Ministernotomy or minithoracotomy for minimally invasive aortic valve replacement: a Bayesian network meta-analysis

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Background: Establishing the relative merits of ministernotomy (MS) and minithoracotomy (MT) approaches to minimally invasive aortic valve replacement (MIAVR) is difficult given the limited available direct evidence. Network meta-analysis is a Bayesian approach that can combine direct and indirect evidence to better define the benefits and risks of MS and MT.

Methods: Electronic searches were performed using six databases from their inception to June 2014. Relevant studies utilizing a minimally invasive approach for aortic valve replacement were identified. Data were extracted and analyzed according to predefined clinical endpoints. Both traditional and Bayesian meta-analysis approaches were conducted.

Results: Compared to full sternotomy, MT was associated with longer cardiopulmonary bypass (CPB) duration (WMD, 9.99; 95% CI, 3.91, 16.07; I^2=55%; P=0.001) and cross-clamp duration (WMD, 7.64; 95% CI, 2.86, 12.42; P=0.002; I^2=74%). When compared to MS using network meta-analysis, no significant difference in duration was detected. Postoperative outcomes including 30-day mortality, stroke, and reoperation for bleeding and wound infection were comparable between MS and MT using both traditional and Bayesian meta-analysis techniques.

Conclusions: The current evidence demonstrates that MIAVR via MS or MT is a safe and efficacious alternative to conventional median sternotomy. MT may be associated with longer CPB and cross-clamp durations, but has similar post-operative outcomes compared to MS. An individualized approach tailored to both the patient and surgical team is likely to provide optimal outcomes.

Keywords: Aortic valve replacement; ministernotomy; minithoracotomy; Bayesian; network meta-analysis

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Introduction

Minimally invasive aortic valve surgery (MIAVR) has been increasingly accepted in the surgical community as a potential alternative to conventional sternotomy, with advantages of reduced trauma, improved cosmesis and reduced hospitalization (1,2). Ministernotomy (MS) is the most common approach to MIAVR and involves a small incision of the sternum, thus allowing access to the cardiac structures (*Figure 1*). However, more recent studies have described the minithoracotomy (MT) approach, which involves an incision between the ribs of the right chest to allow access to the heart (3-5). While several meta-analyses (6) and randomized trials (7-10) to date have demonstrated similar safety and efficacy between MIAVR and conventional aortic valve replacement (CAVR), there are few studies available which have directly compared MS and MT approaches. As such, the decision for selecting

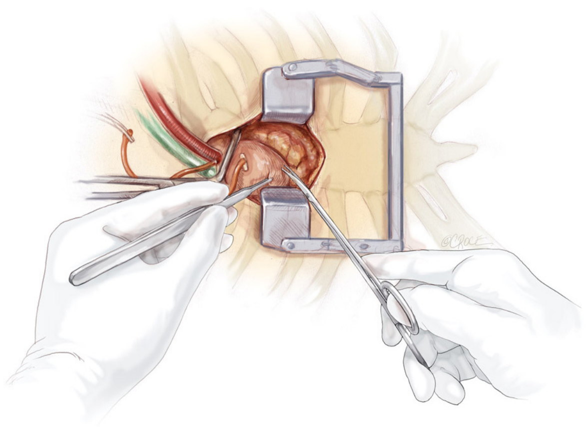

Figure 1 Minimally invasive aortic valve replacement offers an alternative surgical approach to median sternotomy with potential advantages of reduced trauma, intensive care stay, hospitalization, and improved cosmesis.

the MS or MT approach has largely been based on the surgeon's preference.

Network meta-analysis is a Bayesian statistical approach which allows comparison of two treatments or interventions by pooling together a full network of direct head-to-head and indirect evidence to produce a single, integrated effect estimate (11-13). The lack of robust clinical evidence directly comparing MS and MT necessitates a contemporary appraisal and thus, a network meta-analysis was performed to evaluate the current evidence base.

Materials and methods

Literature search strategy

Electronic searches were performed using Ovid Medline, PubMed, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club, and Database of Abstracts of Review of Effectiveness (DARE) from their date of inception to June 2014. To achieve the maximum sensitivity of the search strategy and identify all studies, we combined the terms "minimally invasive" OR "ministernotomy" OR "hemisternotomy" OR "partial sternotomy" OR "minithoracotomy" OR "partial thoracotomy" AND "aortic valve" AND "surgery" as either key words or MeSH terms. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies. All identified articles were systematically assessed using the inclusion and exclusion criteria.

Selection criteria

Eligible randomized controlled trials (RCTs) and propensity-score matched trials for the present systematic review and meta-analysis included those in which patient cohorts underwent minimally invasive aortic valve replacement via MS or MT versus aortic valve replacement by conventional sternotomy (CS). Studies that did not have randomized or propensity-matched cohorts were excluded. When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included for quantitative assessment at each time interval. All publications were limited to those involving human subjects. Abstracts, case reports, conference presentations, editorials, reviews and expert opinions were excluded.

Data extraction and appraisal

All data were extracted from article texts, tables and figures. Two investigators independently reviewed each retrieved article (K.P. and A.X.). Discrepancies between the two reviewers were resolved by discussion and consensus. The final results were reviewed by the senior investigators (M.D.E., T.D.Y.).

Traditional meta-analysis

For traditional pair-wise meta-analysis, the relative risk (RR) was used as a summary statistic. In the present study, both fixed- and random-effect models were tested. χ^2 tests were used to study heterogeneity between trials. I^2 statistic was used to estimate the percentage of total variation across studies, owing to heterogeneity rather than chance, with values greater than 50% considered as substantial heterogeneity. If there was substantial heterogeneity, the possible clinical and methodological reasons for this were explored qualitatively. In the present meta-analysis the results using the random-effects model were presented to take into account the possible clinical diversity and methodological variation between studies. Weighted Pearson's coefficient (r_s) was used to calculate correlation coefficients for meta-regression analysis of outcomes based on midpoint of study periods. All levels of significance (α) were two-sided.

Bayesian network meta-analysis

A Bayesian network meta-analysis was carried out to make indirect comparisons among treatments (MS *vs*. MT *vs*. CS)

Table 1 Characteristics of included randomized or propensity-matched studies comparing minimally invasive versus full sternotomy

First author	Year	Country	Study period	Type of study	Sample size*	Mini (n)	Full (n)	Predominant type of mini-approach	Median follow-up
Neely	2014	USA	2002-2014	PSM	1,319	552	552	Upper MS	NR
Merk	2014	Germany	2003-2012	PSM	2,051	477	477	'J' or inverted 'T' upper MS	3.1 ± 2.7^{M} years
Furukawa	2014	Germany	2009-2012	PSM	984	404	404	Partial upper MS	Until patient discharge
Ahangar	2013	India	2010-2012	RCT	60	30	30	Right anterolateral MT	NR
Gilmanov	2013	Italy	2004-2011	PSM	709	182	182	Right anterior MT	Until patient discharge
Glauber	2013	Italy	2005-2010	PSM	637	138	138	Right anterior MT	30 months
Bang	2012	South Korea	1997-2010	PSM	838	73	73	Upper MS	NR
Johnston	2012	USA	1995-2004	PSM	2,689	832	832	J upper MS	6.5 ± 3.0 yrs^{M}
Ruttman	2010	Austria	2006-2009	PSM	315	87	87	Anterolateral MT	Mini =17.7, Full =20.1
Calderon	2009	France	2003-2007	RCT	78	39	39	Reversed-L MS	NR
Tabata	2007	USA	1996-2005	PSM	140	41	41	Upper MS	NR
Moustafa	2007	Kuwait	NR	RCT	60	30	30	Reversed L-shaped MS	NR
Sharony	2004	USA	1995-2002	PSM	466	233	233	Right anterior MT	NR
Dogan	2003	Germany	NR	RCT	40	20	20	Partial upper MS	NR
Bonacchi	2002	Italy	1999-2001	RCT	80	40	40	Reversed-C MS	9.7 ± 5.7 months^{M}
Machler	1999	Austria	1996-1997	RCT	120	60	60	L-shaped MS	294 days^{M} (R, 30-745)
Aris	1999	Spain	NR	RCT	40	20	20	Reversed L-shaped MS	6 days

^{M}, mean; R, range; *, sample size after propensity-score matching; PSM, propensity-score matched study; RCT, randomized controlled trial; MS, ministernotomy; MT, minithoracotomy; NR, not reported; n, number of patients.

when direct comparisons were scarce. Estimates of relative effects and all model parameters were obtained via a random-effects network within a Bayesian framework using Markov Chain Monte Carlo simulation from the posterior distributions. Four parallel Markov Chain Monte Carlo simulations were run for a period of at least 50,000 interactions, until convergence was obtained. Inconsistency of evidence was assessed using node-splitting analysis when possible.

All analyses were conducted using R version 2.15.2 and GeMTC package version 0.4. If the difference between random effects variance and inconsistency variance was large (P<0.05), then significant heterogeneity was present.

Results

Quality of included studies

Our literature search identified 17 relevant studies, including seven randomized controlled trials (7,8,10,14-17) and ten propensity-score matched observational studies (4,18-26) (*Table 1*). A total of 6,516 patients were analysed, including 3,258 in the MIAVR group and 3,258 in the CAVR group. Seven studies included at least 100 patients in each arm (4,18-20,22,25,26), while ten studies included fewer than 100 patients in each arm (7,8,10,14-17,21,23,24). MS was directly compared with CS in 12 studies (7,8,10,15-19,21,22,24,26), while five studies (4,14,20,23,25) directly compared MT with CS. There were no randomized or propensity-matched studies that directly compared MS with MT approaches. Three studies reported mean or median follow-up greater than 12 months (4,18,22).

The cardiopulmonary bypass (CPB) duration was reported in all studies except one (10), while cross-clamp duration was reported in all studies. The total operation duration was reported in nine studies (7,8,10,14-16,18,19,23).

Study or Subgroup	MIAVR Mean	MIAVR SD	MIAVR Total	CAVR Mean	CAVR SD	CAVR Total	Weight	Mean Difference IV, Random, 95% CI
Ministernotomy								
Aris	95	20	20	83	19	20	6.4%	12.00 [-0.09, 24.09]
Bang	106.3	45.3	73	101.9	39.6	73	5.9%	4.40 [-9.40, 18.20]
Calderon	77.1	13.4	39	71.3	20.4	39	7.5%	5.80 [-1.86, 13.46]
Dogan	115	6.5	20	107	5.4	20	8.2%	8.00 [4.30, 11.70]
Furukawa	79	20	404	80	24	404	8.3%	-1.00 [-4.05, 2.05]
Johnston	73	32	832	95	37	832	8.2%	-22.00 [-25.32, -18.68]
Merk	82.2	25.7	477	82.3	21.7	477	8.3%	-0.10 [-3.12, 2.92]
Moustafa	85.67	6.79	30	90	8.3	30	8.2%	-4.33 [-8.17, -0.49]
Neely	106	0	124	0	0	0		Not estimable
Tabata	122.2	48.5	41	112.1	39.8	41	4.6%	10.10 [-9.10, 29.30]
Subtotal (95% CI)			**2060**			**1936**	**65.6%**	**0.47 [-7.02, 7.97]**
Heterogeneity: Tau² = 113.11; Chi² = 178.77, df = 8 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 0.12 (P = 0.90)								
Minithoracotomy								
Ahangar	122.1	20.8	30	121.8	18.6	30	6.9%	0.30 [-9.68, 10.28]
Gilmanov	117.5	41.9	182	104.1	34.6	182	7.4%	13.40 [5.51, 21.29]
Glauber	121.6	45	138	107.1	32.3	138	7.1%	14.50 [5.26, 23.74]
Ruttman	151.4	43.1	87	129	66.9	87	5.2%	22.40 [5.68, 39.12]
Sharony	110	34	233	104	33	233	7.8%	6.00 [-0.08, 12.08]
Subtotal (95% CI)			**670**			**670**	**34.4%**	**9.99 [3.91, 16.07]**
Heterogeneity: Tau² = 25.16; Chi² = 8.86, df = 4 (P = 0.06); I² = 55%								
Test for overall effect: Z = 3.22 (P = 0.001)								
Total (95% CI)			**2730**			**2606**	**100.0%**	**4.00 [-2.15, 10.15]**
Heterogeneity: Tau² = 116.67; Chi² = 223.67, df = 13 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 1.27 (P = 0.20)								

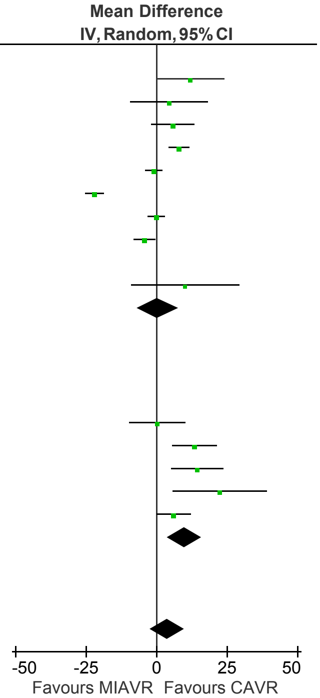

Figure 2 Forest plot of the weighted mean difference (WMD) in cardiopulmonary bypass (CPB) duration between minimally invasive (MIAVR) and conventional aortic valve replacement (CAVR). The estimate of the WMD of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% confidence interval (CI). On each line, the mean and standard deviation (SD) of CPB durations in individual studies is shown for both treatment and control groups. For each subgroup, the sum of the statistics, along with the summary WMD, is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. IV, inverse variance.

Early mortality (30-day) was reported in all studies except one (14). Stroke outcomes were not reported in five studies (7,8,10,14,17), while reoperation for bleeding outcomes were not reported in three studies (14,17,18). Wound infection rates were reported in all studies except three (7,19,26). Other outcomes including transfusions, atrial fibrillation, pacemaker implantations, myocardial infarctions, tamponade, pneumonia, pleural effusions, respiratory and renal failures were reported in fewer than 10 studies, and these outcomes were considered to have insufficient data for Bayesian network meta-analysis in the present study.

Assessment of operational data

Across all included studies using traditional pairwise meta-analysis, there was no significant difference in CPB duration between MIAVR and CAVR cohorts (WMD, 4.00; 95% CI, –2.15-10.15; P=0.20; I^2=94%). For the MS subgroup, this trend was maintained with no difference in CPB duration between cohorts (WMD, 0.47; 95% CI, –7.02-7.97; P=0.80; I^2=94%). However, CPB duration was found to be significantly longer in the MT subgroup compared with matched CAVR patients (WMD, 9.99; 95% CI, 3.91-16.07; I^2=55%; P=0.001) (*Figure 2*). Bayesian network meta-analysis did not show significant differences between MS and MT approaches (WMD, –9.59; 95% CI, –24.03-5.47; *Table 2*).

Pairwise meta-analysis demonstrated that MIAVR had significantly longer cross-clamp duration than CAVR (WMD, 4.01; 95% CI, 0.31-7.70; P=0.03; I^2=93%) (*Figure 3*). Subgroup analysis showed that this difference was only significant in the MT group (WMD, 7.64; 95% CI, 2.86-12.42; P=0.002; I^2=74%) and not the MS group. A similar trend was obtained via Bayesian analysis, where the difference between the MT and CAVR groups almost reached significance (WMD, –7.88; 95% CI, –15.60-0.05; *Table 2*).

Assessment of mortality

There was no difference in 30-day mortality rates between MIAVR and CAVR across all included studies (RR, 0.74;

Table 2 Network meta-analysis of direct and indirect evidence comparisons of MIAVR and CAVR for aortic valve replacement

Outcome	Pooled OR (95% CI) or WMD (95% CI)		
	CS *vs.* MS	CS *vs.* MT	MS *vs.* MT
CPB	–0.30 (–8.64, 7.50)	–9.84 (–22.42, 2.01)	–9.59 (–24.03, 5.47)
Cross-clamp	–2.25 (–8.40, 3.52)	–7.88 (–15.60, 0.05)	–5.62 (–15.16, 4.40)
30-day mortality	1.81 (0.85, 4.07)	1.16 (0.43, 3.08)	0.63 (0.18, 2.17)
Strokes	1.51 (0.69, 3.59)	0.88 (0.34, 2.97)	0.59 (0.17, 2.34)
Reoperation for bleeding	1.01 (0.65, 1.77)	1.01 (0.52, 2.01)	1.00 (0.41, 2.24)
Wound infection	1.18 (0.49, 3.45)	2.09 (0.73, 8.37)	1.67 (0.39, 9.20)

MIAVR, minimally invasive aortic valve replacement; CAVR, conventional aortic valve replacement; OR, odds ratio; WMD, weighted mean difference; CI, confidence interval; CPB, cardiopulmonary bypass; CS, conventional sternotomy; MS, ministernotomy; MT, minithoracotomy.

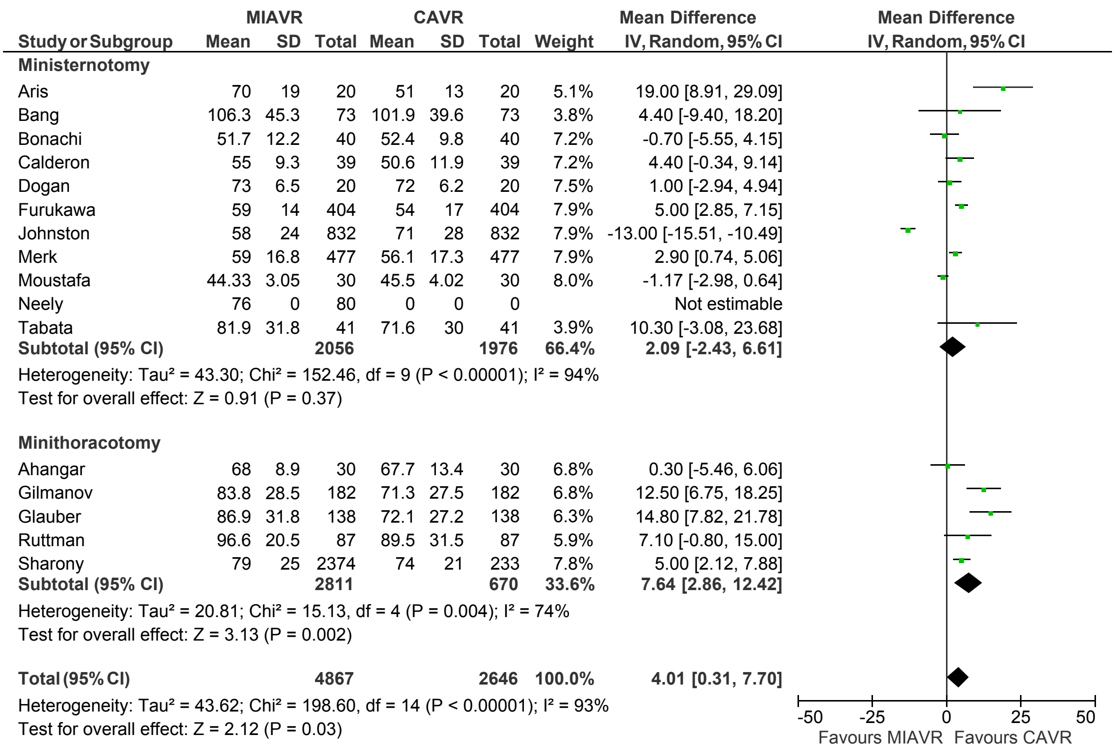

Figure 3 Forest plot of the weighted mean difference (WMD) in cross-clamp duration between minimally invasive (MIAVR) and conventional aortic valve replacement (CAVR). The estimate of the WMD of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% confidence interval (CI). On each line, the mean and standard deviation (SD) of cross-clamp durations in individual studies is shown for both treatment and control groups. For each subgroup, the sum of the statistics, along with the summary WMD, is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. IV, inverse variance.

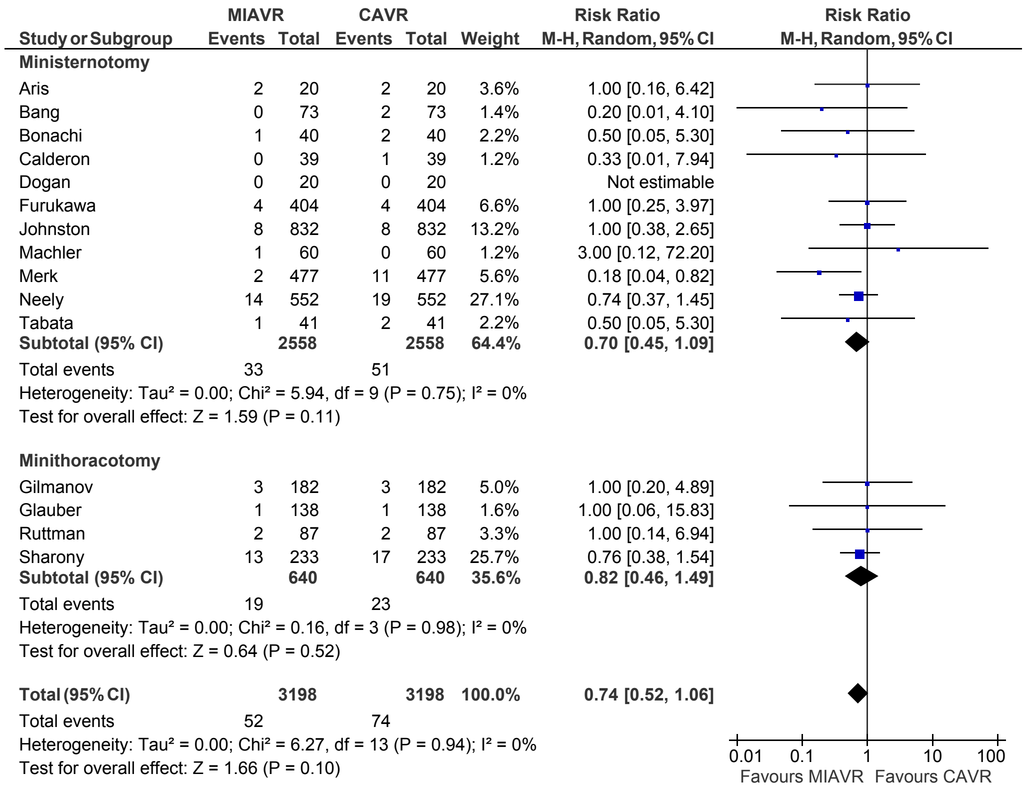

Figure 4 Forest plot of the risk ratio (RR) of 30-day mortality in patients undergoing minimally invasive (MIAVR) versus conventional aortic valve replacement (CAVR). The estimate of the RR of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% confidence interval (CI). On each line, the number of events as a fraction of the total number is shown for both treatment and control groups. For each subgroup, the sum of the statistics, along with the summary RR, is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. M-H, Mantel-Haenszel.

95% CI, 0.52-1.06; P=0.10; I^2=0%). From subgroup analysis, there was also no difference between MS and CAVR (RR, 0.70; 95% CI, 0.45-1.09; P=0.11; I^2=0%) or MT and CAVR (RR, 0.82; 95% CI, 0.46-1.49; P=0.52; I^2=0%) (*Figure 4*). Similar results were obtained using network meta-analysis, with no difference between MS and MT detected (OR, 0.63; 95% CI, 0.18-2.17; *Table 2*).

Assessment of safety

From the studies included for analysis of stroke outcomes, no difference was detected between MIAVR and CAVR cohorts (RR, 0.81; 95% CI, 0.55-1.21; P=0.31; I^2=0%) (*Figure 5*). Subgroup testing via pairwise analysis did not reveal differences between MS and CS (RR, 0.74; 95% CI, 0.47-1.17; P=0.20; I^2=0%) or MT and CS (RR, 1.09; 95% CI, 0.48-2.51; P=0.83; I^2=0%). Likewise for reoperations for bleeding, no difference was found between MIAVR and CAVR overall (RR, 1.02; 95% CI, 0.80-1.31; P=0.85; I^2=0%) (*Figure 6*), nor was there any difference between MS and CS (RR, 1.04; 95% CI, 0.79-1.39; P=0.76) or MT and CS (RR, 0.97; 95% CI, 0.58-1.60; P=0.89). Wound infection rates were also found to be equivalent when comparing MS with CS (RR, 0.83; 95% CI, 0.39-1.76; P=0.62) and MT with CS (RR, 0.60; 95% CI, 0.25-1.43; P=0.25) (*Figure 7*).

From network multiple-treatment meta-analysis, there was equivalent safety between MS and MT in terms of stroke (OR, 0.63; 95% CI, 0.18-2.17), reoperation for bleeding (OR, 1.00; 95% CI, 0.41-2.24), and wound infection rates (OR, 1.67; 95% CI, 0.39-9.20).

Meta-regression analysis

Random effects meta-regression analysis considering variables of interest one at a time showed that midpoint of study period only significantly negatively correlated with

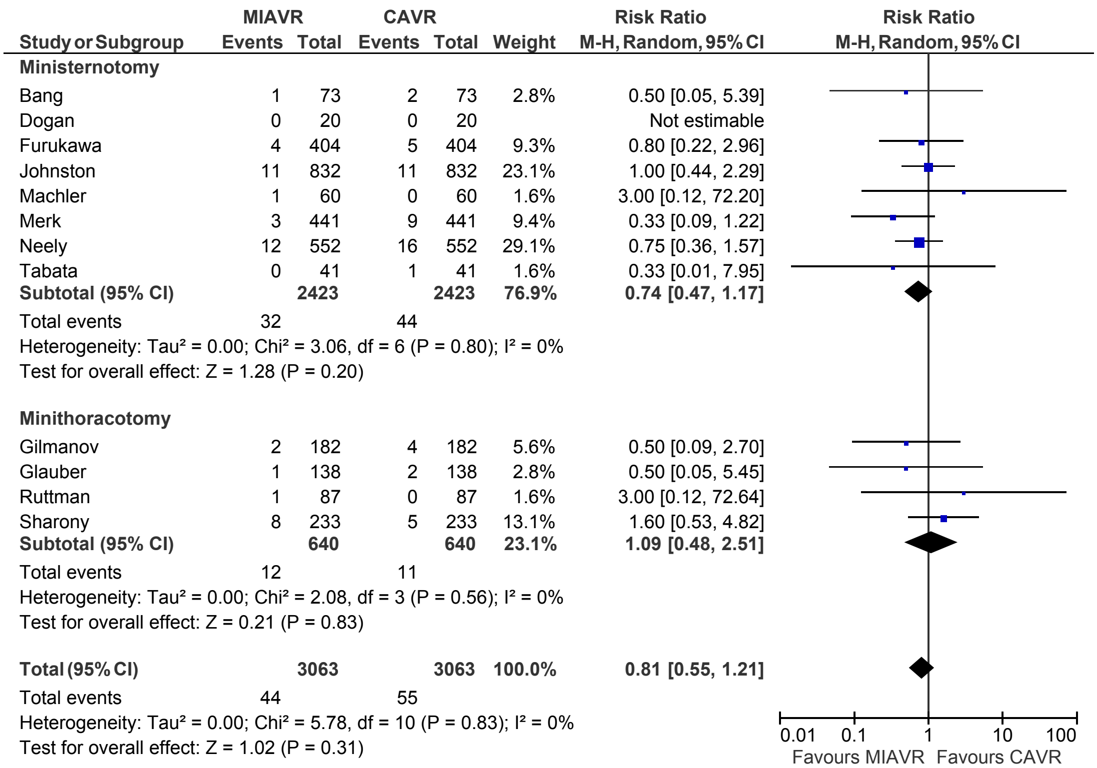

Figure 5 Forest plot of the risk ratio (RR) of postoperative strokes in patients undergoing minimally invasive (MIAVR) versus conventional aortic valve replacement (CAVR). The estimate of the RR of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% confidence interval (CI). On each line, the number of events as a fraction of the total number is shown for both treatment and control groups. For each subgroup, the sum of the statistics, along with the summary RR, is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. M-H, Mantel-Haenszel.

30-day mortality rates (Pearson's coefficient, r=–0.5515; P=0.0409; *Figure 8*). No significant correlation was found between midpoint of study period and CPB duration (P=0.3415), cross-clamp duration (P=0.6011), stroke (P=0.2048), reoperation for bleeding (P=0.9669) and wound infection rates (P=0.4175).

Discussion

There have been few studies to date that have discussed the results of MS versus MT for MIAVR directly. In the only direct comparative study, Miceli *et al.* (27) investigated 251 MT and 155 MS patients and concluded that MT was associated with lower postoperative atrial fibrillation and shorter hospitalization. In contrast, subgroup analysis of a recent meta-analysis (2) suggested that MS may be associated with superior mortality outcomes compared to MT patients. These studies are susceptible to the inherent biases of non-randomized, observational designs that make it difficult to conclusively compare the different surgical approaches. Furthermore, conventional direct meta-analysis fails to measure the relative efficacy of MS, MT and CS, as it only synthesizes studies with the same comparator group. Instead, a Bayesian network meta-analysis can be used to provide a valid statistical comparison between different interventions by combining the network of direct head-to-head and indirect comparative evidence (11,12). As such, both traditional frequentist and Bayesian chain meta-analysis of higher quality randomized and propensity score-matched studies were performed to assess the relative safety and efficacy of MS, MT and CS.

While MS had similar CPB and cross-clamp duration compared with CS, MT was associated with significantly longer CPB and cross-clamp durations. There are several reasons as to why partial thoracotomy may be associated with slightly longer operational outcomes. Firstly,

Study or Subgroup	MIAVR Events	MIAVR Total	CAVR Events	CAVR Total	Weight	Risk Ratio M-H, Random, 95% CI
Ministernotomy						
Bang	7	73	6	73	5.6%	1.17 [0.41, 3.30]
Bonachi	0	40	3	40	0.7%	0.14 [0.01, 2.68]
Calderon	0	39	2	39	0.7%	0.20 [0.01, 4.04]
Dogan	1	20	1	20	0.8%	1.00 [0.07, 14.90]
Furukawa	23	404	26	404	20.6%	0.88 [0.51, 1.52]
Johnston	46	832	36	832	33.6%	1.28 [0.84, 1.96]
Machler	5	60	3	60	3.2%	1.67 [0.42, 6.66]
Moustafa	2	30	5	30	2.5%	0.40 [0.08, 1.90]
Neely	9	552	10	552	7.6%	0.90 [0.37, 2.20]
Tabata	1	41	0	41	0.6%	3.00 [0.13, 71.56]
Subtotal (95% CI)		**2091**		**2091**	**76.0%**	**1.04 [0.79, 1.39]**
Total events	94		92			
Heterogeneity: Tau² = 0.00; Chi² = 6.64, df = 9 (P = 0.67); I² = 0%						
Test for overall effect: Z = 0.30 (P = 0.76)						
Minithoracotomy						
Gilmanov	8	182	11	182	7.7%	0.73 [0.30, 1.77]
Glauber	9	138	6	138	6.0%	1.50 [0.55, 4.10]
Ruttman	4	87	5	87	3.7%	0.80 [0.22, 2.88]
Sharony	8	233	8	233	6.6%	1.00 [0.38, 2.62]
Subtotal (95% CI)		**640**		**640**	**24.0%**	**0.97 [0.58, 1.60]**
Total events	29		30			
Heterogeneity: Tau² = 0.00; Chi² = 1.22, df = 3 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
Total (95% CI)		**2731**		**2731**	**100.0%**	**1.02 [0.80, 1.31]**
Total events	123		122			
Heterogeneity: Tau² = 0.00; Chi² = 7.93, df = 13 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.85)						

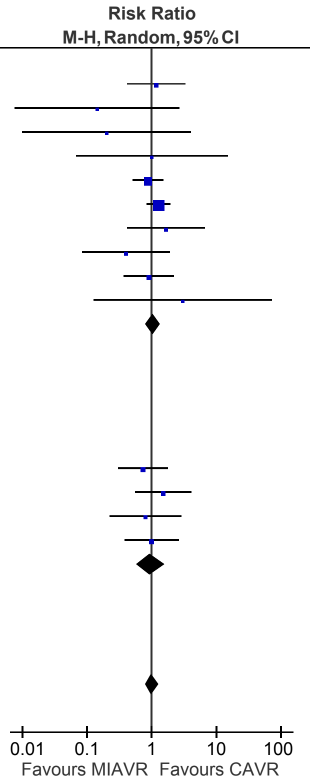

Figure 6 Forest plot of the risk ratio (RR) of reoperations for bleeding in patients undergoing minimally invasive (MIAVR) versus conventional aortic valve replacement (CAVR). The estimate of the RR of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% confidence interval (CI). On each line, the number of events as a fraction of the total number is shown for both treatment and control groups. For each subgroup, the sum of the statistics, along with the summary RR, is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. M-H, Mantel-Haenszel.

compared to MS and CS, MT may provide a limited vision of the aortic valve due to greater distance from the thoracic access. This may reduce maneuverability and increase the difficulty of using long-shaft instruments. The increased complexity of the MT procedure compared to MS and CS approaches could also explain the longer bypass and cross-clamp durations observed. Furthermore, the MT approach has only been used extensively in recent years, with a greater number of centers now experienced with the MS approach, thus traversing the learning curve associated with minimally invasive surgical techniques. While the evidence indicates that MT operations may be longer, it is important to note that the absolute difference is approximately 10 and 5 minutes for CPB and cross-clamp respectively, which may not be clinically significant. The increasing use of sutureless implantation technique may facilitate these minimally invasive approaches in the future, and thus may reduce CPB and cross-clamp durations even further (28). However, whether sutureless AVR is associated with comparable short and long term results with conventional AVR remains to be investigated by prospective randomized studies.

Randomized and propensity-matched evidence to date suggests that MIAVR is an equally safe and efficacious alternative to median sternotomy for aortic valve replacement. No significant differences in 30-day mortality, stroke, reoperations for bleeding and wound infections were found for MIAVR overall. These results were also consistent with Bayesian network meta-analysis, suggesting that both MS and MT approaches are safe, efficacious and comparable. There have been some previous concerns that the standard MT approach requires retrograde arterial perfusion through the femoral artery, which has been associated with increased risk of stroke (29,30). However, this risk is not consistently reported across the literature,

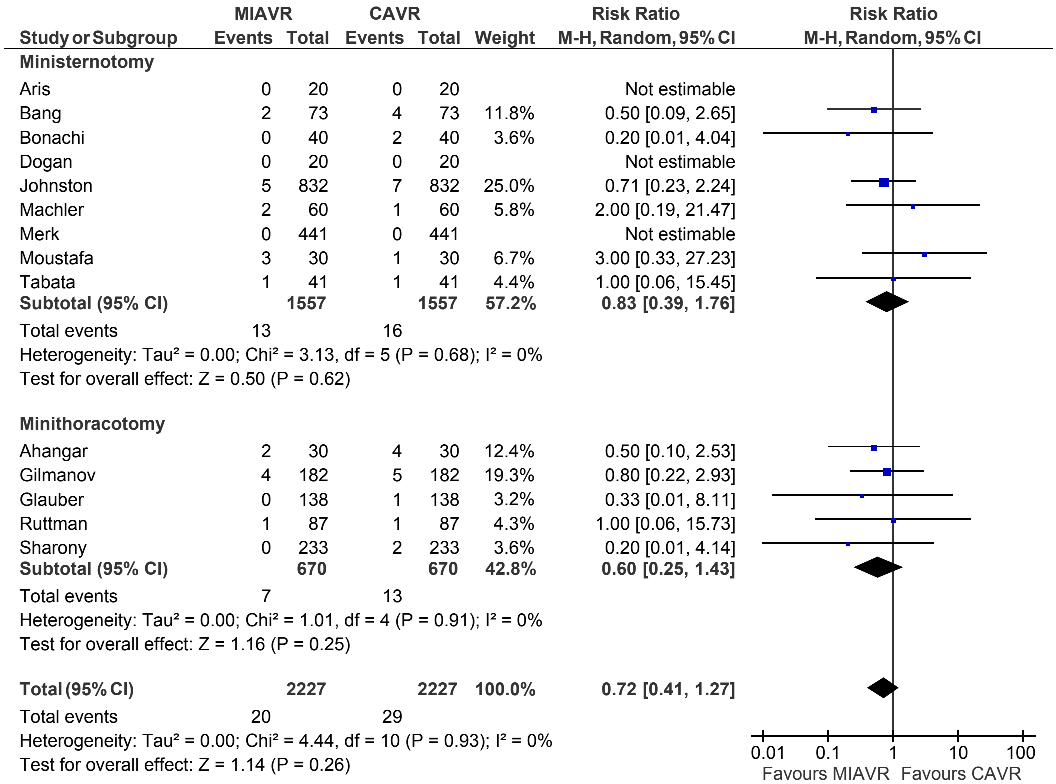

Figure 7 Forest plot of the risk ratio (RR) of wound infections in patients undergoing minimally invasive (MIAVR) versus conventional aortic valve replacement (CAVR). The estimate of the RR of each trial corresponds to the middle of the squares, and the horizontal line shows the 95% confidence interval (CI). On each line, the number of events as a fraction of the total number is shown for both treatment and control groups. For each subgroup, the sum of the statistics, along with the summary RR, is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. M-H, Mantel-Haenszel.

with other institutions reporting excellent stroke outcomes with femoral cannulation (31). Given the inconsistent data available on femoral versus central cannulation, it is likely that the optimal cannulation strategy should be individualized to the specific patient. Retrograde arterial flow can also lead to iliac artery dissections, another complication which may be associated with MT and can lead to increased mortality rates. Thus MS utilizing central aortic cannulation may also result in improved safety and mortality outcomes. In contrast to MS which involves a small sternal incision, MT avoids incision of the sternum and rib bones, and thus would reduce wound complication rates and chance of infection (6). While these potential complications do warrant concern, the results of our current meta-analysis show both MS and MT are safe and efficacious approaches for AVR with similar complication profiles.

While other outcomes are not well reported by the included studies and thus not available for Bayesian analysis, they must still be considered and factored when making the clinical decision to opt for a MS or MT approach. Firstly, the MS approach involves splitting the sternum, often in one or two directions. Consequently, a greater amount of time is required for the sternum to heal, and this may potentially prolong hospitalization (6). With a sternal incision, even if it is smaller, the time required for the bone to heal also means that restrictions are imposed on patients for a period following the operation to avoid excess mechanical stress. While proponents of MS suggest that MT may be associated with more pain, due to stretching of intercostal nerves (32), muscles and parietal pleura, the ease of delivering intercostal nerve block must also be considered. Given the complex learning curve and the apparent evidence of equivalent safety in MS and MT, it seems the best approach is one that is individualized not only to the patient but also to the technical skill and

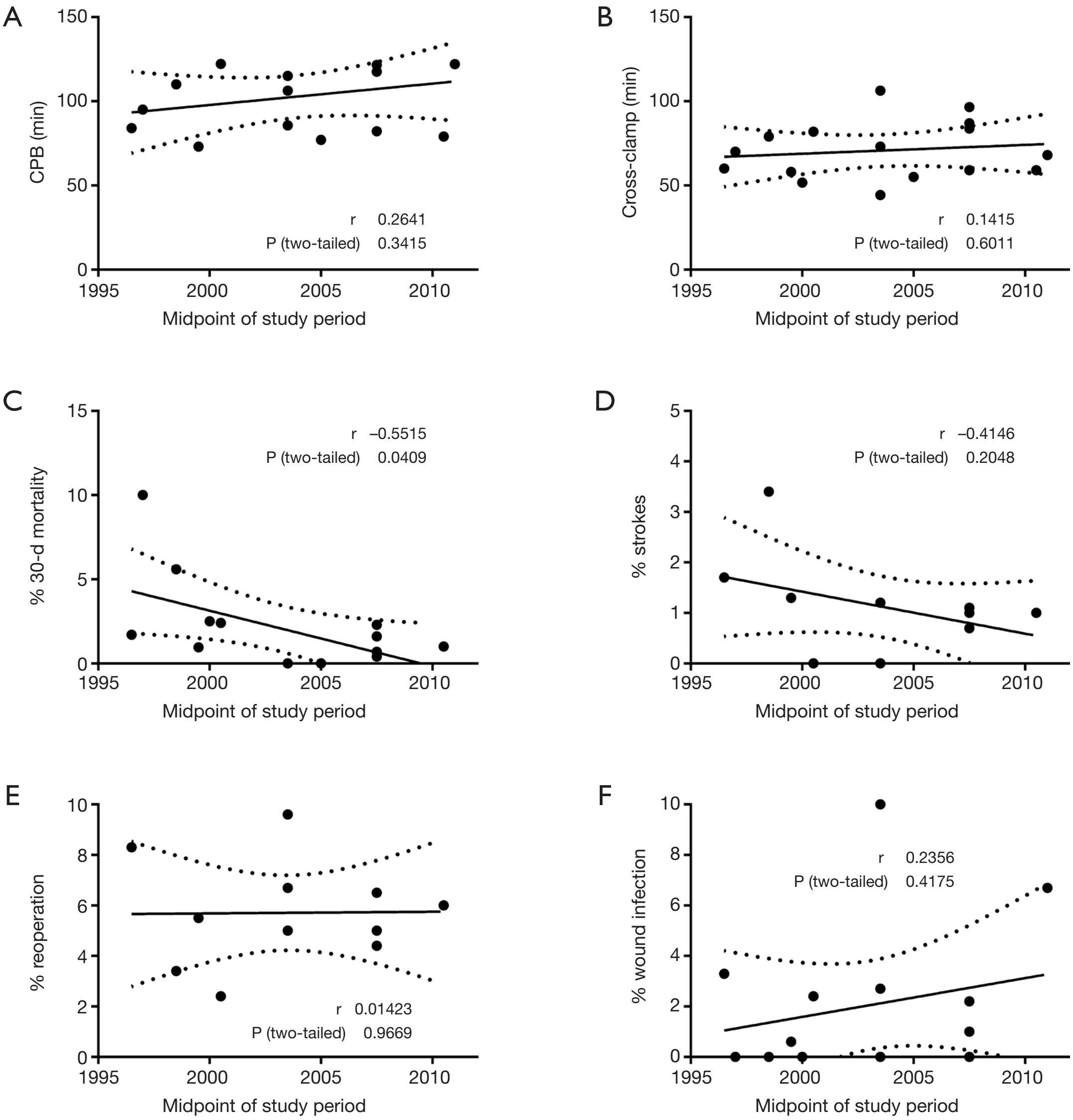

Figure 8 Meta-regression analyses showing significant correlation between the midpoint of the study period and 30-day mortality rate. The solid line indicates the correlation trend line, while dotted lines indicate the 95% confidence interval.

experience of the heart team involved.

Limitations

The present network meta-analysis has several constraints. Firstly, Bayesian analysis could not be performed on all outcomes including intensive care stay, hospitalization length and pain scoring, due to incomplete or inconsistent reporting of outcomes. Other relevant patient outcome measures including quality of life scores and cost-effectiveness economic analyses were rarely carried out. As such, these outcomes could not be compared between MS, MT and CS approaches for MIAVR. Secondly, there were no randomized or propensity-matched studies that directly compared MS and MT approaches. As such, inconsistency could not be statistically assessed using node-splitting methods. To maximize exchangeability of the included studies, carefully chosen randomized and propensity-matched trials were included with matched baseline characteristics. The more conservative results obtained using an inconsistency model, as opposed to a consistency model, were also presented. Despite these measures there was still significant heterogeneity detected in the operative parameters including CPB and cross-clamp duration, which may be due to different patient cohort characteristics and selection criteria among the studies. The heterogeneity may also reflect the variation in experience and expertise of different centers, given that MIAVR is associated with a significant learning curve. Thirdly, although mortality and morbidity outcomes were favorable in the short term, there is a shortage of robust long term clinical data.

Future adequately powered, prospective studies directly comparing MS and MT with consistent and complete reporting will be necessary to inform future policies and evidenced-based guidelines. Additionally, collaborative pooling of individual patient data, propensity-matched analyses and adequately powered randomized studies will assist in patient selection, risk stratification and prognosis. Multi-institutional registries and prospective studies investigating sutureless AVR, overseen by the International Valvular Surgery Study Group (IVSSG), have great potential to overcome the limitations of smaller sized observational studies.

Conclusions

The current evidence demonstrates that MIAVR via MS or MT is a safe and efficacious alternative to CAVR. Traditional and Bayesian analyses were consistent and did not yield any statistical differences between MS and MT approaches, except for longer CPB and cross-clamp durations with MT. Continual improvements in the long term safety and efficacy of sutureless valve technology may facilitate elimination of such differences in operative times. An individualized approach tailored to both the patient and surgical team is recommended for optimal outcomes.

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