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Coronary Artery Bypass Surgery With or Without Mitral Valve Annuloplasty in Moderate Functional Ischemic Mitral Regurgitation

Final Results of the Randomized Ischemic Mitral Evaluation (RIME) Trial

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Background—The role of mitral valve repair (MVR) during coronary artery bypass grafting (CABG) in patients with moderate ischemic mitral regurgitation (MR) is uncertain. We conducted a randomized, controlled trial to determine whether repairing the mitral valve during CABG may improve functional capacity and left ventricular reverse remodeling compared with CABG alone.

Methods and Results—Seventy-three patients referred for CABG with moderate ischemic MR and an ejection fraction >30% were randomized to receive CABG plus MVR (34 patients) or CABG only (39 patients). The study was stopped early after review of interim data. At 1 year, there was a greater improvement in the primary end point of peak oxygen consumption in the CABG plus MVR group compared with the CABG group (3.3 mL/kg/min versus 0.8 mL/kg/min; $P<0.001$). There was also a greater improvement in the secondary end points in the CABG plus MVR group compared with the CABG group: left ventricular end-systolic volume index, MR volume, and plasma B-type natriuretic peptide reduction of 22.2 mL/m², 28.2 mL/beat, and 557.4 pg/mL, respectively versus 4.4 mL/m² ($P=0.002$), 9.2 mL/beat ($P=0.001$), and 394.7 pg/mL ($P=0.003$), respectively. Operation duration, blood transfusion, intubation duration, and hospital stay duration were greater in the CABG plus MVR group. Deaths at 30 days and 1 year were similar in both groups: 3% and 9%, respectively in the CABG plus MVR group, versus 3% ($P=1.00$) and 5% ($P=0.66$), respectively in the CABG group.

Conclusions—Adding mitral annuloplasty to CABG in patients with moderate ischemic MR may improve functional capacity, left ventricular reverse remodeling, MR severity, and B-type natriuretic peptide levels, compared with CABG alone. The impact of these benefits on longer term clinical outcomes remains to be defined.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00413998. (*Circulation*. 2012;126:2502-2510.)

Key Words: bypass surgery, coronary artery ■ coronary disease ■ mitral valve regurgitation ■ myocardial ischemia ■ surgery

Functional ischemic mitral regurgitation (MR) occurs in up to 40% of patients after myocardial infarction.^{1,2} It is usually mild or moderate in severity but is associated with an increased incidence of heart failure and death.^{1,2} It is caused by left ventricular (LV) remodeling and dilatation after myocardial infarction, which tethers and pulls the mitral valve apart, resulting in MR; the mitral valve is

normal in structure but is incompetent as a result of a dilated and dysfunctional left ventricle.^{3,4} The majority have significant 3-vessel coronary artery disease and benefit from coronary artery bypass grafting (CABG). The long-term outcome with coronary artery revascularization alone remains poor, with a reported increased incidence of heart failure and death of up to 50%.^{5,6}

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The ischemic mitral valve can be repaired during CABG with the use of an annuloplasty ring, which achieves mitral valve competency by restoring the size of the mitral annulus and increasing mitral leaflet coaptation.⁷ The benefits of mitral valve repair (MVR) over and above that of CABG alone are uncertain. Observational studies have reported a reduction in the severity of MR with the addition of MVR to CABG, but an improvement in functional capacity or survival has not been demonstrated^{8–10} These studies are limited by the absence of randomization, and in many cases, the use of suboptimal surgical techniques for repairing the ischemic mitral valve, resulting in significant recurrence rates of MR.¹¹

The Randomized Ischemic Mitral Evaluation (RIME) Trial was designed to determine whether the addition of MVR to CABG in moderate ischemic MR may improve functional capacity and LV reverse remodeling compared with CABG alone.

Methods

Study Design

A multicenter, single-blinded, randomized, controlled trial was conducted which recruited patients from 6 centers in the United Kingdom and 1 in Poland. A core team of principal investigators met weekly to ensure the proper running of the trial. An independent data monitoring and safety committee provided study oversight and reviewed all adverse events. The Clinical Trials and Evaluation Unit at the Royal Brompton Hospital provided study coordination at all participating centers, data collection and management, and statistical analysis. The study protocol was approved centrally by the Charing Cross Multicenter Research Ethics Committee and locally by ethics committees and research departments of the participating centers. All patients provided written informed consent. The investigators had direct access to the primary data.

Study Patients

Patients were eligible for enrollment if they had been referred for CABG and had moderate ischemic MR measured by echocardiography alone either at rest or peak exercise. The definition of moderate ischemic MR followed the guidelines of the American College of Cardiology (ACC), the American Heart Association (AHA), and the American Society of Echocardiography (ASE), and was defined as an effective regurgitant orifice area of 0.20 to 0.39 cm², a regurgitant volume of 30 to 59 mL per beat, a regurgitant fraction of 30% to 49%, or a vena contracta width of 0.30 to 0.69 cm.¹² An integrative approach was used to determine moderate MR, and ≥ 1 of the above criteria had to be satisfied to be eligible for enrollment.

The exclusion criteria were severe LV dysfunction (ejection fraction <30%), structural abnormalities of the mitral valve (including papillary muscle rupture), significant aortic valve disease, previous or active endocarditis, New York Heart Association (NYHA) class IV symptoms, unstable angina, acute pulmonary edema or cardiogenic shock, significant comorbidities (severe renal impairment, liver impairment, chronic obstructive airways disease) or other associated conditions that significantly increase the risk of surgery, and previous cardiac surgery.

Study Procedures

Investigations were performed at baseline and 1 year after surgery. This involved a cardiopulmonary exercise test, echocardiography, a cardiovascular magnetic resonance (CMR) scan, and a plasma B-type natriuretic peptide (BNP) blood test. All investigations were

performed locally at participating centers following a standardized protocol. Symptom-limited cardiopulmonary exercise testing with respiratory gas exchange measurements was performed using a modified Bruce protocol on an upright treadmill. Continuous breath-by-breath respiratory gas analysis was performed. Peak oxygen consumption was defined as the highest 30-second average oxygen consumption during the last 60 seconds of exercise. Echocardiography was performed both at rest and at peak exercise. A minimum of 3 cardiac cycles were recorded for all images. Quantification of mitral regurgitation severity was performed using the proximal isovelocity surface area technique. CMR imaging was performed following a previously published protocol.^{13,14} MR volume was determined by subtracting the aortic outflow volume measured by phase contrast velocity mapping from the LV stroke volume measured by a contiguous stack of short axis cine images from the base to apex of the left ventricle. All images of echocardiography and CMR performed at participating centers were sent to the core laboratories at the Royal Brompton Hospital for analysis. Echocardiographic scans were analyzed using Philips iE33 software and CMR scans using CMR Tools 2010 by accredited specialists (K.M.J.C., I.R., S.R.H.).

Randomization was performed after completion of baseline investigations in patients who met the eligibility criteria. This was done by a telephone call from participating centers to the randomization center at the Royal Brompton Hospital Clinical Trials and Evaluation Unit. Patients were randomized in a 1:1 ratio to receive CABG plus MVR or CABG only. A randomization list was used, which was stratified according to the age (<70 years, and ≥ 70 years) and sex of the patient.

All patients received CABG in which the pedicled left internal mammary artery was grafted to the left anterior descending coronary artery, and all significantly narrowed and graftable coronary vessels were bypassed. In patients randomized to CABG plus MVR, the mitral valve was inspected to confirm the absence of any structural abnormalities. MVR was performed using a complete annuloplasty ring. The recommended ring was the Carpentier-McCarthy-Adams IMR ETlogix Annuloplasty Ring (Edwards Lifesciences, Irvine, CA), but alternative annuloplasty rings were also permissible if they were a complete rigid or semirigid annuloplasty ring. The size of the ring was selected by measurement of the anterior mitral valve leaflet. If an alternative complete ring was used, it was downsized by 2 sizes. For example, if the anterior leaflet corresponded to a ring size of 30 mm, a 26-mm ring was used. The aim of the surgery was to achieve a leaflet coaptation length of at least 8 mm between the anterior and posterior mitral valve leaflets, with no more than trace mitral regurgitation at the end of the operation.

All patients were maintained on optimal medical therapy after their operation, which included aspirin, a statin, an angiotensin-converting enzyme inhibitor, and a β -blocker, unless contraindicated.

Study End Points

The primary end point was the peak oxygen consumption at 1 year. The secondary end points were the left ventricular end systolic volume index (LVESVI) measured by cardiovascular magnetic resonance, MR volume, and plasma BNP levels at 1 year.

The physiologist conducting the cardiopulmonary exercise test to determine the primary end point of peak oxygen consumption was blinded to the patient's treatment group. Because of the nature of the surgical intervention, it was not possible to blind either the patient or the clinician looking after the patient.

Statistical Analysis

We calculated that we would need to enroll 100 patients into the study for a 90% power to detect a difference of at least 2.5 mL/kg/min (standard deviation 3.5) in the primary end point of peak oxygen consumption at 1 year, assuming a 3% operative mortality and a further drop-out of 10% at 1 year as a result of mortality or noncompliance.

Two planned interim analyses were performed. The first interim analysis was performed when 50 patients had been randomized, of which 38 patients had been randomized for at least 1 year. Of these

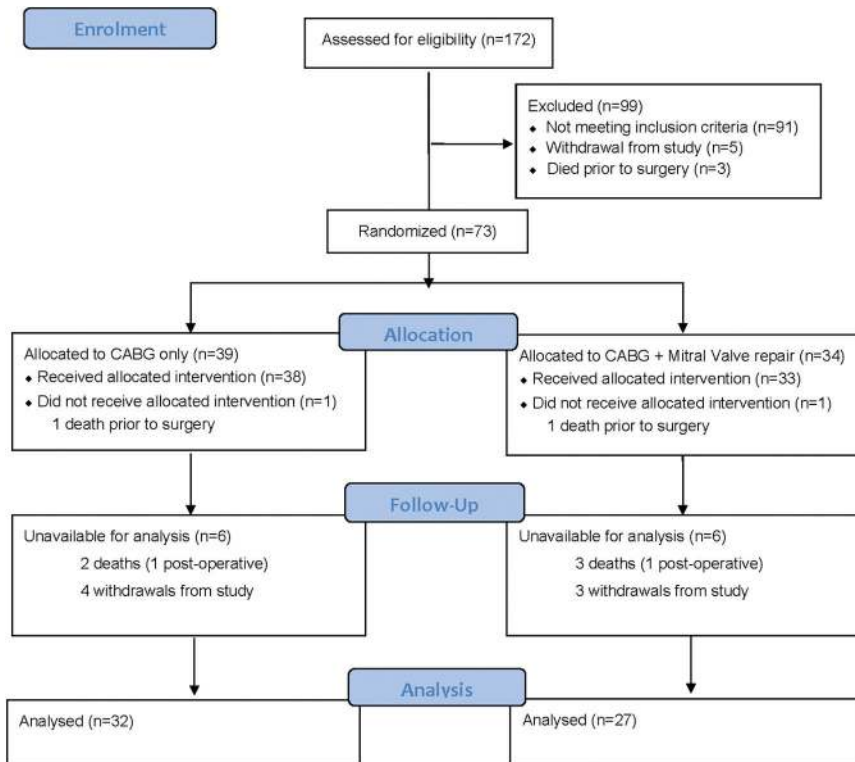


Figure. Flow diagram of enrollment, intervention allocation, follow-up, and analysis. CABG indicates coronary artery bypass grafting.

38 patients, there were 2 withdrawals from the study. Follow-up interim analysis was performed in the 36 available patients and involved only the secondary end points (LVESVI, MR volume, and BNP levels). The second interim analysis was performed when 70 patients had been randomized, of which 68 patients received their allocated treatment (there were 2 deaths before surgery) and 60 patients had been randomized for at least 1 year. Of these 60 patients, there were 4 deaths (2 of which were postoperative) and 4 withdrawals from the study. Follow-up interim analysis was performed in the 52 available patients and involved only the primary end point (peak oxygen consumption). In both interim analyses, the CABG plus MVR group demonstrated improved end points compared with the CABG only group, with the difference in the primary end point of peak oxygen consumption being highly significant ($P=0.008$). The results of both interim analyses were known to the data monitoring and safety committee and the core team of principal investigators. A pragmatic decision was made to stop enrollment after the results of the second interim analysis. At this time, 73 patients had been randomized. The main reasons for stopping the trial early were the demonstration of a benefit in the CABG plus MVR group and that the trial had also reached the end of its planned recruitment period.

Statistical analysis was performed using XLSTAT Version 2012.5.01. All major comparisons were performed using the intention to treat principle. The primary comparison was of the difference in end points between the 2 groups at 1 year. All statistical tests were 2-tailed. Comparisons of continuous data between the 2 treatment groups were made using the 2-sample t test or the Mann-Whitney test as appropriate for independent samples. Categorical comparisons were made using the χ^2 test or Fisher exact test as appropriate. A probability value of 0.05 or less was considered as statistical significance. Tests for normality were done using the Shapiro-Wilk test. Continuous data are presented as means \pm standard deviations if normally distributed, and medians with first and third quartiles (Q1–Q3) if not normally distributed. Numbers and percentages are presented for categorical data.

Results

Study Population

A total of 172 patients were recruited into the RIME Trial between March 15, 2007 and July 29, 2011 and assessed for

eligibility (Figure). Of these, 99 patients were excluded from the study (91 did not meet the eligibility criteria, 5 withdrew from the study, and 3 died before surgery). Of the patients who did not meet the eligibility criteria, 71 had MR that was less than moderate in severity, 11 had MR that was greater than moderate, and 9 had MR of a nonischemic etiology.

Seventy-three patients were randomized (34 to receive CABG plus MVR and 39 to receive CABG only). The baseline characteristics of these patients were well balanced (Tables 1 and 3). The MR volume, LVESVI, and BNP levels appeared numerically higher in the CABG plus MVR group, but this did not reach statistical significance ($P=0.26$, 0.25 , and 0.16 , respectively).

In the CABG plus MVR group, the mean effective regurgitant orifice area and MR volume measured by echocardiography at rest was 0.21 ± 0.09 cm² and 35.5 ± 13.3 mL/beat, respectively, whereas that measured at peak exercise was 0.24 ± 0.09 cm² and 40.7 ± 16.1 mL/beat, respectively. In the CABG-only group, the mean effective regurgitant orifice area and MR volume measured by echocardiography at rest was 0.18 ± 0.10 cm² and 30.3 ± 13.8 mL/beat, respectively, whereas that measured at peak exercise was 0.20 ± 0.07 cm² and 34.2 ± 12.5 mL/beat, respectively (Table 1).

Study Treatments

In the CABG plus MVR group, 33 patients received their allocated treatment; 1 patient died before surgery. In the CABG only group, 38 patients received their allocated treatment; 1 patient died before surgery (Figure).

Patients in both groups received similar numbers of coronary artery bypass grafts, with most patients in both groups receiving at least 3 coronary artery bypass grafts (91% in the CABG plus MVR group and 92% in the CABG group;

Table 1. Patient Characteristics

Variable	CABG (n=39)	CABG+MVR (n=34)
Age, y	70.4±7.9	70.9±10.5
Female sex, n (%)	10 (26)	9 (26)
Body mass index	27.4±5.0	25.3±6.4
Medical history, n (%)		
Atrial fibrillation	4 (10)	2 (6)
Previous myocardial infarction	28 (72)	25 (74)
Previous stroke	1 (3)	2 (6)
Peripheral vascular disease	5 (13)	4 (12)
Hypertension	23 (59)	17 (50)
Diabetic on treatment	15 (38)	12 (35)
Chronic pulmonary disease	1 (3)	2 (6)
NYHA class, n (%)		
I	1 (3)	1 (3)
II	25 (64)	22 (65)
III	13 (33)	11 (32)
Mitral regurgitation*		
Effective regurgitant orifice area, cm ²	0.18±0.10	0.21±0.09
Regurgitant volume, mL/beat	30.3±13.8	35.5±13.3
Vena contracta width, cm	0.4±0.1	0.4±0.1
Tricuspid regurgitation,* n (%)		
None	18 (46)	12 (36)
Mild	18 (46)	18 (52)
Moderate	3 (8)	4 (12)
Left ventricle*		
LVESD, mm	43.3±9.5	45.7±7.4
LVEDD, mm	56.5±12.0	56.5±12.6
Ejection fraction, %	40.3±16.1	40.0±17.3

CABG indicates coronary artery bypass grafting; MVR, mitral valve repair; NYHA, New York Heart Association; LVESD, left ventricular end systolic diameter; and LVEDD, left ventricular end diastolic diameter.

*Mitral regurgitation, tricuspid regurgitation, and left ventricle values displayed were measured by echocardiography.

$P=0.85$; Table 2). All patients received complete coronary artery revascularization. The CABG plus MVR group had significantly longer operation times, with a median cardiopulmonary bypass time of 147 minutes compared with 84 minutes in the CABG group ($P<0.001$). The aortic cross clamp time was also significantly longer in the CABG plus MVR group, with a median time of 95 minutes compared with 51 minutes in the CABG group ($P<0.001$).

Patients in the CABG plus MVR group all received a complete rigid or semirigid annuloplasty ring. The Carpentier-McCarthy-Adams IMR ETlogix Annuloplasty Ring was used in 28 patients (85%), and the Carpentier-Edwards Physio Annuloplasty Ring was used in 5 patients (15%). The median ring size used was 28 mm. Postoperative transesophageal echocardiography revealed no mitral regurgitation in 30 patients (91%) and mild mitral regurgitation in 3 patients (9%). The mean mitral leaflet coaptation length was 7.1 ± 1.2 mm.

Postoperative Course

The median duration of intubation in the CABG plus MVR group was 28 hours compared with 17 hours in the CABG group ($P=0.004$). An intra-aortic balloon pump was used in 33% of patients in the CABG plus MVR group compared with 29% of patients in the CABG group ($P=0.57$; Table 2).

Patients in the CABG plus MVR group received significantly greater amounts of blood transfusion postoperatively, a median of 900 mL compared with 153 mL in the CABG group ($P=0.016$). The amount of postoperative blood loss and transfusion of blood products (platelets and fresh frozen plasma) were similar in both groups (Table 2).

Comparing CABG plus MVR against CABG alone, the incidence of hemofiltration was 12% versus 8% ($P=0.70$), stroke 3% versus 0% ($P=0.47$), reoperation for bleeding or cardiac tamponade 12% versus 5% ($P=0.41$), and 30-day mortality 3% versus 3% ($P=1.00$; Table 2). Patients in the CABG plus MVR group had a longer hospital stay after their surgery compared with those in the CABG group, a median of 15 days versus 9 days ($P=0.05$).

Follow-Up

Final follow-up was completed on July 16, 2012. In the CABG plus MVR group, there were 3 deaths after surgery and before the 1-year follow-up investigations. Three patients withdrew from the study and declined follow-up. Twenty-seven patients were therefore available for analysis. In the CABG group, there were 2 deaths after surgery and before the 1-year follow-up investigations. Four patients withdrew from the study and declined follow-up. Thirty-two patients were therefore available for analysis (Figure).

Survival at 1 year was similar in both groups: 91% in the CABG plus MVR group versus 95% in the CABG group ($P=0.66$). Hospital admissions for heart failure at 1 year were also similar in the 2 groups: 3% in the CABG plus MVR group versus 8% in the CABG group ($P=0.62$). The incidence of atrial fibrillation was 4% in the CABG plus MVR group and 6% in the CABG group ($P=1.00$).

Study End Points

The study end points were all measured at 1 year after surgery. The primary end point was the change in peak oxygen consumption at 1 year. This showed a mean increase of 3.3 mL/kg/min or 22% in the CABG plus MVR group, compared with a mean increase of 0.8 mL/kg/min or 5% in the CABG group ($P<0.001$; Table 3).

The secondary end points were the change in LVESVI, MR volume, and BNP levels at 1 year. These all demonstrated significantly greater improvements in the CABG plus MVR group compared with the CABG group. The LVESVI decreased by 22.2 mL/m² or 28% in the CABG plus MVR group compared with a decrease of 4.4 mL/m² or 6% in the CABG group ($P=0.002$; Table 3).

The MR volume decreased by 28.2 mL/beat or 80% in the CABG plus MVR group compared with a decrease of 9.2 mL/beat or 29% in the CABG group ($P=0.001$; Table 3). In the CABG plus MVR group, 74% (20 patients) had no MR, 22% (6 patients) had mild MR, and 4% (1 patient) had moderate MR. In the CABG only group, 9% (3 patients) had

Table 2. Intra- and Postoperative Results

Variable	CABG (n=38)	CABG+MVR (n=38)	P Value
Surgery			
No. of coronary bypass grafts, n (%)			
2	3 (8)	3 (9)	
3	28 (74)	23 (70)	
4	7 (18)	7 (21)	
CPB time (min), median (Q1–Q3)	84 (70–106)	147 (133–169)	<0.001
Aortic cross clamp time (min), median (Q1–Q3)	51 (41–55)	95 (90–110)	<0.001
Intensive care			
Intra-aortic balloon pump use, n (%)	11 (29)	11 (33)	0.57
Intubation time (hours), median (Q1–Q3)	17 (12–20)	28 (17–102)	0.004
Blood loss and transfusion, median (Q1–Q3)			
Blood loss, mL	755 (479–933)	672 (511–1006)	0.89
Blood transfused, mL	153 (0–818)	900 (225–1439)	0.016
Platelet transfused, mL	0 (0–0)	0 (0–306)	0.08
Fresh frozen plasma transfused, mL	0 (0–0)	0 (0–636)	0.42
Complications, n (%)			
Hemofiltration	3 (8)	4 (12)	0.70
Re-operation for bleeding or tamponade	2 (5)	4 (12)	0.41
Stroke	0 (0)	1 (3)	0.47
30-d mortality	1 (3)	1 (3)	1.00

CABG indicates coronary artery bypass grafting; MVR, mitral valve repair; CPB, cardiopulmonary bypass; and Q1–Q3, first and third quartiles.

no MR, 41% (13 patients) had mild MR, 47% (15 patients) had moderate MR, and 3% (1 patient) had moderate-severe MR. The mean transmitral gradient was 4.2 ± 1.9 mm Hg in the CABG plus MVR group.

BNP levels decreased by 557.4 pg/mL or 75% in the CABG plus MVR group compared with a decrease of 394.7 pg/mL or 58% in the CABG group ($P=0.003$; Table 3).

Symptoms

At 1 year after surgery, patients in the CABG plus MVR group had a median NYHA functional class of I compared with a median NYHA functional class of II in the CABG group ($P=0.03$). In the CABG plus MVR group, 76% were in NYHA functional class I, 20% in NYHA class II, and 4% in NYHA class III. In the CABG group, 21% were in NYHA

functional class I, 64% in NYHA class II, and 15% in NYHA class III.

Discussion

We evaluated the efficacy of concomitant CABG plus MVR compared with CABG alone in patients with moderate ischemic MR. As our primary end point we used peak oxygen consumption, a recognized objective measure of functional capacity, and also a prognostic indicator in heart failure.^{15,16} We used CMR, the gold standard in LV volume assessment, to measure our main secondary end point of LVESVI.¹³ The severity of MR was quantified both by echocardiography and CMR using established techniques.^{14,17} In addition, we measured BNP levels, an established marker of LV failure and prognosis.¹⁸

Table 3. Study End Points at 1 Year

End Points	CABG (n=32)			CABG+MVR (n=27)			P Value*
	Baseline	1 Year	Δ	Baseline	1 Year	Δ	
Primary end point							
Peak VO ₂ , ml/kg/min	15.1±3.3	15.9±2.5	0.8±2.9	14.8±3.2	18.1±2.9	3.3±2.3	<0.001
Secondary end points							
LV ESVI, ml/m ² †	71.8±16.1	67.4±20.4	-4.4±17.4	78.4±26.5	56.2±14.9	-22.2±25.6	0.002
MR volume, ml/beat†	31.9±14.8	22.7±14.6	-9.2±19.1	35.4±24.0	7.2±3.5	-28.2±24.6	0.001
BNP (pg/ml)	681.4±197.3	286.7±132.0	-394.7±213.6	748.1±158.3	190.7±117.8	-557.4±182.9	0.003

Data are presented as mean±SD. CABG indicates coronary artery bypass grafting; MVR, mitral valve repair; VO₂, oxygen consumption; LV ESVI, left ventricular end-systolic volume index; MR, mitral regurgitant; BNP, B-type natriuretic peptide; and Δ, mean change at 1 year from baseline.

*P value is of mean change in values at 1 year from baseline (Δ) in the CABG+MVR group vs the CABG group.

†Values shown were measured by cardiovascular magnetic resonance.

The addition of MVR by annuloplasty to CABG reduced MR severity, LV volumes, and BNP levels, and these translated into an improvement in functional capacity and symptoms at 1 year. However, the addition of MVR to CABG required longer operation times, including time on cardiopulmonary bypass, increased blood transfusion, and intubation times, and resulted in a longer hospital stay. There was also a trend toward higher complication rates in the CABG plus MVR group, although the differences were not significant. The results of this study support the addition of MVR to CABG in patients with moderate ischemic MR undergoing CABG, but the benefits of the combined procedure must be balanced against a possible increased risk of morbidity in the perioperative period.

The results of the RIME Trial are consistent with the only other published randomized trial that reported an improvement in NYHA functional class and LV dimensions measured by echocardiography with CABG plus MVR compared with CABG only in moderate ischemic MR.¹⁹ However, quantitative grading of MR severity and objective assessment of functional capacity were not used in that study. Another randomized, controlled trial is ongoing, sponsored by the National Heart, Lung, and Blood Institute, and is expected to report in 2014 (ClinicalTrials.gov NCT00806988).

A high usage of an intra-aortic balloon pump was observed in this study (33% in the CABG plus MVR group and 29% in the CABG group). This reflected the clinical practice of many clinicians in the RIME Trial who inserted an intra-aortic balloon pump electively either before or at the end of the operation to optimize postoperative hemodynamics in higher risk patients undergoing cardiac surgery. The increased intubation time and blood transfusion in the CABG plus MVR group is likely to reflect the longer operation and cardiopulmonary bypass times in this group. The aortic cross clamp and cardiopulmonary bypass times were comparable with that reported in other studies.^{7,20} Longer periods on cardiopulmonary bypass may result in increased lung injury, necessitating a longer intubation time, and greater hemodilution, necessitating increased blood transfusion.²¹ However, the clinicians looking after the patients were unblinded to their treatment group; it is possible that more caution may have been shown toward patients who had the combined procedure. For example, clinicians may have been more inclined to keep patients who had CABG plus MVR ventilated overnight as opposed to early extubation a few hours after surgery, as would be the case for most CABG patients, and this may have contributed to the longer intubation times in this group. Clinicians may also have had a different threshold for blood transfusion for patients who had a combined procedure, which may have contributed to the higher blood transfusion rates in this group, and may have been more inclined to discharge patients who had CABG only home earlier compared with those who had CABG plus MVR. In addition, some clinicians routinely anticoagulate patients who receive a mitral annuloplasty ring for 3 months after surgery, and this may have been a factor contributing to the longer hospital stay in this group.

The primary pathology in ischemic MR is ischemic heart disease, causing LV dysfunction and dilatation.²² MR occurs secondary to the dysfunctional and dilated LV.⁴ Complete

coronary artery revascularization is the recognized treatment for this condition, particularly as the MR is usually not severe. The results of the RIME Trial suggest that correction of moderate degrees of MR in addition to coronary artery revascularization is also important to allow adequate LV reverse remodeling and improve functional capacity and symptoms. The improvement in peak oxygen consumption from 14.8 mL/kg/min at baseline to 18.1 mL/kg/min at 1 year in the CABG plus MVR group moves the group from Weber's Functional Class C at baseline, indicating moderate-to-severe impairment in aerobic capacity, to Class B at 1 year, indicating mild-to-moderate impairment in aerobic capacity.²³ This is in contrast to the CABG only group, who did not demonstrate a significant change in peak oxygen consumption and remained in Weber's Functional Class C.

Peak oxygen consumption is also an important prognostic indicator in heart failure.²⁴ Previous studies have reported an improvement in survival with increasing peak oxygen consumption values, and it is of note that peak oxygen consumption increased significantly in the CABG plus MVR group.^{25,26} In contrast, patients in the CABG only group did not demonstrate a significant improvement in peak oxygen consumption at 1 year, suggesting a continued adverse prognosis in this group, which is consistent with that reported in observational studies of patients with ischemic MR undergoing CABG only.²⁷

The results of the RIME Trial are in contrast to that observed in the Surgical Treatment for Ischemic Heart Failure (STICH) Trial, where a greater reduction in LVESVI in the CABG plus surgical ventricular restoration group compared with the CABG-only group did not translate into improved functional capacity as assessed by the 6-minute walk test, or to improved survival and reduced hospital admissions.²⁸ However, the STICH Trial addressed a different group of patients with predominantly ischemic cardiomyopathy and without MR in the majority of patients studied, and peak oxygen consumption was not assessed in that study. It is of interest to note that the reduction in LVESVI in the CABG group in the STICH Trial was 6%, which is similar to that in the CABG group in our study (6%), but the reduction in LVESVI in the CABG plus surgical ventricular restoration group in the STICH Trial was 19%, which is less than that in the CABG plus MVR group in our study (28%). A criticism of the STICH Trial concerns the quality of the surgery, which did not achieve adequate LV volume reduction, and which, as a consequence, may have limited its potential clinical benefits. The degree of reduction in LVESVI of 28% in the CABG plus MVR group in our study is consistent with that reported in other studies.²⁰

The reduced LV reverse remodeling in the CABG only group compared with the CABG plus MVR group in our study is consistent with animal studies reporting that the presence of MR promotes continued LV remodeling and prevents LV reverse remodeling. In 1 study in sheep with moderate MR, mitral valve repair decreased the intracellular signals promoting LV remodeling and decreased LV volumes, whereas leaving moderate MR led to an increase in the intracellular signals promoting LV remodeling and no significant change in LV volumes.²⁹

The addition of MVR to CABG in ischemic MR has proved controversial, because most studies have failed to demonstrate long-term benefits in functional capacity and survival over and above that of coronary artery revascularization alone, and many surgeons are concerned about possible increased morbidity and mortality with the combined procedure.^{9,10} However, these studies were observational in nature and nonrandomized. They were also limited by significant recurrence of MR after MVR, which may have been attributable to suboptimal surgical techniques, including the use of flexible mitral annuloplasty bands rather than complete annuloplasty rings, inadequate downsizing of the annuloplasty rings resulting in residual MR, and incomplete coronary artery revascularization.^{8,10,11,30} In the RIME Trial, a standardized and reproducible surgical protocol ensured that important surgical principles were followed, including the use of a complete rigid or semirigid annuloplasty ring, standardized sizing of the annuloplasty ring achieving leaflet coaptation and valve competency, and complete coronary artery revascularization. The recurrence of MR was very low in the RIME Trial, which is consistent with other studies that have used the same surgical techniques, although this could also be explained by the fact that our patients had moderate, rather than severe, ischemic MR at baseline.^{7,19}

Of interest is the finding that 50% of patients in the CABG group showed a small improvement in MR severity, 47% remained unchanged, and 3% progressed to moderate-to-severe MR at 1 year. A similar observation was previously made in another study, where at 18 months after CABG in patients with moderate MR, the mean MR grade was 1.1.³¹ The small improvement in MR severity observed in a proportion of patients is likely to be the result of improved LV function after complete coronary artery revascularization. One of the concerns about leaving moderate ischemic MR at the time of CABG is that the MR may increase in severity with time and require reoperation.⁶ Although this has not been observed in our study, the follow-up extends to only 1 year after surgery, and a longer follow-up period is necessary. However, the continued presence of MR, even when mild in severity, continued to have an adverse impact on LV reverse remodeling and functional capacity.

BNP is an established test in patients with heart failure and has been shown to correlate with the severity of heart failure and prognosis.³² It has also been shown to be predictive of survival and heart failure symptoms in both ischemic heart disease and organic MR.^{18,33–35} Its use in ischemic MR has not been previously reported. A BNP level above 100 pg/mL is reported to be diagnostic of heart failure.³⁶ The very significant elevation in BNP levels at baseline in both groups of patients confirms the presence of significant LV dysfunction and ischemic heart disease in the patients studied.¹⁸ It reinforces the concept that ischemic MR is primarily a disease of the left ventricle and not the mitral valve. Previous studies have reported that BNP activation in organic MR is related to increased LV volumes and not to the severity of MR.^{34,37,38} Despite the significant reductions in plasma BNP levels in both groups, they remained significantly elevated at 1 year, above the 100 pg/mL threshold diagnostic of heart failure (190.7 pg/mL in the CABG plus MVR group and

286.7 pg/mL in the CABG group). These patients were still in the highest risk group for cardiovascular mortality, congestive heart failure, and stroke. The persistent elevation in BNP levels in the CABG plus MVR group, despite successful correction of the MR and complete coronary artery revascularization, suggests persistent LV dysfunction at 1 year. However, myocardial recovery can continue up to 2 years after successful coronary artery revascularization.³⁹ Nevertheless, these results are consistent with studies reporting a worse outcome after surgical repair of functional ischemic MR compared with structural ischemic MR.^{40,41} The underlying pathophysiologic mechanisms responsible for functional ischemic MR are likely to have a continued adverse impact on long-term survival, even after successful correction of the MR and coronary artery revascularization.

The quantitative grading of severity for ischemic MR used in the RIME Trial followed published guidelines by the AHA/ACC/ASE.¹² It has recently been suggested that a lower threshold of severity should be used in ischemic MR to reflect the adverse prognosis with lesser degrees of mitral regurgitation in ischemic as compared with organic causes.¹⁷ If this change in grading of severity were to be universally adopted, the eligibility criteria used in the RIME Trial would be considered as indicating severe rather than moderate ischemic MR. As surgical interventions are generally recommended for severe rather than moderate severities of disease, the results of the RIME Trial would support such a proposed change. It should be noted that the majority of patients enrolled into the RIME Trial were at the lower end of the moderate MR range as defined by the AHA/ACC/ASE (Table 1).

Study Limitations

There are several limitations in the RIME Trial. The trial was stopped early after a benefit was demonstrated in the CABG plus MVR group during interim analyses, and this is likely to have inflated the treatment effect. It was not possible to blind either the patient or the clinician looking after the patient to their allocated treatment group because of the nature of the intervention. However, the end points were all objective measurements, and the physiologists performing and determining the primary end point of peak oxygen consumption were blinded to the treatment group. The end points were determined at 1 year after surgery. It is possible that with time, greater recurrence of mitral regurgitation may occur, which could compromise the benefits of the MVR. There are reports of significant recurrent MR after complete rigid or semirigid ring annuloplasty, which only become apparent after 3 years.⁸ A longer follow-up of this study is therefore necessary. Also, LV reverse remodeling is reported to continue for up to 2 years after coronary artery revascularization, and it is possible that patients in the CABG-only group may demonstrate greater reverse remodeling with time.³⁹ The study was also not designed and not adequately powered to evaluate clinical events and survival. However, the primary end point of peak oxygen consumption is a recognized prognostic indicator.¹⁶ Nevertheless, an evaluation of survival benefit will be needed in a larger randomized, controlled trial, or in the absence of that, a meta-analysis of several random-

ized, controlled trials to determine whether there is a survival benefit with concomitant CABG plus MVR.

Recruitment into the RIME Trial took longer than anticipated, and there were challenges from both clinicians and patients. Some surgeons who routinely performed CABG using an off-pump technique were reluctant to randomize patients, in case they were randomized to the CABG plus MVR group, which would necessitate going on cardiopulmonary bypass to perform the operation. Other surgeons who were more inclined to repair the mitral valve were reluctant to randomize patients, in case they were randomized to the CABG-only group. Some patients did not consent to taking part in the trial because they did not want the type of surgery they received to be decided by randomization, preferring their surgeon to make the decision or to make the decision themselves.

Conclusion

In summary, the RIME Trial compared CABG plus MVR against CABG alone in patients with moderate ischemic MR. The addition of MVR to CABG significantly improved functional capacity at 1 year and reduced LV volumes, MR severity, and BNP levels.

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CLINICAL PERSPECTIVE

The role of mitral valve repair (MVR) during coronary artery bypass grafting (CABG) in patients with moderate ischemic mitral regurgitation is uncertain. We randomized 73 patients referred for CABG with moderate ischemic mitral regurgitation and an ejection fraction >30% to receive either CABG plus MVR (34 patients) or CABG only (39 patients). At 1 year, patients in the CABG plus MVR group had a significantly greater improvement in functional capacity as measured by peak oxygen consumption, and greater left ventricular reverse remodeling as measured by the left ventricular end-systolic volume index, reduction in mitral regurgitation severity, and B-type natriuretic peptide levels, compared with the CABG-only group. However, operation duration, blood transfusion, intubation duration, and hospital stay duration were greater in the CABG plus MVR group. There was also a trend towards higher complication rates in the CABG plus MVR group, although this was not statistically significant. Deaths at 30 days and 1 year were similar in both groups, as was the incidence of hospitalization for heart failure. The results of this study support the addition of MVR to CABG in patients with moderate ischemic mitral regurgitation undergoing CABG, but the benefits of the combined procedure must be balanced against a possible increased risk of morbidity in the perioperative period. The impact of the benefits reported in this study on longer term clinical outcomes remains to be defined.

SUPPLEMENTAL MATERIAL

APPENDIX

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