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Original Article

Inequalities for women diagnosed with distal arch and descending thoracic aortic aneurysms: results from the Effective Treatments for Thoracic Aortic Aneurysms (ETTAA) cohort study

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Abstract

Background: Women with thoracic aortic aneurysms within the arch or descending thoracic aorta have poorer survival than men. Sex differences in relative thoracic aortic aneurysm size may account for some of the discrepancy. The aim of this study was to explore whether basing clinical management on aneurysm size index (maximum aneurysm diameter/body surface area) rather than aneurysm size can restore equality of survival by sex.

Methods: The Effective Treatments for Thoracic Aortic Aneurysms (ETTAA; ISRCTN04044627) study was a prospective, observational cohort study. Adults referred to National Health Service hospitals in England with new/existing arch or descending thoracic aorta aneurysms greater than or equal to 4 cm in diameter were followed from March 2014 to March 2022. Baseline characteristics and survival to intervention and overall were compared for men and women. Survival models were used to assess the association between all-cause survival and sex, with and without adjustment for aneurysm diameter or aneurysm size index.

Results: A total of 886 thoracic aortic aneurysm patients were recruited: 321 (36.2%) women and 565 (63.8%) men. The mean(s.d.) aneurysm diameter was the same for women and men (5.7(1.1) *versus* 5.7(1.2) cm respectively; $P = 0.751$), but the mean(s.d.) aneurysm size index was greater for women than for men (3.32(0.80) *versus* 2.83(0.63) respectively; $P < 0.001$). Women had significantly worse survival without intervention: 110 (34.3%) women and 135 (23.9%) men (log rank test, $P < 0.001$). All-cause mortality remained greater for women after adjustment for diameter (HR 1.65 (95% c.i. 1.35 to 2.02); $P < 0.001$), but was attenuated after adjustment for aneurysm size index (HR 1.11 (95% c.i. 0.89 to 1.38); $P = 0.359$). Similar results were found for all follow-up, with or without intervention, and findings were consistent for descending thoracic aorta aneurysms alone.

Conclusion: Guidelines for referral to specialist services should consider including aneurysm size index rather than diameter to reduce inequity due to patient sex.

Introduction

Thoracic aortic aneurysms (TAAs) are often asymptomatic, but can cause considerable mortality and morbidity when progression to aortic rupture or dissection occurs[1]. The estimated annual incidence is 5.3 (95% c.i. 3.0 to 8.3) TAAs per 100 000, with a prevalence of 0.16% (95% c.i. 0.12% to 0.20%)[2]. These figures are probably underestimated, due to misattribution of sudden death from the rupture of asymptomatic TAAs to other causes[3]. When diagnosed early, small TAAs can be monitored until the risk of rupture approaches the risk of intervention, which can be performed using endovascular stent grafting (ESG) or open surgical repair (OSR)[3].

Women are less likely to have TAAs identified than men, but are up to three times more likely to have TAAs that dissect or rupture at smaller sizes[4,5]. Degenerative TAAs in women also demonstrate faster growth rates[6,7]. Sex differences in relative TAA size may account for some of the discrepancies observed and it has been suggested that use of indexing may improve the prediction of dissection risk[8,9]. Although international guidelines

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Table 1 Patient characteristics and co-morbidities at baseline by sex

Variable	Female ($n = 321$)	Male ($n = 565$)	P
Age (years), mean(s.d.)—missing 0	72.8 (9.9)	69.7 (11.2)	<0.001
Height (cm), mean(s.d.)—missing 12 women, 23 men	161.6 (7.7)	176.3 (8.4)	<0.001
BMI (kg/m^2), mean(s.d.)—missing 16 women, 26 men	26.7 (5.3)	27.7 (4.5)	0.003
Formal/informal care—missing 5 women, 2 men	49 (15.5)	54 (9.6)	0.009
Smoking—missing 1 women, 6 men			
Current smoker	53 (16.6)	60 (10.7)	0.045
Ex-smoker	176 (55.0)	327 (58.5)	
Never smoked	91 (28.4)	172 (30.8)	
Connective tissue disorder—missing 0	20 (6.2)	35 (6.2)	0.983
Extra-cardiac arteriopathy—missing 4 women, 11 men	33 (10.4)	100 (18.0)	0.003
Type I/II diabetes—missing 0 women, 3 men	22 (6.8)	61 (10.8)	0.050
Treated coronary artery disease—missing 7 women, 10 men	47 (15.0)	121 (21.8)	0.014
Hypertension—missing 1 women, 1 men	271 (84.7)	504 (89.4)	0.042
Heart valve disease—missing 6 women, 9 men	74 (23.5)	91 (16.4)	0.010
Chronic obstructive pulmonary disease—missing 4 women, 1 men	84 (26.5)	79 (14.0)	<0.001
NYHA classification of breathlessness—missing 9 women; 27 men			
I	113 (36.2)	246 (45.7)	0.001 (I/II *versus* III/IV)
II	117 (37.5)	198 (36.8)	
III	65 (20.8)	85 (15.8)	
IV	17 (5.5)	9 (1.7)	
EQ-5D-5L index, mean(s.d.)—missing 1 women, 6 men	0.68 (0.3)	0.74 (0.2)	0.001

Values are *n* (%) unless otherwise indicated. *P* values are for comparisons excluding missing data. NYHA, New York Heart Association; EQ-5D-5L, EuroQoL, five dimensions, five levels.

recognize that the thoracic aorta is smaller for women, only the European Society for Vascular Surgery suggests that the threshold for surgery could be reduced and all highlight that the quality of the available evidence remains low[10–12]. Further research is encouraged, including sex-based analysis of large national and international registries of TAAs[13].

The Effective Treatments for Thoracic Aortic Aneurysms (ETTAA) study was a prospective, observational study of patients presenting with TAAs in the arch and descending thoracic aorta in England[3,14]. Although the primary aim was to compare clinical and quality of life outcomes for different management protocols, it also found that women had poorer survival outcomes, despite similar-sized TAAs. This data set provides an opportunity to assess the differences in presentation, treatment, and outcomes for women compared with men and to assess the need for changes in guidelines to address their poorer survival. The aims of this study were to: describe differences between men and women referred for investigation and treatment in the ETTAA study; explore effects of sex on overall and aneurysm-related (AR) survival; assess the ability of stratification by aneurysm size index (ASI) to restore equality of survival by sex; and explore patient and aneurysm characteristics that impact on survival, in addition to sex and aneurysm size.

Methods

Declaration of Helsinki

The authors confirm that the ETTAA study complies with the Declaration of Helsinki, that the West Midlands—South Birmingham Research Ethics Committee approved the research protocol, and that informed consent was obtained from all participants.

Original Effective Treatments for Thoracic Aortic Aneurysms study

Details of the ETTAA study (ISRCTN04044627) have been published and are further described in the *Supplementary Methods*[3,14]. The study recruited adults (greater than or equal to 18 years) presenting to UK National Health Service (NHS) hospitals with new or existing TAAs greater than or equal to 4 cm in diameter in the arch, descending, or thoracoabdominal aorta. The main exclusion criteria were acute dissection ± malperfusion syndromes and previous intervention for the same aneurysm. Within the ETTAA study, patient sex was recorded as a dichotomous variable (male/female).

Baseline variables included patient characteristics (age, height, BMI, need for formal/informal care, and smoking), aneurysm characteristics (maximum aneurysm diameter and location in the aorta), co-morbidities (connective tissue disorders, diabetes, extra-cardiac arteriopathy, treated coronary heart disease, heart valve disease, hypertension, chronic obstructive pulmonary disease, and New York Heart Association (NYHA) classification of breathlessness), and cardiac medication (*Table 1* and *Tables S1–S4*). Extra-cardiac arteriopathy was defined as the presence of any of the following: claudication; carotid occlusion or greater than 50% stenosis; or previous or planned intervention on the abdominal aorta, limb arteries, or carotids. Treatment for coronary artery disease included coronary artery bypass grafting, percutaneous coronary intervention, and medication. Medical treatment was heterogeneous and often involved multiple drugs. Collection of serum creatinine and haemoglobin levels was not mandated in the ETTAA study and levels were unavailable for more than half the patients and so were not analysed in the present study. ASI was calculated as maximum aneurysm diameter (cm) divided by body surface area (m^2) using the formula of Du Bois and Du Bois[8,15].

The primary outcomes were all-cause and AR mortality. Deaths were classified as AR or non-AR by local investigators when they occurred during the ETTAA study interval. Deaths recorded in Hospital Episode Statistics (HES) after this interval were classified as AR when ICD-10 codes included I710, I711, I712, I715, I716, I718, or I719. Two time frames were considered: first, to any surgical intervention (ESG or OSR); and second to the end of the study (with or without surgical intervention).

Extended follow-up for patients in the Effective Treatments for Thoracic Aortic Aneurysms study

Follow-up for the ETTAA study was completed on 30 June 2019. The ETTAA study has Health Research Authority approval (IRAS 140264) and Research Ethics Committee approval (13/WM/0507) and these remain active to allow for collection and analysis of NHS Digital data. Linking ETTAA study data to nationwide electronic health records via the UK National HES, follow-up for surgical intervention and survival was extended to March 2022[16].

Statistical methods

To assess the imbalance in baseline variables on a common scale, standardized mean differences (SMDs) were calculated as the mean differences between men and women, divided by the standard deviations of the pooled data. A value of one (or −1) meant that the mean difference between the sexes was one standard deviation. A difference of ±0.1 in the SMD was used as an informal threshold for imbalance[17].

To explore survival for women and men with similar aneurysm size, patients were split into three equal-sized strata according to diameter and survival was summarized using stratified Kaplan–Meier plots. Patients were then split into three equal-sized strata according to ASI and the analysis was repeated.

Cox proportional hazard models were used to assess whether all-cause survival was associated with sex, with and without adjustment for aneurysm size or ASI, in the two time frames. To analyse all-cause mortality up to surgical intervention, competing risk models were used, with death as the event of interest and intervention (ESG or OSR) the competing risk[18].

Associations between AR deaths and sex were analysed using competing risk models, with deaths from causes other than AR events (and intervention for the first time frame) treated as competing risks.

To explore variables that impacted on survival, in addition to sex and aneurysm size, patient characteristics and co-morbidities were added to the model based on improvement in fit according to the Akaike Information Criterion (AIC). Interactions between time and each covariate were used to assess non-proportional hazards.

The primary analysis used only patients with complete baseline data; 109 (12.3%) patients had at least one missing baseline variable. In the sensitivity analysis, the results for the main analyses were checked using multiply (×15) imputed data for missing baseline variables (see the *Supplementary material*)[19]. To assess whether patient height was better than body surface area in explaining sex-specific differences in survival, the main analyses were repeated using maximum aneurysm diameter divided by height (aneurysm height index (AHI)). The main analyses were repeated using patients with aneurysms with maximum aneurysm diameter in the descending thoracic aorta.

Results

Differences between sexes at presentation

Between March 2014 and June 2018, 886 TAA patients were recruited: 321 (36.2%) women and 565 (63.8%) men. Women were a mean of 3.1 (95% c.i. (1.6 to 4.6) years older than men ($P < 0.001$) and more likely to require formal/informal care (*Table 1*). Women were shorter than men (mean difference −14.7 cm (95% c.i. −15.9 to −13.6); $P < 0.001$) and had a lower BMI (mean difference −1.0 kg/m^2 (95% c.i. −1.7 to −0.4); $P = 0.003$).

Table 1 shows important differences between men and women at presentation. Women were significantly more likely to have concomitant heart valve disease, chronic obstructive pulmonary disease, and NYHA classification of breathlessness III/IV; in addition, they were more likely to be current smokers. Men were significantly more likely to have concomitant extra-cardiac arteriopathy, type I/II diabetes, and treatment for coronary artery disease. Although most patients had hypertension, it was slightly more prevalent in men. Men were significantly more likely to be treated for both hypertension (87.1% *versus* 81.3% for men and women respectively; $P = 0.021$) and hypercholesterolaemia (61.6% *versus* 51.1% for men and women respectively; $P = 0.002$) (*Table S1*).

The EuroQoL, five dimensions, five levels (EQ-5D-5L) questionnaire was completed at baseline by 879 patients[20]. Mean health-related quality of life was significantly lower for women (difference in EQ-5D-5L index −0.06 (95% c.i. −0.01 to −0.02); $P = 0.001$) (*Table S3*).

There were minimal differences between women and men regarding the location where the maximum aneurysm diameter occurred (in the descending thoracic aorta/thoracoabdominal aorta for 81.6% for women *versus* 83.5% for men; $P = 0.466$) and the maximum aneurysm diameter (mean(s.d.) 5.7(1.1) cm for women and 5.7(1.2) cm for men; $P = 0.751$) (*Table S4*). Women had a significantly higher ASI than men (mean(s.d.) 3.32(0.80) *versus* 2.83(0.63) cm/m^2 respectively; $P < 0.001$).

Figure S1 shows SMDs between men and women for important baseline variables. Using this common scale, women and men were well matched for location and maximum diameter of the aneurysm and prevalence of connective tissue disorders, with minor imbalance for age and cardiac/respiratory symptoms and co-morbidities. However, there was marked imbalance between the sexes regarding ASI.

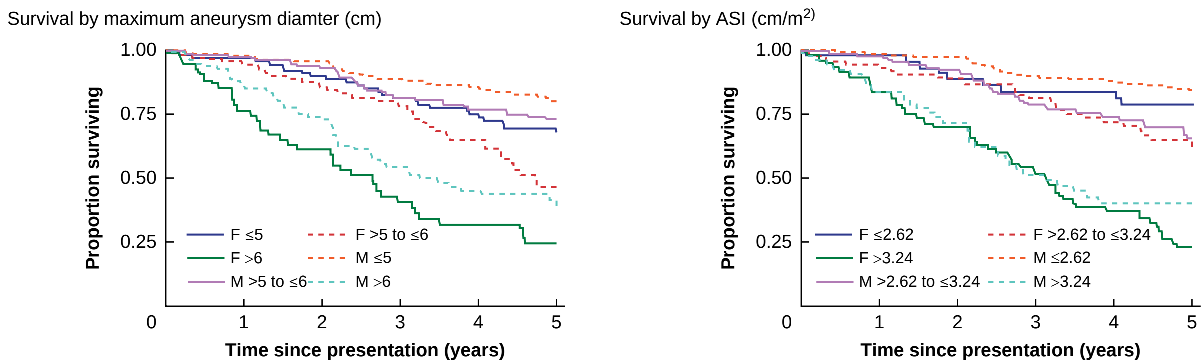
Differences in patient management

During follow-up to March 2022, 60 (18.7%) women and 120 (21.2%) men had ESG as a first procedure, whereas 71 (22.1%) women and 120 (21.2%) men had OSR as a first procedure. The remaining 190 (59.2%) women and 325 (57.5%) men were in the CM (48 (15.0%) women and 64 (11.3%) men) or WW (142 (44.2%) women and 261 (46.2%) men) groups at the end of follow-up or died without surgical intervention. There were no differences between the sexes regarding the management group at the end of the study (chi-squared test, $P = 0.258$) and the time to treatment (log rank test, $P = 0.969$).

Survival during the first time frame (up to intervention) by sex

During extended follow-up, 110 (34.3%) women and 135 (23.9%) men died without intervention; 48 of 110 (43.6%) deaths among women were categorized as AR, compared with 48 of 135 (35.6%) deaths among men. There was a significant difference between the sexes regarding overall survival without surgical intervention (log rank test, $P < 0.001$) (*Fig. S2*). Stratifying into three equally sized groups by maximum diameter or ASI, 107 (33.3%) women were in the largest third for maximum diameter, but 148 (48.5%) women were in the largest third for ASI (*Table S5*). *Figure 1* (left panel) shows that women with the smallest aneurysms (less than or equal to 5 cm) had similar survival to men with aneurysms greater than 5 to less than or equal to 6 cm (middle third) and that survival for men with large aneurysms (greater than 6 cm) was between that for women with medium (greater than 5 to less than or equal to 6 cm) and large (greater than 6 cm) aneurysms. In contrast, when stratifying patients according to ASI, survival patterns for the two sexes were broadly aligned (*Fig. 1*, right panel). For example, survival probability at 2 years for women and men with medium-sized aneurysms was 85.1% (95% c.i. 75.1% to 91.3%) and 91.2% (95% c.i. 85.3% to 94.8%) respectively and the corresponding survival probabilities for a medium-sized ASI were 89.6% (95% c.i. 80.8% to 94.4%) and 89.6% (95% c.i. 82.6% to 93.9%) respectively.

The patterns for AR survival were similar, although the smaller number of events, especially for small aneurysms, meant that the



No. at risk

F ≤5	103	83	75	65	58	39
F >5 to ≤6	111	68	59	49	36	21
F >6	107	42	32	19	14	8
M ≤5	179	146	138	126	120	83
M >5 to ≤6	190	142	123	102	88	59
M >6	196	78	54	38	28	19

No. at risk

F ≤2.62	54	41	37	33	33	25
F >2.62 to ≤3.24	103	74	67	57	44	25
F >3.24	148	68	54	36	25	14
M ≤2.62	223	176	166	151	142	101
M >2.62 to ≤3.24	186	113	96	79	68	42
M >3.24	130	59	40	26	18	14

Fig. 1 All-cause survival without surgical intervention stratified by sex and maximum aneurysm diameter (left panel) and by sex and aneurysm size index (right panel)

ASI, aneurysm size index.

Table 2 HRs (or sub-distribution HRs) for all-cause and aneurysm-related mortality for sex alone (unadjusted) and for sex adjusted for aneurysm diameter or aneurysm size index

Outcome model	HR (95% c.i.) for sex	*P*	HR (95% c.i.) for sex adjusted for aneurysm diameter	*P*	HR (95% c.i.) for sex adjusted for aneurysm size index	*P*
Without intervention—all-cause mortality (SHR)*	1.54 (1.20,1.98)	0.001	1.56 (1.21,2.01)	0.001	1.24 (0.94,1.65)	0.132
Without intervention—aneurysm-related mortality (SHR)*	1.82 (1.22,2.72)	0.003	1.89 (1.26,2.84)	0.002	1.26 (0.81,1.95)	0.314
With/without intervention—all-cause mortality†	1.56 (1.28,1.91)	<0.001	1.65 (1.35,2.02)	<0.001	1.11 (0.89,1.38)	0.359
With/without intervention—aneurysm-related mortality (SHR)†	2.13 (1.57,2.90)	<0.001	2.35 (1.71,3.23)	<0.001	1.47 (1.05,2.07)	0.026

*Includes follow-up until intervention or end of study. †Includes all follow-up with or without surgical intervention. SHR, sub-distribution HR.

improved alignment was mostly evident for people with large aneurysms, among whom there were more deaths (*Figs S3, S4*).

Table 2 shows that for both all-cause and AR mortality, the significant effect of sex on survival without intervention was slightly inflated when adjusted for maximum aneurysm diameter, but was attenuated and non-significant when adjusted for ASI.

Survival with or without surgery (all follow-up) by sex

An additional 64 (48.9%) women and 96 (40.0%) men died after intervention (see *Fig. S5* for post-surgery outcomes). Overall, 172 (53.6%) women and 224 (39.7%) men died by the end of extended follow-up, with Kaplan–Meier all-cause mortality curves showing non-overlapping confidence intervals for women and men (log rank test, $P < 0.001$) (*Fig. S6*). *Figure 2* again shows better alignment between the two sexes when survival was stratified for ASI than when stratified by maximum aneurysm diameter.

Differences between the sexes were observed for AR survival, although the smaller number of events and the intervening surgery for some patients meant the improved alignment was less clear (*Figs S7, S8*).

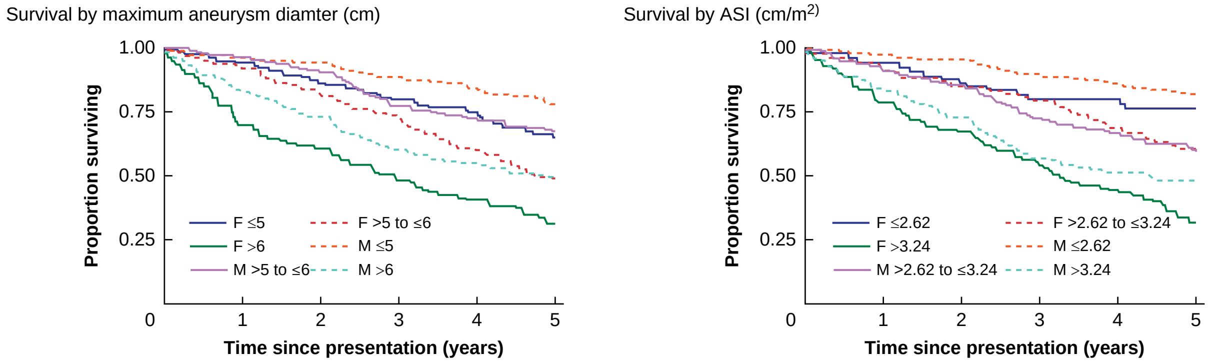
Table 2 shows that the effect of sex on all-cause and AR mortality was slightly increased when adjusted for maximum diameter, but was attenuated when adjusted for ASI.

Adjustment for additional confounders

Table 3 shows additional variables that had an important effect on survival outcomes after adjusting for sex and ASI. In most cases, older age showed the next strongest relationship, with estimated HRs between 1.03 and 1.07 per year increase in age (1.34 to 1.97 per decade). For all-cause death, both age and respiratory dysfunction (increasing NYHA classification of breathlessness and chronic obstructive pulmonary disease) were consistently significant across analyses. Patients reporting use of formal/informal care also had a 53% increased hazard of all-cause mortality without intervention. These associations suggest increased risk due to frailty (*Table 3* and *Table S6*).

Sensitivity analysis

Using multiple imputation for missing data changed estimates of effects slightly, but conclusions remained consistent (*Tables S7–S9*). Repeating the main analysis using AHI rather than ASI to



No. at risk

	0	1	2	3	4	5
F ≤5	103	97	89	82	76	52
F >5 to ≤6	111	102	89	79	63	38
F >6	107	75	64	49	39	23
M ≤5	179	172	169	159	151	103
M >5 to ≤6	190	183	170	145	131	97
M >6	196	161	140	112	102	70

No. at risk

	0	1	2	3	4	5
F ≤2.62	54	51	46	43	42	33
F >2.62 to ≤3.24	103	94	88	81	67	39
F >3.24	148	116	98	77	61	37
M ≤2.62	223	217	213	199	189	134
M >2.62 to ≤3.24	186	169	154	131	119	81
M >3.24	130	108	93	71	64	47

Fig. 2 Overall all-cause survival stratified by sex and maximum aneurysm diameter (left panel) and by sex and aneurysm size index (right panel)
ASI, aneurysm size index.

Table 3 HRs (or sub-distribution HRs) with 95% confidence intervals for outcomes for additional variables adjusted for sex and aneurysm size index

Variable	Outcome model			
	Without intervention—all-cause mortality (SHR)*	Without intervention—aneurysm-related mortality (SHR)*	With/without intervention—all cause mortality†	With/without intervention—aneurysm-related mortality (SHR)†
Female sex	1.10 (0.82,1.47)	1.30 (0.82,2.05)	0.94 (0.75,1.19)	1.47 (1.05,2.07)
Aneurysm size index (per cm/m^2)	1.43 (1.20,1.72)	1.92 (1.50,2.46)	1.90 (1.65,2.18)	2.17 (1.80,2.61)
Age (per year)	1.07 (1.05,1.10)	1.03 (1.00,1.06)	1.05 (1.04,1.06)	–
NYHA classification of breathlessness (per class)	1.32 (1.11,1.56)	–	1.29 (1.13,1.47)	–
Chronic obstructive pulmonary disease	1.47 (1.06,2.04)	–	1.54 (1.19,1.98)	–
Formal/informal care	1.53 (1.08,2.17)	–	–	–

All models include sex and aneurysm size index; other variables included if appropriate (see the Methods section). *Includes follow-up until intervention or end of study. †Includes all follow-up with or without surgical intervention. SHR, sub-distribution HR; NYHA, New York Heart Association.

adjust maximum diameter showed similar patterns, but was less effective in aligning survival for women and men (*Tables S10, S11*).

Repeating the analysis using the 734 patients (262 women and 472 men) with descending thoracic aorta aneurysms, there was no change in the overall conclusions. The biggest changes in results from analysis of the full data set occurred when there were fewer deaths (for example for AR death) and when there were multiple causes of death (for example post-intervention when deaths were also related to intervention, age, and co-morbidities) (*Fig. S5*). The smaller number of deaths when restricting to AR causes meant that the estimates were less precise (*Tables S12–S14*).

Discussion

Analysis of this large, multicentre, prospective cohort demonstrates important differences in age, co-morbidities, and quality of life between women and men at the point of referral for investigation of TTAs. Although maximum aneurysm diameter, aneurysm location, and type and timing of intervention are similar, there was a marked and highly significant difference in ASI between men and women. Adjustment for ASI, as a marker of size at baseline relative to patient's size, largely accounts for the difference in survival outcomes, both before intervention is carried out and for the duration of follow-up with/without intervention. Adjustment for maximum aneurysm diameter does not attenuate the increased risk for women, suggesting that use of diameter thresholds in current guidelines may be insufficient for risk stratification[10,11,21]. Rather, use of ASI may be a better basis for recommendations around referral for investigation and subsequent intervention. ASI has been criticized due to changing weight over time, with adjustment for height and volumetry proposed[22]. Adjustment for patient height is also effective in aligning survival outcomes for the two sexes, albeit less so in the ETTAA study. Further to ASI, age and respiratory co-morbidity, as well as frailty (reflected by need for care and low BMI), should play a part in clinical decision-making. Irrespective of sex, there is some evidence that the effect of size decreases over time and the effect of age increases over time, which reflects increasing risk due to multiple age-related co-morbidities in this cohort. The maximum aneurysm diameter occurred in the descending thoracic aorta for over 80% of patients, meaning that the results for this subgroup are consistent with those for the full data set.

The Yale group reports a protective effect for men in a large single-centre study of men with aortic disease[5] and advocates the use of ASI for risk stratification[8]. Inferior outcomes for women are also reported throughout the spectrum of cardiovascular disease[23,24]. The causes for this discrepancy, including for TAAs, are likely to be multifactorial, including: delayed diagnosis; differences in risk factors, aetiology, and disease progression; under-representation in the research guiding treatment; and subsequent suboptimal management of cardiovascular risk[25–29]. The International Registry of Acute Aortic Dissection (IRAD) reports delayed diagnosis for women presenting with aortic dissection, attributed to a lower likelihood of presentation with 'typical' chest pain symptoms[30]. Hereditable causes of aortopathies have different aortic risk profiles for men and women[31,32]. For women with a degenerative TAA under surveillance, enhanced extracellular matrix degradation, adverse arterial haemodynamics, and hypertension have been identified as contributors to faster growth[6,7,33–35]. The Canadian Thoracic Aortic Collaborative has identified female sex as an independent risk factor for perioperative death, stroke, and complications after thoracic aortic repair, despite use of less complex procedures[36], and increased risk of 30-day and 1-year mortality for women was also observed after treatment of descending TAAs within the Society for Vascular Surgery Vascular Quality Initiative registry[37]. Despite adjustment for ASI, women with TAAs also remain at greater risk of dissection[8]. Further investigation of mechanisms underlying differences in outcomes for women and men are required, so that inequalities can be addressed in current risk stratification, surveillance, and treatment strategies.

The results of the ETTAA study should be applicable to countries with similar populations and services to the UK, as 30 cardiac centres participated and there were few patient exclusion criteria. Data collection was prospective and mandated variables were reasonably complete and checked for errors. Registration with electronic health records ensured mid- to long-term follow-up (3.5–8 years). Robust statistical methods were used, including consideration of competing risks and differences between those undergoing intervention and those in conservative management groups.

The ETTAA study is based on a heterogeneous population of patients with TAAs and analysis stratified by sex and size results in few deaths in some strata. This was particularly difficult when assessing post-intervention risks, as death may result from operative complications, aneurysm features, co-morbidity, or a combination of these. Causes of death for patients who died during the ETTAA study were checked with hospitals, whereas deaths occurring after the ETTAA study finished were available from routinely recorded national registry data only and were more likely to be misclassified[38]. This may partly account for the weaker patterns in the analysis of survival for AR death. Lastly, it cannot be ruled out that some selection bias occurred during recruitment. Further research using routine electronic health records could provide insight into differences in age and other characteristics at referral to cardiac services between the sexes.

Risk stratification by a size-adjusted index (for example ASI or AHI) is more successful at reducing inequities in outcomes between women and men than stratification by aneurysm diameter. Selection of a surgical threshold based on ASI or a related measurement should be strongly considered during the construction of future clinical guidelines.

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Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The ETTAA Working Group supports the principles of data sharing. Applications to access data should be submitted via the corresponding author. Access to anonymized data may be granted after review.

Author contributions

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