Thoracoabdominal aortic aneurysm in women: many questions remain regarding their poor outcome

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Thoracoabdominal aortic aneurysms (TAAAs) affect approximately 5.9/100,000 persons per year, with a male:female ratio of approximately 1.5–1.7:1. Data exploring sex-related variations in epidemiology and clinical presentation are scarce, as women are normally under-represented in clinical trials. As female hormones and their receptors greatly impact the functions of the vascular cells and aneurysm etiology and extent, the age at surgery and comorbidities also differ between men and women. Additionally, female patients have smaller anatomic structures, including visceral/infrarenal aorta and iliac arteries, than most men. Thus, aneurysms of a certain diameter can represent more advanced disease in women comparatively, than the same-sized aneurysms in males, and be the cause of delayed and often emergent treatment. Adjusting the aortic diameter threshold is recommended for surgery using aortic size index (ASI) [aortic diameter in cm/body surface area (BSA) in m^2] or aortic height index (AHI) (aortic diameter in cm/patient height in m) indices in patients who are significantly shorter or taller than average, but no specific sex-related size criteria have been indicated so far for TAAA. Data about TAAA outcomes are conflicting, but female sex has been demonstrated to be an independent risk factor for increased major postoperative complications (i.e., bleeding, acute limb ischemia, renal failure, bowel ischemia, spinal cord ischemia) with longer hospital and intensive unit care stay and in-hospital and 30-day mortality following endovascular treatment and increased long-term mortality following open repair. Despite this evidence, sex does not influence TAAA management strategies and currently the allocation to open or endovascular repair is based on anatomy and clinical setting. In light of these disadvantaged outcomes, further efforts are needed to better understand the sex-related differences in the TAAA diagnosis and management in order to allow prompt and appropriate treatment of female patients.

Keywords: Thoracoabdominal aortic aneurysm (TAAA); sex; aneurysm (aorta); aortic operation

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Introduction

Thoracoabdominal aortic aneurysms (TAAAs) are rare diseases affecting approximately 5.9/100,000 persons per year and represent approximately 10% of all aortic aneurysms (1). Data exploring sex-related differences in TAAA epidemiology are scarce, but according to previously published series, the male:female ratio is approximatively 1.5–1.7:1 (2-4). There exists an increasing consensus that sex impacts health and disease processes across a lifespan, but in vascular surgery, there has not yet been a differentiation of indications for treatment or management strategies (5). Screening programs for aortic aneurysms recommend a single ultrasound scan for men aged 65 years and older, as similar initiatives in women were not cost-effective (6). However, the Society for Vascular Surgery and the '2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease' recommend screening women younger than 65 years if they have multiple cardiovascular risk factors, or later (between 65 and 75 years) if they are ex-smoker/smokers or have a positive family history (1,7). Certainly, as medical management and understanding of the disease evolves, screening recommendations will change.

Customized surveillance strategies have been indicated for female patients who are known to have an abdominal aneurysm, with a reduced threshold for annual ultrasound surveillance (4.0 to 4.9 cm in men and 4.0 to 4.4 cm in women), but no similar indications have been given for TAAA (1). Moreover, current indications for treatment are the same in both sexes and based on aortic size (>6 cm), aneurysm features that are associated with increased risk of rupture (i.e., symptoms, penetrating aortic ulcers, saccular aneurysms) or growing rate, although recent evidence may suggest reducing the surgical threshold to protect patients against the adverse aortic related events (dissection, rupture, and aortic death) that may occur even at smaller diameter (1,8). Generally, the diagnosis of aneurysms in women is delayed. When aneurysms are discovered, women tend to be older-aged, have more comorbidities, and more frequently need emergent treatment than their male counterparts (9). Data on clinical and procedural results are conflicting: on the one hand, some authors find no relationship between outcomes and sex, but on the other hand, several reports find that female sex represents an independent risk factor for increased peri-procedural complications, morbidity, in-hospital and 30-day mortality after endovascular repair and increased long-term mortality after open repair even after adjustment for age and comorbidities (1,9-11). In this setting, it is worth investigating and better defining the sex-related differences in the TAAA diagnosis and management to allow prompt and appropriate treatment of female patients improving their survival and quality of care.

Etiology and pathophysiology

The sex-related differences in TAAA presentation and natural history are difficult to address, as women are normally under-represented in clinical trials and there are no studies describing differences in the histopathology of aortic diseases between the two sexes (12). Most TAAAs have a degenerative etiology, but they can also present as the evolution of aortic dissection or as a complication of connective tissue diseases. In men, the incidence of chronic aneurysmal dissection and degenerative aneurysms overlaps. Conversely, in women, atherosclerotic aneurysms occur three times more than those consequent to dissections (13). Additionally, women are normally diagnosed with TAAA at an older age than men (13). It is unclear if this is due to female hormones, an ascertainment bias, as women are less regularly sent for diagnostic studies, or the physiologic size difference of 'normal caliber' aortas between women and men, so that women have progressed further in their disease before they meet threshold diameters.

The effects of female hormones and their receptors on vascular cells before and after menopause are frequently cited as a cause for sex differences, but the nuances of this relationship are complicated. At a young age, female patients are protected by estrogens that may delay the formation of plaques until after menopause by reducing low-density lipoproteins (LDLs) and inflammatory processes in vessels, inhibiting collagen production, smooth muscle proliferation, and endothelial dysfunction (14). It is not completely understood if matrix deposition and plaque stability are affected by the decrease in estrogen level or by the growth factors that activate the estrogen receptor (ER), but notably after menopause, female patients present with increased arterial stiffness with consequent higher risk of organ damage (2,15).

Preoperative clinical profile

It has been reported that women have more preoperative comorbidities than men presenting with TAAA. Women are normally older at diagnosis, and often suffer concurrently from other advanced cardiovascular comorbidities as hypertension and coronary artery disease (CAD) (9,13). Indeed, in a recent paper by Edman and colleagues, women with TAAAs had increased preoperative frailty, recent unintentional weight loss (11% *vs.* 5%, P=0.002) and limited physical activity tolerance (46% *vs.* 31%, P<0.0001) compared to men (16). One of the most detailed analyses on this topic comes from Spiliotopoulos and colleagues who examined sex-related outcomes in 3,353 open TAAA repairs and demonstrated that women presented for treatment at an older age and were more likely to have pulmonary disease than men, and that these factors were predictors of adverse events postoperatively (13). Additionally, despite the great difference in distribution and prevalence in adult men and women across different countries, type 2 diabetes appears to attenuate the protective effect of the female sex in the development of cardiac diseases. However, it also adversely impacts female endothelial response, impairs the beneficial hemodynamic effects of estrogen, and disrupts the balance of expression and activity of ERs (17).

Genetic syndromes and arteritis

Several medical conditions may predispose women to develop aneurysms. Turner syndrome, a genetic disease linked to a partial or complete loss of a second X chromosome, develops in patients who present phenotypically as women. They may suffer from congenital cardiovascular defects in up to 50% of cases, including bicuspid aortic valve and coarctation of the aorta, and are at increased risk for progressive aortic root dilatation, aneurysm formation, or dissection of the ascending aorta (18). Also, Takayasu arteritis, a rare inflammatory disorder of the aorta and arch branch vessels, has a predilection for women (80–90% of affected patients) in their thirties and predominates in Asian populations. This condition commonly causes stenosis of the aorta and supra-aortic vessels but can also be associated with aortic abdominal and descending thoracic aorta aneurysm formation (18). Marfan syndrome is equally prevalent in the two sexes, although men are at a higher risk of aortic complications than non-pregnant women. The study by Meijboom and colleagues suggests the need to reduce the threshold for elective aortic root replacement in women as dissection and rupture due to progressive root dilation seem to occur at smaller diameters than in men (19).

Anatomical specificities by sex

Aortic diameter and anatomy

From an anatomical point of view, most women have naturally smaller anatomic structures than most men, including coronary arteries, native valve orifice area, and aortic diameter, such that an aneurysm of a certain small diameter can represent more advanced disease in women than the same-sized aneurysm comparatively in men (20,21). Downward or upward adjustment of aortic diameter thresholds for surgery is recommended for both male and female patients who are significantly shorter or taller than average. Adjustments should be made for patients whose height, body surface area (BSA), or both is between 1 to 2 standard deviations of the mean (1). Nevertheless, no specific sex-related threshold has been indicated so far for TAAA.

Z-score may represent a useful tool to express the deviation of a given anatomic measurement from a sex-specific population mean, and clarify the precise surgical threshold for women, but only once the bias related to measurement error, BSA equation used, and variations between alternative Z-score nomograms are improved and standardized in adult patients (22). In the meantime, aortic diameters should be normalized using a ratio of aortic diameter to BSA [aortic size index (ASI) defined as aortic diameter in cm/BSA in m^2], or aortic diameter to the patient's height [aortic height index (AHI) defined as aortic diameter in cm/patient height in m], or to height by calculating a ratio of the cross-sectional area of the aorta (cm) to the patient's height (m) (1). Moreover, in terms of anatomy, female patients have shown to be more challenging compared to men: not only are female visceral/infrarenal aortic and iliac arteries diameters smaller, but infrarenal necks are shorter and more angulated, as too are the iliac arteries (23). Furthermore, the prevalence of thoracic aortic aneurysms in patients with known abdominal aortic aneurysms is higher in women than in men (48% in women *vs.* 23% in men, P<0.0001) (24).

Aneurysm growth and extent

The aortic growth rate may not represent a reliable indicator for intervention, however, contrasting evidence has been reported amongst the sexes (8). Indeed, some reports show that degenerative aneurysms in women display a faster increase in diameter, contrary to those associated with hereditable conditions such as bicuspid aortic valve, Marfan syndrome, familial thoracic aorta aneurysms, dissections, or other genetic syndromes (1,11). On this subject, in their study about the role of sex on TAAA growth in 82 consecutive unoperated patients, Chung *et al.* reported that the growth rate was twice faster in women than in men (1.19–1.15 mm/year in women *vs.* 0.59–0.66 mm/year in men, P<0.02), giving more credence to the notion of a lower threshold for disease in women (11). Finally, men and women seem also to differ in terms of aneurysmal extent, as men are more likely to undergo extent II and IV repairs, whereas women more often need extent I and III repairs (13,16).

Treatment

TAAA still represents a technical challenge, but no specific sex-related management strategies have been suggested thus far (25). Medical treatment consists of risk factors and blood pressure control (level 1a), statins, and antiplatelet therapy (level 2a) (1). Patient anatomy also influences their allocation to open surgical repair with extracorporeal circulation, fenestrated-branched endovascular aortic repair (F-BEVAR), or parallel grafts and hybrid repair with a combination of open and endovascular techniques. The setting for repair also influences surgical strategy. In the case of rupture, the endovascular approach may be hampered by patient instability—because it requires sequential stenting of side branches without the possibility for rapid control of hemorrhage, and the need for customized grafts (1).

Open surgery

The surgical techniques of TAAA repair have been previously extensively described and treatment modalities are based on the extent of the aortic disease according to Crawford classification, with no differences in operative and protective strategies between sexes (21). However, the optimal conduct of open TAAA repair requires an attentive evaluation of patient risk factors, and focused efforts should be held to mitigate the perioperative complications. For instance, knowing that women are at increased risk of respiratory failure, proper patient evaluation and preparation with improvement of baseline lung function before highly complex surgery can contribute to optimizing the surgical outcome (26,27).

Endovascular treatment

In the last two decades, the development of the endovascular devices for complex aortic repair has enabled treatment for even high surgical risk patients. As women are under-represented in vascular trials, endografts have not been specifically shaped to address the specific challenges encountered in women (10,12). Women on average have smaller anatomic structures, including smaller infrarenal aortic diameter and aortic lumen at the visceral vessels. Therefore, these procedures are more complex in women leading to increased interventional times {530 [interquartile range (IQR), 425–625] *vs.* 420 (IQR, 350–510) min, P<0.001}, fluoroscopy times (124.1±49.0 *vs.* 107.3±43.5 min, P=0.017) and contrast usage [200 (IQR, 150–270) *vs.* 175 (IQR, 130–225) mL, P=0.005] (28).

Deery *et al.* reported that female patients are more likely to require iliac access when treated endovascularly, and a recent study by Grandi *et al.* (29,30). showed that the anatomical feasibility of off-the-shelf multibranched Zenith t-Branch is negatively influenced by female sex [odds ratio (OR), 2.9; 95% confidence interval (CI): 1.5–5.4; P=0.001] and limited by the infrarenal aortic diameter (45% in women *vs.* 6% in men, P<0.001) or the aortic lumen at the visceral vessels (19% in women *vs.* 17% in men, P=0.741). Due to these anatomical factors, women often experience intraoperative complications due to unplanned intraoperative maneuvers (45.6% *vs.* 28.1%, P=0.043) or to graft delivery issues (24.6% *vs.* 4.9%, P<0.001), and, after implantation, display an increased rotational deviation of branched endografts and higher rates of type IA endoleaks (8,10,28). Conversely, according to Torsello and colleagues, the chimney technique may be more beneficial for women than F-BEVAR considering the potentially higher risk of access complications when using those devices (31).

Sex-related outcomes

As men and women differ in their preoperative risk profiles, so too do their postoperative outcomes. Data from the 'American College of Surgeons National Surgery Quality Improvement Program' encompassing 17,763 abdominal, thoracic, or TAAA patients demonstrated increased rates of major postoperative complications in women (10.8% *vs.* 7.7%, P<0.001) leading to longer intensive care unit stays (4.4 *vs.* 3.1 days, P=0.024) and increased need for dialysis (5.8% *vs.* 1.2%, P=0.024) after both open and endovascular repair (32). However, center-specific reports tend to be more variable. Controlling for baseline risk factors in the data analysis appears to impact the magnitude of risk. When analyzing data regarding sex differences after open TAAA repair some authors do not report difference in major adverse events, but reduced preoperative pulmonary function in women has been shown to contribute to an increased risk for respiratory failure in the perioperative period and need for tracheostomy (OR, 3.73; 95% CI: 1.53–9.10) (*Table 1*) (9,13,26).

Additionally, after open repair, women seem to be at a higher risk of unplanned readmission (14.8% *vs.* 10%, P=0.051), and discharge to a non-home facility (20.6% *vs.* 10.7%, P<0.001) compared with men in reports where those outcomes are collected (2). Conversely, F-BEVAR procedures have been shown to be associated with higher rates of major bleeding complications and acute limb ischemia in the female subgroup, as well as increased rates of bowel (10.5% *vs.* 2.7%, P=0.013) and

Table 1 Outcomes and mortality after open TAAA repair in female *vs.* male population

Author, year	Size of cohort	Female, n (%)	Complications	Survival/death rate
Latz *et al.*, 2021 (9)	516 patients TAAA I–III	280 (54.3)	Same rate of major adverse events	Survival at 5 years was 50% for women and 67% for men (log-rank P<0.001)
Girardi *et al.*, 2019 (26)	783 patients (DTA or TAAA repair)	321 (41.0)	Female sex is an independent risk factor for a composite of major adverse events (OR, 2.68; 95% CI: 1.41–5.11) and need for tracheostomy (OR, 3.73; 95% CI: 1.53–9.10)	Operative mortality was not different between women and men (5.6% *vs.* 6.2%; P=0.536) Women had significantly lower 5-year survival
Flink *et al.*, 2016 (2)	1,541 patients (AAA, TAA, TAAA)	4,048 (22.8)	The rate of discharge to a non-home facility was nearly double in women compared with men (20.6% *vs.* 10.7%, P<0.001)	–
Latz *et al.*, 2019 (33)	233 patients (TAAA IV)	85 (36.5)	No sex-based difference in combined major in-hospital events	Decreased survival in women compared with men after discharge (hazard ratio, 2.1; 95% CI: 1.2–3.5; P=0.008)
Murana *et al.*, 2016 (34)	542 patients	250 (46.1)	–	Female sex is an independent risk factor for 30-day mortality (OR, 2.52; 95% CI: 1.27–4.99)

TAAA, thoracoabdominal aortic aneurysm; DTA, descending thoracic aorta; OR, odds ratio; CI, confidence interval; AAA, abdominal aortic aneurysm; TAA, thoracic aortic aneurysm.

spinal cord ischemia (15.8% *vs.* 3.8%, P=0.001) (28,35). This difference in neurological outcomes may relate to the fact that while men are predominantly treated for pararenal aneurysms, female patients often need more extensive aortic repair and coverage of the distal thoracic aorta, which represents an important risk factor for this complication (36). This further emphasizes the role of an understanding of baseline anatomy and risk in drawing sex-based comparisons.

Finally, female sex is associated with an 8-fold increased risk of renal function deterioration (OR, 8.1; 95% CI: 6.1–10.8) (37). Reintervention rates after endovascular approaches, as well as the 5-year estimate of freedom from late reintervention, seem to be similar among sexes (*Table 2*) (38). Furthermore, the results after open and endovascular TAAA repair seem dissimilar in terms of survival. de Guerre *et al.* analyzed data extracted from the National Surgical Quality Improvement Program (NSQIP), demonstrating that women display higher rates of peri-operative mortality and major complications after complex endovascular repair compared with male patients, but not after complex open surgical repair (40).

However, the nature of this dataset is such that specific anatomic details cannot be controlled for. Indeed, after adjustment for potential risk factors including age, symptoms, comorbidities, and female sex proved to be independently associated with higher in-hospital mortality (12.3% *vs.* 2.7%, P=0.004) and 30-day mortality rate (OR, 1.8) when patients are treated with endovascular surgery (32,35). The 3-year survival was reported to be the same between the two sexes (*Tables 3-5*) (41). Conversely, the long-term outcomes after open repair suggested that female sex represents an independent predictor of decreased survival (hazard ratio, 1.5; 95% CI: 1.2–1.9; P=0.001) when adjusted for age, aneurysm extent, creatinine, chronic obstructive pulmonary disease, and rupture rate (9).

Transgender people and aneurysms

Sex may determine differences in patients' behaviors and lifestyles, which could affect exposure to cardiovascular risk factors, but it is still unclear if transgender people should be compared with their natal sex or the adopted one when analyzing the development and the natural course of aortic diseases. Additionally, as sex hormones influence metabolism, vascular function, and inflammatory responses, cross-sex hormone therapy may have effects on general cardiovascular health. Currently, available data are limited and inadequate due to a lack of large cohort studies and control populations (42). It has been found that the use of estrogens in transgender women predisposes to myocardial infarction and ischemic stroke, but further

Table 2 Outcomes in female patients compared with male patients after endovascular TAAA repair

Author, year	Size of cohort	Female, n (%)	Outcomes (female *vs.* male)
Heidemann *et al.*, 2020 (36)	877 patients	166 (18.9)	Higher rates of major bleeding complications and acute limb ischemia
Forbes *et al.*, 2023 (28)	242 patients	57 (23.5)	Bowel ischemia 10.5% *vs.* 2.7% (P=0.013)
			Spinal cord ischemia 15.8% *vs.* 3.8%, (P=0.001)
Isernia *et al.*, 2022 (38)	176 patients	88 (50.0)	Technical success rate 86.2% *vs.* 96.6% (P=0.016)
Timaran *et al.*, 2016 (37)	79 patients	16 (20.3)	Intensive care unit stay median, 3 (IQR, 2–5) *vs.* 2 (IQR, 1–3) days (P=0.05)
			Hospital stay median, 4.5 (IQR, 3–6.5) *vs.* 3 (IQR, 2–4) days (P<0.01)
			Reinterventions rate 25% *vs.* 5% (P=0.02)
			Renal function deterioration: 8-fold increased risk (OR, 8.1; 95% CI: 6.1–10.8)
			Female sex independent factor for reinterventions at 30 days (OR, 7.4; 95% CI: 6.7–8.1)
Liao *et al.*, 2020 (39)	136 patients	20 (14.7)	Estimated blood loss 660.0 *vs.* 311.6 mL (P<0.01)
			Transfusion 1.4 *vs.* 0.3 units (P<0.01)
			Operative 295.7 *vs.* 215.7 min (P<0.01)
			Fluoroscopy times 84.3 *vs.* 58.7 min (P<0.01)
			Length of stay 5.6 *vs.* 3.3 days (P=0.03)
Rieß *et al.*, 2019 (35)	959 patients	163 (17.0)	Acute renal failure (RR, 1.71; 95% CI: 1.06–2.77)
			Paraplegia (RR, 2.71; 95% CI: 1.28–5.77)
			Bleeding/anemia requiring transfusion (RR, 1.76; 95% CI: 1.39–2.22)

TAAA, thoracoabdominal aortic aneurysm; IQR, interquartile range; OR, odds ratio; CI, confidence interval; RR, relative risk.

Table 3 In-hospital mortality after endovascular treatment of TAAA in female *vs.* male patients

Author, year	Size of cohort	Female, n (%)	Death rate (female *vs.* male)
Rieß *et al.*, 2019 (35)	959 patients	163 (17.0)	10.4% *vs.* 3.6% (P<0.001)
Forbes *et al.*, 2023 (28)	242 patients	57 (23.5)	12.3% *vs.* 2.7% (P=0.004)
Witheford *et al.*, 2020 (41)	100 patients	50 (50.0)	16% *vs.* 6% (P<0.05)

TAAA, thoracoabdominal aortic aneurysm.

Table 4 Thirty-day mortality after endovascular treatment of TAAA in female *vs.* male patients

Author, year	Size of the cohort	Female, n (%)	Death rate (female *vs.* male)
Witheford *et al.*, 2020 (41)	100 patients	50 (50.0)	16% *vs.* 6% (P<0.05)
Rieß *et al.*, 2019 (35)	959 patients	163 (17.0)	12.3% *vs.* 5.4 % (P=0.002)

TAAA, thoracoabdominal aortic aneurysm.

Table 5 Mortality beyond 90 days after endovascular treatment in female and male patients

Author, year	Size of cohort	Female, n (%)	Death rate (female *vs.* male)
Rieß *et al.*, 2019 (35)	959 patients	163 (17.0)	14.1% *vs.* 7.2% (P=0.006)
Forbes *et al.*, 2023 (28)	242 patients	57 (23.5)	6-year survival was 60.2% for all patients (95% CI: 53.0–68.5%) and was similar between sexes (hazard ratio, 0.95; P=0.83)
Witheford *et al.*, 2020 (41)	100 patients	50 (50.0)	Same survival at 3-year follow-up

CI, confidence interval.

investigation on the vascular response to hormonal therapy is needed to confirm the relationship and the pathogenic mechanism by which sex steroids endanger vascular health to provide better aortic care for the transgender population (42).

Future perspective

In the light of the disadvantaged outcomes from delayed diagnosis (with more severe comorbidities and older age of female patients), a comparatively more challenging extent of disease and access, and the need for emergent treatment, more vigilant preoperative surveillance may be needed in women. However, concrete data to support this is not yet available. Nevertheless, the data reported above highlights that much more can be done to improve the outcomes of aortic surgery in the female population, and that further efforts are needed to develop new gender-specific strategies. Tailored screening programs for early diagnosis and the control of risk factors and comorbidities, would represent a promising starting point.

Conclusions

Women and men undergoing TAAA repair have significant and consistent differences in preoperative characteristics and risk factors, including aneurysm etiology and anatomy, age, comorbidities, and setting for surgery. Data on the outcomes are currently inconsistent and conflicting. Therefore, further efforts are needed to better understand the sex-related differences in TAAA diagnosis and management, to allow prompt and appropriate treatment of female patients, thereby improving their outcomes.

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Footnote

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