

1 **Title:**

2 **Should the mitral valve be repaired for moderate ischemic mitral**
3 **regurgitation at the time of revascularization surgery?**

4 **A Systematic Review and Meta-Analysis**

5

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24

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37

38 **Glossary of abbreviations**

39	CABG	Coronary artery bypass graft
40	CPB	Cardiopulmonary bypass
41	COPD	Chronic obstructive pulmonary disease
42	IMR	Ischemic mitral regurgitation
43	LV	Left ventricle
44	LVEF	Left ventricular ejection fraction
45	LVEDD	Left ventricular end diastolic dimension
46	LVESD	Left ventricular end systolic dimension
47	LVESV	Left ventricular end systolic volume
48	MR	Mitral regurgitation
49	MVr	Mitral valve repair
50	NYHA	New York Heart Association
51	RCT	Randomized controlled trial
52	WMD	Weighted mean difference

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59 **Abstract**

60 Ischemic mitral regurgitation (IMR) is associated with increased mortality and
61 recurrent congestive heart failure following Coronary Artery Bypass Graft (CABG)
62 surgery. Although evidence shows that mitral surgery should be undertaken in severe
63 MR during CABG, the treatment of moderate IMR remains controversial. We
64 conducted a meta-analysis to determine the outcomes of CABG alone and combined
65 with mitral valve repair (MVr) in moderate IMR.

66 A literature search was conducted through Pubmed, Ovid and Embase, revealing 643
67 articles. Eleven studies (seven observational studies and four randomized controlled
68 trials) were ultimately included for analysis. A total of 1,406 patients were included
69 (CABG alone=864 and CABG plus MVr=542).

70

71 There was no difference in operative mortality (OR 1.56, 95% CI 0.92 - 2.71) or long-
72 term survival at 1 year or 5 years (HR 0.98, 95% CI 0.71-1.35, p=0.49) between the
73 two groups, and little evidence of heterogeneity was found in the studies ($I^2 = 0.0$, $p =$
74 0.562). There was a significantly greater improvement in MR grade (WMD -1.15,
75 95% CI -1.67 – -.064, $p < 0.001$) and left ventricular systolic diameter (WMD -3.02,
76 95% CI -4.85 – -1.18, $p = 0.001$) following CABG and MVr compared to CABG
77 alone. No difference in post-operative functional class or ejection fraction was found.

78

79 Our results show that in the context of moderate IMR, adding MVr to
80 revascularization reduces MR grade on follow-up echocardiography and promotes
81 ventricular remodeling, with no improvement in long-term survival or functional
82 class.

83

84

85 **Introduction**

86 Following a myocardial infarction, as many as half of patients develop mitral
87 regurgitation^{1,2}. Adverse myocardial remodelling leads to annular dilatation, papillary
88 muscle displacement and poor leaflet coaptation, despite structurally normal mitral
89 valve leaflets³⁻⁵.

90

91 In the context of severe ischemic mitral regurgitation (MR), a mitral valve
92 procedure at the time of Coronary Artery Bypass Graft (CABG) surgery is
93 necessary^{6,7}. However, the treatment for moderate MR in the context of
94 ischemic heart disease is less clear-cut. The latest American Association for
95 Thoracic Surgery (AATS) guidelines suggest that mitral repair with an
96 undersized complete rigid ring annuloplasty “may be considered” during
97 coronary artery bypass graft (CABG) surgery, but not necessarily “preferred”
98 over revascularization alone⁸. The benefits of mitral valve surgery for moderate
99 ischemic MR during CABG have not been clearly established.

100

101 Some studies suggest that CABG alone can treat moderate MR and that there
102 is no need to intervene⁹. The important considerations when comparing
103 CABG alone with CABG plus mitral valve repair (MVr) are to assess whether
104 there is a change in operative mortality or long-term survival and whether
105 MVr can reduce rates of MR recurrence more than CABG alone.

106

107 Our aim was to review the current literature on the subject of moderate IMR and
108 compare CABG alone with MVr plus CABG via a meta analysis to analyze the
109 outcomes of the two surgical options.

110

111 **Materials and methods**

112 *Search Methodology*

113 We conducted a literature search of PubMed, Medline and Ovid using the terms
114 “ischemic” + “mitral regurgitation” or “incompetence” and “repair” or “plasty” and
115 “coronary artery bypass” or “revascularization”. Only articles written in English were
116 included.

117

118 *Inclusion criteria*

119 Both retrospective and prospective studies were included, without the exception of
120 randomized control trials (RCT).

121

122 A standardized checklist was devised amongst the authors to analyze each of the
123 papers for potential inclusion. The studies were then distributed amongst six of the
124 authors and reviewed for similarity in design, methods, patient characteristics and
125 outcomes measured according to the checklist. Studies comparing two distinct groups
126 (CABG alone and MVr plus CABG) were included. Many studies from the original
127 search which also included degenerative MR in their patient population were
128 manually removed from the study pool.

129

130 Only studies that included patients exclusively with moderate MR were included. The
131 definition of moderate MR followed guidelines from the American College of

132 Echocardiography and American Heart Association^{10,11}. In studies where different
133 degrees of MR were included in the study population, papers were checked amongst
134 the authors to see if patients with moderate IMR could be isolated for analysis.

135

136 *Surgical technique*

137 Studies that merely reported outcomes from cohorts of patients receiving a variety of
138 combinations of surgery, but did not conduct statistical comparisons between the
139 short and long-term outcomes of the two modes of therapy in our study question, were
140 excluded. Other studies were scrutinized and included only if distinct MVr plus
141 CABG and CABG alone groups were separately compared within the statistical
142 analysis.

143

144 Subsequent papers were scrutinized for the type of mitral surgery performed. The
145 studies included were consistent in using undersized ring annuloplasty techniques for
146 most MVr cases although this was not a strict inclusion criterion. A few studies also
147 included MV replacement as the method of MV intervention in the ‘MVr plus CABG
148 group’, which was not an exclusion criterion, so long as MVr remained a significant
149 operative technique.

150

151 *Outcomes*

152 Primary outcome measures were operative mortality, which included in-hospital
153 mortality or mortality within 30 days, post operative MR grade and post operative
154 New York Heart Association (NYHA) class. Papers were also analyzed for long-term
155 survival, which was set at 5 years. Secondary outcome measures were left ventricular

156 ejection fraction (LVEF), LV dimensions, including left ventricular end
157 systolic/diastolic diameters (LVESD/LVEDD) and volumes (LVESV/LVEDV).

158

159 *Statistical Methods*

160 The odds ratio was used as the summary statistic for operative mortality. A random
161 effects meta-analysis¹² was used to find an overall odds ratio comparing MVr plus
162 CABG with CABG alone for 30-day operative mortality due to the expected
163 heterogeneity between the studies.

164

165 Similarly, a random effects meta-analysis was used to find an estimate of the overall
166 hazard ratio for long-term mortality comparing MVr plus CABG with CABG alone
167 patients. Where studies did not present the hazard ratio but gave a Kaplan Meier curve
168 and numbers at risk for overall mortality, the method by Parmar and the spread sheet
169 applying this method were used to give an estimate of and the standard error of the
170 log hazard ratio¹³.

171

172 To assess for differences in MR grade, NYHA class, LVEF and other LV dimensions,
173 standardized difference in the means analysis was conducted with 95% confidence
174 intervals.

175

176 Heterogeneity was investigated using Cochrane's test and the I^2 statistic¹⁴. Funnel
177 plots were generated to assess for publication bias. Peter's test for small studies was
178 conducted to rule out large effects from potentially non-significant studies¹⁵. Meta
179 regression analysis was used to investigate the effects of covariates, especially
180 variations in patient characteristics.

181

182 All the reporting methods applied followed guidance from the prescribed
183 recommended items in systematic reviews meta-analyses (PRISMA) statement¹⁶.
184 Statistical analysis was conducted using the Stata 13.0 software (Stata Corp., College
185 Station, TX, US).

186

187 **Results**

188 Initially, 643 studies were identified containing the search terms. The article titles
189 and abstracts were initially screened for suitability, after which only sixty-nine
190 articles remained for full text review (Figure 1). From these articles, eighteen were
191 excluded for including patients with severe MR. An additional twenty-five were
192 excluded for a lack of direct comparison between distinct MVr plus CABG and
193 CABG alone treatment groups. Finally, fifteen articles were excluded due to
194 inconsistencies in study design or reporting.

195

196 Eleven studies (Table 1) were eventually included which fulfilled the criteria, seven
197 of which were retrospective and the remaining four being randomized prospective
198 studies. This included a total of 1,406 patients: 542 (38.5%) MVr plus CABG cases
199 and 864 (61.5%) CABG alone cases. Funnel plot analysis and Peter's test revealed
200 little evidence of publication bias (figure 2).

201

202 Pre-operative data for co-variates, which was available for both MVr plus CABG and
203 CABG alone groups, was well reported in most studies (Table 1). Out of the eleven
204 studies, age, gender, diabetes and pre-operative LVEF was reported in ten. Previous
205 myocardial infarction (MI) was reported in nine, renal failure in six, chronic

206 obstructive pulmonary disease (COPD) in six and pre-operative MR grade in eight.
207 With regards to NYHA class, six studies reported a mean NYHA class and five
208 studies reported the proportion of patients with NYHA of grades III/IV.

209

210 All the studies included patients with moderate MR exclusively, the majority of which
211 were measured by transthoracic or transoesophageal echocardiography, with two
212 reporting a mixture of echocardiography and ventriculography as assessment
213 methods^{17,18}. Two of the studies did not report the timing or method of valvular
214 assessment, however the remaining nine are clear that MR grading was performed on
215 studies in the pre-operative non-anaesthetized resting patient. Chan et al¹⁹ was the
216 only study to measure MR grade at peak exercise as well as at rest.

217

218 *Operative characteristics*

219 All studies reported the use of a standard median sternotomy and a combination of
220 left internal mammary artery to left anterior descending artery anastomosis and other
221 vein and arterial revascularization strategies. Although not all the studies reported the
222 exact methodology of treatment in the CABG alone group, the majority of patients in
223 the CABG alone group were managed with the use of CPB. All patients in the MVr
224 plus CABG group received mitral valve intervention in the same operation. All
225 studies that reported their operative times (7/11), found a significantly higher cross-
226 clamp and CPB time in the MVr plus CABG compared to the CABG alone group.

227

228 With regards to operative technique (Table 2), eight out of eleven studies exclusively
229 used ring annuloplasty in all patients in the MVr plus CABG group. Only two of the
230 studies included a small number of patients receiving a mitral valve replacement,

231 amounting to 12% in Prifti et al²⁰ and 14% in Harris et al¹⁸. Harris et al reported that
232 3 of the patients receiving a replacement (60%) received a mechanical prosthesis
233 whereas Prifti and colleagues did not report the rate of mechanical valve use.

234

235 There was a relative heterogeneity in the type of ring annuloplasty used amongst the
236 studies (Table 2) but the majority used undersized annuloplasty techniques. Four
237 studies reported using repair techniques other than ring annuloplasty^{17,20-22}, two of
238 which did not report the rate and types of other repair techniques used^{17,22}. One study
239 (Di Donato²¹) reported using suture annuloplasty in 50% of MVr plus CABG patients.
240 Prifti and colleagues²⁰ used a variety of repair techniques in their 43 mitral repair
241 patients, including leaflet resection (58%), chordal transfer/shortening (14%) and
242 papillary muscle shortening (7%).

243

244 *Operative mortality*

245 Nine studies reported operative mortality (four of which RCTs) with very little
246 heterogeneity between them. No difference was found between the two treatment
247 groups when comparing the four RCTs (OR 0.89, 95% CI 0.28 – 2.81, p=0.84) and
248 five retrospective studies (OR 1.82, 95% CI 0.93 – 3.54, p=0.36) separately (figure
249 3A). Furthermore, when combining all ten studies via a random-effects meta-analysis,
250 no difference in operative mortality was detected (OR 1.56, 95% CI 0.90 – 2.71,
251 p=0.58).

252

253 *Mid-term and long-term survival*

254 Out of the eleven studies, five quoted data for one-year survival, two of which were
255 RCTs, and five studies (one RCT) had survival data for up to five years. Meta-

256 analyses found no difference between MVr plus CABG and CABG alone for one-year
257 survival (HR 1.26, 95% CI 0.55–2.92, p=0.52) (figure 3B) or five-year survival (HR
258 0.98, 95% CI 0.71–1.35, p=0.88).

259

260 *NYHA class*

261 Out of all the studies, only Golland and colleagues provided data on changes in the
262 mean NYHA class. From the other studies, only four (Diken, Di Donato, Fattouch and
263 Hamouda^{21–24}) quoted mean post-operative NYHA class. Since analysis of the pre-
264 operative covariates showed that the studies were comparable, analysis of post-
265 operative NYHA class provides useful outcome for comparison between the two
266 treatment arms.

267

268 Another five papers^{17–19,25,26} quoted the post-operative percentage of patients in
269 NYHA classes III and IV. No difference was detected when analysing the RCTs (OR
270 0.71, 95% CI 0.32 – 1.56, p=0.39) and observational studies (2.13, 95% CI 0.92 –
271 4.95, p=0.08) separately, or when combining them together via a random-effects
272 meta-analysis (OR 1.20, 95% CI 0.57 – 2.51, p=0.64) (figure 4C).

273

274 *Echocardiographic data*

275 Four studies reported the mean post-operative MR grade^{21–23,27} and seven studies
276 reported mean LVEF^{20–26} across the MVr plus CABG and CABG alone groups.
277 Similar to the NYHA class analysis, only Golland and colleagues calculated the within
278 subject change between pre- and post-operative MR grade and LVEF values and
279 provided an overall mean change.

280

281 When analyzing mean post op MR grade across four studies, there was a significantly
282 lower MR grade in the MVr plus CABG group compared to CABG alone (weighted
283 mean difference (WMD) -1.15, 95% CI -1.67 – -.064, $p < 0.001$) (figure 4A).

284 Although significant heterogeneity was detected amongst the studies ($I^2 = 90\%$), all
285 four papers analyzed found significantly larger improvements in MR grade favouring
286 the MVr plus CABG group in their respective studies.

287

288 There was no significant difference in LVEF between the two treatment groups,
289 which was consistent when analysing the three RCTs^{23,26,28} (WMD 0.24, 95% CI -
290 3.22 – 3.69, $p = 0.89$) and four retrospective studies^{20–22,24} (WMD 2.12, 95% CI -0.46 –
291 4.70, $p = 0.11$) separately, and when combining them through a random-effects meta-
292 analysis (WMD 1.42, 95% CI -0.54 – 3.39, $p = 0.155$) (figure 4B).

293

294 Left ventricular dimensions were reported in a total of eight studies. Six studies^{20–}
295 ^{24,26} (two RCTs) reported systolic and diastolic diameters. A more significant
296 improvement in LVESD was noticed in the MVr plus CABG group compared to
297 CABG only (WMD -3.02, 95% CI -4.85 – -1.18, $p = 0.001$), although moderate
298 heterogeneity was present in the analysis ($I^2 = 67\%$) (figure 5A).

299

300 Five studies (two RCTs) reported post-operative LV systolic volumes^{19,21,24,26,28}.

301 Only Chan and Smith reported volumes as indices of body surface area. Amongst
302 these five studies, meta-analysis found no difference between MVr plus CABG and
303 CABG only for LVESV (WMD -4.68, 95% CI -12.41 – 3.05, $p = 0.24$) (figure 5B).

304

305 The analysis of LVEDD found no significant difference in the combined analysis of
306 six studies (WMD -0.70, 95% CI -2.87 – 1.47 p=0.53), although a significantly
307 smaller LVEDD was found in the MVr plus CABG group when analysing the RCTs
308 only (WMD -3.50, 95% CI -6.14 – -0.86, p=0.009) (figure 5C).

309

310 **Discussion**

311 Compared to previous studies, our present analysis shows that the addition of mitral
312 surgery to CABG not only improves residual MR at follow-up, but can also promote
313 reverse LV remodelling. Echocardiography-based studies have found persisting MR
314 after CABG alone in moderate IMR^{29,30}. Although reverse left ventricular remodelling
315 does take place after CABG alone and can reduce MR at follow up, it appears that in
316 certain cases persisting MR can be significant. This may reflect the complex
317 pathology surrounding IMR, and suggest that reverse left ventricular remodelling
318 alone without surgical correction of the valve is not sufficient to reverse MR.

319

320 The type of techniques used to repair ischemic MR differ from those used to repair
321 myxomatous valves. The region of infarction and subsequent scar tissue formation
322 can cause mitral valve leaflets to tether in an asymmetrical fashion³¹. Repair
323 techniques that use only down-sized annuloplasty rings may not achieve a more
324 durable repair. Studies have shown that adding a subvalvular repair in addition to an
325 annuloplasty ring results in better freedom from recurrent MR and improved long-
326 term survival in patients with moderate-severe ischemic MR³².

327

328 Similar to the data reported in most studies, our results show no significant difference
329 between operative mortality and long-term survival in both surgical groups. Indeed,

330 none of the nine studies which reported operative mortality in our meta-analysis
331 found a significant difference between the two treatment arms. The latest results from
332 the CTSnet trial also found no difference in mortality between the two groups,
333 although higher rates of neurologic events and supraventricular arrhythmias in the
334 MVr plus CABG group were reported³³.

335

336 The meta-analysis by Benedetto et al³⁴, published in 2009, addressed a very similar
337 study question to ours, comparing CABG with combined CABG and MVr amongst
338 nine different studies. They too found an improved MR grade and NYHA class in the
339 combined surgery group. However, almost half the studies exclusively contained
340 patients with severe MR. A more recent meta-analysis by Kopjar and colleagues³⁵
341 compared CABG alone and MVr plus CABG in moderate IMR across nine studies.
342 The study found a reduction in recurrent MR with mitral intervention, but no survival
343 or functional class improvement. More recently published analyses in the subject
344 field have been more heterogenic in their inclusion of moderate and severe MR
345 pathologies as well as repair and replacement techniques in their methodologies^{36,37}.

346

347 The CTSnet trial by Smith et al²⁵ conducted the largest trial to date (N=150 vs 151)
348 and found no added benefit in adding MVr to CABG when analyzing survival or
349 LVESV index. In the publication of their 2 year follow up data³³, these conclusions
350 were confirmed, although residual MR at follow up was significantly lower than the
351 MVr plus CABG group. These findings reflected in the recently published update to
352 the AATS guidelines where it is stated that repair of the ischemic valve in moderate
353 IMR may be considered⁸. Echocardiographic data from our study found more

354 significant reverse left ventricular remodelling in the MVr plus CABG group in end
355 systolic dimensions. Our results may add to the findings of the trial in suggesting that
356 a stronger argument for mitral intervention in moderate IMR exists.

357

358 Our findings agree with the Randomized Ischaemic Mitral Evaluation (RIME) trial by
359 Chan et al³⁸ which found a significantly reduced LVESVI when adding MVr to
360 CABG compared to CABG alone. The trial also measured peak oxygen consumption,
361 plasma B-type natriuretic peptide and regurgitant volume, and found improvements in
362 all these outcomes following MVr plus CABG compared to CABG alone, as well as
363 NYHA class. Similarly, Fattouch et al²³ found significant improvements in LV
364 reverse remodelling, as well as MR grade and NYHA class in the combined MVr and
365 CABG group compared to CABG alone.

366

367

368 The trial by Bouchard et al²⁶ was significantly smaller (N = 31), and also found no
369 differences between the two groups when analyzing residual MR grade, NYHA class,
370 operative mortality and LV dimensions, although the MR grade was transiently better
371 at 3 months in the MVr plus CABG group and remained unchanged at 12 months.

372

373 *Limitations*

374 As with all meta-analyses, the challenge remains to control for differences in study
375 designs. Differences in follow up time can confound the results. Only 5 studies
376 included were consistent in following patients at exactly 12 months^{21,23,25,27,38}, with
377 the remainder of the studies following patients between a range of 6 – 104 months
378 post operatively. The meta analyses of echocardiographic outcomes carried at least

379 moderate heterogeneity, in particular LV dimensions, which may reflect the use of
380 non-indexed parameters in the retrospective studies. Another cause of heterogeneity
381 may be variation in the definition of moderate MR amongst the studies, including
382 different ranges for vena contracta diameter and regurgitant jet area, despite clear
383 consensus guidelines in this field ¹⁰. This emphasizes the need for future studies to
384 incorporate a standardized method for grading moderate MR.

385

386 Whether the improvement in echocardiographic parameters translates to an
387 improvement in patient's symptomatology remains debatable. All of the studies
388 analyzed lack comprehensive quality of life assessments in their post-operative
389 assessment to demonstrate the efficacy of adding MV repair to CABG.

390

391 This is also compounded by the inconsistency amongst the studies in the reporting of
392 functional class change. In most studies these were reported as isolated post-operative
393 means, and statistical tests were carried out to assess differences between these
394 means. Only one study reported the NYHA and residual MR outcomes as a mean of
395 the change between pre- and post-operative values calculated per patient¹⁷.

396

397 It is clear that both methods of surgery improve the NYHA class of patients, and in
398 many studies the change in NYHA class between pre and post-operative assessment
399 was found to be significant in both treatment arms, which emphasizes the need of
400 more elaborate assessment metrics to identify potential differences.

401

402

403

404 *Conclusions*

405 We conclude that adding MVr to CABG for moderate IMR results in improved long-
406 term echocardiographic parameters but studies have yet to demonstrate an impact on
407 functional class and improved quality of life. The evidence does remain strong that
408 CABG alone for moderate IMR can reduce MR grade and promote reverse LV
409 remodelling. Larger studies with more standardized and controlled composite end
410 points are required to better define the role of MVr in patients with moderate ischemic
411 MR undergoing CABG surgery.

412

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