What Is the Role of Minimally Invasive Mitral Valve Surgery in High-Risk Patients? A Meta-Analysis of Observational Studies

Marco Moscarelli, MD, Khalil Fattouch, MD, PhD, Roberto Casula, MD, Giuseppe Speziale, MD, PhD, Patrizio Lancellotti, MD, PhD, and Thanos Athanasiou, MD, PhD

National Heart and Lung Institute and Department of Surgery and Cancer, Imperial College London, London, United Kingdom; GVM Care and Research, Villa Maria Eleonora, Palermo; GVM Care, Anthea Hospital, Bari, Italy; Department of Cardiology, University of Liège Hospital, Liege, Belgium; and the GVM Care and Research Group

Background. **Minimally invasive valve surgery is related to certain better postoperative outcomes. We aimed to assess the role of minimally invasive mitral valve surgery in high-risk patients.**

Methods. **A systematic literature review identified eight studies of which seven fulfilled criteria for meta-analysis. Outcomes for a total of 1,254 patients (731 were conventional standard sternotomy and 523 were minimally invasive mitral valve surgery) were submitted to meta-analysis using random effects modeling. Heterogeneity and subgroup analysis with quality scoring were assessed. The primary end point was early mortality. Secondary end points were intraoperative and postoperative outcomes and long-term follow-up.**

Results. **Minimally invasive mitral valve surgery conferred comparable early mortality to standard sternotomy ($p = 0.19$); it was also associated with a lower number of units of blood transfused (weighted mean difference, −1.93; 95% confidence interval [CI], −3.04 to −0.82; $p = 0.0006$) and atrial fibrillation rate (odds ratio, 0.49; 95% CI, 0.32 to 0.74; $p = 0.0007$); however, cardiopulmonary bypass time was longer (weighted mean difference, 20.88; 95% CI, −1.90 to 43.65; $p = 0.07$). There was no difference in terms of valve repair rate (odds ratio, 1.51; 95% CI, 0.89 to 2.54; $p = 0.12$), and the incidence of stroke was significantly lower in the high-quality analysis with no heterogeneity (odds ratio, 0.35; 95% CI, 0.15 to 0.82; $p = 0.02$; χ^2, 1.67; I^2, 0%; $p = 0.43$).**

Conclusions. **Minimally invasive mitral valve surgery is a safe and comparable alternative to standard sternotomy in patients at high risk, with similar early mortality and repair rate and better postoperative outcomes, although a longer cardiopulmonary bypass time is required.**

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As a result of the aging of the cardiac surgery population, physicians have to deal with individuals of accumulated comorbidity. Cardiac surgeons have been mastering minimally invasive surgery techniques for several years with favorable results [1], and these benefits may be particularly evident in patients at high risk who, more than others, are prone to experience adverse events postoperatively. However, minimally invasive surgery may be associated with an increased incidence of stroke and aortic dissection, as well as significantly longer cardiopulmonary bypass (CPB) time [2], which can be classified as technical- or learning curve–related drawbacks. So far, there are virtually no prospective randomized trials comparing minimally invasive valve surgery (MIMVS) and standard sternotomy (ST) in an unbiased way, and the majority of evidence rely on observational studies. Moreover, definition of the level of risk has been a controversial issue, mainly because the currently available tools of risk prediction in cardiac surgery such as EuroSCORE II [3] and The Society of Thoracic Surgery Predicted of Risk of Mortality [4] lose calibration and discrimination in the upper boundaries or deciles of surgical risk. Hence, defining where to draw the "red line" above which patients should be considered at high risk remains a challenge and an issue of debate. The aims of this study are to identify (1) whether minimally invasive mitral valve surgery (MIMVS) may offer a mortality advantage in patients at increased risk for surgery when compared with the counterpart, ST; (2) whether the repair rate is the same; (3) whether the reduced rate of postoperative complications observed in the general MIMVS population is maintained or even improved in these subgroups; and finally (4) whether there are any differences in terms of long-term efficacy.

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Address correspondence to Dr Moscarelli, Department of Surgery and Cancer, Imperial College, Paddington, London, W2 1NY, United Kingdom; email: m.moscarelli@imperial.ac.uk.

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Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
CPB = cardiopulmonary bypass
MIMVS = minimally invasive mitral valve surgery
OR = odds ratio
PRC = packed red cells
ST = sternotomy
WMD = weighted mean difference

Material and Methods

Literature Search

A literature search was performed using PubMed, Ovid, Embase, Medline, and Cochrane databases using the MeSH terms "minimally invasive mitral valve" and "high-risk," and we included in the MeSH terms all the EuroSCORE II risk factors. In addition, our search was extended to include the clinicaltrials.gov database and "gray" literature for further rigor. The "related articles" function in PubMed was also used to ensure completeness. The last date for this search was February 1, 2015 (Fig 1).

Inclusion and Exclusion Criteria

All articles reporting outcomes for MIMVS (experimental group) and ST (control group) were included. Studies were excluded from the review if (1) inconsistency of data did not allow valid extraction; (2) data were duplicated; (3) the experimental or control group was robotic mitral valve intervention; and (4) the trial or study was carried out on animal models. Based on these criteria, two assessors (M.M., K.F.) independently selected studies for further examination by title and abstract review. All potentially eligible studies were retrieved in full for further evaluation. Any disagreement was resolved by discussion with a third author (T.A.). Statistical concordance testing was performed using Cohen's kappa coefficient to measure interrate agreement.

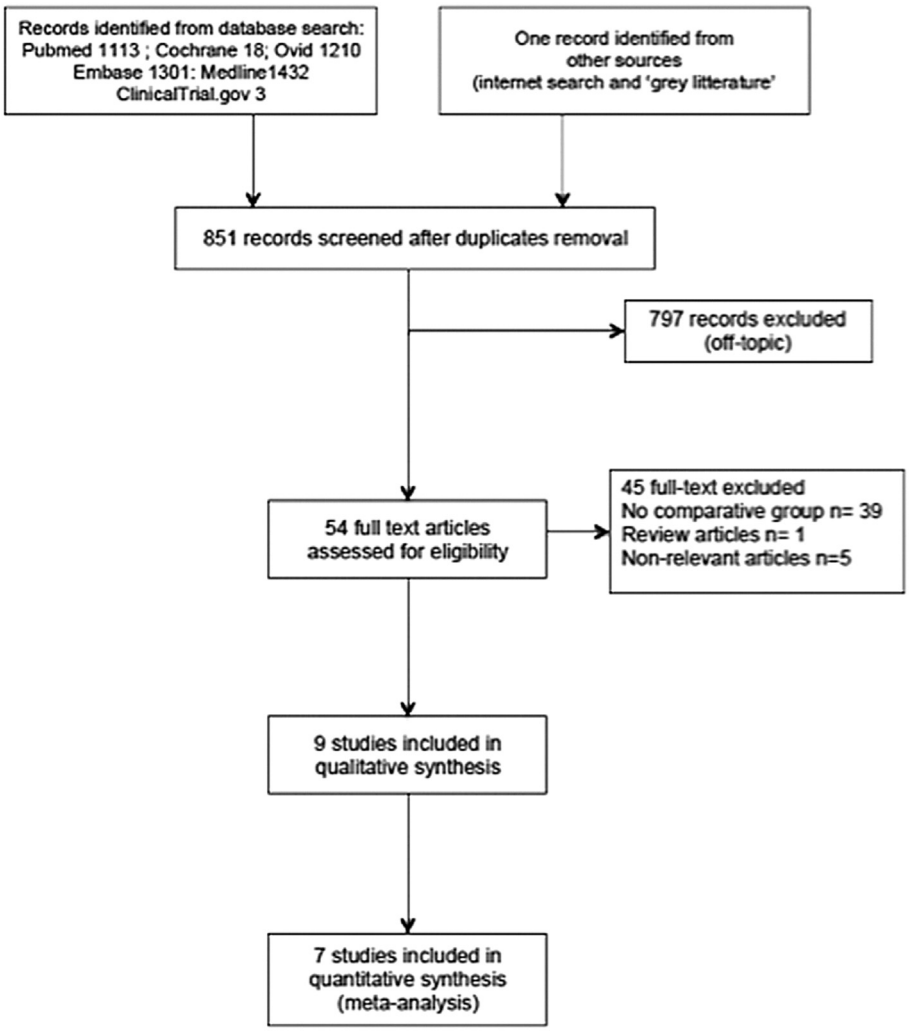

Fig 1. Search strategy.

Data Analysis

Two authors (M.M., K.F.) independently extracted the following data from each paper using a predefined protocol including first author, year of publication, study type, number of subjects, and study population demographics. Specific outcome data, where possible, were extracted for the following: (1) primary end points: early mortality (including 30-day or in-hospital mortality), and (2) secondary end points, including CPB time, mitral repair rate, number of units of packed red cells (PRC) transfused, reopening for bleeding, prolonged intubation (defined as more than 48 hours), atrial fibrillation (AF), acute renal failure, atrioventricular block requiring pacemaker implantation, and length of stay. Meta-analysis was performed in line with recommendations from the Cochrane Collaboration and in accordance with both PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines [5, 6]. Analysis was conducted by use of Review Manager version 5.1.7 for Windows (The Cochrane Collaboration, Software Update, Oxford, UK) and STATA v.11 statistical analysis software (StataCorp, College Station, TX). Data were analyzed using a weighted DerSimonian–Laird random effects model. Continuous data were investigated using weighted mean difference (WMD) as the summary statistic, reported with 95% confidence intervals (CI). The point estimate of the WMD was considered statistically significant at a probability value of less than 0.05, if the 95% CI did not include the value zero. Categorical variables were analyzed using the odds ratio (OR). An OR of less than 1 favored the treatment group, and the point estimate of the OR is considered statistically significant at the probability value of less than 0.05 level, if the 95% CI does not include the value 1.

Heterogeneity

Interstudy heterogeneity was explored using the χ^2 statistic, but the I^2 value was calculated to quantify the degree of heterogeneity across trials that could not be attributable to chance alone. When I^2 was more than 50%, significant statistical heterogeneity was considered to be present. Three strategies were used to assess data validity and heterogeneity: (1) subgroup analysis of higher-quality studies (quality score $>$ 7); (2) funnel plots to evaluate publication bias; and (3) meta-regression to assess the effect of covariates on the log OR for the primary outcome of interest.

Quality Scoring

Quality assessment of each study was performed by attributing a quality assessment score using a modification of the Newcastle–Ottawa scale [6] that included all 17 EuroSCORE II risk factors. Studies attaining greater than the median score of 7 (from a maximum of 17) were defined as having "higher matching quality" and were included in the subgroup analysis. Modified Newcastle–Ottawa scoring criteria are shown in Table 1.

Table 1. Criteria for Quality Assessment

Quality Checklist
Selection
1. Assignment for treatment—any criteria reported? (If yes, 1 star)
2. How representative was the reference group (ST) in comparison to the general population for mitral surgery? (If yes, 1 star; no star if the patients were selected or selection of group was not described)
3. How representative was the reference group (MIMVS) in comparison to the general population for mitral surgery? (If drawn from the same community as the reference group, 1 star; no star if drawn from a different source or selection of group was not described)
Comparability[a]
4. Groups comparable for risk factors 1, 2, 3, 4, 5, 6, 7, 8, 9 (if yes, 1 star was assigned for each of these; no star was assigned if the groups differed)
5. Groups comparable for risk factors 10, 11, 12, 13, 14, 15, 16, 17 (if yes, 1 star was assigned for each of these; no star was assigned if the two groups differed)
Outcome assessment
6. Clearly defined outcome of interest (if yes, 1 star)
7. Follow-up (1 star if described)

[a] Comparability includes all the EuroSCORE II risk factors. Comparability variables were (1) age; (2) sex; (3) renal function; (4) extracardiac arteriopathy; (5) poor mobility; (6) previous cardiac surgery; (7) chronic lung disease; (8) active endocarditis; (9) critical preoperative state; (10) insulin-dependent diabetes mellitus; (11) New York Heart Association; (12) Canadian Cardiovascular Society class IV; (13) left ventricular function; (14) recent myocardial infarction; (15) pulmonary hypertension; (16) urgency; and (17) combined.

MIMVS = minimally invasive mitral valve surgery; ST = standard sternotomy.

Risk of Bias Analysis

A domain-based evaluation of risk of bias was performed in accordance with the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [7]. Two authors (M.M., K.F.) subjectively reviewed all studies included in this review and assigned a value of "yes," "no," or "unclear" to the following questions: (1) Was the allocation sequence adequately generated? (2) Was allocation adequately concealed? (3) Was there blinding of participants, personnel, and outcome assessors? (4) Were incomplete outcome data sufficiently assessed? (5) Are reports in the study free of the suggestion of selective outcome reporting? "Risk of bias" plots were performed using Review Manager version 5.1.7 for Windows (The Cochrane Collaboration, Software Update).

Results

Our search revealed seven studies [8–14] fulfilling these inclusion criteria, producing a pooled data set of 1,254 patients of whom 731 underwent ST and 523 underwent MIMVS (Table 2). There was 100% concordance between reviewers, equating to a Cohen's kappa coefficient of 1. Five studies were retrospective observational in design [8, 10, 12–14], and two were propensity-matched studies

Table 2. Study Characteristics

Author, Year (total patients), Study Type	Inclusion Criteria	Exclusion Criteria	MI/ST (n)	Mean Age (years)		Sex (male)		Ejection Fraction < 0.30 (n)		Infective Endocarditis (n)		Serum Creatinine (g/dL)		COPD (n)		Redo (n)		CCF (NYHA III/IV) (n)	
				MI	ST	MI	ST	MI	ST	MI	ST	MI	ST	MI	ST	MI	ST	MI	ST
Mihos et al 2014 (n = 50), retrospective observational	a	A, C	22/28	65 ± 12	62 ± 16	17	18	NS	NS	22[a]	28[a]	1.23 ± 0.8	1.61 ± 1.7	9	10	4	2	NS	NS
Tang et al 2013 (n = 180), propensity-matched	a, b, c, d,	A	90/90	60.02 ± 1.38	60.42 ± 1.43	NS	NS	NS	NS	16	11	2.5 ± 0.2[a]	2.5 ± 0.2[a]	20	18	34	34	80	79
Iribarne et al 2012 (n = 175), retrospective observational	a	A, B	70/105	78.6 ± 3.3[a]	79.4 ± 3.9[a]	43	70	NS	NS	3	4	1.0 ± 0.04	1.1 ± 0.04	13	4	0	0	18	39
Holzhey et al 2011 (n = 286), propensity-matched	a, b, c, d	A, D	143/143	76 ± 3.9[a]	76 ± 3.6[a]	7	7	7	7	6	8	NS	NS	13	12	21	22	NS	NS
Sharony et al 2006 (n = 277), retrospective observational	a, b	A	100/177	NS	64.9 ± 1.0	NS	30	NS	48	NS	NS	NS	NS	NS	56	100[a]	177[a]	NS	275
Bolotin et al 2004 (n = 71), retrospective observational	a	A	38/33	67.9 ± 1.5	62.9 ± 2.0	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	38[a]	33[a]	24	20
Burfeind et al 2002 (n = 215), retrospective observational	a	A, C	60/155	60 ± 14	58 ± 16	33	122	NS	NS	NS	NS	NS	NS	NS	NS	60[a]	155[a]	NS	NS

[a] Indicates the main risk factor considered in the study.

Inclusions: a = MI through right mini-thoracotomy with endo-clamp or direct clamping or fibrillating heart; b = tricuspid valve surgery; c = atrial septal defect or patent foramen ovale; d = atrial fibrillation ablation; e = intention to treat analysis.

Exclusions: A = standard contraindications: right-sided chest surgery, femoral vessel difficulties, minimally invasive mitral valve surgeons not available; B = reoperation; C = concomitant tricuspid; D = very low ejection fraction.

CCF = congestive cardiac failure; COPD = chronic obstructive pulmonary disease; MI = minimally invasive; NS = not specified for propensity analysis; NYHA = New York Heart Association; ST = sternotomy.

Table 3. Results of Overall Meta-Analysis

Outcome	N			Mean Difference	Overall Effect			Heterogeneity		
	Studies	MIMVS	ST		Odds Ratio	95% CI	*p* Value	χ^2	*p* Value	I^2
Primary outcome										
Early mortality	7	523	731		0.55	0.23 to 1.34	0.19	15.90	0.01	62%
Secondary outcomes										
CPB time[a]	6	523	731	20.88		−1.90 to 43.65	0.07	354.36	<0.00001	99%
Number of units PRC transfused[a]	4	293	294	−1.93		−3.04 to −0.82	0.0006	15.29	0.002	80%
Repair	6	463	576		1.51	0.89 to 2.54	0.12	16.60	0.005	70%
Stroke	4	363	493		0.55	0.21 to 1.42	0.22	4.78	0.19	37%
Reopening for bleeding	5	385	521		0.91	0.34 to 2.42	0.85	6.46	0.17	38%
Prolonged intubation[b]	4	325	366		0.68	0.43 to 1.08	0.11	3.24	0.36	8%
AF[ab]	3	255	261		0.49	0.32 to 0.74	0.0007	0.52	0.77	0%
Acute renal failure[b]	3	303	338		0.60	0.28 to 1.25	0.17	2.86	0.24	30%
AV block requiring PM implant[b]	3	255	261		0.53	0.24 to 1.20	0.13	2.93	0.23	32%
Total LOS	3	251	281	−0.69		−6.32 to 4.94	0.81	491.04	<0.00001	100%

[a] Denotes significance. [b] Part of high-quality studies analysis (compared more than 7 EuroSCORE II risk factors or quality score > 7).

AV = atrioventricular; CI = confidence interval; CPB = cardiopulmonary bypass; LOS = length of stay; MIMVS = minimally invasive mitral valve surgery; PM = pacemaker; PRC = packed red cells; ST = sternotomy.

[9, 11]. Two studies, although observational, included two very homogeneous populations [8, 10]. One study reported an amalgamated secondary outcome for minimally invasive mitral and aortic valve surgery; thus, relevant data could not be retrieved [12]. Another study reported amalgamated outcomes for both primary (mortality) and secondary outcomes for minimally invasive mitral and aortic valve surgery, so it was subsequently excluded from our quantitative analysis to avoid any contamination of the experimental group and reduce clinical heterogeneity [15].

Definition of "High Risk"

As neither the EuroSCORE II nor The Society of Thoracic Surgery Predicted of Risk of Mortality was reported for each study, we defined "high risk" as patients with established risk factors who qualified to be included in the EuroSCORE II. Mihos and colleagues [8] included infective endocarditis and chronic obstructive pulmonary disease (40.9%) and redo operations (18.1%); Tang and associates [9] included patients with chronic renal failure and New York Heart Association functional class IV (43%), redo operations (37.7%), infective endocarditis (17.7%), and chronic obstructive pulmonary disease (22.2%); Iribarne and coworkers [10] included patients older than 75 years and those with chronic obstructive pulmonary disease (18.5%); Holzhey and colleagues [11] included patients older than 70 years and those with redo operations (14.7%), chronic obstructive pulmonary disease (8.6%), infective endocarditis (4.9%), and left ventricular ejection fraction of less than 30% (4.9%); and Sharony and associates [12], Bolotin and coworkers [13], and Burfeind and colleagues [14] included specifically redo patients (Table 2). Combined procedures (tricuspid valve) were also included in the studies by Tang and coworkers [9], Holzhey and colleagues [11], and Sharony and associates [12]. Moreover, the modified Newcastle–Ottawa scale based on 17 EuroSCORE II risk factors was used to both check comparability and numbers of risk factors included.

Primary Outcome

A summary of both primary and secondary end points is shown in Table 3. We observed no difference in terms of early mortality between MIMVS and ST (OR, 0.55; 95% CI, 0.23 to 1.34; $p = 0.19$); however, heterogeneity was observed (χ^2, 15.90; $p = 0.01$; I^2, 62%; Fig 2A).

Secondary End Points

Minimally invasive mitral valve surgery was associated with prolonged CPB time (WMD, 20.88; 95% CI, −1.90 to 43.65; $p = 0.07$), but a similar mitral valve repair rate (OR, 1.51; 95% CI, 0.89 to 2.54; $p = 0.12$); however, the number of PRC units transfused per patient was significantly lower (WMD, 1.93; 95% CI, −3.04 to −0.82; $p = 0.0006$) as was the incidence of AF (OR, 0.49; 95% CI, 0.32 to 0.74; $p = 0.0007$). There was no significant difference with regard to all the other secondary outcomes considered; heterogeneity was found with regard to CPB time, mitral repair

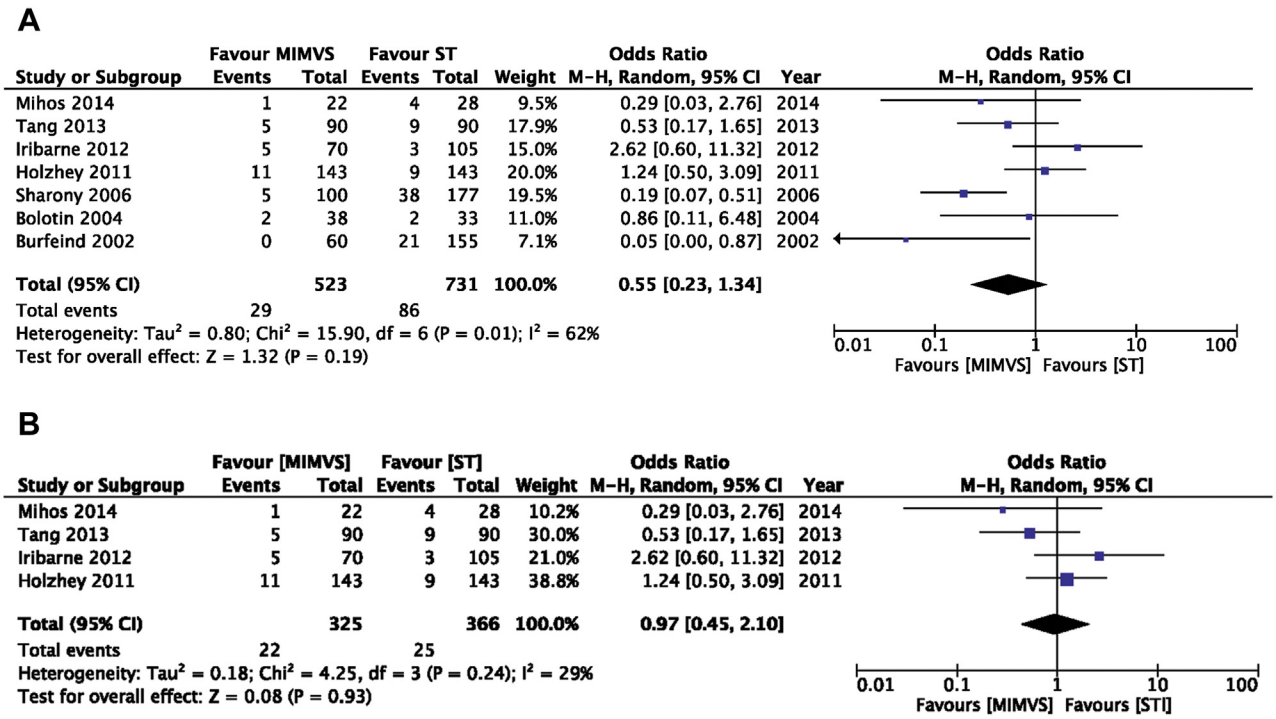

Fig 2. Forest plots of minimally invasive mitral valve surgery (MIMVS) versus standard sternotomy (ST): (A) overall early mortality and (B) high-quality studies. (CI = confidence interval.)

rate, number of PRC units transfused, and length of stay (Table 3).

Quality Scoring and Sensitivity Analysis

HIGH-QUALITY STUDIES. By using a modified version of the Newcastle–Ottawa scale, we assigned 1 point for each EuroSCORE II risk factor included and comparable between the MIMVS and ST groups. The overall quality of studies is outlined in Table 4. Of the seven studies included in this review, four were considered to be of high quality, scoring above the median of 7 points (Table 4) [8–11]. Analysis of high-quality studies did not demonstrate a significant difference in terms of the primary outcome early mortality (OR, 0,98; 95% CI, 0.45 to 2.10; $p = 0.93$), but most importantly, no heterogeneity was detected for this primary outcome (χ^2, 4.25; I^2, 29%; $p = 0.29$; Table 5; Fig 2B.). It seems that study quality can be a factor contributing to statistical heterogeneity among studies. In terms of secondary outcomes, as per overall analysis, the number of PRC units transfused per patient was lower (WMD, 1.57; 95% CI, −3.04 to −0.10; $p = 0.04$); moreover, the incidence of stroke was statistically significantly lower (OR, 0.35; 95% CI, 0.15 to 0.82; $p = 0.02$) with no heterogeneity (χ^2, 1.67; I^2, 0%; $p = 0.43$). Also, there was no difference with regard to mitral valve repair rate (OR, 1.07; 95% CI, 0.68 to 1.69; $p = 0.760$) with no heterogeneity (χ^2, 5.76; I^2, 48%; $p = 0.12$); however, a difference in CPB time was observed (WMD, 33.45; 95% CI, −19.58 to 86.48; $p = 0.04$), but heterogeneity was found ($p < 0.00001$; Table 5).

Table 4. Quality Scoring[a]

	Selection			Comparability		Outcome		
Authors (no. of patients)	1	2	3	4	5	6	7	Total
Mihos 2014 (n = 50)	…	…	…	******	***	*	*	11
Tang 2013 (n = 180)	…	…	…	********	***	*	*	13
Iribarne 2012 (n = 175)	…	…	…	****	**	*	*	8
Holzhey 2011 (n = 286)	…	…	…	*******	***	*	*	12
Sharony 2006 (n = 277)	…	…	…	…	…	*	…	1
Bolotin 2004 (n = 71)	…	…	…	…	*	*	…	2
Burfeind 2002 (n = 215)	…	…	…	*	…	*	…	2

[a] Quality scoring system based on EuroSCORE II modified Newcastle–Ottawa scale. Asterisks indicate points scored for risk factor comparability variables.

Table 5. Results of High-Quality Studies (More Than 7 EuroSCORE II Risk Factors or Quality Score > 7)

Outcome	N			Mean Difference	Overall Effect			Heterogeneity		
	Studies = 4	MIMVS	ST		Odds Ratio	95% CI	*p* Value	χ^2	*p* Value	I^2
Primary outcome										
Early mortality		325	366		0.97	0.45 to 2.10	0.93	4.25	0.24	29%
Secondary outcomes										
CPB time		325	366	33.45		−19.58 to 86.48	0.22	354.36	<0.00001	99%
Number of units PRC transfused[a]		255	261	−1.57		−3.04 to −0.10	0.04	7.55	0.02	74%
Repair		325	366		1.07	0.68 to 1.69	0.76	5.76	0.12	48%
Stroke[a]		303	338		0.35	0.15 to 0.82	0.02	1.67	0.43	0%
Reopening for bleeding		325	366		1.19	0.65 to 2.18	0.58	4.67	0.20	36%
Prolonged intubation[b]		325	366		0.68	0.43 to 1.08	0.11	3.24	0.36	8%
AF[ab]		255	261		0.49	0.32 to 0.74	0.0007	0.52	0.77	0%
Acute renal failure[b]		303	338		0.60	0.28 to 1.25	0.17	2.86	0.24	30%
AV block requiring PM implant[b]		255	261		0.53	0.24 to 1.20	0.13	2.93	0.23	32%

[a] Denotes significance. [b] High-sensitivity studies already part of the overall meta-analysis results.

AF = atrial fibrillation; AV = atrioventricular; CI = confidence interval; CPB = cardiopulmonary bypass; MIMVS = minimally invasive mitral valve surgery; PM = pacemaker; PRC = packed red cells; ST = sternotomy.

HETEROGENEITY ASSESSMENT: BIAS EXPLORATION. In accordance with Cochrane guidelines [7], risk of bias analysis was performed for all studies included in this review (Fig 3A). Overall, a high level of bias was detected attributable to the nonrandomized, unblinded nature of the majority of studies. In addition, to established bias assessment a score was given for each of the following: (1) multicenter trial, (2) propensity-matched study, and (3) confounder adjustment. No study fulfilled all three of these criteria (Fig 3A). Two studies were propensity matched [9, 11], and two others were corrected for potential confounders [8, 10]. Funnel plots were used to assess for publication bias for all primary and secondary outcomes. Minor funnel plot asymmetry was identified for primary outcome (Fig 3B); no funnel plot asymmetry was observed for the secondary outcomes stroke, PRC transfused per patients, postoperative AF, prolonged ventilation time, and reopening for bleeding.

Meta-Regression for Primary Outcome

Meta-regression analysis was performed for early mortality. Variables assessed were EuroSCORE preoperative risk factors and postoperative complications. Significant beneficial association for MIMVS in relation to early mortality was found between the log OR and redo operation ($p = 0.039$; β, −0.77), postoperative AF ($p = 0.013$; β, 0.85), reopening for bleeding ($p = 0.009$; β, 0.88), and postoperative renal failure ($p = 0.008$; β, 0.88).

Comment

This study is the first meta-analysis to date comparing patients with comorbidities undergoing either MIMVS or ST. Although minimally invasive technique is associated with a steep learning curve, several favorable results have been reported in the context of patients who are at increased risk for surgery [16–18]. However, a precise definition of the level of risk is somewhat difficult to achieve, as it depends on multiple factors, not only patients' features. We identified patients with comorbidities that are traditionally associated with an increased morbidity and mortality after surgery and defined this subset of patients as "high risk" for the purpose of our analysis. We demonstrated that MIMVS is at least as safe as the standard approach in terms of early mortality. Our findings are in line with the International Society of Minimally Invasive Surgery 2010 recommendation [2]. However, we did not observe any difference in terms of stroke; in fact in the high-quality studies subgroup analysis, the incidence was even lower in the MIMVS group with no heterogeneity.

High-quality studies analysis included series in which redo patients, although represented, were not predominant. Thus, central cannulation was mainly used in the studies by Iribarne and colleagues [10] and Tang and coworkers [9], and either femoral or central cannulation was used in the study by Mihos and associates [8], whereas all patients were operated on using femoral cannulation in the study by Holzhey and associates [11].

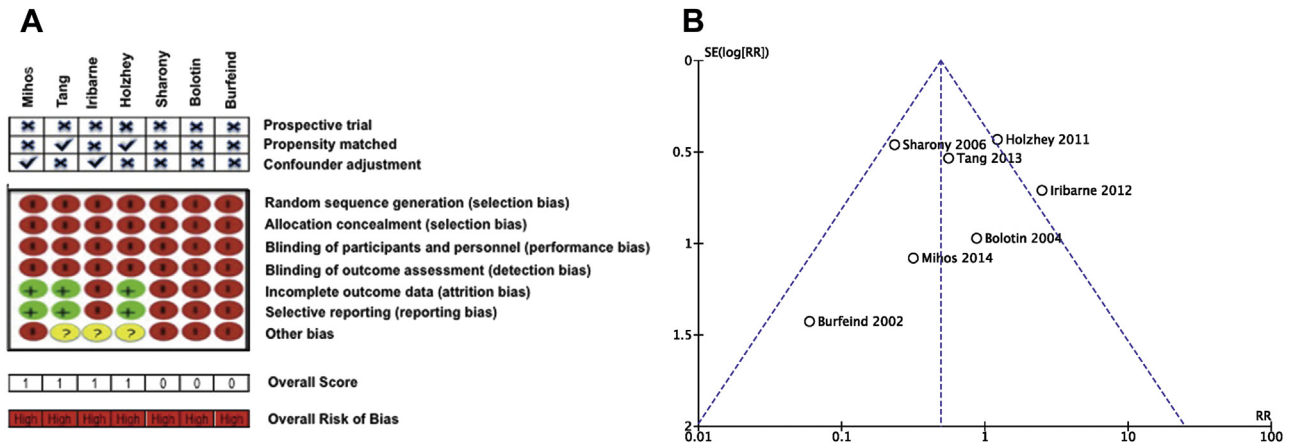

Fig 3. (A) Risk of bias assessment. (B) Funnel plot overall early mortality. (RR = risk ratio; SE = standard error.)

Moreover, a transthoracic aortic clamp was preferred over an intraaortic balloon clamp in all four series. In studies that included mainly redo operation patients [12–14], both ventricular fibrillation arrest and endo-clamping were used, although direct clamping was reported in some cases in one series [12].

As in other reports [1, 19], CPB time was significantly longer in the MIMVS group, but heterogeneity was evident as expected for continuous parameters. Overall meta-analysis also showed a reduced rate of post-operative AF with no heterogeneity. We also did not observe any differences in terms of achieving mitral valve repair between the two groups.

Four studies [8–11] reported follow-up, with two providing long-term follow-up [9, 11] (>5 years), but only Tang and colleagues [9] observed significantly longer survival rate for the MIMVS group.

This meta-analysis study allowed inclusion of 1,254 patients who would be difficult to accumulate prospectively for this particular topic. This study has, however, several limitations. Among the seven studies included, none were randomized controlled trials. Although MIMVS is associated with a significant learning curve and volume–outcome relationship, it was not possible to quantify the impact of this on the outcomes reported in this study; however, most of the cohorts included in the meta-analysis have published on a similar topic before and that could be interpreted as a high-volume experience. Nevertheless, bias in favor of the ST technique cannot be ruled out. To minimize the baseline heterogeneity of the population included in this meta-analysis because a EuroSCORE mean was not possible to calculate, we used a modification of the Ottawa–Newcastle scale based on comparability of all EuroSCORE II risk factors (Table 1). Another limitation of this study is that this meta-analysis included relatively limited mitral-specific long-term outcomes. In terms of follow-up, four studies reported data; of these, two included long-term survival [9, 11]. Only survival was reported, with no mention of freedom from reintervention—either catheter-based procedures or redo operation—or New York Heart Association functional class; hence, the long-term impact of MIMVS on high-risk patients in terms of durability of repair or freedom from reintervention on the mitral valve as well as functional class could not be assessed. Further studies are required to investigate the potential subgroup of patients in whom MIMVS may be of greater benefit.

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STATISTICAL COMMENTARY

Moscarelli and colleagues [1] provide a systematic review and meta-analysis of observational studies of minimally invasive mitral valve surgical procedures in high-risk patients. By combining results across seven studies meeting the inclusion criteria, they show comparable early mortality between minimally invasive mitral valve procedures and standard sternotomy. In addition, they report similar repair rates and better postoperative outcomes despite longer cardiopulmonary bypass times.

This report is noteworthy for several reasons. First, it reflects the high standards of conduct and reporting of systematic reviews and meta-analyses required by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). The implementation of standards adds to the reproducibility of studies such as this. Second, the authors clearly report their literature search strategy, which included searching multiple databases; their approach to data extraction (two readers); and the classification used for assessing the quality of the original studies and threats to bias. Third, they follow standard approaches to data analysis in the setting of a meta-analysis to assess variations in results among the original studies (heterogeneity), and they then use plots to demonstrate the distribution of results. These methods and reporting standards should now be consistently implemented across meta-analyses of randomized trials and observational studies.

Beyond reporting, why pay attention to this article? Importantly, this report demonstrates the potential for systematic review and meta-analysis to add power to address questions for which the original individual studies did not provide sufficient evidence. This is particularly helpful for side effects, adverse events, and measures that go beyond the original efficacy or effectiveness of interventions. Efficacy and effectiveness studies are typically powered to estimate the magnitude of the main effect (benefit) and are not powered to quantify the magnitude of even important adverse events (possible harms). The seven studies included in this analysis ranged from 22 patients undergoing minimally invasive procedures and 28 undergoing sternotomy, up to 143 in the minimally invasive procedures group and 143 in the comparison sternotomy group. The combined analysis, which weighted the studies according to the original precision of estimates, provides a summary across all 1,254 patients (523 minimally invasive mitral valve procedures and 731 standard sternotomy).

In addition to summarizing the published evidence, a systematic review and meta-analysis ideally can identify gaps in the literature, or implications for future studies to address uncertainties remaining after the systematic review. Here the authors note that subgroups of patients for whom minimally invasive procedures may be of greater benefit cannot be identified at present. Better and more consistent reporting of comorbidity, and the stratification of original studies on levels of risk, may help address this gap. Alternatively, by use of the data in the existing studies, an individual patient data meta-analysis with a central data center could implement analysis with the use of common definitions across the studies in a combined repeated analysis. This approach can use a multilevel analysis that controls for the original study design while also analyzing individual level data. This approach further reduces variation among studies introduced by the use of differing cutpoints and approaches to analysis. Consistent definitions of risk strata may be more easily implemented in such an analysis. Additional data will help refine approaches to assessing the tradeoff of surgical approaches for high-risk patients with comorbidities.

Graham A. Colditz, MD

Department of Surgery
Division of Public Health Science
Washington University School of Medicine
660 S Euclid Ave
St. Louis, MO 63108
email: colditzg@wustl.edu

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