Review

Mitral Valve Repair or Replacement for Ischaemic Mitral Regurgitation: A Systematic Review

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A literature review was undertaken according to Cochrane guidelines to identify whether mitral valve repair (MV-Repair) or replacement (MV-Replacement) is more effective in patients with moderate to severe ischaemic mitral regurgitation. The literature suggests MV-Repair may have improved 30-day mortality and long-term survival. All 12 studies identified, however, were non-randomised, retrospective, and at significant risk of bias due to heterogeneous surgical techniques and mismatched patient characteristics. Data describing the need for reoperation were not sufficiently well reported to analyse. Functional outcomes and health-related quality of life were not reported. In conclusion, high-quality randomised comparison of MV-Repair and MV-Replacement is urgently needed.

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Keywords. Mitral valve; Mitral valve repair; Mitral valve replacement; Statistics; Meta analysis

Introduction

Chronic ischaemic mitral regurgitation (IMR) occurs in up to 40% of patients following myocardial infarction [1], and is a major risk factor for adverse outcomes such as impaired ventricular function or death [2]. The characteristic echocardiographic and macroscopic appearance of IMR is a result of complex changes in the geometry and function of the left ventricle and annulus. This is usually caused by myocardial infarction in the distribution of the circumflex or right coronary artery, producing a variable combination of annular dilatation (Carpentier type I dysfunction) and systolic leaflet restriction (Carpentier type IIIb dysfunction) [3].

Few surgeons would advocate either mitral valve (MV) repair or replacement for mild IMR because coronary artery bypass graft (CABG) alone often results in satisfactory resolution of the mitral regurgitation. Outcomes following CABG alone in patients with mild MVR are only marginally worse than in patients with no mitral regurgitation [4] and it has been estimated that only about 3% of patients will subsequently require admission for congestive heart failure [5].

The difficulty arises in determining the management of patients with moderate or severe IMR as CABG alone does not cure the valve insufficiency in this group. Moderate to severe IMR is associated with significantly reduced survival following CABG [6,7] and about half of patients with moderate IMR undergoing CABG will require future admission for congestive heart failure [5]. Many surgical groups involved in the study of IMR have advocated doing a randomised trial of CABG alone versus CABG with mitral valve intervention in patients with at least moderate IMR [6–8]. One recent randomised study has already reported significant improvement in terms of symptoms and reversed remodelling at a mean follow-up of three years following mitral valve repair and CABG compared to CABG alone [9]. Although an improvement in survival has only been demonstrated in case series [10,11], several other randomised trials are currently recruiting patients (NCT00838786, NCT00806988, NCT00443365, NCT00613548, NCT00919256).

The choice of surgical intervention to treat patients with moderate to severe IMR remains problematic as there is no consensus in the literature about whether MV repair (MV-Repair) or MV replacement (MV-Replacement) is more effective. Consequently, we aimed to review the findings of previous studies which have compared these techniques. Our review aims to estimate whether there are

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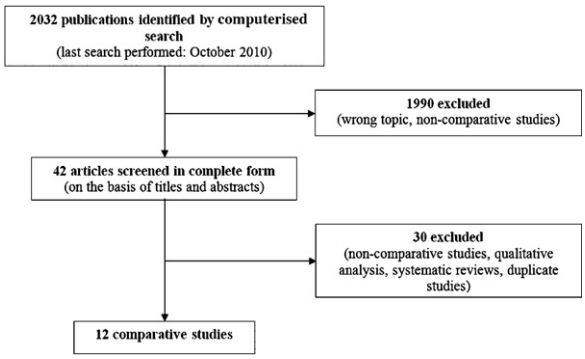

Figure 1. *Summary of the results of literature search*

differences between patients with IMR undergoing MV-Repair or MV-Replacement with respect to (a) operative mortality, (b) need for reoperation, (c) survival, (d) function and (e) health-related quality of life (HRQoL).

Materials and Methods

Literature Search

A literature search was performed in Pubmed, Embase, Ovid and Google Scholar for studies published between 1965 and 2010 without language restriction. The following Medical Subject Headings (MeSH) were used: mitral valve*, replantation*, heart valve prosthesis*, heart valve prosthesis implantation*, ischemia*, myocardial ischemia*, and mitral valve insufficiency*. Complementary searches were also performed with the following free text: "mitral valve repair", "mitral valve replacement", and "mitral regurgitation". The related articles function was used to broaden the search. The Cochrane library was also searched using the above terms. All the review articles whose subject was mitral valve replacement or repair, as well as their reference lists were also assessed (Fig. 1).

Outcomes of Interest

The outcomes defined in the protocol were early (30-day) mortality, re-operation for any reason, survival (time of censoring or time to death from any cause), functional outcomes [12] and HRQoL.

Inclusion and Exclusion Criteria

Any comparative study reporting an effect size for an outcome of interest, or data that allowed an effect size to be calculated, for patients with IMR treated with MV-Repair versus MV-Replacement was eligible. When there were several reports of the same study, data from the most recent report was included for each outcome and all papers were used gather information on patient and study characteristics. No language restrictions were applied. Review articles were used only to identify original studies. Studies in which it was not possible to extract the outcome of interest were excluded.

Data Extraction

Three reviewers (SS, MM and CR) independently extracted study characteristics and outcomes according to a pre-defined protocol [13]. For binary outcomes such as 30-day mortality and reoperation rate, numbers of events and denominators were extracted. Extraction of survival data was performed using previously published methods [14]. The available methods for extracting survival data from observational studies have different limitations [14]. It was not possible to use the same method for all studies because of variation in the ways in which survival data were reported. We used the first, more robust, methods described by Tierney et al. in preference to later methods [14].

Assessing the Risk of Bias to Included Studies

When reviewing observational studies and poorly designed randomised trials, it is important to consider the risk that the reported effect size estimates are confounded. Consequently, several confounding factors may need to be considered when comparing MV-Replacement and MV-Repair techniques. These factors relate to the mitral valve disease itself; the myocardium and its arteries; patient demographics, cardiovascular and general health; and the skill and experience of the individual surgeon and institution in performing MV-Replacement and MV-Repair.

There are three main ways in which these confounding factors can be controlled in observational studies. Confounding factors can be controlled by the study design, by matching the groups being compared on key factors or by restricting eligibility to patients with similar characteristics. Secondly, multivariable regression modelling can be used to control for confounding factors in the analyses. Finally, propensity analysis (a variation on multivariable regression modelling) can be used [15]. All of these methods have limitations and it should be assumed that adjusted effect estimates are still more or less confounded [16].

Included studies that reported survival data were classified according to whether or not they reported effect sizes (hazard ratios) adjusted for any confounding factor (adjusted versus unadjusted studies).

Other bias domains were not assessed because studies were invariant on these domains [17]. Given the nature of the intervention blinding would be difficult (all studies at risk of performance and detection) but outcomes were considered unlikely to be at risk of detection bias. Retrospective cannot distinguish the incipient cohort and the cohort available for analysis. All retrospective studies should also be considered potentially at risk of selective outcome reporting.

Publication bias was not formally considered because it is not clear how to interpret the methods developed for RCTs when applied to non-randomised studies. If a retrospective analysis has not been approved by a regulatory body, for example an Institutional Review Board (often not required for analyses of fully anonymised data), or prospectively registered, it may be impossible to identify that the analysis ever took place [18].

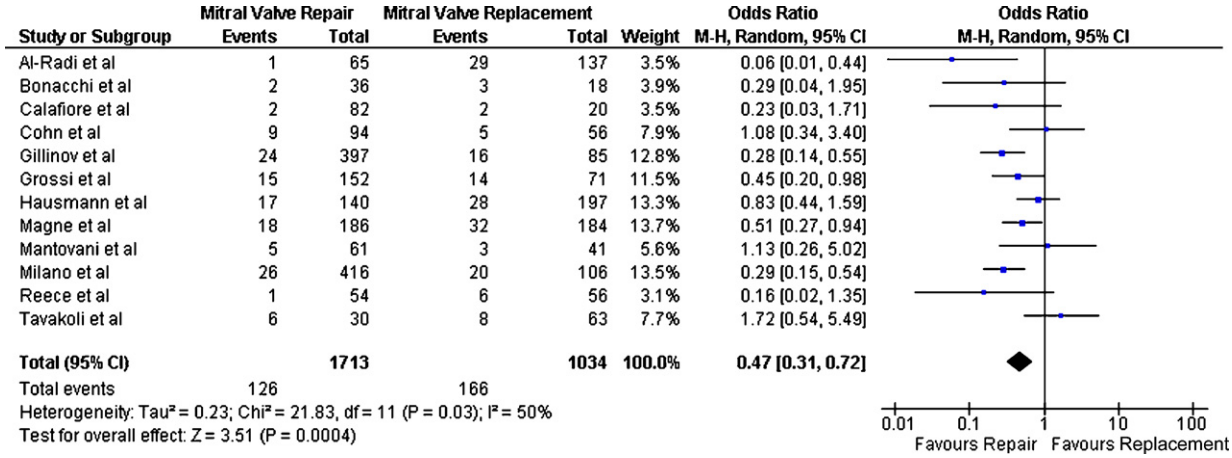

Figure 2. *Forest plot comparing 30-day mortality after MV-Repair or Replacement.*

Statistical Analysis

The odds ratio (OR) was used as the summary statistic for binary variables and the hazard ratio (HR) for survival data. Survival data were aggregated at maximum follow up and constant hazards were assumed. An OR or HR of <1 favoured MV-Repair. Confidence intervals for individual studies are displayed in the forest plots but should be interpreted with caution [19]. Heterogeneity of treatment effects between studies was assessed using the I^2 statistic. This represents the proportion of total variation observed between the trials attributable to differences between trials rather than sampling error or chance. The degree of heterogeneity was graded as low ($I^2 < 25\%$), moderate ($I^2 = 25$–75%) or high ($I^2 > 75\%$) [20]. We used a random-effects model which assumes that there is variation between studies as this model better accounts for heterogeneity between studies [21,22]. Analysis was conducted using Review Manager Version 5.2 (The Cochrane Collaboration, Update Software, Oxford). In order to investigate the sensitivity of the results to variations in risk of confounding, sub-group analysis for studies reporting survival data was performed comparing adjusted and unadjusted studies.

Results

Eligible Studies

The literature search identified 2032 studies, which were published between 1965 and 2010. On the basis of title and abstracts, 42 articles were obtained and reviewed in full. Twelve articles met the inclusion and exclusion criteria (Fig. 1) [4,8,23–32]. All were retrospective and non-randomised. All studies reported 30-day mortality [4,8,23–32], five reported re-operation rates [8,23,28,29,31] and ten reported survival [4,8,23–29,32]. Functional outcomes and health related quality of life were not reported by any study. The studies described a total of 2747 patients of whom 1711 (62.3%) underwent MV-Replacement and 1036 (37.7%) underwent MV-Repair.

Characteristics of the eligible studies are described in Tables 1–4. Tables 2–4 include the characteristics considered to be the most important potential confounding factors, classified into surgical factors, disease severity, and co-morbidity.

As there was considerable heterogeneity in study design, surgical techniques and patient population because of the risk of bias, we judged that it was inappropriate to report pooled effect sizes [18]. Forest plots were used to display results. Meta-analysis was only used to explore heterogeneity amongst studies reporting survival data.

30-day Mortality

Nine of the 12 studies suggested MV-Repair was superior to MV-Replacement [4,8,23,24,26–28,30,32]. The degree of heterogeneity was moderate ($I^2 = 50\%$) (Fig. 2). When funnel plots of the data were examined visually there were three outlying studies [8,28,31]. When these studies were excluded heterogeneity was significantly reduced ($I^2 = 9\%$). These studies either did not perform complete ring-annuloplasty or specify the proportion of patients who underwent complete ring-annuloplasty. When all studies were excluded that either did not perform complete ring-annuloplasty in the majority of cases or specify the proportion of patients who underwent complete ring-annuloplasty [8,24,28–31], heterogeneity in the remaining group, who all performed complete ring anuloplasty in over two-thirds of patients, heterogeneity was low ($I^2 = 15\%$). It was not possible to explore if the severity of valve pathology, or co-morbidities had a similar impact on heterogeneity because of the data reported.

Need for Reoperation

Five studies reported the number of patients who required reoperation [8,23,28,29,31]. Unfortunately, insufficient information was available on the cause and time of re-operation. Al-Radi et al. reported that nine of the 65 patients in the MV-Repair group underwent reoperation between two days and nine months post-operatively for recurrent regurgitation, and four of 137 patients in the MV-Replacement group underwent reoperation between two months and two years for paravalvular leak (two patients),

Table 1. *Surgical Characteristics.*

	Replacement		Repair						
	Preservation Technique	Bioprosthesis	Partial/Suture Annuloplasty (SA)	Ring Annuloplasty (RA)	Papillary Muscle (PM) Intervention	Chordi (Ch) Intervention	Alfieri Technique	Resection	Undersizing
Magne	Pos Pres 121/184(66%) BiL Pres 37/184(20%)	39/184 (21%)	None	CarE RA 145/186 (78%) Carpentier-McCarthy-Adam IMR Etlogix RA 35/186(19%) Duran RA 6/186(3%)	NS	Ch Sh/Tr 7/186(4%) Ch Re 6/186(3%)	1/186 (0.5%)	4/186 (2%)	24 mm RA 17/186 (9%) 26 mm RA 60/186 (32%) 27 mm RA 6/186 (3%) 28 mm RA 67/186 (36%) 30 mm RA 21/186 (11%) 31–33 mm 15/186 (8%)
Milano	NS	30/106 (28%)	Kay SA Technique 24/416(6%)	St Jude Seguin RA 381/416(92%)	NS	NS	NS	NS	NS
Bonacchi	Pos Pres 18/18 (100%)	NS	NS	30/36(83%)	PM Sh 2/36(5%) PM Re 2/26(5%)	Ch Tr 2/36(5%)	2/36(5%)	17/36(47%)	Coaptation length 1 cm (UN)
Al-Radi	Pos Pres 75/137(55%) BiL Pres 22/137(16%)	88/137(64%)	(UN)	(UN)	PM Sh (UN) PM Re (UN)	For CC IIb, IIc (UN)	For CC IIb, IIc (UN)	Quadrangular Resection (UN)	Moderate (UN)
Reece	Miller's Preservation Technique (UN)	NS	NS	(UN)	PM Sh (UN) PM Re (UN)	NS	NS	NS	28 mmRA Males (UN) 26 mm RA Females (UN)
Mantovani	Pos Pres 41/41(100%)	10/41(24%)	NS	CarE RA (UN)	None	NS	NS	NS	Moderate (UN)
Calafiore	Pos Pres 20/20(100%)	11/20(55%)	SA 15/82(18%) Posterior Annuloplasty 67/82(82%)	None	NS	NS	5/82(6%)	NS	NS
Tavakoli	Pos Pres (UN)	4/63(6%)	Wooler's SA Technique (UN)	(UN)	PM Sh (UN)	NS	(UN)	Resection for Ch avulsion (UN)	Downsizing RA alone 6/30(20%)

Prifti	Pos Pres 6/6(100%)	NS	Pericardial Patch 6/43(14%)	CarE RA 7/43(16%)	PM Sh 3/43(7%)	Ch Sh 5/49(10%) Ch Tr 1/43(2%)	NS	Leaflet Resection 25/43(58%)	Coaptation length 1 cm (UN)
Grossi	Pos Pres (UN)	58/71(82%)	SA 35/152(23%)	117/152(77%)	NS	NS	NS	NS	NS
Gillinov	NS	50/85(59%)	Bovine Pericardial Patch 112/397(28%) Autologous Pericardial Patch 2/397(0.5%)	CarE RA 134/397(34%) CosE RA 140/397(35%)	Pm Sh34/397(10%) PM Re12/397(3%)	Ch Sh 27/397(7%) Ch Tr 9/397(2%)	1/397(0.25%)	17/397(4%)	26 mm in 80/397(30%) 28 mm in 73/397(28%)
Hausmann	NS	92/197(47%)	Kay/Wooler's SA Technique 61/140(44%) Panneth SA Technique 15/140(11%) Gerbode SA Technique 30/140(21%) Posterior/Anterior Commisuro-plasty Technique 34/140(24%)	None	NS	NS	NS	NS	NS
Cohn	Pos Pres 56/56(100%)	40/56(71%)	Pericardial Patch 1/94(1%)	CarE 32/94(34%) Duran RA 48/94(51%)	(UN)	(UN)	NS	(UN)	NS

BiL Pres, Bileaflet Preservation; CarE, Carpentier-Edwards; CC, Carpentier Classification; Ch, Chordi; Ch Sh, Chordi Shortening; Ch Tr, Chordi Transfer; CosE, Cosgrove-Edwards; NS, Not Stated; PM, Papillary Muscles; PM Sh, PM Shortening; PM Re, PM Reimplantation; Pos Pres, Posterior Preservation; RA, Ring Annuloplasty; SA, Suture Annuloplasty; UN, Yes, In an Unknown Proportion of Patients.

Table 2. *Matching: Demographic Characteristics.*

	Demographics			Surgical Factors					Acuity			
	Age	Sex	BSA/BMI	Different Surgeons	More Than One Institution	Concomitant CABG	Other Concomitant Procedure	Previous Cardiac Surgery	Shock or Preoperative Intraortic Balloon Pump	Emergency	Recent MI < 30 days	Recent MR < 30 days
Magne	M, S	M, S	M, S	NS	NC	S	E	E	NS	E	NS	E
Milano	S	S	M, S	I	I	I	E	S	NS	E, M	UM	NS
Bonacchi	NS	NS	NS	NS	NC	I	NS	NS	NS	NS	NS	NS
Al-Radi	S	M, S	S	I	NC	NS	NS	NS	E	E	S	S
Reece	M	UM	NS	NS	NC	I	NS	NS	E	E	NS	NS
Mantovani	M	M	NS	NS	NC	I	E	NS	NS	NS	E	NS
Calafiore	M	M	NS	NS	NC	NS	E	M	M	NS	M	NS
Tavakoli	NS	NS	NS	NS	NC	I	NS	NS	NS	NS	NS	NS
Prifti	NS	NS	NS	NS	NC	I	NS	NS	NS	NS	NS	NS
Grossi	M	M	NS	I	NC	M	NS	M	NS	M	NS	S
Gillinov	M, S	M	NS	I, S	NC	NS	E	M	UM	S	S	NS
Hausmann	M	NS	NS	NS	NC	NS	NS	NS	NS	NS	NS	NS
Cohn	UM	M	NS	NS	NC	NS	NS	M	NS	NS	NS	M

BMI, Body Mass Index; BSA, body surface area; CABG, Coronary Artery Bypass Graft; E, controlled using exclusion criteria; I, controlled using inclusion criteria; M, matched; MI, myocardial infarction; MR, mitral regurgitation; NC, not controlled because of study design; NS, not stated; S, statistically controlled; UM, unmatched.

Table 3. *Matching: Atherosclerotic Load.*

	Systemic and Vascular Comorbidities							Coronary Pathology												
								Clinical Presentation							Angiographic Findings					
	CVD	CRI	PVD	DM	COPD	Hypertension	Dyslipidemia	Previous MI	Recent MI	MI <30 days	Unstable Angina	Crescendo Angina	Chronic Angina	CCS Class	3 Vessel Dx	2 Vessel Dx	1 Vessel Dx	LM Dx	LAD Dx	Cx Dx	RCA Dx
Magne	M, S	S	NS	M, S	M, S	M, S	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Milano	S	S	S	M, S	S	M, S	M, S	S	UM	UM	NS	NS	NS	NS	M, S	S	S	M	NS	NS	NS
Bonacchi	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Al-Radi	M, S	M	M	M, S	M, S	M, S	M, S	S	M, S	S	NS	S	M, S	M, S	S	S	S	S	S	S	S
Reece	M	M	M	M	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Mantovani	M	M	M	M	M	M	M	M	E	E	M	NS	M	M	M	M	M	NS	NS	NS	NS
Calafiore	M	M	M	M	NS	UM	NS	M	M	M	M	M	M	NS	NS	NS	NS	NS	NS	NS	NS
Tavakoli	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Prifti	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Grossi	NS	NS	NS	M	NS	NS	NS	NS	NS	NS	UM	UM	UM	UM	NS	NS	NS	NS	NS	NS	NS
Gillinov	NS	M, S	NS	M	UM	M	NS	NS	UM	UM	NS	NS	NS	NS	UM	UM	UM	M	UM	M	UM
Hausmann	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Cohn	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

CCS, Canadian Cardiovascular Society Angina Score; COPD, Chronic Obstructive Pulmonary Disease; CRI, Chronic Renal Impairment; CVD, Cerebrovascular Disease; CX Dx, Circumflex Disease; Dx, Disease; DM, Diabetes Mellitus; E, controlled using exclusion criteria; I, controlled using inclusion criteria; LAD Dx, Left Anterior Descending Disease; LM Dx, Left Main Stem Disease; M, matched; MI, myocardial infarction; NC, not controlled because of study design; NS, not stated; PVD, Peripheral Vascular Disease; RCA Dx, Right Coronary Artery Disease; S, statistically controlled; UM, unmatched.

Table 4. *Matching: Severity of Valve Pathology.*

	Heart Failure										Arrhythmias		Valve Pathology				
	Clinical Heart Failure			Physiological and Echocardiographic Parameters of Heart Failure							Arrhythmias Unspecified	AF					
	CHF Admissions	CHF	NYHA	EF	LVEDP	PAP	Dilated Cradiomyopathy	Akinesia	Hypokinesia	Significant TR			Aetiology	Severity	Ruptured Papillary Muscles	Leaflet or Chordae Pathology	Prior MV Procedure
Magne	NS	S	S	S	NS	NS	E	NS	NS	E	NS	M, S	I	S	NS	NS	E
Milano	NS	NS	S	M, S	NS	NS	NS	NS	NS	NS	NS	NS	I	M	E	NS	E
Bonacchi	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	I	NS	NS	NS	NS
Al-Radi	NS	M, S	M, S	M, S	NS	NS	NS	NS	NS	NS	NS	M, S	I	NS	E	NS	E
Reece	M	NS	NS	M	NS	NS	NS	NS	NS	NS	M	M	I, M	NS	E	NS	NS
Mantovani	NS	M	M	M, S	NS	M	NS	NS	NS	E	M	M	I	M	NS	NS	NS
Calafiore	NS	UM	UM	UM	UM	NS	M	M	M	NS	NS	M	I	M	NS	NS	NS
Tavakoli	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	I	NS	NS	NS	NS
Prifti	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	I	I/E	NS	NS	NS
Grossi	NS	S	UM	M	NS	NS	NS	NS	NS	NS	NS	NS	I	NS	UM	UM	NS
Gillinov	NS	NS	S	UM	NS	NS	NS	S	S	NS	NS	M, S	I	I/E, S	S	NS	NS
Hausmann	NS	NS	NS	M	M	NS	NS	NS	NS	NS	UM	UM	I	NS	NS	E	NS
Cohn	NS	NS	UM	M	NS	NS	NS	NS	NS	NS	NS	NS	I	NS	NS	NS	NS

AF, Atrial Fibrillation; CHF, Congestive Heart Failure; E, controlled using exclusion criteria; EF, Ejection Fraction; I, controlled using inclusion criteria; LVEDP, Left Ventricular End-Diastolic Pressure; M, matched; MV, mitral valve; NC, not controlled because of study design; NS, not stated; NYHA, New York Heart Assossiation Heart Failure Score; PAP, Pulmonary Artery Wedge Pressure; S, statistically controlled; TR, Tricuspid Regurgitation; UM, unmatched.

endocarditis and thrombus [8]. Mantovani et al. reported that one of the 61 patients in the MV-Repair group and four of the 41 patients in the MV-Replacement group underwent re-operation within 30-days for bleeding, that one patient in the MV-Repair group subsequently underwent reoperation for ring-dehiscence and one for bleeding, and three patients in the MV-Replacement group subsequently underwent reoperation, for endocarditis and thromboembolism [29]. Bonacchi et al. reported that one of 36 patients in the MV-Repair group underwent reoperation within 30 days of the operation because the repair failed and one of the 18 patients in the MV-Replacement group underwent reoperation within three months for prosthesis dehiscence [23]. Hausmann et al. reported that none of the 197 patients in the MV-Replacement group underwent reoperation, but five of the 140 patients in the MV-Repair group underwent reoperation at an unspecified time (four because of persistent regurgitation and one because of endocarditis) [28]. Finally, Tavakoli et al. reported that no patients in the MV-Repair group underwent re-operation but two of the 63 patients in the MV-Replacement group underwent re-operation at one and five years post-operatively for unspecified reasons [31].

Survival

Ten included studies reported survival beyond 30-days [4,8,23–29,32]. Six studies reported mortality adjusted for the effect of confounding factors [4,8,26,27,29,32]. Seven studies showed a trend towards longer survival following MV-Repair compared to MV-Replacement at maximum follow-up [4,8,23,24,26,27,32]. The observed variation in point estimates for HR was large, with several outlaying studies. The pooled HR for all 10 studies was 0.69 (95% CI 0.40–1.00), favouring MV-Repair but not statistically significant. The degree of heterogeneity was moderate ($I^2 = 68\%$) (Fig. 3). Many of the same studies accounted for the heterogeneity in long term outcomes as for peri-operative outcomes [8,28], however other studies also contributed significantly to heterogeneity [26]. When these studies were excluded heterogeneity was significantly reduced ($I^2 = 5\%$). There were no obvious common characteristics to account for the heterogeneity. All 10 studies reporting longer term survival also reported 30-day mortality; nine had consistent findings for both outcomes (seven favouring MV-Repair and two favouring MR-Replacement) [4,8,23–27,29,32] and one was inconsistent (favouring MV-Repair for 30-day mortality but MV-Replacement for longer term survival) [28]. Studies that reported HRs adjusted for confounding factors (HR 0.55, 95% CI 0.35–0.87) tended to favour MV-Repair more strongly than studies that reported unadjusted HR (HR 1.11, 95% CI 0.82–1.51) (Fig. 3).

Discussion

The risk of bias to the included studies precludes robust synthesis of their individual findings quantitatively [33]. Nevertheless, the forest plots (Figs. 2 and 3) qualitatively suggest that MV-Repair tends to be associated with

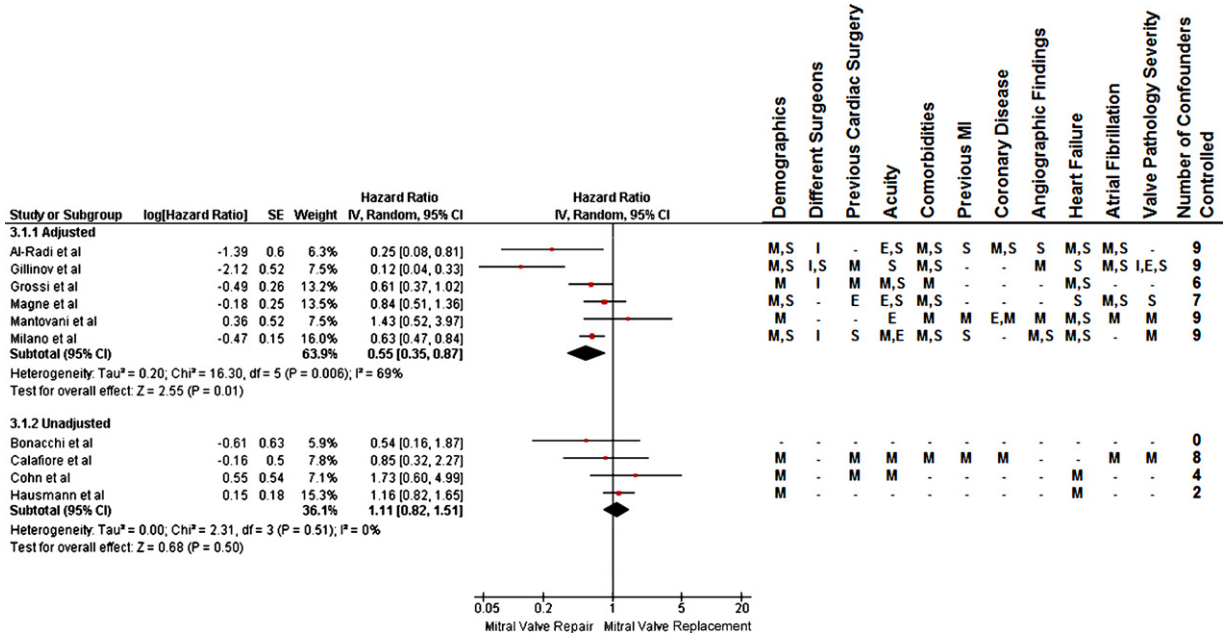

Figure 3. *Forest plot comparing survival during follow-up after MV-Repair or MV-Replacement. Subgroup analysis was performed for studies which reported adjusted versus unadjusted hazard ratios. In the attached table we show if each of the 11 factors identified as confounders in the studies which adjusted reported mortality were controlled in the included studies. We also show how they were controlled. I, controlled using inclusion criteria; E, controlled using exclusion criteria; M, matched; S, survival statistically adjusted.*

lower peri-operative mortality and longer survival than MV-Replacement in patients with IMR. HRs calculated for studies adjusted for confounding tended to be more, rather than less, extreme than HRs for unadjusted other studies, but were nevertheless moderately heterogeneous. The heterogeneity of outcomes in both the peri-operative, and long-term survival analysis can be explained by a relatively small number of studies. The underlying reasons however are not clear. Analysis of the heterogeneity in the peri-operative group suggests that surgical technique may be responsible; however this is not supported by long-term data. This may be for two reasons, either other factors such as patient co-morbidities are more important in the long-term, whilst surgical technique is more important in the short-term; or this is coincidental and completely different variables are responsible. This is entirely feasible, given that complete ring-annuloplasty is generally more widely used in more recent studies. However, we are unable to explore this further because sufficiently detailed information on variables such as the severity of valve disease or co-morbidities is not reported in the majority of the studies.

Data describing the numbers of patients who required reoperation were reported by a minority of studies and were incompletely reported. Reoperation should be analysed as survival free from reoperation in order properly to take into account different durations of follow-up and the time when reoperations occurred. The data reported by authors did not allow this. No clear trends in the relative reoperation rate between interventions was apparent although reoperation for persistent mitral regurgitation predictably appeared to be more common following MV-Repair whilst thrombotic complication and endocarditis appear to be more common following MV-Replacement. Reoperation because of bleeding occurred with similar frequency following both interventions. None of the studies reported either functional or HRQoL outcomes.

We have not reported a quantitative pooled effect estimate for any outcome because of the likely heterogeneity between studies relating to study design features and risk of bias. We have nevertheless presented forest plots because it has been suggested that this is the least biased reporting method to describe the results of individual studies. Bias can have two effects, first to shift the estimate for an individual study or the pooled estimate away from the true effect and, second, to introduce additional uncertainty; confidence intervals only reflect sampling error [16,19].

Given the nature of the existing evidence, what conclusions can be drawn? First, substantial differences in mortality (both early and longer term) between MV-Repair and MV-Replacement are plausible. The second conclusion is that, despite the substantial magnitude of the observed differences, the risk of bias to the current evidence means that there is still great uncertainty about the relative short and long term effects of carrying out MV-Repair versus MV-Replacement.

It is possible that the superior operative mortality and survival in patients undergoing MV-Repair could be explained by differences in patient characteristics. However, the sub-group analysis, splitting included studies according to whether they attempted to adjust for confounding, does not support this. Studies that reported adjusted HRs tended to be more favourable to MV-Repair than unadjusted ones.

Comparison of Study Findings with Existing Literature

Moderate or severe IMR has been reported in approximately 3% of patients undergoing CABG [5,34]. The referral of higher risk patients and the greater use of preoperative dynamic cardiac imaging is likely to increase the number of patients undergoing CABG who are diagnosed with moderate to severe IMR, particularly as the evidence supporting surgical management is consolidated [35].

Several studies have demonstrated symptomatic improvement in patients with moderate to severe IMR by adding MVR-Repair to CABG [34,36]. The durability of repair seen in degenerative disease has not, however, been replicated in patients with IMR following MV-Repair [10,11,23,34,36–40]. Furthermore, under-sizing annuloplasty may prevent diastolic annular relaxation resulting in flow-limiting lesions and restricted exercise capacity [41]. Residual regurgitation is often reported after restrictive annuloplasty in patients with tethering of the valve leaflets [24,42–47]. Whilst procedures to address leaflet tethering such as chordal cutting, the Dor Procedure, papillary muscle slings and relocation have been described, these are difficult to standardise and apply [48–50].

MVR-Repair has historically been preferred to MV-Replacement which was associated with poor outcomes. Routine sparing of the sub-valvular apparatus, however, has resulted in reproducible reductions in peri-operative mortality [51–53] following MVR-Replacement. Many patients groups do not appear to benefit from MV-Repair over MV-Replacement, particularly patients with greater co-morbidity [26,54], although it has been difficult to identify these groups prior to intervention [55]. Consequently a randomised-controlled trial comparing MV-Repair and MV-Replacement is increasingly advocated in the cardiac literature [8,30,55].

Study Strengths and Limitations

This is the first systematic review, identifying all published studies to address this clinically important subject. In the absence of randomised evidence it has a role in informing clinical decision making and defining the focus of future research.

An inherent problem of non-randomised studies is that the difference in effectiveness between the interventions being compared could be due to confounding factors. We were conscious of this when conducting our analysis and performed sub-group analysis of studies which attempted to control confounding factors. Although adjusted studies appeared to favour MV-Repair more strongly than MV-Replacement, all techniques to control confounding factors in non-randomised trials are vulnerable to the effects of unidentified confounding factors and residual confounding.

Heterogeneity is an important consideration when carrying out meta-analysis. It can arise from a variety of sources, e.g. differences in study design, study population or methods of statistical analysis. Heterogeneity is particularly important in the analysis of survival data which is not constantly analysed and reported in the literature. We described heterogeneity using I^2.

We did not account for differences in surgical techniques between studies in our analysis. Despite many of the studies being published before the routine application of undersized rigid ring annuloplasty, there are relatively high rates of ring annuloplasty utilisation and low rates of other procedures such as Alfieri stitch, surgical annuloplasties or leaflet resections which might have compromised the comparison of the repair versus replacement. There were also high rates of bioprosthesis utilisation in the replacement group with at least posterior leaflet preservation in most cases (Table 1).

Implications for Future Research

This study highlights the considerable uncertainty that exists in the literature about the long-term outcomes associated with MV-Repair and MV-Replacement. Future research should focus on randomised comparisons of the gold-standard MV-Repair and MV-Replacement techniques (ring-annuloplasty versus bio-prosthesis with preservation of the subvalvular apparatus). To facilitate a fair comparison, patients with IMR secondary to ruptured papillary muscles should be excluded. In the absence of randomised evidence standardised reporting systems for outcome of interest should be developed, and non-randomised studies must be adjusted or propensity-matched for potential confounding factors.

None of the included studies addressed functional outcomes and HRQoL. In a patient population where life expectancy is commonly limited because of significant co-morbidities, these should be important considerations when discussing surgical management with prospective patients. Future research should include these outcomes.

Conclusion

This review suggests that MV-Repair is associated with lower 30-day mortality and may be associated with improved longer term survival. However, there is considerable uncertainty about this finding because included studies were heterogeneous and at risk of confounding and other biases.

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