Surgical Repair of Moderate Ischemic Mitral Regurgitation—A Systematic Review and Meta-analysis

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Thorac Cardiovasc Surg

Abstract

Introduction Moderate mitral regurgitation (MR) of ischemic etiology has been associated with worse outcomes after coronary artery bypass grafting (CABG). Studies comparing concomitant mitral valve replacement/repair (MVR/Re) with CABG and standalone CABG have reported conflicting results. We performed a systematic review and meta-analysis of the published literature.

Patients and Methods We searched using PubMed, Cochrane, EMBASE, CINAHL, and Google scholar databases from January 1960 to June 2016 for clinical trials comparing CABG to CABG + MVR/Re for moderate MR. Pooled risk ratio or mean difference (MD) with 95% confidence intervals (CI) for individual outcomes were calculated using random effects model and heterogeneity was assessed using Cochrane's Q-statistic.

Results A total of 11 studies were included. Mean follow-up was 35.3 months. All-cause mortality (Mantel–Haenszel [MH] risk ratio [RR]: 0.96, 95% CI: 0.75–1.24, $p = 0.775$), early mortality (MH RR: 0.65, 95% CI: 0.39–1.07, $p = 0.092$), and stroke rates (MH RR 0.65, 95% CI: 0.21–2.03, $p = 0.464$) were similar between CABG and CABG + MVR/Re groups. Adverse event at follow-up was lower with CABG (MH RR: 0.90, 95% CI: 0.61–1.32, $p = 0.584$). MD of change from baseline in left ventricular (LV) end-systolic dimension (MD: − 2.50, 95% CI: − 5.21 to − 0.21, $p = 0.071$) and LV ejection fraction (MD: 0.48, 95% CI: − 2.48 to 3.44, $p = 0.750$) were not significantly different between the groups. Incidence of moderate MR (MH RR: 3.24, 95% CI: 1.79–5.89, $p < 0.001$) was higher in the CABG only group.

Conclusion Addition of MVR/Re to CABG in patients with moderate ischemic MR did not result in improvement in early or overall mortality, stroke risk, or intermediate markers of LV function when compared with CABG alone.

Keywords
- mitral valve insufficiency
- coronary artery bypass grafting
- moderate mitral regurgitation
- coronary artery disease
- mitral valve repair

received
September 11, 2016
accepted after revision
November 6, 2016

DOI http://dx.doi.org/10.1055/s-0036-1598012.
ISSN 0171-6425.

Introduction

The prevalence of ischemic mitral regurgitation (MR) is increasing and the current estimated prevalence is approximately 1.6 to 2.9 million patients in the United States alone.[1] Functional MR occurs in approximately 20% of patients with chronic coronary artery disease (CAD),[2] more commonly after an inferior myocardial infarction (MI).[3] Though there are clear guidelines for repair of degenerative MR, repair of functional MR secondary to ischemia has always been a topic of debate. The pathophysiology of ischemic MR differs from primary MR due to myxomatous mitral valve, rheumatic disease, or endocarditis.[4,5] Ischemic MR is generally considered a disease of the ventricle with a potential for improvement following coronary artery bypass grafting (CABG).[6] The 2014 European Society of Cardiology guidelines[7] recommend mitral valve surgery in patients with moderate MR undergoing CABG (Class IIa) and the recent American College of Cardiology (ACC)/American Heart Association (AHA) valvular heart disease guidelines recommend considering repair for moderate and severe ischemic MR at the time of CABG[8] (Class IIb). Concomitant mitral valve surgery and CABG results in increased aortic cross-clamp and surgical bypass time, predisposing to longer hospital stay and increased periprocedural complications.[9,10] However, these must be balanced against the fact that the presence of moderate regurgitation after CABG is associated with worse outcomes.[11] Left ventricular (LV) remodeling is not uniform after CABG, and therefore, it is difficult to predict the improvement in MR after surgery and this further complicates the decision process.[12,13] In view of this conflicting evidence, we aimed to perform a systematic review and meta-analysis to assess whether concomitant mitral valve surgery with CABG improves clinical outcomes when compared with CABG alone.

Materials and Methods

Literature Search

We performed an electronic search using the terms "ischemic MR," "functional MR," "moderate MR" "mitral valve replacement (MVR)," "mitral valve repair (MVRe)," "mitral valve regurgitation," "mitral valve insufficiency," and their combinations using PubMed, Cochrane, EMBASE, CINAHL, and Google scholar databases for studies published between January 1960 and June 2016 comparing mitral valve surgery to conventional therapy with CABG alone. The detailed search strategy for PubMed is shown in ►**Supplementary Appendix 1** [available online only].

The systematic review and meta-analysis was performed and reported according to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines (►**Supplementary Checklist 1** [available online only]).[14] Search strategy is shown as PRISMA flowchart (►**Supplementary Fig. 1** [available online only]) and Medline search is shown in ►**Supplementary Appendix 1** [available online only]. We also performed handsearch by reviewing the reference sections of the included studies, review articles, and editorials. As per Cochrane guidelines, we excluded conference abstracts with unpublished data.

Eligibility Criteria

Studies selected met the following criteria for eligibility: randomized controlled trials (RCTs), retrospective or prospective observational studies; all patients had moderate MR before surgery; compared two groups, one group with isolated CABG and the other with CABG plus MVR MVR/Re; included only adult patients; and published in English language. We excluded studies that included patients with trace, mild, and severe MR, mixed pathology of MR with only minimal subgroup of ischemic MR, concomitant procedure other than atrial septal defect, atrial fibrillation ablations, or tricuspid repair.

Definitions

Functional ischemic MR was defined as per the American Society of Echocardiography guidelines[15] in some studies and by semiquantitative methods in other studies and is reported in ►**Table 1**. The term functional ischemic MR implies regurgitation secondary to failure of coaptation of anatomically normal leaflets and chordae or secondary to regional or global LV remodeling secondary to CAD.[6] All-cause mortality was defined as death from any cause during follow-up and early mortality as death within 30 days of surgery or during hospitalization.

Data Collection

We included patient demographics, sample size, and type of study in a structured abstract (►**Table 1**). We abstracted patient data including sample size, mean age, mortality data, and risk estimates for different analyses. Two reviewers (M.A.N. and S.A.) independently reviewed the studies for inclusion. Any disagreement was resolved by consensus opinion.

Outcomes

We assessed the outcomes including all-cause mortality, early mortality, LV end-systolic dimension (LVESD), LV ejection fraction (LVEF) and LV end-systolic volume index (LVESVi), New York Heart Association (NYHA) class, stroke, MR grade, reoperations, adverse events, and readmissions at follow-up. We also compared aortic cross-clamp times (CCTs), cardiopulmonary bypass (CPB) time, and usage of intra-aortic balloon pump (IABP) between the two groups.

Statistical Analysis

Statistical analysis was performed using Comprehensive Meta-Analysis (CMA) version 3.3.07. Categorical events data were pooled using random effects model, with the pooled effect size represented as Mantel–Haenszel (MH) risk ratio (RR) with 95% confidence interval (CI) limits. Mean difference (MD) was used for reporting outcomes with continuous variables. The isolated CABG group was considered as the experimental group and so any RR (with 95% CI) < 1 favors that cohort. Publication bias was assessed visually using the funnel plot. Cochrane's Q statistics was calculated and used to determine the heterogeneity of included studies for each end point. I^2 values of < 25, 25 to 50, and 50 to 75% were considered as low, moderate, and high heterogeneity, respectively. An exclusion sensitivity analysis was included for heterogeneity when necessary. A p-value of < 0.05 was

considered statistically significant. A metaregression was performed when required to examine the impact of moderator variables on specific outcomes.

Results

Study Characteristics

A total of 2,577 unique studies were identified in the initial search using the search criteria as specified in ►**Supplementary Appendix 1** [available online only]. After applying inclusion and exclusion criteria as specified earlier, 11 studies,[16–26] including 4 RCTs and 7 observational studies qualified for the final analysis. The mean follow-up duration was 35.3 months. A total of 873 patients had isolated CABG and 527 patients received CABG with MVR/Re. ►**Table 1** summarizes the demographic characteristics of individual studies and ►**Supplementary Table 1** [available online only] summarizes overall results of studies comparing isolated CABG to CABG with MVR/Re in patients with moderate MR.

All-Cause Mortality

All-cause mortality was reported in 10 studies. The RR for all-cause mortality was not different (MH RR: 0.96, 95% CI: 0.75–1.24, $p = 0.775$) between the two groups (►**Fig. 1A**). Funnel plot showed minimal bias (►**Supplementary Fig. 2A** [available online only]>) and heterogeneity of the included studies was low ($I^2 = 9$). Sensitivity analysis with exclusion of the study[22] with the maximum strength did not change the results of the analysis (MH RR 0.99, 95% CI: 0.74–1.32, $p = 0.925$). Analysis of pooled RRs of only RCTs showed no difference in all-cause mortality between the two groups (MH RR 1.08, 95% CI: 0.62–1.88, $p = 0.775$ for RCTs) (►**Fig. 1B**). Exclusion of studies with low EF[21,22] at baseline did not alter the results (MH RR 0.83, 95% CI: 0.63–1.09, $p = 0.180$). Also, exclusion of studies where a small proportion of patients received concomitant MVR[18,21] did not alter the results (MH RR 0.91, 95% CI: 0.69–1.19, $p = 0.475$). A metaregression of follow-up time on RR for all-cause mortality (►**Fig. 1C**) was insignificant ($p = 0.106$).

Early Mortality

Eight studies reported early mortality comparing CABG and CABG with MVR/Re (►**Fig. 2A**). Early mortality was not significantly different between the two groups (MH RR: 0.65, 95% CI: 0.39–1.07, $p = 0.092$). An exclusion sensitivity analysis excluding the study with maximum weight[18] showed a trend in favor of CABG but was not statistically significant (MH RR: 0.44, 95% CI: 0.19–1.03, $p = 0.058$), though there was a strong trend in favor of the CABG alone group. Funnel plot of the included studies showed minimal bias (►**Supplementary Fig. 2B** [available online only]). Heterogeneity was low ($I^2 = 0$) among the included studies.

Major Adverse Events at Follow-up

Five studies that reported adverse events at follow-up were analyzed (►**Fig. 2B**). There was no difference in major adverse cardiac events (MACE) between the isolated CABG group (MH RR: 0.90, 95% CI: 0.61–1.32, $p = 0.584$) and the CABG with MVR/Re group. Heterogeneity was low ($I^2 = 42\%$).

Neurological Events/Stroke at Follow-up

Four studies reported major neurological events/stroke at follow-up (►**Fig. 2C**). Incidence of stroke showed a favorable trend toward the CABG group but without achieving statistical significance (MH RR 0.65, 95% CI: 0.21–2.03, $p = 0.464$). Heterogeneity was low ($I^2 = 0$).

Mitral Regurgitation Grade at Follow-up

A total of 10 studies reported moderate-to-severe MR grade at follow-up with one study reporting separately for LVEF < 40 and $> 40\%$ (►**Fig. 2D**). Incidence of moderate-to-severe MR at follow-up was higher in the CABG alone group when compared with CABG + MVR/Re (MH RR: 3.24, 95% CI: 1.79–5.89, $p < 0.001$). Heterogeneity was moderate ($I^2 = 36\%$).

Left Ventricular End-Systolic Dimension

During the follow-up period, five studies reported LVESD (►**Fig. 3A**). MD between pre- and post-LVESD trended toward improvement with the addition of MVR/Re to CABG but did not reach statistical significance (MD: − 2.50, 95% CI: − 5.21 to − 0.21, $p = 0.071$). Heterogeneity was high however limiting confidence in this result ($I^2 = 67\%$).

Left Ventricular Ejection Fraction

A total of seven studies reported LVEF during the follow-up (►**Fig. 3B**). The LVEF improved in both the groups. Calculated MD between pre- and post-LVEF in CABG was not significantly different from CABG + MVR/Re (MD: 0.48, 95% CI: − 2.48 to 3.44, $p = 0.750$). Heterogeneity was high ($I^2 = 77\%$).

Left Ventricular End-Systolic Volume Index

Two studies reported LVESVi at follow-up (►**Fig. 3C**). Change in LVESVi between pre- and post-CABG was not significantly different when compared with change in LVESVi between pre- and post–CABG + MVR/Re (MD: − 9.56, 95% CI: − 24.19 to 5.07, $p = 0.200$). Heterogeneity was high ($I^2 = 84\%$).

New York Heart Association Class

Three studies reported NYHA class at follow-up (►**Fig. 3D**). MD in NHYA class between pre- and post-CABG favored the addition of MVR/Re (MD: − 0.85, 95% CI: − 1.58 to − 0.12, $p = 0.023$). However, heterogeneity was high ($I^2 = 90\%$).

Intra-aortic Balloon Pump Usage

Intraoperative IABP usage was reported in four studies (►**Fig. 4A**). Comparison of the two arms with CABG and CABG with MVR/Re showed no significant difference (MH RR: 0.74, 95% CI: 0.46–1.20, $p = 0.224$). Heterogeneity was low ($I^2 = 0$).

Aortic Cross-clamp Time

Five studies reported aortic CCT between the two groups (►**Fig. 4B**). MD was in favor of the CABG group (MD: − 42.53 minutes, 95% CI: − 62.27 to − 22.79, $p < 0.001$). Calculated heterogeneity was high ($I^2 = 96\%$).

Cardiopulmonary Bypass Time

Intraoperative CPB was compared between the CABG and CABG with MVR/Re groups and was reported in five studies

Table 1 Patient demographics

Study	Type of study (NOS)	Total number of patients	Age (mean or median) (y)		Isolated CABG (*n*)	CABG ± MVR/Re (*n*)	Maximum follow-up time (mean or median) (mo)	Assessment/definition of functional moderate MR	Type of imaging used to document MR grade	Number of mitral valve replacements *N* (%)
			CABG	CABG ± MVR/Re						
Prifti et al (2001)	Prospective cohort	99	64.5 (6)	63.4 (5)	50	49	34	Quantitative/mild-to-moderate (grade II, RF = 30–39%), moderate (grade III, RF = 40–50%)	Color flow Doppler	5 (10%)
Harris et al (2002)	Retrospective cohort	176	69 (10)	66 (11)	142	34	61.2 (CABG) 56.4 (CABG + MVR/Re)	Quantitative/the average of two maximum RJA and RJA/LAA as well as the average of all three dimensions were correlated	Ventriculography from cardiac catheterization or TTE	5 (15%)
Di Donato et al (2003)	Retrospective cohort	60	64 (10)	66 (8)	30	30	12	Semiquantitative model with moderate MR diagnosed with grade II	TTE	None
Wong et al (2005)	Retrospective cohort	251	Overall group 71.7		220	31	51.6.	Moderate (3 +) MR selected after excluding other etiologies. Technique not mentioned	TTE	None
Fattouch et al (2009)	RCT	102	66 (7)	64 (9)	54	48	32.	Moderate (2 +) MR when radius of PISA was between 5 and 8 mm. Quantitative Doppler used to assess severity of MR	TTE, TEE intraoperatively	None
Goland et al (2009)	Retrospective cohorts	83	69 (11)	68 (9)	55	28	61.2	Semiquantitative fashion based on the size and geometry of the regurgitant jet plus LV dysfunction (LVEF, < 0.50) and a history of MI	Left ventriculography alone (11%), TTE alone (19%), or both (70%)	None
Jeong et al (2012)	Retrospective cohort	140	65 (9)	64 (9)	77	63	44.	ASE guidelines with ERO of 1 5–30 mm^2 obtained with the PISA method	TTE	None
Chan et al (2012)	Single-blinded RCT	73	70 (8)	71 (11)	39	34	12	Quantitative/ASE guidelines with (1) ERO of 0.20–0.39 cm^2, (2) a regurgitant volume of 30–59 mL/beat, (3) a regurgitant fraction of 30–49%, or (4) a vena contracta width of 0.30–0.69 cm (≥ one criteria should be met)	TTE	None
Bouchard et al (2014)	RCT	31	65 (12)	69 (7)	16	15	12	Semiquantitative/jet area/LA area 3 100%. Further quantitative assessment done with ERO using PISA	TTE	None
Diken et al (2014)	Retrospective cohort	84	63 (8)	62 (8)	39	45	18	Quantitative based on regurgitant jet area, vena cava width and PISA. Confirmed by ventriculography	TTE and ventriculography	None

Table 1 (*Continued*)

Study	Type of study (NOS)	Total number of patients	Age (mean or median) (y)		Isolated CABG (*n*)	CABG ± MVR/Re (*n*)	Maximum follow-up time (mean or median) (mo)	Assessment/definition of functional moderate MR	Type of imaging used to document MR grade	Number of mitral valve replacements *N* (%)
			CABG	CABG ± MVR/Re						
Michler et al (2016)	RCT	301	65 (11)	64 (10)	151	150	12	Quantitative/ASE guidelines two-thirds criteria (1) ERO of 0.2 to less than 0.4 cm^2, (2) a vena contracta width of 3 to less than 7 mm, and (3) a ratio of the MR jet area to the LAA of 20% to less than 40%	TTE	None

Abbreviations: ASE, American Society of Echocardiography; CABG, coronary artery bypass grafting; ERO, effective regurgitant orifice; LAA, left atrial area; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; MVR, mitral valve replacement; MVRe, mitral valve repair; NOS, Newcastle–Ottawa scale; PISA, proximal isovelocity surface area; RCT, randomized controlled trial; RF, regurgitation fraction; RJA, regurgitant get area; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram.

(►**Fig. 4C**). MD was in favor of the CABG group (MD: − 48.87 minutes, 95% CI: − 71.95 to − 25.78, $p < 0.001$). I^2 was 94% showing high heterogeneity.

Cardiac Reoperations at Follow-up

Three studies reported cardiac reoperations (►**Fig. 4D**) during follow-up and the RR was not different between the two groups. (MH RR 0.52, 95% CI: 0.18–1.45, $p = 0.209$). Calculated heterogeneity was moderate ($I^2 = 35\%$).

Readmissions at Follow-up

Two studies reported readmission rates (►**Supplementary Fig. 2C** [available online only]) and this was not statistically significant between the two groups (odds ratio 1.02, 95% CI: 0.94–1.12, $p = 0.593$). Heterogeneity was low ($I^2 = 0$).

Discussion

Much of the evidence for managing valvular heart disease rests on expert opinion and analysis of retrospective data, given the small size and relative rarity of RCTs for the surgical management of valvular heart disease.[8] This disparity is even more apparent in managing patients with secondary MR from ischemic heart disease.[8] The 2014 ACC/AHA guidelines[8] and the European Society of Cardiology guidelines[7] recommend surgical intervention of the mitral valve in moderate secondary MR as Classes IIb and IIa, respectively, with a level of evidence C (expert opinion) citing a lack of evidence to make stronger recommendations. A few small RCTs[16,17,23] and a recent modest sized randomized trial[27] have sought to address this gap in the field of incidental moderate ischemic MR at the time of CABG, with mixed results and limitations in their power to detect hard clinical end points.[28] The results of this review therefore help consolidate the literature and provide much needed information on both the long- and short-term outcomes of patients undergoing concomitant mitral valve surgery for moderate MR at the time of CABG.

The major findings of this analysis are a decrease in recurrence of moderate-to-severe MR with the addition of valve intervention to CABG coupled with an improvement in NYHA class. However, NYHA class was reported in only two studies with high heterogeneity limited confidence in the results. Moreover, there was no difference in early and all-cause mortalities, stroke, reoperations, readmissions, or even intermediate markers of remodeling such as LVESD, LVEF, or LVESVi. Overall mortality was also not different between the two groups when we excluded studies with baseline low EF.

There was an increase in aortic cross-clamp and cardiopulmonary bypass times associated with addition of mitral valve surgery to CABG in patients with moderate ischemic MR but fortunately this did not increase early mortality or MACE. Thus, overall, it appears that the addition of mitral valve surgery for moderate MR at the time of CABG reduces the risk of subsequent significant MR, but this did not translate into an improvement in ventricular remodeling or hard clinical outcomes.

Functional MR as a result of CAD is widely considered to be a disease primarily of the ventricle, with adverse ventricular remodeling after MI/ischemia contributing to abnormal

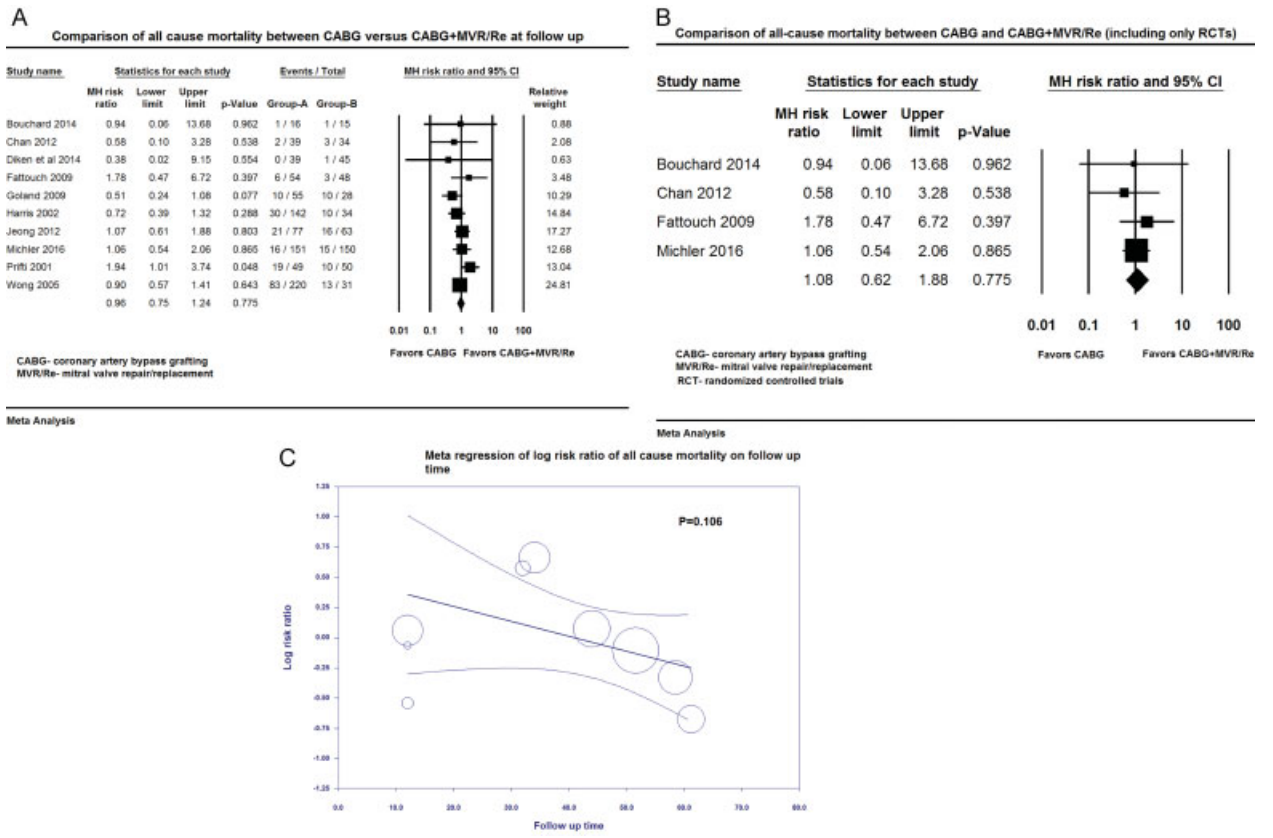

Fig. 1 (**A**) Comparison of all-cause mortality between CABG and CABG + MVR/Re including all studies; (**B**) comparison of all-cause mortality between CABG and CABG + MVR/Re including only RCTs; and (**C**) metaregression of follow-up time on all-cause mortality. CABG, coronary artery bypass grafting; MVR/Re, mitral valve replacement/repair; RCTs, randomized controlled trials.

papillary muscle and chordal architecture and function, abnormal leaflet closing forces and annular dilation.[29] Progressive LV remodeling leads to LV dilatation, and therefore, the LV becomes more spherical by mechanisms already described.[30] This further worsens the severity of MR by increasing the preload and wall tension, which in turn contributes to heart failure. It has long been recognized that the presence of any degree of ischemic MR is an independent prognostic marker of adverse outcomes.[11] In a study of 1,190 patients, moderate-to-severe ischemic MR was associated with 30% mortality at follow-up compared with 6.5% in patients with no MR.[31]

Based on this poor natural history, patients with moderate MR undergoing CABG are frequently offered simultaneous MVR/Re with studies showing no difference between MVR and MVRe.[32] Advocates of this approach cite the detrimental effect of residual MR after CABG toward outcomes and the potential benefit that improving the MR may have on symptoms and LV remodeling.[11] This is largely based on retrospective data and three small randomized trials from Chan et al ($n = 73$), Fattouch et al ($n = 102$), and Bouchard et al ($n = 31$).[16,17,23] However, these trials showed improvements only in intermediate end points such as echocardiographic parameters of remodeling; no improvements were seen in long-term hard clinical end points. These randomized trials did report symptomatic improvement in these patients, but these trials were underpowered to elicit a difference in mortality, and long-term outcomes were not affected.[33] In our study, there was no difference in the surrogate markers of LV function such as LVESD, LVEF, and LVESVi. This suggests that the LV performance does not change significantly over and beyond the benefits accrued from revascularization alone with the addition of MVR/Re in patients with moderate ischemic MR. This may likely explain the lack of mortality benefit observed in these patients.

Supporters of the more conservative approach of foregoing MVR/Re and performing only CABG in patients with moderate MR quote the hypothesis[34] that the mitral valve in these patients acts a "pop-off" valve for the failing left ventricle and correction of the valve is associated with worse outcomes. Also, the aortic CCT and CPB times are increased with the addition of mitral valve surgery to CABG. Previously studies have suggested that concomitant MVR/Re and CABG has been associated with increased major adverse events when compared with CABG alone.[10] However, this was not observed in our study, where despite the higher bypass and CCTs in this group, there was no increase in early mortality or incidence of major adverse events. This suggests that there may not be significant harm from the addition of mitral valve intervention to CABG. One could speculate that this risk would be even lower if the valve is repaired as opposed to replace although we cannot make that conclusion based on our study as there were only one to two studies that included a very minor proportion of patients with concomitant MVR.

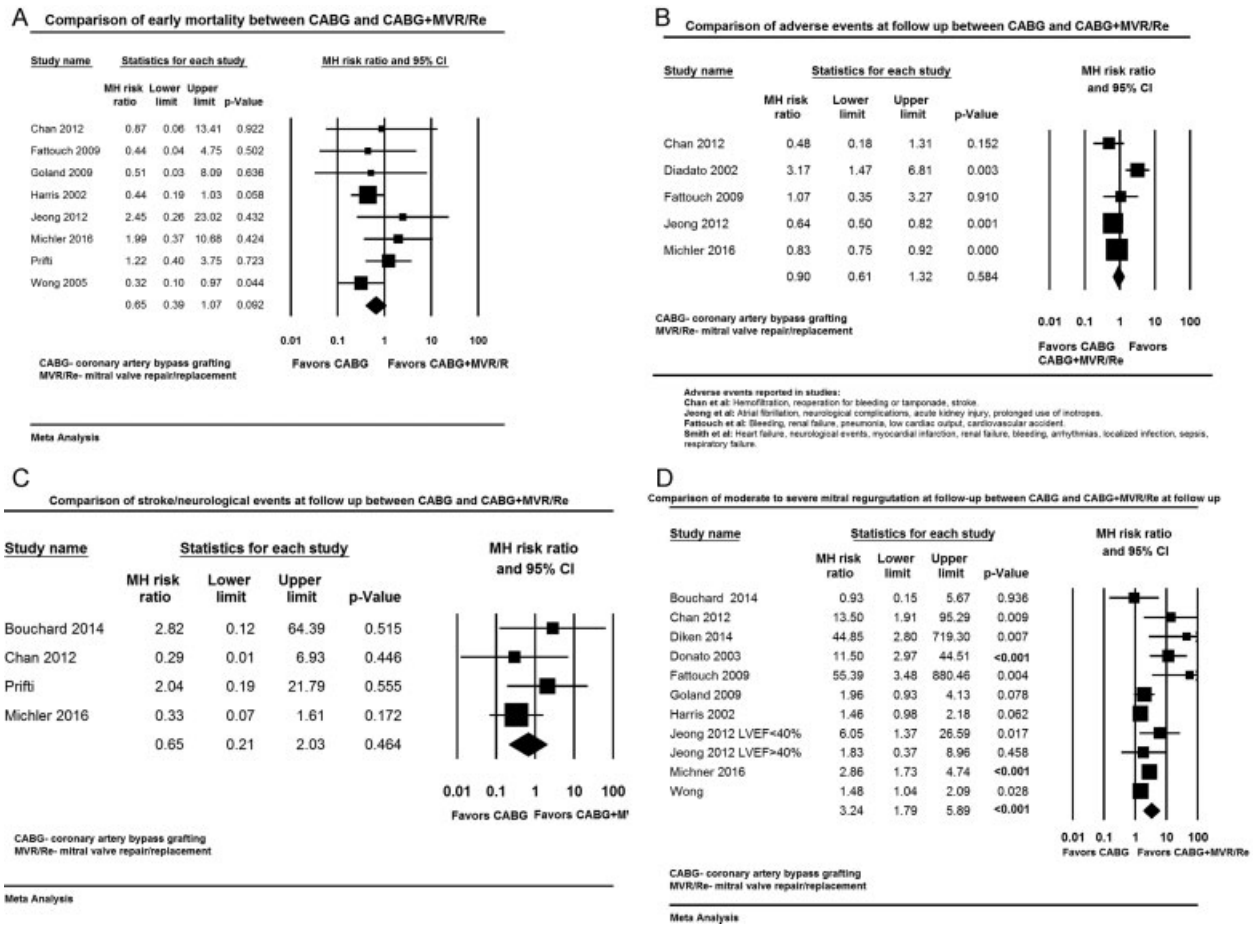

Fig. 2 (**A**) Comparison of early or inhospital mortality between CABG and CABG + MVR/Re; (**B**) comparison of adverse events at follow-up between CABG and CABG + MVR/Re; (**C**) comparison of neurological events at follow-up between CABG and CABG + MVR/Re; and (**D**) comparison of moderate-to-severe regurgitation between CABG and CABG + MVR/Re at follow-up. CABG, coronary artery bypass grafting; MVR/Re, mitral valve replacement/repair.

With viable hibernating myocardium, revascularization has the potential to improve LV function and reverse LV remodeling and thereby improve MR. Roshanali et al[35] reported that if reversibility of myocardium could be shown by dobutamine stress echocardiogram (DSE), these patients could benefit from CABG alone. However, in their recent study, they found that viability prediction by DSE does not essentially reflect the long-term outcomes in patients receiving isolated CABG for moderate ischemic MR.[36] The largest randomized trial of moderate MR undergoing CABG reported their 1- and 2-year outcomes recently and the addition of MVR/Re to CABG did not result in improvement in symptoms, mortality at 1 year or LVESVi at either 1 or 2 years.[27] There was, however, a higher risk of neurological events and longer hospital stay associated with the addition of MVR/Re and a longer bypass time. There was expectedly a significantly lower incidence of residual moderate-to-severe MR in the MVR/Re group compared with the CABG only group (11.2 vs. 31%, respectively). Similar results were obtained in our meta-analysis but compared with the recent modest sized randomized trial; our analyses of the composite data suggest that there is no increase in MACE or stroke with the addition of MVR/Re. It remains to be seen how residual MR affects long-term clinical outcomes in this randomized trial participants. In our meta-analysis, all-cause mortality was not impacted by the follow-up duration on metaregression. Although there is clear lack of evidence to support concomitant mitral surgery for moderate ischemic MR at this time, there may be a subgroup of patients who might benefit from this. Intuitively, one might expect patients with large scar or aneurysm burden to benefit from concomitant mitral valve surgery, since a significant degree of reverse remodeling is unlikely without viable myocardium. However, this hypothesis remains largely unproven and identifying these and other patients who may benefit continues to remain a challenge. Until further data become available, our analysis provides the most comprehensive summary of the available literature.

Limitations

The limitations of this meta-analysis are similar to those inherent to a meta-analysis of retrospectively collected data including all the inherent biases and limitations the original studies may contain. Most of the studies included were retrospective cohorts with only a few RCTs. As a result of this, we could not adjust for confounding variables that were

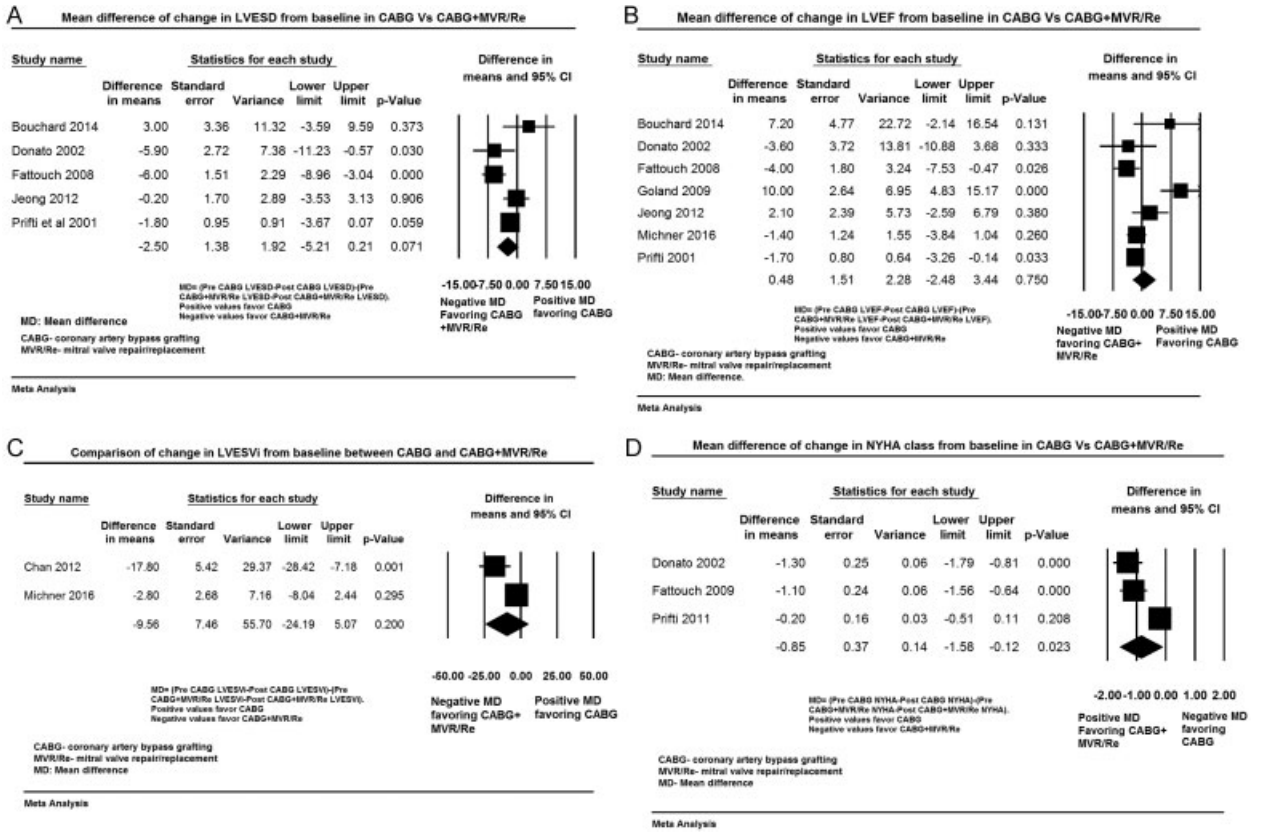

Fig. 3 (**A**) Comparison of mean difference between pre- and postleft ventricular end-systolic dimension between CABG and CABG + MVR/Re groups at follow-up; (**B**) comparison of mean difference between pre- and postleft ventricular ejection fraction between CABG and CABG + MVR/Re groups at follow-up; (**C**) comparison of mean difference between pre- and postleft ventricular end-systolic volume index between CABG and CABG + MVR/Re groups at follow-up; and (**D**) comparison of mean difference between pre- and post-NYHA class between CABG and CABG + MVR/Re groups at follow-up. CABG, coronary artery bypass grafting; MVR/Re, mitral valve replacement/repair; NYHA, New York Heart Association.

not adjusted for in the primary studies. The variably defined major perioperative adverse outcomes limited us from reporting MACE at follow-up. The included studies were conducted over a varying period of time and improvement in surgical techniques and medical therapy over this period may have had a confounding role. To avoid this, we performed a metaregression for outcomes of interest. Assessment of myocardial viability was not performed universally in all the studies and that may be a major limiting factor in the outcomes of these studies. This may be a major limitation factor in interpretation of the results of our meta-analysis. Mitral valve surgery included both replacement and repair, and therefore, we could not compare these techniques. There were a very few studies that reported replacement and we did not have patient level data for indirect comparison of repair with replacement. Some of the differences in outcomes could be due to the use of repair as opposed to replacement, which has recently been shown in a large randomized trial[32] to have higher recurrent MR compared with valve replacement in ischemic MR. The variable definitions used for MR could possibly be a source of potential bias in our meta-analysis. However, historically, the accurate determination of mitral regurgitant severity is often challenging and dynamic, but the performance of valve surgery for the MR suggests (but does not prove) that it was at least of moderate intensity for the surgeon to justify the higher risk of additional mitral valve surgery. Finally, publication bias is an inherent limitation of meta-analyses.

Conclusion

In summary, the results of our systematic review and meta-analysis of the published literature on concomitant mitral valve surgery for moderate ischemic MR at the time of surgical revascularization do not support the addition of MVR/Re to standard CABG surgery. This approach is associated with no demonstrable benefit in terms of hard clinical end points such as stroke, early or long term mortality, or surrogate markers of ventricular remodeling. There was however a decrease in recurrent significant MR and potential improvement in NYHA class with mitral valve intervention. Whether this translates into long-term benefit is uncertain, but there does not appear to be a benefit in the short term after surgery. Fortunately, there appeared to be no significant increase in perioperative or short-term major adverse events despite a longer bypass and aortic CCT. Further research should focus on identifying subgroups of patients with moderate ischemic MR who may benefit from mitral surgery with CABG, such as

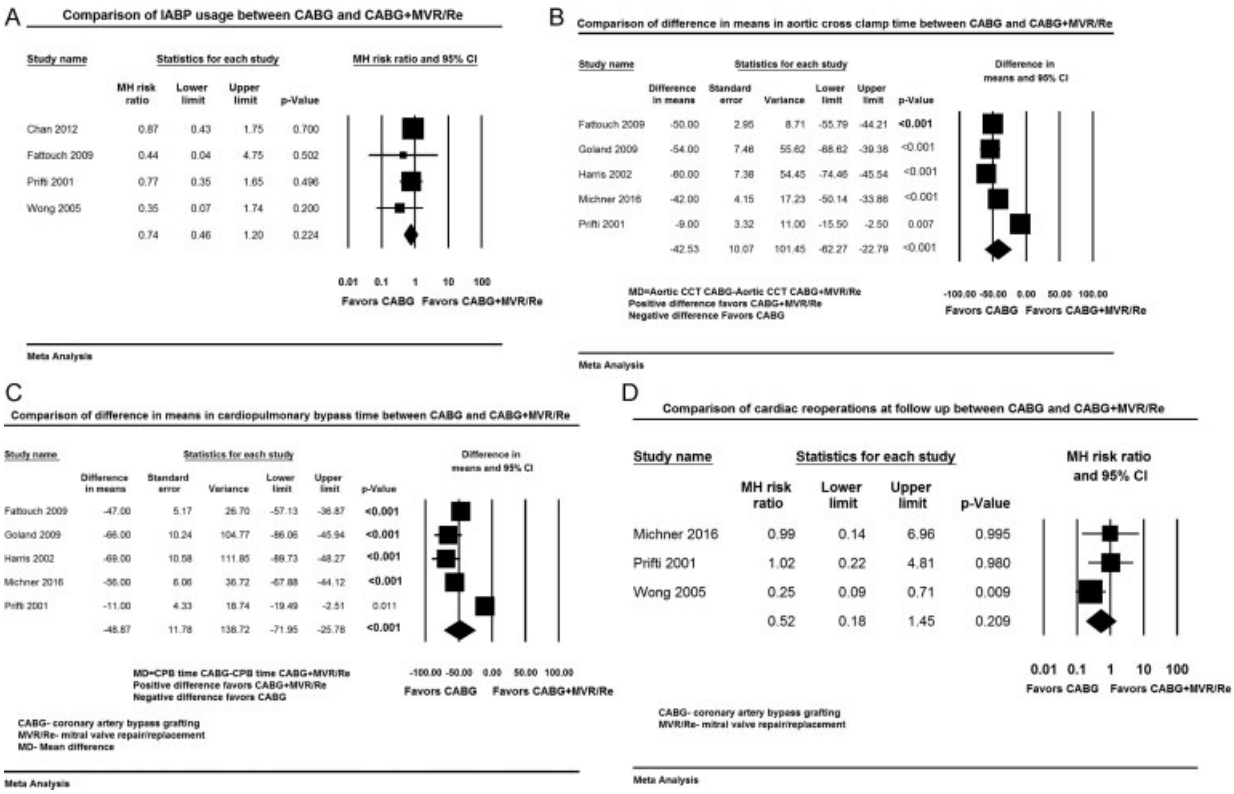

Fig. 4 (**A**) Comparison of intra-aortic balloon pump usage between CABG and CABG + MVR/Re; (**B**) Mean difference in aortic cross-clamp time between CABG and CABG + MVR/Re; (**C**) difference in means in cardiopulmonary bypass time between CABG and CABG + MVR/Re; and (**D**) comparison of cardiac reoperations at follow-up between CABG and CABG + MVR/Re. CABG, coronary artery bypass grafting; MVR/Re, mitral valve replacement/repair.

those with large areas of infarct without viable myocardium, who would theoretically not be expected to benefit from revascularization alone.

Note

All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. We would like to thank Dr. Aryan Mooss for his expert opinion. We would like to acknowledge Baskaran Krishnamoorthy for reviewing the article for English language, spelling and grammar corrections.

References

1 Borger MA, Alam A, Murphy PM, Doenst T, David TE. Chronic ischemic mitral regurgitation: repair, replace or rethink? Ann Thorac Surg 2006;81(3):1153–1161
2 Robbins JD, Maniar PB, Cotts W, Parker MA, Bonow RO, Gheorghiade M. Prevalence and severity of mitral regurgitation in chronic systolic heart failure. Am J Cardiol 2003;91(3): 360–362
3 Kumanohoso T, Otsuji Y, Yoshifuku S, et al. Mechanism of higher incidence of ischemic mitral regurgitation in patients with inferior myocardial infarction: quantitative analysis of left ventricular and mitral valve geometry in 103 patients with prior myocardial infarction. J Thorac Cardiovasc Surg 2003;125(1):135–143
4 Otto CM. Timing of surgery in mitral regurgitation. Heart 2003; 89(1):100–105
5 Anantha Narayanan M, Mahfood Haddad T, Kalil AC, et al. Early versus late surgical intervention or medical management for infective endocarditis: a systematic review and meta-analysis. Heart 2016;102(12):950–957
6 Tolis GA Jr, Korkolis DP, Kopf GS, Elefteriades JA. Revascularization alone (without mitral valve repair) suffices in patients with advanced ischemic cardiomyopathy and mild-to-moderate mitral regurgitation. Ann Thorac Surg 2002;74(5):1476–1480, discussion 1480–1481
7 Kolh P, Windecker S, Alfonso F, et al; European Society of Cardiology Committee for Practice Guidelines; EACTS Clinical Guidelines Committee; Task Force on Myocardial Revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery; European Association of Percutaneous Cardiovascular Interventions. 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur J Cardiothorac Surg 2014;46(4):517–592
8 Nishimura RA, Otto CM, Bonow RO, et al; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. Circulation 2014;129(23):e521–e643
9 Herlitz J, Brandrup-Wognsen G, Caidahl K, et al. Mortality and morbidity among patients who undergo combined valve and coronary artery bypass surgery: early and late results. Eur J Cardiothorac Surg 1997;12(6):836–846

10 Lee R, Li S, Rankin JS, et al; Society of Thoracic Surgeons Adult Cardiac Surgical Database. Fifteen-year outcome trends for valve surgery in North America. Ann Thorac Surg 2011;91(3):677–684, discussion 684
11 Schroder JN, Williams ML, Hata JA, et al. Impact of mitral valve regurgitation evaluated by intraoperative transesophageal echocardiography on long-term outcomes after coronary artery bypass grafting. Circulation 2005;112(9, Suppl):I293–I298
12 Christenson JT, Simonet F, Bloch A, Maurice J, Velebit V, Schmuziger M. Should a mild to moderate ischemic mitral valve regurgitation in patients with poor left ventricular function be repaired or not? J Heart Valve Dis 1995;4(5):484–488, discussion 488–489
13 Penicka M, Linkova H, Lang O, et al. Predictors of improvement of unrepaired moderate ischemic mitral regurgitation in patients undergoing elective isolated coronary artery bypass graft surgery. Circulation 2009;120(15):1474–1481
14 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535
15 Zoghbi WA, Enriquez-Sarano M, Foster E, et al; American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16(7):777–802
16 Chan KM, Punjabi PP, Flather M, et al; RIME Investigators. 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. Circulation 2012;126(21):2502–2510
17 Fattouch K, Guccione F, Sampognaro R, et al. POINT: efficacy of adding mitral valve restrictive annuloplasty to coronary artery bypass grafting in patients with moderate ischemic mitral valve regurgitation: a randomized trial. J Thorac Cardiovasc Surg 2009;138(2):278–285
18 Harris KM, Sundt TM III, Aeppli D, Sharma R, Barzilai B. Can late survival of patients with moderate ischemic mitral regurgitation be impacted by intervention on the valve? Ann Thorac Surg 2002; 74(5):1468–1475
19 Michler RE, Smith PK, Parides MK, et al; CTSN. Two-year outcomes of surgical treatment of moderate ischemic mitral regurgitation. N Engl J Med 2016;374(20):1932–1941
20 Wong DR, Agnihotri AK, Hung JW, et al. Long-term survival after surgical revascularization for moderate ischemic mitral regurgitation. Ann Thorac Surg 2005;80(2):570–577
21 Prifti E, Bonacchi M, Frati G, et al. Should mild-to-moderate and moderate ischemic mitral regurgitation be corrected in patients with impaired left ventricular function undergoing simultaneous coronary revascularization? J Card Surg 2001;16(6):473–483
22 Jeong DS, Lee HY, Kim WS, Sung K, Park PW, Lee YT. Off pump coronary artery bypass versus mitral annuloplasty in moderate ischemic mitral regurgitation. Ann Thorac Cardiovasc Surg 2012; 18(4):322–330
23 Bouchard D, Jensen H, Carrier M, et al. Effect of systematic downsizing rigid ring annuloplasty in patients with moderate ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2014;147(5): 1471–1477
24 Goland S, Czer LS, Siegel RJ, et al. Coronary revascularization alone or with mitral valve repair: outcomes in patients with moderate ischemic mitral regurgitation. Tex Heart Inst J 2009;36(5): 416–424
25 Diken AI, Altıntaş G, Yalçınkaya A, Lafçı G, Hanedan O, Cağlı K. Surgical strategy for moderate ischemic mitral valve regurgitation: repair or ignore? Heart Surg Forum 2014;17(4):E201–E205
26 Di Donato M, Frigiola A, Menicanti L, et al. Moderate ischemic mitral regurgitation and coronary artery bypass surgery: effect of mitral repair on clinical outcome. J Heart Valve Dis 2003;12(3): 272–279
27 Smith PK, Puskas JD, Ascheim DD, et al; Cardiothoracic Surgical Trials Network Investigators. Surgical treatment of moderate ischemic mitral regurgitation. N Engl J Med 2014;371(23): 2178–2188
28 Sundt TM. Surgery for ischemic mitral regurgitation. N Engl J Med 2014;371(23):2228–2229
29 Otsuji Y, Handschumacher MD, Schwammenthal E, et al. Insights from three-dimensional echocardiography into the mechanism of functional mitral regurgitation: direct in vivo demonstration of altered leaflet tethering geometry. Circulation 1997;96(6): 1999–2008
30 Acker MA. Should moderate or greater mitral regurgitation be repaired in all patients with LVEF <30%? Mitral valve repair in patients with advanced heart failure and severe functional mitral insufficiency reverses left ventricular remodeling and improves symptoms. Circ Heart Fail 2008;1(4):281–284
31 Aronson D, Goldsher N, Zukermann R, et al. Ischemic mitral regurgitation and risk of heart failure after myocardial infarction. Arch Intern Med 2006;166(21):2362–2368
32 Acker MA, Parides MK, Perrault LP, et al; CTSN. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. N Engl J Med 2014;370(1):23–32
33 O'Gara PT. Randomized trials in moderate ischemic mitral regurgitation: many questions, limited answers. Circulation 2012; 126(21):2452–2455
34 Braunwald E. Heart Disease: A Textbook of Cardiovascular Medicine. Philadelphia, PA: Saunders; 1980:1943–1980
35 Roshanali F, Mandegar MH, Yousefnia MA, Alaeddini F, Wann S. Low-dose dobutamine stress echocardiography to predict reversibility of mitral regurgitation with CABG. Echocardiography 2006; 23(1):31–37
36 Roshanali F, Shoar S, Shoar N, Naderan M, Alaeddini F, Mandegar MH. Low-dose dobutamine stress echocardiography cannot predict mitral regurgitation reversibility after coronary artery bypass grafting. J Thorac Cardiovasc Surg 2014;148(4):1323–1327