Male–female differences in acute thoracic aortic dissection: a systematic review and meta-analysis

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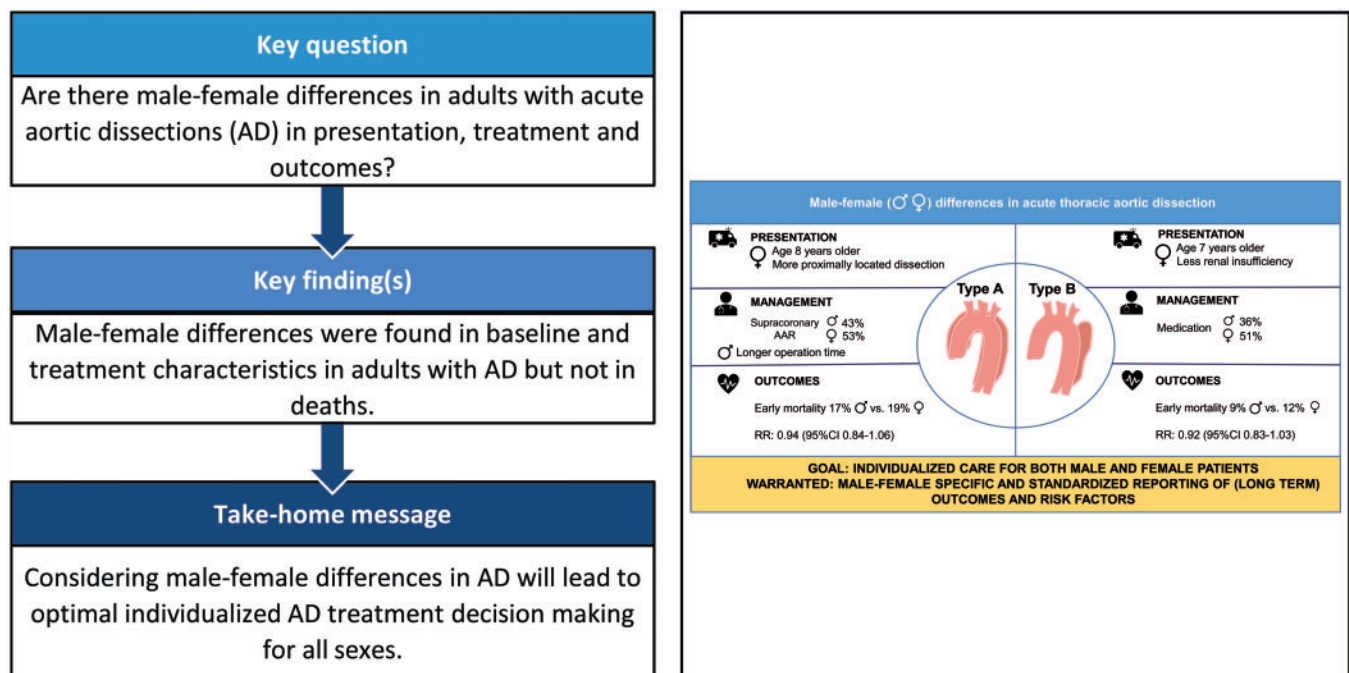
Abstract

OBJECTIVES: This study aims to systematically review published literature on male–female differences in presentation, management and outcomes in patients diagnosed with acute thoracic aortic dissection (AD).

METHODS: A systematic literature search was conducted for studies published between 1 January 1999 and 19 October 2020 investigating mortality and morbidity in adult patients diagnosed with AD. Patient and treatment characteristics were compared with odds ratios (ORs) and standardized mean differences and a meta-analysis using a random-effects model was performed for early mortality. Overall survival and reoperation were visualized by pooled Kaplan–Meier curves.

RESULTS: Nine studies investigating type A dissections (AD-A), 1 investigating type B dissections (AD-B) and 3 investigating both AD-A and AD-B were included encompassing 18 659 patients. Males were younger in both AD-A ($P < 0.001$) and AD-B ($P < 0.001$), and in AD-A patients males had more distally extended dissections [OR 0.57, 95% confidence interval (CI) 0.46–0.70; $P < 0.001$]. Longer operation times were observed for males in AD-A (standardized mean difference 0.29, 95% CI 0.17–0.41; $P < 0.001$) while male patients were less often treated conservatively in AD-B (OR 0.65, 95% CI 0.58–0.72; $P < 0.001$). The pooled early mortality risk ratio for males versus females was 0.94 (95% CI 0.84–1.06, $P = 0.308$) in AD-A and 0.92 (95% CI 0.83–1.03, $P = 0.143$) in AD-B. Pooled overall mortality in AD-A showed no male–female difference, whereas male patients had more reinterventions during follow-up.

CONCLUSIONS: This systematic review shows male–female differences in AD patient and treatment characteristics, comparable early and overall mortality and inconsistent outcome reporting. As published literature is scarce and heterogeneous, large prospective studies with standardized reporting of male–female characteristics and outcomes are clearly warranted. Improved knowledge of male–female differences in AD will help shape optimal individualized care for both males and females.

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Keywords: Thoracic aorta · Acute aortic dissection · Sex and gender

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ABBREVIATIONS

AD	Acute thoracic aortic dissection
AD-A	Acute type A aortic dissection
AD-B	Acute type B aortic dissection
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
KM	Kaplan–Meier
OR	Odds ratio

INTRODUCTION

Acute thoracic aortic dissection (AD) is a cardiovascular emergency with in-hospital mortality of 26–58% for type A dissections (AD-A) and 11–31% for type B dissections (AD-B) [1]. AD has an estimated annual incidence of 4.6–7.2 per 100 000 inhabitants [2–4]. Although male–female differences in cardiovascular disease are gaining attention, the disparities between males and females in AD have not been extensively studied. As AD is a potentially fatal disease, accurate diagnosis and patient-tailored treatment are essential to improve the survival. In this respect, it is important to elucidate male–female differences in AD.

Unfortunately, published evidence on male–female differences in AD concerns mainly single-centre retrospective series with limited sample size and follow-up, and therefore limited value in advancing knowledge on male–female differences. Previous research from the International Registry of Aortic Dissections (IRAD) found differences in clinical profiles between male and female patients for AD-A and AD-B [5]. In addition, surgically managed females with AD-A had higher in-hospital mortality compared to males [5]. On the contrary, Fukui *et al.* [6] concluded that there were no differences in early and late outcomes between male and female patients undergoing surgery for AD-A.

As it remains unclear whether male–female differences exist in AD, and current published evidence is fragmented, the aim of this study was to systematically review published literature conducted in adult AD patients investigating male–female differences in presentation, treatment, and mortality and morbidity.

PATIENTS AND METHODS

Protocol and registration

A systematic review and meta-analysis were conducted according to PRISMA guidelines [7]. The protocol was registered on PROSPERO (ID number: CRD42020155926). A systematic literature search was conducted by the Erasmus University Medical Centre librarian on 19 October 2020 in the scientific databases Embase, PubMed, Web of Science and the Cochrane Library. Studies published between 1 January 1999 and 19 October 2020 were eligible for inclusion. The complete search strings are available in Supplementary Material, Appendix SI.

Study selection

Original research papers investigating patient characteristics, and/or treatment characteristics, and/or outcome after Stanford type A and/or type B acute aortic dissection [8] were eligible for inclusion if male–female differences were mentioned in the title and/or abstract. Studies needed to be written in English, conducted in adult human patients receiving any treatment for AD and describe a study population of at least 30 AD patients. Studies describing a specific study population, such as connective tissue disease, specific age group, obstetric population, reoperations, previous cardiac surgery, malperfusion syndromes, specific operative techniques and traumatic dissections were excluded. Furthermore, studies focusing on non-acute dissections (≥14 days) were excluded. Two researchers independently screened the eligible studies using pre-specified inclusion and exclusion criteria (F.M. and A.L.G.). In case of disagreement, an agreement was negotiated and where necessary, a third researcher was consulted (J.W.R.-H.). The reference lists of included studies were cross-checked for relevant studies.

Endpoints and definitions

Aortic dissections were defined as acute when patients were diagnosed within 14 days after symptom onset [9]. The primary outcomes included male–female differences in early and overall mortality, secondary outcomes were male–female differences in
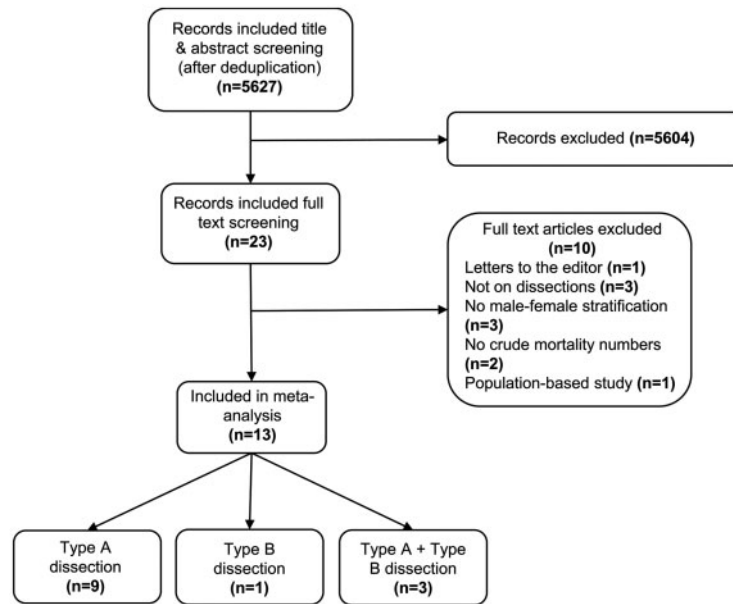
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Figure 1: Flowchart of study selection.

presentation, management, early morbidity (including stroke, acute renal failure and re-exploration for bleeding) and late reoperation. Early mortality and morbidity were defined as in-hospital or within 30 days. Early mortality was defined differently in included studies; therefore, in-hospital mortality and 30-day mortality were summarized as 'early mortality'.

Data collection

The extracted data were collected in Microsoft Excel 2016 (v16.0, Microsoft Corporation, 2016) independently by F.M. and checked by A.L.G. The patient and treatment characteristics, and early and late events were extracted from the included studies. The complete list of extracted variables and definitions is available in Supplementary Material, Appendix SII.

Risk of bias in individual studies

The quality of the included studies was assessed independently by 2 reviewers according to the 'Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies' [10].

Synthesis of results

The patient and treatment characteristics were pooled using an inverse-variance weighted approach. Categorical data were presented as percentages and continuous data as the mean or median, both including the corresponding 95% confidence intervals (CIs). In order to compare baseline and treatment characteristics between males and females, odds ratios (ORs) were used for categorical data, and standardized mean differences for continuous data. When the standard deviation was not reported in studies, it was estimated [11]. For early mortality and morbidity, risk ratios and the corresponding 95% CI comparing males to females were computed. A random-effects model was used based on the DerSimonian–Laird method [12] for all meta-analyses. All meta-analyses were performed using statistical and computing

programme *R* (R Foundation for Statistical Computing, Vienna, Austria. Version 3.5) using the 'Metafor' package [13]. *P*-values <0.05 were considered statistically significant.

Between study heterogeneity was assessed using the Cochrane *Q* statistic and the I^2 test [14]. For the Cochrane *Q* statistic, a *P*-value of <0.05 was considered statistically significant.

If reported, survival and reoperation during follow-up were depicted in pooled Kaplan–Meier (KM) curves for males and females separately, derived from the originally published KM curves using the method described by Guyot *et al.* [15]. The Engauge Digitizer v10.0 [16] was used to produce a list of coordinates of the KM curve, and an algorithm written in R was used to reconstruct the original patient data.

Publication bias was assessed with funnel plots and a trim-and-fill analysis, when the number of studies included in the analysis reached the minimum requirement of 10 studies.

Three sensitivity analyses on early mortality in AD-A were performed: (i) based on region by exclusion of studies performed in Asia; (ii) including studies that encompassed only surgical patients; and (iii) including good quality studies according to our scoring method.

RESULTS

Study selection

The flowchart of study selection is shown in Fig. 1. The studies comprised 13 papers [5, 6, 17–27]: 9 on AD-A, 1 on AD-B and 3 on type A and type B dissections combined, encompassing a total of 18 659 patients. All included studies were retrospective cohort studies and the publication years ranged from 2004 to 2019. The studies including AD-A and AD-B [5, 26, 27] presented patient characteristics on the whole population; however, treatment strategy and mortality were reported for AD-A and AD-B separately. In 8/12 studies on AD-A, only surgical patients were included [6, 17–19, 21–24], whereas in 4/4 studies on AD-B, all diagnosed patients were included [5, 25–27]. Two studies were not included in the meta-analysis for early mortality: Liu *et al.*

[26] as the mortality numbers were not clearly reported and Sabashnikov *et al.* [22] since mortality was only reported for the matched population. The study quality was graded as 'good' for 6/13 studies [5, 6, 18, 19, 21, 23], as 'fair' for 6/13 studies [17, 20, 22, 24, 25, 27] and 'poor' for 1 study [26]. An overview of the individual study characteristics and quality assessment is presented in Supplementary Material, Appendices SIII and SIV.

Patient characteristics and presentation

Pooled patient characteristics and presentation are shown in Tables 1 and 2.

Treatment strategy

Figure 2 shows pooled proportions of males and females by treatment strategy for AD-A based on 4 studies [5, 20, 26, 27] (Fig. 2A) and AD-B patients based on 4 studies [5, 25–27] (Fig. 2B). A sensitivity analysis for AD-A was performed by excluding 1 study as outlier [27], which resulted in an OR of 1.70 (95% CI 0.94–3.07; $P = 0.080$) for surgical repair, 0.25 (95% CI 0.05–1.21; $P = 0.090$) for endovascular repair and 0.62 (95% CI 0.34–1.13; $P = 0.116$) for conservative treatment, comparing males to females (Supplementary Material, Appendix SV).

Operative characteristics

Of the 8 studies [6, 17–19, 21–24], the pooled operative characteristics of surgically treated AD-A patients are shown in Table 3. No operative characteristics were available on AD-B patients.

Early and late outcomes

The forest plots of early mortality in male versus female patients for AD-A and AD-B are shown in Fig. 2. Results of meta-analyses for early mortality, morbidity and the sensitivity analyses are depicted in Table 4.

Forest plots of the meta-analyses for early morbidity in AD-A and an overview of all reported early outcomes in AD-A and AD-B are shown in Supplementary Material, Appendices SVI and SVII.

Overall mortality for AD-A was described in 6/12 studies [6, 18–20, 23, 26], of which none found a significant difference between males and females. For AD-B patients, 1/1 reporting study [26] found no significant male–female difference in late mortality. Late reoperation for AD-A was described in 2/12 studies [6, 23] and none for AD-B.

Pooled KM estimates for overall survival [6, 18–20, 23] and reoperation [6, 23] for AD-A patients are depicted in Fig. 4. Overall survival between male and female AD-A patients was not different, while more reoperations in male patients were observed compared to females.

Risk factor analyses

Six [6, 17, 19, 21, 23, 26] out of the 13 included studies performed risk factor analyses for early and/or late mortality, none of which found sex/gender to be an independent risk factor. Suzuki *et al.* [23] and Friedrich *et al.* [19] included male–female-specific risk

factor analyses. Suzuki *et al.* [23] found different independent risk factors for late mortality: older age and preoperative cerebrovascular disease in males and tamponade, chronic obstructive pulmonary disease (COPD) and longer operation time in females. In Friedrich *et al.* [19], the independent preoperative and intraoperative risk factors for early mortality were cardiopulmonary resuscitation, longer cardiopulmonary bypass time and a higher amount of transfused red blood cells for males, and COPD, peripheral arterial disease, higher amount of transfused red blood cells and intubation prior to surgery for females. In a model including preoperative risk factors only, coronary heart disease and cardiopulmonary resuscitation were found as independent risk factors for both males and females, and additionally for females of older age, and hypolipoproteinaemia [19].

Risk of bias across studies

The publication bias could only be assessed for the meta-analysis of early mortality in surgical AD-A patients, as it contained more than 10 studies and was eligible for risk of bias analyses. The funnel plot and trim-and-fill are shown in Supplementary Material, Appendix SVIII. In the trim-and-fill analysis, we observed that 2 hypothetical studies were possibly missing that would have had higher mortality in male patients.

DISCUSSION

This systematic review shows that existing literature on potential differences between males and females in presentation, management and outcome of acute aortic dissection is scarce and reporting not uniform and incomplete. Clear male–female differences were observed in presentation and treatment; however, early or overall mortality was comparable.

Presentation

Our findings confirm the observations in the population-based Oxford Vascular study that the age of onset in AD is ~10 years later in females compared to males [3]. A later age of onset is in line with the incidence of cardiovascular disease in general, such as acute coronary syndrome [28]. Literature suggests that the risk of cardiovascular disease is lower in premenopausal females than in postmenopausal females [29], due to the protective effect of oestrogen. Oestrogen decreases the proportion of collagen [30] and stimulates the formation of fibrillin [31] in the aortic wall, thereby decreasing the wall stiffness of the aorta and other arteries [30, 32]. It seems plausible that this protective effect of oestrogen also plays an important role in AD.

Active smoking was more common in males [20, 23, 26, 27]. Population-based studies on risk factors for aortic diseases [2, 33] found that smoking was a significant risk factor for the incidence of AD. However, Sidloff *et al.* [34] showed that smoking was not associated with age-standardized mortality in thoracic aortic disease. The association between smoking and abdominal aneurysms on the other hand has been well established [35]. This finding emphasizes that the aorta is a heterogeneous entity and different factors influence aneurysm formation in the thoracic and abdominal aorta [36].

Two AD-A studies [17, 20] found a higher prevalence of hypertension in females. Hypertension was found to be the most

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Table 1: Pooled estimates of baseline characteristics of AD-A and AD-B patients

Variables	AD-A						AD-A + AD-B						AD-B		Significant
	Males, pooled estimate (95% CI)	Females, pooled estimate (95% CI)	OR/SMD (95% CI)	P-value	Studies	I^2 (%)	Males, pooled estimate (95% CI)	Females, pooled estimate (95% CI)	OR/SMD (95% CI)	P-value	Studies	I^2 (%)	Males	Females	
Age (mean)	59.6 (58.5–60.7)	67.7 (65.4–70.0)	−0.62 (−0.77 to −0.48)[a]	<0.001	9	80.4	53.6 (47.4–60.6)	58.5 (50.5–67.7)	−0.39 (−0.49 to 0.30)[a]	<0.001	3	15.2	62.8	69.8	[25] (1/1)
Mean BSA (m²)	1.99 (1.83–2.15)	1.59 (1.37–1.84)	0.79 (0.15–1.44)[a]	0.016	3	96.3	-	-	-	-	-	-	-	-	-
Mean BMI (kg/m²)	26.0 (25.1–26.9)	25.1 (23.4–26.8)	0.23 (0.01–0.45)[a]	0.040	5	80.0	25.9	25.3	-	-	1	-	-	-	-
History of hypertension (%)	69.6 (58.7–82.5)	76.0 (68.5–84.3)	0.78 (0.60–1.00)[b]	0.052	7	44.5	74.5 (67.3–82.5)	75.6 (72.4–78.9)	0.93 (0.67–1.31)[b]	0.693	3	55.6	78.9	79.2	[25] (0/1)
Diabetes mellitus (%)	5.35 (3.15–9.08)	6.30 (4.33–9.16)	0.89 (0.50–1.60)[b]	0.700	7	60.3	7.10 (2.17–23.2)	7.24 (4.32–12.2)	0.98 (0.54–1.79)[b]	0.958	3	60.7	14.8	18.0	[25] (1/1)
Hyperlipidaemia (%)	14.4 (9.50–21.7)	16.0 (12.0–21.4)	0.94 (0.73–1.20)[b]	0.615	5	11.0	-	-	-	-	-	-	-	-	-
Smoking (%)	39.5 (23.5–66.3)	14.4 (6.39–32.5)	4.27 (0.85–21.4)[b]	0.077	4	97.1	61.6 (51.5–73.7)	9.22 (2.27–37.4)	15.1 (5.18–43.8)[b]	<0.001	2	74.5	-	-	-
COPD (%)	6.24 (4.00–9.75)	7.98 (5.61–11.4)	0.74 (0.49–1.10)[b]	0.138	5	18.8	-	-	-	-	-	-	21.4	26.2	[25] (1/1)
History of cerebrovascular disease (%)	6.88 (2.65–17.8)	9.30 (4.17–20.8)	0.85 (0.49–1.47)[b]	0.559	3	33.7	-	-	-	-	-	-	-	-	-
Chronic kidney disease (%)	8.26 (2.84–24.0)	7.24 (3.35–15.7)	1.38 (0.82–2.33)[b]	0.224	5	46.1	-	-	-	-	-	-	-	-	-
Congestive heart failure (%)	-	-	-	-	-	-	3.39 (2.12–5.45)	4.26 (1.60–11.3)	0.70 (0.41–1.20)[b]	0.199	3	15.1	17.9	20.4	[25] (1/1)
Marfan syndrome (%)	4.12 (3.34–5.07)	2.67 (1.87–3.82)	1.57 (1.13–2.19)[b]	0.007	5	2.11	3.48 (1.33–9.11)	2.88 (0.91–9.12)	1.37 (0.75–2.50)[b]	0.300	2	0.0	-	-	-
Bicuspid aortic valve (%)	-	-	-	-	-	-	3.07 (2.03–4.63)	3.92 (2.06–7.47)	0.80 (0.34–1.88)[b]	0.615	2	10.0	-	-	-
Previous aortic aneurysm (%)	-	-	-	-	-	-	18.9 (10.4–34.4)	14.5 (10.9–19.3)	1.23 (0.86–1.77)[b]	0.256	2	18.5	-	-	-
Previous aortic dissection (%)	-	-	-	-	-	-	3.26 (0.99–10.7)	2.94 (0.85–10.2)	1.33 (0.74–2.38)[b]	0.341	2	0.0	-	-	-

'-' indicates the variable was not reported in any of the included studies.

[a]SMD.

[b]OR.

AD-A: acute type A aortic dissection; AD-B: acute type B aortic dissection; BMI: body mass index; BSA: body surface area; CI: confidence interval; COPD: chronic obstructive pulmonary disease; OR: odds ratio; SMD: standardized mean difference.
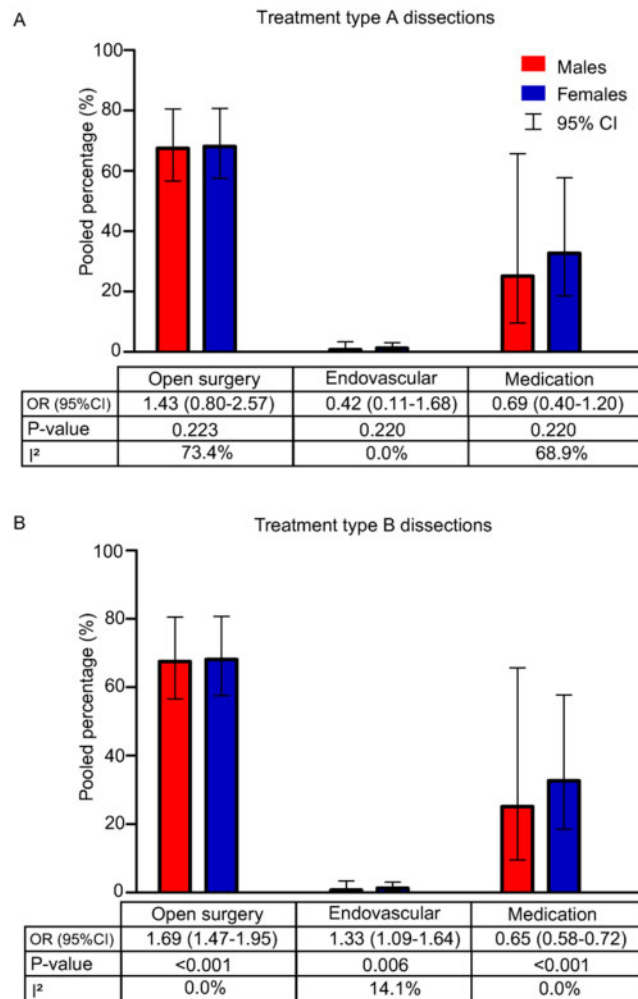
Figure 2: Meta-analysis of treatment in acute type A aortic dissection (**A**) and acute type B aortic dissection (**B**) patients. CI: confidence interval; OR: odds ratio.

important modifiable risk factor in the development of AD in prospective population-based studies [3, 33]. An increased prevalence of hypertension in female AD patients can be explained by the older age at presentation since systolic blood pressure and prevalence of hypertension increase with age [37]. Hypertension is a well-known risk factor for AD and other cardiovascular diseases and might be more important in females compared to males, independently of age [28].

Three AD-A studies [6, 17, 18] showed that males presented with higher 'creatinine levels'. As the absolute differences were small, we assume these differences to be physiological.

Female patients were diagnosed more frequently with more proximally located dissection, such as DeBakey type II [6, 17, 23]. One explanation for the proximally extended dissections could lie in geometric differences in the aorta. Rylski *et al.* [38] found that with increasing age, healthy females have a greater increase in the ascending aorta and aortic arch diameters than healthy males. Furthermore, the body surface area-adjusted diameters of the aforementioned aortic segments were greater in females than in males [38]. As observed in clinical trials on cardiovascular disease, female patients are often underrepresented [39]. Whether a referral delay of female patients with a high risk of AD plays a role in these studies remains to be elucidated. A second

explanation could be that biomechanical differences between males and females in the aortic wall influence the extension of the dissections. Mean wall thickness in both the ascending and the descending aorta is higher in males [40] and the peak wave velocity is lower in healthy females [41]. In addition, the blood flow dynamics in the aorta are significantly different between males and females [42].

Management

This systematic review suggests that females receive conservative treatment more frequently than males in both AD-A and AD-B. The reasons for conservative treatment in AD-A were described in the original papers. First, refusal of emergency surgery was seen more often in females [5, 27]. Other reasons were advanced age, comorbidity, intramural haematoma, preoperative death [1, 5] or irreversible brain damage [20]. Apart from preoperative status and comorbidities, it is possible that literature reporting on poor outcomes for female patients after surgery [43] may influence the physician's choice for a conservative approach.

Procedural times seemed longer in male surgically treated AD-A patients compared to females. This can be explained by more simplified procedures in females, such as the supracoronary

Table 2: Pooled estimates of patient presentation of AD-A and AD-B patients

Variables	AD-A						AD-A + AD-B						AD-B		Significant
	Males, pooled estimate (95% CI)	Females, pooled estimate (95% CI)	OR/SMD (95% CI)	P-value	Studies	I²(%)	Males, pooled estimate (95% CI)	Females, pooled estimate (95% CI)	OR/SMD (95% CI)	P-value	Studies	I²(%)	Males	Females	
Hypotension/shock at presentation (%)	17.6 (11.7–26.6)	19.6 (13.7–28.0)	0.86 (0.7–1.05)[a]	0.136	5	0.0	6.07 (2.38–15.5)	3.97 (0.46–34.3)	1.24 (0.44–3.44)[a]	0.685	2	33.6	4.93	4.31	[25] (0/1)
Tamponade (%)	19.4 (15.2–24.8)	21.9 (19.2–25.0)	0.87 (0.75–0.99)[a]	0.042	4	0.0	-	-	-	-	-	-	-	-	-
Pericardial effusion (%)	33.0 (16.9–64.3)	42.5 (35.4–50.9)	0.70 (0.29–1.71)[a]	0.436	2	78.7	20.8 (15.3–28.4)	30.8 (22.6–42.0)	0.61 (0.50–0.75)[a]	<0.001	3	0.0	-	-	-
Cerebral ischaemia (%)	8.87 (5.33–14.8)	11.3 (7.94–16.2)	0.91 (0.74–1.11)[a]	0.350	3	0.87	-	-	-	-	-	-	-	-	-
Presentation ≥24 h (%)	-	-	-	-	-	-	39.4 (13.9–112.1)	45.7 (20.5–101.9)	0.74 (0.58–0.96)[a]	0.024	2	3.94	-	-	-
Abrupt onset of pain (%)	-	-	-	-	-	-	87.5 (84.1–91.0)	86.4 (68.9–108.4)	0.78 (0.12–4.97)[a]	0.791	2	88.8	-	-	-
Chest pain (%)	-	-	-	-	-	-	78.3 (73.3–83.5)	77.9 (71.3–85.2)	1.07 (0.81–1.41)[a]	0.646	3	32.8	-	-	-
Back pain (%)	-	-	-	-	-	-	57.5 (52.9–62.6)	58.6 (48.6–70.8)	0.95 (0.69–1.31)[a]	0.760	3	61.8	-	-	-
Abdominal pain (%)	-	-	-	-	-	-	18.4 (13.9–24.4)	15.8 (7.65–32.8)	1.22 (0.72–2.05)[a]	0.462	2	51.7	-	-	-
Any focal neurological deficits (%)	-	-	-	-	-	-	11.4 (7.38–17.7)	6.31 (0.92–43.1)	1.74 (0.37–8.19)[a]	0.481	2	77.4	-	-	-
Syncope (%)	-	-	-	-	-	-	3.06 (0.18–52.5)	4.54 (0.38–54.8)	0.86 (0.59–1.26)[a]	0.440	2	0.0	-	-	-
Altered consciousness/coma (%)	-	-	-	-	-	-	8.07 (6.76–9.63)	11.9 (9.47–14.9)	0.66 (0.48–0.91)[a]	0.012	2	0.0	-	-	-
Pulse deficit (%)	-	-	-	-	-	-	22.4 (14.6–34.5)	12.6 (6.57–24.2)	1.99 (1.47–2.69)[a]	<0.001	2	0.0	-	-	-
Mean creatinine (mg/dl)	1.23 (1.12–1.34)	0.97 (0.87–1.07)	0.38 (0.20–0.56)[b]	<0.001	5	73.4	-	-	-	-	-	-	-	-	-
Renal insufficiency (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DeBakey type II (%)	14.3 (9.18–22.2)	23.3 (16.7–32.5)	0.57 (0.46–0.70)[a]	<0.001	4	0.0	-	-	-	-	-	-	23.6	19.9	[25] (1/1)
Max. diameter ascending aorta (mm), mean	54.4 (51.4–57.5)	53.4 (51.1–55.8)	0.06 (-0.20 to 0.32)[b]	0.654	2	0.0	-	-	-	-	-	-	-	-	-
Aortic regurgitation (%)	27.7 (18.4–41.6)	25.6 (15.9–41.2)	1.09 (0.95–1.24)[a]	0.211	5	0.0	-	-	-	-	-	-	-	-	-

'-' indicates the variable was not reported in any of the included studies.

[a]OR.

[b]SMD.

AD-A: acute type A aortic dissection; AD-B: acute type B aortic dissection; CI: confidence interval; OR: odds ratio; SMD: standardized mean difference.

Table 3: Operative characteristics of AD-A patients

	Males, pooled estimate (95% CI)	Females, pooled estimate (95% CI)	OR/SMD (95% CI)	P-value	Studies reported	I^2 (%)
Isolated supracoronary ascending aortic replacement (%)	43.3 (25.2–74.5)	53.0 (34.3–81.9)	0.70 (0.58–0.84)[a]	<0.001	3	36.1
Bentall procedure (%)	23.8 (19.8–28.7)	17.3 (15.4–19.4)	1.49 (1.19–1.86)[a]	<0.001	5	30.0
David procedure (%)	5.33 (3.18–8.93)	3.19 (2.22–4.58)	1.95 (1.31–2.91)[a]	0.001	4	15.5
Aortic valve repair or replacement (%)	10.8 (4.18–28.1)	9.50 (5.58–16.2)	1.36 (0.87–2.11)[a]	0.174	2	0.0
Aortic valve replacement (%)	11.0 (6.37–19.0)	8.95 (4.34–18.5)	1.54 (1.05–2.26)[a]	0.028	4	0.0
Total arch replacement (%)	13.4 (7.26–24.9)	8.91 (5.71–13.9)	1.76 (1.09–2.84)[a]	0.021	6	79.9
Concomitant CABG (%)	10.9 (7.94–14.9)	9.95 (7.26–13.6)	1.08 (0.65–1.81)[a]	0.772	5	45.8
Total operation time (min), mean	321.6 (289.0–357.8)	271.0 (226.9–323.7)	0.29 (0.17–0.41)[b]	<0.001	6	69.5
Cardiopulmonary bypass time (min), mean	173.2 (148.2–202.4)	161.3 (135.7–191.6)	0.19 (0.13–0.24)[b]	<0.001	7	0.0
Aortic cross-clamp time (min), mean	104.0 (97.8–110.5)	91.2 (84.3–98.6)	0.25 (0.11–0.39)[b]	<0.001	6	73.1
DHCA/circulatory arrest time (min), mean	28.6 (25.1–32.6)	28.4 (26.1–31.0)	0.07 (-0.06 to 0.19)[b]	0.293	6	62.3

a OR. b SMD.

AD-A: acute type A aortic dissection; CABG: coronary artery bypass graft; CI: confidence interval; DHCA: deep hypothermic circulatory arrest; OR: odds ratio; SMD: standardized mean difference.

artery replacement alone [17, 19, 21], while male patients more often underwent extensive repair with valve replacement [17–19, 27]. As stated earlier, male patients seemed to have more widespread dissections. Additionally, the increased age and comorbidities in females may have led to the decision of less complicated procedures, resulting in comparable surgical mortality.

Outcomes

The included AD-A studies showed no significant effect of sex/gender on early or overall mortality. Contrasting these findings are 3 population-based studies on AD [2, 4, 44]. McClure *et al.* [2] found a higher hospital mortality in females compared to males across a 12-year study period for AD-A (45.65 per 100 000 in males vs 64.21 in females) and Smedberg *et al.* [4] found an overall 30-day mortality in AD of 26% in males and 21% in females (P < 0.001). The Kaiser Permanente Registry of Aortic Dissections showed a significantly higher incidence of aorta-related morbidity and mortality for females versus males (50% vs 34%, P = 0.01) [44]. As our systematic review concerned hospital-based studies, all patients, who did not reach the hospital or were not operated on, were excluded by design. A possible explanation for the increased mortality in the population-based studies may be that females in worse conditions are more often denied surgical treatment and/or females die more frequently before reaching the hospital. The Oxford Vascular Study [3] confirms that females with acute aortic dissection die more frequently (61.1%) than males (38.9%) (P = 0.07) before reaching the hospital and in Smedberg *et al.* [4], the proportion of females was higher in patients who died out of the hospital than in admitted patients (42% vs 36%, P = 0.001).

Male patients had higher reoperation rates during follow-up in 2 AD-A studies [6, 23]. This can be explained by the different types of dissections in male and female patients: DeBakey type I dissections, which were more prevalent among males, require a late operation more frequently than DeBakey type II dissections [43].

Our meta-analysis revealed no significant difference between males and females with AD-B for early mortality. A study on male–female differences in thoracic endovascular aortic repair [45], not included in our systematic review, found non-significance on late mortality between male and female AD-B patients.

Furthermore, we found that male AD-B patients more often had complications that involved aortic branch vessels. Male patients more often had acute renal failure, paraplegia and limb ischaemia. Imaging characteristics on artery involvement were only available in Maitusong *et al.* [27], which show more involvement of the coeliac trunk and the superior mesenteric artery in male patients.

Male–female specific risk factors

Two AD-A studies performed male–female-specific risk factor analyses [19, 23] that showed different independent risk factors for late mortality such as COPD in females and cerebrovascular disease in males. Male–female risk factor differentiation would allow for the development of male–female-specific risk profiles to optimize treatment decision-making and outcomes. Therefore, we recommend male–female-specific sub-analyses in future risk factor studies for AD.

Sex versus gender

According to working definitions of the World Health Organization, sex refers to the biological characteristics [46] and gender to the socially constructed characteristics that define us being female or male [47]. Several biological factors may play a role in the incidence and prognosis of AD in males and females as previously described: hormones, vascular haemodynamics and cardiovascular risk factors. However, the sociological aspect of male–female differences also may not be underestimated. Jansen Klomp *et al.* [48] found that AD was less likely to be recognized in females by physicians. In addition, it seems that female AD patients die more often out of the hospital [3, 4]. These diagnostic delays might be due to a gender bias; females can be less likely to access medical care and/or to be recognized by physicians. Awareness of patients and physicians of the existing gender biases will hopefully decrease the gender gap.

Clinical relevance

Considering the 13 included studies, the in-hospital outcomes between male and female patients seem similar. However, as it is
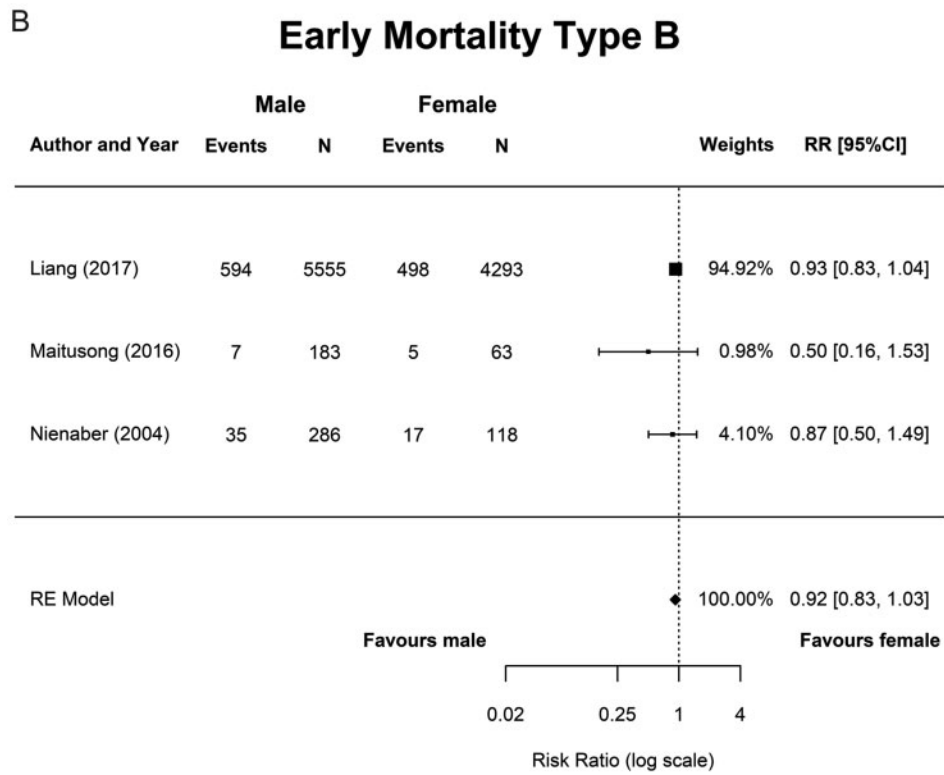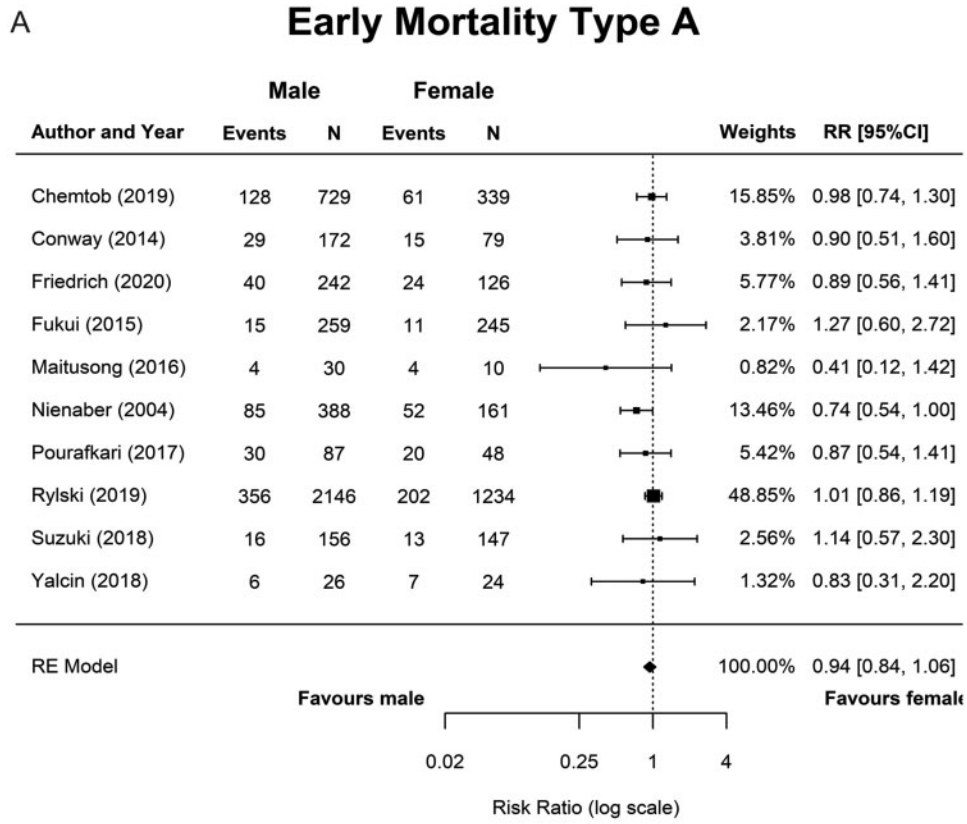
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A

Early Mortality Type A

Author and Year	Male		Female			Weights	RR [95%CI]
	Events	N	Events	N			
Chemtob (2019)	128	729	61	339		15.85%	0.98 [0.74, 1.30]
Conway (2014)	29	172	15	79		3.81%	0.90 [0.51, 1.60]
Friedrich (2020)	40	242	24	126		5.77%	0.89 [0.56, 1.41]
Fukui (2015)	15	259	11	245		2.17%	1.27 [0.60, 2.72]
Maitusong (2016)	4	30	4	10		0.82%	0.41 [0.12, 1.42]
Nienaber (2004)	85	388	52	161		13.46%	0.74 [0.54, 1.00]
Pourafkari (2017)	30	87	20	48		5.42%	0.87 [0.54, 1.41]
Rylski (2019)	356	2146	202	1234		48.85%	1.01 [0.86, 1.19]
Suzuki (2018)	16	156	13	147		2.56%	1.14 [0.57, 2.30]
Yalcin (2018)	6	26	7	24		1.32%	0.83 [0.31, 2.20]
RE Model						100.00%	0.94 [0.84, 1.06]

Favours male   Favours female

0.02   0.25   1   4

Risk Ratio (log scale)

B

Early Mortality Type B

Author and Year	Male		Female			Weights	RR [95%CI]
	Events	N	Events	N			
Liang (2017)	594	5555	498	4293		94.92%	0.93 [0.83, 1.04]
Maitusong (2016)	7	183	5	63		0.98%	0.50 [0.16, 1.53]
Nienaber (2004)	35	286	17	118		4.10%	0.87 [0.50, 1.49]
RE Model						100.00%	0.92 [0.83, 1.03]

Favours male   Favours female

0.02   0.25   1   4

Risk Ratio (log scale)

Figure 3: Meta-analysis of early mortality in male versus female surgically treated acute type A aortic dissection patients (**A**) and acute type B aortic dissection patients receiving any treatment (**B**). CI: confidence interval; RE Model: random-effects model; RR: risk ratio.

Table 4: Meta-analyses for early mortality and morbidity in AD-A and AD-B

Cohort	Outcome	Males (95% CI)	I^2 (%), Q-test[a]	Females (95% CI)	I^2, Q-test[a]	RR male vs female (95% CI)	P-value RR	I^2 (%), Q-test[a]	Studies
AD-A	Early mortality all diagnosed patients (%)	36.9 (25.9–52.6)	90.9, <0.001	52.6 (34.6–80.1)	92.9, <0.001	0.78 (0.66–0.93)	0.006	0.0, 0.723	3
AD-A	Early mortality surgical patients (%)	16.8 (13.7–20.6)	83.2, <0.001	19.3 (14.1–26.4)	89.5, <0.001	0.94 (0.84–1.06)	0.308	0.0, 0.718	10
AD-A	Early mortality surgical patients (%) (sensitivity 1)[b]	19.8 (16.6–23.6)	78.1, <0.001	23.4 (17.4–31.3)	87.5, <0.001	0.94 (0.84–1.05)	0.282	0.0, 0.731	7
AD-A	Early mortality surgical patients (%) (sensitivity 2)[c]	14.8 (12.1–18.0)	73.8, <0.001	14.9 (11.2–19.7)	79.8, <0.001	1.00 (0.88–1.13)	0.965	0.0, 0.982	7
AD-A	Early mortality surgical patients (%) (sensitivity 3)[d]	14.6 (11.4–18.7)	83.4, <0.001	14.8 (9.7–22.5)	91.4, <0.001	0.95 (0.84–1.08)	0.450	0.0, 0.515	6
AD-A	Stroke (%)	13.1 (10.2–16.8)	54.1, 0.069	12.7 (9.16–17.8)	59.7, 0.042	0.99 (0.79–1.23)	0.911	0.0, 0.904	5
AD-A	Acute renal failure (%)	17.1 (12.2–24.0)	82.3, <0.001	12.3 (8.5–17.9)	68.0, 0.010	1.24 (0.93–1.66)	0.135	19.5, 0.286	5
AD-A	Re-exploration for bleeding (%)	18.1 (12.9–25.3)	81.0, <0.001	12.9 (8.7–19.2)	65.8 <0.02	1.34 (1.08–1.67)	0.010	0.0, 0.645	5
AD-B	Early mortality all diagnosed patients (%)	9.46 (6.56–13.6)	76.2, 0.015	11.6 (10.7–12.6)	0.0, 0.426	0.92 (0.83–1.03)	0.143	0.0, 0.543	3
AD-B	Early mortality surgically[e] treated patients (%)	6.21 (0.45–85.7)	92.6, 0.001	11.4 (3.05–42.3)	65.8, 0.088	0.77 (0.26–2.31)	0.637	27.2, 0.241	2

[a]The *P*-value of the *Q*-test is reported.
[b]Exclusion of studies performed in Asia: Fukui *et al.* [6], Maitusong *et al.* [27] and Suzuki *et al.* [23].
[c]Exclusion of studies which included all diagnosed patients: Nienaber *et al.* [5], Maitusong *et al.* [25], Pourafkari *et al.* [20], leaving studies which included only surgical patients.
[d]Inclusion of studies with a good study quality.
[e]Surgical treatment included open surgical repair and endovascular treatment.
AD-A: acute type A aortic dissection; AD-B: acute type B aortic dissection; CI: confidence interval; RR: risk ratio.
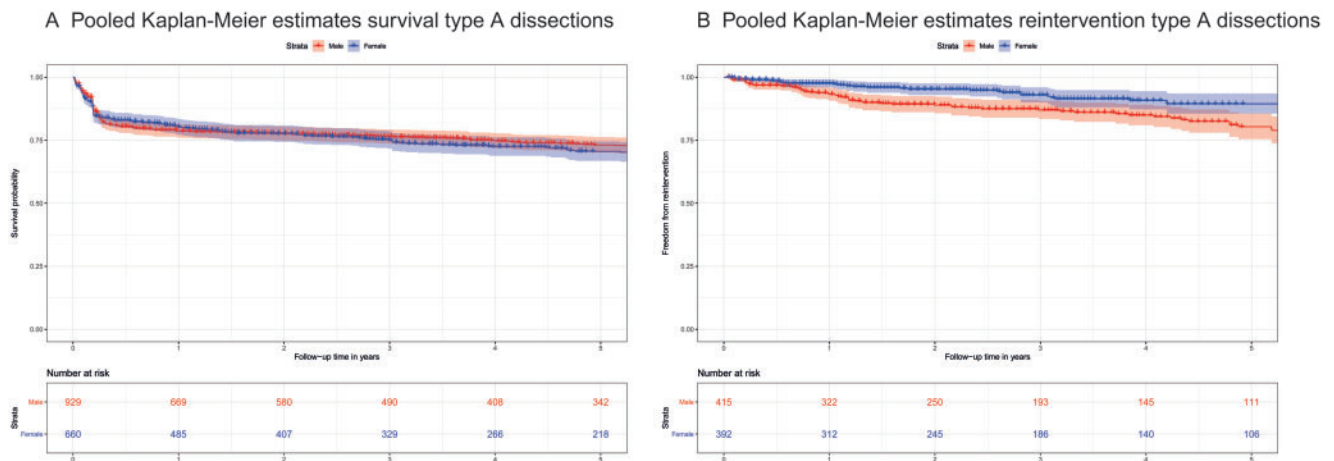

Figure 4: Pooled Kaplan–Meier estimates survival (**A**) and reinterventions (**B**) in acute type A aortic dissection patients.

plausible that the diagnosis of AD is more frequently missed in females [2, 4, 48], awareness of less typical symptoms is required. Furthermore, close monitoring of patients with hypertension, especially females, is crucial in the prevention of AD. In case of presentation with AD, male patients with cerebrovascular disease and coronary heart disease are at high risk of mortality, whereas female patients with tamponade and COPD require attention. Physicians' awareness of these differences will help them to actively ascertain relevant sex-specific risk factors, whilst preventing adverse outcomes.

Limitations

All included studies were retrospective hospital-based studies with inherent selection bias. The amount of out-of-hospital death and these patients' clinical profiles remain unknown.

The quality of included studies was graded fair in some studies, mainly because clear definitions of variables and outcomes were not reported.

Significant heterogeneity was detected between the studies, which may have influenced the results of the meta-analyses.

Between study differences may be due to disparities in management, operative techniques or health care systems in the participating countries, and differences in variable definitions.

Finally, there are limitations inherent of meta-analyses and combining data from retrospective studies, which should be acknowledged [49].

Recommendations

Prospective cohort studies studying male–female differences with a focus on late outcomes are recommended. The study quality should be improved by following international guidelines for study and outcome reporting, and by using standardized variable definitions. As AD is a rare disease, international collaboration and data sharing need to be stimulated to increase the power of studies. Furthermore, translational science can help elucidate underlying mechanisms for male–female disparities, such as hormonal changes or histological differences in the vascular wall. At the same time, gender-related factors that may affect diagnosis and referral patterns are important to consider moving forward. Most importantly, we recommend male–female-specific reporting of outcomes and risk factors in AD studies to fill the current knowledge gap.

CONCLUSION

This systematic review shows male–female differences in baseline and treatment characteristics in AD, however, comparable early and overall mortality. Published literature is scarce and heterogeneous and large prospective studies with more details and complete registration are clearly warranted. Improved knowledge of male–female differences can lead to the recognition of high-risk patients and help shape optimal individualized care for both males and females.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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Author contributions

Frederike Meccanici: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Visualization; Writing—original draft. **Arjen L. Gökalp:** Conceptualization; Data curation; Investigation; Methodology; Resources; Software; Validation; Writing—review & editing. **Carlijn**

G.E. Thijssen: Conceptualization; Validation; Writing—review & editing. **Mostafa M. Mokhles:** Validation; Writing—review & editing. **Jos A. Bekkers:** Validation; Writing—review & editing. **Roland van Kimmenade:** Validation; Writing—review & editing. **Hence J. Verhagen:** Validation; Writing—review & editing. **Jolien W. Roos-Hesselink:** Conceptualization; Funding acquisition; Supervision; Validation; Writing—review & editing. **Johanna J.M. Takkenberg:** Conceptualization; Funding acquisition; Methodology; Supervision; Validation; Writing—review & editing.

Reviewer information

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