

Influence of proximal aortic neck diameter on durability of aneurysm sealing and overall survival in patients undergoing endovascular aneurysm repair. Real-world data from The Gore Global Registry for Endovascular Aortic Treatment (GREAT)

Dominic. P.J. Howard^{1,2} D Phil, Conor .D. Marron¹ MD, Ediri. Sideso² MD, Phillip. Puckridge¹ MD, Eric. L.G. Verhoeven³ MD, PhD, James.I. Spark¹ MD, on behalf of the Global Registry for Endovascular Aortic Treatment (GREAT) Investigators

¹ Dept. of Vascular and Endovascular Surgery, Flinders Medical Centre, Adelaide, Australia

² Dept. of Vascular Surgery, Oxford University Hospitals NHS Trust, Oxford, UK

³ Dept. of Vascular and Endovascular Surgery, Paracelsus Medical University, Nuremberg, Germany

Word Count: 5491

Correspondence:

Professor Ian Spark
Department of Vascular and Endovascular Surgery
Flinders Medical Centre
Adelaide
Australia
ian.spark@sa.gov.au

What does this study/review add to the existing literature and how will it influence future clinical practice?

Aortic neck diameter is an anatomical feature that is potentially linked to proximal seal failure and adverse outcome following standard EVAR. We have shown that large aortic diameter is independently associated with delayed type IA endoleak in patients undergoing standard EVAR and is also associated with lower 5-year survival. With increasing clinical focus on long-term stent-graft seal durability, aortic neck diameter is a parameter that should be considered as more intensive long-term surveillance maybe required.

Abstract

Objective/Background: Aortic neck diameter is an independent anatomical feature that is poorly understood, yet potentially linked to proximal seal failure and adverse outcome following standard EVAR. The aim of this study was to assess whether large proximal aortic neck (LAN) diameter is associated with adverse outcome using prospectively collected individual patient data from The Global Registry for Endovascular Aortic Treatment (GREAT).

Methods: 3166 consecutive patients, from 78 global centres, receiving Gore Excluder stent-grafts for infra-renal abdominal aortic aneurysm repair between 2011 and 2017 were included. Patient demographics, biometrics, operative details, and clinical outcome were analyzed. Patients were divided into two groups; normal baseline proximal aortic neck (NAN) diameter ($<25\text{mm}$ on CT-aortography), and LAN ($\geq 25\text{mm}$). Clinical follow-up (including imaging) was available for 76.5% of patients at 5-years post-intervention. Primary endpoints analyzed were type IA endoleak and any aortic re-intervention out to 5 years post-procedure. A composite endpoint of type IA endoleak, re-intervention, aortic rupture or aortic-related mortality was also assessed.

Results: 1977 (62.4%) patients were classified NAN and 1189 (37.6%) were LAN. Immediate technical success was achieved in 3164/3166 ($>99.9\%$) of cases. Freedom from type IA was achieved in 99.3% at 1-year and 97.3% at 5-years (lower in LAN vs NAN – 96.8% (CI 93.7-98.4) vs 98.6% (CI 94.5-99.6), $p=0.007$). Freedom from aortic re-intervention was 93.7% at 1-year and 83.2% at 5-years (78.6% (CI 66.0-87.0) LAN vs 86.0% (CI 81.8-89.3) NAN, $p=0.11$). Freedom from primary composite endpoint was 95.9% at one year and 84.9% at 5-years (81.3% (CI 69.2-89.0) LAN versus 87.0% (CI 81.6-91.0) NAN, $p=0.066$). 5-year Survival was lower in the LAN group; 64.6% (CI 50.1-75.7) vs 76.5% (CI 70.7-81.3), $p=0.03$).

Conclusion: LAN is associated with delayed type IA endoleak occurrence and lower overall survival.

Key words: Abdominal aortic aneurysm (AAA); Endovascular aneurysm repair (EVAR); Aneurysm neck; Outcome analysis

Introduction

Endovascular abdominal aortic aneurysm repair (EVAR) commenced in the early 1990s¹ and is associated with short-term advantages compared to open repair, including shorter hospital stay, more rapid return to independent activity, and early overall survival benefit.²⁻⁴ These benefits relate to the minimally invasive nature of the procedure. However, at the medium - long-term follow up (4-15 years post procedure) benefits in terms of both aneurysm-related and overall mortality are lost.⁵⁻⁶ High-pressure endoleaks and graft migration are the key culprits for stent-graft failure, aneurysm re-pressurization, and subsequent morbidity.⁵⁻⁷ With increasing awareness of this, there is a recent shift in focus to achieving long-term durability rather than just immediate operative sealing following stent-graft deployment. Operating within “instructions for use” (IFU) and performing detailed planning in order to choose optimal sealing zones are crucial,⁸ but the understanding of patient factors associated with endoleak formation are limited. These include progressive aneurysmal degeneration and sealing zone dilatation, both of which lead to subsequent EVAR failure, in addition the potential impact of cardiovascular co-morbidity and medication use on endoleak formation are poorly understood.

The infra-renal aortic neck is arguably the most important feature to consider when planning endovascular intervention and the exact nature of its morphology often dictates both immediate and long-term aneurysm sealing success. Several adverse aortic neck features are known to be associated with poor proximal seal durability, including short neck length, excessive angulation, circumferential thrombus, and reverse tapering.⁹ However progressive aortic neck dilatation due to underlying aneurysmal degeneration is an independent feature that is poorly understood, yet potentially linked to proximal seal failure and adverse short-term outcome.¹⁰⁻¹² Eurostar analysis has shown that up to 32% of patients experience neck dilatation following EVAR and risk factors for this include the use of larger diameter main body devices and excessive device oversizing.¹³ At 2 year follow-up Cao et al. found preoperative proximal neck diameter to be correlated with future aortic neck dilatation.¹¹

94 Despite this link, immediate technical success and short-term re-intervention rates have not
95 been found to be influenced by pre-operative neck diameter.¹⁴⁻¹⁵ Mid- to long-term data are
96 scarce, conflicting, and limited to studies with less than 300 subjects.¹⁶⁻¹⁷ As neck dilatation
97 is a slow process, issues with proximal fixation and sealing may not become apparent for
98 several years after the initial procedure.

99
100 The aim of this study was to assess whether large proximal aortic neck diameter is associated
101 with stent-graft failure at mid-long term follow-up. Particular outcomes focused on were type
102 IA endoleak occurrence, requirement for endovascular re-intervention, aortic rupture and
103 overall survival. As an aortic diameter of 25mm or greater is considered abnormal and
104 potentially pre-aneurysmal,¹⁸ we used this diameter as a cut-off for defining large proximal
105 aortic necks. Current AAA screening policies use 25mm diameter as the cut-off for abnormal
106 aortic diameter, and 30mm for the definition of an aortic aneurysm. Therefore, to understand
107 aortic disease progression and what influences EVAR failure, we aimed to compare patients
108 with a normal aortic neck diameter sealing zone to those with an abnormal pre-aneurysmal
109 diameter. Prospectively collected individual patient data from The Global Registry for
110 Endovascular Aortic Treatment (GREAT) were used for this study.¹⁹

Materials and Methods

The Global Registry for Endovascular Aortic Treatment (GREAT) is a prospective observational multicenter cohort registry that was initiated in 2011. GREAT is the largest stent-graft registry to-date, having enrolled over 5000 consecutive patients undergoing intervention with Gore thoracic and abdominal aortic stent-grafts from 78 centres in Europe, the United States, Australia, New Zealand and Brazil. GREAT has broad inclusion criteria with no exclusion criteria to reflect real world practice. Inclusion criteria are all patients with an indication for endovascular aneurysm repair who agree to sign informed consent. Patients needed to be at least 18 years old. All consenting patients receiving Gore stent-grafts were included, including those receiving grafts for non-standard indications and devices deployed outside instruction for use (IFU). This particular study focuses on 3166 consecutive patients who received Gore Excluder stent-grafts for infra-renal abdominal aortic aneurysm repair from January 2011 to January 2017. For abdominal aortic aneurysm repair subjects were considered to be outside IFU if:

1. The proximal neck length was less than 15 mm and an infra-renal aortic neck treatment diameter range outside of 19-29 mm.
2. The infra-renal neck angle was greater than 60 degrees. Neck angle was defined as the angle between the longitudinal axis of AAA neck and the longitudinal axis of the AAA sac.
3. Distal segment iliac vessel lengths of less than 30 mm with less than 10 mm less than or equal to 18.5 mm in diameter.
4. The main body was sized of less than 10% (undersize) or greater than 21% (oversize) compared to the aortic inner diameter.
5. The iliac limb extensions were sized less than 7% or greater than 25% compared to the iliac inner diameter.

Data collection and processing

Patient demographics, past medical history, biometrics, treatment indication, case planning, operative details, and clinical outcome were analyzed. Aorto-iliac planning measurements were performed by physicians and local gore endovascular representatives at each registry centre. All measurements were performed using 3D reconstructed thin-sliced CT angiograms and dedicated endovascular stent graft planning software (inner wall – to – inner wall orthogonal diameters and centerline construction for lengths). Collected data were recorded on a web-based electronic report form (iMedidata, Medidata Worldwide Solutions, Inc., New York, NY, USA) to ensure reliability, and secure authentication and traceability. Data management was performed by the Gore Clinical Research Department (W.L. Gore & Associates). The database is maintained by Gore and all data is available for investigators to access at any time upon request. This analysis was conducted by GORE but at the direction of the authors. There was an a priori analysis plan agreed upon and executed by GORE. The authors directed the Gore team throughout the process as to what variables were analysed and how it was conducted. All collected data were reviewed and if missing or inconsistent data were detected, relevant queries were posed to the investigators for resolution. Monitoring visits were performed at each enrollment site to verify necessary study documents, including signed informed consent for each patient. Consistency between electronically imported data and source documents was also examined.

Patients were divided into two groups for analysis; those classified as having normal proximal aortic neck diameter (<25mm on preoperative cross-sectional CT aortography), and those classified as having large aortic necks (≥25mm diameter).

Outcome ascertainment and Follow-up

Follow up was accomplished according to the protocol of each institution. A GREAT electronic database connects all sites online. Sites are trained to use the database and input follow up data in real time as subjects return for their follow up. No specific imaging tests at particular time points were required. Serious adverse events either related or unrelated to the stent-graft were recorded. Endoleaks, stent-graft migration, aortic dilatation, aortic-related re-intervention, serious device events by pathology and aorto-iliac segment, cardiovascular

morbidity and mortality were recorded. Aortic-related re-intervention includes any aortic operative re-intervention (endovascular or open) in the location of the stent graft placement (i.e. endoleak intervention, re-lining, renal or aorto-iliac intervention). Hospital readmission and the time and cause of death were flagged and recorded for all cases from countries where hospital and mortality coding are available. This was accessible for the vast majority of participants. Complications, morbidity, and mortality were also reported in real time by each site using the online GREAT electronic database. Follow-up to 5 years was available, providing contemporary mid-long term data on stent-graft durability and individual patient outcome.

The primary endpoint analyzed was type IA endoleak in isolation out to 5 years post-procedure. We also analysed a primary composite endpoint of: Type IA endoleak, aortic-related re-intervention, aortic rupture or aortic-related mortality out to 5 years post-procedure. Aortic related mortality was defined as one of the following:

- 1.) Procedure Death
- 2.) Death days < 30
- 3.) Death before hospital discharge date
- 4.) If there was reintervention and patient died within 30 days
- 5.) If death and cause of death was stated to be due to Aortic Rupture or Aortic Endoleak or one of the following: Aortic Aneurysm, Aortic Aneurysm Repair, Aortic Dilatation, Aortic Disorder, Aortic Dissection, Aortic Embolus, Aortic Occlusion, Aortic Stenosis, Aortic Stent Insertion, Aortic Surgery, Aortic Thrombosis.

Freedom from these endpoints were assessed using Kaplan-Meier analysis for subjects with proximal aortic diameter of less than 25mm and greater or equal to 25mm. Secondary endpoints analyzed included any aortic-related complication (endoleak of any type; stent-graft migration, fracture, or compression; aortic rupture), and overall mortality. These were assessed at 30-days, and out to 5 years post-procedure. Only endoleaks matching the ISO definition of serious (requiring intervention) were included.

209

210 ***Stent-graft design***

211 The Gore Excluder stent-graft is a third generation device that has now been used for 18
212 years in more than 250,000 patients with proven safety, efficacy, and long-term durability.²⁰⁻

213 ²² It features a flexible, catheter-mounted introduction, and infra-renal attachment with barbs.

214 It consists of two primary modular components(trunk-Ipsilateral Leg Endoprosthesis and the
215 Contralateral Leg Endoprosthesis) and two ancillary components (Aortic and Iliac Extender
216 Endoprostheses). The graft material is expanded polytetrafluoroethylene (ePTFE) and
217 fluorinated ethylene propylene (FEP), and is attached to and supported by nitinol wire along
218 its external surface. Nitinol anchors and an ePTFE / FEP sealing cuff are located at the
219 proximal (aortic) end of the Trunk-Ipsilateral Leg component. The device conforms to
220 ISO14155 standard.

221

222 ***EVAR Procedure***

223 All patients had a preoperative stent-graft plan featuring length and diameter of the chosen
224 stent-grafts according to their aortic and iliac dimensions. The procedure was performed
225 under local, regional, or general anesthesia and via percutaneous or surgical-cut down
226 access according to operator's preference. Heparin and antibiotic were administered
227 according to each institution's standard regimen. The need for and details of level and/or
228 orientation repositioning were documented for every procedure. Adjunctive procedures (e.g.,
229 proximal cuff extender implantation) needed were also documented. A completion angiogram
230 was routinely performed to document final position of the stent-graft and to exclude endoleak.
231 Immediate technical success was defined as successful deployment of the stent-graft with
232 no type I/III endoleak, unintentional coverage of visceral aortic branches or internal iliac
233 arteries at the end of the procedure, and with successful removal of the delivery system.

234

235 ***Statistical analysis***

236 Statistical analysis was performed by the Gore Clinical Research Department. All variables
237 are reported descriptively. Categorical variables are expressed as total count with

percentage. Continuous variables are presented as mean with standard deviation. Group differences in continuous variables were examined with Student t test (or ANOVA) or Mann-Whitney U test (or Kruskal Wallis Test) for parametric and non-parametric variables, respectively. Group differences in categorical variables were examined with Fisher Exact test or Chi squared test, as appropriate. Cumulative patient survival and freedom from endpoints during follow-up were subjected to Kaplan–Meier analysis adjusted for significant potential confounding variables, and are presented as percentages with confidence intervals (CI). Not all endpoints were available for all patients at particular time points, so the numbers at risk differ for individual Kaplan–Meier analyses. All patients without imaging follow-up were censored in the relevant Kaplan-Meier analyses. To assess the independence of co-variate influence on outcome, univariate and multivariate stepwise Cox regression analysis was also performed. All data were analyzed using statistical SAS software, version 9.2 of the SAS System for Windows (Copyright 2002–2016 by SAS Institute INC., Cary, NC, USA).

Ethical Approval

All included patients provided written informed consent for their participation in the study. The trial was conducted according to the Declaration of Helsinki and the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines, and approved by the ethical committee of each participating institution. ClinicalTrials.gov Identifier: NCT01658787

Results

Over 5000 patients with thoracic and abdominal aortic pathology were entered into the GREAT registry since 2011, of which 3166 consecutive patients received a Gore Excluder stent-graft for treatment of an infra-renal abdominal aortic aneurysm. 85.6% of subjects were male, and mean (SD) age at time of procedure was 73.4 (8.3) years. 89.5% of patients were Caucasian, 3.3% African American, and 0.6% Asian/Oriental (Table 1). Prior cardiovascular disease and the prevalence of vascular risk factors were significant, with 81.1% of subjects having known pre-morbid hypertension, 56.2% having a smoking history, 18.8% with treated diabetes mellitus, and 16.1% having pre-intervention renal impairment (Table 1).

1977 (62.4%) patients were classified as having normal proximal aortic neck (NAN) diameters (<25mm maximal cross-sectional diameter on CT angiography) and 1189 (37.6%) were deemed to have large proximal aortic necks (LAN) (≥ 25 mm). Some significant differences were found in patient demographics, past medical history, and risk factor burden between the NAN and LAN groups. In particular, patients in the LAN group were slightly older (mean age 73.9 versus 73.0, $p=0.008$), with higher male predominance (88.6% versus 83.8%, $p<0.001$). Risk factors and cardiovascular disease burden were substantial in both groups. The majority of variables were similar between groups, with the notable exceptions of renal insufficiency (more common in the LAN group - 19.3% versus 14.2%, $p<0.001$), and a history of COPD, previous malignancy, stroke, and congestive cardiac failure, all of which were both more common in the LAN group (table 1).

Specific aortic aneurysm anatomical details are documented in table 2. Mean (SD) maximal aneurysm diameter was 57.2 (10.6) mm, and this was greater in the LAN group (59.3mm versus 55.7mm, $p<0.001$). Mean neck length was 29.7mm, averaging 28.1mm in the LAN group and 30.0mm in the NAN group. Distal iliac diameters averaged between 13.8 and 15.3mm, and were marginally larger in the LAN group (table 2). Mean (SD) infra-renal neck angle was 30.8 (23.6) Degrees, and this was similar in both groups (30.5 LAN versus 31.0 NAN, $p=0.823$).

288

289 Procedure and device specifics are also detailed in table 2. Over 99.1% of cases had
290 standard femoral access with percutaneous access being utilized in 48.8%, and this was
291 similar between groups (table 2). Iliac conduit access was used for the remaining 0.9%. The
292 Gore C3 Excluder main body trunk was used in 94.3% of cases (similar between groups).
293 The median number of device components implanted during a primary procedure was 3
294 (range 1-10), and this was higher for patients in the LAN group ($p<0.001$). Device and
295 extension piece specifics were similar between groups, except aortic extension / cuff
296 placement, which was required in 10.4% of the LAN group versus 7.7% of the NAN group,
297 $p=0.01$. The requirement for a large diameter main body trunk ($\geq 28.5\text{mm}$) was (as expected)
298 greater in the LAN group (92.4% versus 23.2%, $p<0.001$). 163/1189 (13.7%) in the LAN group
299 and 239/1977 (12.1%) in the NAN group were treated outside IFU ($p=0.24$). Immediate
300 technical success was achieved in 3164/3166 ($>99.9\%$) of cases, with two cases requiring
301 conversion to open repair, both of which were in the NAN group.

302

303 Clinical follow-up (with imaging) was achieved in 76.5% of patients who reached 5-year
304 follow-up post-intervention. Completeness of imaging follow-up during the study period is
305 shown in table 3. Mean (SD) hospital stay was 4.1 (5.3) days and this did not significantly
306 differ between groups. At 30-days post-procedure 111/3166 (3.5%) patients had had a major
307 complication, and this was similar between groups (4.0% LAN versus 3.2% NAN, $p=0.289$)
308 (table 4). These complications included 89 patients who required an additional endovascular
309 intervention or aortic-related surgical procedure, 9 patients who had a cerebrovascular event,
310 and 17 patients who died from any cause. Device-specific complications of any type at 30-
311 days (any endoleak, migration, compression, fracture, or aortic rupture) occurred in 52/3166
312 (1.6%) patients, with the majority being type I or II endoleaks. These were similar between
313 groups.

314

315 Hospital readmission and mortality was flagged and recorded for all cases. Freedom from
316 any aortic-related re-intervention was achieved in 93.7% at 1-year and 83.2% at 5-years.

Higher levels of re-intervention were found in the LAN group but this did not reach significance; freedom from re-intervention 78.6% (CI 66.0-87.0) in the LAN group versus 86.0% (CI 81.8-89.3) in the NAN group, $p=0.11$ (figure 1). Freedom from type IA endoleak was achieved in 99.3% at 1-year and 97.3% at 5-years. This was lower in the LAN group compared to the NAN group at 5 years post-intervention - 96.8% (CI 93.7-98.4) vs 98.6% (CI 94.5-99.6), $p=0.007$ (figure 2). A sensitivity analysis including only patients with at least 1 year follow-up confirmed a similar significant association (supplemental figure 1). Univariate and stepwise multivariate Cox regression analysis was performed to assess the independence of aortic neck diameter association with type IA endoleak formation (table 5). Potential confounding covariates included were; age, gender, aortic neck length and angulation, under- and over-sizing outside instructions for use (IFU), and iliac vessel diameter and length outside IFU. In univariate analysis, outside IFU deployment and aortic neck diameter were significantly associated with type 1A endoleak occurrence. When included in the model as co-variables, aortic neck diameter remained independently associated with type IA endoleak formation (table 5).

Freedom from the primary composite endpoint (any of type IA endoleak, aortic-related re-intervention, aortic rupture, or aortic-related mortality) was achieved in 95.9% at one year and 84.9% at 5-years. This trended towards a lower freedom in the LAN group compared to the NAN group at 5 years - 81.3% (CI 69.2-89.0) versus 87.0% (CI 81.6-91.0), $p=0.066$ (figure 3). Freedom from aortic-related mortality in isolation was 99.1% at one year and 98.5% up to 5 years. At 5 years post intervention, this was similar between groups (figure 4): 97.9% in the LAN group (CI 95.7-99.0) versus 98.8% in the NAN group (CI 97.6-99.5), $p=0.234$. Overall survival at one year was 93.5%, and 72.0% at 5 years. This was significantly lower in the LAN group; 64.6% (CI 50.1-75.7) vs 76.5% (CI 70.7-81.3), $p=0.03$ (figure 5).

Discussion

The Gore GREAT registry is the largest prospective stent-graft registry to-date. It is separated from other medical registries by minimal exclusion criteria, having over 5000 consecutive patients enrolled, and extended length of follow-up. The active tracking of long-term device performance and associated patient outcomes will continue to provide key insights into real-world clinical practice, which is vital to advancing the future of endovascular repair and improving outcome. Patient ascertainment from 78 centres in Europe, the United States, Australia, New Zealand and Brazil should ensure robust and representative data is collected on patients from a variety of demographic backgrounds.

This is the first study to use a cut-off at 25mm for aortic neck diameter, and this is because an aortic diameter of 25mm or greater is abnormal and pre-aneurysmal tissue. In accordance with this, all current AAA screening policies use 25mm diameter as the cut-off for abnormal aortic diameter. If one wants to truly understand aortic disease progression and what influences EVAR failure, it is essential to compare normal sealing zones with abnormal. We, therefore, feel that this is the correct anatomical distinction to use. All previous studies investigating aortic neck diameter, have used larger cut-offs, such as using 36mm diameter stent-grafts.^{23,24} These cases represent a very small minority of patients undergoing EVAR in the real-world (only 177/3166 (5.6%) of patients in GREAT had aortic neck diameters greater or equal to 30mm) which leads to limited study numbers, reduced power for useful analysis, and limited overall clinical relevance.

Several key findings should be mentioned. First, a third of patients were found to have large proximal aortic neck diameters (≥ 25 mm). This is, therefore, a relatively common finding and is associated with other anatomical features, including a larger maximal aortic aneurysm diameter and slightly larger distal iliac diameters. However, adverse neck length and neck angulation were not found to be associated with neck diameter. Subjects with larger proximal aortic necks tended to require additional device components, particularly a higher likelihood

for aortic cuff component placement, compared to those with normal neck diameters. Despite this, successful device deployment and immediate aneurysm sealing was achieved in over 99% of cases.

Second, short-term adverse outcome was uncommon with only 3.5% of patients suffering any form of major complication at 30-days. The majority of these were the requirement for an additional endovascular procedure for correction of early type 1 or II endoleaks. Baseline proximal aortic neck diameter was not associated with the occurrence of major complications or device-specific complications within 30 days of intervention.

Third, when focusing on complications potentially influenced by proximal aortic neck diameter, there was a lower freedom from type IA endoleak in the LAN group. This was not realized until after 2 years of follow-up, which may explain why previous studies with shorter follow-up have failed to identify this. The association was found to be independent on Cox regression analysis. This finding may be explained by progressive aortic neck dilatation in the LAN group, although we do not have aortic neck dimension data during follow-up to confirm this.

Fourth, there was also a trend towards a reduced freedom from aortic re-intervention and the primary composite endpoint (any of type IA endoleak, aortic-related re-intervention, aortic rupture, or aortic-related mortality) in patients with large proximal aortic necks. These findings may point towards a higher aneurysm seal failure rate in patients with large baseline aortic neck diameters, and raise the question of whether in young patients, with life expectancies exceeding 10 years, this maybe an adverse feature for standard endograft usage.

Fifth, isolated aortic-related mortality up to five years post-procedure was very low and not associated with baseline aortic neck diameter. Overall survival was however significantly lower in the large aortic neck diameter group. This would suggest that large aortic neck

diameter is associated with increased mortality from non-aortic aetiologies, potentially cardiovascular and cerebrovascular disease.

Finally, patients being treated for large abdominal aortic aneurysms are predominantly elderly men with multiple cardiovascular risk factors and co-morbidity. The age at treatment appears to be steadily increasing, as does co-morbidity that is known to influence long-term outcome. Over 80% of patients in this study had hypertension, over a third had treated coronary heart disease, and a sixth had renal insufficiency at baseline. These shifts in patient cohort epidemiology will continue to impact on clinical decision making and make endovascular strategies more appealing in order to avoid the up-front cardiovascular strain imposed by open surgery. Although one could question the relevance of long-term EVAR durability in elderly patients with comorbidity, all-cause mortality out to 5-years post intervention was less than 30% overall. Therefore, the majority of patients do live long enough to warrant robust and effective treatment.

Limitations

Limitations of the present study should be acknowledged. Data, although prospectively collected, were retrospectively analyzed. In order to reflect real world practice, follow-up schemes and re-intervention protocols were per local centre protocol and therefore were variable. Selection bias is also inherent due to the observational design of the study. Completeness of follow-up is a limitation of our study as only 75% of patients have imaging follow-up data out to 5 years post procedure. This is, however, one of the highest follow-up rates for any registry focused on vascular disease in recent times. As near 100% hospital readmission and mortality follow-up was achieved, there is unlikely to be significant bias with regards to serious morbidity and mortality. Aortic-related mortality was determined following post-mortem and death certificate analysis of all deaths within the study period. Cause of death is not 100% accurate as post-mortem rates for out-of-hospital deaths range from 40-60% and therefore death certificate inaccuracies can potentially occur.

Conclusion

In this large, real-world, prospective registry, the Gore Excluder stent-graft successfully treated patients across the disease spectrum with infra-renal abdominal aortic aneurysms. Adverse outcome, re-intervention, and aortic-related mortality out to five years were low overall. However, patients with large proximal aortic neck diameters were found to have higher rates of delayed type IA endoleak and reduced survival out to five years follow-up. There was also a trend towards greater re-intervention and aortic-related complications in these patients. These findings may be explained by progressive aortic neck dilatation and subsequent proximal seal failure. With increasing clinical focus now on long-term stent-graft seal durability, proximal aortic neck diameter is a parameter that should be considered as more intensive long-term surveillance will be required in these patients. Our findings raise the question as to whether young patients, with predicted life expectancies exceeding 10 years, should receive standard endovascular intervention if they have large aortic neck diameters at baseline.

Acknowledgements: Many thanks to Beth Tohill at the Gore Clinical Research Office for data extraction.

Sources of Funding: GREAT was funded by W.L. Gore & Associates.

Conflicts of interest: Eric L.G. Verhoeven has received educational grants and is a consultant for Cook Inc., W.L. Gore & Associates, Siemens and Atrium-Maquet.

References

1. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. *Ann Vasc Surg*, 1991;5:491–499
2. Greenhalgh RM, Brown LC, Kwong GP, et al. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial *Lancet*. 2004;364: 843–848
3. Prinssen M, Verhoeven EL, Buth J, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. *N Engl J Med*. 2004;351:1607–1618

4. Bertrand M1, Godet G, Koskas F, et al. Endovascular treatment of abdominal aortic aneurysms: is there a benefit regarding postoperative outcome? *Eur J Anaesthesiol.* 2001;18(4):245-50.
5. Paravastu SC, Jayarajasingam R, Cottam R, et al. Endovascular repair of abdominal aortic aneurysm. *Cochrane Database Syst Rev.* 2014;23;1:CD004178.
6. Patel, Rajesh et al. 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.* 2016;388:2366 - 2374
7. De Bruin JL, Baas AF, Buth J, et al. DREAM Study Group. Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. *N Engl J Med.* 2010;362(20):1881-9
8. Schanzer A1, Greenberg RK, Hevelone N, et al. Predictors of abdominal aortic aneurysm sac enlargement after endovascular repair. *Circulation.* 2011;123(24):2848-55
9. Dillavou ED, Muluk SC, Rhee RY, et al. Does hostile neck anatomy preclude successful endovascular aortic aneurysm repair? *JVS.* 2003;38:657-663
10. Napoli V, Sardella SG, Bargellini I, et al. Evaluation of the proximal aortic neck enlargement following endovascular repair of abdominal aortic aneurysm: 3-years experience. *Eur Radiol,* 2003;13:1962–1971
11. Cao P, Verzini F, Parlani G, et al. Predictive factors and clinical consequences of proximal aortic neck dilatation in 230 patients undergoing abdominal aorta aneurysm repair with self expandable stent-grafts. *J Vasc Surg.* 2003;37:1200-1205.
12. Dillavou ED, Muluk S, Makaroun MS, et al. Is neck dilatation after endovascular aneurysm repair graft dependent?: Results of 4 US Phase II trials. *Vasc Endovasc Surg,* 2005;39:47–54
13. Leurs LJ, Kievit J, Dagnelie PC, et al. Influence of infrarenal neck length on outcome of endovascular abdominal aortic aneurysm repair. *JEVT.* 2006;13:640-8
14. Chisci E, Kristmundsson T, de Donato G, et al. The AAA with a challenging neck: outcome of open versus endovascular repair with standard and fenestrated stent-grafts. *JEVT.* 2009;16:137-46.
15. Verhoeven BA, Waasdorp EJ, Gorrepati ML, et al. Long-term results of Talent endografts for endovascular abdominal aortic aneurysm repair. *JVS.* 2011;53:293-8.
16. Jim J, Rubin BG, Geraghty PJ, Criado FJ, Fajardo A and Sanchez LA. A 5-year comparison of EVAR for large and small aortic necks. *JEVT.* 2010;17:575-84.
17. Jordan WD, Jr., Ouriel K, Mehta M, Varnagy D, Moore WM, Jr., Arko FR, et al. Outcome-based anatomic criteria for defining the hostile aortic neck. *JVS.* 2015;61:1383-90 e1

- 501 18. Devaraj S, Dodds S. Ultrasound Surveillance of Ectatic Abdominal Aortas. *Annals of*
502 *The Royal College of Surgeons of England*. 2008;90(6):477-482.
- 503 19. WL Gore and Associates. GORE Excluder AAA Endoprosthesis 2012 annual clinical
504 update. February 2012. [http:// www.goremedical.com/resources](http://www.goremedical.com/resources/dam/assets/AH1406-EN8.pdf)
505 [/dam/assets/AH1406-EN8.pdf](http://www.goremedical.com/resources/dam/assets/AH1406-EN8.pdf), Accessed December 23, 2012.
- 506 20. Sayeed S, Marone LK, Makaroun MS. The Gore Excluder endograft device for the
507 treatment of abdominal aortic aneurysms. *J Cardiovasc Surg (Torino)*. 2006;47:251-
508 260.
- 509 21. Bos WT, Tielliu IF, Van Den Dungen JJ, et al. Results of endovascular abdominal
510 aortic aneurysm repair with selective use of the Gore Excluder. *J Cardiovasc Surg*
511 *(Torino)*. 2009;50:159-164.
- 512 22. Ghotbi R, Sotiriou A, Mansur R. New results with 100 Excluder cases. *J Cardiovasc*
513 *Surg (Torino)*. 2010;51:475-48
- 514 23. Oliveira NFG, Bastos Goncalves FM, Van Rijn MJ, de Ruiter Q, Hoeks S, de Vries
515 JPM, van Herwaarden JA and Verhagen HJM. Standard endovascular aneurysm
516 repair in patients with wide infrarenal aneurysm necks is associated with increased
517 risk of adverse events. *J Vascular Surg*. 2017;65:1608-1616.
- 518 24. Gargiulo M, Gallitto E, Wattez H, Verzini F, Bianchini Massoni C, Loschi D, Freyrie
519 A and Haulon S. Outcomes of endovascular aneurysm repair performed in
520 abdominal aortic aneurysms with large infrarenal necks. *J Vascular Surg*.
521 2017;66:1065-1072.
- 522
- 523
- 524
- 525
- 526
- 527

528 Table 1. Demographics, past medical history, and risk factors by maximal proximal aortic
529 neck diameter

	Total	Aortic neck <25mm	Aortic neck ≥25mm	P Value
Number of Subjects	3166	1977	1189	
Mean (SD) age, year	73.4(8.28)	73.0(8.30)	73.9(8.22)	0.008
Male	2710(85.6%)	1656(83.8%)	1054(88.6%)	<0.001
Mean (SD) Weight (kg)	83.1(17.07)	82.2(16.83)	84.6(17.36)	<0.001
Mean (SD) Height (cm)	173.6(9.05)	173.0(9.19)	174.6(8.73)	<0.001
Mean (SD) BMI	27.5(5.08)	27.4(5.10)	27.7(5.05)	0.082
Race				
American Indian	8(0.3%)	3(0.3%)	5(0.3%)	
Asian / Oriental	20(0.6%)	4(0.3%)	16(0.8%)	
African American	106(3.3%)	38(3.2%)	68(3.4%)	
Middle Eastern	7(0.2%)	1(0.1%)	6(0.3%)	
Pacific Islander	9(0.3%)	6(0.5%)	3(0.2%)	
White or Caucasian	2835(89.5%)	1080(90.8%)	1755(88.8%)	0.066
Hypertension	2558/3153(81.1%)	1591/1970(80.8%)	967/1183(81.7%)	0.496
Hypercholesterolemia	2027/3062(66.2%)	1277/1912(66.8%)	750/1150(65.2%)	0.373
Tobacco Use	1730/3080(56.2%)	1087/1924(56.5%)	643/1156(55.6%)	0.636
Coronary Artery Disease	1288/3104(41.5%)	783/1945(40.3%)	505/1159(43.6%)	0.070
Cardiac Arrhythmia	659/3116(21.1%)	397/1947(20.4%)	262/1169(22.4%)	0.181
Congestive Heart Failure	278/3106(9.0%)	150/1941(7.7%)	128/1165(11.0%)	0.002
Diabetes Mellitus	591/3145(18.8%)	381/1965(19.4%)	210/1180(17.8%)	0.268
Peripheral Vascular Disease	611/3094(19.7%)	369/1938(19.0%)	242/1156(20.9%)	0.200
Stroke	305/3126(9.8%)	172/1953(8.8%)	133/1173(11.3%)	0.021
Transient Ischemic Attack	183/3095(5.9%)	109/1943(5.6%)	74/1152(6.4%)	0.354
Carotid Disease	382/2993(12.8%)	235/1865(12.6%)	147/1128(13.0%)	0.732
Renal Insufficiency	506/3141(16.1%)	278/1962(14.2%)	228/1179(19.3%)	<0.001
COPD	817/3107(26.3%)	483/1942(24.9%)	334/1165(28.7%)	0.020
Cancer	711/3120(22.8%)	412/1950(21.1%)	299/1170(25.6%)	0.004
Coronary Artery Bypass Graft	500/3144(15.9%)	306/1964(15.6%)	194/1180(16.4%)	0.523
Erectile Dysfunction (male only)	177/1508(11.7%)	113/942(12.0%)	64/566(11.3%)	0.688
Valvular Heart Disease	235/3099(7.6%)	133/1933(6.9%)	102/1166(8.7%)	0.057
Thromboembolic Event	196/3095(6.3%)	112/1934(5.8%)	84/1161(7.2%)	0.110
Renal Dialysis	45/3148(1.4%)	24/1968(1.2%)	21/1180(1.8%)	0.200
Paraparesis	32/3153(1.0%)	21/1969(1.1%)	11/1184(0.9%)	0.709
Degenerative Connective Tissue Disease	54/3033(1.8%)	37/1894(2.0%)	17/1139(1.5%)	0.353
Paraplegia	14/3158(0.4%)	8/1970(0.4%)	6/1188(0.5%)	0.685

Table 2. Patient Anatomy, Intervention specifics and Device Usage By Maximum Proximal Aortic Neck Diameter

	<25mm	≥25mm	P-value
Number of Subjects	1977	1189	
Anatomy, mm			
Mean (SD) AAA diameter	55.7(10.86)	59.3(11.63)	<0.001
Mean (SD) Proximal neck length	30.0 (2.28)	28.1 (1.62)	0.004
Mean (SD) Proximal neck Diameter	21.7(2.26)	27.8(2.75)	<0.001
Mean (SD) Left iliac distal diameter	13.8(4.35)	15.0(4.73)	<0.001
Mean (SD) Right iliac distal diameter	14.3(4.83)	15.3(4.80)	<0.001
Mean (SD) Infra-renal neck angle, degrees	31.0(25.15)	30.5(20.90)	0.823
Access			
Femoral	1959(98.9%)	1185(99.4%)	0.167
Percutaneous	968(48.9%)	581(48.7%)	0.936
Device Specifics			
Non-C3 Excluder Trunk Implanted	123/1977(6.2%)	62/1189(5.2%)	0.239
C3 Excluder Trunk Implanted	1859/1977(93.9%)	1130/1189(94.8%)	0.287
Contralateral Leg Implanted	1949/1977(98.4%)	1167/1189(97.9%)	0.271
Aortic Extender / Cuff Implanted	153/1977(7.7%)	124/1189(10.4%)	0.010
Iliac Extender Implanted	278/1977(14.0%)	154/1189(12.9%)	0.373
EXCLUDER Trunk ≥28.5 mm Implanted	459/1977 (23.2%)	1101/1189(92.4%)	<0.001
Devices Implanted at Initial Procedure (per Subject)			
Median (Range)	3.0 (1-8)	3.0(1-10)	<0.001
Treated outside IFU	239 (12.1%)	163 (13.7%)	0.24
Immediate Technical Success	1976/1977(>99.9%)	1188/1189(>99.9%)	
Mean (SD) Hospital Stay, Days	3.9(6.09)	4.3(5.51)	0.161

549 Table 3. Completeness of Imaging Follow-up

550

551

552

	1 Month	6 Months	1 Year	2 Years	3 Years	4 Years	5 Years
Number subjects eligible for follow-up	3149	3094	2609	1799	969	465	268
Number subjects Imaged	3138 (99.7%)	2360 (76.3%)	1717 (65.8%)	1205 (67.0%)	671 (69.2%)	362 (77.8%)	205 (76.5%)
Number subjects lost to Imaging follow-up	11	734	892	594	298	103	73

553 Table 4. 30-Day Outcome by Maximal Proximal Aortic Neck Diameter

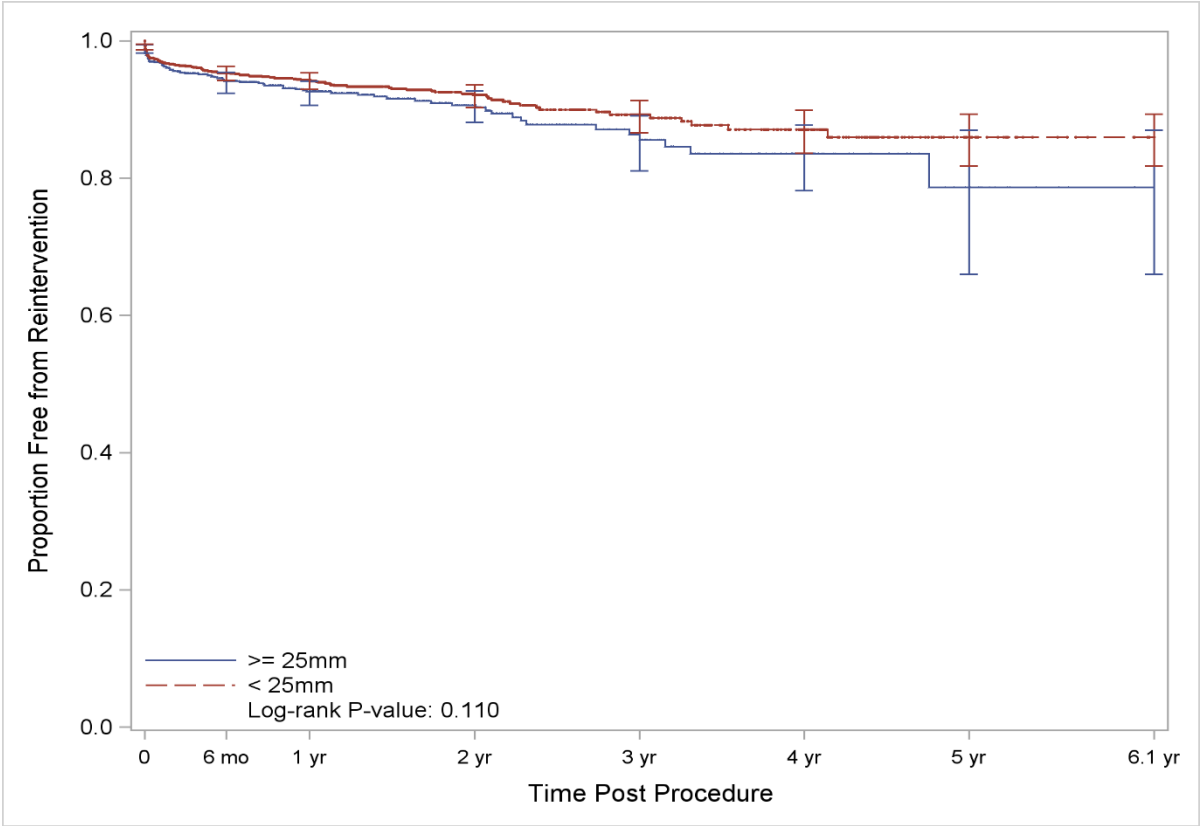
	<25mm	≥25mm	P-value
Number of Subjects Enrolled	1977	1189	
Stroke	3(0.2%)	6(0.5%)	0.071
Paraplegia/Paraparesis/Spinal Cord Ischemia	2(0.1%)	1(0.1%)	0.880
All Reinterventions	53(2.7%)	36(3.0%)	0.567
Conversion to Open Repair and/or Explant	2(0.1%)	2(0.2%)	
Additional Graft	3(0.2%)	3(0.3%)	
Other Procedure/Surgery	49(2.5%)	31(2.6%)	
Device Related Reinterventions	14(0.7%)	8(0.7%)	0.908
Mortality	10(0.5%)	7(0.6%)	0.757
Any Above	64(3.2%)	47(4.0%)	0.289
Endoleak	16(0.8%)	9(0.8%)	0.943
Type IA	4(0.2%)	4(0.3%)	
Type IB	5(0.3%)	3(0.3%)	
Type II	7(0.4%)	2(0.2%)	
Type III	0(0%)	0(0%)	
Type IV	0(0%)	0(0%)	1.000
Migration	0(0%)	1(0.1%)	0.553
Fracture	0(0%)	0(0%)	1.000
Compression	1(0.1%)	0(0%)	0.442
Aortic Rupture	0(0%)	0(0%)	1.000
Any Above	33(1.7%)	19(1.6%)	0.859

Table 5. Cox Regression Analysis for development of Type 1A Endoleak

Covariate	N used in model	Hazard Ratio	P-Value Univariate	P-Value Multivariate
Age	2678	1.06	0.0692	
Gender	2678	0.73	0.6680	
Max Infrarenal Neck Angle	2678	1.00	0.9841	
Proximal Neck Length (cm)	2678	0.75	0.1886	
Outside IFU	2678	4.56	0.008	0.013
Neck Diameter	2678	2.3	0.007	0.025

Potential confounding covariates included in the multivariate analysis were; age, gender, aortic neck length and angulation, under- and over-sizing outside instructions for use (IFU), and iliac vessel diameter and length outside IFU.

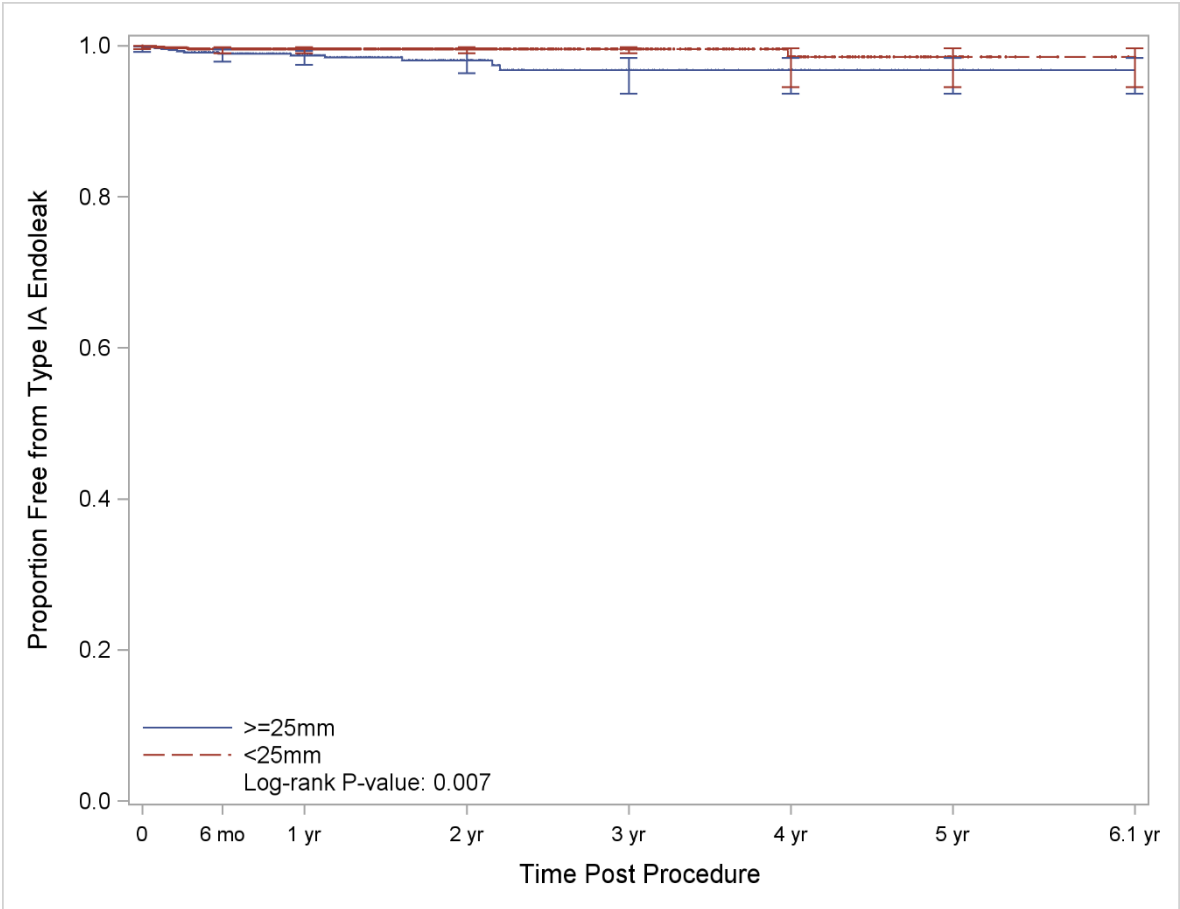
Figure 1



Numbers At Risk

<25mm	1977	1317	1171	897	439	213	103	25
≥25mm	1189	743	660	496	240	108	48	11

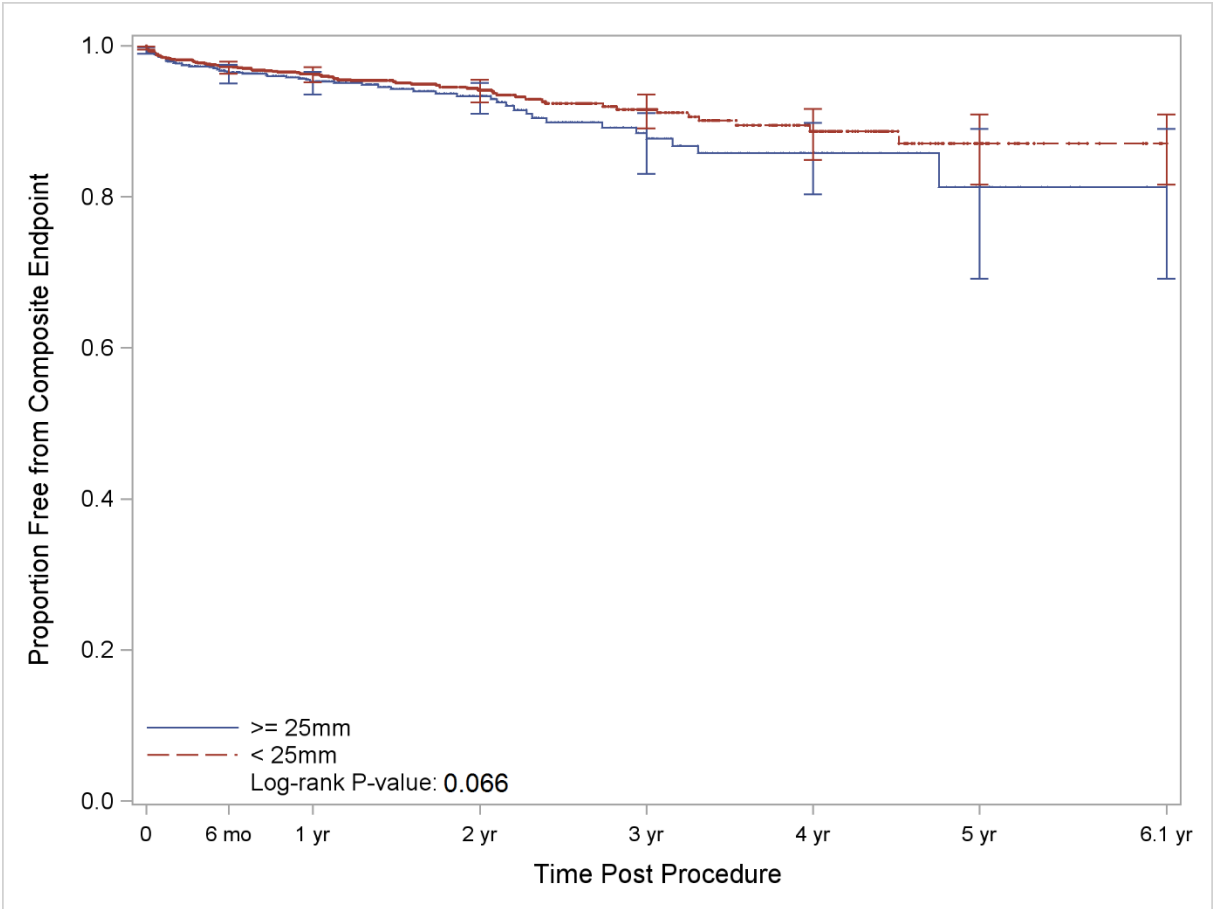
Figure 2



Numbers At Risk

<25mm	1977	1531	1175	1053	792	370	188	91
≥25mm	1189	893	660	579	434	193	96	47

Figure 3.

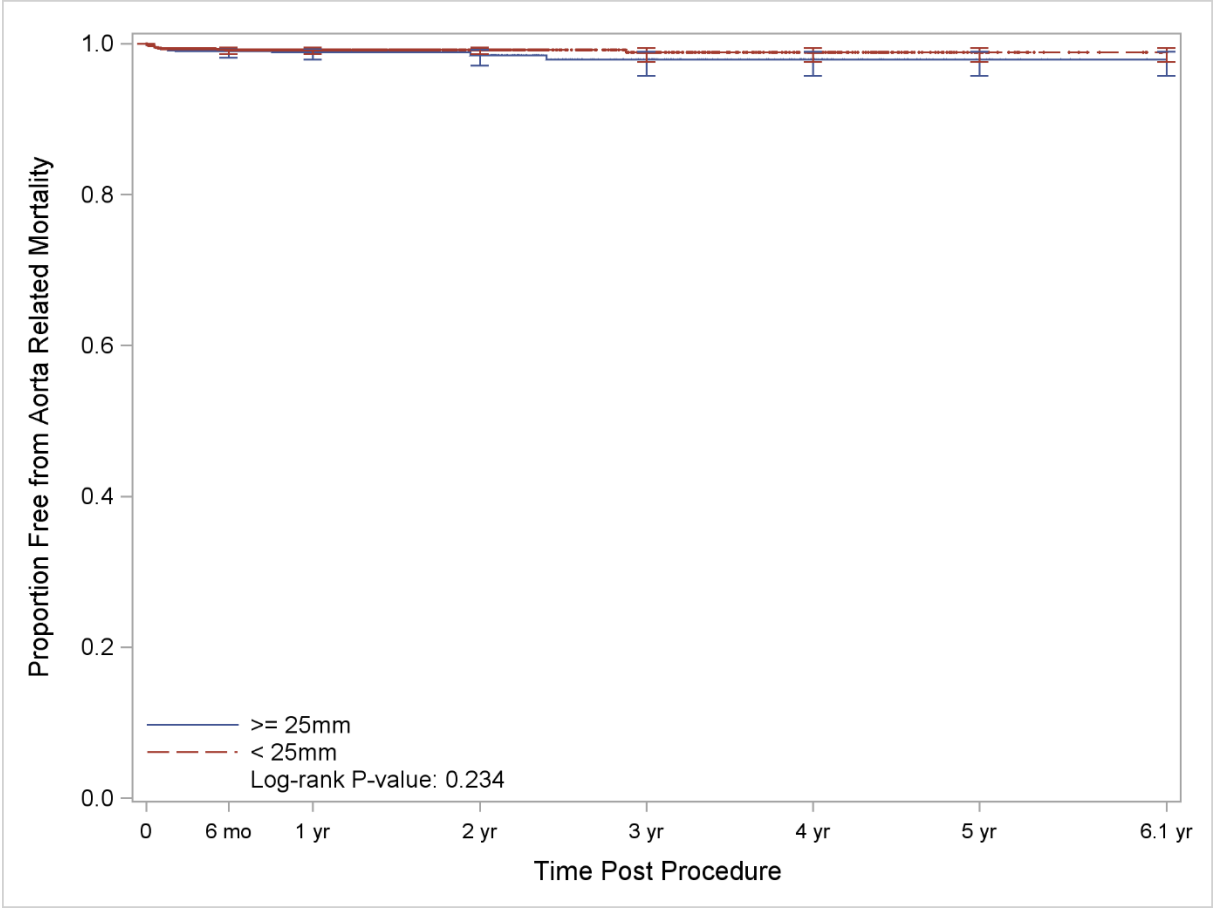


Primary composite endpoint encompasses Type IA endoleak, device-related re-intervention, aortic rupture, or aortic-related mortality

Numbers At Risk

<25mm	1977	1656	1352	1205	925	452	222	106
≥25mm	1189	768	685	515	249	115	51	12

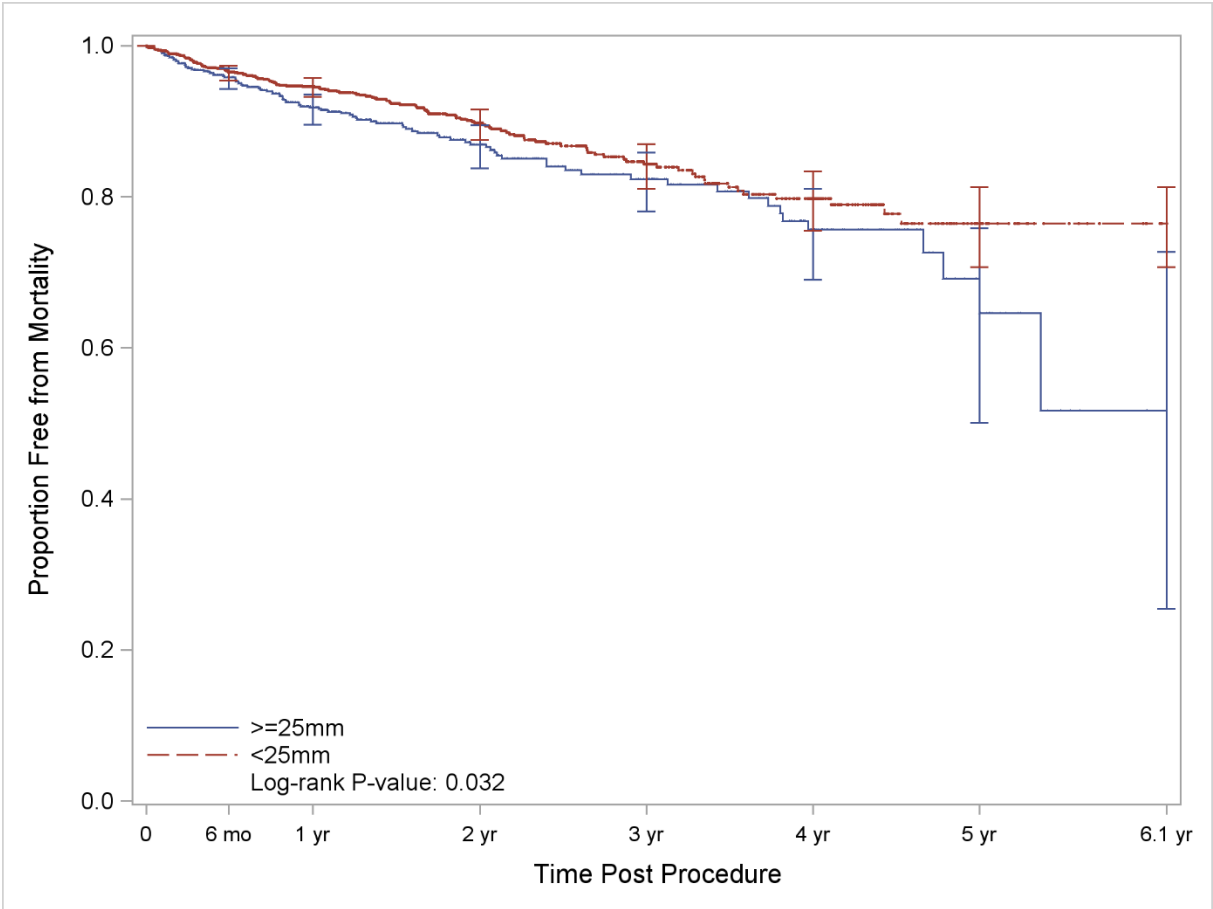
Figure 4.



Numbers At Risk

<25mm	1977	1668	1368	1230	955	478	244	123
≥25mm	1189	993	780	702	530	261	130	62

Figure 5.



Numbers At Risk

<25mm	1977	1668	1367	1230	952	476	243	123
≥25mm	1189	993	779	701	526	259	129	62

Figure Legends

Figure 1. 5-year freedom from aortic re-intervention by maximal proximal aortic neck size with numbers at risk tabulated below

Figure 2. 5-year freedom from type 1A endoleak by maximal proximal aortic neck size with numbers at risk tabulated below

Figure 3. 5-year freedom from primary composite endpoint by maximal proximal aortic neck size with numbers at risk tabulated below

Figure 4. 5-year freedom from aortic-related mortality by maximal proximal aortic neck size with numbers at risk tabulated below

Figure 5. 5-year freedom from all-cause mortality by maximal proximal aortic neck size with numbers at risk tabulated below