

Restrictive mitral annuloplasty with or without coronary artery bypass grafting in ischemic mitral regurgitation

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Abstract

Aims In patients with ischaemic mitral regurgitation (MR), the impact of mitral valve surgery with concomitant coronary artery bypass grafting (CABG) on post-operative survival and left ventricular (LV) reverse remodelling remains unknown. Therefore, we investigated these outcomes following restrictive mitral annuloplasty (RMA) with and without CABG in those patients.

Methods and results This study included 309 patients with chronic MR and ischaemic cardiomyopathy for whom concomitant CABG was indicated ($n = 225$) or not indicated ($n = 84$) with RMA. The primary endpoint was all cause mortality during the follow-up, and the secondary endpoint was defined as the composite of mortality and re-admission for heart failure. Linear mixed model was used to analyse serial echocardiographic changes in LV function. To reduce the impact of treatment bias and potential confounding in the direct comparisons between patients who underwent RMA with and those who underwent it without CABG, we established weighted Cox proportional-hazards regression models with inverse-probability-of-treatment weighting. Pre-operatively, there were no intergroup differences in age (RMA with CABG, 67 ± 9 vs. RMA without CABG, 68 ± 11 , $P = 0.409$) and logistic EuroSCORE II (16 ± 14 vs. 15 ± 15 , $P = 0.496$). The 30-day mortalities were 2.7% and 3.6%, respectively ($P = 0.67$). During follow-up with a mean duration of 72 ± 37 months (range, 5.6–179), there were 157 deaths and 105 re-admissions for heart failure. Overall 1-year and 5-year survival rates were $83 \pm 2\%$ and $58 \pm 3\%$, respectively. Patients who did not receive CABG with RMA had a significantly lower 5-year survival rate (45% vs. 63%, $P = 0.049$) and freedom from adverse events defined as mortality and/or admission for heart failure (19% vs. 43%, $P < 0.001$) than those who did. After adjustments for clinical covariates with inverse-probability-of-treatment weighting, concomitant CABG was identified as an independent protective factor for adverse events (hazard ratio: 0.53; 95% confidence interval: 0.44–0.64; $P < 0.001$). Along with significant MR reduction, LV function parameters changed over time after surgery in both groups, with greater improvements in patients who underwent RMA with CABG (time effect, $P < 0.001$; and interaction effect, $P = 0.002$).

Conclusions RMA can be performed with an acceptable operative mortality, irrespective of indications for CABG. Patients with ischaemic MR for whom CABG is indicated with RMA are more likely to show better long-term and event-free survival and greater improvements in LV systolic function. The optimal revascularization strategy should be discussed with a heart team whenever indicated in patients with ischaemic MR; otherwise, they may miss the opportunity to benefit from concomitant CABG during subsequent RMA.

Keywords Ischaemic mitral regurgitation; Coronary artery bypass grafting; Restrictive mitral annuloplasty; Cardiomyopathy; Left ventricular reverse remodelling

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Introduction

Ischaemic mitral regurgitation (MR) complicates the course of 13–50% of cases of acute myocardial infarctions (MIs) and adds volume overload to a decompensated left ventricle; it results in a poor prognosis in the long-term follow-up and has been identified as an independent predictor of heart failure and reduced long-term survival.^{1,2} The data indicating that correcting MR prolongs life or improves symptoms are sparse; therefore, the current consensus guidelines do not strongly recommend mitral valve surgery in patients with chronic secondary MR, unless coronary artery bypass grafting (CABG) is indicated.³ In accordance with the guidelines, a recent randomized clinical trial demonstrated that the rates of death from any cause, cardiovascular causes, and hospitalization for cardiovascular causes were significantly lower over 10 years in patients who underwent CABG in addition to receiving medical therapy than those who received medical therapy alone.⁴ Therefore, we hypothesized that the prognoses of patients with ischaemic MR in whom CABG is not indicated must be worse than the prognoses in those who also undergo CABG at the time of the mitral valve surgery. To date, however, the long-term outcomes of patients who undergo mitral valve surgery with and those who undergo it without CABG have not been sufficiently reported. Thus, to test our hypothesis, we investigated and compared the long-term clinical outcomes of patients with ischaemic MR who underwent restrictive mitral annuloplasty (RMA) with and without concomitant CABG, with a focus on the indication of concomitant CABG.

Methods

Patients

The basic patient characteristics and surgical data were obtained from the surgical database of Osaka Cardiovascular Surgery Research Group, which is a prospective database. A total of 598 patients with chronic secondary MR who underwent RMA between 1999 and 2015 were identified, and, of them, those with non-ischaemic aetiology ($n = 131$) and those with less left ventricular (LV) remodelling with an ejection fraction $> 40\%$ ($n = 158$) were excluded from this study. Finally, 309 patients with chronic MR secondary to ischaemic cardiomyopathy, which was defined as severely

impaired LV systolic function with an ejection fraction $\leq 40\%$, were included. Of these, concomitant CABG with RMA was indicated and performed in 225 patients, while in the remaining 84 patients, only RMA was performed. A flow diagram depicting the selection of the patient population is shown in *Figure 1*. Prior to surgical referral, all patients were treated with optimized medical regimens for heart failure, including beta-blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and diuretics. The investigation conformed to the principles outlined in the Declaration of Helsinki. The final study protocol was approved by an institutional ethical committee, and all participants provided written informed consent.

Echocardiography

Two-dimensional and Doppler echocardiography were performed preoperatively (baseline), at 1 and 12 months postoperatively, and annually thereafter. The anatomical and Doppler parameters were measured according to the recommendations of the *American Society of Echocardiography*.

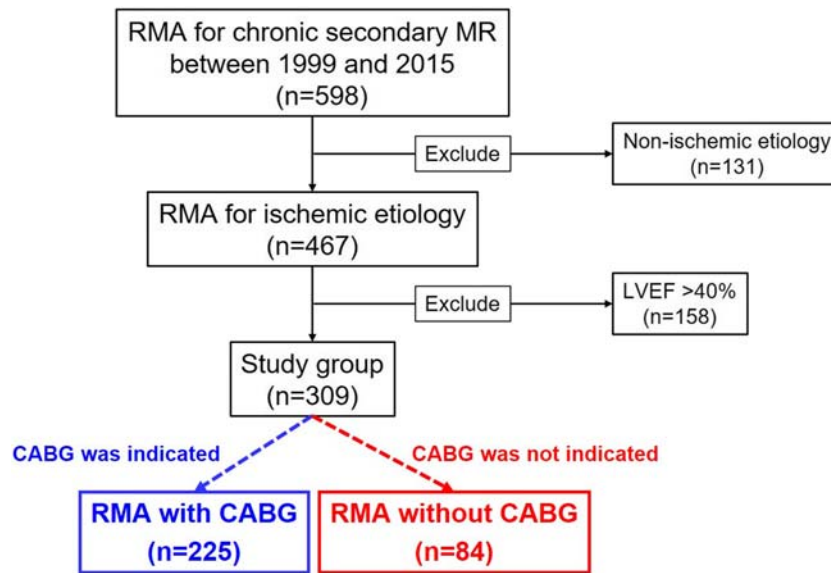
Surgical procedures

The surgical procedures were performed with the use of a standard cardiopulmonary bypass. All patients underwent stringent RMA after careful assessments of the inter-commissural distance and height of the anterior leaflet. No other adjunct procedures were performed on the mitral valve itself. The indication for CABG was influenced by the cardiac and coronary anatomies, myocardial viability, and previous history of either percutaneous coronary intervention (PCI) or CABG; however, the final decision was made at the discretion of the attending surgeon. In patients in whom concomitant CABG was indicated, whenever possible, *in situ* right or left internal thoracic artery was utilized to bypass to the left anterior descending artery. The decision to perform concomitant procedures, such as surgical ventricular restoration, papillary muscle approximation, or aortic valve replacement, was made at the discretion of the attending surgeon.

Outcomes, definitions, and clinical follow-up

The primary endpoint was all-cause mortality during the follow-up, and the secondary endpoint was defined as the

Figure 1 CONSORT flowchart for selection of patients with ischaemic cardiomyopathy who underwent RMA during the study period. MR, mitral regurgitation; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; RMA, restrictive mitral annuloplasty.



composite of mortality and re-admission for heart failure. The diagnosis of post-operative recurrent heart failure was based on clinical symptoms, physical signs, or radiological evidence of pulmonary congestion. Additionally, we also evaluated the longitudinal changes in LV function parameters and MR severity on serial echocardiography. Clinical follow-up examinations were completed in all patients (100%), with a mean follow-up duration of 72 ± 37 months (range: 5.6–179) in the survivors. The overall cumulative follow-up period was 1371 patient years.

Statistical analysis

Continuous variables were summarized as mean \pm standard deviation and compared with the use of Welch's *t*-test for the two study groups (i.e. RMA with CABG and RMA without CABG). Likewise, categorical variables were summarized as frequencies with proportions and compared using chi-squared test or Fisher's exact test, as appropriate. The echocardiographic variables over time were analysed using a mixed-effects model for repeated measures, including factors for group, time, and interaction between group and time. Each time and patient were treated as a random effect, while assessment time points were treated as categorical factors. The variance-covariance matrix in the linear mixed-effects model was assumed to be unstructured.

Survival analysis was performed using the Kaplan–Meier method for estimation and a log-rank test for comparison between the patient groups. To reduce the impact of treatment bias and potential confounding in the direct comparisons

between patients who underwent RMA with and those who underwent it without CABG, we established weighted Cox proportional-hazards regression models with inverse-probability-of-treatment weighting (IPTW) because of the observational nature of this study.^{5,6} In that technique, the weights for patients who underwent RMA with CABG were the inverse of the propensity score, and the weights for patients who underwent RMA without CABG were the inverse of (1-propensity score). The probability of undergoing RMA with CABG (propensity score) for each patient was calculated using multivariate logistic regression analysis based on clinically relevant covariates that are listed in *Table 2*. In order to measure the covariate balance, we checked the standardized mean differences before and after matching. When standardized mean difference was <0.1 (10%), we considered it to indicate a negligible imbalance between the two groups. The results are summarized as hazard ratios (HRs) and 95% confidence intervals (CIs). Statistical analyses were performed using JMP 7.0 (SAS Institute, Cary, NC, USA) and R (R Foundation for Statistical Computing, version 3.5.0, Vienna, Austria).

Results

Patient demographics and surgical data

The baseline characteristics of the patients and surgical data are summarized in *Table 1*. Pre-operatively, there were no intergroup differences in the age, sex, body surface area, logistic EuroSCORE II, and prevalence of emergency surgery,

Table 1 Patient demographics

	RMA with CABG (n = 225)	RMA without CABG (n = 84)	P value
Clinical variables			
Age, years	67 ± 9	68 ± 11	0.409
Male, n (%)	180 (80%)	72 (86%)	0.249
Body surface area, m ²	1.63 ± 0.18	1.62 ± 0.16	0.838
Emergent operation, n (%)	33 (15%)	12 (14%)	0.933
Redo operation, n (%)	14 (6.2%)	15 (18%)	0.002
Catecholamine use, n (%)	18 (8.0%)	13 (15%)	0.052
Logistic EuroScore II, %	15 ± 15	16 ± 14	0.496
History of coronary revascularization			
Pre-op CABG, n (%)	12 (5.3%)	12 (14%)	0.009
Prior coronary intervention, n (%)	90 (40%)	76 (90%)	<0.001
None	135 (60%)	7 (8.3%)	<0.0001
Single	44 (20%)	25 (30%)	
Multiple	46 (20%)	52 (62%)	
Number of PCI history, n	0.9 ± 1.5	2.3 ± 1.6	<0.0001
Comorbidities, n (%)			
eGFR < 30 mL/min/1.73m ²	64 (28%)	29 (35%)	0.370
Diabetes	130 (58%)	39 (46%)	0.075
Echocardiographic data			
LVESD, mm	54 ± 8	56 ± 8	0.039
LVEF, %	29 ± 8	27 ± 8	0.034
Mitral regurgitation grade, n (%)			
Mild	38 (17%)	9 (11%)	0.069
Moderate	118 (52%)	38 (45%)	
Severe	69 (31%)	37 (44%)	
Medications, n (%)			
Statin	111 (49%)	45 (54%)	0.507
Beta-blockers	127 (56%)	59 (70%)	0.026
ACE inhibitors and/or ARB	141 (63%)	62 (74%)	0.063
Surgical data			
Graft selection, n (%)			
No ITA use	24 (11%)	-	-
Single ITA use	151 (67%)	-	-
Bilateral ITA use	50 (22%)	-	-
Distal anastomoses, n	2.8 ± 1.2	-	-
Mitral annuloplasty ring, n (%)			
Partial ring	9 (4.0%)	3 (3.6%)	0.862
Complete ring	216 (96%)	81 (96%)	
Ring size, n (%)			
24 mm	63 (28%)	43 (51%)	0.001
26 mm	102 (45%)	33 (40%)	
28 mm	52 (23%)	8 (9.6%)	
30 mm	7 (3.1%)	0 (0%)	
32 mm	1 (0.4%)	0 (0%)	
Concomitant procedures, n (%)			
SVR	58 (26%)	38 (45%)	0.001
PM approximation	26 (12%)	26 (31%)	<0.0001
Aortic valve replacement	18 (8.0%)	8 (9.5%)	0.668

ACE, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blockers; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ITA, internal thoracic artery; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; PM, papillary muscle; RMA, restrictive mitral annuloplasty; SVR, surgical ventricular reconstruction.

chronic kidney disease, and diabetes between the groups. However, patients in whom concomitant CABG was not indicated were more likely to be dependent on inotropic agents and have larger LV dimensions, lower LV ejection fraction, and past histories of PCI and cardiac surgeries. Additionally, the patients who underwent RMA without CABG tended to undergo RMA with a smaller ring and undergo concomitant procedures such as surgical ventricular reconstruction and papillary muscle approximation more frequently.

After adjusting for the clinically relevant baseline and surgical profiles with the use of IPTW, there were no inter-group

differences in the baseline and surgical covariates, with the standardized difference for each of the covariates being less than 0.10 (10%) (Table 2).

Early and late outcomes

The 30-day mortality was 2.7% in patients who underwent RMA with CABG and 3.6% in those who underwent RMA without CABG ($P = 0.67$). During the follow-up, there were 157 deaths and 105 re-admissions for heart failure, and the

Table 2 Patient demographics before and after adjustments with IPTW

	Original cohort (crude)			IPTW		
	RMA with CABG (n = 225)	RMA without CABG (n = 84)	SMD	RMA with CABG (n = 313)	RMA without CABG (n = 288)	SMD
Clinical variables						
Age, years	67 ± 9	68 ± 11	0.100	67 ± 9	68 ± 12	0.061
Male, n (%)	180 (80%)	72 (86%)	0.152	255 (82%)	237 (82%)	0.020
Body surface area, m ²	1.63 ± 0.18	1.62 ± 0.16	0.026	1.62 ± 0.17	1.61 ± 0.17	0.097
Emergency operation, n (%)	33 (15%)	12 (14%)	0.011	44 (14%)	42 (14%)	0.009
Redo operation, n (%)	14 (6.2%)	15 (18%)	0.363	33 (11%)	29 (9.6%)	0.063
Catecholamine use, n (%)	18 (8.0%)	13 (15%)	0.234	32 (10%)	29 (9.6%)	0.062
Logistic EuroScore II, %	15 ± 15	16 ± 14	0.088	16 ± 15	16 ± 18	0.002
Comorbidities, n (%)						
eGFR < 30 mL/min/1.73 m ²	64 (28%)	29 (35%)	0.131	90 (29%)	90 (30%)	0.059
Diabetes	130 (58%)	39 (46%)	0.229	170 (54%)	168 (55%)	0.001
Echocardiographic data						
LVESD, mm	54 ± 8	56 ± 8	0.258	55 ± 8	55 ± 9	0.009
LVEF, %	29 ± 8	27 ± 8	0.271	28 ± 8	28 ± 8	0.005
Mitral regurgitation grade, n (%)						
Mild	38 (17%)	9 (11%)	0.297	46 (15%)	42 (14%)	0.092
Moderate	118 (52%)	38 (45%)		155 (50%)	148 (49%)	
Severe	69 (31%)	37 (44%)		112 (36%)	114 (38%)	
Concomitant procedures, n (%)						
SVR	58 (26%)	38 (45%)	0.415	106 (34%)	105 (37%)	0.059
PM approximation	26 (12%)	26 (31%)	0.488	54 (17%)	55 (19%)	0.047
Aortic valve replacement	18 (8.0%)	8 (9.5%)	0.054	28 (9.0%)	30 (10%)	0.050

CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; IPTW, inverse-probability-of-treatment weighting; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; PM, papillary muscle; RMA, restrictive mitral annuloplasty; SMD, standardized mean difference; SVR, surgical ventricular reconstruction.

overall 1-year and 5-year survival rates were 83 ± 2% and 58 ± 3%, respectively. In unadjusted comparisons, patients who underwent RMA without CABG had significantly lower 5-year survival rate than those who underwent RMA with CABG (45% vs. 63%, $P = 0.049$) and freedom from composite

adverse events (19% vs. 43%, $P < 0.001$) (Figure 2). Patients in whom concomitant CABG was not indicated were more likely to die from heart failure (Figure 3).

After adjustments with IPTW, patients who underwent RMA with CABG demonstrated a lower risk of all-cause

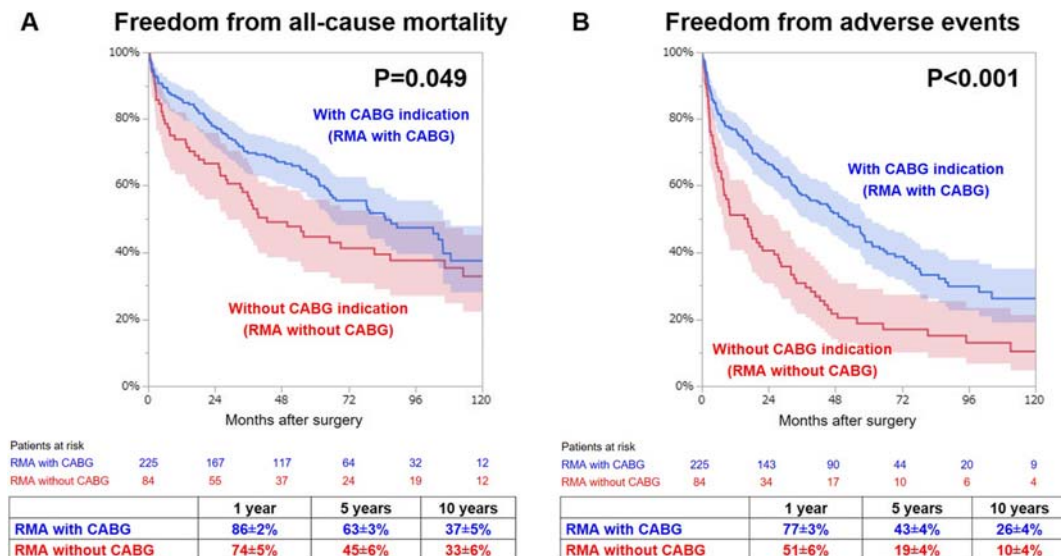
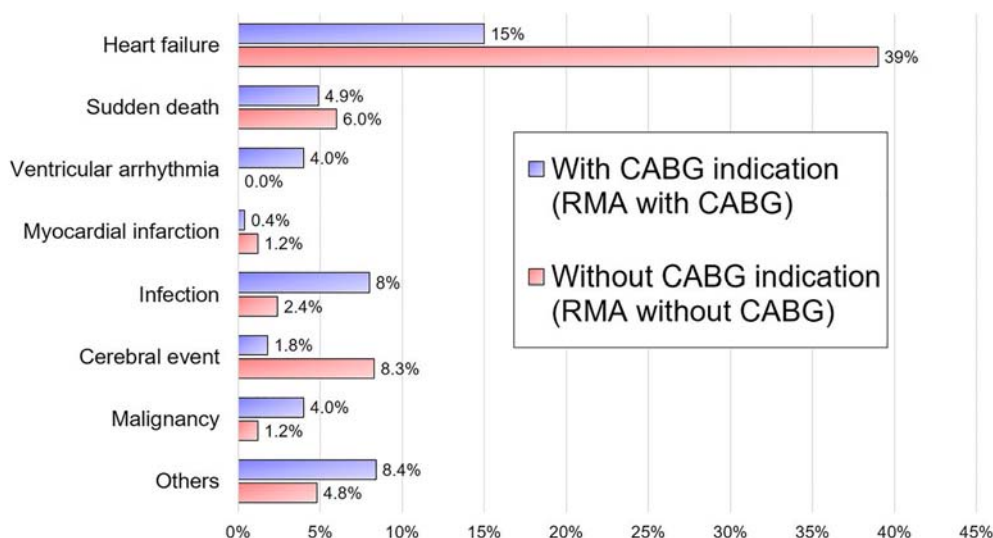
Figure 2 Freedom from all-cause mortality (A) and composite adverse events (B) according to the study groups. CABG, coronary artery bypass grafting; RMA, restrictive mitral annuloplasty.

Figure 3 Cause of death according to the study groups. CABG, coronary artery bypass grafting; RMA, restrictive mitral annuloplasty.

mortality (HR: 0.58; 95% CI: 0.47–0.73; $P < 0.001$) and composite adverse events (HR: 0.54; 95% CI: 0.45–0.66; $P < 0.001$) when compared with those who underwent RMA without CABG. The adjusted outcomes by various statistical methods are summarized in *Table 3* and highlight that the results were consistently in favour of patients who underwent RMA with CABG in terms of long-term survival, regardless of the statistical methods used.

Longitudinal echocardiographic assessment

Serial echocardiography demonstrated significant changes in LV end-systolic dimensions and LV ejection fraction in both the groups, with greater degrees of changes observed in patients who underwent RMA with CABG (*Figures 4A and 4B*). If we exclude the patients who underwent concomitant surgical ventricular reconstruction with RMA, the difference in the amounts of changes in LV function became more distinct (*Figure 4C and 4D*).

Table 3 Adjusted hazard ratios of death and composite events in patients who underwent restrictive mitral annuloplasty with coronary artery bypass grafting compared with those who underwent restrictive mitral annuloplasty without coronary artery bypass grafting

Outcomes	HR	95% CI	<i>P</i> value
Overall mortality			
Crude (original cohort)	0.72	0.51–1.00	0.050
IPTW	0.78	0.63–0.97	0.024
Overall mortality and/or heart failure readmission			
Crude (original cohort)	0.51	0.38–0.68	<0.001
IPTW	0.53	0.44–0.64	<0.001

CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting.

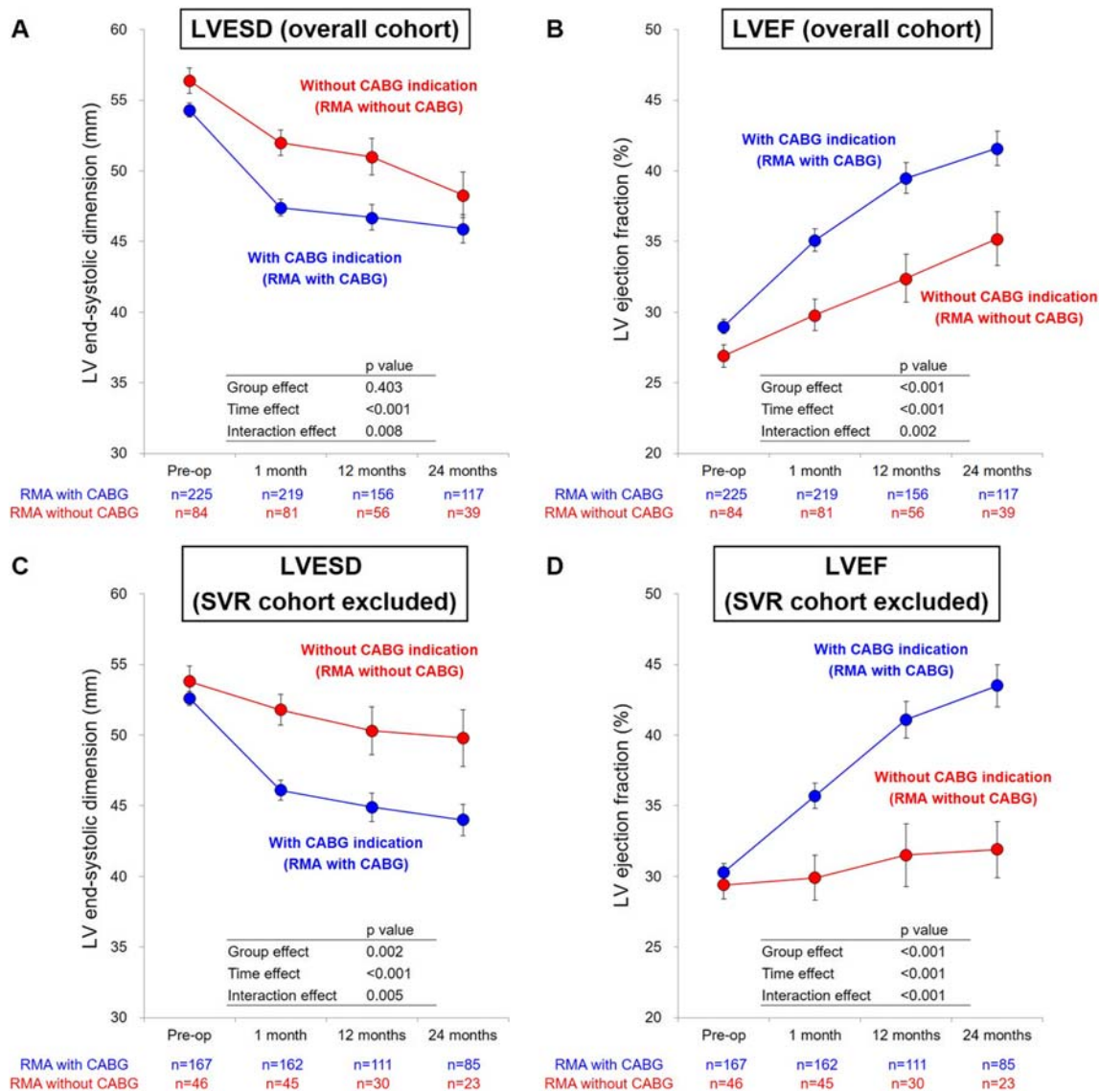
The grade of MR significantly changed at 1 month after the surgery, irrespective of the indication of CABG (time effect $P < 0.001$). Thereafter, the severity of MR was equal to or greater than moderate grade and did not substantially change during the follow-up up to 2 years after the surgery, with no intergroup differences at any follow-up time point (interaction effect $P = 0.116$, group effect $P = 0.273$) (*Figure 5*).

Discussion

The major findings of this study are the following: (i) in patients with chronic MR secondary to ischaemic cardiomyopathy, surgery could be performed with acceptable operative mortality irrespective of the indication of CABG; (ii) patients who underwent RMA without CABG had significantly lower 5-year survival rate and freedom from composite adverse events than those who underwent RMA with CABG; (iii) significant changes in LV end-systolic dimensions and LV ejection fraction in both groups, with greater degrees of changes observed in patients who underwent RMA with CABG; (iv) MR grade significantly changed post-operatively in both groups, and the change was sustained for up to 2 years with no intergroup difference; and (v) concomitant CABG with RMA was identified as an independent protective factor in both mortality and composite adverse events, which was further confirmed after adjustments with the IPTW method.

According to the current consensus guidelines, in patients with chronic severe secondary MR who remain symptomatic despite guideline-directed medical therapy, mitral valve surgery is reasonable (Class IIa recommendation) when CABG is indicated or can be considered (Class IIb) as an isolated procedure, indicating that the degree of recommendation for

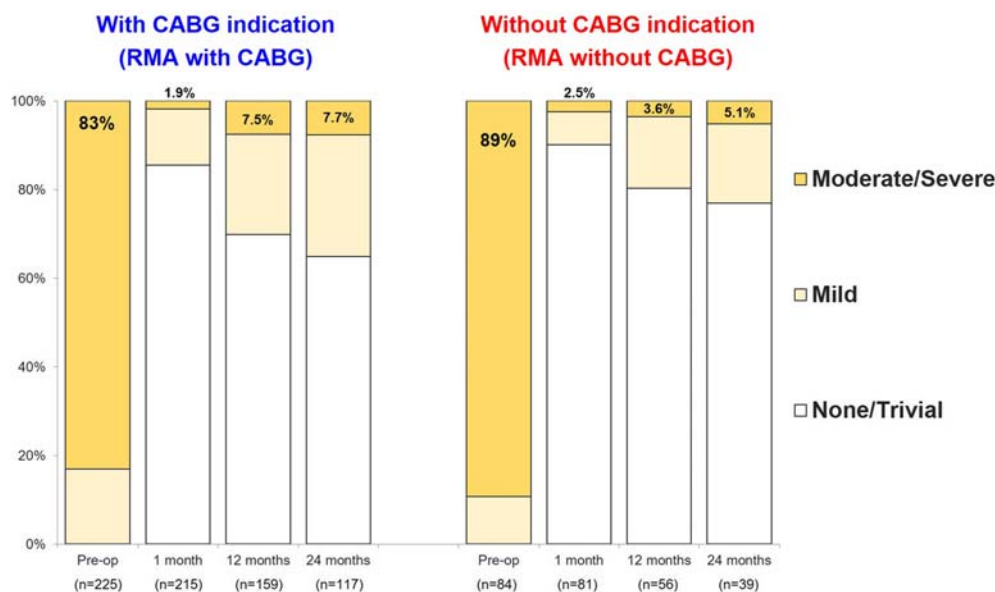
Figure 4 Longitudinal changes in (A) LVESD and (B) LVEF according to the study groups. Longitudinal changes in (C) LVESD and (D) LVEF according to the CABG indication in patients who did not undergo concomitant SVR. CABG, coronary artery bypass grafting; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; RMA, restrictive mitral annuloplasty; SVR, surgical ventricular reconstruction.



mitral valve surgery is altered by the indication of CABG and weakened when CABG is not indicated.³ One reason for it is that the correction of MR may be of little benefit because of the underlying ischaemic injury; in other words, MR may reflect ischaemia or advanced LV dysfunction and, therefore, not have an independent impact on survival.⁷ In fact, it has not been clearly demonstrated that reduction or correction of MR alters the natural course of the underlying LV disease or improves survival.^{8–13} The guideline's recommendations also imply that patients with ischaemic MR will benefit from concomitant CABG with mitral valve surgery; however, no previous study has addressed this issue. To the best of our knowledge, this is the first study to compare the long-term

clinical outcomes between patients in whom concomitant CABG was indicated with RMA and those of patients in whom concomitant CABG was not indicated with RMA. In this study, we observed poorer prognoses in patients in whom CABG was not indicated at the time of RMA, which was not surprising given the differences in the patient characteristics in terms of higher prevalence previous cardiac surgeries and use of inotropic agents, and more impaired LV functions in them. Notably, the unfavourable prognosis in these patients was further confirmed after adjusting for clinically relevant covariates with the IPTW technique. This can be partly explained by the findings of a recent randomized clinical trial that demonstrated that the rates of death from any cause,

Figure 5 Longitudinal changes in the grade of MR according to the study groups. CABG, coronary artery bypass grafting; RMA, restrictive mitral annuloplasty; MR, mitral regurgitation.



cardiovascular causes, and hospitalization for cardiovascular causes were significantly lower over 10 years in patients who underwent CABG in addition to receiving medical therapy than the rates in those who received medical therapy alone.⁴

One of the novel aspects of this study was the demonstration that LV systolic function had substantially changed post-operatively, irrespective of the indication for CABG. This finding is interesting because it can be speculated that patients in whom CABG was not indicated did not have sufficient preoperative myocardial viability and, therefore, were less likely to manifest post-operative ameliorations in LV function. However, the changes in LV function observed in these patients might largely have stemmed from significant volume reduction and restoration of LV attributed to the concomitant surgical ventricular reconstruction. Indeed, when we exclude patients who underwent concomitant surgical ventricular reconstruction with RMA, the degree of changes in LV function was small in patients in whom CABG was not indicated. Nevertheless, these changes following RMA alone were—although modest—significant. The mechanisms of ameliorations in LV function following RMA alone may be related to the reduction in afterload following unloading of the ventricular volume secondary to correction of MR. This speculation is supported by the findings from our previous publication, in which we demonstrated that decrease in afterload along with reduction in volume overload was responsible for postoperative reverse LV remodelling following RMA.¹⁴

The incidence of moderate or severe recurrent MR was not significantly different between the groups at any follow-up time point and was substantially lower than the recently

reported values of 32.6% and 58.8% at 1 and 2 years, respectively, in a recent prospective randomized clinical study.¹⁵ The difference in the MR recurrence rate can be explained by a combination of the differences in the baseline LV function, MR severity, degree of leaflet tethering, and the size of mitral ring implanted. In fact, the average ring size utilized in a previous study was 27.9 mm, which was larger than the 25.8 mm ring used in our study.¹⁵ Additionally, the significant post-operative decrease in LV end-systolic dimensions and the sustenance of the ameliorations during follow-up might have contributed to the lower rate of recurrent MR in the present study. It is worth noting, however, that the patients in whom CABG was not indicated experienced lower survival and freedom from composite adverse events despite comparable changes in MR during the follow-up, indicating that correction of MR did not always translate into modification of the underlying pathophysiology and, thereby, prevention of re-admission for heart failure. The greater positive impact of concomitant CABG with RMA on composite adverse events over the impact on mortality (adjusted HR: 0.53 and 0.78, respectively) can be attributed, at least in part, to the significantly higher prevalence of re-admissions for heart failure observed in patients without CABG indications during the follow-up. These findings may emphasize—in order to improve the outcomes in patients with chronic secondary MR—the importance of picking a treatment strategy that can reverse LV remodelling along with, or even followed by, changes in MR rather than elimination of MR alone by correcting the mitral valve annular dilatation with RMA.

Despite the poor prognosis in patients with chronic ischaemic MR following primary PCI, there are no established

guidelines regarding the routine follow-up of these patients. It is well known that multi-vessel coronary artery disease is documented in approximately half the patients who present with acute MI and undergo primary PCI while non-culprit lesions are left untreated; therefore, these patients should be closely followed-up. However, optimal management of non-culprit lesions in these settings continues to be a matter of debate, and no consensus has been reached yet.^{16,17} In the present study, 62% of the patients in whom CABG was not indicated underwent subsequent PCI following primary PCI for acute MI, most of which were carried out in a non-acute setting (data not shown). In contrast, only 20% of the patients in whom CABG was indicated with RMA underwent repeat PCI pre-operatively, and the remaining 80% were referred to surgery with non-culprit lesions left untreated. Based on these findings, we suggest that when myocardial revascularization is needed in patients with ischaemic MR, the optimal strategy should be discussed among cardiologists, interventionists, and surgeons and CABG may be considered, whenever indicated. This suggestion is supported by the findings of Kang *et al.* who demonstrated that, compared with PCI, surgical revascularization is associated with an improved long-term event-free survival for patients with ischaemic MR.¹⁸ Furthermore, Castleberry *et al.* reviewed the clinical outcomes of patients diagnosed with significant coronary artery disease and moderate or severe ischaemic MR over 20 years who were treated either with only medical treatment, PCI, or CABG, or CABG plus mitral valve surgery, and found that CABG with or without mitral valve surgery was associated with lower mortality than either PCI or medical treatment alone.¹⁹

Although surgical mitral valve repair or replacement is considered for the treatment of choice for patients with symptomatic chronic secondary MR, many patients are not offered surgery based on their high surgical risk status.²⁰ Meanwhile, several percutaneous device therapies that reproduce surgical tools have been designed for reducing MR severity without sternotomy/thoracotomy or cardiopulmonary bypass. Edge-to-edge mitral valve repair with the MitraClip system (Abbott Vascular, Santa Clara, CA, USA) is the most widely used percutaneous system with more than 70 000 implants performed to date.^{21–23} Observational studies suggest that MitraClip treatment of secondary MR is safe and associated with improved symptoms, quality of life, and functional status in heart failure patients.²² In the randomized EVEREST II (*Endovascular Valve Edge-to-Edge Repair Study*) of MitraClip vs. conventional surgery, MitraClip was shown to be safer than but not as effective as conventional surgery in reducing MR and LV volumes.²³ This is likely attributable to the fact that the surgery resulted in greater reduction of MR severity than MitraClip. Of note, that patients included in EVEREST II were low-risk candidates for surgery mainly affected by primary MR (73.4%). Glower *et al.* then reported that the MitraClip significantly reduced MR, improved clinical symptoms, and decreased LV dimensions at 12 months

in high surgical risk cohort.²⁴ Here, we should be aware that patients with LV ejection fraction < 20% or LV end-systolic diameter > 5.5 cm (EVEREST II) or >6.0 cm (high risk) were excluded because of a concern that the MitraClip could not grasp both mitral leaflets in markedly dilated ventricles. Nevertheless, these results raise a question as to how we should treat high-risk patients with chronic secondary MR especially when concomitant CABG was not indicated.

Two recent randomized controlled clinical trials have investigated the impact of MitraClip on the outcomes of heart failure patients: *Percutaneous Repair with the MitraClip Device for Severe Secondary Mitral Regurgitation* (MITRA-FR) and *Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation* (COAPT). Both trials randomized patients to MitraClip plus guideline-directed medical therapy (GDMT) or GDMT alone. There were no intergroup differences in the composite of death from any cause or hospitalization for heart failure in MITRA-FR, whereas the MitraClip offered a significant reduction in heart failure hospitalizations and mortality in COAPT.^{21,25} As a consequence of these conflicting results, guidelines are divided over recommendations for the MitraClip. The European guidelines suggest the use of MitraClip only for symptomatic patients with severe secondary MR despite optimal GDMT who are at high or prohibitive surgical risk (Class IIb recommendation, Evidence Level C),²⁶ whereas the American guidelines do not give any indications for transcatheter treatment of this entity.²⁷ Notably, in patients with chronic secondary MR, the absolute changes in the LV ejection fraction ($44 \pm 11\%$ to $44 \pm 11\%$) and LV end-systolic dimension (46 ± 9 to 44 ± 9 mm) from baseline to 1 year after the MitraClip were substantially smaller than those observed in the present study, irrespective of indication for concomitant CABG.²⁸ These data suggest that surgical annuloplasty rather than transcatheter device therapy may be recommended, whenever indicated, to achieve favourable LV reverse remodelling. Most importantly, each case should be discussed among a dedicated heart team to provide optimal care until further analyses and ongoing trial (i.e. *A Clinical Evaluation of the Safety and Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation*, RESHAPE-HF2) are conducted. Additional research will help to clarify the role of MitraClip in improving prognosis of patients with heart failure and chronic secondary MR.

Limitations

The main limitations of this study include the non-randomized retrospective design and the small sample size. To minimize the potential bias related to patient selection, we excluded patients with a low degree of LV

remodelling and ischaemic MR secondary to non-ischaemic cardiomyopathy and restricted our analysis to only those with advanced cardiomyopathy secondary to ischaemic aetiology. However, the decision to perform concomitant CABG with RMA was strongly affected by several important baseline demographic and clinical profiles (e.g. myocardial viability, coronary anatomy, and surgical risks) as well as surgeons' discretion. Although we tried to rigorously adjust selection bias using the IPTW technique, unmeasured confounders, procedure bias, or detection bias may have affected our results. Concomitant surgical procedures may have influenced the results as well, although such concomitant procedures are usually required in very sick patients who present with severely deteriorated clinical and pathophysiological statuses. Furthermore, when the adjustment was further augmented by the concomitant surgery (i.e. surgical ventricular reconstruction, papillary muscle approximation, and aortic valve replacement), the concomitant CABG was still independently associated with better outcomes after surgery in the matched cohort (data not shown).

We only analysed patients with functional MR secondary to advanced cardiomyopathy considered suitable by referring cardiologists to undergo restrictive annuloplasty. No information is available regarding the number of patients not referred for surgical intervention during the same time period because of the extremely high risk considered by their primary care physician. Finally, the lack of data for myocardial viability and coronary severity (i.e. syntax score) at baseline did not allow us to make the right comparisons between the study groups and elucidate the mechanisms for the poorer prognoses in patients without CABG.^{29,30} Some would claim that patients without CABG and severe ischaemic MR might have presented with excessive myocardial scarring or coronary anatomies (e.g. diffuse disease and mid-distal vessel disease) that would not be suitable for surgical revascularization and these patients would do worse than those who have viable myocardium or good distal targets.

Conclusions

In patients with ischaemic MR, surgery can be accomplished with an acceptable operative mortality irrespective of the indication for CABG. Concomitant CABG with RMA was associated with better long-term survival, event-free survival, and a greater improvement in LV systolic function, which supports the current consensus guideline. The optimal revascularization strategy should be discussed with a heart team whenever indicated in patients with ischaemic MR; otherwise, they may miss the opportunity to benefit from concomitant CABG during subsequent RMA.

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Conflict of interest

None declared.

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