akinetic LV wall, the LV is closed with a direct suture or in case of a remaining defect, using an endoventricular patch.

Functional mitral regurgitation at the time of LVR

Functional MR is frequently observed in patients with ischaemic heart failure, but although its presence is known to be associated with poor survival, the management of MR at the time of LVR remains controversial.[127] On the one hand, LVR may reduce tethering forces and thus severity of MR by reducing LV volumes and restoring LV geometry. Additionally, the reduction in LV wall stress and myocardial oxygen demand may increase mitral leaflet coaptation due to improved LV function and hence closing forces. On the other hand, LVR may lead to distortion of LV geometry and the subvalvular apparatus and consequently induce or exacerbate MR. Moreover, ongoing LV remodelling after LVR may lead to development or recurrence of functional MR if left untreated at the time of surgery.[129, 130]

Results after LVR combined with RMA

In our institution, concomitant mitral valve repair is performed in patients with MR ≥ grade 2 on preoperative echocardiography, and in patients with an increase of MR to ≥ grade 2 on intraoperative transoesophageal echocardiography directly after LVR. Other concomitant procedures are performed when indicated. In a previous report, Klein et al. demonstrated sustained improvement in LVEF, reduction of LV volumes, and favourable clinical outcomes (approximately 80% survival) 36 months after this integrated approach of LVR with concomitant mitral valve repair and other procedures.[131]

Cardiac support device

Rationale and surgical technique

The CorCap CSD (Acorn Cardiovascular, St. Paul, MN, USA) is an external fabric mesh device for patients with heart failure due to non-ischaemic cardiomyopathy. The CSD is implanted surgically around the heart and reduces LV wall stress by providing circumferential diastolic support, in order to prevent further LV remodelling.

The CSD can be used in combination with mitral valve repair. In our hospital, the CSD implantation was performed in patients with non-ischaemic MR and advanced LV remodelling,

i.e. preoperative LV end-diastolic diameter (LVEDD) ≥ 65mm or indexed LVEDD ≥ 30mm/m^2. The CSD is than implanted after mitral valve surgery has been performed, on the beating heart along the atrioventricular groove. At the end of the surgical procedure, the CSD is tailored to meet the preoperative LV dimensions measured on transoesophageal echocardiography. Currently, the CorCap CSD has been taken off the market and is no longer used.

Results after CSD combined with RMA

The Acorn trial has studied the effect of a CSD in 192 patients with non-ischaemic MR and heart failure (EF ≤ 35%, LV end-diastolic diameter ≥ 60mm and a 6-minute walking test < 450m, NYHA functional class III or IV). Patients were randomised to receive either RMA alone (n = 102) or RMA with implantation of a CSD (n = 91). At 5-year follow-up, LV volumes were decreased in both strata, but addition of a CSD resulted in a more extensive decrease in LV volumes. Change in MR grade and LVEF were similar between both groups and CSD did not improve survival. The results of the Acorn trial are discussed in more detail in Chapter 2.

In another study, Braun and co-workers from our institution reported outcomes of 69 patients with non-ischaemic MR and heart failure, who received optimal medical therapy combined with mitral valve repair (n = 28) or – in case of advanced LV remodelling – mitral valve repair and concomitant CSD implantation (n = 41). Overall actuarial survival at 1 and 5 years was 86 ± 4% and 63 ± 7%, respectively. Addition of the CSD to mitral valve repair resulted in similar clinical outcome compared to mitral valve repair alone, a greater decrease in LV end-diastolic volume (33 versus 18%, p = 0.007) and a trend towards less recurrent MR.

Other concomitant procedures

Tricuspid regurgitation is frequently observed in patients with functional MR. In patients undergoing mitral valve surgery, tricuspid valve repair should be considered in case of severe tricuspid regurgitation and in patients with mild or moderate tricuspid regurgitation and annular dilatation (≥ 40 mm or ≥ 20mm/m^2).[57] Tricuspid valve repair for these indications was found to reverse right ventricular remodelling and improve functional status without increasing the operative risk.[132] In heart failure patients with LV ejection fraction ≤ 30%, an implantable cardiac defibrillator is advised, to reduce sudden death due to cardiac arrhythmias.[13]

Thesis outline

The aim of this thesis was to study the surgical treatment of patients with functional MR, focusing on identification of patients likely to benefit from each treatment strategy, in order to be able to further personalise the surgical approach and optimise outcomes for each patient.

Chapter 2, provides an overview of the different surgical and interventional treatment strategies for patients with both ischaemic and non-ischaemic MR. The rationale, indication, surgical technique, results and limitations of each of these techniques is discussed by experts in the field.

Studies regarding the surgical treatment of ischaemic MR are presented in chapters 3 and 4. Chapter 3 is a comment on the two-year results of the Cardio-Thoracic Surgery Network trial comparing mitral valve repair versus mitral valve replacement. In chapter 4, long-term outcomes after mitral valve repair with revascularization for ischaemic MR are evaluated. This study specifically focuses on the mortality-adjusted incidence of recurrent MR, the clinical impact of recurrent MR and its pre-operative determinants.

Chapter 5 presents the long-term outcomes after an integrated medico-surgical approach for patients with non-ischaemic MR, focusing on the prevalence and prognostic impact of LV reverse remodelling and recurrent MR. Furthermore, the analysis of preoperative risk factors for adverse clinical outcomes are presented.

In chapter 6, ten-year outcomes of patients with heart failure due to a post-infarction anteroseptal LV aneurysm, who underwent an integrated approach of LVR with concomitant procedures – mitral and tricuspid valve reconstruction, coronary revascularization and arrhythmia surgery – are presented.

In chapter 7, mitral valve exercise haemodynamics are assessed in patients who underwent an RMA, and related to LV geometry and function, and to clinical outcomes.

In chapter 8, analyses the incidence and clinical impact of vasoplegia after mitral valve repair for patients with ischaemic and non-ischaemic MR.

Finally, chapter 9 provides a summary, clinical implications, conclusions and future perspectives.

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