Outcome of the pivotal study of the Aptus endovascular abdominal aortic aneurysms repair system

Manish Mehta, MD,[a] John Henretta, MD,[b] Marc Glickman, MD,[c] David Deaton, MD,[d] Thomas C. Naslund, MD,[e] Bruce Gray, DO,[f] Richard McCann, MD,[g] William Jordan, MD,[h] and **Ronald Fairman, MD,[i]** *Albany, NY; Ashville, NC; Norfolk, Va; Washington, D.C.; Nashville, Tenn; Greenville, SC; Durham, NC; Birmingham, Ala; and Philadelphia, Pa*

Objective: **Endovascular treatment of abdominal aortic aneurysm (AAA) is associated with benefits over open surgery, yet limitations remain with current endovascular devices. This study was performed to assess outcomes of AAA repair with the Aptus endograft and EndoAnchors (Aptus Endosystems, Sunnyvale, Calif).**

Methods: **This prospective, multicenter, single-arm investigational device exemption trial was conducted at 25 sites in the United States. A total of 155 patients were enrolled in the trial (mean age, 73 ± 8 years; male, 93.5%; mean AAA diameter, 53.6 ± 7.9 mm). The Aptus endograft is a two-component system: a multilumen, modular endograft with two docking limbs (Aptus Endograft System) and the Heli-FX Aortic Securement System comprising an electronically controlled applier (Heli-FX Applier) with helical EndoAnchors provided in a cassette and a deflectable sheath (Heli-FX Guide) designed for delivery of the applier to the target location for EndoAnchor implantation. The main eligibility criteria included proximal neck length of ≥12 mm, diameter of 19 to 29 mm, and infrarenal angulation of ≤60 degrees. The primary safety end point was freedom from major adverse events at 30 days, and the primary effectiveness end point was successful aneurysm treatment at 12 months. Thrombus-related events (TRE) were defined as limb occlusion or thromboembolism from the endograft. Subjects were observed for a median of 4.2 years, with imaging end points analyzed by a core laboratory and adverse events adjudicated by a clinical events committee.**

Results: **Among 155 enrolled subjects, 153 (98.7%) underwent successful implantation of the Aptus endograft and a median of five EndoAnchors; two subjects were converted to open surgical repair during the initial procedure. Overall, the primary safety and effectiveness end points were met in 98.1% and 97.4% of the subjects, respectively. Aneurysm-related mortality was 0.6%, with one postdischarge cardiac death 18 days after implantation. There were no AAA ruptures. There were no fractures of stents or EndoAnchors. There was one type I endoleak and one type III endoleak. Stent graft migration was noted in five subjects, none associated with sac enlargement, type I endoleak, or EndoAnchor dislocation from the endograft. AAA sac shrinkage of ≥5 mm at 1, 2, and 3 years was observed in 60.3%, 72.9%, and 81.7%, respectively. Sixty-one subjects (39.4%) experienced 113 TRE, associated with 80 reinterventions (in 58 subjects) unassociated with limb loss or death. A root cause analysis of TRE identified small, out-of-specification docking limbs with graft infolding and high local shear, resulting in thrombus formation within the endograft with subsequent distal embolization in some cases.**

Conclusions: **Early results of the Aptus endograft trial met its safety and effectiveness end points; however, a high rate of TRE was observed because of manufacturing discrepancies. The findings confirm a low rate of type I and type III endoleaks, migration, and non-TRE reintervention with a high rate of aneurysm sac regression during midterm follow-up. (J Vasc Surg 2014;60:275-85.)**

From the Department of Vascular and Endovascular Surgery, Albany Medical College, Albany[a]; the Department of Vascular Surgery, Mission Health, Asheville[b]; the Department of Vascular Surgery, Sentara Heart Hospital, Norfolk[c]; the Department of Vascular Surgery, Georgetown University, Washington, D.C.[d]; the Department of Vascular Surgery, Vanderbilt University, Nashville[e]; the Department of Vascular Surgery, Greenville Hospital System, Greenville[f]; the Department of Vascular Surgery, Duke University, Durham[g]; the Department of Vascular Surgery, University of Alabama Birmingham, Birmingham[h]; and the Department of Vascular Surgery and Endovascular Therapy, University of Pennsylvania, Philadelphia.[i]

Author conflict of interest: D.D. is a consultant for Aptus. B.G. is an advisor to Abbot, Gore, and Trivascular. W.J. receives research funding for clinical trials participation from Medtronic, Gore, Cook, Endologix, Trivascular, Cordis, and Aptus and is a consultant for Medtronic, Gore, Endologix, and Aptus. M.M. receives an honorarium from and is a speaker for Gore, Trivascular, Aptus, Endologix, and IDEV; he receives research funding for clinical trial participation from Gore, Medtronic, Aptus, Lombard, Bolton, Abbott, Cordis, Terumo, ev3, Trivascular, Maquet, and Harvest. R.M. is a speaker for Medtronic and Gore and participates in clinical trials for Gore, Medtronic, and Aptus. T.C.N. is a consultant for Gore.

Reprint requests: Manish Mehta, MD, MPH, Director of Endovascular Services, Institute for Vascular Health and Disease, 43 New Scotland Ave, MC-157, Albany, NY 12208 (e-mail: mehtam@albanyvascular.com).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214/$36.00

http://dx.doi.org/10.1016/j.jvs.2014.02.017

Abdominal aortic endografts have been commercially available in the United States since 1999, and during the next decade, endovascular aneurysm repair (EVAR) supplanted open surgery for most patients with abdominal aortic aneurysm (AAA).[1] Randomized clinical trials and population-based studies demonstrated a reduction in early morbidity and mortality for EVAR compared with open surgical AAA repair.[2-5] The paradox of an early mortality advantage for EVAR counterbalanced by late survival loss appears in part to be due to a high rate of secondary reinterventions and even aneurysm rupture after EVAR.[6,7] Persistent endoleaks, endograft migration, limb occlusion, and aneurysm sac enlargement continue to plague EVAR.[8-11]

The Aptus endograft with EndoAnchors (Aptus Endosystems, Sunnyvale, Calif) is unique in its use of endovascular anchors that are independent of the endograft itself for the device fixation at the proximal aortic neck. The Aptus endograft with EndoAnchors was designed to overcome some of the limitations of currently available devices for treatment of AAA. The use of active fixation with EndoAnchors at the proximal attachment site allows the use of a lower radial force proximal stent, with the potential to reduce early and late aortic neck complications including neck dilation, endoleak, and migration. After the completion of a feasibility trial, a U.S. investigational device exemption premarket approval study was begun.[12] The purpose of this study was to evaluate the safety and effectiveness of the Aptus endograft and EndoAnchors for treatment of AAA.

METHODS

The device. The Aptus AAA Endovascular Repair System comprises two components: a modular bifurcated endograft that uses two docking limbs (Aptus Endograft System) and the Heli-FX Aortic Securement System comprising an electronically controlled applier (Heli-FX Applier) with helical EndoAnchors provided in a cassette and a deflectable sheath (Heli-FX Guide) designed for delivery of the applier to the target location for EndoAnchor implantation. The endograft has a short proximal stent with relatively low radial force at the top of the main body for sealing and the EndoAnchors for fixation (Fig 1). The main body of the endograft is composed of woven polyester fabric and a proximal nitinol self-expanding sealing stent. Each limb is fully supported with a nitinol self-expanding stent running the length of the graft. The helically shaped EndoAnchors are manufactured from MP35N-LT (nickel-cobalt-chromium alloy) and are approximately 4.5 mm in length. The low-profile delivery system for the endograft comes in two sizes: 16F outer diameter for 22-, 24-, and 26-mm-diameter main body devices and all iliac lumens; and 18F outer diameter for the 29- and 32-mm-diameter main body devices. The EndoAnchor delivery system has an outer profile of 16F. The system is described in greater detail in the feasibility trial publication.[12]

Fig 1. The proximal aspect of the main body, with EndoAnchors penetrating the graft through the interstices of the proximal stent ring.

The endograft implantation procedure begins with standard femoral or iliac artery access and introduction of the main body delivery system. Once it is at the desired aortic level, the main body is partially deployed by releasing the proximal stent, unsupported main body, and contralateral gate, while the proximal stent and ipsilateral gate are still tethered to the delivery catheter to stabilize the endograft until EndoAnchor fixation is achieved. After cannulation of the contralateral gate, the Heli-FX Guide is advanced through the contralateral access artery and positioned within the aortic neck. Directing the guide toward the desired location for EndoAnchor implantation, the Heli-FX Applier is advanced through the guide until it is in contact with the endograft, and the EndoAnchor is deployed under fluoroscopic visualization. In this manner, EndoAnchors are implanted around the circumference of the proximal neck, at the physician's discretion. The EndoAnchor is designed to penetrate the endograft and aortic wall to reach the adventitia. The contralateral limb is introduced and deployed before the completion of main body deployment. After release of the main body and removal of its delivery system, endograft implantation is completed by introduction and deployment of the ipsilateral iliac limb.

Study design. This prospective, multicenter, single-arm study was performed at 25 U.S. investigative sites under a Food and Drug Administration investigational device exemption. The study was conducted in accordance with Good Clinical Practice guidelines and was approved by the Food and Drug Administration and each center's Institutional Review Board. Written informed consent was obtained from each subject. Anatomic eligibility criteria included proximal neck length of $\geq$12 mm, diameter of 19 to 29 mm, and infrarenal angulation of $\leq$60 degrees (Table I). Subjects were observed with computed tomography (CT) imaging at 1, 6, and 12 months and then yearly thereafter through 60 months after implantation.

Table I. Eligibility criteria

Inclusion criteria
1. Age 21 years or older
2. Male or nonpregnant female patient; if a woman with childbearing potential, pregnancy test result must be negative before enrollment into the study
3. Willing and able to give informed consent
4. Infrarenal AAA with a maximum diameter ≥4.5 cm
5. Infrarenal AAA with at least 12-mm-length of nonaneurysmal proximal neck
6. Infrarenal AAA with a proximal neck internal diameter between 19 and 29 mm
7. Infrarenal AAA with an internal diameter at the aortic bifurcation ≥18 mm
8. Infrarenal AAA with an angle of ≤60 degrees relative to the long axis of the aorta
9. Bilateral iliac artery distal fixation sites ≥10 mm in length. The resultant repair should preserve patency in at least one hypogastric artery.
10. Bilateral iliac arteries with an internal diameter between 9 and 20 mm
11. Bilateral femoral/iliac arteries with morphology (minimal thrombus, calcium, or tortuosity) compatible with standard vascular access techniques, and vessel size must accommodate a 16F (5.3 mm) or 18F (6.0 mm) delivery system
12. Candidate for elective surgical AAA repair based on the opinion of the investigator
13. Patient agrees to return to the treating investigator for all scheduled follow-up visits and is capable of returning to the hospital for follow-up
14. Life expectancy >2 years

Exclusion criteria
1. Myocardial infarction within past 10 weeks
2. Active systemic infection
3. Ruptured or leaking AAA
4. Mycotic or inflammatory AAA
5. Connective tissue disorders
6. Concomitant thoracic or thoracoabdominal aortic aneurysms
7. Requires emergent AAA surgery
8. Previous AAA repair
9. Patients with a body habitus that would prevent imaging required by the study
10. Patient has significant comorbid conditions that, in the opinion of the investigator, pose undue risk of general anesthesia or endovascular surgery
11. Patient requires additional planned major procedure at the time of AAA repair or within 30 days before or after AAA repair
12. Dialysis dependent renal failure or creatinine concentration >2.5 mg/dL
13. Allergy to or intolerance of radiopaque contrast agents that cannot be adequately pretreated or would prevent imaging required by the study
14. Patients with a known sensitivity or allergy to polyester, nickel, titanium, tantalum, chromium, molybdenum, or cobalt
15. Patients who cannot discontinue oral anticoagulation or antiplatelet therapy at the time of the study procedure
16. Patients with history of bleeding diathesis or hypercoagulable condition
17. Patients with thrombus, calcification, or plaque ≥2 mm in thickness or ≥50% (180-degree) continuous coverage of the vessel circumference in the intended seal zone
18. Patients with irregularly shaped calcification or plaque that may compromise the fixation and sealing at the proximal or distal implantation sites
19. Mental impairment or other conditions that may not allow the subject to understand the nature, significance, or scope of the study
20. Participation in another trial of an investigational drug or device that has not yet completed follow-up requirements

AAA, Abdominal aortic aneurysm.

The primary safety end point of the study was the percentage of subjects experiencing one or more major adverse events (MAE) occurring within 30 days of the index procedure. MAE were defined with the criteria specified by the Society for Vascular Surgery Outcomes Committee in the Lifeline Registry, defined by the occurrence of death, myocardial infarction, stroke, renal failure, respiratory failure, or paralysis.[13]

The primary effectiveness end point of the study was the composite of delivery success and absence of type I or type III endoleaks requiring intervention after the index procedure, migration, open surgical conversion, or aneurysm rupture within 1 year of the index procedure. Delivery success was defined as successful implantation of the Aptus endograft with a main body and two iliac limbs and delivery of at least two EndoAnchors at an appropriate treatment site within the proximal aortic neck. Bench testing demonstrated that displacement force with two or more EndoAnchors was similar to that achieved with a surgically constructed anastomosis.[14]

Aneurysm sac enlargement or shrinkage was defined when the maximum sac diameter changed by more than 5 mm, and migration was defined by endograft stent movement of more than 10 mm, both relative to the 30-day CT scan as read by the core laboratory. Adverse events were adjudicated by an independent Clinical Events Committee; this included all thrombus-related events (TRE), defined as any graft limb occlusions or distal thromboembolic event thought to originate from the endograft. Integrity of the EndoAnchors and endograft stents was assessed on the plain film radiographs by the core laboratory. Unanticipated adverse device effects were defined as those serious adverse events associated with the device that were not previously identified in nature, severity, or incidence. A Data

Safety Monitoring Board was organized to determine whether the rate of adverse events was unreasonable and to establish monitoring criteria and time points for their assessment. The Data Safety Monitoring Board proposed stopping rules based on the predetermined expected frequency of adverse events.

Statistical analysis. The study was designed to demonstrate superiority of the Aptus AAA Endograft System in comparison to the 30-day MAE rate of 11.1% for the 323-subject open surgical AAA repair Lifeline Registry data set (primary safety end point)[13] and to demonstrate aneurysm treatment success greater than a performance goal of 80% at 1 year (primary effectiveness end point).[15-19] Assumptions used for sample size calculations included a one-sided α of .025, 80% power, and withdrawal rates of 5% and 15% at 30 days and 1 year, respectively. The estimated MAE rate at 30 days was 4.6% for the primary safety end point, and the estimated treatment success for the effectiveness end point was 90.3%. Under these assumptions, the sample sizes for the primary safety and effectiveness end points were 155 and 135 subjects, respectively. Thus, the overall sample size was driven by safety and was set at 155 subjects.

A χ^2 test was used to compare categorical variables (with Fisher exact test when the number of cases in any group was less than five), and these are reported as percentages. Continuous variables were assessed with the Student *t*-test and are reported as mean ± standard deviation (range). For all analyses, a two-tailed *P* value of $<.05$ was considered significant.

RESULTS

Between September 2007 and January 2009, 155 subjects were enrolled, and 153 (98.7%) were implanted with the complete Aptus Endograft System. A single subject underwent conversion to open surgical repair before the placement of EndoAnchors after unsuccessful cannulation of the contralateral gate. A second subject was converted to another endovascular device after misdeployment of the Aptus main body. Among the 155 subjects, the mean age was 73 ± 8 years (range, 57-91 years), and 145 (93.5%) were men. Aneurysms ranged in size from 4.2 to 9.4 cm, with a mean of 5.4 ± 0.8 cm. The average proximal aortic neck length was 22.1 ± 10.8 mm, with a range of 2 to 50 mm. The proximal neck length was <12 mm and <10 mm in 17% and 12% of subjects, respectively. The average infrarenal neck angulation was 32.1 ± 14.0 degrees, with a range of 3.1 to 71.7 degrees.[a] Baseline comorbidities and anatomic characteristics are summarized in Tables II and III. The median length of follow-up was 3.4 years, with an interquartile range of 3.1 to 3.8 years.

A total of 155 main bodies, 332 iliac limbs, and 7 aortic cuffs were implanted. The median number of EndoAnchors was five per subject, with a range of 0 to 14 (Fig 2). The average time to deploy the device was 69 ± 34 minutes, including 17 ± 12 minutes to deploy the EndoAnchors. The mean total procedure duration was 135 ± 60 minutes. The mean procedural blood loss was 207 ± 218 mL, with a median of 150 mL. The length of intensive care unit stay averaged 0 ± 1 day, with a range of 0 to 5 days.

Among the 155 subjects, successful device delivery was completed in 153 (98.7%); the two failures included one open surgical conversion after failure to cannulate the contralateral gate and one implantation of a nonstudy endograft after misdeployment of an Aptus main body. In the latter case, the Aptus endograft was released from the delivery system before deployment of EndoAnchors, the study device was dislodged distally into the aneurysm sac, and a nonstudy endograft (Excluder; W. L. Gore,

Table II. Baseline characteristics of the subjects

Age, years	
Mean ± standard deviation	73 ± 8
Median	73
Minimum, maximum	57, 91
Gender, n/N (%)	
Male	145/155 (93.5)
Female	10/155 (6.5)
Comorbid conditions, n/N (%)	
Coronary artery disease	88/155 (56.8)
Previous myocardial infarction	52/155 (33.5)
Congestive heart disease	11/155 (7.1)
Valvular heart disease	15/155 (9.7)
Chronic obstructive pulmonary disease	34/155 (21.9)
History of smoking	124/155 (80.0)
Current smoker	34/155 (21.9)
Stroke	17/155 (11.0)
Renal insufficiency	9/155 (5.8)
Peripheral arterial disease	31/155 (20.0)

Table III. Anatomic characteristics of the subjects as determined by the core laboratory

Neck length, mm	
Mean ± standard deviation	22.1 ± 10.8
Median	19.9
Minimum, maximum	2.0, 50.0
Neck angle, degrees	
Mean ± standard deviation	32.1 ± 14.0
Median	30.5
Minimum, maximum	3.1, 71.7
Neck diameter, mm—landing zone	
Mean ± standard deviation	22.8 ± 2.5
Median	22.5
Minimum, maximum	17.5, 29.5
Aneurysm maximum diameter range, n/N (%)	
<45 mm	0/155 (0.0)
45-49 mm	43/155 (27.7)
50-59 mm	85/155 (54.8)
60-69 mm	21/155 (13.5)
70-79 mm	5/155 (3.2)
80-89 mm	0/155 (0.0)
≥90 mm	1/155 (0.6)
Minimum access vessel diameter, mm	
Mean ± standard deviation	7.0 ± 1.4
Median	7.0
Minimum, maximum	3.7, 11.0

[a]Investigator-submitted data were used to determine anatomic inclusion or exclusion. Core laboratory data are presented here.

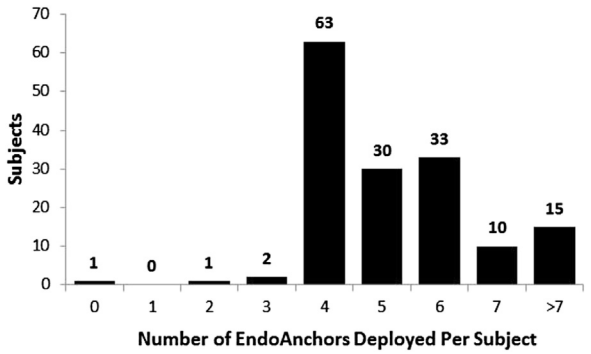

Fig 2. The number of EndoAnchors (810) implanted in 154 subjects.

Table IV. Subjects experiencing one or more major adverse events (*MAE*) within 30 days, 1 year, and 3 years of index procedure

Event	*Through 30 days, n/N (%)*	*Through 1 year, n/N (%)*	*Through 3 years, n/N (%)*
Death	1/155 (0.6)	5/155 (3.2)	15/155 (9.7)
Myocardial infarction	2/155 (1.3)	7/155 (4.5)	10/155 (6.5)
Stroke	0/155 (0.0)	3/155 (1.9)	7/155 (4.5)
Renal failure	0/155 (0.0)	2/155 (1.3)	6/155 (3.9)
Respiratory failure	0/155 (0.0)	1/155 (0.6)	3/155 (1.9)
Paralysis	0/155 (0.0)	0/155 (0.0)	0/155 (0.0)
Any MAE	3/155 (1.9)	14/155 (9.0)	30/155 (19.4)

Flagstaff, Ariz) was deployed through the study device to complete the repair. The 30-day mortality rate was 0.6%, with one postdischarge cardiac death that occurred 18 days after an index procedure complicated by rupture of an iliac artery during balloon angioplasty of a graft limb. Overall survival at 1, 2, and 3 years was 96.8%, 96.1%, and 91.6%, respectively. Freedom from aneurysm-related mortality was 99.4% at 1 year, accounted for by the death that occurred within 30 days of implantation. There was one additional aneurysm-related death beyond 3 years due to hemorrhagic stroke adjudicated to be related to warfarin prescribed to treat a pulmonary embolism subsequent to an AAA-related reintervention. There were no device-related deaths or AAA ruptures in the study. Type I and type III endoleaks within the first year of follow-up were observed in one subject each. The primary effectiveness end point of 1-year treatment success was achieved in 151 of 155 subjects (97.4%); thus, the study met its primary effectiveness end point by exceeding the 90.3% estimated rate of treatment success.

MAE occurred in three subjects (1.9%) within 30 days and in 14 subjects (9.0%) within 1 year (Table IV). The observed 30-day MAE rate was significantly lower than the 11.1% rate in the Lifeline open surgical control group ($P = .0003$); thus, the study met its primary safety end point.

There were no EndoAnchor or stent fractures identified in any subject. There were no reported balloon ruptures during inflation at the proximal endograft attachment site. There was no migration of the EndoAnchors relative to the endograft in any subject. Endoleaks as assessed by the core laboratory are reported in Table V. There was one type I endoleak within the first year after implantation (0.6%), for which the subject did not meet the proximal neck inclusion criteria. This subject underwent reintervention with placement of four additional EndoAnchors 8 months postoperatively, without resolution of the endoleak. Chimney grafts were deployed in this subject 10 months thereafter, and the endoleak resolved. There was one type III endoleak that occurred in a subject who had inadvertent caudal deployment of the main body requiring placement of an aortic extender cuff during the initial procedure (0.6%). The unanchored main body migrated distally relative to the aortic cuff, as observed on the 6-month CT scan, which also identified sac enlargement. This subject was successfully treated 7 months after the index procedure, with deployment of an aortouni-iliac device within the original endograft and a femoral-femoral bypass.

Type II leaks were observed in 49 of 149 subjects (32.9%) at 30 days and in 23 of 131 subjects (17.6%) at 1 year. Endograft migration >1 cm was reported by the core laboratory in five subjects. Two subjects exhibited endograft migration on the 2-year follow-up CT scan, neither with evidence of endoleak or EndoAnchor dislocation or requiring reinterventions. One of the two was associated with significant mural preoperative aortic neck thrombus that might have precluded EndoAnchor penetration into the aortic wall (Fig 3). Aortic neck thrombus >2 mm in thickness is a criterion of exclusion into the trial. On 3-year follow-up CT imaging, two subjects demonstrated endograft migration from the proximal fixation site. In both subjects, there was no evidence of EndoAnchor dislocation; they remained in the same location with respect to the endograft, and there were no demonstrable type I endoleaks. It could not be determined whether the EndoAnchors failed to adequately penetrate the aortic wall on implantation, the EndoAnchors became dislodged from the aortic wall over time, or the caudal displacement of the endograft was attributable to aortic neck elongation alone. A fifth subject presented with migration at 4-year follow-up, again without evidence of endoleak or EndoAnchor dislocation and not requiring reintervention. Aneurysm sacs decreased in 60.3% of subjects at 1 year and in 81.7% at 3 years. Sacs enlarged in 1.5% of subjects at 1 year and in 3.7% at 3 years (Table VI). Overall, a total of five subjects (3.2%) exhibited >5 mm sac enlargement, of which four occurred in conjunction with type II endoleaks and one in conjunction with the type III endoleak noted before.

Sixty-two subjects experienced 114 adverse events that met the definition of unanticipated adverse device effects through the median follow-up of 4.2 years. TRE accounted for the unanticipated adverse device effects in 61 of these 62 subjects (98.4%). Overall, 32 subjects (20.6%) experienced a total of 49 device-related thrombotic events within 1 year of implantation (average of 1.5 events per subject), and 56 subjects (36.1%) experienced 104 device-related

Table V. Endoleaks as assessed by the core laboratory

Endoleak type	*30 days, n/N (%)*	*6 months, n/N (%)*	*1 year, n/N (%)*	*2 years, n/N (%)*	*3 years, n/N (%)*
I	0/149 (0.0)	0/140 (0.0)	0/131 (0.0[a])	0/104 (0.0)	0/78 (0.0)
II	49/149 (32.9)	33/140 (23.6)	24/131 (18.3)	11/104 (10.6)	10/78 (12.8)
III	0/149 (0.0)	1/140 (0.7)	0/131 (0.0)	0/104 (0.0)	0/78 (0.0)
IV	0/149 (0.0)	0/140 (0.0)	0/131 (0.0)	0/104 (0.0)	0/78 (0.0)
V	0/149 (0.0)	0/140 (0.0)	0/131 (0.0)	0/104 (0.0)	0/578 (0.0)
Indeterminate	1/149 (0.7)	4/140 (2.9)	4/131 (3.1)	2/104 (1.9)	4/78 (5.1)

[a]A type I endoleak was observed on a nonprotocol-required computed tomography (CT) scan performed within the first year after the index procedure. This scan was not reviewed by the core laboratory and thus does not appear in the table.

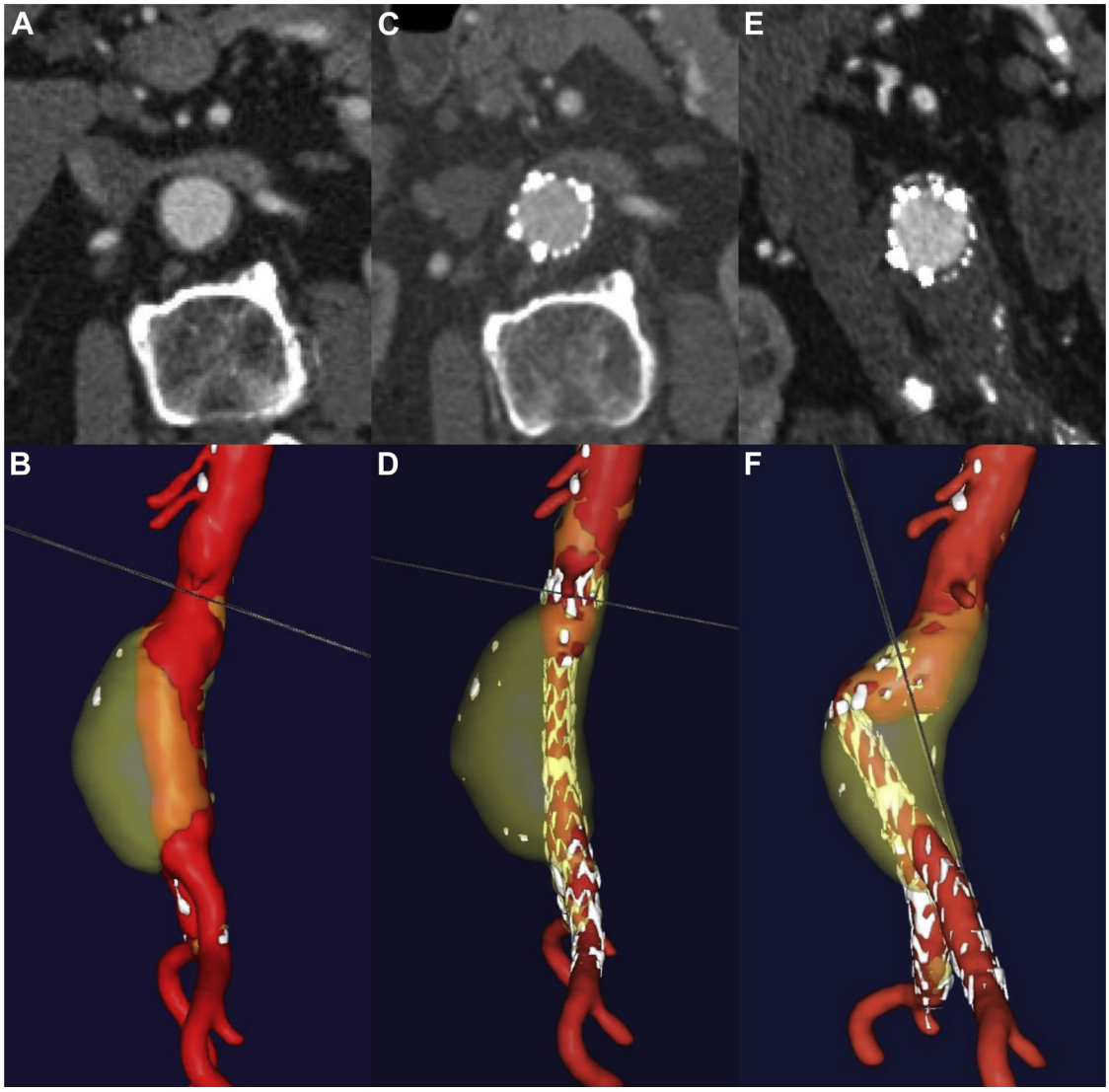

Fig 3. Computed tomography (CT) images from a subject with endograft migration. **A,** Preoperative image of aortic neck with significant mural thrombus. **B,** Preoperative three-dimensional reconstruction. **C,** A 1-month image demonstrating reasonable apposition of graft to aortic wall but poor penetration of EndoAnchors. **D,** A 1-month three-dimensional reconstruction with top stent of endograft immediately caudal to the left renal artery. **E,** A 30-month image demonstrating poor EndoAnchor penetration and proximal stent located in mural thrombus. **F,** A 30-month three-dimensional reconstruction illustrating caudal migration of the endograft well below the left renal artery.

Table VI. Aneurysm sac diameter change by core laboratory analysis at each follow-up time point

	6 months (n = 140), No. (%)	*1 year (n = 131), No. (%)*	*2 years (n = 107), No. (%)*	*3 years (n = 82), No. (%)*
Decrease by >5 mm	62 (44.3)	79 (60.3)	78 (72.9)	67 (81.7)
No change[a]	77 (55.0)	50 (38.2)	26 (24.3)	12 (14.6)
Increase by >5 mm	1 (0.7)	2 (1.5)	3 (2.8)	3 (3.7)

[a]A change of ≤5 mm in the aneurysm sac diameter.

thrombotic events within 3 years (average of 1.9 events per subject). Median time from implantation to first event in affected subjects was 355 days (interquartile range, 176-691 days; range, 17-1477 days). The rate of limb occlusion on a per subject basis was 4.5% (seven subjects) at 1 year and 7.7% (12 subjects) at 3 years. Distal embolic events linked to the endograft occurred in 15 subjects (9.7%) within 1 year and 23 subjects (14.8%) within 3 years. Imaging identified nonocclusive thrombus in association with symptoms (or asymptomatic thrombus that was treated prophylactically) in 15 subjects (9.7%) through 1 year and 33 subjects (21.3%) through 3 years (Fig 4).

A total of 122 secondary interventions were performed in 74 subjects (47.7%), 92 (75.4%) of which were performed in 58 of the 61 subjects (95.1%) with TRE (Table VII). No TRE resulted in minor or major amputations, either at the time of the event or as a result of treatment for the event. Six subjects (3.29%) underwent open surgical conversion: one during the index procedure after inability to cannulate the contralateral gate, one for migration discovered on the 2-year follow-up CT scan, one for aortoenteric fistula remote from the location of the EndoAnchors, and three for device occlusion (Table VIII). Three subjects (1.9%) had implantation of a nonstudy endograft device, one after the aforementioned misdeployment of the Aptus main body device during the index procedure, one for endograft limb occlusion, and one for the aforementioned type III endoleak after disunion of the unanchored main body and aortic extender cuff.

Endograft explantation was necessary in six subjects. Among these, one underwent explantation at the index procedure after inability to cannulate the contralateral gate, mentioned previously. The other five explants were performed for thrombotic occlusion in three subjects, endograft migration and kinking in one subject, and aortoenteric fistula remote from the site of EndoAnchor implantation in the last subject.

TRE root cause analysis. After the identification of the high rate of TRE, a root cause analysis was performed. The root cause analysis indicated that the high rate of graft-related thrombotic events was caused by undersized docking lumens in the main body endografts, resulting from a manufacturing stitching process that allowed luminal narrowing. The out-of-specification and undersized docking lumens, when implanted within the ipsilateral or contralateral stent graft main body docking lumen, led to focal flow lumen diameter reductions and significant infolding of the stent graft material. An explanted endograft from an open surgical conversion demonstrated this constriction and infolding of the fabric within the docking lumens (Fig 5).

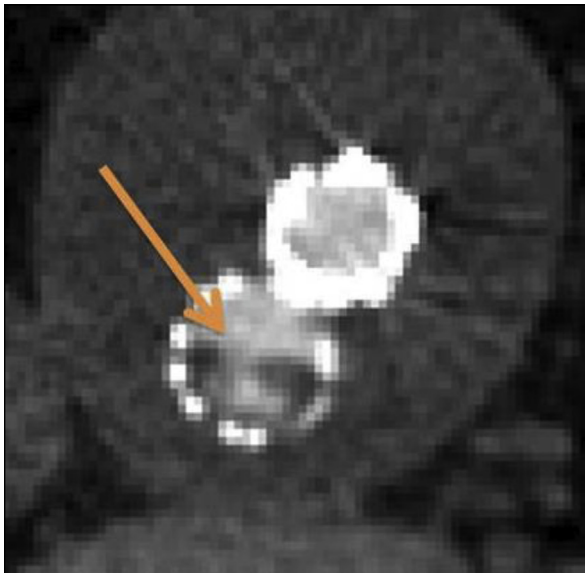

Fig 4. Computed tomography (CT) image of endograft limb with irregular luminal thrombus (*arrow*).

We hypothesize that narrow and highly irregular luminal surfaces resulted in a high fluid shear environment that led to platelet aggregation within the lumen, having the potential to progress to limb occlusion or to embolize in the distal vasculature. This was confirmed in ex vivo bench experiments using fresh male bovine blood. Worst-case undersized docking regions were evaluated, yielding shear rates double those observed in nonnarrowed devices that met specification. Thrombus formation was assessed in main body devices with three different luminal diameters: 9.9 mm, 11.9 mm, and 13.3 mm. Each was perfused at a similar blood flow rate. The highest blood shear rate group (9.9 mm diameter) was associated with the greatest amount of thrombus compared with the medium-shear (11.9 mm) and low-shear (13.3 mm) groups. Applying these shear conditions to other marketed endografts demonstrated similar platelet-rich thrombus formation. Repeating the experiments with platelet-depleted blood demonstrated no thrombus formation, supporting the hypothesis that platelet-rich thrombus formation was the cause of the high rate of TRE.

After identification of the presumed cause of the high frequency of TRE, the manufacturer shared the findings with the Clinical Events Committee, the Data Safety

Table VII. Conversions and reinterventions

	Procedure to 30 days, No. (%)	*30 days to 6 months, No. (%)*	*6 to 12 months, No. (%)*	*12 to 24 months, No. (%)*	*24 to 36 months, No. (%)*	*36 to 48 months, No. (%)*
Subjects at start of interval	155	152	146	143	126	104
Conversion to open repair	1 (0.6)	0 (0)	0 (0)	1 (0.7)	2 (1.6)	2 (1.9)
Conversion to nonstudy endovascular device	1 (0.6)	0 (0.0)	1 (0.7)	0 (0)	1 (0.8)	0 (0)
TRE-related reinterventions	0 (0.0)	13 (8.6)	22 (15.1)	25 (17.5)	24 (19.0)	6 (5.8)
Other AAA-related reinterventions	3 (1.9)	0 (0.0)	5 (3.4)	10 (7.0)	7 (5.6)	3 (2.9)
Total AAA-related reinterventions[a]	3 (1.9)	13 (8.6)	27 (18.5)	35 (24.6)	31 (24.6)	9 (8.7)

AAA, Abdominal aortic aneurysm; *TRE,* thrombus-related event.
[a]The two conversions occurring within 30 days were completed during the index procedure; therefore, they are not counted in the total of "secondary" interventions.

Table VIII. Conversions to open surgical repair or to a nonstudy endograft during the course of study

Days after index procedure	*Event*	*Conversion*
0	Misdeployment of main body	Implant nonstudy device
0	Failure to cannulate gate	Open surgical repair
203	Type III endoleak between main body and aortic cuff	Aortouni-iliac device
467	Device occlusion	Open surgical repair
934	Device occlusion	Open surgical repair
938	Limb thrombus deposition	Aortouni-iliac device
1004	Migration and subsequent kinking	Open surgical repair
1181	Device occlusion	Open surgical repair
1282	Aortoenteric fistula	Open surgical repair

Monitoring Board, and the principal investigators. The parties developed a strategy that included modification of the surveillance schedule with more frequent follow-up examinations with additional imaging at the discretion of the investigator. Investigators chose numerous treatments to address TRE in their study subjects. In evaluating treatment of the first episode of TRE in 94 limbs, covered stents were employed in 33 limbs (35.1%), bare metal stents in 11 (11.7%), and open surgical revascularization or endograft explant and revascularization in 17 (18.1%). Twenty-one limbs (22.3%) underwent other interventions including thrombectomy, thrombolysis, endarterectomy, percutaneous transluminal angioplasty, and native vessel stenting. Twelve limbs (12.8%) were observed without direct intervention, either with or without (10 and two limbs, respectively) antithrombotic medication.

The placement of a balloon-expandable stent within an iliac lumen in an affected docking region has the potential to address part of the root cause of TRE as the irregular luminal surface can be smoothed; however, a diameter increase would not be obtained because of the constriction of the undersized main body endograft docking lumen. Covered stents may offer the potential for better smoothing than bare metal stents. None of the 33 limbs treated with a covered stent experienced recurrent TRE. By contrast, recurrences developed in two of 11 limbs (18.1%) treated with bare metal stents and in eight of 21 limbs (38.1%) in which the offending endograft was not directly addressed with an intervention (Table IX).[b]

DISCUSSION

The two decades after the advent of EVAR witnessed great advances in endograft technology, operator proficiency, and patient selection. Early reports documented clinical benefit over traditional open surgical aneurysm repair, with reductions in perioperative adverse events, length of hospital stay, and time to return to baseline activity levels.[20-22] Nevertheless, the longer term durability of the procedure remains inferior to that of open surgical repair, and early morbidity and mortality benefits have not persisted during long-term follow-up.[5,6,23] As well, the applicability of current devices is limited to patients with relatively specific aortoiliac anatomic configurations and access vessels of adequate diameter to accommodate the relatively large bore delivery systems. Outcome is inferior when the limits of an endograft are extended beyond its intended use, particularly when the proximal neck is highly angulated, short, or large in diameter.[24-27]

The Aptus endograft and EndoAnchors were designed to function in tandem to offer a durable solution to proximal aortic neck challenges, thereby increasing the applicability of EVAR to a broader patient population. The design concept separates sealing and fixation, relying on a conformable top stent ring without great radial force to achieve sealing while the EndoAnchors accomplish fixation. The absence of a high–radial force stent and the use of securing EndoAnchors may reduce the incidence of proximal aortic neck enlargement commonly encountered after EVAR, although there are scant objective data on which to support this supposition.[28] Noting the durability of open surgical aneurysm repair, the EndoAnchors were designed to mimic a traditional surgically sutured anastomosis. The data from this study confirmed a low rate of type I endoleak and endograft migration. Further, aneurysm sac contraction occurred in more than 60% of

[b]Statistical testing omitted because of the post hoc analysis.

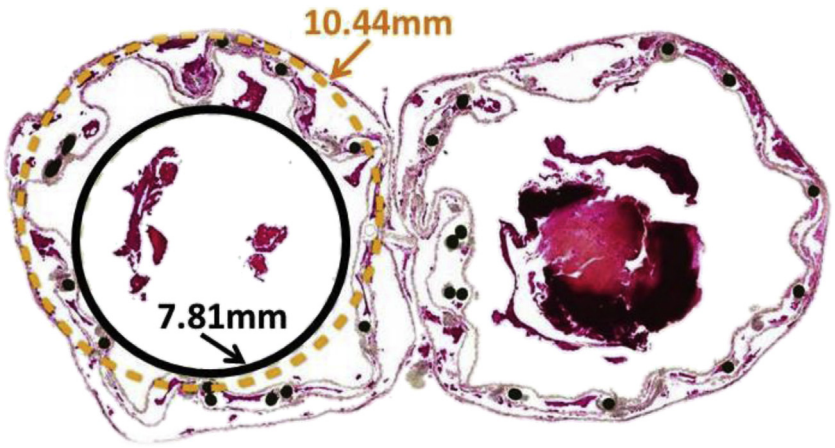

Fig 5. Infolding of graft fabric evident on an explanted device, with the histologic section at the level of the docking limbs. The *black circle* is the lumen diameter when it is reconstructed from nadir to nadir; the *orange circle* represents the nominal diameter.

Table IX. Treatment of thrombus-related events (*TRE*), by limb

Treatment	*Events (n = 94), No. (%)*	*Recurrent TRE, n/N (%)*	*Follow-up after intervention Median (minimum, maximum)*
Explant of device	3 (3.2)	0/3 (0.0)	39 (39, 42)[a]
Bypass revascularization	14 (14.9)	2/14 (14.3)	871 (117, 1482)
Covered stent in device	33 (35.1)	0/33 (0.0)	656 (165, 1483)
Bare metal stent in device	11 (11.7)	2/11 (18.2)	812 (531, 1463)
Stent in native artery	3 (3.2)	2/3 (66.7)	873 (414, 973)
Other intervention	18 (19.1)	6/18 (33.3)	833 (0, 1364)
Medication alone	10 (10.6)	3/10 (30.0)	1134 (269, 1324)
Total without intervention	2 (2.1)	1/2 (50.0)	739 (701, 776)[b]
Total with intervention	92 (97.9)	15/92 (16.3)	742 (0, 1483)

[a]Per protocol, subjects exit the study on completion of a 30-day follow-up after conversion.
[b]Follow-up is from time of TRE in limbs without intervention.

subjects 1 year and in more than 80% 3 years after implantation, a rate that surpasses the reports of other devices and is indirect evidence of reliable sealing. Endograft migration was noted in just more than 3% of subjects. Neither EndoAnchor dislocation nor a type I endoleak was recognized in any of these cases. Possible root causes for endograft migration without EndoAnchor dislocation include inability of EndoAnchors to fully penetrate the aortic wall at the time of implantation, EndoAnchor penetration into aortic neck thrombus alone, EndoAnchor dislocation from the aortic wall over time, and elongation of the aortic neck. Whereas the current study defined success by deployment of two or more EndoAnchors, commercially four or six EndoAnchors are recommended, depending on the diameter of the endograft. The primary safety and effectiveness end points of the clinical trial were met; the Aptus system was associated with a lower rate of MAE compared with standard open surgical repair, and the effectiveness of the system as measured by 1-year treatment success was comparable to that of other marketed devices.

The rate of endograft-related thrombotic events was unexpectedly high, although direct comparison of rates to published data is hindered because relatively few prior publications have rigorously searched for or reported such events.[8,29] Although it is not reflected in the MAE rate, TRE were associated with significant clinical sequelae. All but one of five endograft explants performed postoperatively were required because of limb-related complications. A root cause analysis identified the main body docking limb sewing process and out-of-specification lumen diameters as the underlying problem for thromboembolism. Mating of the iliac limbs into the smaller than anticipated docking zones produced a diameter reduction along with infolding of the fabric, both of which increased shear rate and turbulence. Computational fluid dynamics modeling suggested that high shear rate and platelet aggregation within the proximal iliac limbs could occur in out-of-specification gates. The development of platelet-rich thrombi at sites of high shear is well known in many settings, most notably carotid stenosis, in which nonocclusive thrombi embolize distally or progress to in situ vascular occlusion, or both.[30,31] The same phenomenon is also seen in kinked endograft limbs or those narrowed in small aortic bifurcations. A recent study demonstrated a correlation between

higher peak flow velocities and thrombotic events in endograft patients.[32]

Design modifications were facilitated by the precise identification of the underlying cause of the high rate of TRE. A new supporting suture sewing method and enhanced quality assurance processes reduced the shear to a level at or below that of other endograft devices. Clinically, these changes appear to have reduced the rate of TRE to very low levels, reported to be near zero in a report of the early European experience with the newer generation devices.[33]

TRE did not affect the rate of primary end point variables of the study because they are a component of neither MAE nor the effectiveness measures as recommended in societal guidelines.[16,34,35] This is not surprising because the earlier years of EVAR focused on endoleaks, migration, and device integrity issues. Only relatively recently has the rate of endograft limb problems risen to the forefront. A review of published rates of endograft limb occlusion reveals a frequency ranging from 0% to 6%, depending on the particular device and length of follow-up. Reports of embolic complications after EVAR are scant, but two series suggest that the frequency approximates 1%.[8,29] Authors of subsequent revisions of reporting standard documents may consider recommending the addition of endograft-related thromboembolic complications to the list of MAE after EVAR. The analysis of TRE data from the current study is likely to be generalizable to other endografts. When TRE occur with thrombus detected in an endograft, it appears that outcome is best if the problem is directly addressed. Noninterventional management alone was associated with a significant rate of recurrent thromboembolism, and covered stents seemed to provide the best long-term protection.

This clinical trial is limited by many of the shortcomings inherent in studies performed to gain regulatory approval for a medical device. The study population is more limited than would be encountered once a device reaches the marketplace. As such, the findings must be evaluated in the context of the inclusion and exclusion criteria. This is of particular importance in the current study because clinicians may elect EndoAnchor use for patients with the most challenging aortic neck anatomy, a subpopulation that would have been excluded from this study. Similar to most recent investigational device exemption studies, this study does not include a concurrent control group. For this reason, clinical and imaging outcome observations may not be entirely comparable to those of other studies that employed different eligibility criteria. Any comparisons between the current study and other studies should be considered in this regard.

CONCLUSIONS

The Aptus endograft with EndoAnchors is a promising new alternative, with the potential to treat patients with more challenging proximal aortic necks with a system that structurally resembles a hand-sewn surgical anastomosis. Whereas patients with hostile aortic neck anatomy were, for the most part, excluded from enrollment in this study, it is axiomatic that EndoAnchors alone can be used in commercially available endografts, and the a study is ongoing for the stand-alone EndoAnchor indication.[36] The high rates of limb thrombosis and distal thromboembolism appear to have been addressed with a design modification, borne out by early clinical data. Ultimately, the long-term outcome in patients treated with the Aptus system must await the availability of data from ongoing and future clinical trials that are designed to carefully assess the risk-benefit equation of endovascular repair of infrarenal AAA over the broad range of anatomy encountered.

AUTHOR CONTRIBUTIONS

Conception and design: MM, RF, DD
Analysis and interpretation: MM
Data collection: MM, RF, DD
Writing the article: MM, JH, MG
Critical revision of the article: MM, TN, WJ
Final approval of the article: MM, DD
Statistical analysis: MM, MG, RM
Obtained funding: Not applicable
Overall responsibility: MM

REFERENCES

1. Schwarze ML, Shen Y, Hemmerich J, Dale W. Age-related trends in utilization and outcome of open and endovascular repair for abdominal aortic aneurysm in the United States, 2001-2006. J Vasc Surg 2009;50:722-9.
2. Greenhalgh RM, Brown LC, Kwong GP, Powell JT, Thompson SG. 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;364:843-8.
3. Prinssen M, Verhoeven EL, Buth J, Cuypers PW, van Sambeek MR, Balm R, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. N Engl J Med 2004;351:1607-18.
4. Anderson PL, Arons RR, Moskowitz AJ, Gelijns A, Magnell C, Faries PL, et al. A statewide experience with endovascular abdominal aortic aneurysm repair: rapid diffusion with excellent early results. J Vasc Surg 2004;39:10-9.
5. De Bruin JL, Baas AF, Buth J, Prinssen M, Verhoeven EL, Cuypers PW, et al. Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. N Engl J Med 2010;362:1881-9.
6. Greenhalgh RM, Brown LC, Powell JT, Thompson SG, Epstein D, Sculpher MJ. Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med 2010;362:1863-71.
7. Harris PL, Buth J. An update on the important findings from the EUROSTAR EVAR registry. Vascular 2004;12:33-8.
8. Makaroun MS, Tuchek M, Massop D, Henretta J, Rhee R, Buckley C, et al. One year outcomes of the United States regulatory trial of the Endurant Stent Graft System. J Vasc Surg 2011;54:601-8.
9. Hobo R, Buth J. Secondary interventions following endovascular abdominal aortic aneurysm repair using current endografts. A EUROSTAR report. J Vasc Surg 2006;43:896-902.
10. Greenberg RK, Chuter TA, Cambria RP, Sternbergh WC III, Fearnot NE. Zenith abdominal aortic aneurysm endovascular graft. J Vasc Surg 2008;48:1-9.
11. Adelman MA, Rockman CB, Lamparello PJ, Jacobowitz GR, Tuerff S, Gagne PJ, et al. Endovascular abdominal aortic aneurysm (AAA) repair since the FDA approval. Are we going too far? J Cardiovasc Surg (Torino) 2002;43:359-67.
12. Deaton DH, Mehta M, Kasirajan K, Chaikof E, Farber M, Glickman MH, et al. The phase I multicenter trial (STAPLE-1) of the

Aptus endovascular repair system: results at 6 months and 1 year. J Vasc Surg 2009;49:851-7.
13. Zwolak RM, Sidawy AN, Greenberg RK, Schermerhorn ML, Shackelton RJ, Siami FS. Lifeline registry of endovascular aneurysm repair: open repair surgical controls in clinical trials. J Vasc Surg 2008;48:511-8.
14. Melas N, Perdikides T, Saratzls A, Saratzls N, Kiskinis D, Deaton DH. Helical EndoStaples enhance endograft fixation in an experimental model using human cadaveric aortas. J Vasc Surg 2012;55:1726-33.
15. Lifeline registry of endovascular aneurysm repair: long-term primary outcome measures. J Vasc Surg 2005;42:1-10.
16. Summary of Safety and Effectiveness Data (SSED). Endologix Power Link System; 2004.
17. Summary of Safety and Effectiveness Data (SSED). EXCLUDER Bifurcated Endoprosthesis; 2002.
18. Summary of Safety and Effectiveness Data (SSED). Zenith AAA Endovascluar Graft; 2003.
19. Summary of Safety and Effectiveness Data (SSED). The AneuRx Stent Graft System; 1999.
20. Zarins CK, White RA, Schwarten D, Kinney E, Dietrich EB, Hodgson KJ, et al. AneuRx stent graft versus open surgical repair of abdominal aortic aneurysms: multicenter prospective clinical trial. J Vasc Surg 1999;29:292-308.
21. Matsumara JS, Brester DC, Makaroun MS, Naftel DC. A Multicenter controlled clinical trial of open versus endovascular treatment of abdominal aortic aneurysm. J Vasc Surg 2003;37:262-71.
22. Greenberg RK, Chuter TAM, Sternberg WC, Fearnot NE. Zenith AAA endovascular graft: intermediate-term results of the US multicenter trial. J Vasc Surg 2004;39:1209-18.
23. Becquemin JP, Pillet JC, Lescalie F, Sapoval M, Goueffic Y, Lermusiaux P, et al. A randomized controlled trial of endovascular aneurysm repair versus open surgery for abdominal aortic aneurysms in low- to moderate-risk patients. J Vasc Surg 2011;53:1167-73.
24. Sternbergh WC, Carter G, York JW, Yoselevitz M, Money SR. Aortic neck angulation predicts adverse outcome with endovascular abdominal aortic aneurysm repair. J Vasc Surg 2002;35:482-6.
25. Leurs LJ, Kievit J, Dagnelie PC, Nelemans PJ, Buth J. Influence of infrarenal neck length on outcome of endovascular abdominal aortic aneurysm repair. J Endovasc Ther 2006;13:640-8.
26. AbuRahma AF, Campbell J, Stone PA, Nanjundappa A, Jain A, Dean LS, et al. The correlation of aortic neck length to early and late outcomes in endovascular aneurysm repair patients. J Vasc Surg 2009;50:738-48.
27. Schanzer A, Greenberg RK, Hevelone N, Robinson WP, Eslami MH, Goldgerg RJ, et al. Predictors of abdominal aortic aneurysm sac enlargement after endovascular repair. Circulation 2011;123:2848-55.
28. Rodway AD, Powell JT, Brown LC, Greenhalgh RM. Do abdominal aortic aneurysm necks increase in size faster after endovascular than open repair? Eur J Vasc Endovasc Surg 2008;35:685-93.
29. Maldonado TS, Rockman CB, Riles E, Douglas D, Adelman MA, Jacobowitz GR, et al. Ischemic complications after endovascular abdominal aortic aneurysm repair. J Vasc Surg 2004;40:703-9.
30. Markl M, Wegent F, Zech T, Bauer S, Strecker C, Schumacher M, et al. In vivo wall shear stress distribution in the carotid artery: effect of bifurcation geometry, internal carotid artery stenosis, and recanalization therapy. Circ Cardiovasc Imaging 2010;3:647-55.
31. Colace TV, Muthard RW, Diamond SL. Thrombus growth and embolism on tissue factor–bearing collagen surfaces under flow: role of thrombin with and without fibrin. Arterioscler Thromb Vasc Biol 2012;32:1466-76.
32. Karthikesalingam A, Kumar S, Anandarajah JJ, Hinchliffe RJ, Poloniecki JD, Thompson MM, et al. Predictive value of peak systolic velocity for the development of graft limb complications after endovascular repair. J Endovasc Vasc Ther 2012;19:428-33.
33. de Vries JPPM. Results of EVAR with endostapling. Presented at the 34th Annual Charing Cross International Symposium, London, UK, April 15, 2012.
34. Chaikof EL, Blankensteijn JD, Harris PL, White GH, Zarins CK, Bernhard VM, et al. Reporting standards for endovascular aortic aneurysm repair. J Vasc Surg 2002;35:1048-60.
35. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European Society for Vascular Surgery. Eur J Vasc Endovasc Surg 2011;41(Suppl 1):S1-58.
36. de Vries JP, van de Pavoordt HD, Jordan WD Jr. Rationale of EndoAnchors in abdominal aortic aneurysms with short or angulated necks. J Cardiovasc Surg (Torino) 2014;55:103-7.

Submitted Aug 5, 2013; accepted Feb 13, 2014.