Mitral valve surgery and coronary artery bypass grafting for moderate-to-severe ischemic mitral regurgitation: Meta-analysis of clinical and echocardiographic outcomes

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ABSTRACT

Objective: This meta-analysis was conducted to compare clinical and echocardiographic outcomes following isolated coronary artery bypass grafting (CABG) versus CABG and mitral valve (MV) surgery in patients with moderate-to-severe ischemic mitral regurgitation (IMR).

Methods: Seven databases were systematically searched to identify relevant studies. For eligibility, studies were required to report on the primary endpoint of perioperative or late mortality. Data were analyzed according to predefined clinical endpoints.

Results: Four randomized controlled trials (RCTs) (n = 505) and 15 observational studies (OS) (n = 3785) met the criteria for inclusion. Compared with isolated CABG, concomitant CABG and MV surgery was not associated with increased perioperative mortality (RCTs: relative risk [RR] 0.89, 95% confidence interval [CI], 0.26-3.02; OS: RR 1.40, 95% CI, 0.88-2.23). CABG and MV surgery was associated with significantly lower incidence of moderate-to-severe MR at follow-up (RCTs: RR 0.16, 95% CI, 0.04-0.75; OS: RR 0.20, 95% CI, 0.09-0.48). Late mortality was similar between the surgical approaches in RCTs (hazard ratio [HR] 1.20, 95% CI, 0.57-2.53) and OS (HR 0.99, 95% CI, 0.81-1.21). There were no significant differences in echocardiographic outcomes. These results remained consistent in subgroup analyses restricted to patients with strictly moderate IMR.

Conclusions: In patients with moderate-to-severe IMR, the addition of MV surgery to CABG was not associated with increased perioperative mortality. Although concomitant MV surgery reduced recurrence of moderate-to-severe MR at follow-up, this was not associated with a reduction in late mortality. Larger trials with longer follow-up duration are required to further assess long-term survival and freedom from reintervention. (J Thorac Cardiovasc Surg 2017;154:127-36)

Forest plot for late mortality following CABG versus CABG and mitral valve surgery.

Central Message

In patients with moderate-to-severe ischemic mitral regurgitation, there was no difference in perioperative or late mortality following isolated CABG versus CABG and mitral valve surgery.

Perspective

In patients with moderate-to-severe ischemic mitral regurgitation, the addition of mitral valve (MV) surgery to coronary artery bypass grafting was not associated with increased perioperative mortality. Concomitant MV surgery reduced recurrence of moderate-to-severe mitral regurgitation at follow-up, but this was not associated with a reduction in late mortality.

See Editorial Commentary page 137.

Ischemic mitral regurgitation (IMR) is common after myocardial infarction, occurring in up to 50% of patients.¹ The development of IMR is associated with an increased

risk of mortality and heart failure, and this risk increases with the severity of regurgitation.^{2,3} In IMR, valvular insufficiency is predominantly due to the adverse left ventricular remodeling and annular dilatation that occurs following myocardial injury, resulting in tethered mitral leaflets with poor coaptation.

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Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CI	= confidence interval
CPB	= cardiopulmonary bypass
HR	= hazard ratio
IMR	= ischemic mitral regurgitation
LVEF	= left ventricular ejection fraction
LVESVI	= left ventricular end-systolic volume index
MD	= mean difference
MV	= mitral valve
NYHA	= New York Heart Association
RCT	= randomized controlled trial
RR	= relative risk

Isolated coronary artery bypass grafting (CABG) is well-established as the standard treatment for trivial-to-mild IMR.⁴ However, the optimal management of moderate-to-severe IMR remains controversial.^{4,5} Revascularization alone may sufficiently restore left ventricular function and dimensions, thereby addressing regurgitation without the potentially increased perioperative risk associated with concomitant mitral valve (MV) surgery.^{6,7} However, it remains unclear whether isolated CABG can achieve similar midterm survival outcomes in patients with moderate-to-severe IMR.⁸ The aim of the present meta-analysis was to compare clinical and echocardiographic outcomes following isolated CABG and CABG and MV surgery in patients with at least moderate IMR.

METHODS**Search Strategy and Study Selection**

Electronic searches were performed using Ovid Medline, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Database of Abstracts of Reviews of Effects, and ACP Journal Club from their dates of inception to February 2016. The search terms “mitral” AND (“ischemic” OR “ischaemic”) AND (“repair” OR “annuloplasty” OR “replacement”) AND (“mortality” OR “death” OR “survival”) were entered as keywords and MeSH terms. This was supplemented by hand searching the reference lists of key reviews and all potentially relevant studies.

Two reviewers (A.S. and D.D.) independently screened the title and abstract of records identified in the search. Full-text publications were subsequently reviewed separately if either reviewer considered the manuscript as being potentially eligible. Disagreements regarding final study inclusion were resolved by discussion and consensus.

Eligibility Criteria

Eligible studies were those reporting perioperative mortality or late survival following isolated CABG and CABG and MV surgery in patients with at least moderate IMR. Studies were excluded if they included patients with trivial-to-mild IMR without subgroup analysis by IMR severity.

Studies with fewer than 10 patients in either the isolated CABG or CABG and MV surgery arm were also excluded.

All publications were limited to those involving human subjects and written in English. Abstracts, conference presentations, editorials, and expert opinions were excluded. Review articles were omitted because of potential publication bias and duplication of results. When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included for quantitative assessment.

Data Extraction

All data were independently extracted from text, tables, and figures by 2 investigators (A.S. and D.D.). The final results were reviewed by the senior reviewer (C.C.). The predetermined primary endpoints were perioperative mortality and late survival. Perioperative mortality was defined as death within 30 days after surgery or during the same hospitalization. Secondary outcomes included perioperative morbidity, recurrence of moderate-to-severe MR (grade ≥ 2) at latest follow-up, aortic cross-clamp and cardiopulmonary bypass (CPB) durations, New York Heart Association (NYHA) functional status, and echocardiographic measurements.

Statistical Analysis

Baseline characteristics and operative details were presented as raw values (%), mean $\pm$ standard deviation or median (interquartile range [IQR]) unless otherwise indicated. The relative risk (RR), mean difference (MD), or hazard ratio (HR) were used as the summary statistics, and reported with 95% confidence intervals (CIs). When available, adjusted ratios were used from individual studies. Otherwise, unadjusted ratios were computed from the exposure distribution given in the articles. For survival analysis, HRs and associated variance were obtained or calculated from each study by using techniques described by Parmar et al⁹ and Tierney et al.¹⁰ When direct calculations were not possible due to a lack of presented data, HRs were estimated using Kaplan-Meier graphs. For analysis of continuous data, data presented as median and IQR were converted to mean and standard deviation using the method of Wan et al.¹¹

Meta-analyses were performed by using random-effects models to take into account the anticipated clinical and methodological diversity between studies. The I^2 statistic was used to estimate the percentage of total variation across studies due to heterogeneity rather than chance, with values exceeding 50% indicative of considerable heterogeneity. Mixed-effects meta-regression models were formed by using follow-up duration as a continuous moderator to assess its impact on the incidence of survival and residual MR.

Subgroup analysis was performed by study design to take into account the different levels of evidence provided by observational studies and randomized trials. Sensitivity analysis was performed by IMR severity to specifically assess the impact of concomitant MV surgery in patients with moderate IMR. Publication bias was assessed by using funnel plots comparing log odds ratios with their standard error. The Egger linear regression method and Begg rank correlation test were used to detect funnel plot asymmetry.^{12,13} The Trim-and-Fill method was used to explore the impact of studies potentially missing due to publication bias.¹⁴ Statistical analysis was conducted with Review Manager Version 5.1.2 (Cochrane Collaboration, Software Update, Oxford, United Kingdom) and publication bias assessed by using Comprehensive Meta-Analysis v2.2 (Biostat Inc, Englewood, NJ). All P values were 2 sided, and values $< .05$ were considered statistically significant.

RESULTS

A total of 1125 unique records were identified through the database and bibliographic searches. Of these, 1091

FIGURE 1. PRISMA flow chart for literature search and study selection.

were excluded on the basis of title and abstract content. After screening the full text of the remaining 34 articles, 20 studies met the criteria for inclusion.¹⁵⁻³⁴ The study selection process is summarized in Figure 1.

Of the included studies, 4 were randomized controlled trials (RCTs) and the remainder were observational studies. These included data on a total of 4290 patients, including 3038 who underwent isolated CABG and 1252 patients who underwent combined CABG and MV surgery. For patients who underwent MV surgery, all patients included in the RCTs, and most patients included in the observational studies, underwent mitral valve repair. The mean or median follow-up duration ranged from 12 to 87 months. A full summary of study characteristics is presented in Table 1. Baseline demographic and clinical characteristics of study participants are summarized in Table 2.

Intraoperative Outcomes

In 4 RCTs and 11 observational studies including a total of 1963 patients, CABG and MV surgery was associated with significantly longer CPB (MD 48.12; 95% CI, 38.05-58.15; $P < .001$; Figure 2, A) and aortic cross-clamp (MD 39.13; 95% CI, 32.39-45.86; $P < .001$;

Figure 2, B) durations. These results were consistent in subgroup analyses by study design.

Perioperative Mortality

In 3 RCTs including a total of 474 patients, concomitant MV surgery was not associated with significantly increased perioperative mortality compared with CABG alone (RR 0.89; 95% CI, 0.26-3.02; $P = .85$; $I^2 = 0\%$; Figure 3, A). Likewise, in 14 observational studies including a total of 1975 patients, perioperative mortality was not significantly increased with the addition of concomitant MV surgery (RR 1.40; 95% CI, 0.88-2.23; $P = .16$; $I^2 = 35\%$; Figure 3, B).

Perioperative Morbidity

In 3 RCTs including a total of 203 patients, CABG and MV surgery was not associated with significantly increased risk of stroke (RR 1.65; 95% CI, 0.27-10.22; $P = .53$; $I^2 = 0\%$).¹⁶⁻¹⁸ Likewise, in 2 observational studies including a total of 182 patients, the risk of stroke was not significantly increased with concomitant MV surgery (RR 0.90; 95% CI, 0.23-3.53; $P = .70$; $I^2 = 0\%$).^{20,22} In 2 RCTs including a total of 173 patients, the incidence of acute renal failure was not significantly increased with the addition of MV surgery (RR 1.38; 95% CI, 0.44-4.31;

TABLE 1. Summary of studies comparing isolated coronary artery bypass graft surgery versus concomitant mitral repair for ischemic mitral regurgitation

Study	Study design	No. of patients		Type of mitral surgery	Follow-up, mo	Mean MR grade		Preoperative MR grade inclusion criteria
		CABG	CABG + MVS			CABG	CABG + MVS	
Bouchard 2014	RCT	16	15	MVr (100%)	12 ^M	2 (all patients)		2+ (Moderate Only)
Smith 2014	RCT	151	150	MVr (100%)	12 ^M	2 (all patients)		2+ (Moderate Only)
Chan 2012	RCT	38	33	MVr (100%)	12 ^M	2 (all patients)		2+ (Moderate Only)
Fattouch 2009	RCT	54	48	MVr (100%)	32 ± 18	2 (all patients)		2+ (Moderate Only)
Castleberry 2014	OS	1651	243	MVR or MVr (% NR)	64.4 ^M	2.25*	3.46*	≥ 2+ (Moderate to Severe)
Sa 2013	OS	26	16	MVR (100%)	NR	NR	NR	NS (Moderate to Severe)
Deja 2012	OS	42	49	MVr (98%); MVR (2%)	56 ^M	NR	NR	NS (Moderate to Severe)
Jeong 2012	OS	77	63	MVr (100%)	44 ± 34.5	NR	NR	3+ (Moderate Only)
Silberman 2011	OS	108	87	MVr (100%)	87 ± 50	3.1 ± 0.3*	3.8 ± 0.4*	≥ 3+ (Moderate to Severe)
de Waroux 2009	OS	42	34	MVr (100%)	51 ± 44	2.2 ± 0.4	2.4 ± 0.5	≥ 3+ (Moderate to Severe)
Goland 2009	OS	55	28	MVr (100%)	61.2 ± 43.2	3 (all patients)		3+ (Moderate Only)
Mihaljevic 2007	OS	54	54	MVr (100%)	48 ^M	3.24	3.19	≥ 3+ (Moderate to Severe)
Bonacchi 2006	OS	36	40	MVr (100%)	32.4 ± 11	2.5 ± 0.5*	3.3 ± 0.6*	≥ 2+ (Moderate to Severe)
Buja 2006	OS	50	39	MVR (56%); MVr (44%)	34.9 [5.3-104]	NR	NR	≥ 3+ (Moderate to Severe)
Kang 2006	OS	57	50	MVr (100%)	41 ± 27 (CABG) 37 ± 22 (MVr + CABG)	2.5 ± 0.5	2.8 ± 0.4	2+/3+ (Moderate to Severe)
Kim 2005	OS	168	187	MVr (100%)	NR	2.63*	3.81*	≥ 3+ (Moderate to Severe)
Wong 2005	OS	220	31	MVr (100%)	51.6 ^m	2.3 ± 0.7*	3.1 ± 0.3*	3+ (Moderate Only)
Diodato 2004	OS	51	51	MVr (100%)	39 ± 25 (CABG) 37 ± 25 (MVr + CABG)	NR	NR	≥ 2+ (Moderate to Severe)
Harris 2002	OS	142	34	MVr (85%); MVR (15%)	61.2 ± 3.6 (CABG) 56.4 ± 7.2 (MVS + CABG)	2.1 ± 0.3*	2.6 ± 0.5*	2+/3+ (Moderate Only)

Data presented as n (%), mean ± standard deviation, or median [interquartile range], unless stated otherwise. CABG, Coronary artery bypass graft; MVS, mitral valve surgery; MR, mitral regurgitation; RCT, randomized controlled trial; MVr, mitral valve repair; OS, observational study; MVR, mitral valve replacement; NR, not reported; NS, not specified; M, median; m, mean. * $P < .05$.

$P = .58$; $I^2 = 0\%$).^{17,18} Similarly, in 3 observational studies including a total of 433 patients, there was no significant difference in acute renal failure between the 2 groups (RR 1.08; 95% CI, 0.28-4.19; $P = .91$; $I^2 = 79\%$).^{20,22,31}

Meta-analyses could not be performed for other morbidity endpoints due to the lack of outcome reporting across studies.

Survival

In 3 RCTs involving a total of 462 patients, there was no difference in survival at follow-up between patients who underwent isolated CABG and those who underwent CABG and MV surgery (HR 1.20; 95% CI, 0.57-2.53; $P = .62$; $I^2 = 0\%$; Figure 4, A). Similarly, in 14 observational studies involving a total of 3828 patients, the 2 surgical cohorts had similar survival at the time of latest follow-up (HR 0.99; 95% CI, 0.81-1.21; $P = .92$; $I^2 = 47\%$; Figure 4, B). Aggregated survival was calculated by using either Kaplan-Meier curves assuming constant censoring^{18,28} or with censoring information,^{19,23-25,27,34}

events and P value,^{17,22,26,29,30} adjusted HR,²¹ or unadjusted HR,^{16,31} as per methods described by Tierney and colleagues.¹⁰

Recurrence of Moderate-to-Severe Mitral Regurgitation

In 4 RCTs including a total of 459 patients, CABG and MV surgery was associated with significantly lower incidence of moderate-to-severe (grade ≥ 2) regurgitation at latest follow-up (RR 0.16; 95% CI, 0.04-0.75; $P = .02$; $I^2 = 68\%$; Figure 5, A). This result was also demonstrated in an analysis of 4 observational studies including a total of 312 patients (RR 0.25; 95% CI, 0.12-0.50; $P < .001$; $I^2 = 21\%$; Figure 5, B).

Echocardiographic Outcomes

Due to limited data from observational studies, meta-analyses of echocardiographic outcomes were limited to RCTs. In 3 RCTs including 402 patients, CABG and MV surgery was not associated with significantly greater

TABLE 2. Baseline characteristics of participants in studies comparing isolated coronary artery bypass graft surgery versus concomitant mitral repair for ischemic mitral regurgitation

Study	Age		Male (%)		HTN (%)		Diabetes (%)		AF (%)		Prior MI (%)		LVEF %	
	CABG	CABG + MVr	CABG	CABG + MVr	CABG	CABG + MVr	CABG	CABG + MVr	CABG	CABG + MVr	CABG	CABG + MVr	CABG	CABG + MVr
Bouchard 2014	65 ± 12	69 ± 7	88	75	56	73	50	27	13	20	75	60	41.5 ± 17.4	45.7 ± 11.4
Smith 2014	65.2 ± 11.3	64.3 ± 9.6	66	71	NR	NR	44	51	23*	13*	64	69	41.2 ± 11.6	39.3 ± 10.9
Chan 2012	70.4 ± 7.9	70.9 ± 10.5	74	74	59	50	38	35	10	6	72	74	40.3 ± 16.1	40.0 ± 17.3
Fattouch 2009	66 ± 7	64 ± 9	65	63	43	54	59	58	NR	NR	100	100	43 ± 9	42 ± 10
Castleberry 2014	66 (58-73)*	66 (58-74)*	65	54	69	61	36	35	NR	NR	NR	NR	48 (35-60)*	45 (31-60)*
Sa 2013	NR	NR	54	56	85	94	42	25	NR	NR	46	50	47 ± 3	45 ± 5
Deja 2012	64 (56-70)	60 (54-68)	88	90	50	59	55*	27*	NR	NR	74	82	30 (25-35)*	22 (19-28)*
Jeong 2012	65.4 ± 9.1	63.9 ± 9.1	69	83	69	59	46	49	4*	18*	100	100	41.5 ± 12.3	38.3 ± 12.0
Silberman 2011	68 ± 9*	63 ± 10*	70	78	64	61	44	53	12	7	NR	NR	NR	NR
de Waroux 2009	61.4 ± 10.1	64.0 ± 8.4	79	76	29	24	24	41	NR	NR	NR	NR	34.4 ± 10.1	33.0 ± 12.5
Goland 2009	69 ± 11	68 ± 9	64	80	65	61	36	29	NR	NR	44	61	39 ± 11	37 ± 11
Mihaljevic 2007	66 ± 9.2	66 ± 9.6	59	69	70	71	42	32	0	0	89	83	NR	NR
Bonacchi 2006	64.5 ± 6	64.6 ± 6	70	57	53	63	38	41	NR	NR	NR	NR	27 ± 5	27.6 ± 5
Buja 2006	75 ± 7.4	72 ± 9.1	64	62	72	74	42	41	38	31	88	85	38 ± 13*	50 ± 14*
Kang 2006	63 ± 9	61 ± 10	68	74	NR	NR	56	52	0	12	NR	NR	36 ± 9	36 ± 11
Kim 2005	71 ± 11	72 ± 9	67	71	64	62	40	40	NR	NR	48*	63*	43 ± 15*	38 ± 14*
Wong 2005	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	42.2 ± 15.3	39.0 ± 13.6
Diodato 2004	69 ± 11*	65 ± 10*	51	47	69	82	NR	NR	NR	NR	67	78	31 ± 11	35 ± 12
Harris 2002	68.8 ± 9.8	65.6 ± 10.8	54	44	76	68	46	50	NR	NR	80	76	38.7 ± 12.6	38.0 ± 13.8

HTN, Hypertension; AF, atrial fibrillation; MI, myocardial infarction; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass graft; MVr, mitral valve repair. NR, not reported. * $P < .05$.

increase in left ventricular ejection fraction (LVEF) at follow-up (MD 0.19; 95% CI, -3.26 to 3.65; $P = .91$).^{15,16,18} In 2 RCTs including 339 patients, the decrease in left ventricular end-systolic volume index (LVESVI) was not significantly greater following CABG and MV surgery (weighted mean difference [WMD] -3.59; 95% CI, -17.98 to 10.81; $P = .63$).^{16,17} In 2 RCTs including 88 patients, the decrease in residual regurgitant volume was not significantly different between patients who underwent CABG and MV surgery and those who underwent isolated CABG (WMD -4.78; 95% CI, -26.61 to 17.06; $P = .67$; $I^2 = 94\%$).^{15,17}

NYHA Functional Status

In 3 RCTs including a total of 330 patients, the proportion of patients in NYHA class III/IV at follow-up were similar following isolated CABG or CABG and MV surgery (RR 0.67; 95% CI, 0.25-1.82; $P = .43$; $I^2 = 18\%$).¹⁵⁻¹⁷ This result was also demonstrated in an analysis of 4

observational studies including a total of 292 patients (RR 1.23; 95% CI, 0.78-1.93; $P = .37$; $I^2 = 5\%$).^{26,27,33,35}

Subgroup Analysis: Moderate MR

Subgroup analysis was conducted to assess studies in which all patients had only moderate IMR. This included 4 RCTs and 4 observational studies, reporting on a total of 1155 patients.^{15-18,22,25,31,34} Within this group, combined CABG and MV surgery was found to be associated with significantly increased perioperative mortality in observational studies (RR 1.81; 95% CI, 1.03-3.15; $P = .02$; $I^2 = 0\%$) but not within RCTs (RR 0.89; 95% CI, 0.26-3.02; $P = .85$; $I^2 = 0\%$). Patients who underwent combined CABG and MV surgery still had significantly reduced recurrence of MR at latest follow-up in both RCTs (RR 0.16; 95% CI, 0.04-0.75; $P < .001$; $I^2 = 68\%$) and observational studies (RR 0.26; 95% CI, 0.11-0.65; $P = .004$; $I^2 = 38\%$). There remained no difference between the surgical approaches with regard

FIGURE 2. Forest plot displaying the mean difference (MD) in aortic cross-clamp (2A) and cardiopulmonary bypass (CPB) durations (2B) for isolated coronary artery bypass graft (CABG) surgery versus CABG and mitral valve (MV) surgery. The MD in each study corresponds to the middle of the squares, the horizontal lines show the 95% confidence intervals (CIs), and the pooled MD is represented by the middle of the solid diamond. A test of heterogeneity between studies is given below the summary statistics. SD, Standard deviation; RCT, randomized controlled trial.

to long-term survival (HR 1.09; 95% CI, 0.84-1.42; $P = .53$; $I^2 = 0\%$) or NYHA functional status (RR 1.16; 95% CI, 0.61-2.21; $P = .65$; $I^2 = 37\%$).

Meta-Regression Analyses

Meta-regression analyses demonstrated that duration of follow-up was not a significant moderator for long-term survival ($P = .60$) and residual MR ($P = .20$). Meta-regression

analyses could not be performed for other endpoints due to the paucity of studies.

Publication Bias

Neither the Begg rank correlation test ($P = .51$) nor Egger linear regression method ($P = .40$) suggested publication bias was a significant factor when perioperative mortality was selected as an endpoint. Likewise,

FIGURE 3. Forest plot displaying relative risk (RR) for perioperative mortality following isolated coronary artery bypass graft (CABG) surgery versus CABG and mitral valve (MV) surgery in randomized controlled trials (3A) and observational studies (3B). The RR of individual studies correspond to the middle of the squares, the horizontal lines show the 95% confidence intervals (CIs), and the pooled RR is represented by the middle of the solid diamond. A test of heterogeneity between studies is given below the summary statistics. *RCT*, Randomized controlled trial.

publication bias was not found to significantly influence results for late mortality (Begg rank correlation test, $P = .97$; Egger linear regression method, $P = .51$).

DISCUSSION

Despite the prevalence of IMR in patients referred for surgical revascularization and its association with poorer clinical outcomes, the optimal management of moderate-to-severe IMR remains unclear.³ The present meta-analysis assessed the safety and efficacy of isolated CABG versus combined CABG and MV surgery in patients with moderate-to-severe IMR. Concomitant MV surgery was not associated with an increase in perioperative mortality. However, the addition of MV surgery to CABG resulted in significantly reduced recurrence of moderate-to-severe MR at latest follow-up. There was no significant difference in late mortality or NYHA functional status between patients who underwent isolated CABG or those who underwent CABG and MV surgery. These findings were replicated in subgroup analysis conducted to assess the impact of concomitant MV surgery in patients with strictly moderate IMR.

CPB and aortic cross-clamp durations were found to be significantly higher in patients undergoing CABG + MV surgery. This is an intuitive finding given the increased complexity of a combined procedure. Longer CPB and aortic cross-clamp durations have been linked with a number of complications, including microemboli, increased transfusion requirements, coagulation defects, and immunosuppression.³⁵⁻³⁷ In the present meta-analysis, increased operative durations did not translate to an increase in adverse perioperative events. However, it must be emphasized that the present study was unable to assess key perioperative morbidity outcomes, such as major bleeding, reoperation, myocardial infarction, and wound infection. In particular, there were a very limited number of studies assessing neurological events and the event rate may have been too low to enable sufficiently powered analysis. Indeed, in 2 of the included RCTs, the point estimate for stroke suggested a possible trend toward increased risk following combined CABG + MV surgery.^{16,17} As such, given the paucity of endpoints reported in current studies, it is not possible to exclude an increased risk of perioperative morbidity with the addition of concomitant MV surgery.

FIGURE 4. Forest plot displaying hazard ratio (HR) for late mortality following isolated coronary artery bypass graft (CABG) surgery versus CABG and mitral valve (MV) surgery in randomized controlled trials (4A) and observational studies (4B). The HR of individual studies correspond to the middle of the squares, the horizontal lines show the 95% confidence intervals (CIs), and the pooled HR is represented by the middle of the solid diamond. A test of heterogeneity between studies is given below the summary statistics. RCT, Randomized controlled trial; SE, standard error.

Key findings from the present study demonstrated that the proportion of patients with residual MR of at least moderate severity was significantly lower following concomitant mitral intervention. However, this was not associated with any significant advantage with regard to survival or functional status at the time of latest follow-up. This represents an unexpected finding given the association previously demonstrated between persistent MR and increased mortality.³⁸ It is possible the limited sample size and follow-up durations of the included studies, particularly the RCTs, may not have provided sufficient time or statistical power to highlight the clinical benefit of reduced residual MR. Alternatively, surgical revascularization alone may have sufficiently improved adverse left ventricular remodeling and contractility so as to mitigate the adverse impact of residual MR.^{6,7} The latter suggestion was supported by our meta-analysis of echocardiographic outcomes, which demonstrated similar pooled LVEF and LVESVI in patients who underwent either isolated CABG or CABG and MV surgery. Nonetheless, larger randomized trials with longer follow-up durations

are required to clarify this discrepancy between echocardiographic and clinical outcomes.

The present meta-analysis highlighted the considerable variability that exists with regard to the definition of “moderate” IMR. Although the American Society of Echocardiography and American Heart Association/American College of Cardiology have proposed standardized guidelines for the determination of MR grade,^{39,40} these were only adopted by several studies.^{16,17} Most included studies graded MR severity according to local institutional criteria, using a wide range of cutoffs for jet regurgitant area, vena contracta diameter, and/or proximal isovelocity surface area. This likely contributed to the considerable heterogeneity present in several of our analyses. To standardize comparative data across institutions, it is imperative that future studies use well-defined echocardiographic grading criteria according to established guidelines.

Results of the present meta-analysis were limited by several restraints, and should be interpreted with caution. First, there were only 4 RCTs, and observational studies

FIGURE 5. Forest plot displaying relative risk (RR) for recurrence of moderate-to-severe mitral regurgitation following isolated coronary artery bypass graft (CABG) surgery versus CABG and mitral valve (MV) surgery in randomized controlled trials (5A) and observational studies (5B). The RR of individual studies corresponds to the middle of the squares, the horizontal lines show the 95% confidence intervals (CIs), and the pooled RR is represented by the middle of the solid diamond. A test of heterogeneity between studies is given below the summary statistics. RCT, Randomized controlled trial.

provided a significant proportion of clinical data. As observational studies did not use propensity-score matching or report adjusted estimates, it was not possible to account for potential baseline differences between the 2 surgical arms. In recognition of this limitation, we performed subgroup analyses by study design. Second, due to the lack of reporting, it was not possible to assess quality-of-life scores or measures of resource utilization and cost-effectiveness, such as length of intensive care unit stay, despite these being increasingly key considerations in clinical practice. Third, follow-up periods and endpoint definitions differed between institutions, and some studies may have underestimated adverse events due to incomplete follow-up. Although meta-regression analyses did not demonstrate significant interaction between follow-up duration and survival or residual MR, there was not enough data to perform meta-regression for other outcomes such as NYHA functional class. Last, due to the lack of available data, residual MR was assessed using a binary approach rather than through a longitudinal, competing risks method.

In conclusion, available data in the current literature demonstrated that MV surgery in addition to CABG was not associated with increased perioperative mortality in patients with moderate-to-severe IMR. Compared with isolated CABG, concomitant MV surgery was associated with reduced recurrence of moderate-to-severe MR at follow-up. However, there was no significant difference between the 2 treatment approaches with regard to late

mortality or NYHA functional status. Larger trials with longer follow-up duration are required to further assess overall survival and freedom from reintervention, as well as the impact of both surgical approaches on quality of life and health care costs.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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