Minimally Invasive versus Conventional Surgery of the Ascending Aorta and Root: A Systematic Review and Meta-Analysis.

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Key question: *How do the intraoperative and perioperative outcomes of minimally invasive surgery of the aorta compare to median sternotomy?*

Key findings

- *Mortality was similar for both groups*
- *There was some evidence of improved outcomes for minimally invasive patients.*

Take home message: *Minimally invasive surgery of the aorta appears to be safe, but the quality of the available evidence is low. Randomised studies are needed.*

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Summary

Limited uptake of minimally invasive surgery (MIS) of the aorta hinders assessment of its efficacy compared to median sternotomy (MS). The objective of this systematic review is to compare operative and perioperative outcomes for MIS vs MS. Online databases Medline, EMBASE, Cochrane Library, and Web of Science were searched from inception until July 2018. Both randomized and observational studies of patients undergoing aortic root, ascending aorta, or aortic arch surgery by MIS vs MS were eligible for inclusion. Primary outcomes were 30-day mortality, reoperation for bleeding, perioperative renal impairment and neurological events. Intraoperative and postoperative timing measures were also evaluated. Thirteen observational studies were included comparing 1,101 MIS and 1,405 MS patients. The overall quality of evidence was very low for all outcomes. Mortality and the incidence of stroke was similar between the two cohorts. Meta-analysis demonstrated increased length of cardiopulmonary bypass (CPB) time for patients undergoing MS (standardized mean difference (SMD) 0.36, 95% confidence interval (CI) 0.15-0.58, p=0.001). Patients receiving MS spent more time in hospital (SMD 0.30, 95% CI 0.17-0.43, p<0.001), and intensive care (SMD 0.17, 95% CI 0.06-0.27, p<0.001). Reoperation for bleeding (risk ratio (RR) 1.51, 95% CI 1.06-2.17, p=0.024) and renal impairment (RR 1.97, 95% CI 1.12-3.46, p=0.019) were also greater for MS patients. There was substantial heterogeneity in meta-analyses for CPB and aortic cross-clamp timing outcomes. MIS may be associated with improved early clinical outcomes compared to MS, but the quality of the evidence is very low. Randomized evidence is needed to confirm these findings.

Key words: *Minimally invasive; Aortic surgery; Meta-analysis*

Introduction

Median sternotomy (MS) is the gold-standard surgical approach for dealing with thoracic aortic pathology, offering excellent exposure for access to the aorta and central cannulation [1]. The technical complexity and steep learning curves associated with minimally invasive surgery (MIS) of the aorta act as barriers, hindering the widespread adoption of these methods. Nevertheless, the proposed reduction in postoperative pain and hospital stay, alongside improved cosmesis in minimally invasive aortic valve surgery [2,3] make MIS techniques attractive.

Well-established operations of the aortic root, such as the Bentall-De-Bono [4] and valve-sparing root replacement (David) [5] procedures can now be performed via much smaller incisions. Additionally, minimal access techniques have proven to be diverse approaches, allowing the surgeon to carry out isolated or concomitant procedures of the aortic arch [6,7]. Numerous case series assessing MIS have found it to be safe in selected patients [8,9,10]. However, the paucity of comparative studies investigating MIS vs MS makes it difficult for surgeons to assess the true benefit of minimally invasive techniques in thoracic aorta surgery.

The aim of this study is to comprehensively review the current body of evidence comparing MIS of the aorta with analogous procedures performed via MS. We performed a systematic review and meta-analyses to evaluate if MIS for pathologies of the aorta is a safe and feasible alternative to the current approach in terms of its perioperative outcomes.

Material and Methods

The protocol for this review can be found on the PROSPERO website, registration number: **CRD42018102726**

Selection Criteria

Both randomized and observational studies of patients undergoing aortic root, ascending aorta, or aortic arch surgery comparing minimal access versus a MS were eligible for inclusion. Minimal access was defined as any incision type other than MS [11]. Studies were excluded if they did not have a comparison group, if they included patients receiving isolated aortic valve or abdominal aortic procedures only, or if more than 10% of study participants were emergency cases or had previous cardiac surgery. Studies performing concomitant procedures were included if the data for patients undergoing procedures of interest could be identified, or if 80% or more of the study patients underwent procedures of interest. No restriction was made on language or study size. Where multiple publications were available for the same cohort study, we used the data from the publication reporting the largest cohort and/or the most up to date results. To reduce the risk of publication bias, studies presenting only an abstract without a full text were included.

Primary outcomes were 30-day mortality, reoperation for bleeding, perioperative renal impairment and neurological events. Intraoperative and postoperative timing measures were also evaluated.

Literature Search Strategy

Electronic searches were performed using Ovid Medline, Embase, the Cochrane Library, and the Web of Science from inception until July 2018. We combined the terms: (aorta **or** aortic **or** aortic root **or** aortic arch **or** ascending aorta) **AND** (surgical **or** surgeries **or** replacement **or** operation **or** ministernotomy **or** hemisternotomy **or** hemi-sternotomy **or** mini-sternotomy). All terms were searched as both text words and subject headings. The full search strategy is supplied in **Supplementary Appendix 1.** To look for further relevant literature we used the phrases "minimally invasive aortic surgery", "minimally invasive aortic root/arch surgery", and "minimally invasive ascending aorta surgery" to search websites and journals of relevance such as CTSnet and Annals of Cardiothoracic Surgery. The reference lists of included studies were reviewed to identify further potentially relevant studies. An expert cardiothoracic surgeon (H.V) was consulted regarding the existence of any unpublished material.

Data Extraction and Critical Appraisal of Evidence

Two reviewers (T.R & P.R) independently reviewed retrieved citations using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). For all relevant records, full papers were retrieved and read in full by two reviewers independently (T.R & P.R). Discrepancies were resolved by consensus, and where necessary inclusion of a third reviewer (J.S). Data extraction was completed by T.R and checked by P.R.

Statistical Analysis

We calculated the weighted arithmetic mean of patient baseline characteristics to look for differences between groups. For binary outcomes, we estimated the summary risk ratio (RR) and 95% confidence intervals from the reported number of events and participants from eligible studies. For continuous outcomes, we anticipated substantial variation between studies in terms of methods, technique, and operations performed making the raw mean difference less valid in a meta-analysis [12]. We therefore estimated the standardised mean difference (SMD) and its standard error (SE) from the reported means, standard deviations (SD) and numbers of participants [13], which accounts for some of these differences. If medians and inter-quartile ranges (IQR) were presented, the median was substituted for the mean and the SD was estimated from the IQR [14] if we considered the distribution looked normal (i.e. the IQR was reasonably symmetrical about the median). Both fixed-effect and random-effects models were estimated and presented. Because of the technical differences in surgery of the aortic root and ascending aorta when compared to the aortic arch, we performed subgroup analysis and meta-regression for each outcome to assess if there was evidence of a difference between studies including and excluding arch procedures. The I^2 statistic was used to estimate the percentage variation in the average treatment effect due to differences between studies [15]. We considered a value greater than 50% to represent substantial heterogeneity, and we considered potential reasons for such variation. The effect of small-study effect and publication bias was assessed using visual inspection of funnel plots [16]. P-values were two-tailed. Stata Version 15.1 (StataCorp LLC) was used for all statistical analysis.

Assessment and Evaluation of the Quality of Evidence

The risk of bias was assessed using the Risk of Bias in Non-Randomized Trials- of Interventions (ROBINS-I) tool [17]. ROBINS-I examines seven domains of bias: confounding, selection bias, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes, and bias in the selection of the reported result. Studies are judged to be at ‘low’, ‘moderate’, ‘serious’, or ‘critical’ for risk of bias. Studies judged ‘critical’ were excluded from synthesis. The quality of evidence for each of the main outcomes was assessed using the GRADE scoring system [18], using GRADEpro software (available from www.gradepro.org).

Results

Study selection and Characteristics of Included Studies

Literature searches of online databases yielded 4430 citations and an additional 33 records were found from other sources. Of these, 143 relevant articles were read in full and assessed against the inclusion criteria, and 15 were included in the review [19,20,21,22,23,24,25,26,27,28,29,30,31,32,33]. After assessment of the risk of bias two studies were rated as having critical risk of bias and were not included in further analysis [27,29], thus leaving 13 studies for descriptive analysis. One further study was excluded from quantitative synthesis as no useable data existed for either binary or continuous outcomes [21]. Twelve studies were included in the quantitative synthesis, comprising 1,101 patients in the MIS and 1,405 in the MS group. This information is shown in Figure 1 [34].

Table 1 illustrates the characteristics of the inclu7ded studies. Three studies were only reported in abstracts from posters and conferences [20,21,30]. Less than 100 patients were investigated in three included articles [21,23,31]. Only one study involved more than 500 participants [25]. Mean follow-up time was provided for only 4 studies [20,28,31,33].

Patient Characteristics

The weighted means of patient baseline characteristics were similar between MIS and MS groups (Supplementary Table 1): for example age (57.6 vs 58.0 years), sex (72.6% vs 74.6% male), left ventricular ejection fraction (58.8% vs 58.1%), New York Heart Association functional class ≥3 (9.5% vs 11.2%), bicuspid aortic valve (58.1% vs 59.1%), hypertension (61.4% vs 63.9%), diabetes mellitus (7.2% vs 7.7%) and chronic obstructive pulmonary disease (7.1% vs 7.7%). The percentage of patients with aortic insufficiency (AI) grade ≥3 was higher in the MIS group (57.3% vs 48.2%), although this was reported by only two studies [28,33]. One study included 3 (1.5%) patients requiring emergency procedures [28], all remaining studies only included elective procedures.

Interventions

The indication, procedure, and concomitant procedures performed in the studies are summarised in Supplementary Table 2. The indication for operation varied between studies for the MIS and MS cohorts, though 10 articles reported aortic dilatation or aneurysm as an indication [19,20,23,24,25,26,28,31,32,33]. Aortic root replacement was performed in 12 institutions [19,20,21,22,23,25,26,28,30,31,32] and ascending aorta replacement was performed in six centres [22,24,25,28,30,32]. Four studies reported operations of the aortic arch [24,28,32,33], with only one explicitly stating that they performed complete arch replacement [28]. There were differences in the proportion of patients in the MIS and MS cohorts receiving each primary aortic intervention in seven studies [20,22,23,25,28,30,32]. The Bentall procedure was performed by six institutions [19,20,22,26,30,32], and eight institutions operated on the aortic valve concomitantly [22,23,24,25,28,30,32,33]. Other additional procedures were performed by three institutions [23,28,33] and included mitral valve surgery and coronary artery bypass grafting. The proportion of patients receiving each of these concomitant procedures was in general greater for the MS cohort in two studies [23,33], whilst in one study MIS patients were more likely to undergo additional surgery [28].

The ‘J’ ministernotomy to the third or fourth intercostal space was used in all but one study, instead opting for a right or right lateral thoracotomy [24]. One study also performed MIS through an ‘inverted-T’ ministernotomy [19]. The cannulation technique and strategies for myocardial protection varied widely between studies. They are presented in Supplementary Table 3. Only one study fully described their cannulation technique for both MIS and MS cohorts [22].

Five studies commented that they gained experience with aortic surgery via MS prior to progressing to MIS [18,22,24,26,28]. Four studies stated that a single surgeon performed the procedures at their institution for both MS and MIS groups [21,22,24,26]. In one study, five surgeons performed aortic surgery via MS, whilst only two of this five operated on the MIS group [28]. The remaining studies did not report issues related to the surgical learning curve.

Risk of Bias in Included Studies

All included studies were non-randomized and their risk of bias is shown in Supplementary Table 4. We judged two studies to be at critical risk of bias due to the presence of strong unadjusted confounding [27,29]. Ten included studies were at ‘serious’ risk of bias [20,21,22,23,24,25,26,28,29,32], mainly due to confounding, one was at ‘moderate’ risk of bias [33], and one study provided insufficient information to make a risk of bias judgement [29]. Three studies undertook propensity-score matched analyses [24,25,28] and three studies used matched-pair analysis to control for specific patient baseline characteristics [22,32,33].

Synthesis of Evidence by Outcome

The timing outcomes and the main clinical findings for the included studies are presented in Supplementary Table 5 and Supplementary Table 6 respectively. Results of meta-analyses for perioperative mortality, reoperation for bleeding, renal impairment, stroke, aortic cross-clamp (AoX) time, CPB time, and length of intensive care unit (ITU) and hospital stay are presented in Table 2. The quality of the overall body of evidence was very low for all outcomes as defined by GRADE criteria [18].

The reported use of packed red blood cells (pRBC) suggested a skewed distribution, invalidating the method of converting medians to means, making meta-analysis unfeasible.

Perioperative Mortality

There were more observed postoperative deaths in the MS cohort, however the number of events occurring across all 12 studies was low and thus there was little evidence that rates of post-operative mortality differed between MIS and MS (RR 1.74, 95% CI 0.70-4.37, *p*=0.24; Figure 2). There was no evidence that mortality was influenced by the inclusion of arch procedures (p for difference= 0.772). There was no evidence of heterogeneity (I^2= 0.0%, *p*= 0.99). The funnel plot demonstrated no visual asymmetry (Supplementary Figure 1).

Reoperation for Bleeding and Use of Blood Products.

Reoperation for bleeding occurred more commonly in MS patients (RR 1.51, 95% CI 1.06-2.17, *p*=0.024; I^2= 0.0, *p*= 0.83; Figure 3). There was some evidence that reoperation was influenced by the inclusion of arch surgery (RR 2.00, 95% CI 1.01-3.93 for studies including arch surgery, RR 1.36, 95% CI 0.89-2.07 for studies excluding arch surgery, p for difference = 0.0368). The funnel plot for the reoperation outcome demonstrated asymmetry which is suggestive of small-study effect or publication bias [35,36] (Figure 4).

A greater number of pRBC units were transfused in the MS compared with MIS cohort, in eight of the nine studies reporting this outcome [19,22,24,26,28,31,32,33]. Mean number of units transfused across studies ranged from 1.3 to 6.7 units to 0.89 to 4.9 units for MS and MIS patients, respectively.

Renal Impairment and Neurological Events

There was some evidence to suggest that postoperative renal impairment was greater in the MS cohort (RR 1.97, 95% CI 1.12-3.46, *p*=0.019; I^2= 0.0, *p*=0.99; Supplementary Figure 2a). There was no evidence that renal impairment was influenced by the inclusion of arch procedures (p for difference = 0.836). The funnel plot for the renal impairment outcome appeared symmetrical (Supplementary Figure 2b).

Four studies reported perioperative stroke [25,28,30,32] but there were few events and so there was no evidence of a difference in the incidence of stroke for MIS vs MS patients (RR 1.06, 95% CI 0.50-2.26, *p*=0.887; I^2 = 0.0, *p*=1.0; Supplementary Figure 3a). There was no evidence that the incidence of stroke was influenced by the inclusion of arch procedures (p for difference =0.951). The funnel plot appeared symmetrical for the stroke outcome (Supplementary Figure 3b). One study found postoperative delirium to be increased for MS patients [33].

Aortic cross-clamp & cardiopulmonary bypass Time

Patients undergoing MS for their aortic pathology had longer AoX times (SMD 0.16, 95% CI -0.03-0.36, *p*=0.091; I^2 = 70.7, *p*<0.001; Supplementary Figure 4a). However, there was substantial heterogeneity between the studies and there was little evidence of difference between groups in the random effects model. The funnel plot appeared symmetrical (Supplementary Figure 4b).

There was some evidence to suggest that patients in the MS cohort were subject to increased CPB time, but the heterogeneity between studies was substantial (SMD 0.36, 95% CI 0.15-0.58, *p*=0.001; I^2=76.5, *p*=0.001; Supplementary Figure 5a). No asymmetry was observed in the funnel plot for this outcome (Supplementary Figure 5b).

There was no evidence the inclusion of arch procedures influenced the AoX (p for difference = 0.614) or CPB time (p for difference = 0.849).

Length of ICU and Hospital Stay

Patients undergoing MS spent more time in ICU (SMD 0.17, 95% CI 0.06-0.27, p<0.001; I^2= 7.2%, p=0.37; Supplementary Figure 6a). There was no strong evidence of a difference in ICU length of stay with the inclusion of arch procedures (p for difference = 0.085). There was no evidence of asymmetry in the funnel plot (Supplementary Figure 6b).

The length of hospital stay was longer for the MS group (SMD 0.30, 95% CI 0.17-0.43, p<0.001; I^2=16.5, p=0.30; Supplementary Figure 7a). There was no evidence the inclusion of arch procedures influenced the hospital length of stay (p for difference = 0.753). The funnel plot was symmetrical (Supplementary Figure 7b).

Discussion

To the best of our knowledge, the present study represents the first systematic review and meta-analysis comparing outcomes of all aortic surgery by MIS versus MS. The overall quality of the body of evidence was very low [18] for all outcomes, thus all findings should be interpreted with caution. We found no significant difference in mortality between MIS and MS, although MIS was associated with reduced rates of reoperation for bleeding, renal impairment, ICU stay, hospital length of stay and CPB time. There was no significant difference in AoX time between patient groups. The incidence of stroke was low and meta-analysis did not demonstrate a difference between MIS and MS patients. Although meta-analysis was not possible, fewer pRBC units were transfused for MIS patients in all but one study that reported the outcome [23]. We found no strong evidence that the inclusion of arch procedures influenced all outcomes except reoperation for bleeding. Our review highlights that MIS of the aorta is a highly versatile approach that facilitates surgery of the aortic root, ascending aorta, and aortic arch for a diversity of indications. Despite the limitations of the available evidence, our findings suggest that MIS of the aorta may be a feasible alternative to MS. Robust randomised studies are needed to support this conclusion.

The strengths of this systematic review include the comprehensive search to identify all available evidence and the rigorous methods of study selection, with two independent reviewers. Our systematic review was conducted according to the highest standards of review conduct [37]. We designed a comprehensive and sensitive search strategy, with input from two professional information scientists, to identify as many relevant studies as possible and reduce the risk of publication bias. We searched multiple electronic databases, additional relevant sources, and references of relevant studies were inspected for further studies. We did not impose date or language restrictions. Study selection was performed independently by two reviewers and data extraction was carried out by one reviewer and checked by another. We used the ROBINS-I [17] tool to assess the risk of bias in included observational studies, the most comprehensive tool for assessing risk of bias in non-randomized studies of interventions. We assessed the overall quality of the body of evidence according to GRADE recommendations and followed Cochrane recommendations for conducting meta-analyses [13].

The reduction in the CPB time for MIS patients in our review contradicts current trends in minimally invasive cardiac surgery [2,38]. It is well-established that prolonged time on CPB increases the risk of neurological [39] and perioperative renal impairment [40]. There was substantial heterogeneity in this meta-analysis, with the Levack study [25] contributing the most weight to the estimate. We could not identify specific study characteristics that could explain the observed heterogeneity in CPB times across studies. One possible explanation for this finding is that patients receiving MIS may have undergone procedures that demanded less time on CPB when compared to the MS group. Moreover, many of the institutions in the included studies gained sufficient experience of aortic surgery via MS before graduating to MIS. This would have the effect on minimising the surgeon learning curve for performing MIS of the aorta. Therefore, surgeons with less experience of MIS may require longer CPB time than in the included studies of this review. However, it is noteworthy that most institutions opted for a ministernotomy. This incision enables the surgeon to visualise a similar operating field when compared to MS. Therefore, the difference in CPB time should not vary considerably for MIS of the aorta versus MS, and the clinical significance of any difference is probably minimal.

Our study also reports a reduction in the number of patients undergoing reoperation for bleeding in the MIS group. Reoperation keeps patients in hospital, and brings with it the risks of reopening the chest [41]. Minimally invasive cardiac surgery has been theorised to reduce bleeding, possibly due to reduced sternal trauma and instability. However, the visually asymmetrical funnel plot indicates the presence of small-study effect or publication bias; the latter of which would result in a favourable interpretation of the benefits of MIS on the rate of reoperation. Selective reporting and publication bias precludes accurate interpretation of the potential benefits of MIS and so it is key that surgeons report all data regardless of the outcome in future studies. Meta-regression analysis suggested that reoperation rates might be lower in studies which included aortic arch surgery. Though interesting, the proportion of arch procedures was relatively low in the included studies, so this finding is likely to be related to other differences between studies.

Although we were unable to quantitatively analyse the transfused pRBC outcome, fewer pRBC units were transfused in the MIS cohort in eight of the nine studies reporting the outcome. This may reflect a tendency of surgeons to pay closer attention to haemostasis in MIS compared to MS, and the possibility that the threshold for giving blood products may have differed for MIS and MS patients. Nevertheless, these results provide some reassurance that MIS of the aorta does not lead to a greater quantity of blood transfusion, which has the potential for minimising morbidity [42] and cost to health services.

There was some evidence that MIS was associated with a reduction in both ICU and hospital length of stay. This finding is consistent with the current literature for minimal access cardiac surgery [2,38,43]. Prolonged periods in ICU are associated with perioperative morbidity and mortality [44], and so minimising this would be an important advantage of MIS of the aorta. Whether the result in our review occurred because of the effect of MIS rather than differences in postoperative care for MIS and MS patients requires consideration. All included studies reporting the length of hospital stay found the time in hospital to be shorter for MIS patients. This could be a consequence of attenuated postoperative pain, although the lack of data on this outcome does not allow us to make firm conclusions. Future studies should endeavour to report this very important outcome.

It is challenging to recommend a means of approaching MIS of the aorta given the marked variation in the way surgeons undertake these procedures (e.g. cannulation and myocardial protection). This is often dictated by surgeon preference given their experiences with similar procedures performed through MS. Surgeons contemplating utilising MIS may wish to first gain sufficient experience with aortic surgery via MS before undertaking MIS. Shreshta and colleagues performed more than 500 David procedures via a MS at their institution and more than 200 minimal access aortic valve replacements prior to undertaking MIS of the aorta [45]. This enabled them to adequately develop a routine approach to these procedures which minimises the challenge of converting to MIS of the aorta. Moreover, the authors initially selected low-risk patients with isolated aortic disease to undergo MIS. We therefore emphasise the need for prolonged experience with MIS of the aorta and careful patient selection in the early stages of a MIS programme.

A limitation of the evidence included in our review is that it is based on single centre, non-randomized studies which are vulnerable to confounding and other biases. There was heterogeneity in the CPB and AoX time that was not explained by the inclusion of arch procedures. Therefore, it is likely that this variation occurred due to other confounding variables such as differences in indication, type of surgery, and the performance of concomitant procedures between studies. To mitigate the impact of concomitant procedures such as aortic valve surgery on the outcomes of MIS, further studies should aim to compare isolated aortic surgery for MIS versus MS. The overall quality of the body of evidence was very low for all outcomes, as defined by the GRADE criteria [18]. As only a few of the studies had long-term follow-up, we were unable to evaluate the differences in long term aortic complications between the two approaches. Moreover, we were not able to assess important measures of patient satisfaction such as quality of life and time to return to work. These outcomes should be addressed in future studies to establish whether MIS of the aorta is of benefit to patients.

Conclusion

Very low quality non-randomized evidence suggests that MIS of the aorta may be associated with improved early clinical outcomes when compared to MS. Randomized controlled trials are essential to confirm these findings.

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Author contributions

Conception, study design and protocol: TR, JS, HV.

Identification of studies: TR (with input from information scientists AR and CB).

Study selection, data extraction, risk of bias and GRADE assessments: TR, PR, JS.

Statistical analyses: SH, TR.

Writing: TR lead, with contributions from JS, SH, VH, DM

Project oversight and supervision: JS (methodological) and VH (clinical expertise).

Critical revisions for important intellectual content: JS, SH, DM, HV, PR, GDA, MC. All authors read and approved the final manuscript.

Fig 1.

PRISMA flow chart of the search and study selection process.

Fig 2.

Early postoperative mortality in patients undergoing minimally invasive surgery (MIS) of the aorta vs median sternotomy (MS). (M-H = Mantel-Haenszel test; D+L= DerSimonian-Laird test.) Solid squares for each study represent the risk ratio (RR) with the size proportional to the weights in meta-analysis. The horizontal lines denote the 95% confidence intervals (95% CI). A RR of 1 (vertical black line) indicates no difference between MIS and MS. The uppermost diamond represents the fixed effect model weighted RR. The bottommost diamond illustrates the random-effects weighted RR. The horizontal tips of the diamond are the confidence interval for the overall effect estimate.

Fig 3.

The requirement to reoperate for bleeding in patients undergoing minimally invasive aortic surgery (MIS) vs median sternotomy (MS). (M-H = Mantel-Haenszel test; D+L= DerSimonian-Laird test.) Solid squares for each study represent the risk ratio (RR) with the size proportional to the weights in meta-analysis. The horizontal lines denote the 95% confidence intervals (95% CI). A RR of 1 (vertical black line) indicates no difference between MIS and MS. The uppermost diamond represents the fixed effect model weighted RR. The bottommost diamond illustrates the random-effects weighted RR. The horizontal tips of the diamond are the confidence interval for the overall effect estimate.

Fig 4

Funnel plot for the reoperation for bleeding outcome. Individual blue circles indicate studies included in the present study. The position of these circles along the horizontal axis represents the effect-estimate/risk ratio (RR). This is plotted against the standard error (SE) of the log-RR which is an estimate of study precision. Asymmetry is suggestive of small-study or publication bias causing overestimation of the effect size in a meta-analysis.

Table 1

Characteristics of studies included in this systematic review & meta-analysis comparing minimally invasive aortic surgery with median sternotomy.

First Author & Year [ref no.]	**Study Period**	**Country, Treatment Centre**	**Study Design**	**n (MIS)**	**n (MS)**	**MIS Incision**	**Mean Follow-up Time (months)**		**Comment**
							MIS	**MS**	
Abjigitova 2018 [19]	1998-2016	The Netherlands, Rotterdam	OC, RSP	26	91	‘J’ ministernotomy or ‘inverted T’ ministernotomy	-	-	
Aharon 2017 [20]	1998-2016	USA, Wynnewood, PA	OC, RSP[a]	26	199	Ministernotomy	22.3	158.3	Type of ministernotomy not defined
Burdett 2014 [21]	2012-2013	UK, Middlesborough	OC, RSP[a]	7	9	Ministernotomy	-	-	Type of ministernotomy not defined
Hastaoglu 2018 [22]	2010-2015	Turkey, Istanbul	MC	54	75	‘J’ ministernotomy”	-	-	

Hillebrand 2018 [23]	2012-2016	Germany, Münster	OC, RSP	33	25	‘J’ ministernotomy	-	-	
Lamelas 2018 [24]	2009-2014	USA, Houston, TX	PSM	74	103	MI right thoracotomy OR right lateral thoracotomy	-	-	
Levack 2017 [25]	1995-2014	USA, Cleveland, OH	PSM	568	1259	‘J’ ministernotomy	-	-	
Mikus 2017 [26]	2010-2015	Italy, Ravenna	OC, RSP	53	185	‘J’ ministernotomy	-	-	
Monsefi 2018 [27]	1991-2015	Germany, Frankfurt	OC, RSP	90	206	‘J’ ministernotomy	36±24	96±48	Critical Risk of Bias
Monsefi 2018 [28]	1991-2016	Germany, Frankfurt	PSM	120	207	‘J’ ministernotomy	36±24	96±48	
Shreshta 2015 [29]	2011-2014	Germany, Hannover	OC, RSP	26	14	‘J’ ministernotomy	40±27	41±26	Critical Risk of Bias

Shreshta 2018 [30]	2011-2016	Germany, Hannover	OC, RSP[a]	210	192	‘J’ ministernotomy	-	-
Sun 2000† [31]	1999-1999	China, Beijing	OC, RSP	8	21	‘J’ ministernotomy	3	3
Tabata 2007 [32]	1996-2005	USA, Boston, MA	MC	128	93	‘J’ ministernotomy	-	-
Wachter 2017 [33]	2007-2012	Germany, Stuttgart	MC	117	75	‘J’ ministernotomy	31±18	31±18

[a]= abstract; MC= matched cohort; MIS= minimally invasive surgery; MS= median sternotomy; OC= observational cohort, RSP= retrospective; PSM= propensity score matched

±= range

†= The authors stated that patients were followed-up for at least 3 months for both cohorts.

Table 2.

Summary of perioperative characteristics and outcomes with quality of evidence assessment for analysed outcomes by the Grades of Recommendation, Assessment, Development and Evaluation Working Group Approach (GRADE).

Population or patient: Patients Undergoing Minimally Invasive Aortic Surgery

Setting: Inpatient Hospital Setting

Interventions: All Minimally Invasive Procedures of The Aortic Root/Arch and Ascending Aorta

Comparator: Median Sternotomy

Outcome	**Quality of Evidence for Outcome (GRADE) With Justification(s)**	**No. of studies**	**No. of patients in MIS**	**Events in MIS group (%)**	**No. of patients in MS**	**Events in MS group (%)**	**RR (95% CI)**		**P value for overall effect**		**Heterogeneity**	
							Fixed	**Random**	**Fixed**	**Random**	***I^2 (%)***	***P* value**
	Major outcomes											
Mortality	⊕○○○ 1, 3, 4	9	1039	0.67	1328	1.73	1.96 (0.81-4.76)	1.74 (0.70-4.37)	0.14	0.24	0.0	0.99
Reoperation for bleeding	⊕○○○ 1, 3, 4, 5	12	1168	4.07	1470	7.10	1.61 (1.13-2.29)	1.51 (1.06-2.17)	0.008	0.024	0.0	0.83

Renal Impairment	⊕○○○ 1, 3, 4	7	899	1.56	1194	3.52	1.99 (1.13-3.51)	1.97 (1.12-3.46)	0.017	0.019	0.0	0.99
Stroke	⊕○○○ 1, 3, 4	4	875	1.49	857	1.52	1.06 (0.50-2.25)	1.06 (0.50-2.26)	0.89	0.89	0.0	1.0
	Operative outcomes						**SMD (95% CI)**					
							Fixed	**Random**				
AoX time	⊕○○○ 1, 2, 3	11	955	-	1275	-	0.26 (0.17-0.34)	0.16 (-0.03-0.36)	<0.001	0.091	70.7	<0.001
CPB time	⊕○○○ 1, 2, 3	11	955	-	1275	-	0.36 (0.15-0.44)	0.36 (0.15-0.58)	<0.001	0.001	76.5	<0.001

Length of ICU stay	⊕○○○ 1, 3	8	805	-	952	-	0.15 (0.06-0.25)	0.17 (0.06-0.27)	<0.001	<0.001	7.2	0.37
Length of Hospital stay	⊕○○○ 1, 3	7	684	-	831	-	0.31 (0.21-0.41)	0.30 (0.17-0.43)	<0.001	<0.001	16.5	0.30

AoX= aortic cross-clamp CI= confidence interval; CPB= cardiopulmonary bypass; ITU= intensive care unit; MIS= minimally invasive surgery; MS= median sternotomy; RR= risk ratio; SMD= standardised mean difference

Quality of Evidence

⊕○○○ = Very Low, ⊕⊕○○ = Low; ⊕⊕⊕○ = Moderate; ⊕⊕⊕⊕ = High

Limitation in Design:

1 Potential risk of bias

2 Heterogeneity- possibly not explained

3 Small number of events and/or small sample size and/or small number of studies reporting outcome

4 Wide confidence intervals for effect estimate suggestive of imprecision

5 Suspicion of publication bias confirmed by funnel plot

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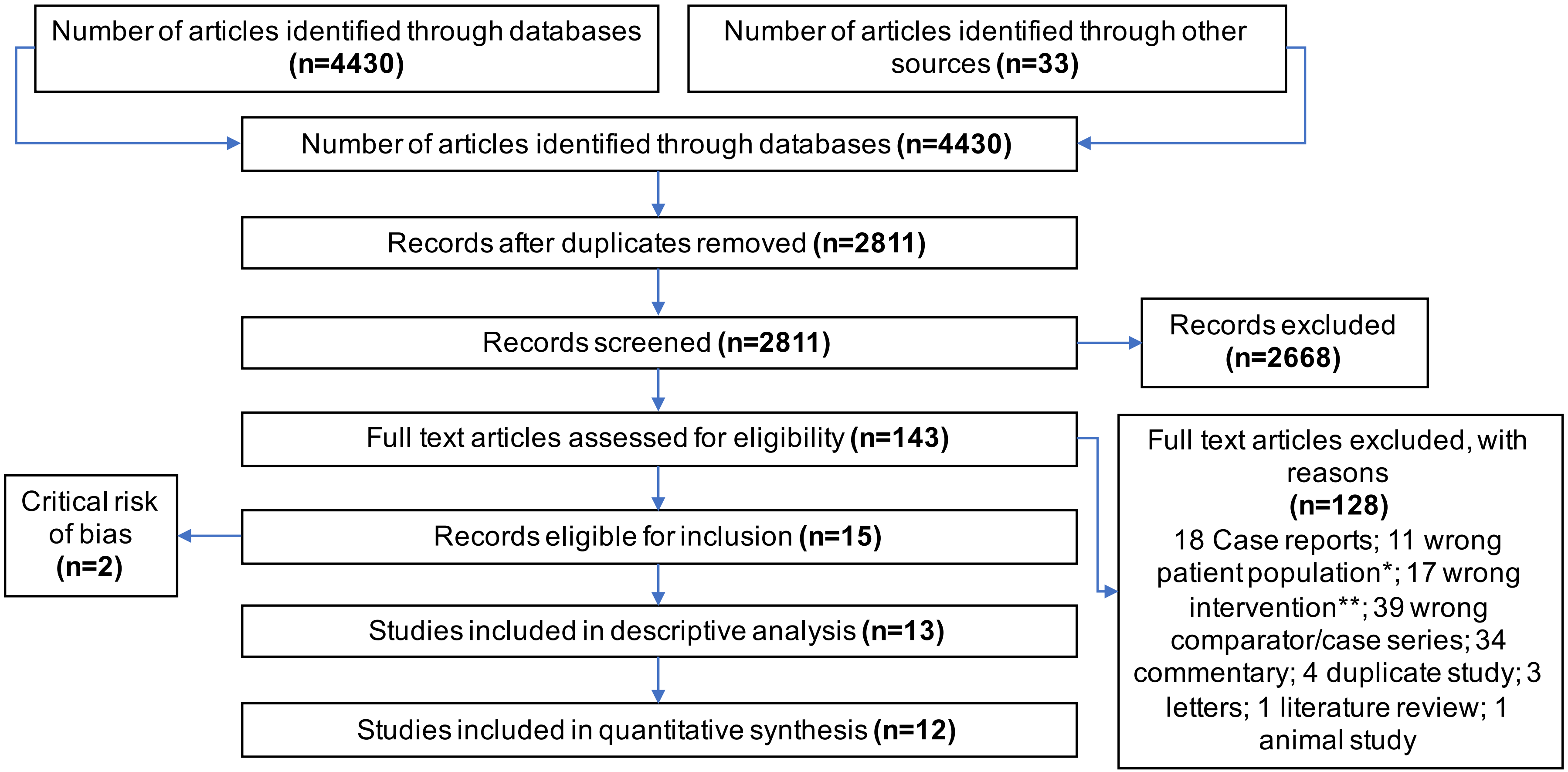
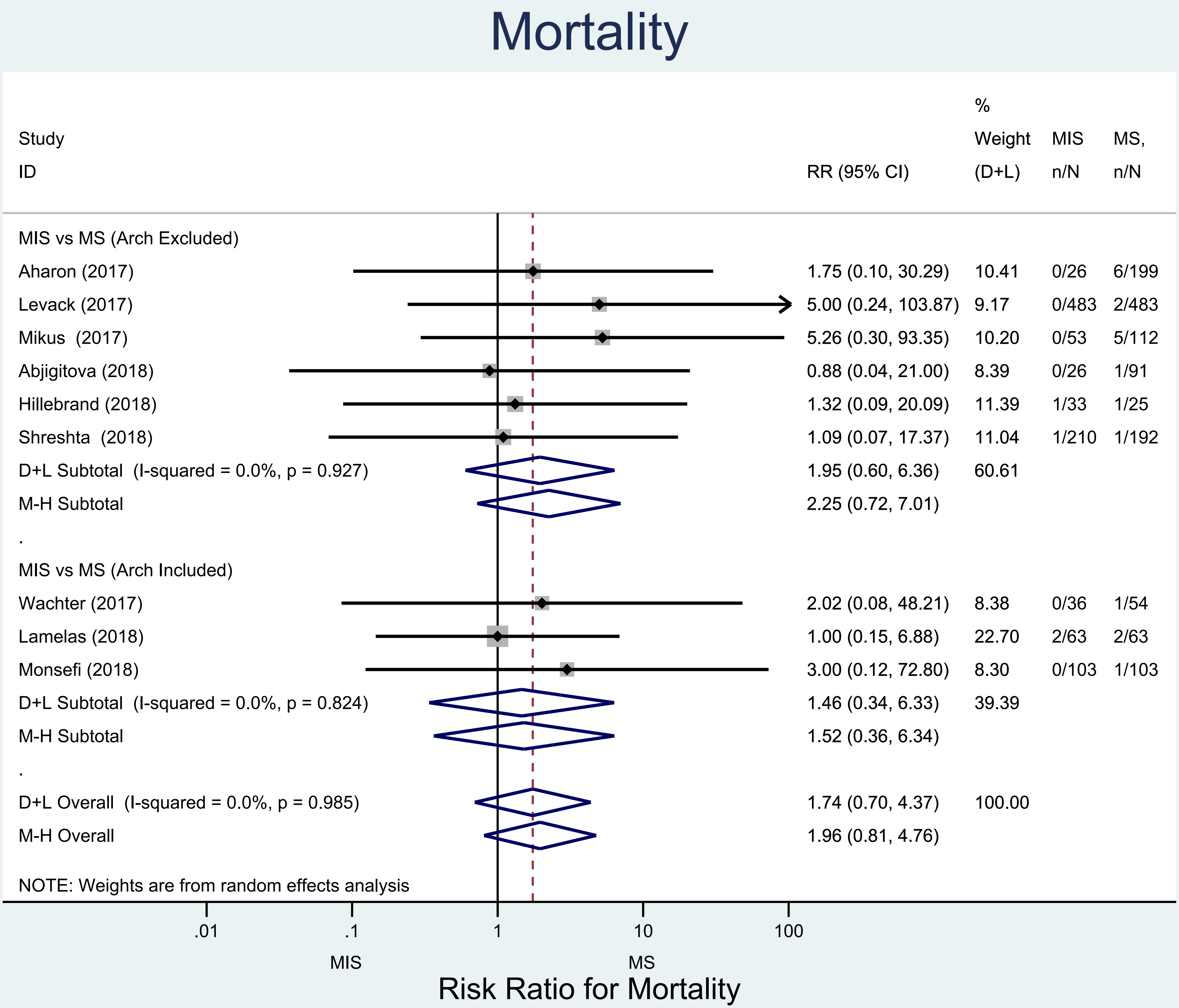
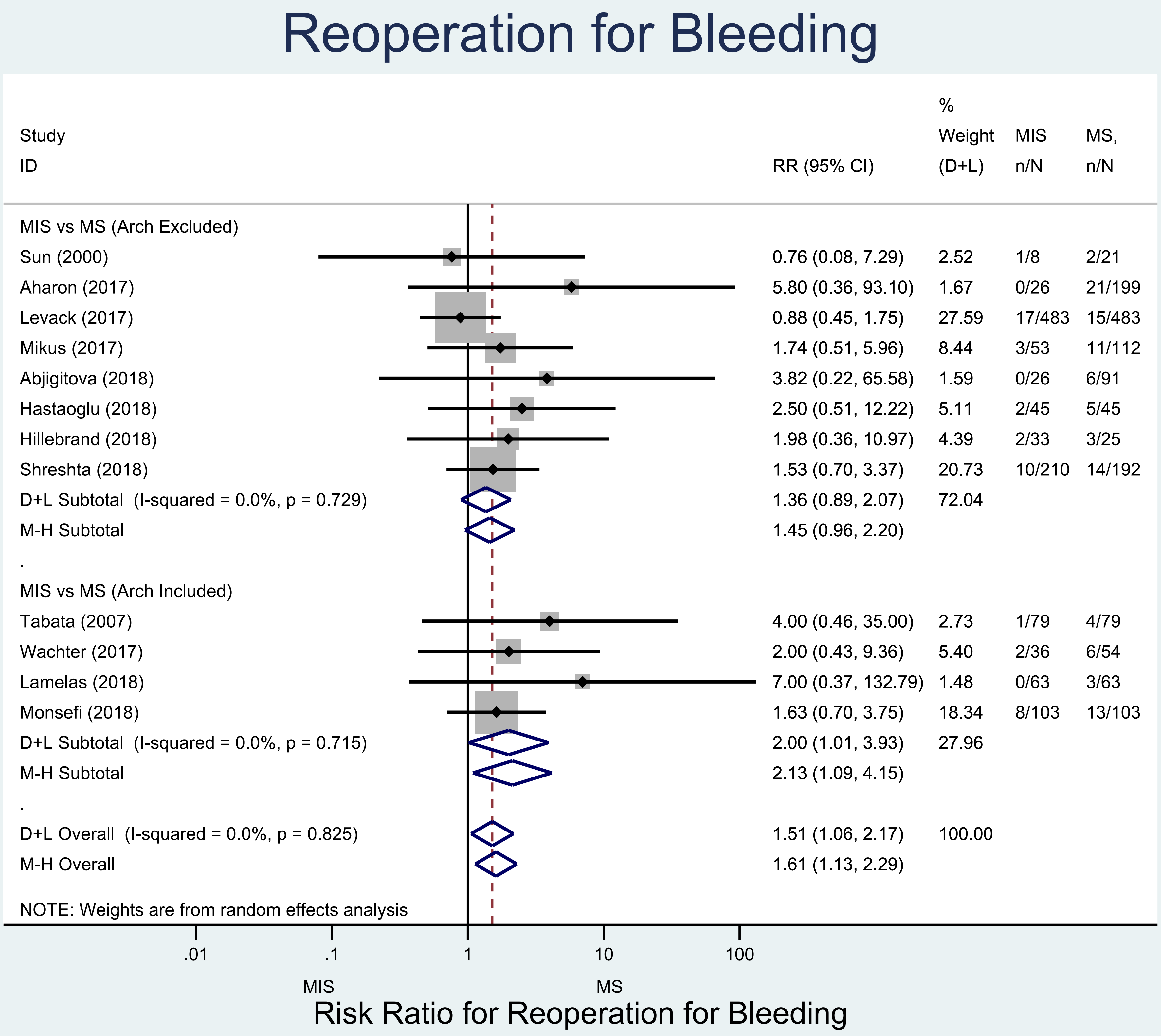
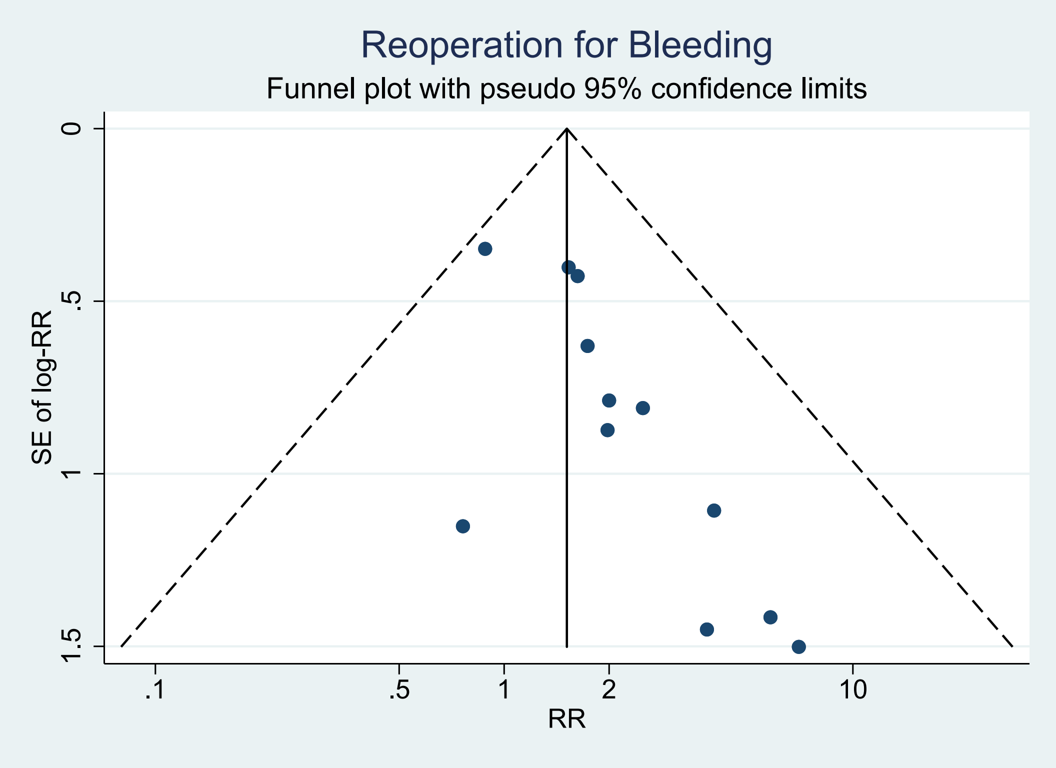


*3 abdominal aorta pathology; 8 non-aortic pathology

**11 not minimally invasive surgery; 3 aortic valve replacement only; 1 coronary artery bypass graft only; 2 endovascular intervention only


Mortality
Study ID
RR (95% CI)
% Weight (D+L)
MIS n/N
MS, n/N
MIS vs MS (Arch Excluded)
Aharon (2017) 1.75 (0.10, 30.29) 10.41 0/26 6/199
Levack (2017) 5.00 (0.24, 103.87) 9.17 0/483 2/483
Mikus (2017) 5.26 (0.30, 93.35) 10.20 0/53 5/112
Abjigitova (2018) 0.88 (0.04, 21.00) 8.39 0/26 1/91
Hillebrand (2018) 1.32 (0.09, 20.09) 11.39 1/33 1/25
Shreshta (2018) 1.09 (0.07, 17.37) 11.04 1/210 1/192
D+L Subtotal (I-squared = 0.0%, p = 0.927) 1.95 (0.60, 6.36) 60.61
M-H Subtotal 2.25 (0.72, 7.01)
.
MIS vs MS (Arch Included)
Wachter (2017) 2.02 (0.08, 48.21) 8.38 0/36 1/54
Lamelas (2018) 1.00 (0.15, 6.88) 22.70 2/63 2/63
Monsefi (2018) 3.00 (0.12, 72.80) 8.30 0/103 1/103
D+L Subtotal (I-squared = 0.0%, p = 0.824) 1.46 (0.34, 6.33) 39.39
M-H Subtotal 1.52 (0.36, 6.34)
.
D+L Overall (I-squared = 0.0%, p = 0.985) 1.74 (0.70, 4.37) 100.00
M-H Overall 1.96 (0.81, 4.76)
NOTE: Weights are from random effects analysis
.01
.1
1
10
100
MIS
MS
Risk Ratio for Mortality


Reoperation for Bleeding
Study ID
RR (95% CI)
% Weight (D+L)
MIS n/N
MS, n/N
MIS vs MS (Arch Excluded)
Sun (2000) 0.76 (0.08, 7.29) 2.52 1/8 2/21
Aharon (2017) 5.80 (0.36, 93.10) 1.67 0/26 21/199
Levack (2017) 0.88 (0.45, 1.75) 27.59 17/483 15/483
Mikus (2017) 1.74 (0.51, 5.96) 8.44 3/53 11/112
Abjigitova (2018) 3.82 (0.22, 65.58) 1.59 0/26 6/91
Hastaoglu (2018) 2.50 (0.51, 12.22) 5.11 2/45 5/45
Hillebrand (2018) 1.98 (0.36, 10.97) 4.39 2/33 3/25
Shreshta (2018) 1.53 (0.70, 3.37) 20.73 10/210 14/192
D+L Subtotal (I-squared = 0.0%, p = 0.729) 1.36 (0.89, 2.07) 72.04
M-H Subtotal 1.45 (0.96, 2.20)
.
MIS vs MS (Arch Included)
Tabata (2007) 4.00 (0.46, 35.00) 2.73 1/79 4/79
Wachter (2017) 2.00 (0.43, 9.36) 5.40 2/36 6/54
Lamelas (2018) 7.00 (0.37, 132.79) 1.48 0/63 3/63
Monsefi (2018) 1.63 (0.70, 3.75) 18.34 8/103 13/103
D+L Subtotal (I-squared = 0.0%, p = 0.715) 2.00 (1.01, 3.93) 27.96
M-H Subtotal 2.13 (1.09, 4.15)
.
D+L Overall (I-squared = 0.0%, p = 0.825) 1.51 (1.06, 2.17) 100.00
M-H Overall 1.61 (1.13, 2.29)
NOTE: Weights are from random effects analysis
.01
.1
1
10
100
MIS
MS
Risk Ratio for Reoperation for Bleeding


Reoperation for Bleeding
Funnel plot with pseudo 95% confidence limits
SE of log-RR
0
.5
1
1.5
.1
.5
1
2
10
RR

Supplementary Appendix 1

Search strategies for the electronic databases used in this review

Search Strategy for Embase & Medline

1. Aorta/
2. ((aortic or aorta) adj4 (operation* or replace* or surgery)).tw.
3. (aortic adj (root or arch or ascending)).tw.
4. 1 or 2 or 3
5. Surgical Procedures, Minimally Invasive/
6. ((surgical or surgery or surgeries or replacement* or operation*) adj3 minim*).tw.
7. ((surgery or surgeries or surgical) adj3 (keyhole or percutaneous or robot-assisted)).tw.
8. (ministernotom* or hemisternotom* or hemi-sternotomy or mini-sternotomy).tw.
9. 5 or 6 or 7 or 8
10. 4 and 9

Search Strategy for Web of Science

1. TS=Aorta
2. TS= ((aortic or aorta) NEAR/4 (operation* or replace* or surgery))
3. TS=(aortic NEAR (root or arch))
4. #3 OR #2 OR #1
5. TS= Surgical Procedures, Minimally Invasive
6. TS=((surgical or surgery or surgeries or replacement* or operation*) NEAR/3 minim*)
7. TS= ((surgery or surgeries or surgical) NEAR/3 (keyhole or percutaneous or robot-assisted)
8. TS= (ministernotom* or hemisternotom* or hemi-sternotomy or mini-sternotomy)
9. #8 OR #7 OR #6 OR #5
10. #9 AND #4

Search strategy for the Cochrane Library

1. Aorta
2. ((aortic or aorta) near (operation* or replace* or surgery))
3. (aortic near (root or arch or ascending))
4. 1 or 2 or 3
5. Surgical Procedures, Minimally Invasive
6. ((surgical or surgery or surgeries or replacement* or operation*) near minim*)
7. ((surgery or surgeries or surgical) near (keyhole or percutaneous or robot-assisted))
8. (ministernotom* or hemisternotom* or hemi-sternotomy or mini-sternotomy)
9. 5 or 6 or 7 or 8
10. 4 and 9

Supplementary Table 1.

Baseline characteristics for the patients included in studies comparing minimally invasive surgery of the aorta with median sternotomy.

Author *et al.* [ref no.]	Mean age in years SD		Sex n (% male)		LVEF % SD		NYHA≥3 n (%)		AI≥3 n (%)		BAV n (%)		HTN n (%)		DM n (%)		COPD n (%)	
	MIS	**MS**	**MIS**	**MS**	**MIS**	**MS**	**MIS**	**MS**	**MIS**	**MS**	**MIS**	**MS**	**MIS**	**MS**	**MIS**	**MS**	**MIS**	**MS**
***Abjigitova* [19]**	57 SD 12	57 SD 13	23 (88.5)	74 (81.3)	60 SD 7.4	60 SD 7.4	-		-		10 (38.8)	28 (30.8)	18 (69.2)	74 (81.3)	1 (3.8)	7 (7.7)	2 (7.7)	12 (13.2)
***Aharon* [20]**	56 SD 12.9	57.6 SD 13.5	23 (88.5)	161 (80.7)	-		-		-		-		-		-		-	
***Burdett* [21]**	-	-	-		-		-		-		-		-		-		-	
***Hastaoglu* [22]**	57.9 SD 12.5	58.4 SD 9.6	33 (73.3)	33 (73.3)	60.9 SD 6.3	61.9 SD 6.0	-		-		-		29 (64.4)	27 (60.0)	8 (17.8)	6 (13.3)	-	
***Hillebrand* [23]**	55.6 SD 13.2	59.1 SD 12.5	24 (72.7)	18 (72.0)	-		-		-		14 (42.4)	2 (8.0)	20 (60.6)	19 (76.0)	5 (15.2)	3 (12.0)	3 (9.1)	3 (12.0)
***Lamelas* [24]**	63.3 SD 13.5	63.2 SD 13.7	37 (58.7)	39 (61.9)	59.0 SD 8.4	58.0 SD 9.4	-		-		40 (63.5)	16 (25.4)	50 (79.4)	50 (79.4)	10 (15.9)	13 (20.6)	5 (7.9)	4 (6.3)
***Levack* [25]**	56 SD 14	55 SD 14	351 (73.0)	364 (75.0)	-		34 (7.7)	32 (7.2)	-		-		293 (61.0)	285 (59.0)	23 (4.8)	30 (6.2)	36 (7.5)	36 (7.5)
***Mikus* [26]**	61 SD 13.3	64 SD 11.7	44 (83.0)	93 (83.0)	61 SD 8.8	58.3 SD 9.7	8 (15.0)	24 (22.0)	-		27 (51.0)	41 (36.0)	32 (60.0)	78 (70.0)	4 (7.0)	9 (8.0)	4 (7.0)	10 (9.0)
***Monsefi* [28]**	57 SD 14	57 SD 13	29 (77.0)	29 (77.0)	60 SD 10	57 SD 10	-		58 (56.0)	56 (54.0)	23 (22.3)	17 (13.1)	51 (50.0)	56 (54.0)	-		-	
***Shreshta* [30]**	60 SD 14	63 SD 13	137 (65.2)	114 (59.4)	-		-		-		-		-		-		-	

***Sun* [31]**	41.6 SD 8.2	40.8 SD 10.1	6 (75.0)	19 (90.5)	60.1 SD 11.5	56.8 SD 12.3	-		-		-		-		-		-	
***Tabata* [32]**	55 SD 13	54 SD 14	60 (76.0)	60 (76.0)	56 SD 11	54 SD 13	13 (16.5)	16 (20.2)	-		35(44.3)	30 (38.0)	-		3(3.8)	2(2.5)	4(5.1)	5(6.3)
***Wachter* [33]**	65.5 SD 9.9	65.9 SD 9.5	27 (75.0)	42 (77.8)	54.6 SD 12.8	60.2 SD 12.6	-		22 (61.1)	20 (37.0)	-		-		5 (13.9)	3 (5.6)	2 (5.6)	6 (11.1)
Minimum	41.6	40.8	58.7	59.4	54.6	54	7.73	7.20	56.0	37.0	22.3	8.0	50.0	54.0	3.8	2.5	5.1	6.3
Maximum	65.9	65.9	88.5	90.5	61	61.91	16.5	22.0	61.1	54.0	63.5	36.0	79.4	81.3	17.8	20.6	9.1	13.2
Weighted Mean	57.6	58.0	72.6	74.6	58.8	58.1	9.48	11.2	57.3	48.2	58.1	59.1	61.4	63.9	7.2	7.7	7.14	7.74

AI= aortic insufficiency; BAV= bicuspid aortic valve; COPD= chronic obstructive pulmonary Disease; DM= diabetes mellitus; HTN= hypertension; LVEF= left ventricular ejection fraction; MIS= minimally invasive surgery; MS= median sternotomy; NYHA= New York Heart Association functional class; SD= standard deviation

Data are presented as number (n) and percentage (%). Mean age in years is presented with its SD. Left ventricular ejection fraction is expressed as a percentage (%) with its SD.

Supplementary Table 2.

The indication for surgery, type of surgery performed, and the utilisation of concomitant procedures for studies comparing minimally invasive surgery of the aorta with median sternotomy.

Author et al. [ref no.]	Indication for surgery		Primary procedure(s)		Concomitant procedures	
	MIS	**MS**	**MIS**	**MS**	**MIS**	**MS**
Abjigitova [19]	Medial degeneration (88.5%); endocarditis (7.7%)	Chronic dissection (9.9%); medial degeneration (72.5%); endocarditis (2.2%); aortitis (1.1%)	Bentall (100%)	Bentall (100%)	All patients received AV replacement	
Aharon [20]	Medial degeneration (57.8%)	Medial degeneration (76.9%)	Bentall (84.6%); David (15.4%)	Bentall (83.9%); David (16.1%)	NI	
Burdett [21]	NI	NI	Isolated aortic root replacement (100%)	Isolated aortic root replacement (100%)	Not included	
Hastaoglu [22]	"Pathology of the proximal aorta"		Ascending aorta replacement (40.0%); AV replacement + aortic root replacement (40%); Bentall (20%)	Ascending aorta replacement (33.3%); AV replacement + aortic root replacement (42.2%); Bentall (24.4%)	See 'primary procedures'	See 'primary procedures'
Hillebrand [23]	Aortic root dilation	Aortic root dilation	Aortic root replacement using a valved conduit. Mechanical conduit (57.6%); biological conduit (42.4%)	Aortic root replacement using a valved conduit. Mechanical conduit (48%); biological conduit (52%)	Mitral valve repair/replacement (9.1%); tricuspid valve repair	Mitral valve repair/replacement (12%); tricuspid valve repair (8%)

					(6.1%); closure of PFO (3%)	
Lamelas [24]	Patients requiring circulatory arrest for pathology of the ascending aorta (aneurysm) with or without AV involvement		Ascending aorta replacement with AV replacement; ascending aorta replacement with AV replacement & hemiarch replacement. No breakdown provided. However, those with aneurysms extending to the arch, who required valve-sparing operation, and those requiring coronary revascularisation received median sternotomy.		AV replacement. No breakdown provided	
Levack [25]	AV regurgitation (69%); AV stenosis (43%); ascending aortic aneurysm or aortic root dilatation (30%)	AV regurgitation (71%); AV stenosis (43%); ascending aortic aneurysm or aortic root dilatation (29%)	Aortic root reimplantation (0.83%); remodelling (0.41%); resuspension (6%); valved conduit (15%); isolated ascending aorta repair (1%); ascending aorta repair with AV repair (1.4%); ascending aorta repair with AV replacement (3.7%); isolated ascending aorta replacement (6%); ascending aorta replacement with AV repair (23%); ascending aorta replacement with AV replacement (43%)	Aortic root reimplantation (12%); remodelling (1%); resuspension (5.2%); valved conduit (19%); isolated ascending aorta repair (0.21%); ascending aorta repair with AV repair (1.4%); ascending aorta repair with AV replacement (6.2%); isolated ascending aorta replacement (7.5%); ascending aorta replacement with AV repair (8.3%); ascending aorta replacement with AV replacement (40%)	See ‘primary procedures’	
Mikus [26]	Chronic aneurysm due to calcified degenerative disease	NI	Bentall-De-Bono (100%)	Bentall-De-Bono (100%)	All patients received AV replacement	

	(45.3%); annuloaortic ectasia (50.9%); infective chronic endocarditis (3.8%)					
Monsefi [28]	Aortic root aneurysm with or without AV incompetence (100%)	Aortic root aneurysm with or without AV incompetence (100%)	Neosinus (96.1%); pseudosinus (0.97%); standard David (2.91%); isolated ascending aorta replacement (72%); ascending aorta + hemiarch replacement (10%); complete arch replacement (12%); elephant trunk (6%)	Neosinus (40.8%); pseudosinus (16.5%); standard David (42.7%); isolated ascending aorta replacement (66%); ascending aorta + hemi-arch replacement (27%); complete arch replacement (3%); elephant trunk (3%)	CABG (5%); ASD closure (2%); mitral valve repair (10%); tricuspid valve repair (3%); leaflet plication of the AV (50%); supra-annular stitch (54%)	CABG (7%); ASD closure (1%); mitral valve repair (2%); tricuspid valve repair (2%); leaflet plication of the AV (42%); supra-annular stitch (17%)
Shreshta [30]	NI	NI	Isolated ascending aortic replacement (19.5%); AV replacement with supra-commissural ascending aorta replacement (30.5%); Bentall (26.2%); David (21.9%)	Isolated ascending aortic replacement (25%); AV replacement with supra-commissural ascending aorta replacement (33.9%); Bentall (27.1%); David procedure (14.1%)	See 'primary procedures'	
Sun [31]	Proximal aortic aneurysm with aortic regurgitation (100%)	Proximal aortic aneurysm with aortic regurgitation (100%)	David (100%)	David (100%)	Not included	

Tabata [32]	Aortic aneurysm (58.2%); chronic aortic dissection (1.3%); calcified aorta (3.8%); bicuspid AV (44.3%); aortic stenosis (40.5%); aortic insufficiency (51.9%); endocarditis (1.3%)	Aortic aneurysm (67.1%); calcified aorta (1.3%); bicuspid AV (38.0%); aortic stenosis (29.1%); aortic insufficiency (59.5%); endocarditis (3.8%)	Aortic root replacement (52.3%); homograft (44.5%); stentless bioprosthetic valve (1.56%); Bentall procedure (4.69%); aortic reimplantation (0.78%);aortic remodelling (0.78%); ascending aorta replacement (41.4%); ascending aorta replacement with no AV procedure (14.8%); ascending aorta replacement concomitant AV replacement (22.7%); ascending aorta replacement with concomitant AV repair (3.9%); ascending aorta with hemi arch replacement (5.5%); ascending aorta with hemi-arch replacement with no valve procedure (3.1%); ascending aorta with hemi arch replacement with AV replacement (1.56%); ascending aorta with hemi arch replacement with AV repair (0.78%); others (0.78%); patch	Ascending aorta, proximal arch and root operations with or without AV procedures. No breakdown provided	See ‘primary procedures’.	See ‘primary procedures’.

			exclusion of sinus of Valsalva (0.78%)			
Wachter [33]	Isolated AI (13.9%); isolated aortic aneurysm (38.9%); combined AI and aneurysm (47.2%)	Isolated AI (9.3%); isolated aortic aneurysm (61.1%); combined AI and aneurysm (27.7%); tumour of the aortic glomus (1.9%)	Elective David with or without additional cusp repair	Elective David with or without additional cusp repair	Atrial ablation (3.4%); aortic arch replacement (1.7%); septal myectomy and atrial ablation (0.9%)	CABG (11.5%); atrial ablation (7.9%); aortic arch replacement (6.8%); surgery on other valves (5.8%).

AI = aortic insufficiency; AV= aortic valve; ASD= atrial septal defect; CABG= coronary artery bypass graft; MIS= minimally invasive surgery; MS= median sternotomy; NI= no information; PFO= patent foramen ovale

Supplementary Table 3.

Authors description of cannulation technique and myocardial protection in the included studies

Author et al. [ref no.]	Description of cannulation		Description of myocardial protection	
	MIS	**MS**	**MIS**	**MS**
Abjigitova 2018 [19]	• Cannulation of the anterior surface of the aortic arch opposite the innominate artery • Cannulation of the right common femoral vein	• Not described	• Antegrade cardioplegia • Left ventricular vent through pulmonary trunk	• Not described
Aharon 2017 [20]	NI		NI	
Burdett 2014 [21]	NI		NI	
Hastaoglu 2018 [22]	• Aortic cannulation	• Aortic cannulation • Innominate artery cannulated using prosthetic graft in patients undergoing ascending aortic replacement.	• Antegrade cardioplegia • 32°C. • Left ventricular vent through right superior vein.	• Antegrade & retrograde cold blood cardioplegia • Ascending aorta replacements performed using UCP at 24°C.

Hillebrand 2018 [23]	• Cannulation of the transition between the ascending aorta and the aortic arch in 32 patients. • Cannulation of right axillary artery in 2 patients. • Venous cannulation through apex of the right atrium in 29 patients. • Bicaval venous cannulation in 4 patients requiring combined procedures.	• Not described	• Selective antegrade or retrograde cardioplegia	• Not described
Lamelas 2018 [24]	• Cannulation of femoral or axillary artery • Venous cannulation of femoral vein	• Not described	• Antegrade cardioplegia	• Antegrade cardioplegia • Cooling to 20°C if aneurysm extended to arch.
Levack 2017 [25]	• Cannulation of the distal aortic arch in most patients.	• Not described	• Antegrade cardioplegia alone. • Left ventricular venting not used.	• Not described

	• Cannulation of the right subclavian artery in a subset of patients at surgeon's discretion.			
Mikus 2017 [26]	• Arterial cannulation: proximal aortic arch. • Venous cannulation: right atrium (using three-stage cannula).	• Not described	• Antegrade hypothermic (4°C) cardioplegia in to aortic root or directly in to the coronary ostia if aortic regurgitation was present. • Left ventricular vent through right superior vein.	• Not described
Monsefi 2018 [28]	• Cannulation of right subclavian artery. • Venous cannulation of right atrium with dual stage venous cannula.	• Not described	• Intermittent retrograde and intermittent antegrade cold blood cardioplegia • Cooling to 28 to 30°C.	• Not described.
Shreshta 2018 [30]	NI		NI	

Sun 2000 [31]	• Cannulation of the left femoral artery • Venous cannulation of left femoral vein in 6 patients and right atrial appendage in 2 patients.	• Not described	• Left ventricular vent through pulmonary trunk.	• Not described
Tabata 2007 [32]	• Cannulation of the ascending aorta, aortic arch, femoral or right axillary artery. • Percutaneous femoral venous or direct right atrial cannulation	• Not described	• Antegrade and retrograde cardioplegia • Left ventricular vent is placed through right superior pulmonary vein or aortic valve after aortotomy.	• Not described
Wachter 2017 [33]	• Cannulation of ascending aorta • Cannulation of right atrial appendage	• Not described	• Antegrade cardioplegia	• Not described

MIS= minimally invasive surgery; MS= median sternotomy; NI= no information

Supplementary Table 4.

Summary of the Risk of Bias in Non-Randomised Studies- of Interventions (ROBINS-I) assessment for studies comparing minimally invasive aortic surgery and median sternotomy.

Author [Ref No.]	Confounding	Selection Bias	Classification of Intervention Bias	Deviations from intended interventions	Missing Data	Measurement of outcomes	Selection of reported result	Overall Judgement
Abjigitova [19]	Serious	Low	Low	Low	Low	Low	Moderate	Serious
Aharon [20]	Serious	Low	NI	NI	NI	NI	NI	Serious
Burdett [21]	NI	Serious	Low	NI	NI	NI	NI	Serious
Hastaoglu [22]	Serious	Low	Low	Moderate	Low	Low	Low	Serious
Hillebrand [23]	Serious	Low	Low	Low	Low	Moderate	Moderate	Serious
Lamelas [24]	Serious	Serious	Low	Low	Low	Low	Moderate	Serious
Levack [25]	Serious	Serious	Low	Low	Moderate	Moderate	Low	Serious
Mikus [26]	Serious	Moderate	Low	Low	Low	Moderate	Moderate	Serious
Monsefi [27]	Critical	Low	Low	Low	Low	Moderate	Moderate	Critical
Monsefi [28]	Serious	Low	Low	Low	Low	Moderate	Moderate	Serious
Shreshta [29]	Critical	Low	Low	Moderate	Serious	Low	Moderate	Critical
Shreshta [30]	NI	NI	Low	NI	NI	NI	Moderate	NI
Sun [31]	Serious	Low	Low	Low	NI	Low	Low	Serious
Tabata [32]	Moderate	Low	Serious	Low	Serious	Low	Low	Serious
Wachter [33]	Moderate	Serious	Low	Low	Low	Low	Moderate	Serious

NI= no information.

Supplementary Table 5.

Timing outcomes for patients receiving minimally invasive surgery of the aorta versus median sternotomy.

First Author & Year [ref no.]	CPB Time (mins)		AoX Time (mins)		Length of ICU Stay (Days)		Length of Hospital Stay (Days)	
	MIS	MS	MIS	MS	MIS	MS	MIS	MS
Abjigitova 2018 [19]	169 IQR 156.0-188.5	186 IQR 161.0-205.0	148 IQR 131.3-160.3	153 IQR 133.0-171.0	3.0 IQR 2.0-4.8	3.0 IQR 2.0-5.0	6.5 IQR 5.0-11.0	8.0 IQR 6.0-11.0
Aharon 2017 [20]	178.0 SD 30.3	216.0 SD 54.4	150.9 SD 24.5	180.3 SD 44.5	-		9.6	10.9
Burdett 2014 [21]	114	108	88	75	-		5.7	8.4
Hastaoglu 2018 [22]	97.1 SD 23.3	85.6 SD 28.4	75.7 SD 22.8	67.4 SD 26.2	1 day:100%	1 day: 80%, 2 days: 20%	4.9 SD 0.9	7.6 SD 5.5
Hillebrand 2018 [23]	166.1 SD 40.6	162.9 SD 45.9	122.2 SD 27.4	113.4 SD 22.6	2.5 SD 3.4	3.9 SD 7.5	13.4 SD 9.3	13.5 SD 10.2
Lamelas 2018 [24]	141.0 IQR 113.0-163.0	177.0 IQR 150.0-201.0	141.0 IQR 113.0-163.0	132.0 IQR 96.0, 155.0	1.21 IQR 0.9-2.9	2.00 IQR 1.7-3.8	6.0 IQR 4.0-7.0	7.0 IQR 6.0-11.0
Levack 2017 [25]	73 SD 28	83 SD 33	57 SD 23	66 SD 27	1.0 IQR 0.8-2.0	1.1 IQR 0.9-2.3	5.2 IQR 4.1-7.2	6.0 IQR 4.8-8.2
Mikus 2017 [26]	81.5 SD 28.4	112.8 SD 43.3	81.5 SD 28.4	94 SD 35.4	3.4 SD 3.9	4.6 SD 6.6	10.5 SD 6.4	10.7 SD 7.7
Monsefi 2017 [28]	184 SD 49	202 SD 40	136 SD 32	151 SD 28	1.1 SD 0.5	1.3 SD 0.8	-	
Shreshta 2018 [30]	-		-		-		-	
Sun 2000 [31]	78.1 SD 6.9	88.6 SD 24.7	58.2 SD 5.2	63.3 SD 12.2	3.0 SD 0.5	2.9 SD 0.7	12.1 SD 5.4	16.1 SD 6.5

Tabata 2007 [32]	156 SD 52	158 SD 61	112 SD 43	116 SD 54	-		5	6
Wachter 2017 [33]	165.5 SD 35.6	173.2 SD 44.1	133.7 SD 23.6	132.8 SD 23.8	2.6 SD 4.9	3.4 SD 6.5	12.4 SD 7.7	13.5 SD 7.7

AoX= aortic cross-clamp; CPB= cardiopulmonary bypass; ICU= intensive care unit; IQR= interquartile range; MIS= minimally invasive surgery; MS= median sternotomy; SD= standard deviation.

Values quoted as either a mean with SD or median with IQR. Hastaoglu et al. report ICU length of stay in terms of a percentage leaving ICU per day.

Supplementary Table 6.

Perioperative outcomes for the current systematic review and meta-analysis of patients receiving minimally invasive surgery of the aorta vs median sternotomy.

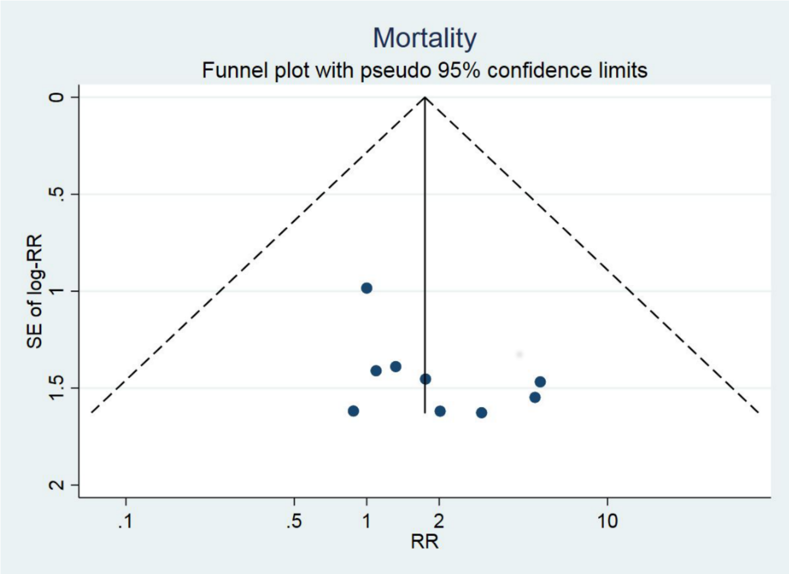
First Author & Year (ref no.)	In Hospital/30-day Mortality n(%)		Reoperation for Bleeding n(%)		Patients Requiring Transfusion n(%)		pRBC use (U)		Neurological Events n(%)		Renal Impairment n(%)	
	MIS	**MS**	**MIS**	**MS**	**MIS**	**MS**	**MIS**	**MS**	**MIS**	**MS**	**MIS**	**MS**
Abjigitova 2018 [19]	0(0)	1(1.1)	0(0)	6(6.6)	11(42.3)	37(40.7)	1.0 IQR 1.0-4.0	2.0 IQR 2.0-4.0	0(0)	0(0)	0(0)	1(1.1)
Aharon 2017 [20]	0(0)	6(3)	21(10.6)	0(0)	-		-		-		0(0)	5(2.5)
Burdett 2014 [21]	0(0)	0(0)	-		1(14.0)	5(56.0)	-		0(0)	0(0)	0	
Hastaoglu 2018 [22]	0(0)	0(0)	2(4.4)	5(11.1)	-		1.31 SD 0.76	1.82 SD 0.49	-		-	
Hillebrand 2018 [23]	1(3.0)	1(3.6)	2(6.1)	3(12.0)	-		1.42 SD 2.46	1.30 SD 3.25	-		-	
Lamelas 2018 [24]	2(3.2)	2(3.2)	0(0)	3(4.8)	-		1.0 IQR 0.0-3.0	3.0 IQR 2.0-5.0	0(0)	0(0)	1(1.6)	4(6.3)
Levack 2017 [25]	0(0)	2(0.4)	17(3.5)	15(3.1)	60(15.0)	78(19.0)	-		3(0.6)	3(0.6)	3(0.6)	6(1.2)
Mikus 2017 [26]	0(0)	5(4.5)	3(6.0)	11(10.0)	26(49.0)	68(60.0)	4.9 SD 6.0	6.7 SD 11.3	-		1(2.0)	4(4.0)
Monsefi 2018 [28]	0(0)	1(1.0)	8(9.0)	13(13.0)	-		1.0 SD 0.5	3.4 SD 4.0	1(2)	1(1.6)	-	
Shreshta 2018 [30]	1(0.48)	1(0.52)	10(4.8)	14(7.3)	-		-		8(3.8)	8(4.1)	1(0.48)	2(1.0)
Sun 2000 [31]	0(0)	0(0)	1(12.5)	2(9.52)	-		0.89 SD 1.14	1.53 SD 1.16	-		-	

Tabata 2007 [32]	0(0)	0(0)	1(1.3)	4(5.1)	27(34.1)	28(35.4)	1.0 SD 1.6	3.4 SD 3.5	1(1.3)	1(1.3)	0(0)	0(0)
Wachter 2017[a] [33]	0(0)	1(1.9)	2(5.6)	6(11.1)	15(41.7)	32(59.3)	1.6 SD 2.7	4.6 SD 15.0	1(2.8)	8(14.8)	7(19.4)	20(37.7)

IQR= interquartile range; MIS= minimally invasive surgery; MS= median sternotomy; n= number; pRBC= packed red blood cells; SD= standard deviation U= units of packed red blood cells.

[a]= neurological impairment reported as postoperative delirium. All other neurological events were stroke.

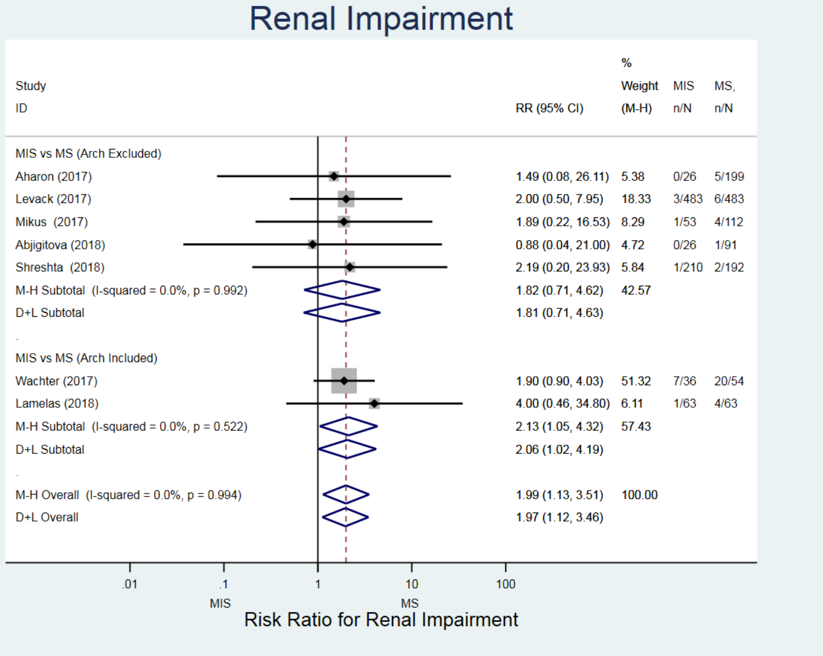
Values quoted as n with percentage (%). Transfused pRBC units are quoted as either mean with SD or median with IQR.



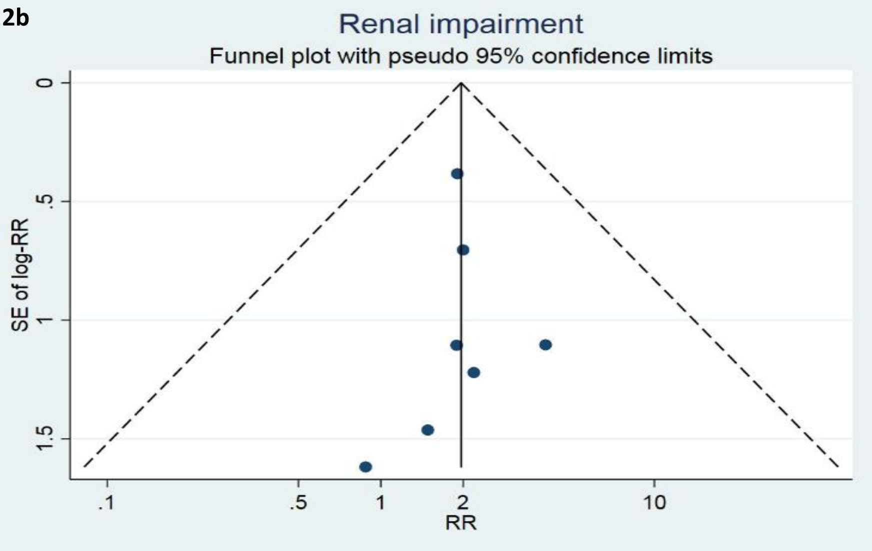
Supplementary Figure 1.

Funnel plot for the perioperative mortality. Individual blue circles indicate studies included in the present study. The position of these circles along the horizontal axis represents the effect-estimate/risk ratio (RR). This is plotted against the standard error (SE) of the log-RR which is an estimate of study precision. Asymmetry is suggestive of small study or publication bias causing overestimation of the effect size in a meta-analysis.

2a

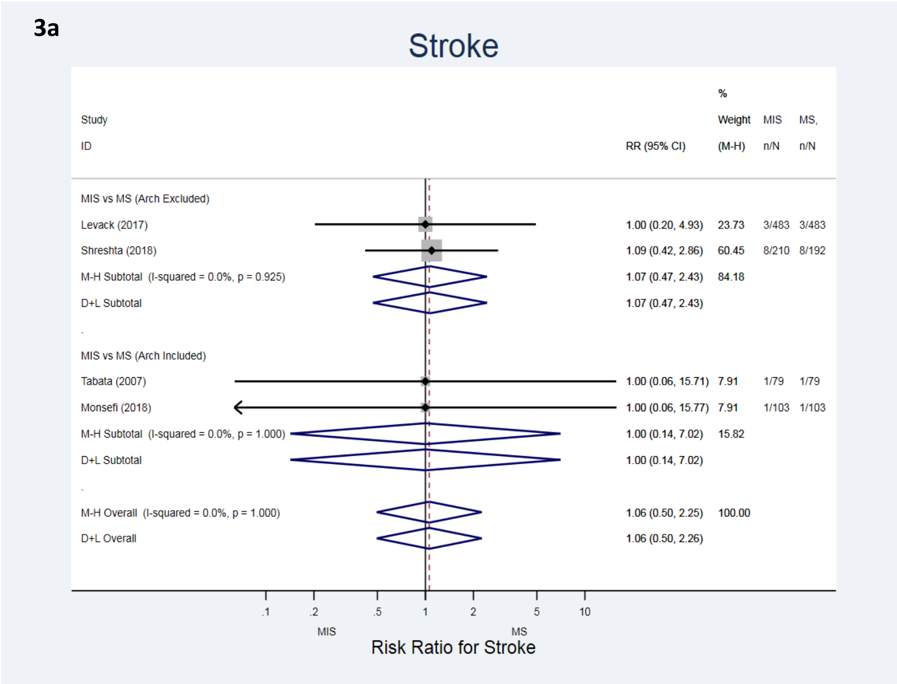


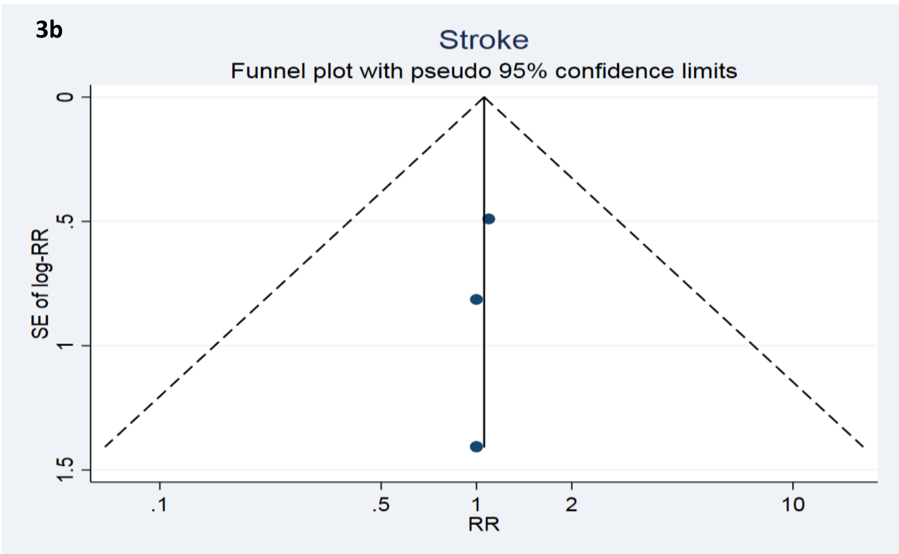
2b



Supplementary Figure 2a & 2b.

2a. Forest plot for the renal impairment this meta-analysis to compare minimally invasive surgery (MIS) of the aorta with median sternotomy (MS). (M-H = Mantel-Haenszel test; D+L= DerSimonian-Laird test.) **2b**. Funnel plots for the renal impairment outcome. Individual blue circles indicate studies included in the present study. The position of these circles along the horizontal axis represents the effect-estimate/risk ratio (RR). This is plotted against the standard error (SE) of the log-RR which is an estimate of study precision. Asymmetry is suggestive of small study or publication bias causing overestimation of the effect size in a meta-analysis.

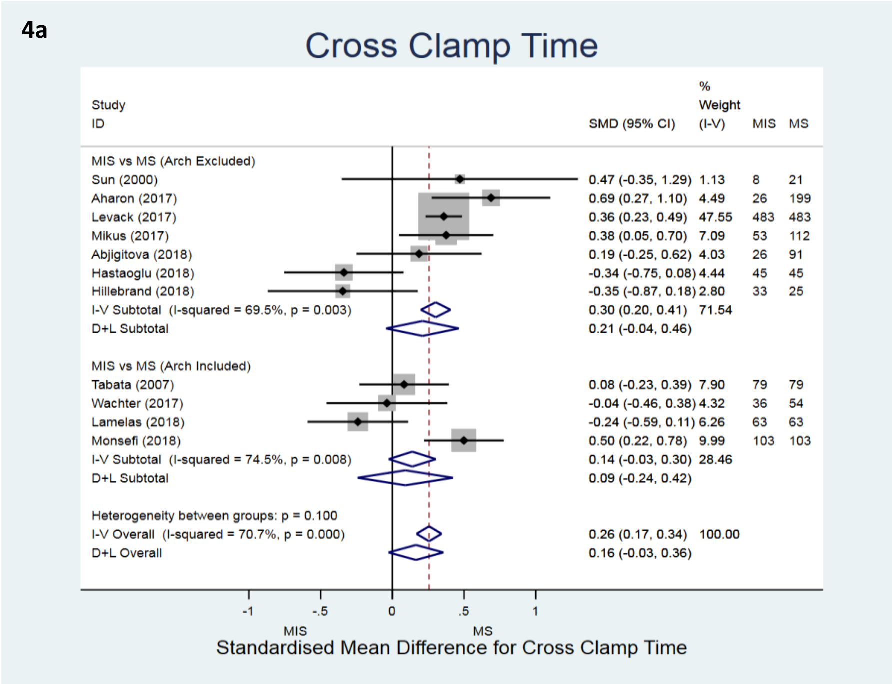




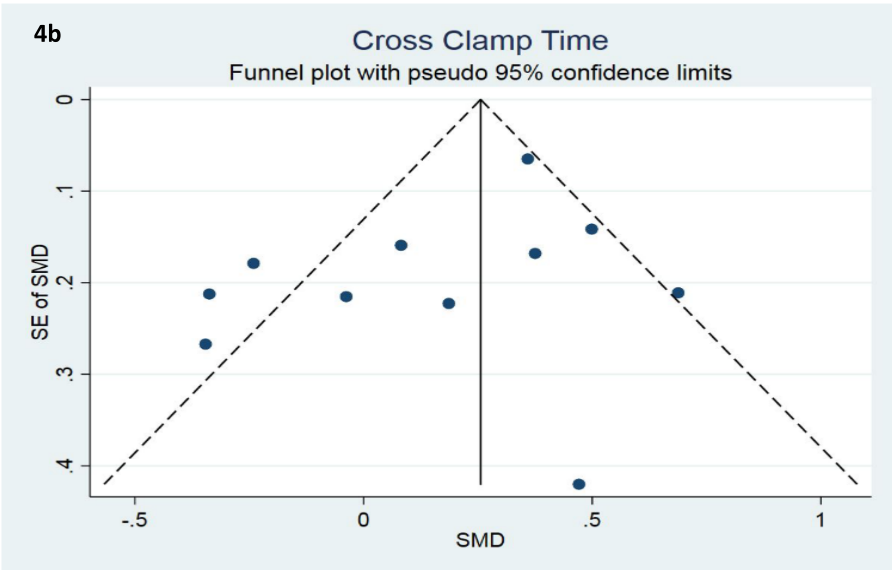
Supplementary Figure 3a & 3b.

3a. Forest plot for the stroke outcome for this meta-analysis to compare minimally invasive surgery (MIS) of the aorta with median sternotomy (MS). (M-H = Mantel-Haenszel test; D+L= DerSimonian-Laird test.) **3b**. Funnel plots for the stroke outcome. Individual blue circles indicate studies included in the present study. The position of these circles along the horizontal axis represents the effect-estimate/risk ratio (RR). This is plotted against the standard error (SE) of the log-SMD which is an estimate of study precision. Asymmetry is suggestive of small study or publication bias causing overestimation of the effect size in a meta-analysis.

4a



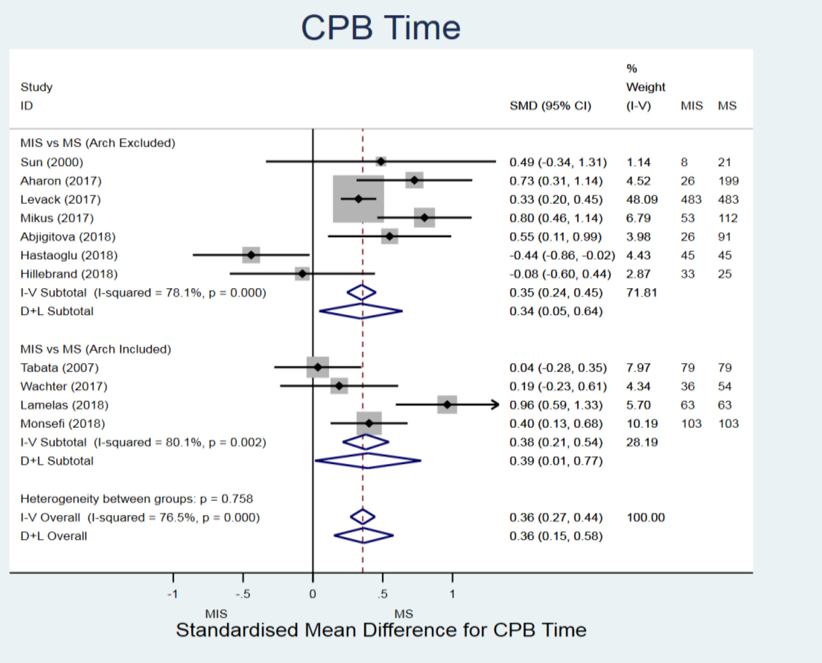
4b



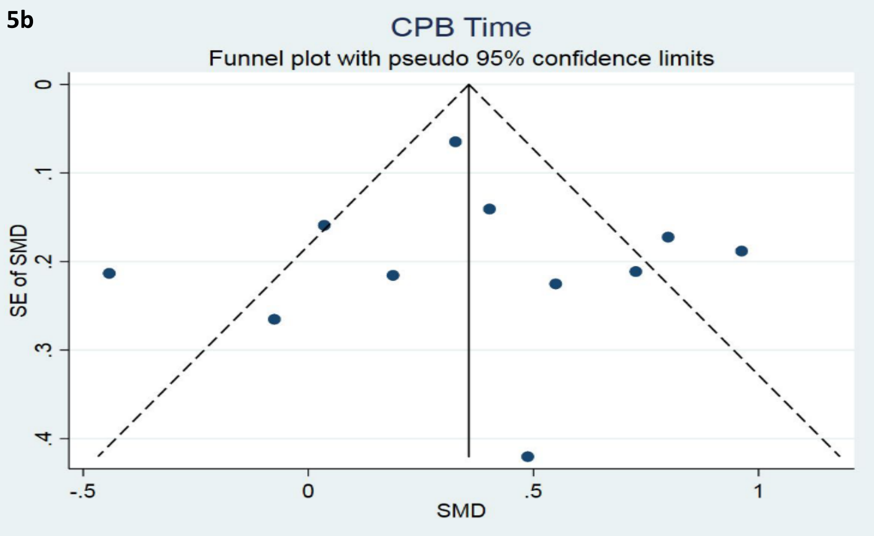
Supplementary Figure 4a & 4b.

4a. Forest plot for the aortic cross clamp (AoX) time outcome for this meta-analysis to compare minimally invasive surgery (MIS) of the aorta with median sternotomy (MS). (M-H = Mantel-Haenszel test; D+L= DerSimonian-Laird test.) **4b**. Funnel plots for the AoX time outcome. Individual blue circles indicate studies included in the present study. The position of these circles along the horizontal axis represents the effect-estimate/standardised mean difference (SMD). This is plotted against the standard error (SE) of the log-SMD which is an estimate of study precision. Asymmetry is suggestive of small study or publication bias causing overestimation of the effect size in a meta-analysis.

5a



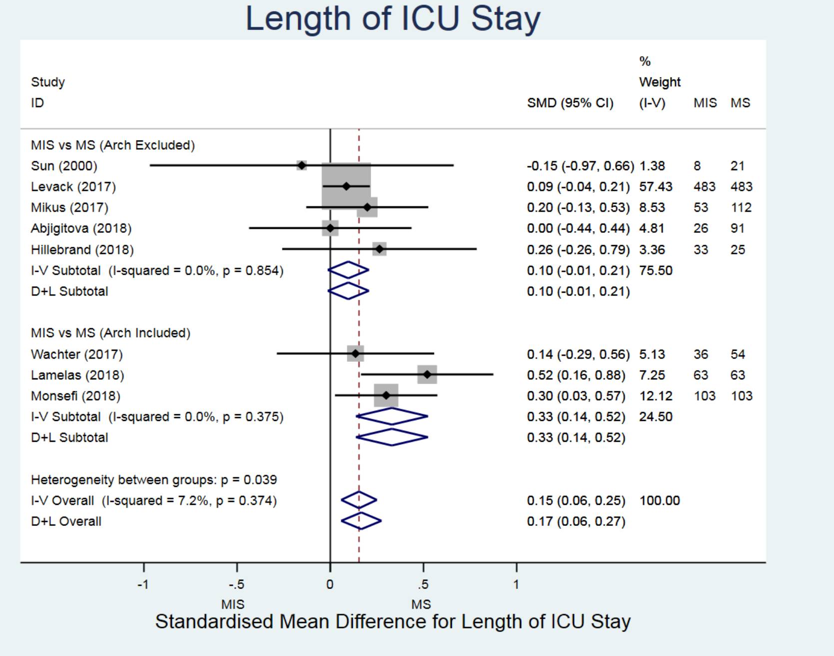
5b



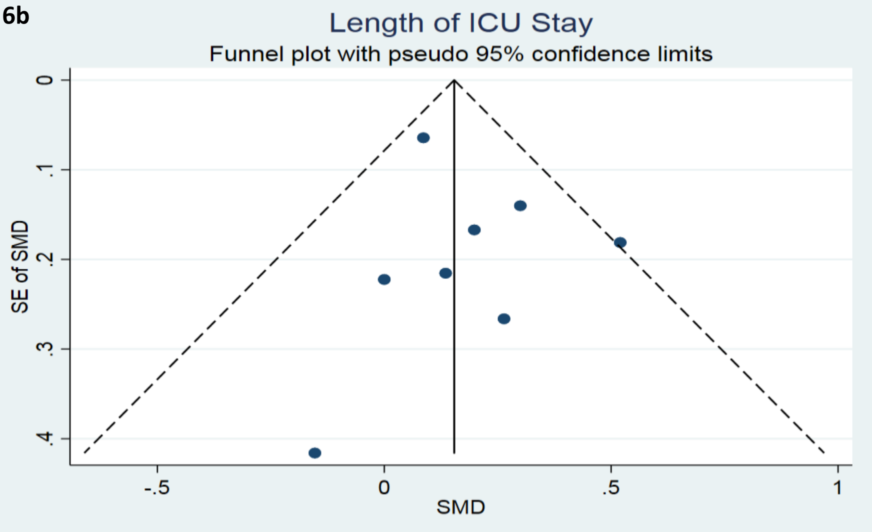
Supplementary Figure 5a & 5b.

5a. Forest plot for the CPB time outcome for this meta-analysis to compare minimally invasive surgery (MIS) of the aorta with median sternotomy (MS). (M-H = Mantel-Haenszel test; D+L= DerSimonian-Laird test.) **5b**. Funnel plots for the CPB time outcome. Individual blue circles indicate studies included in the present study. The position of these circles along the horizontal axis represents the effect-estimate/standardised mean difference (SMD). This is plotted against the standard error (SE) of the log-SMD which is an estimate of study precision. Asymmetry is suggestive of small study or publication bias causing overestimation of the effect size in a meta-analysis.

6a

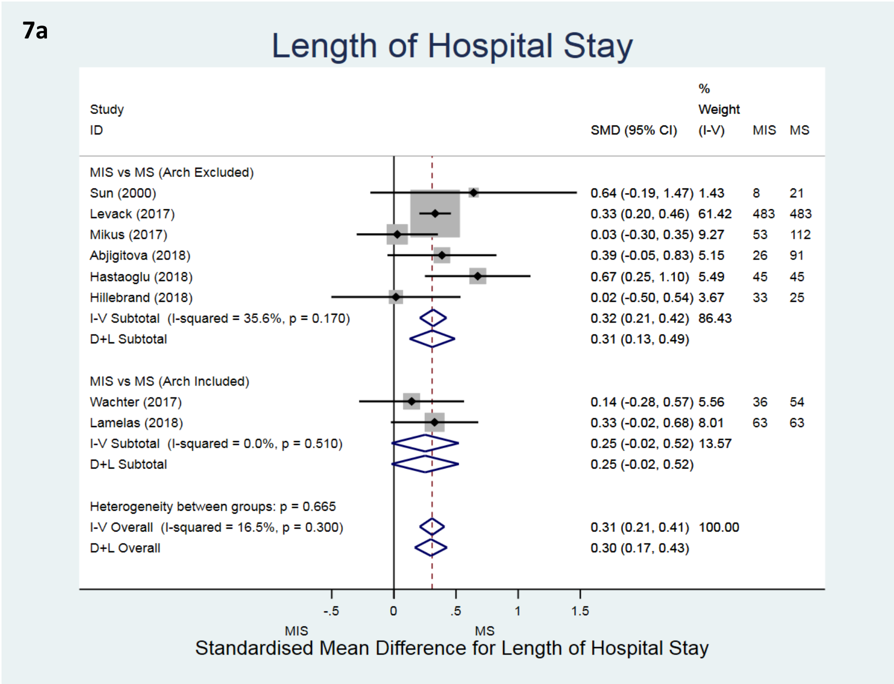


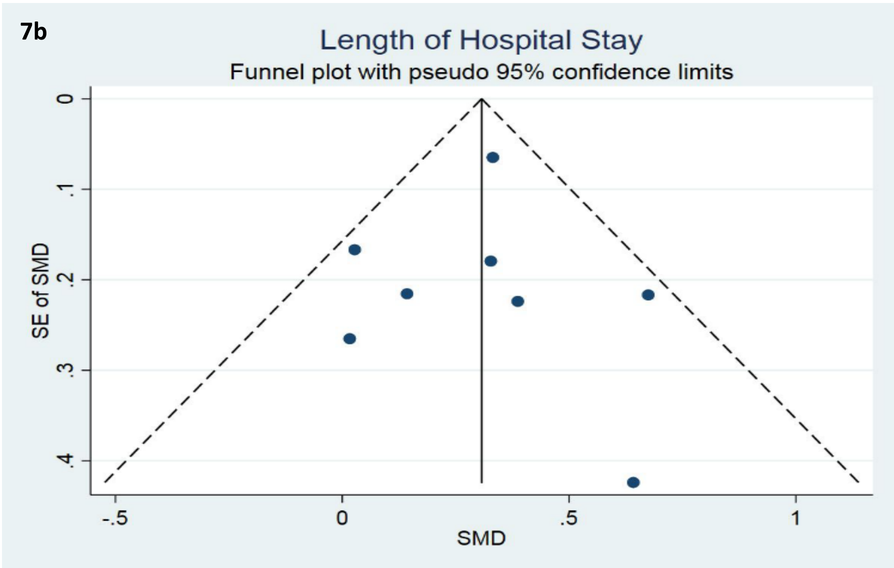
6b



Supplementary Figure 6a & 6b.

6a. Forest plot for the length of ICU stay for this meta-analysis to compare minimally invasive surgery (MIS) of the aorta with median sternotomy (MS). (M-H = Mantel-Haenszel test; D+L= DerSimonian-Laird test.) **6b**. Funnel plots for the length of ICU stay outcome. Individual blue circles indicate studies included in the present study. The position of these circles along the horizontal axis represents the effect-estimate/standardised mean difference (SMD). This is plotted against the standard error (SE) of the log-SMD which is an estimate of study precision. Asymmetry is suggestive of small study or publication bias causing overestimation of the effect size in a meta-analysis.





Supplementary Figure 7a & 7b.

7a. Forest plot for the length of hospital stay for this meta-analysis to compare minimally invasive surgery (MIS) of the aorta with median sternotomy (MS). (M-H = Mantel-Haenszel test; D+L= DerSimonian-Laird test.) **7b**. Funnel plots for the length of hospital stay outcome. Individual blue circles indicate studies included in the present study. The position of these circles along the horizontal axis represents the effect-estimate/standardised mean difference (SMD). This is plotted against the standard error (SE) of the log-SMD which is an estimate of study precision. Asymmetry is suggestive of small study or publication bias causing overestimation of the effect size in a meta-analysis.