Female sex is associated with comparable 5-year outcomes after contemporary endovascular aneurysm repair despite more challenging anatomy

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ABSTRACT

Background: Women with abdominal aortic aneurysms less often meet anatomic criteria for endovascular repair and experience worse perioperative and long-term survival.

Methods: We compared long-term survival, aneurysm-related mortality, and rates of endoleaks and reinterventions between male and female patients in the Endurant Stent Graft Natural Selection Global Postmarket Registry (ENGAGE) using 2:1 propensity score matching.

Results: There were 1130 male patients and 133 female patients, yielding 399 patients after matching (266 male patients, 133 female patients). Female patients were older, with smaller aneurysms, smaller iliac arteries, and shorter, more angulated necks, and they were more often treated outside the device instructions for use (all $P < .001$). Through 5 years, female patients experienced overall mortality comparable to that of well-matched male patients (34% vs 38%, respectively; hazard ratio, 0.89 [0.61-1.29]; $P = .54$) and lower aneurysm-related mortality (0% vs 3%; $P = .047$). Female patients experienced higher rates of any postoperative type IA endoleak through 5 years (10% vs 1%; $P < .001$) but comparable rates of secondary endovascular procedures (14% vs 16%; $P = .40$). Female sex was independently associated with significantly higher risk of long-term type IA endoleaks (hazard ratio, 4.8 [1.2-20.8]; $P = .04$), even after accounting for anatomic factors. No female patient experienced aneurysm rupture during follow-up, and only one female patient underwent conversion to open repair.

Conclusions: Despite more challenging anatomy, female patients in the ENGAGE registry had long-term outcomes comparable to those of male patients. However, female patients experienced higher rates of type IA endoleaks. Although standard endovascular aneurysm repair remains a viable solution for most women, whether high-risk patients may be better served with open surgery, custom-made devices, EndoAnchors (Aptus Endosystems, Sunnyvale, Calif), or chimneys is worthy of further study. (J Vasc Surg 2020;71:1179-89.)

Keywords: Abdominal aortic aneurysm; Sex; Endovascular aneurysm repair; Gender; EVAR

Abdominal aortic aneurysms (AAAs) disproportionately affect men at a 4:1 ratio, but women with AAAs suffer worse outcomes.[1-5] Aneurysms in women rupture four times as frequently and at smaller diameters. Consequently, many argue that women should undergo repair earlier and suggest updating the current sex-neutral 5.5-cm diameter threshold for repair.[2,4,6-8] Indeed, the most recent guidelines from the Society for Vascular Surgery recommend that "young, healthy patients, particularly women, with an AAA between 5.0 and 5.4 cm may benefit from early repair."[8] Women were underrepresented in the early trials that established the current threshold, and recent data suggest that aortic size index, which is adjusted for body surface area, may represent a better metric (although a definitive threshold is yet to be established).[2,4,7,9-13] Replacing the current one-size-fits-all approach with more patient-centered, sex-specific thresholds would dramatically increase the number of

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women eligible for repair. However, before aneurysm repair can be expanded to this vulnerable population, the gap in outcomes after repair needs to be bridged.

Multiple trials and a recent meta-analysis demonstrated higher perioperative and long-term morbidity and mortality for women compared with men after both open and endovascular repair.[4,6,14-17] Women experience higher mortality than men after endovascular repair, but this difference is even more pronounced after open repair. Despite operative mortality after open repair of almost twice that of men, women are less likely to undergo endovascular aneurysm repair (EVAR).[16] Women less often meet device instructions for use (IFU) and are more likely to have unsuitable anatomy, largely because of shorter, more angulated necks and inadequate access vessel size. As a consequence of their smaller vessels, women undergo adjunctive access procedures more frequently than men and experience higher rates of access complications.[18,19] Until the sex gap in outcomes after AAA repair narrows by expanding the eligibility for EVAR or improving outcomes, it will remain difficult to advocate expanding the use of AAA repair in women.

Early pivotal trial results in addition to long-term, real-world data from the Endurant Stent Graft Natural Selection Global Postmarket Registry (ENGAGE) demonstrated low morbidity and mortality, and several series documented success in treating patients with challenging anatomy even outside the IFU.[20-23] In 2013, Dubois et al[24] demonstrated equivalent perioperative results between men and women in the ENGAGE registry. We therefore studied whether this low-profile, widely applicable stent graft would narrow the sex gap and whether the outcomes remained durable over time in the ENGAGE registry.

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective analysis of prospectively collected data from the Endurant Stent Graft Natural Selection Global Postmarket Registry (ENGAGE)
- **Key Findings:** After endovascular aneurysm repair, 133 female patients experienced comparable 5-year mortality to that of 166 matched male patients and lower aneurysm-related mortality, with no ruptures. Female patients experienced higher rates of type IA endoleaks (10 vs 1), even after accounting for anatomic factors, but similar reinterventions.
- **Take Home Message:** Female patients experience long-term outcomes after endovascular aneurysm repair similar to those of men, although alternative strategies may be needed for female patients with adverse neck anatomy.

METHODS

Study design and participants. Full methodologic details of the ENGAGE registry and rationale of data collection have been published previously, as have technical specifications of the Endurant Stent Graft System (Medtronic, Santa Rosa, Calif).[20-23] Briefly, ENGAGE is a prospective, real-world registry of standard infrarenal EVARs, with minimal inclusion and exclusion criteria compared with the extensive requirements of investigational device exemption trials. Informed consent was obtained from all patients at the time of enrollment for authorization of data release. To date, the registry has enrolled a total of 1263 patients at 79 centers over a wide, multinational geographic area in 30 countries spanning six continents. All participating candidate ENGAGE registry sites were required to seek and to obtain Institutional Review Board approval of the protocol if applicable, and the protocol is registered on clinicaltrials.gov (NCT01379222).

Outcomes. Our primary outcome was 5-year survival. Secondary outcomes included procedural results (technical success, length of stay, endoleaks) and 5-year rates of type I and type III endoleaks and secondary procedures. All deaths were reviewed and adjudicated by the Clinical Events Committee, consisting of three independent vascular surgeons or radiologists. Follow-up occurred at 1 month, at 12 months, and then yearly afterward. Computed tomography angiography (CTA) was recommended by trial protocol at 1 month and 1 year, and subsequent follow-up (CTA vs duplex ultrasound) studies were at the discretion of the institutions. The imaging modality most frequently used at the 1-year follow-up visit was CTA (48% of follow-up imaging); but over time, ultrasound use became more frequent, and at the 5-year follow-up only 31% were CTA compared with 52% ultrasound. All CTA images were analyzed using three-dimensional reconstructions.

Statistical analysis. We compared baseline and anatomic characteristics using standard statistical methods, including Student *t*-test or Wilcoxon rank sum test for continuous variables and Cochran-Mantel-Haenszel test for categorical variables.

In our primary analysis, we used propensity score matching to account for differences in baseline characteristics. We generously introduced covariates into our model, including age, hypertension, hyperlipidemia, diabetes, cancer, alcoholism, cardiac disease (coronary artery disease, congestive heart failure, prior myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention), pulmonary disease, renal disease, cerebrovascular disease, peripheral vascular disease, family history of AAA, American Society of Anesthesiologists class, and procedure year. To increase the generalizability of our analysis, anatomic characteristics were not included in our propensity score models. This allowed the previously described anatomic differences between the sexes to persist. We wanted to evaluate whether outcomes

differed between men and women *despite* their inherent differences or whether the advances in endograft technology were able to surmount these differences. Essentially we sought to determine whether modern endografts had narrowed the outcomes gap for all patients or just for patients with more favorable anatomy. Therefore, for our initial analysis, we allowed anatomic differences to persist to better reflect the population at large and performed a secondary analysis (described later) in which we directly examined the effect of patients' anatomy. Each female patient was matched with two male patients by propensity scores using the nearest neighbor method. After matching, the standardized differences were all <10% (the usual threshold) except for pulmonary disease and procedure year of 2011 (11% and 12%, respectively), indicating minimal imbalance. We compared survival estimates of all-cause mortality, aneurysm-related mortality, type I and type III endoleaks, and reinterventions in the matched cohort using the log-rank test, and the hazard ratio (HR) was computed using Cox regression. Cox regression models were tested for violations of the proportional hazards assumption using the proportionality test. There was <15% missingness for all covariates in the propensity score model. Missing data were imputed using the sex-specific median for propensity modeling. Cause of death was adjudicated by the Clinical Events Committee, which consists of three independent vascular surgeons or radiologists.

As a secondary analysis, we sought to determine whether disparate outcomes between the sexes were explained by the inherent anatomic differences or whether female sex would still be independently associated with type IA endoleaks after adjustment for age and anatomy. To do this, we used Cox regression modeling with long-term type IA endoleaks as the outcome. This model adjusted for sex, age, and anatomic factors including aneurysm diameter, proximal neck length, proximal neck diameter, distal neck diameter, iliac diameter, and infrarenal neck angle. Two separate models were made; the first included anatomic data as continuous variables, and the second included the anatomic factors as binary variables based on whether they violated the manufacturer's IFU.

Data management and statistical analysis. The data from the patients in the ENGAGE registry are recorded on a web-based electronic case report (Veracity Clinical Asset Management; Merge Healthcare, Chicago, Ill). Data are entered under the supervision of each site's principal investigator and are managed by the Medtronic Biostatistics and Data Management Department (Santa Rosa, Calif). It reviews 100% of data to detect missing or inconsistent data to generate queries to the investigators for resolution. In addition to this, Medtronic Bakken Research Centre BV (Maastricht, The Netherlands) randomly monitors >40% of patients' source documentation against the data entered. It also performed a verification of all 1263 patient informed consents and essential study documents at each site.

Role of the funding source. The statistical analyses were performed by an independent third party (Baim Institute for Clinical Research, formerly Harvard Clinical Research Institute, Boston, Mass) that had access to all of the data, at the guidance of the authors. The authors did not receive funding from the industry source, wrote the manuscript, and had final responsibility for the decision to submit for publication.

RESULTS

Baseline characteristics and anatomic details. We identified 1263 patients, 1130 male (89%) and 133 female (11%). After matching, there were 133 female patients and 266 male patients. Baseline characteristics before and after matching are presented in Tables I and II, and anatomic characteristics are presented in Table III. Before matching, female patients were older, with lower rates of documented cardiac disease, but were more American Society of Anesthesiologists class 4 patients and more often had a family history of aortic aneurysms (all $P < .05$). Female patients had smaller aneurysms (58 ± 10 mm vs 61 ± 12 mm; $P = .01$); smaller iliac arteries (13 ± 3 mm vs 14 ± 4 mm; $P < .001$); and shorter, smaller, more angulated necks (neck length <10 mm, 4.5% vs 1.9% [$P = .049$]; infrarenal neck angle >60 degrees, 19.7% vs 9.0% [$P < .001$]). Correspondingly, female patients were treated outside the IFU twice as often as men (32% vs 16%; $P < .001$).

Perioperative events. Compared with male patients, female patients experienced higher rates of type I (12.9% vs 6.6%; $P < .01$) and type II endoleaks (20.5% vs 13.7%; $P = .04$) seen on any intraoperative angiogram, but there was no difference in the rates of any endoleaks at the end of the case (type I, 1.5% vs 1.1% [$P = .64$]; type II, 15.9% vs 12.1% [$P = .20$]; Table IV). The Endurant II is a semiporous graft and can have type IV endoleaks that are difficult to differentiate from other leaks until the 1-month scan. Indeed, many of the endoleaks initially thought to be type I may in fact have been type IV as the majority were no longer visible by case end, and only 14 patients (4 women, 10 men) had type I endoleaks at 1-month follow-up (3% and 1%, respectively). Male and female patients experienced comparable procedure times, adjunctive procedures, technical success rates, estimated blood loss, contrast material volume, fluoroscopy time, and postoperative intensive care unit stays. However, female patients underwent hypogastric coiling less frequently (1.5% vs 5.6%; $P = .04$) and experienced longer lengths of post-procedure stay (6 ± 6 days vs 5 ± 5 days; $P < .01$).

Five-year mortality, rupture, and conversion. Matched female and male patients experienced comparable 5-year mortality rates of 34% and 38%, respectively

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Table I. Baseline characteristics of the study cohort

Baseline characteristics	Male patients (n = 1130)	Female patients (n = 133)	*P* value
Age, years, mean ± SD	72.8 ± 8.1	75.7 ± 7.1	<.001
Alcoholism	3.6 (39/1098)	0.8 (1/131)	.089
Cardiac disease	54.7 (618/1129)	45.1 (60/133)	.035
Myocardial infarction	27.6 (297/1077)	18.2 (24/132)	.021
Arrhythmia	16.2 (179/1103)	15.3 (20/131)	.777
Angina	16.1 (177/1102)	12.8 (17/133)	.326
Congestive heart failure	5.6 (62/1099)	6.9 (9/131)	.569
Coronary artery disease	36.4 (396/1088)	21.4 (28/131)	<.001
CABG or PCI	28.9 (322/1113)	12.9 (17/132)	<.001
Valvular heart disease	6.2 (68/1103)	6.0 (8/133)	.946
Pulmonary disease	25.4 (282/1111)	26.0 (34/131)	.887
Renal insufficiency	15.5 (173/1119)	16.5 (22/133)	.745
Carotid artery disease	10.8 (102/943)	11.6 (13/112)	.800
Cerebrovascular/neurologic disease	12.8 (144/1129)	12.8 (17/133)	.993
Transient ischemic attack	4.7 (52/1117)	6.8 (9/132)	.276
Cerebrovascular accident	5.6 (63/1123)	3.0 (4/132)	.213
Paraplegia	0.2 (2/1122)	0.8 (1/133)	.200
Paraparesis	0.9 (10/1123)	0.0 (0/133)	.275
Vascular disease	31.2 (352/1129)	29.3 (39/133)	.662
Previous AAA	1.8 (20/1123)	0.0 (0/133)	.121
Any thoracic aneurysm	1.8 (19/1081)	3.1 (4/127)	.278
Peripheral vascular disease	19.1 (213/1113)	12.9 (17/132)	.080
Thromboembolic event	3.3 (36/1106)	3.8 (5/131)	.734
Bleeding	2.0 (23/1129)	0.0 (0/133)	.097
Liver disease	2.4 (27/1129)	1.5 (2/133)	.518
Gastrointestinal complications	19.0 (214/1129)	27.1 (36/133)	.026
Family history of aneurysms	6.2 (70/1129)	12.0 (16/133)	.012
Additional medical history			
Cardiac disease	0.4 (5/1130)	0.0 (0/133)	.442
Cerebrovascular/neurologic disease	0.3 (3/1130)	0.0 (0/133)	.552
Vascular disease	0.4 (5/1130)	0.0 (0/133)	.442
Gastrointestinal complications	0.2 (2/1130)	0.8 (1/133)	.198
Other	17.8 (201/1130)	27.1 (36/133)	.010
ASA class			.045
1	6.4 (72/1129)	3.0 (4/133)	
2	41.6 (470/1129)	43.6 (58/133)	
3	42.1 (475/1129)	36.8 (49/133)	
SVS score			.007
0	0.1 (1/1084)	0.0 (0/131)	.728
1	14.3 (155/1084)	8.4 (11/131)	.063
2	51.3 (556/1084)	46.6 (61/131)	.307
3	34.3 (372/1084)	45.0 (59/131)	.015

AAA, Abdominal aortic aneurysm; *ASA*, American Society of Anesthesiologists; *CABG*, coronary artery bypass grafting; *PCI*, percutaneous coronary intervention; *SD*, standard deviation; *SVS*, Society for Vascular Surgery.
Categorical variables are presented as percentage (n/N).

Table II. Baseline characteristics of the matched cohort

Measure	Male patients (n = 266)	Female patients (n = 133)	*P* value
Age, years			.881
Mean ± SD (No.)	75.6 ± 8.0 (266)	75.7 ± 7.1 (133)	
Median (Q1-Q3)	76.0 (70.0-81.0)	77.0 (70.0-81.0)	
Range, minimum-maximum	48.0-93.0	57.0-89.0	
Alcoholism	0.4 (1/261)	0.8 (1/131)	.625
Cardiac disease	43.2 (115/266)	45.1 (60/133)	.721
Myocardial infarction	21.9 (56/256)	18.2 (24/132)	.396
Arrhythmia	14.4 (38/263)	15.3 (20/131)	.829
Angina	13.8 (36/261)	12.8 (17/133)	.782
Congestive heart failure	3.8 (10/261)	6.9 (9/131)	.193
Coronary artery disease	27.5 (72/262)	21.4 (28/131)	.193
CABG or PCI	22.5 (59/262)	12.9 (17/132)	.025
Valvular heart disease	3.8 (10/262)	6.0 (8/133)	.328
Pulmonary disease	21.1 (55/261)	26.0 (34/131)	.278
Renal insufficiency	16.3 (43/264)	16.5 (22/133)	.947
Carotid artery disease	10.4 (22/212)	11.6 (13/112)	.732
Cerebrovascular/neurologic disease	11.7 (31/266)	12.8 (17/133)	.744
Transient ischemic attack	4.9 (13/263)	6.8 (9/132)	.446
Cerebrovascular accident	4.9 (13/265)	3.0 (4/132)	.390
Paraplegia	0.0 (0/265)	0.8 (1/133)	—
Paraparesis	0.4 (1/265)	0.0 (0/133)	—
Vascular disease	28.6 (76/266)	29.3 (39/133)	.876
Previous AAA	0.0 (0/265)	0.0 (0/133)	—
Any thoracic aneurysm	1.2 (3/252)	3.1 (4/127)	.199
Peripheral vascular disease	15.2 (40/263)	12.9 (17/132)	.535
Thromboembolic event	3.4 (9/264)	3.8 (5/131)	.837
Bleeding	1.5 (4/266)	0.0 (0/133)	—
Liver disease	1.1 (3/266)	1.5 (2/133)	.751
Gastrointestinal complications	20.7 (55/266)	27.1 (36/133)	.154
Family history of aneurysms	12.0 (32/266)	12.0 (16/133)	1.000
Additional medical history			
Cardiac disease	0.0 (0/266)	0.0 (0/133)	—
Cerebrovascular/neurologic disease	0.4 (1/266)	0.0 (0/133)	—
Vascular disease	0.0 (0/266)	0.0 (0/133)	—
Gastrointestinal complications	0.0 (0/266)	0.8 (1/133)	—
Other	19.5 (52/266)	27.1 (36/133)	.090
ASA class			.962
1	3.8 (10/266)	3.0 (4/133)	
2	42.9 (114/266)	43.6 (58/133)	
3	35.7 (95/266)	36.8 (49/133)	
4	17.7 (47/266)	16.5 (22/133)	
SVS score			.574
0	0.0 (0/255)	0.0 (0/131)	
1	11.4 (29/255)	8.4 (11/131)	
2	45.1 (115/255)	46.6 (61/131)	
3	43.5 (111/255)	45.0 (59/131)	

AAA, Abdominal aortic aneurysm; *ASA*, American Society of Anesthesiologists; *CABG*, coronary artery bypass grafting; *PCI*, percutaneous coronary intervention; *SD*, standard deviation; *SVS*, Society for Vascular Surgery.
Categorical variables are presented as percentage (n/N).

Table III. Anatomic characteristics of the study cohort, including considerations for both United States and European Union instructions for use (*IFU*)

Characteristics	Male patients (n = 1130)	Female patients (n = 133)	*P* value
Maximum aneurysm diameter, mm	60.6 ± 11.8	57.9 ± 9.6	.012
Proximal neck diameter, mm	23.9 ± 3.5	21.8 ± 3.3	<.001
Distal neck diameter, mm	25.1 ± 4.0	22.9 ± 4.1	<.001
Aortic neck length, mm	27.3 ± 12.4	24.5 ± 11.9	.014
Proximal neck length <15 mm	11.5 (128/1117)	16.5 (22/133)	.088
Right iliac artery diameter, mm	14.3 ± 3.5	12.9 ± 3.5	<.001
Left iliac artery diameter, mm	13.9 ± 3.5	12.5 ± 2.9	<.001
Infrarenal neck angle, degrees	29.4 ± 23.3	38.1 ± 26.2	<.001
Implantation outside of IFU	16.1 (182/1130)	32.3 (43/133)	<.001
Proximal neck diameter outside of 19-32 mm	4.3 (48/1124)	17.3 (23/133)	<.001
Proximal neck length <10 mm	1.9 (21/1117)	4.5 (6/133)	.049
Proximal neck length ≥10 mm and <15 mm but infrarenal angle >60 degrees or suprarenal angle >45 degrees	1.9 (21/1117)	3.8 (5/133)	.151
Proximal neck length ≥15 mm but infrarenal angle >75 degrees or suprarenal angle >60 degrees	4.3 (48/1117)	8.3 (11/133)	.041
Distal iliac diameter <8 mm for patients without iliac aneurysm	1.3 (15/1130)	2.3 (3/133)	.393
Distal iliac diameter >25 mm for patients without iliac aneurysm	0.7 (8/1130)	0.0 (0/133)	.331

Categorical variables are presented as percentage (n/N). Continuous variables are presented as mean ± standard deviation.

(HR, 0.89 [0.61-1.29]; $P = .54$; Fig 1). Aneurysm-related mortality was low overall but actually lower in female patients (0% vs 3%; $P = .047$). No female patient experienced aneurysm rupture during follow-up, and only 1 of 133 female patients underwent conversion to open repair (0.7%). Of 1130 male patients, 13 experienced aneurysm rupture (1.2%) at a mean of 1038 days postoperatively (range, 316-1504 days), and 18 underwent open conversion (1.6%).

Five-year endoleaks and secondary procedures. In Kaplan-Meier analysis of the matched cohort, the 5-year rates of any endoleaks were not significantly different between female and male patients (35% vs 27%; $P = .10$). Female and male patients also were not significantly different in their rates of type I or type III endoleaks during 5-year follow-up (13% vs 8%, respectively; $P = .13$). However, female patients experienced significantly higher rates of any long-term type IA endoleaks (10% vs 1%; HR, 7.17 [1.97-26.06]; $P < .001$; Fig 2). Rates of long-term type III endoleaks were similar ($P = .41$). Despite the fact that female patients experienced higher rates of proximal endoleaks, 5-year rates of secondary endovascular procedures were similar between female and male patients (14% vs 16%; HR, 0.77 [0.42-1.42]; $P = .40$; Fig 3).

In univariate analysis, female sex was associated with significantly higher risk of type IA endoleak (HR, 7.2 [2.0-26.1]; $P < .01$). When age and anatomic characteristics were added to the model, female sex remained independently associated with an almost fivefold higher risk of long-term type IA endoleaks (HR, 4.8 [1.2-20.8]; $P = .035$). This risk was consistent regardless of whether anatomic variables were included as continuous or binary variables. Other factors independently associated with higher risk of type IA endoleak were a neck length <10 mm (HR, 18.4 [3.1-109]; $P = .001$) and a neck angle >60 degrees (HR, 6.2 [1.7-23.1]; $P < .01$). There was no interaction between female sex and neck length ($P = .1$) or female sex and neck angle ($P = .4$).

Although female sex was associated with higher rates of type IA endoleaks, this was significantly attenuated in female patients without short or angled necks. Male patients had a 5-year freedom from type IA endoleak rate of 98.7% compared with 94.2% for female patients without either a neck length <10 mm or a neck angle >60 degrees ($P = .06$). However, female patients with either of these factors (24% of the sample) had a 5-year freedom from type IA endoleak rate of 72.5% ($P < .01$ for comparison to other female patients as well as to male patients).

DISCUSSION

Before the introduction of modern, low-profile stent grafts, women less frequently underwent EVAR and experienced inferior short- and long-term outcomes. Our results suggest that the sex gap is narrowed in the patients in the ENGAGE registry, but significant room for improvement remains. Despite more challenging anatomy and a third of female patients undergoing EVAR outside the IFU, female patients experienced long-term survival, aneurysm-free survival, and rates of

Table IV. Perioperative results in the full cohort

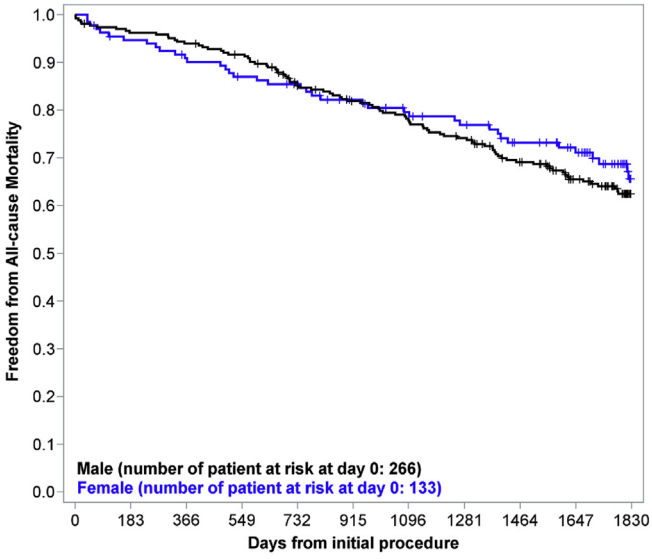
Measurement	Male patients (n = 1130)	Female patients (n = 133)	*P* value
Procedure time, minutes	99.7 ± 44.5	97.4 ± 48.9	.580
Technical success	99.2 (1121/1130)	97.7 (130/133)	.101
Type of anesthesia used			
General	62.4 (705/1129)	60.2 (80/133)	.606
Spinal	20.5 (231/1129)	27.1 (36/133)	.078
Epidural	8.7 (98/1129)	3.0 (4/133)	.023
Local	13.5 (152/1129)	11.3 (15/133)	.482
Estimated blood loss during procedure, mL	208.3 ± 224.6	208.7 ± 177.3	.985
Volume of contrast material, mL	132.7 ± 69.9	122.4 ± 68.5	.119
Total fluoroscopy time, minutes	20.6 ± 12.5	19.4 ± 11.1	.276
Associated procedures performed during implant procedure			
Coil embolization of hypogastric artery	5.6 (63/1130)	1.5 (2/133)	.044
Right hypogastric artery	2.8 (32/1130)	1.5 (2/133)	
Left hypogastric artery	2.7 (31/1130)	0.0 (0/133)	
Both hypogastric arteries	0.0 (0/1130)	0.0 (0/133)	
Coil embolization of IMA	0.6 (7/1130)	0.0 (0/133)	.363
Other	8.8 (99/1130)	9.0 (12/133)	.920
None	85.9 (971/1130)	90.2 (120/133)	.172
Hospital stay, days	6.4 ± 6.1	7.9 ± 9.8	.017
Procedure stay, days	4.72 ± 4.94	5.74 ± 6.05	.005
Duration of ICU stay, hours	10.4 ± 44.6	7.7 ± 18.2	.312
Endoleak at case end	15.5 (174/1125)	21.2 (28/132)	.089
Type I	1.1 (12/1125)	1.5 (2/132)	.642
Type II	12.1 (136/1125)	15.9 (21/132)	.204
Type III	0.3 (3/1125)	0.8 (1/132)	.344
Type IV	1.9 (21/1125)	0.8 (1/132)	.360
Undetermined	0.5 (6/1125)	2.3 (3/132)	.025
Endoleak at any point of case	23.6 (265/1125)	39.4 (52/132)	.003
Type I	6.6 (74/1125)	12.9 (17/132)	.008
Type II	13.7 (154/1125)	20.5 (27/132)	.036
Type III	1.2 (14/1125)	2.3 (3/132)	.333
Type IV	2.0 (22/1125)	0.8 (1/132)	.331
Undetermined	0.6 (7/1125)	3.0 (4/132)	.005

ICU, Intensive care unit; *IMA*, inferior mesenteric artery.
Categorical variables are presented as percentage (n/N). Continuous variables are presented as mean ± standard deviation.

reintervention equivalent to those of their male counterparts. However, female patients had significantly higher rates of proximal endoleaks, even after accounting for the anatomic differences between the sexes.

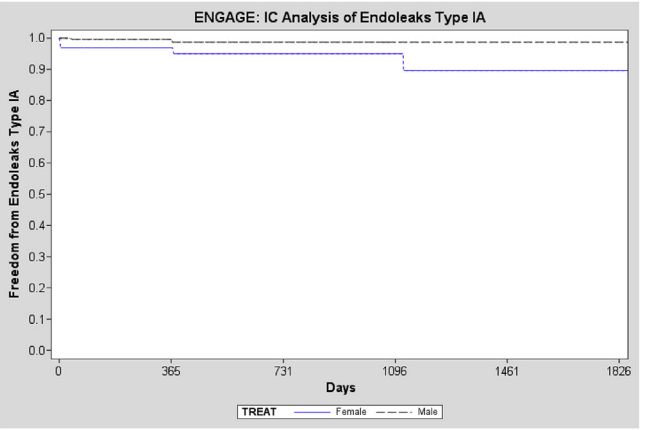
Modern endografts, with lower profile, widely applicable IFU, and conformability, are better suited than their predecessors for the complex anatomy often seen in women. The Endurant stent graft in particular allows wider necks, shorter neck length, smaller access vessels, and greater angulation than other commonly implanted endografts. Previously, Dubois et al[24] published the perioperative results of the ENGAGE registry, demonstrating excellent and equivalent results between male and female patients. We confirm that these results remain durable over time. Despite the challenging anatomy of the female patients in our study, technical success rates were similar to those of other modern endografts and reintervention rates were low, especially at the proximal neck.[25,26] Multiple studies including this one demonstrate that women typically have smaller, more tortuous iliac arteries, emphasizing the need for low-profile, conformable devices to treat aneurysms in this population.[3-5,19]

With significantly more hostile neck anatomy, it is not surprising that female patients experienced significantly higher rates of type IA endoleaks. The anatomy of the infrarenal neck drove much of the increased risk of



All-cause Mortality	0-30 days	31-365 days	366-731 days	732-1096 days	1097-1461 days	1462-1826 days
Female						
# At Risk	133	133	118	105	90	76
SE	0.00%	2.51%	3.08%	3.58%	4.03%	4.69%
Male						
# At Risk	266	259	248	213	191	163
SE	0.83%	1.47%	2.20%	2.60%	2.92%	3.14%

Fig 1. All-cause mortality in the propensity score-matched cohort. $P = .54$ for comparison. *SE,* Standard error.



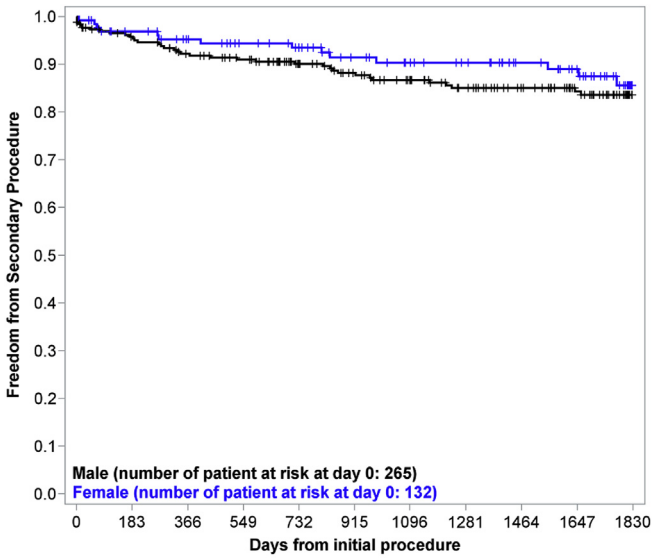
	0-30 days	31-365 days	366-731 days	732-1096 days	1097-1461 days	1462-1826 days
Female						
No. at Risk[1]	132	123	103	91	74	55
Standard Error	1.51%	1.51%	1.91%	1.91%	2.68%	2.68%
Male						
No. at Risk[1]	265	249	225	189	162	136
Standard Error	0%	0.40%	0.70%	0.70%	0.70%	0.70%

Fig 2. Five-year rates of type IA endoleaks in the propensity score-matched cohort. $P = .0005$ for comparison. *ENGAGE,* Endurant Stent Graft Natural Selection Global Postmarket Registry; *IC,* investigational cohort.

proximal endoleaks, with hostile anatomy more common in female patients, but female sex remained independently associated with type IA endoleaks, even after accounting for these anatomic factors. This is consistent with previous studies, which consistently demonstrate inferior outcomes in female patients, especially at the proximal neck.[4,16,27,28] Reassuringly, despite a higher rate of proximal endoleak, no female patient experienced aneurysm rupture within 5 years, and only one patient underwent open conversion. In comparison, the 5 year rupture rate after EVAR in the overall Medicare population was 3.0%.[29] As the purpose of elective aneurysm repair is to prevent aneurysm rupture, the results of the Endurant II stent graft in female patients are excellent. However, the risk of type IA endoleaks and the divergence of the Kaplan-Meier curves over time carry important implications for patients with difficult necks (both men and women).

These data emphasize the challenge that patients with hostile neck anatomy, especially female patients, present. Female patients with short or angled necks experienced 5-year type IA endoleak rates of 25%, which calls into question the safety of standard EVAR in this population. Patients with difficult neck anatomy, especially female patients, deserve careful consideration of their suitability for advanced endovascular options as well as open surgical repair. Fortunately, fenestrated and branched grafts as well as chimney and snorkel techniques present a compelling solution to the problem of hostile neck anatomy by extending the proximal seal zone, surmounting the problems presented by short necks. In highly angulated necks, where even fenestrated devices may be inadequate, adjuncts such as EndoAnchors (Aptus Endosystems, Sunnyvale, Calif) may also help secure the proximal neck. Female patients in particular would benefit from a low-profile, conformable, fenestrated device, given their small access vessels. This should be a focus of device development going forward as the success of low-profile infrarenal devices demonstrates the critical need for similar devices in the juxtarenal space. Fortunately, three-quarters of the women in this study had suitable neck lengths and neck angles, suggesting that standard EVAR remains a viable solution for many patients.

National screening programs for AAA exist in the United States, United Kingdom, Canada, France, and Sweden, but none of these countries recommend screening of women except in the presence of a family history of AAA.[30-33] However, because aneurysms in women behave more aggressively, with higher risk of rupture, modern studies using Markov modeling demonstrated that screening of women would actually be cost-effective despite lower prevalence.[34,35] Women smokers in particular stand to benefit from screening, as the prevalence of AAA in this population probably exceeds that of nonsmoking men.[36] As such, the Society for Vascular Surgery recommends screening of women aged 65 years or older who have smoked or have a family history of AAA.[8,37] The European Society for Vascular Surgery, in contrast, recommends screening only of women with a family history of AAA and states that



Secondary Endovascular Procedure	0-30 days	31-365 days	366-731 days	732-1096 days	1097-1461 days	1462-1826 days
Female						
# At Risk	132	131	112	97	81	67
SE	0.75%	1.89%	2.23%	2.79%	2.79%	3.79%
Male						
# At Risk	265	253	229	192	165	139
SE	0.92%	1.67%	1.88%	2.21%	2.36%	2.53%

Fig 3. Secondary procedures in the propensity score-matched cohort. $P = .40$ for comparison. *SE,* Standard error.

population screening of older, female smokers "may require further investigation."[38]

In addition to concerns about prevalence, the two factors limiting the expansion of screening efforts to women and increasing the number of women undergoing elective aneurysm repair were anatomic unsuitability for EVAR and inferior outcomes with both EVAR and open repair.[39] Previous reports from the Vascular Quality Initiative and Medicare demonstrated higher perioperative and long-term mortality in female patients.[3,4,40,41] In contrast, the results of the ENGAGE registry show that women experienced 66% overall survival at 5 years, no perioperative deaths, and rates of reintervention comparable to those of their male counterparts. Our study adds to the growing body of literature supporting the contention that with modern endografts and the widespread availability of EVAR, screening paradigms for women should be reconsidered.

This analysis must be interpreted in the context of its design. Whereas the sample size of 133 female patients in this analysis is high, female patients represented only 11% of the ENGAGE cohort, which is higher than in other device registries but lower than the 17.6% in the Medicare population.[25,26,29] The substantial proportion of female patients who underwent EVAR despite being outside the device IFU suggests the population is not reflective of a highly selected clinical trial cohort and reflects a real-world experience with the Endurant stent graft. Whereas reinterventions were well captured, the type and indication of the reinterventions merit further study, given the higher risk of proximal endoleaks in female patients. The registry does not capture the indication for reintervention or what the intervention was. As female patients had significantly higher rates of type IA endoleaks but no difference in reintervention rates, this is an important limitation. Further study is needed to determine why female patients have similar reintervention rates despite higher endoleak rates. As not all interventions are equivalent, a better understanding of the nature of the interventions in female patients, especially those with endoleaks, is necessary. In addition, this analysis does not take into account those women whose anatomy precluded them from repair. We also lack long-term data on sac morphology in patients with endoleaks, so we do not know how differences in sac behavior may have contributed to the reintervention rates.

CONCLUSIONS

Despite more challenging anatomy, female patients treated with the Endurant stent graft demonstrated comparable perioperative and long-term outcomes to those of male patients, with similar survival, low rates of conversion and reintervention, and no aneurysm ruptures in follow-up. However, female patients experienced higher rates of type IA endoleaks, even after accounting for anatomic differences. Overall, this analysis of the ENGAGE registry shows that the sex gap has narrowed with the use of modern low-profile conformable devices but highlights the potential for further improvement through the application of EndoAnchor or fenestrated technologies in patients with adverse neck anatomy.

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AUTHOR CONTRIBUTIONS

Conception and design: TO, MS
Analysis and interpretation: TO, MS
Data collection: TO, HV, GP, CP, JT, FV, PM, TF, MS
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Critical revision of the article: TO, HV, GP, CP, JT, FV, PM, TF, MS
Final approval of the article: TO, HV, GP, CP, JT, FV, PM, TF, MS
Statistical analysis: TO, MS
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