Personalised surgical treatment of functional mitral regurgitation

Petrus, A.H.J.

Chapter 4

Impact of recurrent mitral regurgitation after mitral valve repair for functional mitral regurgitation: Long-term analysis of competing outcomes

Annelieke H.J. Petrus, Olaf M. Dekkers, Laurens F. Tops,
Eva Timmer, Robert J.M. Klautz, Jerry Braun

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Abstract

Aims: Recurrent mitral regurgitation (MR) has been reported after mitral valve repair for functional MR. However, the impact of recurrent MR on long-term survival remains poorly defined. In the present study, mortality-adjusted recurrent MR rates, the clinical impact of recurrent MR and its determinants were studied in patients after mitral valve repair with revascularization for functional MR in the setting of ischaemic heart disease.

Methods and results: Long-term clinical and echocardiographic outcome was evaluated in 261 consecutive patients after restrictive mitral annuloplasty and revascularization for moderate to severe functional MR, between 2000 and 2014. The cumulative incidence of recurrent MR ≥ grade 2, assessed by competing risk analysis, was 9.6 ± 1.8% at 1-year, 20.3 ± 2.5% at 5-year, and 27.6 ± 2.9% at 10-year follow-up. Cumulative survival was 85.8% [95% confidence interval (CI) 81.0 – 90.0] at 1-year, 67.3% [95% CI 61.1 – 72.6%] at 5-year, and 46.1% [95% CI 39.4 – 52.6%] at 10-year follow-up. Age, preoperative New York Heart Association Class III or IV, a history of renal failure, and recurrence of MR expressed as a time-dependent variable (HR 3.28 [1.87 – 5.75], p <0.001), were independently associated with an increased mortality risk. Female gender, a history of ST-elevation myocardial infarction, a preoperative QRS duration ≥120 ms, a higher preoperative MR grade, and a higher indexed left ventricular end-systolic volume were in-dependently associated with an increased likelihood of recurrent MR.

Conclusion: Mitral valve repair for functional ischaemic MR resulted in a low incidence of recurrent MR with favourable clinical outcome up to 10 years after surgery. Presence of recurrent MR at any moment after surgery proved to be independently associated with an increased risk for mortality.

Introduction

Functional mitral regurgitation (MR) is a common phenomenon in patients with ischaemic heart disease and results from a combination of increased mitral leaflet tethering and decreased closing forces, due to regional or global left ventricular (LV) remodelling.[1] Presence of functional MR induces volume overload, resulting in further LV remodelling and worsening MR. Consequently, functional MR is a relevant marker of adverse clinical outcome.[2,3]

The treatment of patients with functional MR focuses on both the mitral valve (by curing MR) and the left ventricle (by initiating and sustaining LV reverse remodelling). The most effective surgical strategy to address the mitral valve — either by mitral valve repair or by mitral valve replacement — has been studied in many (predominantly observational) studies, but remains a matter of ongoing debate.[4,5] Arguments in favour of mitral valve repair — generally by restrictive mitral annuloplasty (RMA) — are based on the presumed lower perioperative morbidity and mortality associated with mitral valve repair compared to replacement.[6] On the other hand, high recurrent MR rates reported after mitral valve repair have led to the believe that mitral valve replacement might result in better clinical outcome since it provides a more durable correction of MR.[7–10]

Recently, a randomized controlled trial was conducted by the Cardio-Thoracic Surgery network (CTSN), comparing mitral valve repair and mitral valve replacement for patients with severe functional ischaemic MR.[11,12] This trial did not demonstrate relevant differences with regard to LV reverse remodelling or survival between both groups, despite a clearly higher recurrent MR rate after mitral valve repair (33% at 1-year and 59% at 2-year follow-up) compared to mitral valve replacement (2% at 1-year and 4% at 2-year follow-up). These results have raised the question: Does recurrent MR, in terms of clinical outcome, matter at all?

Although recurrent MR was found to be associated with absence of LV reverse remodelling and adverse clinical outcome in several observational studies,[7–10] the effect of recurrent MR on long-term survival remains poorly defined. Furthermore, previous studies were not able to account for the attrition of patients due to death during follow-up. Given the high mortality in these patients, the true incidence of recurrent MR and its clinical impact may not be fully appreciated.

The aim of the present study was to evaluate long-term outcomes in patients with functional MR in the setting of ischaemic heart disease, who underwent a structured approach of mitral valve repair with revascularization, focusing on mortality-adjusted recurrent MR rates (by competing risk analysis), the clinical impact of recurrent MR and its determinants.

Methods

Study population and study design

Consecutive patients with coronary artery disease scheduled to undergo coronary artery bypass grafting (CABG) and moderate to severe chronic ischaemic MR (grade 3 or 4) due to restrictive systolic leaflet motion (Carpentier IIIb), who underwent mitral valve repair at Leiden University Medical Center between 2000 and 2014, were included. Severity of MR was assessed by echocardiography at rest, or — in patients scheduled for CABG with fluctuating MR or MR grade 2 — during bicycle exercise or intra-operative provocative testing, as previously described.[13–15] Patients with functional MR due to non-ischaemic-dilated cardiomyopathy, patients with organic mitral valve abnormalities or aortic valve disease and patients requiring LV reconstruction surgery for an LV aneurysm were excluded.

Baseline and surgical characteristics, echocardiographic data, and clinical outcome were evaluated for all patients. The study complies with the Declaration of Helsinki, the institutional medical ethics committee approved the protocol and written informed consent was obtained from all participating patients.

Surgical technique

All surgical procedures were performed through midline sternotomy under normothermic cardiopulmonary bypass with intermittent antegrade warm-blood cardioplegia. Conventional multivessel CABG was performed, aiming at complete revascularization. The mitral valve was exposed through a transseptal approach and mitral valve repair was performed with a complete semi-rigid ring (Carpentier Edwards Physio Ring, Edwards Lifesciences, Irvine, CA, USA). Ring size was carefully determined by measuring the anterior leaflet height and then downsizing by two ring sizes (i.e. size 26 when measuring 30). No additional procedures were performed on the mitral valve leaflets, nor on the subvalvular apparatus or the left ventricle itself. Concomitant tricuspid annuloplasty was performed with a Carpentier Edwards Classic or MC3 ring in patients with tricuspid regurgitation ≥ grade 2 or — from the year 2003 onward — in presence of a tricuspid annular diameter >40 mm.

Intra-operative transoesophageal echocardiographic assessment of LV and mitral valve function was performed in all patients. Mitral valve repair was considered successful in case no or mild MR and a leaflet coaptation height of at least 8 mm were observed. If these criteria were not met, further downsizing was performed.

Echocardiography

Two-dimensional and Doppler transthoracic echocardiography was performed preoperatively and before discharge in all patients. Mitral regurgitation severity was semi-quantitatively assessed on a scale from 1 to 4 by colour-flow Doppler in conventional parasternal long-axis and apical two-, three-, and four-chamber images.[16] Left atrial and LV diameters were determined from parasternal long-axis acquisitions and LV volumes were measured in apical two- and four-chamber images and indexed to body surface area (BSA).[17] Left ventricular ejection fraction (LVEF) was calculated by the modified biplane Simpson's method.[17] Transtricuspid pressure gradient was estimated using the modified Bernoulli equation on the transtricuspid continuous-wave signal.[18] Subsequent echocardiographic follow-up was performed in our institution or in the patient's home institution.

Study endpoints and follow-up

Primary endpoint of this study was recurrence of MR. The first Doppler echocardiography demonstrating MR ≥ grade 2 after surgery was considered 'MR recurrence'. Secondary endpoints were all-cause mortality, reinterventions (mitral valve reinterventions, heart transplantation, and implantation of an LV assist device) and hospital readmissions for congestive heart failure (requiring treatment with parenteral diuretics or inotropes).

After surgery, patients were followed by their personal physician at our institution or in the patient's home institution. All available echocardiographic reports were obtained to assess recurrence of MR. Information regarding clinical events was obtained by direct patient interview and patients' medical records. All endpoints were assessed from surgery until 10-year follow-up or until 1 June 2017.

Statistical analysis

Continuous data are expressed as mean ± standard deviation or median with interquartile ranges (IQR) and compared using the paired and unpaired Student's t-test. Categorical variables are described as frequencies and percentages and compared using the χ^2 test or Fisher's exact test. Recurrence of MR and death are not independent endpoints, hence competing risk analysis was performed to assess the cumulative incidence of recurrent MR. Univariable and multivariable Fine and Gray models were used to assess preoperative variables associated with recurrence of MR.[19] The Kaplan–Meier method was used to estimate absolute mortality risk. Univariable and multivariable Cox proportional hazards regression analyses were performed to analyse variables associated with all-cause mortality; MR recurrence was

analysed as time-dependent variable. For the comparison of patients with and without recurrent MR we used recurrent MR as time-dependent covariate to avoid immortal time bias. A level of p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS statistical software version 20.0 (IBM Corp., Armonk, NY, USA) or Stata version 14 (StataCorp., College Station, TX, USA: StataCorp LP).

Table 1. Baseline characteristics (n = 261).

	Whole cohort (n = 261)	Recurrent MR (n = 67)	No recurrent MR (n = 194)	p-value
Clinical data				
Age (years)	69 ± 9	69 ± 8	69 ± 9	0.948
Female	81 (31%)	28 (42%)	53 (27%)	0.027
BSA (m^2)	1.9 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	0.006
NYHA class	2.7 ± 0.8	2.8 ± 0.9	2.6 ± 0.8	0.165
CCS class	1.8 ± 1.3	1.9 ± 1.3	1.8 ± 1.2	0.535
Diabetes	64 (25%)	14 (21%)	50 (26%)	0.424
Renal failure	11 (4%)	6 (9%)	5 (3%)	0.036
COPD	25 (10%)	7 (10%)	18 (9%)	0.779
Hypertension	88 (34%)	24 (36%)	64 (33%)	0.673
Stroke / TIA	29 (11%)	6 (9%)	23 (12%)	0.515
STEMI	180 (69%)	54 (81%)	126 (65%)	0.017
Atrial fibrillation	39 (15%)	6 (10%)	33 (17%)	0.100
QRS duration (ms)	122 ± 33	128 ± 34	120 ± 33	0.075
Previous cardiac surgery	49 (19%)	16 (24%)	33 (17%)	0.214
Pulmonary hypertension	13 (5%)	6 (9%)	7 (4%)	0.083
ICD	20 (8%)	6 (9%)	14 (7%)	0.645
CRT	6 (2%)	1 (1%)	5 (3%)	0.609
Log EuroSCORE I	12.9 ± 12.3	17 ±15	11 ± 11	0.001
Echocardiographic data				
MR grade	3.0 ± 0.7	3.3 ± 0.6	2.9 ± 0.7	0.001
Grade 2	36 (14%)	4 (6%)	32 (16%)	
Grade 3	134 (51%)	32 (48%)	102 (53%)	
Grade 4	91 (35%)	31 (46%)	60 (31%)	
LA dimension (mm)	46 ± 7	46 ± 8	45 ± 7	0.372
LV end-diastolic dimension (mm)	61 ± 8	64 ± 9	60 ± 8	0.002
Indexed to BSA (mm/m^2)	32 ± 5	35 ± 5	32 ± 4	<0.001
LV end-systolic dimension (mm)	50 ± 10	53 ± 10	48 ± 9	<0.001
Indexed to BSA (mm/m^2)	26 ± 6	29 ± 6	25 ± 5	<0.001
LV ejection fraction (%)	37 ± 9	35 ± 8	38 ± 9	0.077
LV end-diastolic volume (ml)	168 ± 59	192 ± 64	159 ± 55	<0.001
Indexed to BSA (ml/m^2)	88 ± 29	103 ± 31	82 ± 26	<0.001
LV end-systolic volume (ml)	108 ± 47	126 ± 48	102 ± 45	<0.001
Indexed to BSA (mm/m^2)	56 ± 24	68 ± 25	53 ± 22	<0.001
Transtricuspid PG (mmHg)	30 ± 11	30 ± 10	31 ± 11	0.975

BSA = body surface area, CCS = Canadian Cardiovascular Society, COPD = Chronic obstructive pulmonary disease, CRT = cardiac resynchronization therapy, ICD = implantable cardioverter-defibrillator, MR = mitral regurgitation, LA = left atrium, LV = left ventricle, PG = pressure gradient, NYHA = New York Heart Association, STEMI = ST-elevation myocardial infarction, TIA = transient ischaemic attack.

Results

Study population

Two hundred and sixty-one patients, who underwent RMA for moderate to severe functional ischaemic MR between 2000 and 2014, were included. Baseline patient characteristics are summarized in Table 1. Mean age was 69 ± 9 years. All patients had coronary artery disease and 69% had a previous ST-elevation myocardial infarction (STEMI); 63% of patients were in New York Heart Association (NYHA) Class III or IV. Preoperative echocardiographic assessment demonstrated MR grade 3 in 51% of patients and grade 4 in 35%. In 36 patients scheduled for CABG with fluctuating MR or MR grade 2, MR increased to grade 3 or 4 during bicycle exercise testing (n = 8) or intra-operative provocative testing (n = 28). Mean LV end-systolic volume indexed to BSA (LVESVI) was 56 ± 24 mL/m^2 and mean LVEF was 37 ± 9%.

Surgical data are summarized in Table 2. Mitral valve repair could be achieved in all patients (mean implanted ring size 26 ± 2). Intra-operative transoesophageal echocardiography demonstrated a competent mitral valve in all patients (no MR in 95%, trace or grade 1 MR in 5% of patients) with a mean leaflet coaptation height of 8 ± 1 mm.

Table 2. Surgical data (n = 261).

	Whole cohort (n = 261)	Recurrent MR (n = 67)	No recurrent MR (n = 194)	p-value
Mitral annular diameter	30 ± 2	30 ± 2	30 ± 2	0.407
Mitral annuloplasty ring size	26 ± 2	27 ± 2	26 ± 2	0.486
24	66 (25%)	18 (27%)	47 (24%)	
26	95 (36%)	18 (27%)	78 (40%)	
28	83 (32%)	27 (40%)	56 (29%)	
30	15 (6%)	3 (5%)	12 (6%)	
32	2 (1%)	1 (1%)	1 (1%)	
Coronary artery bypass grafting	226 (87%)	56 (84%)	170 (88%)	0.402
No. of distal anastomosis	3.0 ± 1.3	3.0 ± 1.2	3.0 ± 1.4	0.773
Tricuspid valve annuloplasty	84 (32%)	20 (30%)	64 (33%)	0.635
AF ablation	33 (13%)	25 (13%)	8 (12%)	0.841
CPB time	191 ± 64	191 ± 58	192 ± 67	0.971
Aortic cross-clamp time	134 ± 46	126 ± 42	136 ± 47	0.207

AF = atrial fibrillation, CPB = cardiopulmonary bypass, MR = mitral regurgitation.

Recurrence of mitral regurgitation

Echocardiographic follow-up was performed in >80% of alive patients for each defined time interval between surgery and 10 years after surgery (Figure 1). After surgery, recurrence of MR ≥ grade 2 was diagnosed in 67 patients, at a median of 1.7 years [IQR 0.5 – 4.7] post-operatively. Recurrent MR was observed at discharge in 10 patients (MR grade 2 in eight patients and grade

3 in two patients), whereas recurrence of MR developed after discharge in 57 patients. The cumulative incidence of recurrent MR was 9.6 ± 1.8% at 1-year, 14.3 ± 2.2% at 2-year, 16.6 ± 2.3% at 3-year, 20.3 ± 2.5% at 5-year, and 27.6 ± 2.9% at 10-year follow-up (**Figure 2**).

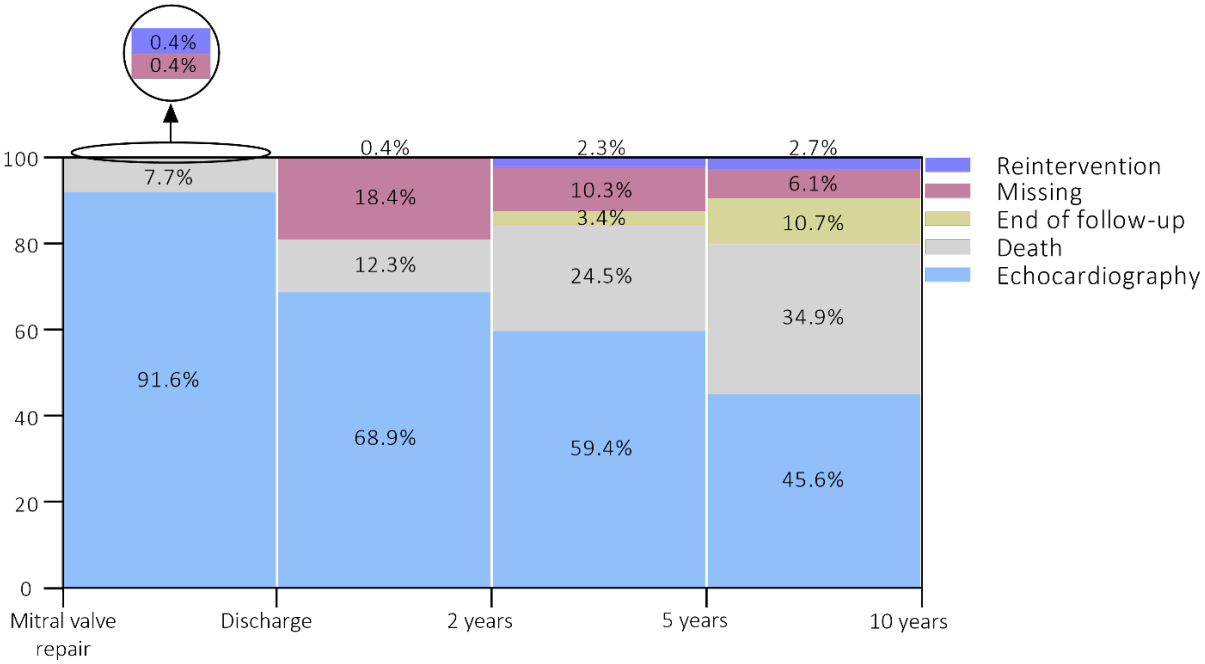


Figure 1. Echocardiographic follow-up.

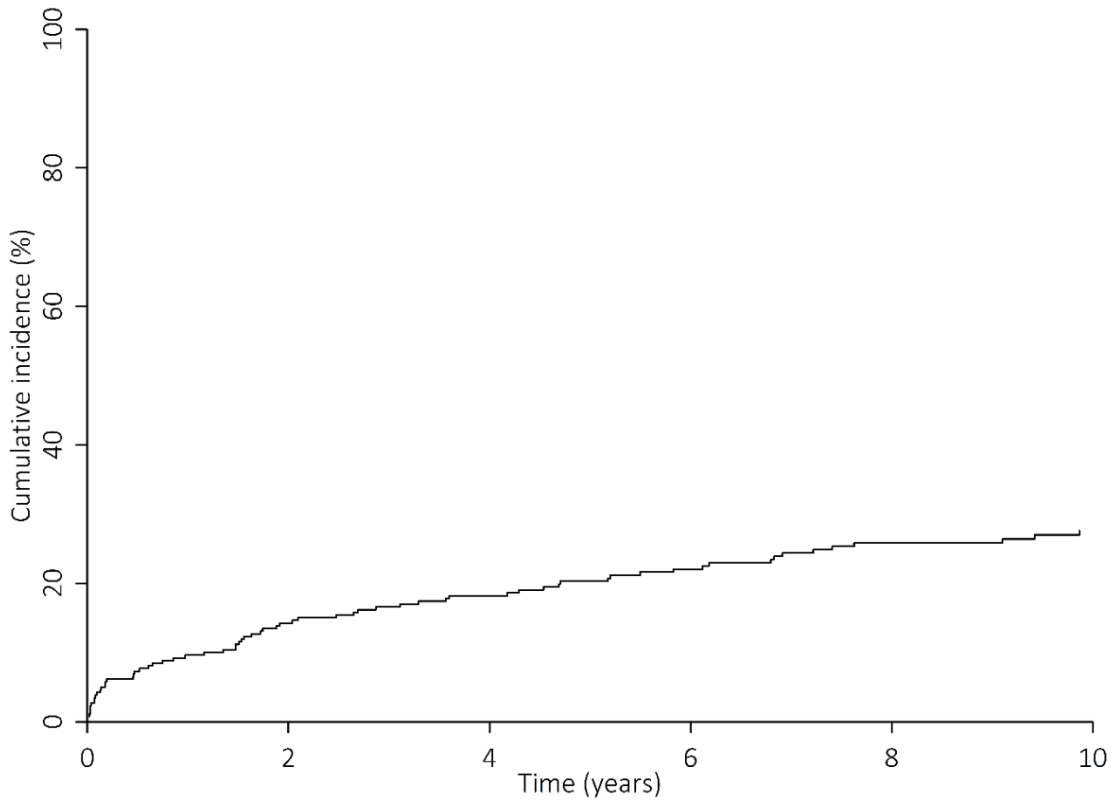


Figure 2. Cumulative incidence of recurrent mitral regurgitation by competing risk analysis.

Clinical outcome

Clinical follow-up was complete and median follow-up duration was 6.8 years [IQR 3.0 – 10.0]. During follow-up, 10 patients (3.8%) underwent a reintervention. In eight patients, the reintervention was performed for recurrent MR, due to ring dehiscence (n = 2), endocarditis (n = 2), and progressive mitral leaflet tethering (n = 4). The mitral annuloplasty ring was removed because of mitral valve stenosis in one patient. Finally, one patient with progressive heart failure underwent LV assist device implantation. Eighty-three hospital survivors (34%) were rehospitalized for congestive heart failure; these patients experienced 156 readmissions (9.8 per 100 patient years). A total of 127 patients died (including 20 in-hospital deaths) Cumulative survival was 85.8% [95% confidence interval (CI) 81.0 – 90.0] at 1-year, 80.1% [95% CI 74.7 – 84.4%] at 2-year, 67.3% [95% CI 61.1 – 72.6%] at 5-year, and 46.1% [95% CI 39.4 – 52.6%] at 10-year follow-up (**Figure 3**).

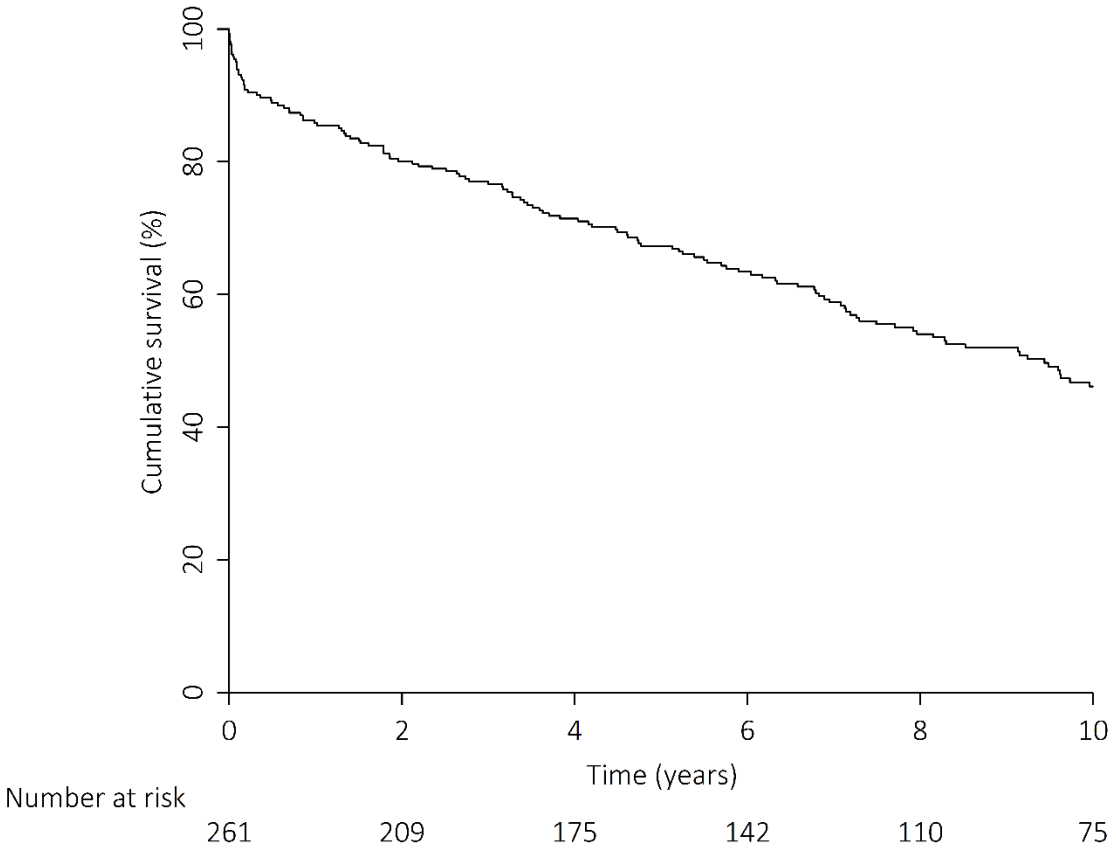


Figure 3. Survival after mitral valve repair.

Predictors for mortality and significance of recurrent mitral regurgitation

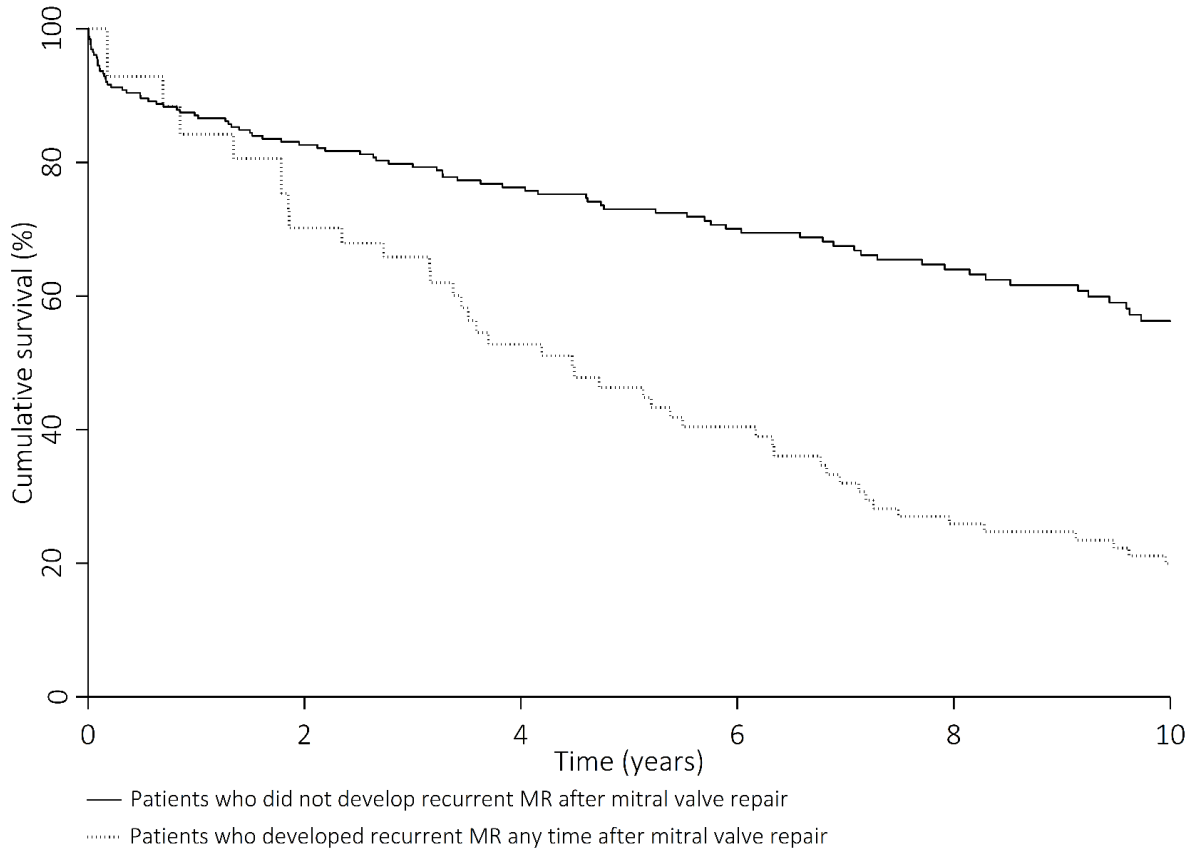
Predictors for all-cause mortality are presented in Table 3. After correction for potential confounders, the following variables were associated with an increased mortality risk: age (HR 1.05 [1.02 – 1.08], p = 0.002), preoperative NYHA Class III or IV (HR 2.08 [1.56 – 3.74], p = 0.015), a history of renal failure (HR 3.35 [1.46 – 7.71], p = 0.004), and recurrence of MR expressed as a time-dependent variable (HR 3.28 [1.87 – 5.75], p <0.001). The clinical impact of recurrent MR on survival is displayed in the Take home figure.

Reinterventions were performed in eight patients (11.9%) with recurrent MR compared with two patients (1.2%) without recurrent MR (p = 0.001). Furthermore, recurrent MR was associated with an increased risk for readmissions for congestive heart failure (HR 2.19 [1.40 – 3.44], p = 0.001); 51% of patients with recurrent MR were readmitted for congestive heart failure (16.8 rehospitalizations per 100 patient years) compared to 30% of patients without recurrent MR (7.2 rehospitalizations per 100 patient years).

Table 3. Predictors for all-cause mortality after surgery (n=261).

	Univariable		Multivariable	
	HR [95% CI]	p-value	HR [95% CI]	p-value
Preoperative clinical data				
Age	1.04 [1.02 – 1.06]	<0.001	1.05 [1.02 – 1.08]	0.002
Female gender	0.97 [0.66 – 1.41]	0.866		
NYHA class III – IV	1.75 [1.13 – 2.71]	0.013	2.08 [1.56 – 3.74]	0.015
Diabetes Mellitus	1.12 [0.75 – 1.67]	0.578		
Renal failure	2.23 [1.13 – 4.40]	0.021	3.35 [1.46 – 7.71]	0.004
STEMI	1.25 [0.84 – 1.85]	0.279		
Atrial fibrillation	1.14 [0.69 – 1.89]	0.610		
Previous cardiac surgery	1.50 [1.00 – 2.27]	0.056	1.48 [0.77 – 2.83]	0.235
QRS duration ≥ 120ms	1.57 [1.10 – 2.26]	0.014	1.30 [0.74 – 2.27]	0.355
CRT	1.96 [0.72 – 5.30]	0.187		
Preoperative echocardiographic data				
MR grade	1.23 [0.96 – 1.58]	0.107		
LV ejection fraction ≥ 30%	1.27 [0.81 – 1.98]	0.293		
LV end-systolic volume indexed to BSA (ml/m^2)	1.01 [1.00 – 1.02]	0.008	1.01 [1.00 – 1.02]	0.070
Operative data				
Mitral annuloplasty ring size	1.00 [0.90 – 1.10]	0.979		
Concomitant CABG	0.83 [0.51 – 1.36]	0.460		
Concomitant TVP	0.96 [0.65 – 1.42]	0.852		
Concomitant AF ablation	0.81 [0.45 – 1.42]	0.448		
CPB time	1.00 [1.00 – 1.01]	0.017	1.00 [1.00 – 1.01]	0.327
Follow-up data				
MR recurrence*	3.15 [2.13 – 4.65]	<0.001	3.28 [1.87 – 5.75]	<0.001

*MR recurrence was analysed as a time-dependent variable. CABG = coronary artery bypass grafting, CI = confidence interval, HR = hazard ratio, TVP = tricuspid valve annuloplasty, other abbreviations as in Table 1.



Take home figure. Two hundred sixty-one patients underwent mitral valve repair for ischaemic functional MR. Recurrence of MR was observed in 67 patients, whereas recurrent MR was absent in 194 patients. Time-dependent Cox regression analysis shows that patients without recurrent MR (solid line) have significantly better survival compared to patients who develop recurrent MR at any time after mitral valve repair (dotted line).

Predictors for recurrent mitral regurgitation

Given that recurrent MR was associated with adverse clinical outcome, we aimed to identify preoperative predictors for MR recurrence. Comparison of clinical characteristics of patients with and without recurrent MR (Table 1) demonstrated that patients with recurrent MR were more often female, had a higher EuroSCORE and more were more likely to have a history of renal failure or STEMI. Comparison of preoperative echocardiographic characteristics showed a higher preoperative MR grade and larger LV dimensions and volumes in patients with recurrent MR compared to patients without recurrent MR (Table 1). Surgical data were not clearly different between both groups (Table 2).

Multivariable regression analysis (according to Fine and Gray's subdistribution hazards model) demonstrated that female gender (subdistribution hazard ratio (sHR) 2.11 [1.12 – 3.99], p = 0.022), a history of STEMI (sHR 2.43 [1.19 – 4.92], p = 0.014), a preoperative QRS duration ≥120 ms (sHR 2.16 [1.14 – 4.09], p = 0.019), a higher preoperative MR grade (sHR 1.59 [1.03 – 2.47], p = 0.037), and a higher LVESVI (sHR 1.02 [1.01 – 1.03], p = 0.001) were all independently associated with an increased likelihood of recurrent MR (Table 4).

Table 4. Predictors of MR recurrence (n=261).

	Univariable		Multivariable	
	sHR [95% CI]	p-value	sHR [95% CI]	p-value
Preoperative clinical data				
Age	1.00 [0.97 – 1.03]	0.988		
Female gender	1.84 [1.13 – 3.01]	0.015	2.11 [1.12 – 3.99]	0.022
NYHA class III/IV	1.09 [0.64 – 1.87]	0.754		
Renal failure	2.62 [1.17 – 5.87]	0.020	1.79 [0.79 – 4.04]	0.161
STEMI	1.99 [1.09 – 3.62]	0.025	2.43 [1.19 – 4.96]	0.014
Atrial fibrillation	0.52 [0.23 – 1.20]	0.124		
Pulmonary hypertension	2.56 [1.05 – 6.24]	0.039	1.84 [0.69 – 4.92]	0.223
QRS duration ≥120ms	2.30 [1.38 – 3.82]	0.001	2.16 [1.14 – 4.09]	0.019
CRT	0.62 [0.08 – 4.64]	0.640		
Preoperative echocardiographic data				
MR grade	1.98 [1.40 – 2.82]	<0.001	1.59 [1.03 – 2.47]	0.037
LV ejection fraction ≥30%	1.49 [0.84 – 2.65]	0.175		
LV end-systolic volume indexed to BSA (ml/m^2)	1.02 [1.01 – 1.03]	<0.001	1.02 [1.01 – 1.03]	0.001
Operative data				
Mitral annuloplasty ring size	1.05 [0.92 – 1.21]	0.460		
Concomitant CABG	0.74 [0.38 – 1.44]	0.379		
CPB time	1.00 [1.00 – 1.00]	0.933		

CI, confidence interval; sHR, subdistribution hazard ratio; other abbreviations as in Table 1 and 2.

Discussion

In the present study, long-term clinical and echocardiographic outcome — specifically focusing on the incidence, clinical impact and determinants of recurrent MR — was evaluated in patients who underwent mitral valve repair for functional ischaemic MR. Main findings of this study are: 1) The overall cumulative incidence of recurrent MR was 9.6 ± 1.8% at 1-year, 20.3 ± 2.5% at 5-year, and 27.6 ± 2.9% at 10-year follow-up; 2) Recurrence of MR during follow-up significantly increased the risk for reoperations, hospital readmissions, and mortality; 3) Female gender, a history of STEMI, preoperative QRS duration ≥ 120 ms, higher preoperative MR grade, and higher preoperative LVESVI were independently associated with an increased likelihood of recurrent MR following mitral valve repair.

Incidence of recurrent mitral regurgitation

Functional MR is a common phenomenon in patients with coronary artery disease and is independently associated with adverse clinical outcome. Mitral valve repair — by implantation of an RMA ring — aims to restore mitral valve competence and initiate LV reverse remodelling, in order to improve clinical outcome in these patients. Although several studies demonstrated that RMA can ensure a durable correction of MR,[20–24] others reported considerable incidences of recurrent MR.[7–10] However, follow-up duration was limited and different surgical techniques were used in these studies. More importantly, none of these studies accounted for the competing risk of death, which may mask the true incidence of recurrent MR.

In the present study, recurrence of MR was assessed up to 10 years after mitral valve repair and we uniquely accounted for death as a competing event. The cumulative incidence of recurrent MR observed in the current study — 10% at 1-year, 14% at 2-year, 20% at 5-year, and 28% at 10-year follow-up — is lower than that observed in many observational studies[7–10] and far lower than the incidence recently reported by the CTSN investigators (33% at 1-year and 59% at 2-year follow-up).[11,12] Although the observed difference may partly be explained by the fact that preoperative MR grade was higher in the CTSN trial (including only patients with severe MR) compared to the present study (including patients with moderate to severe MR), preoperative LVESVI and LVEF were comparable (61 ± 26 mL/m^2 and 42 ± 12% in the CTSN trial, vs. 56 ± 24 mL/m^2 and 37 ± 9% in the present study). The low incidence of recurrent MR observed in the present study, might therefore rather be explained by the structured surgical approach to patients with functional ischaemic MR in our institution. This approach consists of implantation of a semi-rigid annuloplasty ring, stringently downsized by two ring sizes, and aiming at a coaptation length of at least 8 mm. In contrast, in other studies uniformity in ring type and sizing is often lacking and leaflet coaptation at the end of surgery is not routinely

assessed. Furthermore, durability of mitral valve repair may be related to the experience of the surgeon performing the procedure.[4,5] Recurrent MR was observed in 4% of hospital survivors at discharge in the current study, whereas the CTSN trial reported a recurrent MR rate of 30% within 30 days after surgery.[12] Such a high incidence cannot be explained by disease progression and should be considered residual MR due to suboptimal repair rather than recurrent MR.

Clinical outcome and significance of recurrent mitral regurgitation

Follow-up duration in the present study is longer than in any previous report. The observed survival rates — 86% at 1-year, 80% at 2-year, 67% at 5-year, and 46% at 10-year follow-up — are better than short-term survival rates in some previous reports[8,25,26] and comparable to those reported by others.[20–24] We identified four preoperative predictors for adverse long-term survival: age, preoperative NYHA functional Class III or IV, a history of renal failure, and recurrence of MR. Several previous studies have shown that recurrence of MR is associated with absence of LV reverse remodelling and poor clinical outcome.[7–10] However, to the best of our knowledge, this study is the first to demonstrate that recurrence of MR occurring at any moment during the course of follow-up is independently associated with poor long-term clinical outcome, including an increased risk of reoperation, heart failure readmissions, and a three times higher risk of death [HR 3.28 (1.87 – 5.75), p <0.001].

Preoperative predictors for recurrence of mitral regurgitation

Since recurrence of MR independently affects subsequent clinical outcome, preoperative patient selection — based on the likelihood to develop recurrent MR — is crucial to optimize outcome after mitral valve repair. In the current study, female gender, a history of STEMI, preoperative QRS duration ≥ 120 ms, higher preoperative MR grade, and higher preoperative LVESVI were associated with an increased risk for recurrent MR. In line with earlier reports, these parameters can almost all be related to LV remodelling, underlining once again that the extent of remodelling of the LV plays a key role in determining the success of mitral valve repair.[7,10,27–29] These findings can be used in the decision-making process on the optimal treatment of patients with functional ischaemic MR, which should be performed on a case-by-case basis by the Heart Team, as proposed by the current ESC/EACTS guidelines.[4,5]

Clinical implications

The optimal surgical strategy to treat patients with functional MR in the setting of ischaemic heart disease—either by mitral valve repair or by mitral valve replacement — remains a topic of debate. The high incidences of recurrent MR reported after mitral valve repair increasingly lead to the believe that mitral valve replacement might be the better option.

Results of the present study convey two important messages: first, it demonstrates that a structured surgical approach to mitral valve repair results in a low incidence of recurrent MR and favourable clinical outcome up to 10 years after surgery. These findings stress the importance of using a complete semi-rigid annuloplasty ring, proper downsizing and obtaining a supra-physiologic coaptation length. Second, in the subgroup of patients developing recurrent MR after surgery, the risk for poor clinical outcome was significantly increased. These findings may lead to the conclusion that mitral valve replacement should be preferred over mitral valve repair. However, several studies have demonstrated that patients after a successful mitral valve repair (without recurrent MR) have potential for LV reverse remodelling.[20–24] Even the CTSN trial shows a 30% decrease in indexed LV end-systolic volume in patients after successful mitral valve repair, whereas a volume reduction of only 10% was observed in patients after mitral valve replacement.[11,12] Based on these results a durable mitral valve repair seems to be better than a mitral valve replacement. Therefore, the key focus for future studies should be aimed at identifying preoperative parameters to select patients with potential for a durable mitral valve repair. Mitral valve replacement or mitral valve repair with additional subvalvular techniques should be considered only in patients without such potential.

Study limitations

The present study is an observational, retrospective study and may therefore bear associated biases. After the discharge echocardiogram, follow-up was performed either at our institution or in the patient's home institution. Since the quality of echocardiograms performed elsewhere could not be individually confirmed, the possibility exists that some of the patients with follow-up outside our institution had MR recurrence, which was not detected. Furthermore, patients with missing echocardiographic follow-up data could have developed recurrent MR. However, echocardiographic follow-up from surgery up to 10 years after surgery was complete in >80% of alive patients. The contribution of coronary revascularization and mitral valve repair to LV reverse remodelling and thus MR recurrence and outcome cannot be assessed separately. Data on myocardial viability or the extent of scar tissue was very limited in our study population, and therefore, its importance could not be taken into consideration. However, all patients underwent complete revascularization to maximize the potential for LV recovery. Finally, due

to the long-term follow-up (inclusion of patients started in 2000), technical challenges resulted in the limited use of qualitative and semi-quantitative parameters for assessment of MR severity, whereas in the most recent recommendations the use of quantitative parameters is recommended.[28]

Conclusion

In the present study, a structured approach of mitral valve repair for functional MR due to ischaemic heart disease resulted in a low incidence of recurrent MR and favourable clinical outcome up to 10 years after surgery. Presence of recurrent MR at any moment after surgery proved to be independently associated with an increased risk for reinterventions, readmissions for congestive heart failure, and mortality. These findings indicate that mitral valve repair is a suitable treatment option for the vast majority of patients with functional MR. Given the clear clinical impact of recurrent MR, future studies should aim at preoperative identification of patients with a high likelihood of developing recurrent MR.

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