Systematic Review

Sex differences in long-term outcomes following surgery for acute type A aortic dissection: a systematic review and meta-analysis

Nitish Bhatt[1], Rodolfo V. Rocha[2], Farid Foroutan[3], Michael W. A. Chu[4], Maral Ouzounian[2,5], Daniyal N. Mahmood[6], Jennifer Chia-Ying Chung[2,5]

[1]Faculty of Medicine, University of Toronto, Toronto, ON, Canada; [2]Division of Cardiac Surgery, University of Toronto, Toronto, ON, Canada; [3]Ted Rogers Centre for Heart Research, Peter Munk Cardiac Centre, Toronto, ON, Canada; [4]Division of Cardiac Surgery, University of Western Ontario, London, ON, Canada; [5]Division of Cardiovascular Surgery, University Health Network, Toronto, ON, Canada; [6]Division of Vascular Surgery, University of Toronto, Toronto, ON, Canada

Correspondence to: Dr. Jennifer Chia-Ying Chung, MD, MSc. Division of Cardiac Surgery, University of Toronto, Toronto, ON, Canada; Division of Cardiovascular Surgery, University Health Network, 200 Elizabeth St., Toronto, ON M5G 2C4, Canada. Email: Jennifer.Chung@uhn.ca.

Background: Recent reports on sex differences in long-term outcomes after surgery for acute type A aortic dissection (ATAAD) are conflicting. We aimed to aggregate updated data on long-term survival and reoperation stratified by sex.

Methods: A literature search was conducted using Medline, Embase, and Cochrane Central. Studies reporting sex-stratified long-term survival and/or reoperation following surgery for ATAAD between January 1, 2000, to March 15, 2023 were included. Preoperative characteristics, intraoperative variables, and early perioperative outcomes were meta-analyzed using a random effects model and pooled risk ratio (RR) with men as the reference group. Individual patient-level data for long-term outcomes was reconstructed to generate sex-specific pooled Kaplan-Meier curves to assess long-term survival and freedom from reoperation.

Results: A total of 15 studies with 7,608 male and 3,989 female patients were included in this analysis. Female patients were older, had higher rates of hypertension, and had less previous cardiac surgery. Intraoperatively, women received less extensive repairs with lower rates of aortic valve replacement and total arch replacement, and higher rates of hemiarch replacement. There were no sex differences for in-hospital/30-day mortality [risk ratio (RR), 1.18; 95% confidence interval (CI): 0.96, 1.45; P=0.12], stroke (RR, 1.07; 95% CI: 0.90, 1.28; P=0.46), and early reoperation (RR, 0.90; 95% CI: 0.75, 1.09; P=0.28). Female patients had lower long-term survival overall (P<0.001) and amongst survivors at 1-year (P=0.014). Overall survival at 5-year was 82.4% in men and 78.1% in women, and at 10-year was 68.1% for men and 63.4% in women. Male patients had higher rates of long-term reoperation (P<0.001). Freedom for reoperation at 5-year was 88.4% in men *vs.* 93.1% in women.

Conclusions: Though perioperative early outcomes have equalized between the sexes following surgery for ATAAD, differences remain in long-term survival and reoperation.

Keywords: Sex differences; acute type A aortic dissection (ATAAD); long-term outcomes

Submitted Jun 26, 2023. Accepted for publication Sep 25, 2023. Published online Oct 27, 2023.
doi: 10.21037/acs-2023-adw-0098
View this article at: https://dx.doi.org/10.21037/acs-2023-adw-0098

Introduction

Acute type A aortic dissection (ATAAD) is a life-threatening condition with a 50% mortality rate before reaching a specialist center (1), where emergency life-saving surgery then carries an additional 9–26% mortality rate (2-6). Important sex-related differences in presentation and management of ATAAD have been described (7,8). Whether this then translated into in-hospital outcome differences was unclear as there was conflicting data from international registries, multi-center, and single-center studies (9-13). Recent updated analyses from the Canadian Thoracic Aortic Collaborative (CTAC) have demonstrated that while historically women had worse outcomes than men following aortic arch surgery, including surgery for ATAAD, this outcome gap has decreased and been eliminated over time (14). Furthermore, updated data from the International Registry for Aortic Dissections (IRAD) also showed reduction of sex differences in operative mortality amongst surgically treated ATAAD patients (9). In fact, recent systematic reviews and meta-analyses corroborate that early outcomes between the sexes have now become comparable (15,16).

Questions remain as to whether long-term outcomes differ between men and women following surgery for ATAAD. Sex-stratified analyses of patients receiving surgery for ATAAD have shown conflicting evidence (9-11,17), with some showing female sex as an independent predictor of worse long-term mortality (10), while other reports show that, among hospital survivors, women have better long-term outcomes than men (18,19). Aggregation of these studies through meta-analysis may provide clarity.

The first meta-analysis of long-term sex differences in patients undergoing surgery for ATAAD reported comparable overall survival between the sexes and higher rates of reoperation in male ATAAD patients (15). However, this analysis included a limited number of studies (five for long-term mortality and two studies for long-term reoperation). Another meta-analysis reported worse long-term survival in women, but several studies were not included, and long-term reoperation was not assessed (20). Therefore, sex differences in long-term outcomes after ATAAD remain controversial. In this systematic review and meta-analysis, we aim to definitively aggregate updated evidence on sex differences in long-term mortality and reoperation.

Methods

Literature search strategy

A systematic review and meta-analysis were conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (*Figure 1*) (21). A systematic review was initiated by searching Medline, Embase, and Cochrane Central from January 1, 2000, to March 15, 2023. Articles prior to 2000 were excluded due to changing cardiac surgery practice including the widespread combined use of contemporary perfusion techniques and systemic hypothermic circulatory arrest which have improved safety. A professional research librarian from our institution was consulted to review and optimize search terms. Both Medical Subject Heading (MeSH) and title, abstract, subject heading, and keyword were used to create search terms. A complete list of search terms for each database is provided in Appendix 1, Table S1.

Eligibility criteria

Relevant studies that met the inclusion criteria were those that included patients who underwent aortic surgery for the diagnosis of ATAAD, performed long-term follow-up of mortality or reoperation outcomes, and reported outcomes stratified by sex. Exclusion criteria included studies with data limited to a specific patient population (e.g., young patients, older patients, Marfan's patients), acute aortic dissection without differentiation of type A *vs.* type B, chronic dissection, no stratification of outcomes by sex, and no long-term follow-up. Moreover, review articles without original data and conference abstracts were excluded. Title and abstract screening of articles from the systematic literature search was performed independently by two authors (Bhatt N and Rocha RV) in Covidence (Melbourne, Australia). Full-text review was also independently performed by Bhatt N and Rocha RV. Discrepancies in assessment were resolved by discussion and consensus.

Data extraction and critical appraisal

Data was extracted independently from text, tables, and figures. The primary data variables of interest were long-term mortality and reoperation. For studies with published

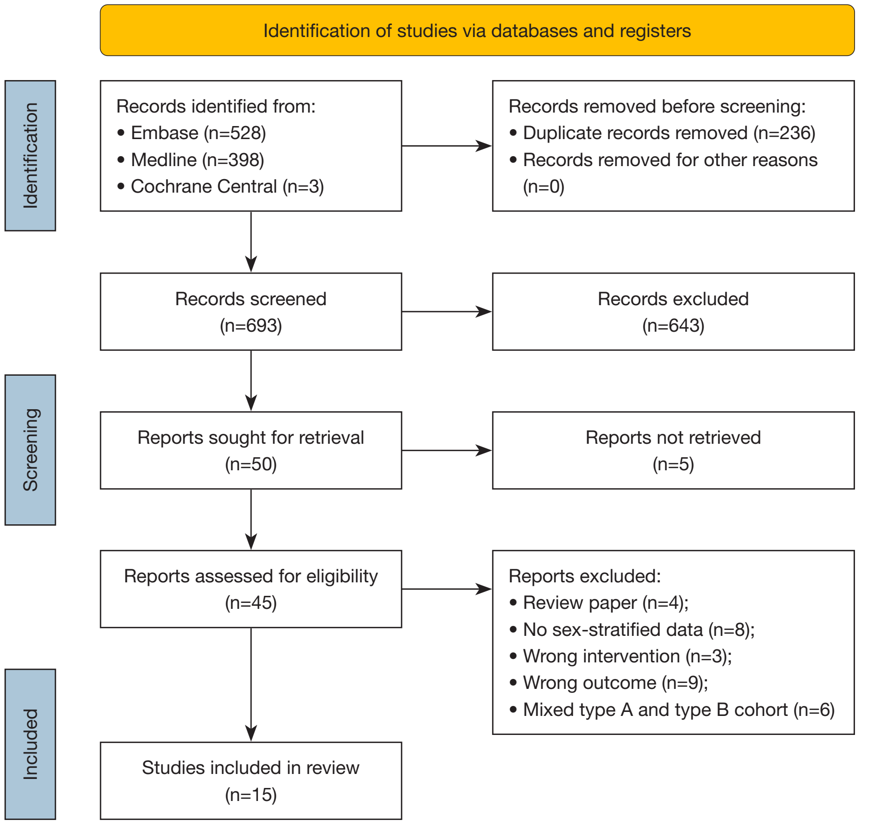


Figure 1 PRISMA flow diagram summarizing systematic review search strategy. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Kaplan-Meier curves comparing outcomes between the sexes, all graphs were saved digitally and the data from the number at risk table was extracted. From published Kaplan-Meier curves, we used a validated algorithm to reconstruct individual patient-level survival data (22). Additionally, preoperative baseline characteristics and intraoperative variables were extracted from included studies. Continuous variables that were reported as median and interquartile range (IQR) were converted to mean ± standard deviation (SD) using a validated estimation method (23). A full list of extracted data variables is provided in Appendix 2, Table S2.

The validated Newcastle-Ottawa Scale (NOS) was used for quality and risk of bias assessment for nonrandomized cohort studies (24). NOS scores graded participant selection (maximum four stars), comparability between studied groups (maximum two stars), and assessment of outcome and follow-up (maximum three stars), for a maximum score of nine stars.

Statistical analysis

Continuous variables were reported as mean ± SD and categorical variables were reported as frequency (percentages). Extracted preoperative and intraoperative variables were aggregated using random effects models in Review Manager (RevMan) (version 5.4). Sex differences were assessed using pooled risk ratio (RR) (categorical variables) or mean difference (continuous variables), with men being the reference group. Heterogeneity across studies was assessed by calculating I^2, with values of <25%, 25–75%, and >75% being interpreted as low, moderate, and high heterogeneity, respectively. Publication bias for preoperative characteristics, intraoperative variables, and early post-operative outcomes was assessed for analyses where at least 10 studies were included by plotting funnel plots in RevMan and performing Egger's test in R statistical software (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria) using the 'metafor' package

Table 1 Characteristics of included studies

Studies	Type	Country/region	Matched	Time	Male, n	Female, n
Gasser *et al.*	Single-center	Austria	No	2000–2020	268	126
Huckaby *et al.*	Multi-center, IRAD	Multi-national	No	1996–2018	1,854	969
Liu *et al.*	Single-center	China	No	2002–2016	167	68
Li *et al.*	Single-center	China	Yes	2009–2014	451	302
Norton *et al.*	Single-center	United States	No	1996–2018	444	206
Rios *et al.*	Single-center	Brazil	No	2006–2016	63	24
Sabashnikov *et al.*	Single-center	United States	Yes	2006–2015	153	87
Suzuki *et al.*	Single-center	Japan	No	2004–2016	156	147
Yousef *et al.*	Single-center	United States	No	2007–2021	361	240
Conway *et al.*	Multi-center, STS database	United States	No	2000–2010	172	79
Friedrich *et al.*	Single-center	Germany	No	2001–2016	242	126
Fukui *et al.*	Single-center	Japan	No	2006–2013	259	245
Chen *et al.*	Multi-center, Taiwan NHIRD	Taiwan	No	2004–2013	2,883	1,286
Santamaria *et al.*	Single-center	Italy	No	2009–2016	98	36
Hirata *et al.*	Single-center	Japan	No	2009–2013	37	48

IRAD, International Registry of Acute Aortic Dissections; STS, Society of Thoracic Surgeons; NHIRD, National Health Insurance Research Database.

(version 4.2.0).

Sex differences in long-term outcomes were analyzed by reconstructing individual patient-level data for survival and reoperation outcomes, which was then aggregated to generate pooled Kaplan-Meier curves and obtain overall estimates of sex-specific survival and freedom from reoperation. We also performed a landmark analysis starting at 1-year following surgery, to exclude the influence of perioperative outcomes and the early patient course, and to assess sex differences in long-term outcomes in patients who were alive at 1-year.

Life expectancy for males and females in the general Canadian population were retrieved from data published by Statistics Canada (25). This data represented life expectancy for all male and female Canadians at a specific age. After adjusting for the average age of male and female patients receiving surgery for ATAAD, yearly life expectancies were plotted against the pooled Kaplan-Meier curve for both sexes.

Two separate sensitivity analyses were performed by excluding studies that performed propensity score matching, and including only studies rated as moderate to good quality according to our NOS assessment (overall score ≥6). All analysis of long-term outcomes was performed using R statistical software and Prism 9 (version 9.4.1; GraphPad, Boston, MA, USA). Significance level was taken as P<0.05.

Results

Quantity and quality of evidence

Our initial systematic search produced 929 studies of which 236 were duplicates and excluded prior to screening. Title and abstract screening resulted in 50 articles which were sought for full text review. The full text for five articles could not be retrieved via institutional library access. The remaining 45 articles underwent full-text review and 15 articles met inclusion criteria and were included in the qualitative synthesis and quantitative analysis. *Table 1* outlines the characteristics of included studies. Across the 15 included studies, there were 7,608 male and 3,989 female patients. Of these, 12 reported single-center retrospective data (10,11,19,26-34), one reported multi-center data 35, and two reported on large multi-center national or

Table 2 NOS for risk of bias assessment in included studies

Studies	Selection (maximum four stars)	Comparability (maximum two stars)	Outcome (maximum three stars)	Total
Gasser *et al.*	***	–	**	5
Huckaby *et al.*	***	**	***	8
Liu *et al.*	**	**	*	5
Li *et al.*	***	**	***	8
Norton *et al.*	***	**	***	8
Rios *et al.*	**	–	*	3
Sabashnikov *et al.*	**	**	**	6
Suzuki *et al.*	***	**	***	8
Yousef *et al.*	***	**	***	8
Conway *et al.*	***	–	***	6
Friedrich *et al.*	***	**	***	8
Fukui *et al.*	****	**	***	9
Chen *et al.*	***	**	***	8
Santamaria *et al.*	***	**	***	8
Hirata *et al.*	**	*	**	5

Total scores greater or equal to six were considered moderate to good quality. NOS, Newcastle-Ottawa Scale.

international datasets (9,17). A total of 13 studies published Kaplan-Meier curves for survival (9-11,19,26-28,30-35) and four studies published curves for reoperation (9,17,19,28) and were subsequently included in the respective pooled Kaplan-Meier analyses. Two studies included cohorts starting from the earliest timepoint and followed patients over the longest time span from 1996–2018 (9,32).

The NOS evaluation is displayed in *Table 2*. Nine of 16 studies included were scored eight or nine points suggesting they have good quality (9,11,17,19,26-29,32). Three studies scored less than six points which was due to no description of comparability of cohorts, or lack of information about the method for outcomes ascertainment and assessment (10,30,33). The 12 studies scored as having moderate to good quality (NOS scores ≥6) included a total of 6,947 men and 3,707 women.

Patient and operative characteristics

Table 3 summarizes pooled number of studies and patients analyzed as well as results for preoperative patient characteristics, intraoperative variables, and perioperative outcomes from the included studies (see Appendix 3, Figures S1-S24). Women were older than men [mean difference, 8.07 years; 95% confidence interval (CI): 7.05, 9.10; P<0.001; ten studies included (10,303 patients)] and had a lower body mass index [mean difference, −1.09; 95% CI: −1.56, −0.62; P<0.001; seven studies (5,379 patients)]; these analyses showed moderate heterogeneity (I^2=62% and I^2=54%, respectively). Women had higher rates of hypertension [risk ratio (RR), 1.06; 95% CI: 1.03, 1.09; P<0.001; ten studies (10,303 patients)] and lower rates of chronic kidney disease [RR, 0.74; 95% CI: 0.59, 0.93; P=0.01; seven studies (9,154 patients)]; these analyses showed moderate heterogeneity (I^2=26% and I^2=38%, respectively). Women were less likely to be currently smoking [RR, 0.47; 95% CI: 0.25, 0.88; P=0.02; five studies (4,144 patients)]; though this analysis showed high heterogeneity (I^2=94%). Women were also less likely to have undergone previous cardiovascular surgery [RR, 0.70; 95% CI: 0.59, 0.84; P<0.001; six studies (9,005 patients)]; this analysis showed low heterogeneity (I^2=0%).

Intraoperatively, females had shorter cardiopulmonary bypass times [mean difference, −11.51 minutes; 95% CI: −20.58, −2.44; P=0.01; nine studies (5,903 patients)]; however, this analysis showed high heterogeneity (I^2=86%).

Table 3 Pooled estimates of preoperative patient characteristics, intraoperative variables, and perioperative outcomes

Variables	Number studies	Male, n	Female, n	RR/MD	95% CI	P value	I^2 (%)
Preoperative variables†							
Age	10	6,792	3,511	8.07	7.05, 9.10	<0.001*	62
BMI	7	3,478	1,901	−1.09	−1.56, −0.62	<0.001*	54
Hypertension	10	6,792	3,511	1.06	1.03, 1.09	<0.001*	26
Prior CVA	4	3,767	1,697	1.78	1.01, 3.15	0.05	76
Prior CKD	7	6,093	3,061	0.74	0.59, 0.93	0.01*	38
CTD	7	6,106	3,105	1.17	0.91, 1.50	0.23	0
CAD	5	1,468	785	0.94	0.77, 1.15	0.57	0
COPD	6	4,165	1,970	1.05	0.82, 1.34	0.71	20
Diabetes mellitus	9	6,524	3,385	1.22	0.94, 1.59	0.13	62
Current smoker	5	2,696	1,448	0.47	0.25, 0.88	0.02*	94
Prior cardiac surgery	6	6,052	2,953	0.70	0.59, 0.84	<0.001*	0
Shock	5	2,955	1,693	1.13	0.99, 1.29	0.07	0
Malperfusion	5	1,382	806	0.94	0.81, 1.10	0.46	21
Intraoperative variables‡							
CPB time	9	3,740	2,163	−11.51	−20.58, −2.44	0.01*	86
Nadir temperature	3	2,566	1,301	0.27	−0.05, 0.59	0.10	0
AVR	6	3,335	1,882	0.80	0.70, 0.90	<0.001*	0
Total arch	9	4,018	2,400	0.73	0.58, 0.93	0.01*	85
Hemiarch	5	2,987	1,641	1.06	1.01, 1.11	0.01*	11
Cannulation							
Aortic	4	2,610	1,422	1.17	0.93, 1.48	0.18	73
Axillary/subclavian	6	3,050	1,627	0.83	0.77, 0.91	<0.001*	0
Femoral	6	3,050	1,627	0.98	0.89, 1.08	0.68	1
Perioperative outcomes							
In-hospital/30-day mortality	11	6,972	3,757	1.18	0.96, 1.45	0.12	46
Stroke	10	6,901	3,686	1.07	0.90, 1.28	0.46	12
Reoperation for bleeding	8	3,588	2,100	0.90	0.75, 1.09	0.28	0

†, analysis of preoperative variables used unmatched data from Sabashnikov *et al.* (34) and Li *et al.* (11); ‡, analysis of intraoperative variables used unmatched data from Sabashnikov *et al.* (34); *, P<0.05. RR, risk ratio; MD, mean difference; CI, confidence interval; BMI, body mass index; CVA, cerebrovascular accident; CKD, chronic kidney disease; CTD, connective tissue disease; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; AVR, aortic valve replacement.

Furthermore, women had less extensive surgery with lower rates of total arch replacements [RR, 0.73; 95% CI: 0.58, 0.93; P=0.01; nine studies (6,418 patients)]; though this analysis showed high heterogeneity (I^2=85%). Women received more hemiarch replacements [RR, 1.06; 95% CI: 1.01, 1.11; P=0.01; five studies (4,628 patients)] and less aortic valve replacements [RR, 0.80; 95% CI: 0.70, 0.90; P<0.001; six studies (5,217 patients)]; these analyses showed

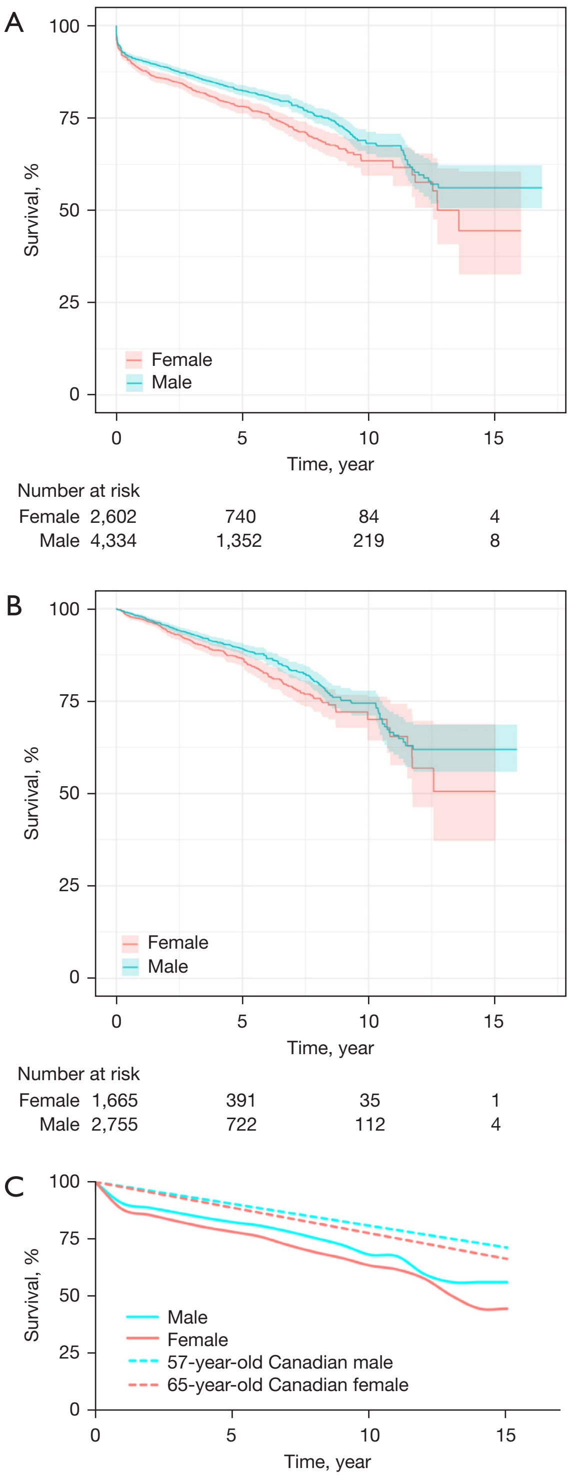


Figure 2 Pooled Kaplan-Meier curve of long-term survival with 95% CI for (A) all patients, (B) patients who survived 1-year post-surgery, and (C) all patients plotted against yearly life expectancy of age- and sex-matched general Canadian population, data retrieved from Statistics Canada (25). CI, confidence interval.

low heterogeneity (I^2=11% and I^2=0%, respectively). Cannulation strategy was also different between the sexes with women receiving axillary cannulation less frequently than men [RR, 0.83; 95% CI: 0.77, 0.91; P<0.001; six studies (4,677 patients)], though rates of femoral cannulation did not differ significantly [RR, 0.98; 95% CI: 0.89, 1.08; P=0.68; six studies (4,677 patients)]; these analyses showed low heterogeneity (I^2=0% and I^2=1%, respectively). No other sex differences in preoperative and intraoperative variables were noted.

For perioperative outcomes, the aggregate studies showed no differences in in-hospital/30-day mortality, perioperative stroke, or early reoperation for bleeding.

In analyses where ≥10 studies were included (i.e., age, hypertension, in-hospital/30-day mortality, and perioperative stroke) we did not note any large asymmetry in funnel plots (Appendix 4, Figures S25-S28) and detected no significant asymmetry in funnel plots by Egger's test for age (P=0.92), hypertension (P=0.35), in-hospital/30-day mortality (P=0.84), and perioperative stroke (P=0.20).

Long-term survival

Overall survival (*Figure 2A*) was significantly worse in women in comparison to men (P<0.001). Using the pooled Kaplan-Meier curves, estimates for 5-year survival were 82.4% in men and 78.1% in women, and for 10-year survival were 68.1% in men and 63.4% in women. Sensitivity analysis showed long-term survival remained poorer for women after removing studies with propensity-matched cohorts (P=0.0004) and studies graded as poor quality (P=0.002). Landmark analysis of patients surviving 1-year post-surgery (*Figure 2B*) also showed poorer survival for women in the long-term (P=0.014), though the difference between the sexes was less with 5-year survival of 90.9% in males *vs.* 88.9% in females and a 10-year survival of 75.1% in males *vs.* 72.0% in females. For reference, the long-term survival curves were superimposed with the expected survival of age- and sex-matched Canadians (*Figure 2C*).

Of the two studies that did not publish Kaplan-Meier curves for survival, Chen and colleagues reported no significant differences between male and female patients in all-cause mortality [35.3% *vs.* 34.7%; odds ratio (OR), 0.99; 95% CI: 0.88, 1.10] across a mean follow up of 2.8±2.7 years (17). Meanwhile, Santamaria and colleagues reported worse long-term survival in female patients (47% *vs.* 24%, P=0.005) across a mean follow-up of 3.25±3 years (29).

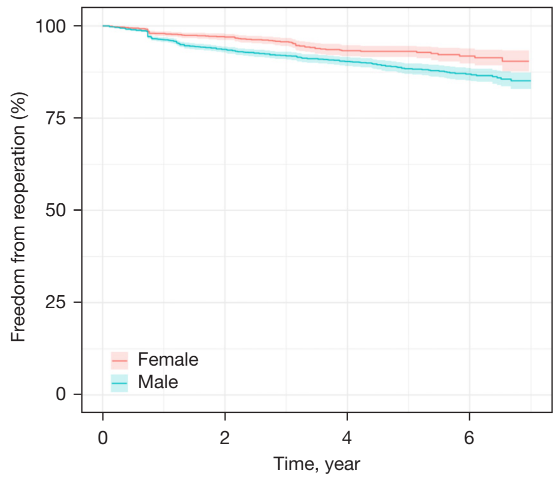


Figure 3 Pooled Kaplan-Meier curve with 95% CI of long-term reoperation for all patients. CI, confidence interval.

Long-term reoperation

Long-term freedom from reoperation (*Figure 3*) was lower in men compared to women (P<0.001). Freedom from reoperation at 5-year was estimated to be 88.4% in men *vs.* 93.1% in women. Sensitivity analysis was not performed for this outcome, as none of the included studies had propensity-matched cohorts and all studies received scores ≥6 on NOS assessment. Although Gasser and colleagues did not publish a Kaplan-Meier curve for freedom from reoperation, they reported higher rates of reoperation during follow-up for men (8.6% *vs.* 4.0%) and this difference was not statistically significant (P=0.08) (10).

Discussion

This meta-analysis evaluated the influence of sex on long-term death and reoperation following surgical treatment of ATAAD using all available updated sex-stratified data. Our literature search identified 15 studies reporting sex-specific data for long-term survival and/or reoperation which included over 11,000 ATAAD patients undergoing surgical repair. We found that men and women now have comparable perioperative outcomes. However, women had worse long-term survival, and men had higher rates of long-term reoperation.

Our study found that women presented on average ~8 years older than men, which is similar to the results reported by two previous meta-analyses (15,20). Furthermore, we found that men received more extensive surgical repair for ATAAD which could potentially be due to more extensive distal disease involving the descending thoracic and abdominal aorta in men (36). Despite similar rates of preoperative malperfusion syndrome, there was a trend towards women presenting with shock, which may have influenced the surgeon's decision to perform a more conservative intervention.

Our study was the first to meta-analyze sex differences in total arch and hemiarch replacements, and arterial cannulation. We found that women received less total arch replacements and more hemiarch replacements. Furthermore, women were less likely to receive axillary cannulation, though there were no sex differences in rates of direct aortic and femoral cannulation. Ohira and colleagues also found that female sex was an independent predictor of axillary non-cannulation and hypothesized this could be due to a combination of lower vessel caliber, increased age, and increased urgency of surgery which prohibited against the typically longer times required to establish axillary cannulation (37). While some studies have found comparable outcomes across all three cannulation strategies (38), two meta-analyses showed axillary cannulation is superior to femoral cannulation for in-hospital mortality and stroke (39,40).

The finding that there were no sex differences in the rates of in-hospital/30-day mortality and perioperative stroke in our analysis was similar to recent reports and meta-analyses (15,16,20). Previously, there was a gender gap reported in perioperative outcomes which has been eliminated over time. Contemporary data from IRAD shows female in-hospital mortality following ATAAD surgery decreased from 27% to 16% (trend P=0.114), and female sex was eliminated as an independent predictor of mortality when considering patients enrolled in the last decade of the study [2006–2017] (9). Moreover, CTAC data also shows equalization between the sexes driven largely by significant improvements for women undergoing urgent aortic arch surgery (30% to 11%, trend P=0.01) (14). This era effect may be due to advances in surgical techniques and improving safety of aortic surgery, which could drive large improvements in outcomes for female patients due to the initial disparities between the sexes. Our updated meta-analysis of all available data, including more contemporary results, can make this effect more definitive.

Despite having comparable in-hospital/30-day mortality, long-term survival was worse in women. One important factor influencing this could be the older age at presentation of women compared to men. Across included studies, the average age at presentation was 65 years for women compared to 57 years for men. In Canada, the general population life expectancy was 22.2 years for women aged 65 and 26.1 years for men aged 57 years (25). Similarly, in the United States, life expectancy was 20.8 years for women aged 65 and 24.2 years for men aged 57 (41). However, the differences in yearly survival between the average Canadian 65-year-old woman and 57-year-old man were smaller than the differences in survival between the sexes following surgery for ATAAD (shown in *Figure 2C*). This suggests that older age at presentation for female patients is an important factor though may not fully account for the sex-based differences in long-term survival.

Furthermore, in our pooled Kaplan-Meier plot, the sex-specific survival curves demonstrated the greatest separation within the first-year post-surgery. Given the dynamic changes in the outcome gap between men and women within the early perioperative period over the past 10–20 years, we sought to neutralize this confounding effect. Therefore, we carried out a landmark analysis of patients alive at 1 year, which showed a smaller difference between men and women, though survival remained significantly poorer in women. In their meta-analysis, Carbone and colleagues found higher risk of mortality at 5- and 10-year for women, though their study did not estimate pooled survival rates at 5- and 10-year (20). Our findings are in contrast to the meta-analysis by Meccanici and colleagues who reported comparable long-term survival between men and women, however their analysis only included five studies and did not analyze differences beyond 5-year post-surgery (15). Overall, the sum of the data suggests that a difference in long-term survival between the sexes after surgery for ATAAD does exist but is not large. Encouragingly, our analysis suggests that this difference is at least partially accounted for by the expected differences in long-term survival of age- and sex-matched cohorts in the general population.

Despite men having more extensive surgery, there was a higher rate of reoperation among them. It has been suggested that this could be due to lower age at presentation, as advanced age may be a reason against performing late reoperation (19,28). Other confounders could be the higher long-term mortality in females, which is a competing risk. Geirsson and colleagues reported more extensive distal dissection and younger age, both more common in men, to be independent predictors of distal reoperations in surgically treated ATAAD patients (42), while An and colleagues also reported advanced age and female sex as protective factors against reoperation amongst patients who survived at least 90 days post-surgery (18). The only previous study to perform meta-analysis of long-term reoperation is Meccanici and colleagues, which included only two studies (15). Nonetheless, they also reported higher rates of reoperation in men.

Limitations

There are several limitations to our current study. Firstly, this is a systematic review of retrospective, observational studies. The majority of included studies have provided data regarding sex differences in unmatched cohorts. However, two included studies provided outcomes data from propensity-matched cohorts (11,34); we performed sensitivity analysis on the effect of including these two propensity-matched cohorts in our meta-analysis and found no significant changes to our results. Secondly, our inclusion criteria limited our analysis to studies providing long-term sex-specific outcomes in surgically treated ATAAD patients. As such, several studies included in previous meta-analyses were excluded from the present analysis. Of these, the most significant exclusion is sex-stratified data from the large, multicenter, international German Registry for Acute Aortic Dissection Type A (GERAADA) which has reported on sex differences in preoperative characteristics, intraoperative variables, and perioperative outcomes, however has not yet published data on long-term follow-up (36). Thirdly, some variables showed high heterogeneity (*Table 3*), including prior cerebrovascular accident and current smoking, which may be due to challenges in the classification and reporting of these variables, as well as total arch and aortic cannulation, which may be due to differences in standard practice between institutions. Finally, there are limitations to the algorithm used to reconstruct individual patient-level data and generate pooled Kaplan-Meier curves. The algorithm assumes a constant rate of censoring over time (22), and some individual studies included in our analysis capture mortality as a censored event when the outcome of interest is reoperation, as such the cumulative probability of reported reoperation may be susceptible to inaccuracy. Nonetheless, our estimated 5- and

10-year reoperation rates were similar to those reported in individual studies.

Conclusions

In this updated meta-analysis of surgically treated ATAAD patients, sex differences in preoperative characteristics and intraoperative management were apparent. Women had worse long-term survival compared to men. This difference remains even amongst patients who survive the first-year post-surgery, though the difference is smaller. Male sex was associated with higher rates of reoperation. Future work is needed to understand if there are any associations between specific preoperative and intraoperative variables and long-term outcomes.

Acknowledgments

The authors thank Ashley Farrell (Library and Information Services, University Health Network, Toronto, ON, Canada) for research librarian support in reviewing and suggesting improvements for the search strategy.
Funding: None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Howard DP, Banerjee A, Fairhead JF, et al. Population-based study of incidence and outcome of acute aortic dissection and premorbid risk factor control: 10-year results from the Oxford Vascular Study. Circulation 2013;127:2031-7.
2. Conzelmann LO, Weigang E, Mehlhorn U, et al. Mortality in patients with acute aortic dissection type A: analysis of pre- and intraoperative risk factors from the German Registry for Acute Aortic Dissection Type A (GERAADA). Eur J Cardiothorac Surg 2016;49:e44-52.
3. Yamasaki M, Yoshino H, Kunihara T, et al. Risk analysis for early mortality in emergency acute type A aortic dissection surgery: experience of Tokyo Acute Aortic Super-network. Eur J Cardiothorac Surg 2021;60:957-64.
4. Trimarchi S, Nienaber CA, Rampoldi V, et al. Contemporary results of surgery in acute type A aortic dissection: The International Registry of Acute Aortic Dissection experience. J Thorac Cardiovasc Surg 2005;129:112-22.
5. Tolenaar JL, Froehlich W, Jonker FH, et al. Predicting in-hospital mortality in acute type B aortic dissection: evidence from International Registry of Acute Aortic Dissection. Circulation 2014;130:S45-50.
6. Pape LA, Awais M, Woznicki EM, et al. Presentation, Diagnosis, and Outcomes of Acute Aortic Dissection: 17-Year Trends From the International Registry of Acute Aortic Dissection. J Am Coll Cardiol 2015;66:350-8.
7. Nienaber CA, Fattori R, Mehta RH, et al. Gender-related differences in acute aortic dissection. Circulation 2004;109:3014-21.
8. Smedberg C, Steuer J, Leander K, et al. Sex differences and temporal trends in aortic dissection: a population-based study of incidence, treatment strategies, and outcome in Swedish patients during 15 years. Eur Heart J 2020;41:2430-8.
9. Huckaby LV, Sultan I, Trimarchi S, et al. Sex-Based Aortic Dissection Outcomes From the International Registry of Acute Aortic Dissection. Ann Thorac Surg 2022;113:498-505.
10. Gasser S, Stastny L, Kofler M, et al. Type A aortic dissection is more aggressive in women. Eur J Cardiothorac Surg 2022;62:ezac040.
11. Li Y, Yang N, Liu S, et al. Sex Differences of Clinical Presentation and Outcomes in Propensity-Matched Patients with Acute Type A Aortic Dissection. Heart Surg Forum 2021;24:E311-6.
12. Chemtob RA, Hjortdal V, Ahlsson A, et al. Effects of Sex on Early Outcome following Repair of Acute Type A Aortic Dissection: Results from The Nordic Consortium for Acute Type A Aortic Dissection (NORCAAD). Aorta (Stamford) 2019;7:7-14.
13. Chung J, Stevens LM, Ouzounian M, et al. Sex-Related Differences in Patients Undergoing Thoracic Aortic

Surgery. Circulation 2019;139:1177-84.
14. Chung JCY, Bhatt N, Stevens LM, et al. Trends in sex-specific differences following aortic arch repair: results from the Canadian Thoracic Aortic Collaborative. Ann Cardiothorac Surg 2023. doi: 10.21037/acs-2023-adw-0163.
15. Meccanici F, Gökalp AL, Thijssen CGE, et al. Male-female differences in acute thoracic aortic dissection: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg 2022;34:616-27.
16. Lawrence KW, Yin K, Connelly HL, et al. Sex-based outcomes in surgical repair of acute type A aortic dissection: A meta-analysis and meta-regression. J Thorac Cardiovasc Surg 2022. [Epub ahead of print]. doi: 10.1016/j.jtcvs.2022.02.005.
17. Chen FT, Chou AH, Chan YH, et al. Sex-related differences on the risks of in-hospital and late outcomes after acute aortic dissection: A nationwide population-based cohort study. PLoS One 2022;17:e0263717.
18. An KR, de Mestral C, Tam DY, et al. Surveillance Imaging Following Acute Type A Aortic Dissection. J Am Coll Cardiol 2021;78:1863-71.
19. Suzuki T, Asai T, Kinoshita T. Clinical differences between men and women undergoing surgery for acute Type A aortic dissection. Interact Cardiovasc Thorac Surg 2018;26:944-50.
20. Carbone A, Ranieri B, Castaldo R, et al. Sex differences in type A acute aortic dissection: a systematic review and meta-analysis. Eur J Prev Cardiol 2023;30:1074-89.
21. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
22. Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012;12:9.
23. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135.
24. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-5.
25. Statistics Canada. Life expectancy and other elements of the complete life table, three-year estimates, Canada, all provinces except Prince Edward Island. 2022. Available online: https://doi.org/10.25318/1310011401-eng
26. Yousef S, Navid F, Zhu J, et al. Sex-based outcomes after surgery for acute type A aortic dissection. J Card Surg 2022;37:4342-7.
27. Friedrich C, Salem MA, Puehler T, et al. Sex-specific risk factors for early mortality and survival after surgery of acute aortic dissection type a: a retrospective observational study. J Cardiothorac Surg 2020;15:145.
28. Fukui T, Tabata M, Morita S, et al. Gender differences in patients undergoing surgery for acute type A aortic dissection. J Thorac Cardiovasc Surg 2015;150:581-7.e1.
29. Santamaria V, Schirone L, Vinciguerra M, et al. Predictors for outcome in type A aortic dissection: A focus on false lumen. Cirugía Cardiovascular 2021;28:71-6.
30. Hirata K, Oda S, Suzuki R, et al. Long-term prognostic value of the combined assessment of clinical and computed tomography findings in type: An acute aortic dissection. Medicine (Baltimore) 2020;99:e23008.
31. Liu YJ, Wang XZ, Wang Y, et al. Correlation between Sex and Prognosis of Acute Aortic Dissection in the Chinese Population. Chin Med J (Engl) 2018;131:1430-5.
32. Norton EL, Kim KM, Fukuhara S, et al. Differences among sexes in presentation and outcomes in acute type A aortic dissection repair. J Thorac Cardiovasc Surg 2023;165:972-81.
33. Rios F, Perez D, Soca G, et al. Predictive Factors of Mortality in Acute Aortic Dissection and Validity of the EuroSCORE Algorithm in a Small-Sized Cardiac Surgery Institution. Braz J Cardiovasc Surg 2020;35:878-83.
34. Sabashnikov A, Heinen S, Deppe AC, et al. Impact of gender on long-term outcomes after surgical repair for acute Stanford A aortic dissection: a propensity score matched analysis. Interact Cardiovasc Thorac Surg 2017;24:702-7.
35. Conway BD, Stamou SC, Kouchoukos NT, et al. Effects of Gender on Outcomes and Survival Following Repair of Acute Type A Aortic Dissection. Int J Angiol 2015;24:93-8.
36. Rylski B, Georgieva N, Beyersdorf F, et al. Gender-related differences in patients with acute aortic dissection type A. J Thorac Cardiovasc Surg 2021;162:528-535.e1.
37. Ohira S, Malekan R, Kai M, et al. Direct Axillary Artery Cannulation for Type A Dissection and Impact of Dissected Innominate Artery. Ann Thorac Surg 2022;113:1183-90.
38. Yousef S, Brown JA, Serna-Gallegos D, et al. Central versus peripheral cannulation for acute type A aortic dissection. J Thorac Cardiovasc Surg 2022. [Epub ahead of print]. doi: 10.1016/j.jtcvs.2022.04.055.

39. Benedetto U, Mohamed H, Vitulli P, et al. Axillary versus femoral arterial cannulation in type A acute aortic dissection: evidence from a meta-analysis of comparative studies and adjusted risk estimates. Eur J Cardiothorac Surg 2015;48:953-9.
40. Ren Z, Wang Z, Hu R, et al. Which cannulation (axillary cannulation or femoral cannulation) is better for acute type A aortic dissection repair? A meta-analysis of nine clinical studies. Eur J Cardiothorac Surg 2015;47:408-15.
41. Arias E, Xu J. United States life tables, 2020. 2022. Available online: https://dx.doi.org/10.15620/cdc:118055
42. Geirsson A, Bavaria JE, Swarr D, et al. Fate of the residual distal and proximal aorta after acute type a dissection repair using a contemporary surgical reconstruction algorithm. Ann Thorac Surg 2007;84:1955-64; discussion 1955-64.

Cite this article as: Bhatt N, Rocha RV, Foroutan F, Chu MWA, Ouzounian M, Mahmood D, Chung JC. Sex differences in long-term outcomes following surgery for acute type A aortic dissection: a systematic review and meta-analysis. Ann Cardiothorac Surg 2023;12(6):514-525. doi: 10.21037/acs-2023-adw-0098

Supplementary

Appendix 1

Table S1 Systematic review search terms

Database	Search terms
Medline/Cochrane Central	(exp Sex Characteristics/OR exp Sex Factors/OR exp Sex/OR Sex Distribution/OR (sex* adj3 difference*).mp,kw. OR (sex* adj3 specific*).mp,kw. OR sex factor*.mp,kw. OR sex characteristic*.mp,kw. OR sex based.mp,kw. OR sex distribution.mp,kw. OR (sex* adj3 stratifi*).mp,kw. OR sex related.mp,kw. OR gender*.mp,kw. OR male*-female*.mp,kw. OR (male* adj2 female*).mp,kw. OR (exp Aortic Dissection/OR m#n adj2 wom#n).mp,kw.) AND ((type a adj3 aort* dissect*).mp,kw. OR dissecting aneurysm.mp,kw.) AND (exp Follow-Up Studies/OR exp Survival Rate/OR exp Survival/OR exp Survival Analysis/OR exp Treatment Outcome/OR exp Reoperation/OR exp Mortality/OR mortality.mp,kw. OR survival.mp,kw. OR reintervention*.mp,kw. OR re-intervention*.mp,kw. OR reoperation*.mp,kw. OR re-operation*.mp,kw. OR exp Death/OR death*.mp,kw. OR Fatalit*.mp,kw. OR Prognos*.mp,kw. OR morbidity.mp,kw. OR follow-up.mp,kw. OR kaplan meier.mp,kw.)
Embase	(exp sex difference/OR exp sex factor/OR exp gender/OR exp "gender and sex"/OR (sex* adj3 difference*).mp,kw. OR (sex* adj3 specific*).mp,kw. OR sex factor*.mp,kw. OR sex characteristic*.mp,kw. OR sex based.mp,kw. OR sex distribution.mp,kw. OR (sex* adj3 stratifi*).mp,kw. OR sex related.mp,kw. OR gender*.mp,kw. OR male*-female*.mp,kw. OR (male* adj2 female*).mp,kw. OR (m#n adj2 wom#n).mp,kw.) AND (exp aortic dissection/OR (type a adj3 aort* dissect*).mp,kw. OR dissecting aneurysm.mp,kw.) AND (exp follow up/OR exp long-term survival/OR exp overall survival/OR exp survival analysis/OR exp mortality/OR exp death/OR exp reoperation/OR mortality.mp,kw. OR survival.mp,kw. OR reintervention*.mp,kw. OR re-intervention*.mp,kw. OR reoperation*.mp,kw. OR re-operation*.mp,kw. OR death*.mp,kw. OR Fatalit*.mp,kw. OR Prognos*.mp,kw. OR morbidity.mp,kw. OR follow-up.mp,kw. OR kaplan meier.mp,kw.)

Appendix 2

Table S2 List of extracted variables

Type	Variables
Preoperative	Age, body mass index, body surface area, cerebrovascular accident, chronic kidney disease/renal insufficiency, connective tissue disease/Marfan's disease, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, hypertension, current smoker, previous cardiac surgery, previous/known aneurysm, shock, malperfusion syndrome, tamponade
Intraoperative	Cardiopulmonary bypass time, aortic valve replacement, total arch replacement, hemiarch replacement, aortic cannulation, axillary/subclavian cannulation, femoral cannulation, nadir temperature
Perioperative outcomes	In-hospital/30-day mortality, stroke/permanent neurological dysfunction, reoperation for bleeding

https://dx.doi.org/10.21037/acs-2023-adw-0098

Appendix 3

Study or Subgroup	Female Mean	Female SD	Female Total	Male Mean	Male SD	Male Total	Weight	Mean Difference IV, Random, 95% CI
Chen 2022	65.1	12.6	1286	56.9	13.1	2883	17.0%	8.20 [7.36, 9.04]
Conway 2015	60.3	13.9	79	54.5	11.9	172	5.9%	5.80 [2.26, 9.34]
Friedrich 2020	67.5	11.8	126	60.4	12	242	8.8%	7.10 [4.54, 9.66]
Fukui 2015	71.5	9.8	245	59.7	13.4	259	10.9%	11.80 [9.76, 13.84]
Gasser 2022	66.5	13.5	126	57.4	15.4	268	7.3%	9.10 [6.11, 12.09]
Huckaby 2021	65.4	13.4	969	58.6	13.3	1854	16.0%	6.80 [5.76, 7.84]
Norton 2021	64.3	15	206	56.7	12.6	444	9.5%	7.60 [5.24, 9.96]
Sabashnikov 2016	67.3	13.5	87	60	15.7	153	5.4%	7.30 [3.53, 11.07]
Suzuki 2018	72.6	10.3	147	63	12.9	156	8.5%	9.60 [6.98, 12.22]
Yousef 2022	65.5	12.7	240	58.6	13.2	361	10.6%	6.90 [4.79, 9.01]
Total (95% CI)			**3511**			**6792**	**100.0%**	**8.07 [7.05, 9.10]**

Heterogeneity: $Tau^2 = 1.43$; $Chi^2 = 23.79$, df = 9 (P = 0.005); $I^2 = 62\%$
Test for overall effect: Z = 15.39 (P < 0.00001)

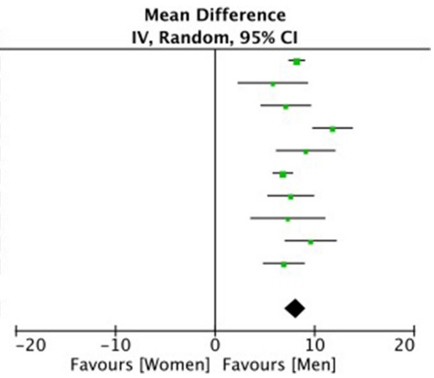


Figure S1 Forest plot for age. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degree of freedom.

Study or Subgroup	Female Mean	Female SD	Female Total	Male Mean	Male SD	Male Total	Weight	Mean Difference IV, Random, 95% CI
Friedrich 2020	25.6	3.8	126	26.9	3.6	242	15.4%	−1.30 [−2.10, −0.50]
Gasser 2022	24.9	5.1	126	26.6	3.3	268	12.7%	−1.70 [−2.67, −0.73]
Huckaby 2021	27.6	5.7	969	28.3	5.5	1854	22.6%	−0.70 [−1.14, −0.26]
Norton 2021	27.8	6.1	206	28.5	5.1	444	12.9%	−0.70 [−1.66, 0.26]
Sabashnikov 2016	25.6	4.7	87	26.5	3.1	153	11.0%	−0.90 [−2.00, 0.20]
Suzuki 2018	22.2	3.2	147	24.3	4.4	156	14.4%	−2.10 [−2.96, −1.24]
Yousef 2022	29.9	6.9	240	30.1	6.5	361	11.0%	−0.20 [−1.30, 0.90]
Total (95% CI)			**1901**			**3478**	**100.0%**	**−1.09 [−1.56, −0.62]**

Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 13.01$, df = 6 (P = 0.04); $I^2 = 54\%$
Test for overall effect: Z = 4.55 (P < 0.00001)

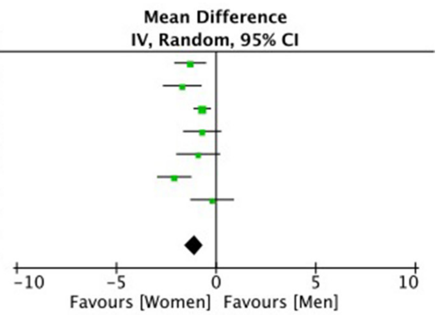


Figure S2 Forest plot for body mass index. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degree of freedom.

Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2022	1048	1286	2170	2883	27.6%	1.08 [1.05, 1.12]
Conway 2015	62	79	136	172	4.1%	0.99 [0.86, 1.14]
Friedrich 2020	92	126	170	242	4.3%	1.04 [0.91, 1.19]
Fukui 2015	210	245	227	259	12.9%	0.98 [0.91, 1.05]
Gasser 2022	85	126	183	268	3.7%	0.99 [0.85, 1.14]
Huckaby 2021	725	969	1286	1854	20.3%	1.08 [1.03, 1.13]
Norton 2021	162	206	314	444	8.1%	1.11 [1.01, 1.22]
Sabashnikov 2016	70	87	111	153	3.9%	1.11 [0.96, 1.28]
Suzuki 2018	119	147	126	156	6.2%	1.00 [0.90, 1.12]
Yousef 2022	193	240	264	361	8.8%	1.10 [1.01, 1.20]
Total (95% CI)		**3511**		**6792**	**100.0%**	**1.06 [1.03, 1.09]**
Total events	2766		4987			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 12.18$, df = 9 (P = 0.20); $I^2 = 26\%$
Test for overall effect: Z = 3.76 (P = 0.0002)

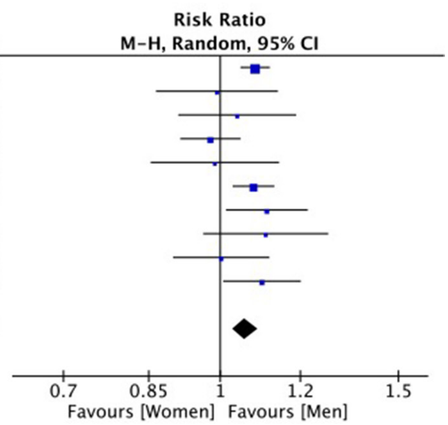


Figure S3 Forest plot for hypertension. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

https://dx.doi.org/10.21037/acs-2023-adw-0098

Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2022	133	1286	251	2883	33.8%	1.19 [0.97, 1.45]
Conway 2015	14	79	29	172	25.9%	1.05 [0.59, 1.88]
Gasser 2022	13	126	8	268	19.7%	3.46 [1.47, 8.13]
Norton 2021	15	206	9	444	20.6%	3.59 [1.60, 8.07]
Total (95% CI)		**1697**		**3767**	**100.0%**	**1.78 [1.01, 3.15]**
Total events	175		297			

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 12.39$, df = 3 (P = 0.006); $I^2 = 76\%$
Test for overall effect: Z = 1.99 (P = 0.05)

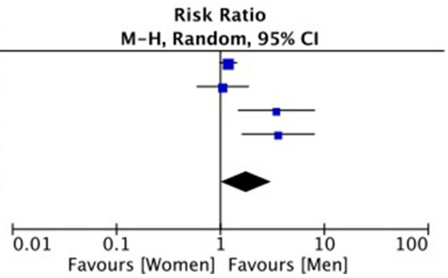


Figure S4 Forest plot for preoperative cerebrovascular accident. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2022	206	1286	585	2883	37.6%	0.79 [0.68, 0.91]
Friedrich 2020	12	126	36	242	10.6%	0.64 [0.35, 1.19]
Huckaby 2021	47	969	101	1854	22.6%	0.89 [0.64, 1.25]
Norton 2021	4	206	24	444	4.4%	0.36 [0.13, 1.02]
Sabashnikov 2016	18	87	57	153	15.9%	0.56 [0.35, 0.88]
Suzuki 2018	13	147	9	156	6.7%	1.53 [0.68, 3.48]
Yousef 2022	2	240	11	361	2.2%	0.27 [0.06, 1.22]
Total (95% CI)		**3061**		**6093**	**100.0%**	**0.74 [0.59, 0.93]**
Total events	302		823			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 9.70$, df = 6 (P = 0.14); $I^2 = 38\%$
Test for overall effect: Z = 2.57 (P = 0.01)

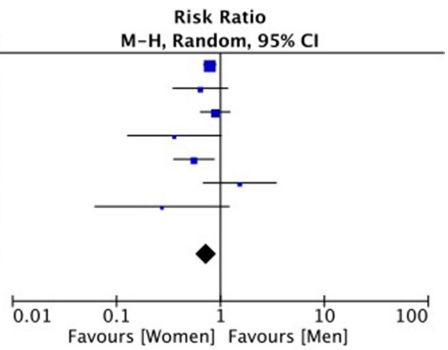


Figure S5 Forest plot for preoperative chronic kidney disease. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2022	45	1286	77	2883	48.2%	1.31 [0.91, 1.88]
Friedrich 2020	2	126	7	242	2.6%	0.55 [0.12, 2.60]
Fukui 2015	5	245	6	259	4.6%	0.88 [0.27, 2.85]
Gasser 2022	2	126	4	268	2.2%	1.06 [0.20, 5.73]
Huckaby 2021	24	969	39	1854	25.0%	1.18 [0.71, 1.95]
Norton 2021	12	206	18	444	12.5%	1.44 [0.71, 2.93]
Suzuki 2018	4	147	10	156	4.9%	0.42 [0.14, 1.32]
Total (95% CI)		**3105**		**6106**	**100.0%**	**1.17 [0.91, 1.50]**
Total events	94		161			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.91$, df = 6 (P = 0.56); $I^2 = 0\%$
Test for overall effect: Z = 1.20 (P = 0.23)

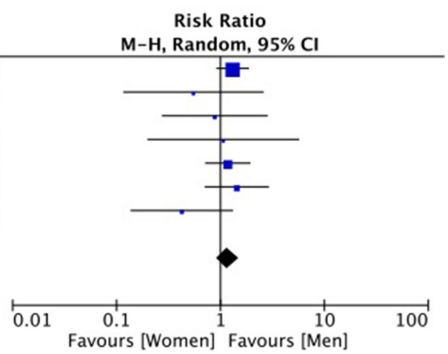
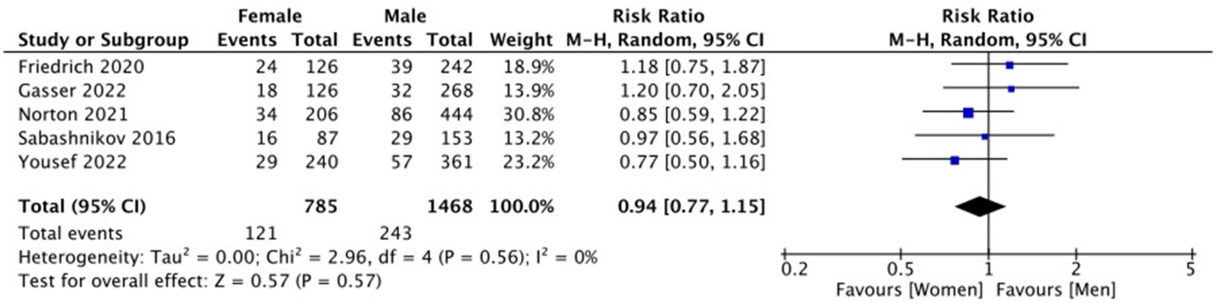


Figure S6 Forest plot for connective tissue disease. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

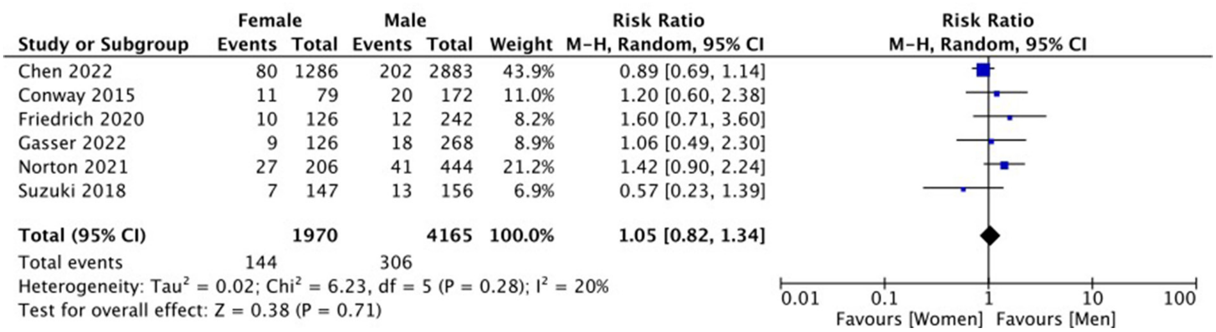
https://dx.doi.org/10.21037/acs-2023-adw-0098



Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Friedrich 2020	24	126	39	242	18.9%	1.18 [0.75, 1.87]
Gasser 2022	18	126	32	268	13.9%	1.20 [0.70, 2.05]
Norton 2021	34	206	86	444	30.8%	0.85 [0.59, 1.22]
Sabashnikov 2016	16	87	29	153	13.2%	0.97 [0.56, 1.68]
Yousef 2022	29	240	57	361	23.2%	0.77 [0.50, 1.16]
Total (95% CI)		**785**		**1468**	**100.0%**	**0.94 [0.77, 1.15]**
Total events	121		243			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.96$, df = 4 (P = 0.56); $I^2 = 0\%$
Test for overall effect: Z = 0.57 (P = 0.57)

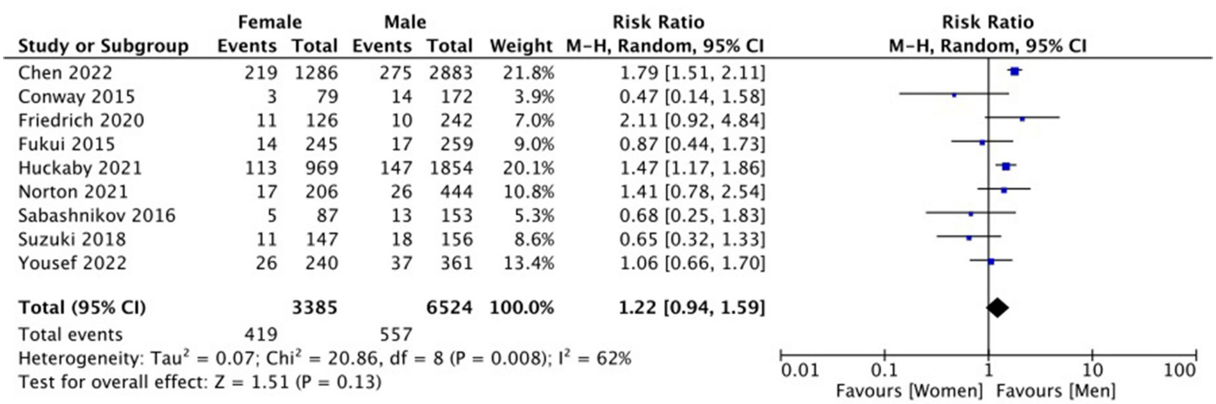
Figure S7 Forest plot for coronary artery disease. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.



Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2022	80	1286	202	2883	43.9%	0.89 [0.69, 1.14]
Conway 2015	11	79	20	172	11.0%	1.20 [0.60, 2.38]
Friedrich 2020	10	126	12	242	8.2%	1.60 [0.71, 3.60]
Gasser 2022	9	126	18	268	8.9%	1.06 [0.49, 2.30]
Norton 2021	27	206	41	444	21.2%	1.42 [0.90, 2.24]
Suzuki 2018	7	147	13	156	6.9%	0.57 [0.23, 1.39]
Total (95% CI)		**1970**		**4165**	**100.0%**	**1.05 [0.82, 1.34]**
Total events	144		306			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 6.23$, df = 5 (P = 0.28); $I^2 = 20\%$
Test for overall effect: Z = 0.38 (P = 0.71)

Figure S8 Forest plot for chronic obstructive pulmonary disease. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.



Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2022	219	1286	275	2883	21.8%	1.79 [1.51, 2.11]
Conway 2015	3	79	14	172	3.9%	0.47 [0.14, 1.58]
Friedrich 2020	11	126	10	242	7.0%	2.11 [0.92, 4.84]
Fukui 2015	14	245	17	259	9.0%	0.87 [0.44, 1.73]
Huckaby 2021	113	969	147	1854	20.1%	1.47 [1.17, 1.86]
Norton 2021	17	206	26	444	10.8%	1.41 [0.78, 2.54]
Sabashnikov 2016	5	87	13	153	5.3%	0.68 [0.25, 1.83]
Suzuki 2018	11	147	18	156	8.6%	0.65 [0.32, 1.33]
Yousef 2022	26	240	37	361	13.4%	1.06 [0.66, 1.70]
Total (95% CI)		**3385**		**6524**	**100.0%**	**1.22 [0.94, 1.59]**
Total events	419		557			

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 20.86$, df = 8 (P = 0.008); $I^2 = 62\%$
Test for overall effect: Z = 1.51 (P = 0.13)

Figure S9 Forest plot for diabetes mellitus. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

https://dx.doi.org/10.21037/acs-2023-adw-0098

Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Friedrich 2020	15	126	56	242	23.1%	0.51 [0.30, 0.87]
Huckaby 2021	177	969	425	1854	27.2%	0.80 [0.68, 0.93]
Li 2021	39	302	243	451		Not estimable
Norton 2021	52	206	144	444	26.3%	0.78 [0.59, 1.02]
Suzuki 2018	14	147	112	156	23.4%	0.13 [0.08, 0.22]
Total (95% CI)		**1448**		**2696**	**100.0%**	**0.47 [0.25, 0.88]**
Total events	258		737			

Heterogeneity: $Tau^2 = 0.36$; $Chi^2 = 47.19$, df = 3 ($P < 0.00001$); $I^2 = 94\%$

Test for overall effect: Z = 2.37 (P = 0.02)

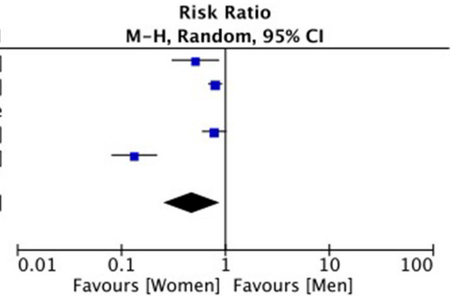


Figure S10 Forest plot for current smoking status. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2022	41	1286	143	2883	25.1%	0.64 [0.46, 0.90]
Friedrich 2020	3	126	9	242	1.8%	0.64 [0.18, 2.32]
Gasser 2022	5	126	10	268	2.6%	1.06 [0.37, 3.05]
Huckaby 2021	85	969	210	1854	50.8%	0.77 [0.61, 0.98]
Norton 2021	10	206	46	444	6.6%	0.47 [0.24, 0.91]
Yousef 2022	22	240	50	361	13.0%	0.66 [0.41, 1.06]
Total (95% CI)		**2953**		**6052**	**100.0%**	**0.70 [0.59, 0.84]**
Total events	166		468			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.01$, df = 5 ($P = 0.70$); $I^2 = 0\%$

Test for overall effect: Z = 4.03 (P < 0.0001)

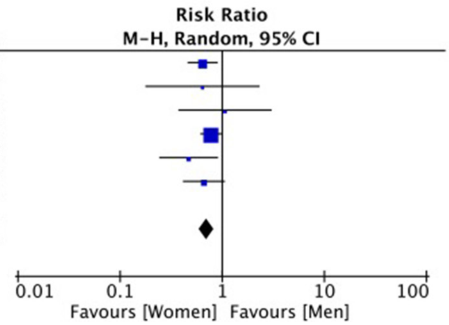


Figure S11 Forest plot for prior cardiac surgery. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Friedrich 2020	10	126	17	242	3.2%	1.13 [0.53, 2.39]
Fukui 2015	48	245	37	259	11.8%	1.37 [0.93, 2.03]
Huckaby 2021	169	969	281	1854	59.6%	1.15 [0.97, 1.37]
Norton 2021	18	206	38	444	6.3%	1.02 [0.60, 1.74]
Suzuki 2018	51	147	55	156	19.2%	0.98 [0.72, 1.34]
Total (95% CI)		**1693**		**2955**	**100.0%**	**1.13 [0.99, 1.29]**
Total events	296		428			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.90$, df = 4 ($P = 0.75$); $I^2 = 0\%$

Test for overall effect: Z = 1.79 (P = 0.07)

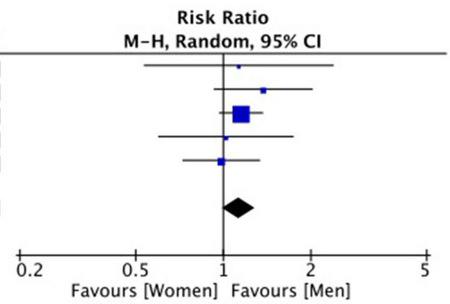


Figure S12 Forest plot for shock. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Gasser 2022	58	126	107	268	28.5%	1.15 [0.91, 1.46]
Norton 2021	42	206	116	444	19.1%	0.78 [0.57, 1.07]
Sabashnikov 2016	26	87	44	153	12.2%	1.04 [0.69, 1.56]
Suzuki 2018	34	147	40	156	12.7%	0.90 [0.61, 1.34]
Yousef 2022	69	240	121	361	27.4%	0.86 [0.67, 1.10]
Total (95% CI)		**806**		**1382**	**100.0%**	**0.94 [0.81, 1.10]**
Total events	229		428			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.04$, df = 4 ($P = 0.28$); $I^2 = 21\%$

Test for overall effect: Z = 0.74 (P = 0.46)

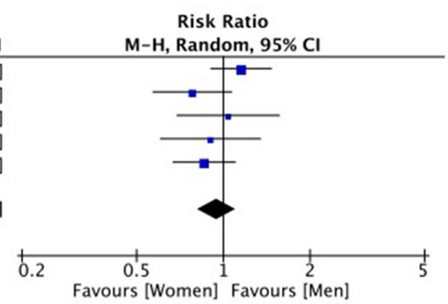


Figure S13 Forest plot for malperfusion. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

https://dx.doi.org/10.21037/acs-2023-adw-0098

Study or Subgroup	Female Mean	Female SD	Female Total	Male Mean	Male SD	Male Total	Weight	Mean Difference IV, Random, 95% CI
Conway 2015	167	128.4	79	182	75.6	172	5.5%	−15.00 [−45.48, 15.48]
Friedrich 2020	156.3	54	126	176.7	60.1	242	11.5%	−20.40 [−32.49, −8.31]
Gasser 2022	213.7	73.5	126	232	73.4	268	10.2%	−18.30 [−33.85, −2.75]
Huckaby 2021	187	66.7	969	202	67.5	1854	13.8%	−15.00 [−20.20, −9.80]
Li 2021	126.2	38.9	262	113.5	39.7	262	13.4%	12.70 [5.97, 19.43]
Norton 2021	213	66	206	232.3	66.8	444	12.0%	−19.30 [−30.25, −8.35]
Sabashnikov 2016	164.7	66.7	87	188	81.6	153	8.8%	−23.30 [−42.37, −4.23]
Suzuki 2018	112.3	32.2	147	116.7	31.9	156	13.3%	−4.40 [−11.62, 2.82]
Yousef 2022	197	73.5	240	207	74	361	11.5%	−10.00 [−22.03, 2.03]
Total (95% CI)			**2242**			**3912**	**100.0%**	**−11.51 [−20.58, −2.44]**

Heterogeneity: $Tau^2 = 147.86$; $Chi^2 = 56.83$, df = 8 ($P < 0.00001$); $I^2 = 86\%$
Test for overall effect: Z = 2.49 (P = 0.01)

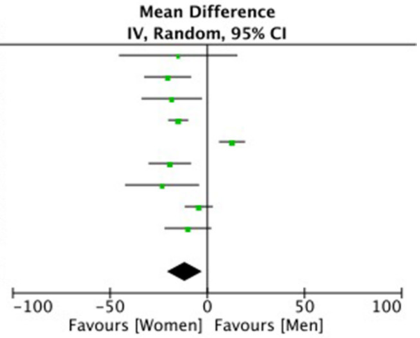


Figure S14 Forest plot for cardiopulmonary bypass time. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degree of freedom.

Study or Subgroup	Female Mean	Female SD	Female Total	Male Mean	Male SD	Male Total	Weight	Mean Difference IV, Random, 95% CI
Gasser 2022	22.1	4.3	126	21.3	5.2	268	10.7%	0.80 [−0.18, 1.78]
Huckaby 2021	22	6	969	21.7	5.9	1854	47.3%	0.30 [−0.16, 0.76]
Norton 2021	19.1	2.5	206	19	3.8	444	42.1%	0.10 [−0.39, 0.59]
Total (95% CI)			**1301**			**2566**	**100.0%**	**0.27 [−0.05, 0.59]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.61$, df = 2 ($P = 0.45$); $I^2 = 0\%$
Test for overall effect: Z = 1.66 (P = 0.10)

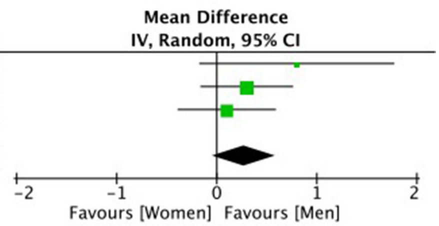


Figure S15 Forest plot for nadir temperature. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degree of freedom.

Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Conway 2015	6	79	15	172	1.8%	0.87 [0.35, 2.16]
Friedrich 2020	15	126	42	242	4.9%	0.69 [0.40, 1.19]
Huckaby 2021	200	969	507	1854	70.5%	0.75 [0.65, 0.87]
Li 2021	67	262	72	262	18.0%	0.93 [0.70, 1.24]
Norton 2021	5	206	9	444	1.3%	1.20 [0.41, 3.53]
Yousef 2022	15	240	22	361	3.6%	1.03 [0.54, 1.94]
Total (95% CI)		**1882**		**3335**	**100.0%**	**0.80 [0.70, 0.90]**
Total events	308		667			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.15$, df = 5 ($P = 0.68$); $I^2 = 0\%$
Test for overall effect: Z = 3.71 (P = 0.0002)

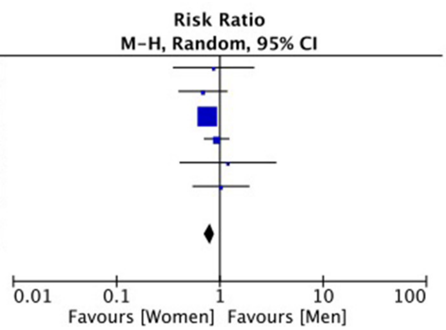


Figure S16 Forest plot for aortic valve replacement. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

 https://dx.doi.org/10.21037/acs-2023-adw-0098

Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Conway 2015	7	79	18	172	5.4%	0.85 [0.37, 1.94]
Friedrich 2020	11	126	37	242	7.5%	0.57 [0.30, 1.08]
Fukui 2015	47	245	116	259	13.1%	0.43 [0.32, 0.57]
Gasser 2022	22	126	56	268	10.4%	0.84 [0.54, 1.30]
Huckaby 2021	119	969	315	1854	14.7%	0.72 [0.59, 0.88]
Li 2021	213	262	216	262	16.0%	0.99 [0.91, 1.07]
Norton 2021	69	206	158	444	14.2%	0.94 [0.75, 1.18]
Suzuki 2018	6	147	12	156	4.5%	0.53 [0.20, 1.38]
Yousef 2022	70	240	141	361	14.1%	0.75 [0.59, 0.95]
Total (95% CI)		**2400**		**4018**	**100.0%**	**0.73 [0.58, 0.93]**
Total events	564		1069			

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 54.03$, df = 8 ($P < 0.00001$); $I^2 = 85\%$
Test for overall effect: Z = 2.55 (P = 0.01)

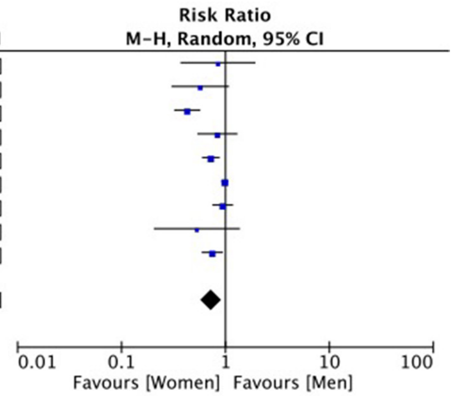


Figure S17 Forest plot for total arch replacement. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Conway 2015	41	79	84	172	3.0%	1.06 [0.82, 1.38]
Huckaby 2021	466	969	848	1854	26.2%	1.05 [0.97, 1.14]
Norton 2021	125	206	262	444	10.8%	1.03 [0.90, 1.18]
Suzuki 2018	141	147	144	156	47.2%	1.04 [0.98, 1.10]
Yousef 2022	165	240	208	361	12.8%	1.19 [1.06, 1.35]
Total (95% CI)		**1641**		**2987**	**100.0%**	**1.06 [1.01, 1.11]**
Total events	938		1546			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.49$, df = 4 ($P = 0.34$); $I^2 = 11\%$
Test for overall effect: Z = 2.51 (P = 0.01)

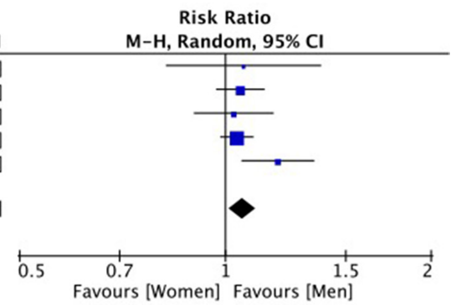


Figure S18 Forest plot for hemiarch replacement. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Conway 2015	27	79	71	172	5.5%	0.83 [0.58, 1.18]
Friedrich 2020	0	126	1	242	0.1%	0.64 [0.03, 15.54]
Gasser 2022	44	126	118	268	9.2%	0.79 [0.60, 1.04]
Huckaby 2021	266	969	652	1854	48.5%	0.78 [0.69, 0.88]
Sabashnikov 2016	65	87	126	153	34.1%	0.91 [0.79, 1.05]
Yousef 2022	23	240	31	361	2.6%	1.12 [0.67, 1.87]
Total (95% CI)		**1627**		**3050**	**100.0%**	**0.83 [0.77, 0.91]**
Total events	425		999			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.21$, df = 5 ($P = 0.52$); $I^2 = 0\%$
Test for overall effect: Z = 4.30 ($P < 0.0001$)

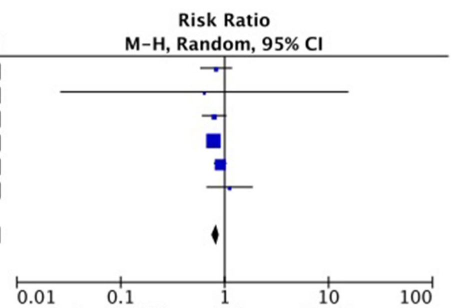


Figure S19 Forest plot for axillary cannulation. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

https://dx.doi.org/10.21037/acs-2023-adw-0098

Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Friedrich 2020	40	126	76	242	22.3%	1.01 [0.74, 1.39]
Huckaby 2021	116	969	164	1854	28.2%	1.35 [1.08, 1.69]
Sabashnikov 2016	21	87	23	153	12.7%	1.61 [0.95, 2.73]
Yousef 2022	199	240	291	361	36.9%	1.03 [0.95, 1.11]
Total (95% CI)		**1422**		**2610**	**100.0%**	**1.17 [0.93, 1.48]**
Total events	376		554			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 11.14$, df = 3 (P = 0.01); $I^2 = 73\%$
Test for overall effect: Z = 1.34 (P = 0.18)

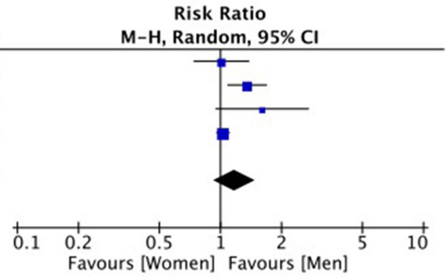


Figure S20 Forest plot for aortic cannulation. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Conway 2015	20	79	31	172	3.9%	1.40 [0.86, 2.30]
Friedrich 2020	32	126	46	242	6.1%	1.34 [0.90, 1.99]
Gasser 2022	55	126	122	268	16.8%	0.96 [0.76, 1.22]
Huckaby 2021	306	969	621	1854	70.9%	0.94 [0.84, 1.06]
Sabashnikov 2016	2	87	3	153	0.3%	1.17 [0.20, 6.88]
Yousef 2022	12	240	21	361	2.0%	0.86 [0.43, 1.71]
Total (95% CI)		**1627**		**3050**	**100.0%**	**0.98 [0.89, 1.08]**
Total events	427		844			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.04$, df = 5 (P = 0.41); $I^2 = 1\%$
Test for overall effect: Z = 0.41 (P = 0.68)

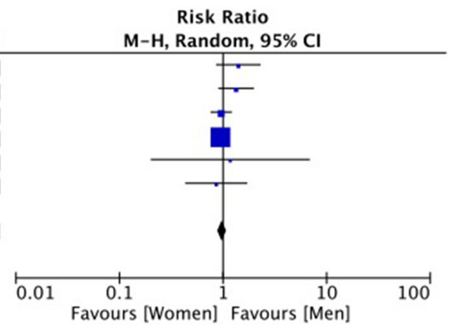


Figure S21 Forest plot for femoral cannulation. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

Study or Subgroup	Female Events	Female Total	Male Events	Male Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2022	16	1286	43	2883	8.4%	0.83 [0.47, 1.48]
Conway 2015	15	79	29	172	8.5%	1.13 [0.64, 1.98]
Friedrich 2020	23	126	38	242	10.5%	1.16 [0.73, 1.86]
Fukui 2015	11	245	15	259	5.6%	0.78 [0.36, 1.65]
Gasser 2022	32	126	37	268	11.7%	1.84 [1.20, 2.81]
Huckaby 2021	162	969	256	1854	19.4%	1.21 [1.01, 1.45]
Li 2021	22	262	9	262	5.7%	2.44 [1.15, 5.21]
Norton 2021	10	206	42	444	6.8%	0.51 [0.26, 1.00]
Sabashnikov 2016	15	71	10	71	6.0%	1.50 [0.72, 3.11]
Suzuki 2018	13	147	16	156	6.4%	0.86 [0.43, 1.73]
Yousef 2022	33	240	34	361	11.0%	1.46 [0.93, 2.29]
Total (95% CI)		**3757**		**6972**	**100.0%**	**1.18 [0.96, 1.45]**
Total events	352		529			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 18.41$, df = 10 (P = 0.05); $I^2 = 46\%$
Test for overall effect: Z = 1.57 (P = 0.12)

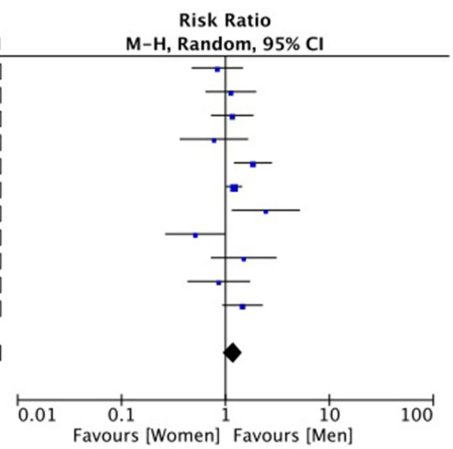


Figure S22 Forest plot for in-hospital/30-day mortality. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

https://dx.doi.org/10.21037/acs-2023-adw-0098

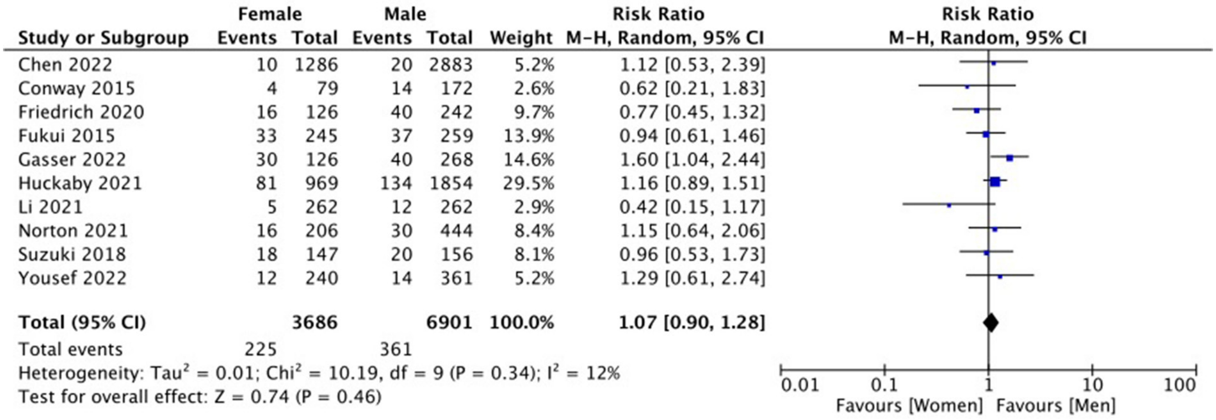


Figure S23 Forest plot for postoperative stroke. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

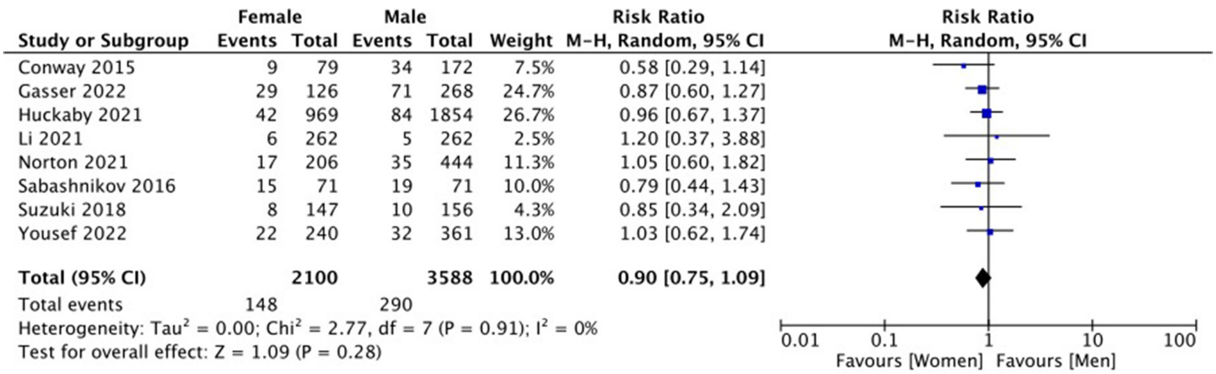


Figure S24 Forest plot for early reoperation for bleeding. M-H, Mantel-Haenszel; CI, confidence interval; df, degree of freedom.

 https://dx.doi.org/10.21037/acs-2023-adw-0098

Appendix 4

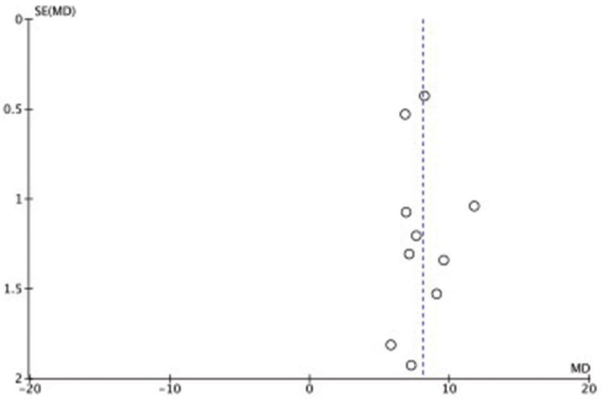


Figure S25 Funnel plot for age. SE, standard error; MD, mean difference.

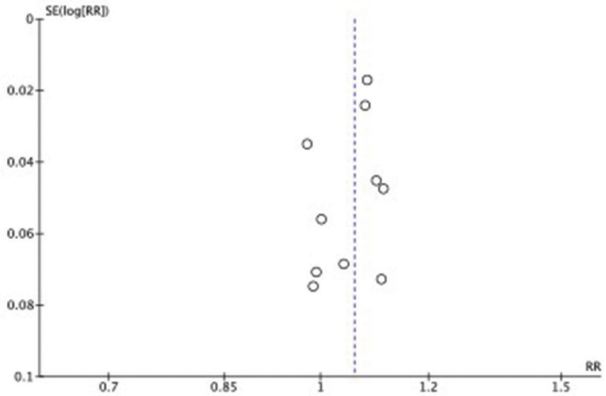


Figure S26 Funnel plot for preoperative hypertension. SE, standard error; RR, risk ratio.

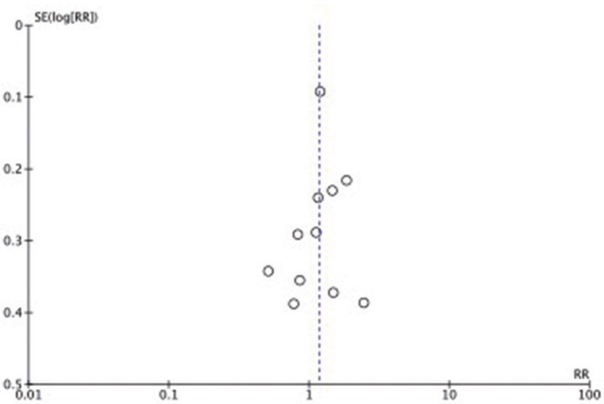


Figure S27 Funnel plot for in-hospital/30-day mortality. SE, standard error; RR, risk ratio.

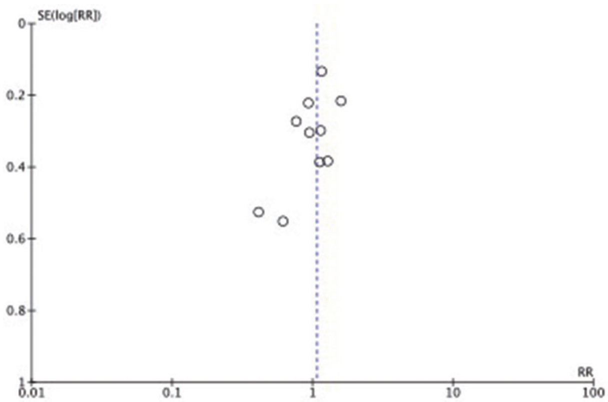


Figure S28 Funnel plot for postoperative stroke. SE, standard error; RR, risk ratio.

https://dx.doi.org/10.21037/acs-2023-adw-0098