# Women undergoing Endovascular Thoracoabdominal Aortic Aneurysm Repair Differ Significantly from their Male Counterparts Pre and Post Operatively

Miranda Witheford[1*], Debra ST Chong[1,2*], Teresa Martin-Gonzalez[1], Katrien Van Calster[3], Meryl Davis[1], Anna Prent[1], Stephan Haulon[4], Tara M Mastracci[1,2]

[1]*Complex Aortic Team, Royal Free London NHS Foundation Trust, London, United Kingdom*

[2]*Division of Surgery and Interventional Science, University College London, UK*

[3]*Aortic Center, CHRU Lille, Lille, France*

[4]*Aortic Center, Hôspital Marie Lannelongue, Université Paris Sud, France*

**These authors contributed equally to this project*

**Corresponding Author:** Dr Tara M Mastracci, *MD MSc FRCSC FACS FRCS*

**Address:** Complex Aortic Team, 9th Floor, Department of Vascular Surgery, Royal Free London NHS Foundation Trust, Pond Street, London, NW3 2QG, United Kingdom

**E-mail:** tara.mastracci@nhs.net

**Telephone Number:** +44 (0) 207 830 2163

**Category:** Original Article

**Short Title:** Endovascular Thoracoabdominal Aneurysm Repair in Women

## ARTICLE HIGHLIGHTS

**Type of Research:** Multicentre retrospective cohort

**Key Findings:** Complex endovascular thoracoabdominal aortic aneurysm repair in fit female and matched male patients at two centres is associated with infrequent perioperative complications in both groups, but elevated 30 day mortality in women (16% versus 6%). At long-term follow-up, women have predominantly type 2 endoleaks, and a reduction in aneurysm diameter, compared to matched men. Matched men and women post complex endovascular thoracoabdominal aneurysm repair have the same 3 year survival.

**Take Home Message:** Endovascular thoracoabdominal aortic aneurysm repair in women is associated with elevated perioperative mortality, but acceptable survival and durability at long-term follow-up.

## TABLE OF CONTENTS SUMMARY

Fenestrated and Branched endovascular repair of thoracoabdominal aortic aneurysms in a cohort of 50 women and 50 matched male patients is associated with increased perioperative mortality in women, but the same long-term survival and durability of repair. The authors suggest that male/female outcome differences after complex aortic aneurysm repair should be placed within the context of preoperative differences in aneurysm extent and patient comorbidities to contextualize postoperative outcomes.

## ABSTRACT

**Objective:** A rational approach to the management of aortic aneurysm disease relies upon weighing the risk of aneurysm rupture against the complications and durability of operative repair. In men, seminal studies of infrarenal aortic aneurysm disease and its endovascular management can provide a reasoned argument for the timing and modality of surgery, which is then extrapolated to the management of thoracoabdominal aortic aneurysms. In contrast, there is less appreciation for the natural history of thoracoabdominal aortic aneurysm disease in women, and its response to therapy.

**Methods:** We used a retrospective cohort design of women, all men, and matched men, fit for complex endovascular thoracoabdominal aneurysm repair at two large aortic centres. We controlled for preoperative anatomic and comorbidity differences, and assessed technical success, postoperative renal dysfunction, spinal ischemia, and early mortality. Women and matched men were reassessed at follow-up for long-term durability and survival.

**Results:** Assessing women and all men undergoing complex endovascular aortic reconstruction, we demonstrate that these groups are dissimilar pre-intervention, with respect to comorbidities, aneurysm extent, and aneurysm size; women have a higher proportion of proximal Crawford extent 1, 2, and 3 aneurysms. Matching men and women for demographic and anatomic differences, we find persistent elevated perioperative mortality in women (16%) undergoing endovascular thoracoabdominal aneurysm repair compared to matched men (6%), however, at 3-year follow-up, both groups have the same survival. Furthermore, women demonstrate more favourable anatomic responses to aneurysm exclusion, with good durability and greater aneurysm sac regression at follow-up, compared with matched men.

**Conclusions:**

Women and unmatched men with thoracoabdominal aortic aneurysm disease differ preoperatively with respect to aneurysm extent and comorbidities. Controlling for these differences, after complex endovascular aneurysm repair, there is elevated early mortality in women compared with matched men. These observations argue for a careful risk stratification of women undergoing endovascular thoracoabdominal aneurysm treatment, balanced with women's good long-term survival and durability of endovascular aneurysm repair.

## INTRODUCTION

Our current understanding of aortic aneurysm disease, both its natural history and response to open or endovascular therapy, has historically relied primarily upon data unsegregated on the basis of sex, with most study participants composed of men [1–3]. The paucity of data in female patients has spurred recent interest in delineating more precise indications for, and outcomes of, treatment. A rational approach to aneurysm management in women must balance the hazards of repair with the probability of mortality from aneurysm rupture; data is needed to weigh these risks.

The rationale for examining women undergoing aortic aneurysm repair relates to perceived increased risk relating to access complications, mortality, suitability for standard endovascular aneurysm repair (EVAR), and rupture risk in women scaled to maximal aneurysm diameter and body size. A recent meta-analysis of open (Open surgical repair; OSR) and endovascular infrarenal aneurysm repair in women demonstrated that, compared with men, women have elevated perioperative mortality (OSR 5.37% vs 2.82%, EVAR 2.31% vs 1.37%), although EVAR maintains its early survival advantage in both sexes [4]. This data is most salient in the context of turndown rates for infrarenal EVAR in women due to anatomic unsuitability [5]. Pooled estimates of infrarenal EVAR suitability differ significantly between men and women [4], and women are less likely than men to undergo EVAR electively for intact aneurysms [6].

It has been posited that outcome differences in women undergoing EVAR relate to advanced age and burden of comorbidities; this has not been universally borne out in the literature. Studies that control for age, comorbidities, ethnicity, and hospital volume, note poorer outcomes in women, including perioperative mortality, length of stay, and readmission [7]. Indeed, although female patients undergoing EVAR tend to be older, they are also healthier, having fewer diagnosed instances of heart disease, diabetes, concurrent smoking,

COPD, and chronic renal dysfunction [8]. There have been several studies where controlling for age, urgency at presentation, comorbidities and risk factors has resulted in equipoise of perioperative and 1-year mortality [6].

There is interplay between a patient's comorbidities, and their aneurysm anatomy, which ultimately determines long-term outcome: successful aneurysm exclusion, prevention of rupture, aneurysm-related mortality, and overall survival. Female sex has been noted to predict failure of AAA exclusion with resultant ongoing risk of rupture [9]. Given the conflicted literature with respect to infrarenal EVAR, we wanted to directly compare outcomes of endovascular repair for more extensive aortic aneurysm disease, in men and women at two aortic centres, as a matched cohort. We felt that endovascular thoracoabdominal aneurysm repair, fenestrated (FEVAR), or branched (BEVAR), with its increasing complexity, greater physiologic demand, greater risk of access complications, or postoperative complications, might exaggerate differences between men and women with respect to endovascular aneurysm repair. This data could then be used to rationalize differing approaches to treatment, possibly with respect to timing of intervention or preferred approach, stratified by sex.

## METHODS

***Population.*** This is a retrospective cohort series utilizing data collected prospectively from two independent centres for aortic surgery (Royal Free Hospital, London, UK; Lille University Hospital, Lille, France.) All patients, male and female, undergoing FEVAR or BEVAR between 2006 and 2017 were identified, and demographic data, including sex, smoking status, coronary artery disease, COPD and chronic renal impairment, was collected prospectively, as were details of individual operations. Patients were only included if they

underwent a planned fenestrated or branched endovascular repair; ruptured, urgent or symptomatic cases, and dissections, were excluded, as were cases where only an infrarenal device was implanted. Thus, only patients with thoracoabdominal aneurysms of Crawford extents 1-5 (Safi modification), and pararenal aneurysms, denoted here as extent 6, were studied. Retrospectively, all female patients ("female all-comers") undergoing FEVAR or BEVAR were matched to case control male patients on the basis of age, aneurysm extent, smoking status, presence of ischemic heart disease, and diagnosis of COPD). Surgery was undertaken by two aortic surgeons (TM, SH) on patients deemed anatomically suitable for FEVAR/BEVAR by standard criteria for use for these devices, and physiologically appropriate for endovascular intervention with acceptable risk for general anesthesia, through a preoperative anesthetic consultation and multidisciplinary team approach, "fit patients". Threshold maximal diameter for intervention was determined by the treating surgeon, but most often followed the rules of >6cm diameter for thoracoabdominal aneurysms, and >5.5cm for pararenal aneurysms. Measurements were made on centreline of flow reconstructed CT scans. Female and matched male patients were equally distributed by operating surgeon (Female TM 23, SH 27; Male TM 28, SH 22), and the groups were matched in distribution over the time interval of assessment from 2006-2017. The endovascular devices utilized for repair included custom-made branched and/or fenestrated devices from Cook Medical (Bloomington, Indiana) and were designed and implanted at the discretion of the local surgeons. As is standard practice in the United Kingdom, this research project was adjudicated through the MRC/HRA decision-making tool (http://www.hra-decisiontools.org.uk/research/) and deemed not to require ethical review board oversight. As such, this project was registered as a local clinical audit, patient consent was waived, and ethics procedures adhered to according to local governance.

***Variables.*** Patient demographics, comorbidities, preoperative aneurysm anatomy by Crawford extent, and aneurysm diameter were gathered for all comers. Aneurysm extent and diameter were assessed by preoperative contrast-enhanced CT scan, reformatted to centreline measurements. As is standard practice at both institutions, following an early postoperative CT assessment within 3 months of the index procedure, patients undergo, at minimum, yearly CT imaging and duplex arterial assessment of their endovascular repairs. Postoperative aneurysm diameter was assessed as the maximal aneurysm diameter at the patient's last follow-up, by contrast-enhanced CT scan, again through centre of flow measurement. Endoleaks were also assessed from these contrast-enhanced CT scans and Duplex ultrasound, and were reported if peri-graft flow was noted by either modality. Endoleaks were assessed for all follow-up scans, and are reported as positive if any endoleak was ever present for an individual patient at any time during follow-up. Target vessel patency, and reinterventions are reported for any stenosis/occlusion reported by either duplex ultrasound or CTA at any time during follow-up. Renal dysfunction/acute kidney injury was assessed on by eGFR at 24 hours post procedure, and clinical follow-up regarding dialysis dependence thereafter, to produce RIFLE scores [10].

***Statistical Analysis.*** Categorical variables are presented as percentages, with raw data in adjacent parentheses, and continuous variables as the mean +/- standard deviation. Differences between groups were assessed using the Chi-square, Student's T-test, or ANOVA. All tests were two-sided and considered significant if $p<0.05$. Statistical analysis was performed using SPSS Statistical Analytics software (IBM Analytics).

## RESULTS

***Preoperative Assessment***

A cohort of all female patients undergoing endovascular repair for thoracoabdominal aortic aneurysm (TAAA), from 2006-2017 at two treating centres was assembled, 50 patients total (8% of all patients undergoing endovascular thoracoabdominal aortic aneurysm repair). These women were classified as requiring complex aortic repair, as they were anatomically unsuitable for infrarenal EVAR, requiring a custom-made fenestrated (FEVAR; 36 patients) or branched (BEVAR; 14 patients) device. Patients undergoing emergency intervention were excluded from analysis. Female patients were then matched to a 50 patient cohort of male patients distributed over the same surgical sites and time period, and requiring complex endovascular aneurysm repair (FEVAR 39 patients; BEVAR 11 patients). They were further matched on the basis of medical comorbidities including the diagnosis of coronary artery disease, COPD, diabetes mellitus, smoking status(Table 1), as well as their aneurysm extent (modified Crawford criteria, with pararenal aneurysms delineated as category 6 in this manuscript). The male and female matched cohorts (100 patients total) were compared to the entire cohort of male patients undergoing complex aortic repair during the same time period (541 patients). As this research project, adjudicated through MRC/HRA, was recognized as a clinical audit, patient consent was waived and procedures adhered to according to local ethics governance.

Female patients undergoing FEVAR or BEVAR (Table 1) are the same age ($\mu$= 71.9 +/- 9.7) as their male (unmatched) counterparts ($\mu$= 72 +/- 8.6), however, they differ significantly with respect to percentage of patients currently using cigarettes, albeit a higher proportion of these women have never smoked (**$p<0.01$ by $\chi 2$ between female and male all-comers cohorts). Women undergoing complex aortic repair, compared with all men, are also are less likely to be diabetic, suffer from coronary artery disease or chronic renal insufficiency (**$p<0.01$). The male cohort of FEVAR/BEVAR patients, matched to our

female cohort for age, smoking status, COPD and diabetes mellitus remains statistically more heavily burdened by chronic renal insufficiency (*$p<0.05$, by $\chi 2$ between matched male and female patients).

An assessment of preoperative distribution of aneurysm extent in women by modified Crawford criteria, with pararenal aneurysms delineated as extent 6 (Figure 1A), demonstrates a representation of all aneurysm categories, with a predominance of extent 4 thoracoabdominal aneurysms (15/50), followed by extent 2 (10/50; percentages of each group next to wedges). In contrast (Figure 1B), in all male patients undergoing FEVAR/BEVAR, patients have predominantly extent 4 TAAA and 6 (pararenal) aneurysms (77/140, 42/140 respectively), with a paucity of more extensive/cephalad aneurysms ($p<0.05$). Female patients can be matched to a male cohort by aneurysm extent and comorbidities, and no longer differ significantly with respect to Crawford aneurysm class (Figure 1C).

***Perioperative Events***

Technical success, defined as aneurysm exclusion, without immediate type 1 or 3 endoleak, and with perfusion to visceral, renal, and lower extremity arterial beds, was 100% in both female and male matched patients at the termination of each procedure. Intraoperative complications in both groups were rare. These consisted of: failure to catheterize and stent the celiac artery, dissection of the celiac, thoracic or visceral aorta, left subclavian artery, or external iliac, and type 2 endoleak. There were no intraoperative deaths.

Early perioperative complications are infrequent, and similar, between women and matched men (Table 2). Postoperative mean renal function (eGFR) within 24 hours of FEVAR or BEVAR (Table 2) in matched men and women is unchanged. For the minority of patients suffering any renal impairment postoperatively (women 14/47, men 13/48, NS), as expressed by RIFLE score, change in postoperative eGFR does not differ significantly either

in degree of eGFR decline, or in total loss of renal function requiring dialysis, between male and female patients. Patients developing renal impairment were primarily in the "Risk" category (women 9/47, men 9/48), expressing a decrease in eGFR <25%, from which all patients recovered. Very few patients (2% total) require new institution of dialysis either temporarily or indefinitely.

Spinal cord injury (Table 2), either immediate or delayed, is also uncommon in patients undergoing FEVAR/BEVAR (9% of all patients), and a there is no significant difference between matched men (12%) and women (6%), given the small cohort, and low frequency of this complication. Spinal cord injury was more often delayed (>24hours) in both matched men and women (>24 hours 6/100 patients, <24 hours 3/100 patients).

Perioperative/early 30d mortality is higher in women (16%) than matched men (6%) ($p<0.05$). The causes of perioperative mortality are primarily attributable to the procedure, including cerebrovascular postoperative events, retrograde type A dissection, sepsis, and multiorgan failure, as well as cardiovascular causes (Table 3). In female and matched male patients (Table 3), detailed assessment of events resulting in mortality demonstrates an association with more proximal/extensive aneurysm disease, presence of a TEVAR (placed as a staged procedure or concurrently), and placement of a BEVAR. These subgroup findings cannot be corroborated statistically in this study, given the small patient numbers. There was no difference in perioperative mortality rate by surgical site.

***Postoperative Follow-up***

Postoperatively, women and matched men underwent follow-up for a median of 957 and 820 days respectively. Follow-up of all patients consisted of clinical assessment, contrast-enhanced CT, and duplex assessment of visceral vessels, with measures of durability including: target vessel patency, secondary reinterventions, aneurysm diameter, and the

presence of endoleak, as well as patient survival. At both institutions, follow-up CT is performed at approximately 1 month postoperatively, and then by CT and duplex at minimum on a yearly basis, baring indications for more aggressive surveillance.

Preoperatively, women and men statistically have the same maximal aneurysm diameter, albeit with the largest aneurysms (>8cm) belonging exclusively to matched men (Figure 2A). However, postoperatively, aneurysm maximal diameters in women are significantly smaller (women $\mu$= 52.1, men $\mu$= 62.9; $p<0.01$), and they have a significantly larger decrease in mean aneurysm diameter (Figure 2A: women mean, large dashes $\mu$= -8.3 mm, matched men mean small dots $\mu$= -2.8 mm; $p<0.05$). In contrast, endoleaks occurred more frequently at any time during follow-up in women (Figure 2B); indeed, 42% of women demonstrated an endoleak recorded at any time during their follow-up. These were predominantly type 2 endoleaks (Figure 2B; raw numbers of patients adjacent to wedges). In matched men post FEVAR/BEVAR, there were fewer endoleaks overall, occurring in 25% of patients, however their distribution was predominantly of type 1b, or c (Figure 2C). Coordinate with this data, there were more reinterventions of any kind over the entire follow-up period in matched men compared with women (18 reinterventions in 15 men, versus 16 reinterventions in 14 women), but this was not significant. Visceral vessel reinterventions at any time during follow-up are rare, and were required in 7 visceral vessels in women, and 9 visceral vessels in men.

Although we have suggested that 30-day survival post FEVAR/BEVAR is reduced in women versus men, thereafter, survival by Kaplan-Meier analysis (Figure 3A) is not statistically different between groups; many patients are however lost to follow-up at 5 years (Figure 3B). Patient mean survival, by days confirmed alive, is also the same, at 1114 days (3.05 years) for women, and 855 days (2.3 years) for men (Figure 3C; $p=0.17$).

## DISCUSSION

This is a retrospective cohort study of complex endovascular aortic repair at two centres, comparing female, matched male, and all male patients fit for repair.

The cohort of women undergoing thoracoabdominal aortic aneurysm repair in our series is fundamentally different from all male patients undergoing intervention for this disease at our institutions. Although it has often been reported that female patients treated with infrarenal EVAR are older than their male counterparts [6], we found that for more extensive thoracoabdominal aortic disease in our cohort, this is not true. Women do, however, have a different burden of medical comorbidities. Current smoking is more common in our female patients, and is a recognized risk factor for aneurysm enlargement, rupture, and worse perioperative or long-term outcomes following EVAR [11,12]. COPD, which is a predictor of AAA development, expansion, poor perioperative outcome and rupture risk, is not different between our female patients and all male patients [13,14]. Diabetes mellitus, chronic renal disease, and coronary artery disease have all been reported to influence perioperative outcome post endovascular AAA repair, or to influence rupture risk for infrarenal AAA, [15–17] and had a higher prevalence amongst all male patients than our female patients. These comorbidities represent complex and competing influences on aneurysm growth, rupture risk, and complications associated with aneurysm repair. Sex differences in comorbidities or their management, rather than an intrinsic sex-related difference in aneurysm pathophysiology, may more accurately explain differences observed in rupture risk, perioperative, and long-term outcome reported for women in the literature.

It is compelling that the anatomic distribution of thoracoabdominal pathology differs significantly between unmatched men and women in our cohort; women who are fit for surgery have more proximal aortic disease, with higher proportions of Crawford extent 1,2, and 3 aneurysms, in contrast to a higher prevalence of extent 4 and pararenal aneurysms in all

male patients. If the difference in anatomic distribution is reflective of the total population, it would imply that these women are likely at increased risk of spinal ischemia, proximal arch complications, and visceral/renal complications owing to the more extensive nature of their repair and an increased number of visceral vessels receiving intervention [18]. It is possible that the general view that endovascular aortic surgery in women is more complex and associated with poorer outcome, is in fact determined by more complex anatomy. Conversely, selection bias towards 'hardier' women, may be influencing anatomic distribution and subsequent perioperative course. Without knowledge of all patients who defer surgery at each institution, this generalization is difficult to make.

It has also been noted that absolute aneurysm size preoperatively is an independent predictor of cardiovascular death, whether or not the aneurysm is repaired [19]. Whilst matched male patients in our study had the same mean preoperative aneurysm diameter, the largest aneurysms overall belonged to the matched male cohort. Women and matched men in our study however had similar long-term survival post repair, an effect which may reflect lower statistical power at longer follow-up due to patient dropout.

It is salient, that although there is a relatively low incidence of perioperative complication in our matched male and female patients, there is initially elevated mortality in women. The reasons for this are not immediately clear. New onset renal failure was extremely uncommon in both groups, as was spinal cord ischemia, despite the extensive operations undertaken. Reports of perioperative renal failure post endovascular thoracoabdominal aneurysm repair vary widely in the literature; some studies report up to 32% of endovascular thoracoabdominal patients demonstrating acute renal insufficiency [20], although in a larger study, only 5% of FEVAR, and 9% of EVAR patients developed a decline in eGFR >25% [21]. Preoperative renal dysfunction is a known risk factor for postoperative renal impairment in aneurysm patients, and we could not match female and

male patients for the presence of renal dysfunction preoperatively, yet both groups had low rates of renal impairment. We cannot account for the effect of renal impairment on patient outcomes in this study. Matched men suffered more frequently from this comorbidity, but had lower perioperative mortality, thus it seems unlikely to have had a negative impact. Similarly, one might expect a higher risk of spinal ischemia in women, compared with the male aneurysm patient, owing to more extensive disease. However, when matched for aneurysm extent, neither women or men in our study suffered from high rates of spinal cord dysfunction. Reported rates of spinal cord injury in the literature range from 2-10% after thoracoabdominal repair, and are stratified by aneurysm, and hence coverage, extent [22,23]. The spinal cord event rates in our series concur with those data; they are also reassuring given the extensive nature of aneurysm disease presented here.

The extensiveness of aortic coverage in our patients compared to all patients with thoracoabdominal aneurysm disease is likely a contributor to their elevated perioperative mortality, with disproportionate impact on the basis of sex. Women suffering death within 30 days of FEVAR/BEVAR in the majority represented individuals with proximal/extensive aneurysm disease of Crawford extents 1-3, requiring branched endovascular devices. The small numbers of female patients undergoing FEVAR/BEVAR in this cohort does not allow for a subgroup analysis of mortality on the basis of sex and aneurysm extent, or an assessment of operative complexity. The literature regarding open repair of thoracoabdominal aneurysms would support elevated perioperative mortality in extent 2 aneurysms, with predictors including age, renal insufficiency, and transfusion requirement[24,25]. The explanation for an elevated perioperative mortality in women undergoing FEVAR/BEVAR, placed in the context of extensive aneurysm disease, may suggest that assessment of interventional complexity, including factors assessing operative time, access site use, and difficulty of target vessel interventions may be required to risk

stratify women undergoing these procedures. These observations suggest that women with complex proximal aortopathy and multiple comorbidities require in-depth discussions of risk.

Although the mean preoperative aneurysm diameter was the same in matched men and women in our study, significant sex-based differences were observed post repair. Women were more likely to suffer from any endoleak, although the majority of these were type 2, whereas matched male patients with endoleaks were of types 1b or c. This is likely also related to our observation that the female cohort had a significant reduction in mean aneurysm diameter postoperatively, and the more distal phenotype of anatomic extent observed in men. There continues to be some debate regarding the significance of type 2 endoleak, however without aneurysm sac enlargement, these are generally regarded as benign [26]. In contrast, the presence of type 1b, and 1c endoleaks, which results in repressurization of the aneurysm sac, should intuitively be associated with continued aneurysm expansion, or at least stabilization of aneurysm diameter. Indeed, this is borne out in our results, as matched male patients, on average, had a reduction in aneurysm diameter post intervention of only 2.9mm, in contrast to female patients with a reduction of 9.3mm. Perhaps this suggests that we should more aggressively treat ectatic iliac anatomy in men, as it is a likely source of diminished durability, but the clinical sequela of this observation remains undetermined, as we measured only overall survival, as opposed to aneurysm-related mortality. With increasing patient numbers and longer follow-up, one might expect divergence in these measures, however this unfortunately remains a limitation of this study. At least at follow-up to five years, there is no significant difference in overall survival between matched male and female patients.

## CONCLUSIONS

We have demonstrated that thoracoabdominal aortic aneurysm disease differs significantly in women and all men fit for complex endovascular repair at two large centres; women have more extensive proximal aortopathy, and a different complement of comorbidities. Our current understanding of aneurysm pathophysiology, including development, expansion, and rupture risk acknowledges the influence of medical comorbidities and their treatment. This implies that a comparison of unmatched women and men may attribute intra/perioperative outcomes to differences in sex-based aortic physiology rather than the protective and disrupting influences of medical comorbidities on aneurysm pathophysiology and response to endovascular therapy. Controlling for anatomic and physiologic variables, both women and matched men undergoing complex aortic reconstruction have low perioperative complication rates. There is, nevertheless, a higher 30-day mortality in women associated with extensive aortic endovascular intervention. Fortunately, survival in both groups up to 3 years is not different between the groups, and women have low reintervention rates, and favourable reductions in aneurysm size over time. Delineating the preoperative phenotypic components, sex and non-sex based, in patients that lead to poor perioperative and long-term outcome after endovascular thoracoabdominal repair, is fundamental to reasoned risk stratification and rational decision-making.

REFERENCES CITED

1. Powell JT. Final 12-year follow-up of Surgeryversus Surveillance in the UK Small Aneurysm Trial. Br J Surg [Internet]. 2007 Jun 1 [cited 2018 Nov 21];94(6):702–8. Available from: http://doi.wiley.com/10.1002/bjs.5778

2. Lederle FA, Johnson GR, Wilson SE, Chute EP, Hye RJ, Makaroun MS, et al. The Aneurysm Detection and Management Study Screening Program. Arch Intern Med [Internet]. 2000 May 22 [cited 2018 Nov 21];160(10):1425. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinte.160.10.1425

3. Patel R, Sweeting MJ, Powell JT, Greenhalgh RM, EVAR trial investigators. Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial. Lancet (London, England) [Internet]. 2016 Nov 12 [cited 2018 Nov 21];388(10058):2366–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27743617

4. Ulug P, Sweeting MJ, von Allmen RS, Thompson SG, Powell JT, Ulug P, et al. Morphological suitability for endovascular repair, non-intervention rates, and operative mortality in women and men assessed for intact abdominal aortic aneurysm repair: systematic reviews with meta-analysis. Lancet [Internet]. 2017 Jun 24 [cited 2018 Nov 21];389(10088):2482–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28455148

5. Sidloff DA, Saratzis A, Sweeting MJ, Michaels J, Powell JT, Thompson SG, et al. Sex differences in mortality after abdominal aortic aneurysm repair in the UK. 2017 [cited 2018 Dec 11]; Available from: www.bjs.co.uk

6. Lo RC, Bensley RP, Hamdan AD, Wyers M, Adams JE, Schermerhorn ML. Gender differences in abdominal aortic aneurysm presentation, repair, and mortality in the Vascular Study Group of New England. J Vasc Surg [Internet]. 2013 May 1 [cited 2018 Nov 21];57(5):1261–1268.e5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0741521412024317

7. Lowry D, Singh J, Mytton J, Tiwari A. Sex-related Outcome Inequalities in Endovascular Aneurysm Repair. 2016 [cited 2018 Nov 21]; Available from: http://dx.doi.org/10.1016/j.ejvs.2016.07.083

8. Machado R, Teixeira G, Oliveira P, Loureiro L, Pereira C, Almeida ; Rui. Endovascular Abdominal Aneurysm Repair in Women: What are the Differences Between the Genders? Brazilian J Cardiovasc Surg Braz J Cardiovasc Surg [Internet]. 2016 [cited 2018 Nov 21];31(3):232–40. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5062709/pdf/rbccv-31-03-0232.pdf

9. Brewster DC, Jones JE, Chung TK, Lamuraglia GM, Kwolek CJ, Watkins MT, et al. Long-term outcomes after endovascular abdominal aortic aneurysm repair: the first decade. Ann Surg [Internet]. 2006 Sep [cited 2018 Dec 11];244(3):426–38. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16926569

10. Lopes JA, Jorge S. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. 2013 [cited 2018 Nov 21]; Available from: https://academic.oup.com/ckj/article-abstract/6/1/8/468698

11. Participants USAT. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. The UK Small Aneurysm Trial Participants. Lancet (London, England) [Internet]. 1998

Nov 21 [cited 2018 Nov 21];352(9141):1649–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9853436

12. Koole D, Moll FL, Buth J, Hobo R, Zandvoort H, Pasterkamp G, et al. The influence of smoking on endovascular abdominal aortic aneurysm repair. J Vasc Surg [Internet]. 2012 Jun 1 [cited 2018 Nov 21];55(6):1581–6. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0741521411029831

13. Axelrod DA, Henke PK, Wakefield TW, Stanley JC, Jacobs LA, Graham LM, et al. Impact of chronic obstructive pulmonary disease on elective and emergency abdominal aortic aneurysm repair. J Vasc Surg [Internet]. 2001 Jan [cited 2018 Nov 21];33(1):72–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11137926

14. Liao KM, Chen CY. Impact of chronic obstructive pulmonary disease on patients with aortic aneurysms: A nationwide retrospective cohort study in Taiwan. BMJ Open [Internet]. 2017 [cited 2018 Nov 20];7(9). Available from: http://bmjopen.bmj.com/

15. Lederle F. The Strange Relationship between Diabetes and Abdominal Aortic Aneurysm. 2012 [cited 2018 Nov 20]; Available from: www.vascularеducation.com

16. Raffort J, Lareyre F, Clément M, Hassen-Khodja R, Chinetti G, Mallat Z. Diabetes and aortic aneurysm: current state of the art. [cited 2018 Nov 20]; Available from: https://academic.oup.com/cardiovascres/article-abstract/114/13/1702/5056750

17. Takeuchi H, Okuyama M, Uchida HA, Kakio Y, Umebayashi R, Okuyama Y, et al. Chronic Kidney Disease Is Positively and Diabetes Mellitus Is Negatively Associated with Abdominal Aortic Aneurysm. PLoS One [Internet]. 2016 [cited 2018 Nov 20];11(10):e0164015. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27764090

18. Orr N, Minion D, Bobadilla JL. Thoracoabdominal aortic aneurysm repair: current endovascular perspectives. Vasc Health Risk Manag [Internet]. 2014 [cited 2018 Nov 21];10:493–505. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25170271

19. Norman PE, Muller J, Golledge J. The cardiovascular and prognostic significance of the infrarenal aortic diameter. J Vasc Surg [Internet]. 2011 Dec 1 [cited 2018 Dec 10];54(6):1817–20. Available from: https://www.sciencedirect.com/science/article/pii/S0741521411016673

20. Chang CK, Chuter TAM, Niemann CU, Shlipak MG, Cohen MJ, Reilly LM, et al. Systemic Inflammation, Coagulopathy, and Acute Renal Insufficiency Following Endovascular Thoracoabdominal Aortic Aneurysm Repair. J Vasc Surg [Internet]. 2009 [cited 2018 Nov 20];49(5):1140–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3276362/pdf/nihms-115141.pdf

21. De Souza LR, Oderich GS, Farber MA, Haulon S, Banga P V, Pereira AH, et al. Editor's Choice - Comparison of Renal Outcomes in Patients Treated by Zenith® Fenestrated and Zenith® Abdominal Aortic Aneurysm Stent grafts in US Prospective Pivotal Trials. Eur J Vasc Endovasc Surg [Internet]. 2017 [cited 2018 Nov 20];53:648–55. Available from: http://dx.doi.org/10.1016/j.ejvs.2017.02.005

22. Awad H, Ramadan ME, Sayed HF El, Tolpin DA. Spinal Cord Injury after Thoracic Endovascular Aortic Aneurysm Repair HHS Public Access. Can J Anaesth [Internet]. 2017 [cited 2018 Nov 20];64(12):1218–35. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5954412/pdf/nihms965061.pdf

23. Leurs LJ, Bell R, Degrieck Y, Thomas S, Hobo R, Lundbom J. Endovascular treatment of thoracic aortic diseases: Combined experience from the EUROSTAR and United

Kingdom Thoracic Endograft registries. 2004 [cited 2018 Nov 20]; Available from: https://www.jvascsurg.org/article/S0741-5214(04)00925-5/pdf

24. LeMaire SA, Price MD, Green SY, Zarda S, Coselli JS. Results of open thoracoabdominal aortic aneurysm repair. Ann Cardiothorac Surg [Internet]. 2012 Sep [cited 2019 Mar 5];1(3):286–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23977510

25. Coselli JS, LeMaire SA, Conklin LD, Köksoy C, Schmittling ZC. Morbidity and mortality after extent II thoracoabdominal aortic aneurysm repair. Ann Thorac Surg [Internet]. 2002 Apr [cited 2019 Mar 5];73(4):1107-15; discussion 1115-6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11996250

26. Sidloff DA, Stather PW, Choke E, Bown MJ, Sayers RD. Type II endoleak after endovascular aneurysm repair. Br J Surg [Internet]. 2013 Sep [cited 2018 Nov 21];100(10):1262–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23939840

## FIGURE LEGENDS

**Figure 1. Female patients undergoing complex endovascular aortic repair have a different anatomic distribution of aneurysm than their male counterparts.**
Preoperative anatomic distribution of aneurysm extent in women (A), by modified Crawford criteria, with pararenal aneurysms denoted as category 6, and in (B) all male patients undergoing FEVAR/BEVAR. Female patients can be (C) matched to a male cohort by aneurysm extent and comorbidities.

**Figure 2. Postoperatively, women and matched male patients have dissimilar maximal aneurysm diameters, and a different distribution of endoleak type.**
Preoperatively, (A) women and men have the same maximal aneurysm diameter, but the mean diameter at latest follow-up differs postoperatively, as does the mean change in aneurysm diameter (Female mean= dashed line, Male mean = dotted line). (B) Endoleaks occurred more frequently at any time during follow-up in women and differed by type from those demonstrated in men.

**Figure 3. Survival post FEVAR/BEVAR in men and women is similar**
Early (A) Kaplan-Meier assessment of postoperative cumulative survival demonstrates a reduced early survival in women post FEVAR/BEVAR versus men, however thereafter, survival is not significantly different between groups. (B) Raw Survival data for female and matched male patients post FEVAR/BEVAR demonstrates low patient follow-up at 5 years, however (C) mean confirmed days alive in patients who undergo follow-up is the same in both groups at 1114 days (3.05 years) for women, and 855 days (2.3 years) for men.

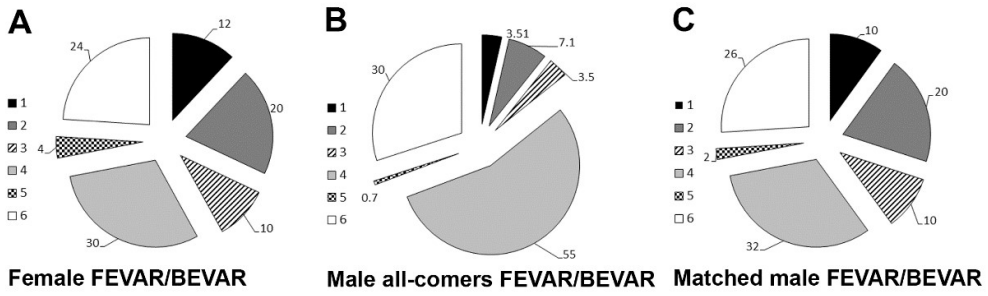
## TABLE LEGENDS

**Table 1. Female Patients undergoing FEVAR or BEVAR are demographically dissimilar from male patients.**

Female patients undergoing FEVAR or BEVAR differ significantly from all male patients undergoing FEVAR/BEVAR, but can be matched according to comorbidities and aneurysm extent.

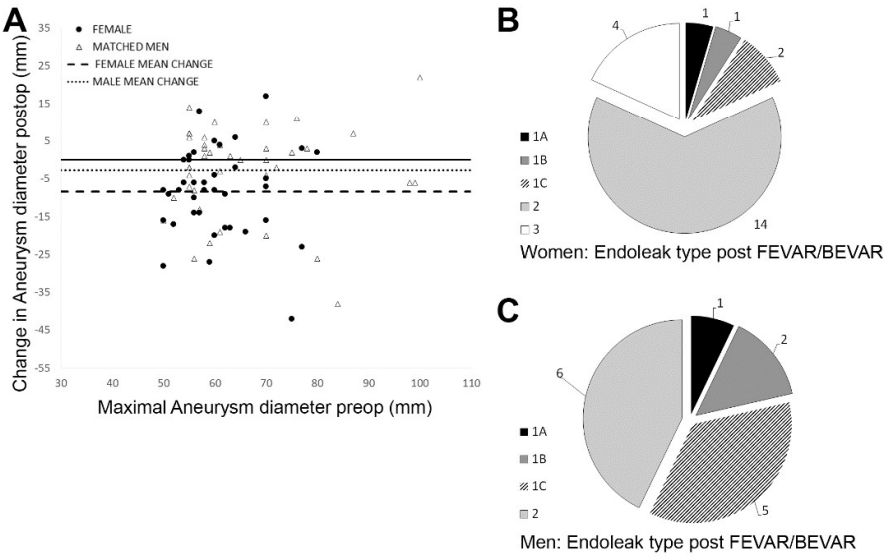
**Table 2. Perioperative complication rates are infrequent and similar between women and matched men undergoing FEVAR/BEVAR.**

**Table 3. Perioperative complications in deceased male and female BEVAR/FEVAR patients frequently involve proximal/complex repairs**


A
12
24
20
4
10
30
1
2
3
4
5
6
Female FEVAR/BEVAR
B
3.51
7.1
3.5
30
0.7
55
1
2
3
4
5
6
Male all-comers FEVAR/BEVAR
C
10
26
20
2
10
32
1
2
3
4
5
6
Matched male FEVAR/BEVAR

1

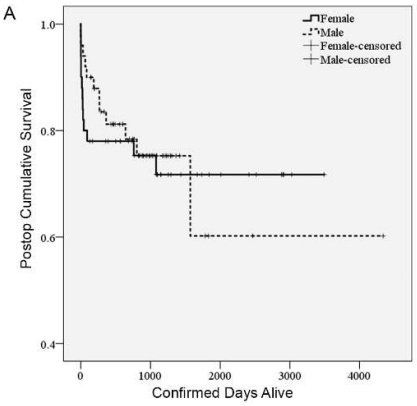
2


A
FEMALE
MATCHED MEN
FEMALE MEAN CHANGE
MALE MEAN CHANGE
Change in Aneurysm diameter postop (mm)
35
25
15
5
-5
-15
-25
-35
-45
-55
30
40
50
60
70
80
90
100
110
Maximal Aneurysm diameter preop (mm)
B
4
1
1
2
14
1A
1B
1C
2
3
Women: Endoleak type post FEVAR/BEVAR
C
1
2
6
5
1A
1B
1C
2
Men: Endoleak type post FEVAR/BEVAR

1

2

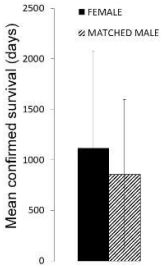
A




B

| | 30d | 1 year | 3 years | 5 years |
|---|---|---|---|---|
| Female | 42(50) | 37(48) | 24(34) | 14(23) |
| Male | 47(50) | 35(44) | 17(28) | 3(15) |
| Total n | 100 | 92 | 62 | 38 |

C




1

2

| | FEMALE PATIENTS | MATCHED MALE COHORT | MALE ALL-COMERS |
|---|---|---|---|
| **Mean Age (std dev)** | 71.9 (9.7) | 72.3 (8.8) | 72 (8.6) |
| **Smoking Status (%)** | | | |
| **Never** | 26 | 16 | 13.6** |
| **Current** | 30 | 30 | 23.6** |
| **Former** | 42 | 54 | 62.9** |
| **Diabetes Mellitus (%)** | 4 | 8 | 20.1** |
| **Coronary Artery Disease (%)** | 28 | 34 | 50** |
| **COPD (%)** | 30 | 32 | 27.1 |
| **Chronic Renal Insufficiency (%)** | 16 | 40* | 43.6** |

**Table I**

| | | Female | Male | Significance |
|---|---|---|---|---|
| **Renal Function** | | | | |
| | Mean % Change eGFR | 0.94 (0.3) | 0.98 (0.6) | - |
| | Renal outcomes by RIFLE score | (n=47) | (n=48) | |
| | 0 | 33 | 35 | - |
| | 1 Risk | 9 | 9 | - |
| | 2 Injury | 4 | 2 | - |
| | 3 Failure | 0 | 1 | - |
| | 4 Loss | 0 | 0 | - |
| | 5 ESRD | 1 | 1 | - |
| **Spinal Cord Injury** | | (n=50) | (n=50) | |
| | Total incidence | 3 | 6 | - |
| | Immediate (<24 hours) | 1 | 2 | - |
| | Delayed (>24 hours) | 2 | 4 | - |
| **30 day Mortality** | | | | |
| | Death within 30 days | 8 (16%) | 3 (6%) | <0.05 |
| | Death attributable to intervention | 7 | 3 | - |
| | Contributors to perioperative death | | | |
| | Mesenteric Ischemia | 1 | 1 | - |
| | Cerebrovascular Accident | 3 | 0 | - |
| | Cardiac (Arrhythmia/MI/Arrest) | 2 | 1 | - |
| | Sepsis | 2 | 2 | - |
| | Multiorgan Failure | 2 | 1 | - |

**Table II**

| Female Perioperative deaths | | | | | | |
|---|---|---|---|---|---|---|
| **Time of death (days postop)** | **Cause of Death** | **Associated perioperative complications** | **Crawford Extent** | **TEVAR** | **BEVAR or FEVAR** | **Related to TAAA repair** |
| **1** | Cerebrovascular Accident | Retrograde Type A Dissection, cardiac failure | 1 | Y | BEVAR | Y |
| **1** | Multiorgan Failure | Iliac Rupture, Cerebrovascular Accident | 6 | N | FEVAR | Y |
| **3** | Cardiac Failure | - | 2 | Y | BEVAR | Y |
| **3** | Spinal Cord Injury | Acute Renal Failure | 3 | Y | BEVAR | Y |
| **16** | Cerebrovascular Accident | Intracerebral Haemorrhage | 2 | Y | BEVAR | Y |
| **24** | Multiorgan Failure | Sepsis, Mesenteric Ischemia | 2 | Y | BEVAR | Y |
| **27** | Sepsis (Pneumonia) | Spinal Cord Injury, Acute Renal Failure | 1 | Y | BEVAR | Y |
| **30** | Cardiac Failure | - | 2 | Y | BEVAR | N |
| **Male Perioperative Deaths** | | | | | | |
| **0** | Multiorgan Failure | Sepsis, Ischemic Leg | 3 | Y | BEVAR | Y |
| **1** | Embolization | Spinal Ischemia, Mesenteric Ischemia, Sepsis | 3 | N | BEVAR | Y |
| **30** | PEA arrest | Spinal ischemia, Acute Renal Failure | 2 | Y | BEVAR | Y |

**Table III**