From the Society for Vascular Surgery

Results of the United States multicenter prospective study evaluating the Zenith fenestrated endovascular graft for treatment of juxtarenal abdominal aortic aneurysms

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Objective: **This study reports the results of a prospective, multicenter trial designed to evaluate the safety and effectiveness of the Zenith fenestrated endovascular graft (Cook Medical, Bloomington, Ind) for treatment of juxtarenal abdominal aortic aneurysms (AAAs).**

Methods: **Sixty-seven patients with juxtarenal AAAs were prospectively enrolled in 14 centers in the United States from 2005 to 2012. Custom-made fenestrated stent grafts were designed with one to three fenestrations on the basis of analysis of computed tomography data sets. Renal alignment was performed with balloon-expandable stents. Follow-up included clinical examination, laboratory studies, mesenteric-renal duplex ultrasound, abdominal radiography, and computed tomography imaging at hospital discharge and at 1 month, 6 months, and 12 months and yearly thereafter up to 5 years.**

Results: **There were 54 male and 13 female patients with a mean age of 74 ± 8 years enrolled. Mean aneurysm diameter was 60 ± 10 mm. A total of 178 visceral arteries required incorporation with small fenestrations in 118, scallops in 51, and large fenestrations in nine. Of these, all 118 small fenestrations (100%), eight of the scallops (16%), and one of the large fenestrations (11%) were aligned by stents. Technical success was 100%. There was one postoperative death within 30 days (1.5%). Mean length of hospital stay was 3.3 ± 2.1 days. No aneurysm ruptures or conversions were noted during a mean follow-up of 37 ± 17 months (range, 3-65 months). Two patients (3%) had migration ≥10 mm with no endoleak, both due to cranial progression of aortic disease. Of a total of 129 renal arteries targeted by a fenestration, there were four (3%) renal artery occlusions and 12 (9%) stenoses. Fifteen patients (22%) required secondary interventions for renal artery stenosis/occlusion in 11 patients, type II endoleak in three patients, and type I endoleak in one patient. At 5 years, patient survival was 91% ± 4%, and freedom from major adverse events was 79% ± 6%; primary and secondary patency of targeted renal arteries was 81% ± 5% and 97% ± 2%, freedom from renal function deterioration was 91% ± 5%, and freedom from secondary interventions was 63% ± 9%.**

Conclusions: **This prospective study demonstrates that endovascular repair of juxtarenal AAAs with the Zenith fenestrated AAA stent graft is safe and effective. Mortality and morbidity are low in properly selected patients treated in centers with experience in these procedures. (J Vasc Surg 2014;60:1420-8.)**

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Endovascular aortic aneurysm repair (EVAR) has gained widespread acceptance in patients with abdominal aortic aneurysms (AAAs). Prospective randomized trials have demonstrated several short-term advantages over open repair, including less blood loss, operative time, hospital stay, mortality, and morbidity.[1-3] The applicability of these procedures is limited in up to 40% of the patients by the presence of inadequate neck or involvement of the visceral arteries. In these patients, open repair remains the standard treatment in most centers.

Fenestrated endografts have been increasingly used to treat complex aneurysms involving one or more visceral branches. These devices are designed with fenestrations or scallops to incorporate segments of the visceral arteries into the proximal sealing zone. Intermediate results at 2 years from the first 30 patients in the U.S. Zenith Fenestrated AAA Endovascular Graft Trial have shown that the procedure is safe, effective, and associated with high technical success.[4] These results are further corroborated by single-center reports, multicenter registries, and systematic reviews indicating that endovascular repair with fenestrated stent grafts can be performed with high technical success and lower morbidity and mortality compared with open conventional repair.[5-13] This article reports the results of all 67 patients enrolled in the trial designed to evaluate the safety and efficacy of the Zenith fenestrated AAA endovascular graft (Cook Medical, Bloomington, Ind) to treat juxtarenal AAAs.

METHODS

Details of the study design and methods have been previously described.[4] The study was a prospective, multicenter, nonrandomized trial conducted in 14 academic centers in the United States (Supplementary Table I, online only). Participation in each center required informed consent approved by the Institutional Review Board and compliance with the study inclusion and exclusion criteria (Supplementary Table II, online only). Sixty-seven patients were enrolled in the study, including 42 patients in the pivotal phase (January 2005 to August 2010) and 25 patients in the extended access phase (October 2010 to April 2012). This report summarizes results from 67 patients as of November 2013.

Device design and alignment stents. Aneurysm morphology was determined by high-resolution computed tomography angiography (CTA) data sets. Infrarenal aortic neck was ≥4 and <15 mm in length. Device design consisted of one to three fenestrations, including small, large, and scallop fenestrations, with a maximum of two fenestrations of the same type (Supplementary Fig 1, online only). The proposed design was reviewed and approved by one of two centers with prior experience in device planning—Cleveland Clinic Foundation and William A. Cook Australia.

Alignment stents were recommended for all vessels accommodated by small fenestrations, were optional for scallops, and were not recommended for large fenestrations. The study was initiated allowing use of any commercially available balloon-expandable stent for alignment of fenestrations. After enrollment of the first 30 patients, a specifically designed bare-metal balloon-expandable stent (Zenith Alignment stent; Cook Medical, Bloomington, Ind) was available for use. The technical details of device implantation have been previously described.[4-7]

Clinical and imaging follow-up. Follow-up consisted of clinical examination and imaging before discharge and at 1 month, 6 months, and 12 months and annually thereafter for the first 5 years. Imaging evaluation included CTA or CT without contrast enhancement, duplex ultrasound of the visceral arteries, and abdominal radiography. All imaging studies were independently evaluated at the investigative sites and core laboratory. Adverse events were reviewed and adjudicated by an independent clinical event committee.

Statistical analysis. Data were managed and analyzed by MED Institute Inc with SAS 9.1 software (SAS Institute, Cary NC). The reporting standards of the Society for Vascular Surgery for endovascular repair of AAAs were used to define technical success, aneurysm sac changes, endoleak, migration, and device integrity.[14] Major adverse events (MAEs) were analyzed by the definition previously described.[4] Renal function deterioration was defined a priori by serum creatinine rise to >2 mg/dL and >30% from baseline, detected on two or more follow-up tests. A more stringent criterion was defined a posteriori by >30% decrease from baseline in estimated glomerular filtration rate (eGFR) in two or more follow-up tests. Other renal events included renal artery stenosis, occlusion, and kidney parenchymal infarct. For renal arteries targeted by a fenestration, primary patency was defined a posteriori as uninterrupted patency from index procedure until occlusion or any renal stent reintervention for stenosis, and secondary patency was defined a posteriori as an occlusion treated by surgical bypass or not suitable to endovascular salvage. Time-dependent outcomes were reported with Kaplan-Meier estimates. Results were reported as percentage for categorical variables and mean ± standard deviation for continuous variables. The Fisher exact test was used for comparing categorical variables. A value of $P < .05$ was used to determine statistical significance.

RESULTS

Study patients. A total of 195 patients underwent imaging review by the planning center to determine eligibility. Of these, 128 patients (66%) were excluded because of stringent anatomic criteria listed in Supplementary Table III (online only). Of the excluded 128 patients, the most common exclusion criterion was inadequacy of infrarenal aortic neck (<4 mm or ≥15 mm in length) in 60 patients (47%).

Sixty-seven patients met all clinical and anatomic criteria and were included in the study. There were 54 male and 13 female patients with a mean age of 74 ± 8 years. Cardiovascular risk factors and anatomic measurements are summarized in Table I. The mean aneurysm diameter was 60 ± 10 mm (range, 47-100 mm). The

Table I. Clinical and anatomic characteristics of patients participating in the Cook Zenith Fenestrated Abdominal Aortic Aneurysm (AAA) Endovascular Graft Trial

Factors	*No. or mean ± SD*	*Percentage[a] or range*
Demographics		
Age, years	74.2 ± 8.1	52-87
Male	54	81
Body mass index	29.5 ± 6.5	18.6-57.6
Cardiovascular risk factors		
Hypertension	60	90
Cigarette smoking	59	88
Coronary artery disease	36	54
Arrhythmia	21	31
Myocardial infarction	20	30
Chronic obstructive pulmonary disease	24	36
Chronic kidney disease stage 3[b]	16	24
Diabetes mellitus	16	24
Peripheral arterial occlusive disease	15	23
Family history of aortic aneurysm disease	12	21
Cerebrovascular disease	11	16
Congestive heart failure	7	10
History of thromboembolic event	7	10
Anatomic characteristics (site assessment)		
Maximum aneurysm diameter, long axis, mm	59.7 ± 9.7	47-100
Maximum aneurysm diameter, short axis, mm	55.9 ± 9.8	37-94
Aortic diameter at the celiac axis, mm	26.5 ± 2.6	22-33
Aortic diameter at SMA, mm	25.5 ± 2.7	20-32
Aortic diameter at midpoint of renal arteries, mm	24.6 ± 2.8	19-31
Aortic diameter at lowest renal artery, mm	24.5 ± 3	19-31
Aortic diameter 15 mm distal to lowest renal artery, mm	31.3 ± 5.3	20-45
Aortic diameter at the aortic bifurcation, mm	26.2 ± 5.8	17-45
Infrarenal neck length, mm	7.5 ± 2.3	4-12
Suprarenal to infrarenal axis neck angulation, degree	12.2 ± 11.8	0-45
Infrarenal neck to aneurysm axis angulation, degree	20.6 ± 14.1	0-45
Diameter of ostia of SMA, mm	8.6 ± 1.7	5-14
Diameter of ostia of right renal artery, mm	6.6 ± 1	4-8
Diameter of ostia of left renal artery, mm	6.7 ± 1	5-10

SD, Standard deviation; *SMA*, superior mesenteric artery.
[a]The denominators for calculation of the percentages did not include patients with missing data or for whom the condition was reported as unknown.
[b]Glomerular filtration rate ≤ 60 mL/min/1.73 m^2.

length of infrarenal aortic neck averaged 7.5 ± 2.3 mm (range, 4-12 mm).

Stent graft design. A total of 178 visceral arteries were incorporated (Table II), including 129 renal arteries (62 right and 67 left) and 49 superior mesenteric arteries (SMAs). Fenestrations designed to incorporate these vessels included 118 small fenestrations for renal arteries, 51 scallops for 40 SMAs and 11 renal arteries, and nine large fenestrations for SMAs. The most common device configuration, used in 40 patients (60%), consisted of two small renal fenestrations and a scallop for the SMA.

Device implantation. Endovascular repair was performed with general endotracheal anesthesia in 52 patients (78%) or local-regional anesthesia in 15 (22%). The femoral arteries were surgically exposed in 57 patients (85%) or accessed percutaneously in nine. One patient (1.5%) required an iliac conduit. Total anesthesia and procedure times were 298 ± 74 minutes (range, 177-623 minutes) and 236 ± 81 minutes (range, 104-554 minutes), respectively. The mean fluoroscopy time was 60 ± 34 minutes (range, 5-233 minutes), and the mean dose of contrast material was 42,748 ± 24,256 mgI (range, 4500-113,700 mgI). The mean time for complete device implantation was 164 ± 69 minutes (range, 50-448 minutes). The mean estimated blood loss was 526 ± 490 mL (range, 50-2400 mL).

Technical success was achieved in all 67 patients, with all intended target vessels stented (100%). Of 178 visceral arteries targeted by fenestrations or scallops, alignment stents were used in 127 (71%) visceral arteries, including all 118 renal arteries incorporated by small fenestrations, eight renal arteries incorporated by scallops, and one SMA targeted by a large fenestration. None of the SMA scallops were aligned by stents despite the use of single-width scallop in the design. A total of 135 balloon-expandable stents were used (Table II), including 115 bare-metal and 20 iCAST covered stents (Atrium, Hudson, NH). Placement of two stents was required in seven renal arteries and one SMA because of kink or inadequate overlap between the fenestration and the first stent. All 178 visceral arteries were patent by completion angiography. Other adjunctive procedures included iliac angioplasty in 12 patients, iliac stent in six, femoral artery repair or endarterectomy in six, and celiac stent in one.

Table II. Device design, fenestration type, and alignment stents in patients participating in the Cook Zenith Fenestrated Abdominal Aortic Aneurysm (AAA) Endovascular Graft Trial

	No.	*%*
Types of fenestrations used for target vessel incorporation		
Renal artery	129	72
Small fenestrations	118	66
Scallops	11	6
SMA	49	28
Scallops	40	22
Large fenestration	9	5
Total number of vessels	178	100
Design of proximal fenestrated stent graft		
2 small fenestrations and 1 scallop	40	60
2 small fenestrations and 1 large fenestration	9	13
2 small fenestrations	6	9
1 small fenestration and 1 scallop	5	7.5
1 scallop	4	6
1 small fenestration	2	3
1 small fenestration and 2 scallops	1	1.5
Total number of devices	67	100
Alignment stents		
Zenith alignment stent (Cook Medical Inc, Bloomington, Ind)	58	43
Express LD stent (Boston Scientific, Bloomington, Minn)	29	21
eV3 IntraTherapeutics stent (Covidien, Plymouth, Calif)	25	19
iCAST Covered stent (Atrium Maquet, Hudson, NH)	20	15
Palmaz Genesis stent (Cordis, Warren, NJ)	2	1.5
Bridge Assurant stent (Medtronic, Minneapolis, Minn)	1	0.7
Total number of alignment stents	135	100

SMA, Superior mesenteric artery.

Early morbidity and mortality (≤30 days). There was one early death (1.5%) on postoperative day 2 from bowel ischemia in a patient treated by two small renal fenestrations and a large SMA fenestration, all with alignment stent placement. The SMA was patent, but the patient had persistent acidosis, and abdominal distention was observed at completion of the procedure. Exploratory laparotomy was performed 2 days after the procedure, when irreversible ischemia and necrosis involving the jejunum, ileum, colon, and rectum were found; the patient died about an hour later.

There were no ruptures or conversions to open repair. Early complications are shown in Supplementary Table IV (online only). Eleven patients (16%) had acute blood loss anemia requiring transfusion. Three patients developed bowel ischemia, including the patient who died and two other patients who were treated medically with fluid resuscitation and antibiotics and had complete resolution. No patient experienced deterioration of renal function within the first 30 days.

Time to ambulation was 1.3 ± 1 days (range, 0-7 days). Regular enteral diet was resumed in 1.4 ± 1 days (range, 0-6 days). Mean length of stay was 0.5 ± 1.1 days (range, 0-6 days) in the intensive care unit and 3.3 ± 2.1 days (range, 1-14 days) in the hospital. Core laboratory review revealed widely patent stent graft and target visceral arteries in all 58 patients who had predischarge CTA available for patency assessment and no type I or type III endoleak in 56 patients with studies available for endoleak assessment. Sixteen patients (29%; 16 of 56) had a type II endoleak noted on predischarge CTA.

All-cause mortality and MAEs. Of the 66 patients who survived the first 30 days, the mean follow-up was 37 ± 17 months (range, 3-65 months). Follow-up was 44 ± 17 months (range, 3-65 months) among the 42 patients enrolled in the pivotal study phase, of whom 35 (83%) completed 2 years and 17 (40%) completed 5 years of follow-up.

There were five deaths during the study (Table III), including the aforementioned aneurysm-related death. Three late deaths were considered by the clinical event committee to be unrelated to the aneurysm repair and one was considered to be indeterminate. Freedom from all-cause mortality was 97% ± 2% at 1 year and 91% ± 4% at 5 years (Table IV). Twelve patients developed 16 MAEs. These included death in five patients; congestive heart failure, bowel ischemia, or myocardial infarction in three patients each; and stroke or bowel obstruction in one patient each. Of the 16 MAEs, four were considered to be events related to the aneurysm repair by independent adjudication. Freedom from any MAE was 90% ± 4% at 1 year and 79% ± 6% at 5 years (Supplementary Fig 2, online only). There were no aneurysm ruptures or conversions to open repair to date.

Renal events. Eight patients developed asymptomatic renal infarcts with no clinical consequence, including seven patients with infarcts diagnosed by predischarge CTA and one who developed infarct associated with occlusion of an accessory renal artery stent at 6 months

Table III. Summary of all-cause mortality and major adverse events (*MAEs*) in the Cook Zenith Fenestrated Abdominal Aortic Aneurysm (AAA) Endovascular Graft Trial

		MAEs[a]	
Type	*Days*	*Cause of deaths or event description*	*Clinical event committee adjudication*
Deaths			
	2	Bowel ischemia	Procedure related
	85	Septic shock, acute MI, and multisystem organ failure	Unrelated
	677	Unknown	Unrelated
	754	Atherosclerotic cardiovascular disease and hypertension	Unrelated
	761	Unknown	Unable to determine
Cardiac			
	76	Anterior septal MI	Unrelated
	140	Congestive heart failure	Unrelated
	314	Congestive heart failure	Unrelated
	625	Congestive heart failure	Unrelated
	245	Cardiac ischemia requiring intervention	Unrelated
	854	Cardiac ischemia requiring intervention	Unrelated
Gastrointestinal			
	0	Bowel ischemia	Procedure related
	8	Bowel ischemia	Procedure related
	25	Bowel ischemia	Procedure related
	383	Bowel obstruction	Unrelated
Neurologic			
	992	Stroke	Unrelated

MI, Myocardial infarction.
[a]One patient may experience more than one MAE.

Table IV. Kaplan-Meier estimates of freedom from stent graft-related events in the Cook Zenith Fenestrated Abdominal Aortic Aneurysm (AAA) Endovascular Graft Trial

	Freedom from adverse event, Kaplan-Meier estimate (standard error)				
	Aneurysm growth[a]	*Endoleaks*[a]	*Secondary interventions*	*MAEs*	*All-cause mortality*
12-month	1.000 (0)	0.668 (0.058)	0.908 (0.036)	0.896 (0.037)	0.970 (0.021)
	(n = 63)	(n = 41)	(n = 57)	(n = 58)	(n = 63)
	(e = 0)	(e = 22)	(e = 6)	(e = 7)	(e = 2)
	(c = 4)	(c = 4)	(c = 4)	(c = 2)	(c = 2)
24-month	1.000 (0)	0.652 (0.059)	0.844 (0.045)	0.862 (0.043)	0.952 (0.027)
	(n = 49)	(n = 31)	(n = 41)	(n = 44)	(n = 49)
	(e = 0)	(e = 23)	(e = 10)	(e = 9)	(e = 3)
	(c = 18)	(c = 13)	(c = 16)	(c = 14)	(c = 15)
36-month	0.935 (0.044)	0.626 (0.062)	0.781 (0.060)	0.791 (0.056)	0.907 (0.041)
	(n = 28)	(n = 18)	(n = 22)	(n = 24)	(n = 30)
	(e = 2)	(e = 24)	(e = 12)	(e = 12)	(e = 5)
	(c = 37)	(c = 25)	(c = 33)	(c = 31)	(c = 32)
48-month	0.935 (0.044)	0.626 (0.062)	0.683 (0.083)	0.791 (0.056)	0.907 (0.041)
	(n = 18)	(n = 12)	(n = 14)	(n = 17)	(n = 19)
	(e = 2)	(e = 24)	(e = 14)	(e = 12)	(e = 5)
	(c = 47)	(c = 31)	(c = 39)	(c = 38)	(c = 43)
60-month	0.880 (0.068)	0.626 (0.062)	0.631 (0.092)	0.791 (0.056)	0.907 (0.041)
	(n = 12)	(n = 7)	(n = 9)	(n = 13)	(n = 14)
	(e = 3)	(e = 24)	(e = 15)	(e = 12)	(e = 5)
	(c = 52)	(c = 36)	(c = 43)	(c = 42)	(c = 48)

c, Cumulative censored; *e*, cumulative events; *MAEs*, major adverse events; *n*, patients at risk.
[a]Based on imaging analysis by the core laboratory.

(Supplementary Table V, online only). Freedom from any renal infarct was 90% ± 4% at 30 days, 88% ± 4% at 1 year, and 88% ± 4% at 5 years. Renal function deterioration by the predefined criteria occurred in three patients, all after 30 days. Two of the three patients had chronic kidney disease stage 3 (GFR ≤ 60 mL/min/1.73 m^2) before repair. Of these, one patient eventually progressed to dialysis without renal artery occlusion or stenosis; this was considered unrelated to aneurysm repair by independent adjudication. Freedom from renal function deterioration by the predefined criteria was 100% at 30 days and 1 year and 91% ± 5% at 5 years (Table IV; Supplementary Fig 3, online only). By

the more stringent criteria (>30% decrease in baseline eGFR), freedom from renal function deterioration was 100% at 30 days, 92% ± 3% at 1 year, and 83% ± 7% at 5 years.

Of 129 targeted renal arteries, there were four renal artery occlusions (3%) in four patients and 12 stenoses (9%) in 10 patients. In addition, one stenosis occurred in one renal artery, which was not targeted by a fenestration or stented. No patient had renal stent kink by core laboratory review of CT scans and radiographs. Of the 10 patients with stenosis in targeted renal arteries, nine had reinterventions. Mean time to occlusion or secondary intervention for stenosis in a target renal artery was 17 ± 16 months (range, 1-51 months). Rate of renal stent occlusion or stenosis was not significantly different for bare-metal stents (13%, 15 of 115) compared with covered stents (5%, 1 of 20; $P = .23$). Freedom from renal artery occlusion was 98% ± 1% at 1 year and 97% ± 2% at 5 years (Supplementary Table V, online only). At 1 and 5 years, primary renal artery patency was 95% ± 2% and 81% ± 5%, respectively, and secondary renal artery patency was 98% ± 1% and 97% ± 2%, respectively (Supplementary Fig 4, online only).

Endoleak and aneurysm sac change. One late type I endoleak (1.5%) was observed for the entire study cohort. The patient had a proximal type I endoleak at 3 years treated with coil embolization, which was confirmed by core laboratory analysis. At last follow-up, aneurysm size remained stable with no evidence of endoleak. Type II endoleaks were noted in 16 of 56 patients (29%) at dismissal, 10 of 49 patients (20%) at 1 year, and six of 32 patients (19%) at 2 years. Most of these were observed with no intervention. There was no type III or type IV endoleak (Supplementary Table VI, online only). Freedom from any endoleak was 67% ± 6% at 1 year and 63% ± 6% at 5 years (Table IV; Supplementary Table VI, online only).

Three patients with type II endoleaks had aneurysm enlargement >5 mm. One patient had reintervention for type II endoleak at 4 years with resolution of endoleak and no additional growth. A second patient was treated for a type II endoleak at 9 months but had persistent type II endoleak at 4 years with aneurysm growth. The third patient was noted to have an increase in aneurysm size at 3 years, with no secondary intervention reported. Decrease in aneurysm sac >5 mm was noted in 38 of 54 patients (70%) at 1 year and 29 of 39 patients (74%) at 2 years (Supplementary Table VII, online only). Freedom from aneurysm growth was 100% at 1 year and 88% ± 7% at 5 years (Table IV; Supplementary Table VII, online only).

Device migration. Two patients had device migration ≥10 mm by core laboratory analysis, which required secondary intervention in one patient. One patient was identified with caudal migration of the fenestrated component at 24 months, resulting in mild deformation and stenosis of the right renal stent, which required reintervention with placement of two renal stents at 883 days. There was no type I or type III endoleak or deterioration of renal function, and the patient had 8-mm decrease in aneurysm sac diameter since implantation of the device. The second patient had migration identified at 5 years, with no endoleak, renal stent stenosis, or deterioration of renal function. In both of these cases, analysis of CTA revealed cranial progression of aortic disease with further dilation of the aortic neck in the fenestrated segment, resulting in loss of fixation and device migration.

Device integrity. Core laboratory analysis of device integrity issues identified barb separation in three patients at 6, 12, and 24 months, respectively; fracture of the proximal Z stent in the inferior apex of a scallop was identified in one patient at 12 months. There were two renal stent fractures affecting an Express LD (Boston Scientific, Minneapolis, Minn) in one (at 12 months) and a Zenith alignment stent in the other (at 6 months). None of the patients with device integrity issues had clinical consequences or required reintervention.

Secondary interventions. Secondary interventions were needed in 15 patients (22%). Freedom from secondary intervention was 91% ± 4% at 1 year, 78% ± 6% at 3 years, and 63% ± 9% at 5 years (Table IV; Supplementary Fig 5, online only).

Secondary interventions were performed to treat renal artery occlusion in two patients and renal stent stenosis in nine. Two patients with renal artery occlusions underwent successful renal artery bypass (the other two patients with renal artery occlusion had stable creatinine levels during follow-up and did not undergo any reintervention). One renal artery stenosis failed an endovascular attempt, and the patient had no other intervention. The remaining eight patients with 10 in-stent stenoses (all within bare-metal stents) underwent angioplasty and additional stent placement. Three patients were treated for type II endoleak by coil embolization in two or laparotomy with ligation of the inferior mesenteric artery in one. One patient had restenting of renal fenestration with covered stent and later coil embolization to treat a proximal type I endoleak.

DISCUSSION

This study represents the updated results of the first prospective, multicenter analysis of endovascular repair with a fenestrated stent graft to treat juxtarenal AAAs. The Zenith fenestrated stent graft is based on a time-tested platform, and the data presented in this study extend our confidence regarding its longer term durability through 5 years. The observations of high technical success (100%), low 30-day mortality (1.5%), no conversion or rupture, only one (1.5%) type I and no type III endoleak, and high secondary target renal stent patency (97%) support the safety, effectiveness, and durability of the Zenith fenestrated stent graft and serve as a benchmark for comparison with other devices or alternative endovascular techniques to treat similar anatomy.

Prospective randomized studies have shown that EVAR has several short-term advantages over open repair, including lower mortality.[1-3] The perioperative survival advantage of endovascular repair is sustained for several years, after which it is lost. Although Level I evidence is not yet available for repair with use of fenestrated stent grafts, it seems logical that an endovascular approach will

have even greater impact, given that open surgery carries greater risk in patients with juxtarenal AAAs who need more extensive reconstruction. Systematic reviews have shown that endovascular repair with fenestrated stent grafts can significantly reduce mortality, morbidity, and renal dysfunction compared with open repair.[12,13] Tsilimparis et al reported that open repair was associated with a fivefold increase in mortality (5% vs 1%) and twofold increase in complications (40% vs 20%), including a 10-fold increase in renal and pulmonary complications.[13]

The argument supporting open repair relates to its long-term durability in contrast to the higher reintervention rates noted for endovascular approaches. Unfortunately, open surgical reports are retrospective, and few if any have critically analyzed late outcomes such as branch patency, renal function changes, aneurysm degeneration, and secondary aortic or laparotomy-related complications. Endovascular repair has been associated with more reinterventions than surgical repair in the Dutch Randomized Endovascular Aneurysm Management (DREAM) and EVAR trials.[1,2] However, these two studies did not include laparotomy-related complications. In the Open vs Endovascular Repair (OVER) trial, which included laparotomy-related problems, there was no difference in reintervention rates, which averaged 20% for both groups.[3] Oderich et al reported late outcomes of open juxtarenal aneurysm repair with use of an endovascular classification based on the estimated number of fenestrations, had the patient been treated by endovascular approach.[15] For patients requiring up to two small fenestrations, implying equipoise to the Zenith fenestrated cohort, freedom from any reintervention was 78% at 3 years, which is identical to the Zenith fenestrated study and similar to the Zenith AAA pivotal study (83%).[16]

The importance of device planning and sizing cannot be overemphasized. In this study, all patients were reviewed by experienced implanters and at the Cook Australia planning center. The proximal landing zone was selected within normal aorta, which was recommended by experienced operators to be >2 cm of parallel aortic wall with at least 4 mm of infrarenal neck and no thrombus, calcium, or angulation. The device was customized to maximize the proximal landing zone within the constraints of the design, which included up to three fenestrations. Successful aneurysm exclusion achieved by a fenestrated stent graft positioned within a normal aortic segment is supported by the rare occurrence of type I or type III endoleak and sac shrinkage achieved in more than 70% of our patients. The stringent anatomic criteria in the study may account for differences in endoleak rate compared with other series of fenestrated endografts and alternative techniques such as snorkel or chimney grafts.[10,17,18]

Despite the rigorous selection process in this study, two patients had migration of the fenestrated component due to cranial progression of aortic disease. England et al reported a much higher migration rate of 22%.[19] It is difficult to determine if the selection process used for device planning in that study was as rigorous as the one used in the Zenith fenestrated trial, but clearly progression of aortic disease should be taken into consideration. The Cleveland Clinic group noted migration >5 mm in only seven of 650 patients (1%) included in a prospective study using selection of >2 cm of proximal landing zone within normal aortic segments.[20]

The need to routinely align fenestrations with stents has been well established since the early reports from Western Australia, which identified more vessel occlusions when stents were not used to align fenestrations.[5] Since then, target vessel patency has been reported to be >95% at 3 to 5 years.[9,10,20] The clinician's choice of type of stent has evolved from bare-metal stents to covered stents on the basis of recent reports of higher patency rates for covered stents (95%) compared with bare-metal stents (89%).[21] In that study, bare-metal stents were more prone to in-stent stenosis in the proximal stent segment, probably because of neointimal hyperplasia from intimal and medial injury triggered by "flaring" of the proximal stent. Conversely, covered stents may have impeded ingrowth of tissue either by acting as a barrier or rendering the arterial wall ischemic. Another advantage of covered stents is protection from type III endoleak if the vessel originates from abnormal aorta.

Preservation of renal function is critical, given that renal insufficiency is an important predictor of mortality after aortic surgery.[1-3] Patients undergoing fenestrated repair are subjected to risk of renal function deterioration from numerous causes.[5-13] Similar to other complex endovascular procedures, common causes of renal dysfunction include progression of parenchymal disease, embolization of atheromatous debris during catheter manipulations, and toxicity from repeated doses of iodinated contrast material, which are needed for device implantation and during surveillance studies. In some patients, renal function is lost from lesions created by the procedure or from device-related complications. Late occlusion of renal stents is infrequent and has been related to dissection, small vessel diameter (<4 mm), or renal occlusive disease.[21] In this trial, freedom from renal function deterioration (91%) and freedom from renal stent occlusion (97%) were high at 5 years.

A few technical lessons should be emphasized from the experience accumulated in this trial and worldwide. Renal artery motion is higher distal to the middle third of the renal artery, indicating that stents should be kept as short in length (<2 cm) as possible.[22] The posterior orientation of a renal artery, especially on the right, may predispose to kinks distal to the stent edge, which can be difficult to detect on completion angiography and more commonly anticipated on the basis of preoperative imaging. In these cases, a short flexible self-expandable stent extension may be added as a bridge between the rigid balloon-expandable stent and the native artery, aiding in compliance mismatch. Debate continues about the need to place alignment stents in SMA or renal scallops. Although there were no instances of occlusion in the Zenith fenestrated trial, others have noted shuttering of the SMA by the fabric of single-width scallops, which may lead to bowel ischemic complications.[8-10] In addition, placement of the distal bifurcated component can result in damage to alignment

stents, which can be avoided by protection of the stent by inflation of an angioplasty balloon during advancement and retrieval of the distal device cannula.

Finally, a variety of creative approaches have been used to extend the indications of EVAR to patients with unfavorable anatomy.[17,18,23] The concept of parallel stent grafts (eg, chimney, snorkel, periscope, or sandwich grafts) to maintain visceral branch patency and to extend the seal zone has been popularized, but concern remains about the effects of "gutter" endoleak on long-term durability as well as branched vessel patency.[17,18] Although technical success is high, two systematic reviews have shown that operative mortality (6% and 4.3%) and rate of type I endoleak (10% and 14%) are unquestionably higher than the results herein described in this trial.[17,18] Another approach that has gained popularity is the use of physician-modified fenestrated stent grafts, but limitations include lack of quality control, inconsistent use of modifications, potential risk of device contamination, and integrity issues that could originate from structural changes in the device.[23]

The primary limitations of this study relate to the nonrandomized design and lack of surgical control group, which preclude any definitive comparison with open surgical repair or alternative endovascular techniques beyond a discussion of historical results. Despite the study's mean follow-up of >3 years, many patients have not reached their 5-year end point, thereby restricting the power of our statistical analysis. The stringent anatomic requirements used in this study should be taken into consideration in comparing results with alternative techniques, such as parallel grafts or open repair. Finally, the predominant use of a bare-metal stent for renal alignment differs from current practice standards and may have accounted for higher rates of renal stenosis in this trial.

CONCLUSIONS

This study presents the results of the Zenith fenestrated trial. Overall, results have shown that endovascular repair of juxtarenal AAAs with a Zenith fenestrated stent graft is safe, effective, and durable. The high technical success, low mortality, rare occurrence of type I or type III endoleak, high target vessel patency, and lack of conversion to open repair or aneurysm rupture relate to the integrity of the device, the proper selection of patients, and the technical abilities of our investigators. These results are similar to what has been achieved with the parent Zenith stent graft for infrarenal aneurysms and to other single-center experiences with fenestrated stent grafts. Still, a rigorous follow-up is recommended in these patients. Continued emphasis should be placed on training, refinement of device design and alignment stents, and evolution of implantation techniques.

The U.S. Zenith fenestrated study represents the ideas and concepts of our mentor, friend, and leader, Dr Roy K. Greenberg, who served as national principal investigator from the inception of the trial to its completion of enrollment in 2012.

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AUTHOR CONTRIBUTIONS

Conception and design: RG, PB
Analysis and interpretation: GO, RG, MF, SL, LS, RF, FJ, PB
Data collection: GO, RG, MF, SL, LS, RF, FJ, PB
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Critical revision of the article: GO, MF, SL, LS, RF, FJ, PB
Final approval of the article: GO, MF, SL, LS, RF, FJ, PB
Statistical analysis: GO, RG, MF, SL, LS, RF, FJ, PB
Obtained funding: Industry-sponsored study
Overall responsibility: GO

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Supplementary Table I (online only). Participating centers in the Cook Zenith Fenestrated Abdominal Aortic Aneurysm (AAA) Endovascular Graft Trial

Institution	*Location*	*Site principal investigator*	*Patients enrolled, No.*
Cleveland Clinic Foundation	Cleveland, Ohio	Sean Lyden, MD	10
Massachusetts General Hospital	Boston, Mass	Christopher Kwolek, MD	8
University of Pittsburgh Medical Center	Pittsburgh, Pa	Michel Makaroun, MD	8
University of North Carolina	Chapel Hill, NC	Mark Farber, MD	8
University of California San Francisco/VA	San Francisco, Calif	Linda Reilly, MD	7
Barnes-Jewish Hospital	St. Louis, Mo	Gregorio Sicard, MD	7
Hospital of the University of Pennsylvania	Philadelphia, Pa	Ronald Fairman, MD	6
Mayo Clinic	Rochester, Minn	Gustavo Oderich, MD	5
New York University	New York, NY	Neal Cayne, MD	2
Dartmouth Hitchcock Medical Center	Lebanon, NH	Mark Fillinger, MD	2
Harborview Medical Hospital	Seattle, Wash	Benjamin Starnes, MD	1
Shands Hospital	Gainesville, Fla	Adam Beck, MD	1
The Indiana Heart Hospital	Indianapolis, Ind	Ali Shahriari, MD	1
University of Massachusetts	Worcester, Mass	Andres Schanzer, MD	1
Total			67

Supplementary Table II (online only). Inclusion and exclusion criteria for the Cook Zenith Fenestrated Abdominal Aortic Aneurysm (AAA) Endovascular Graft Trial

Inclusion criteria
- Aortic or aortoiliac aneurysm with diameter ≥5 cm
- Aortic or aortoiliac aneurysm with a history of growth ≥0.5 cm per year, or clinical indication for AAA repair

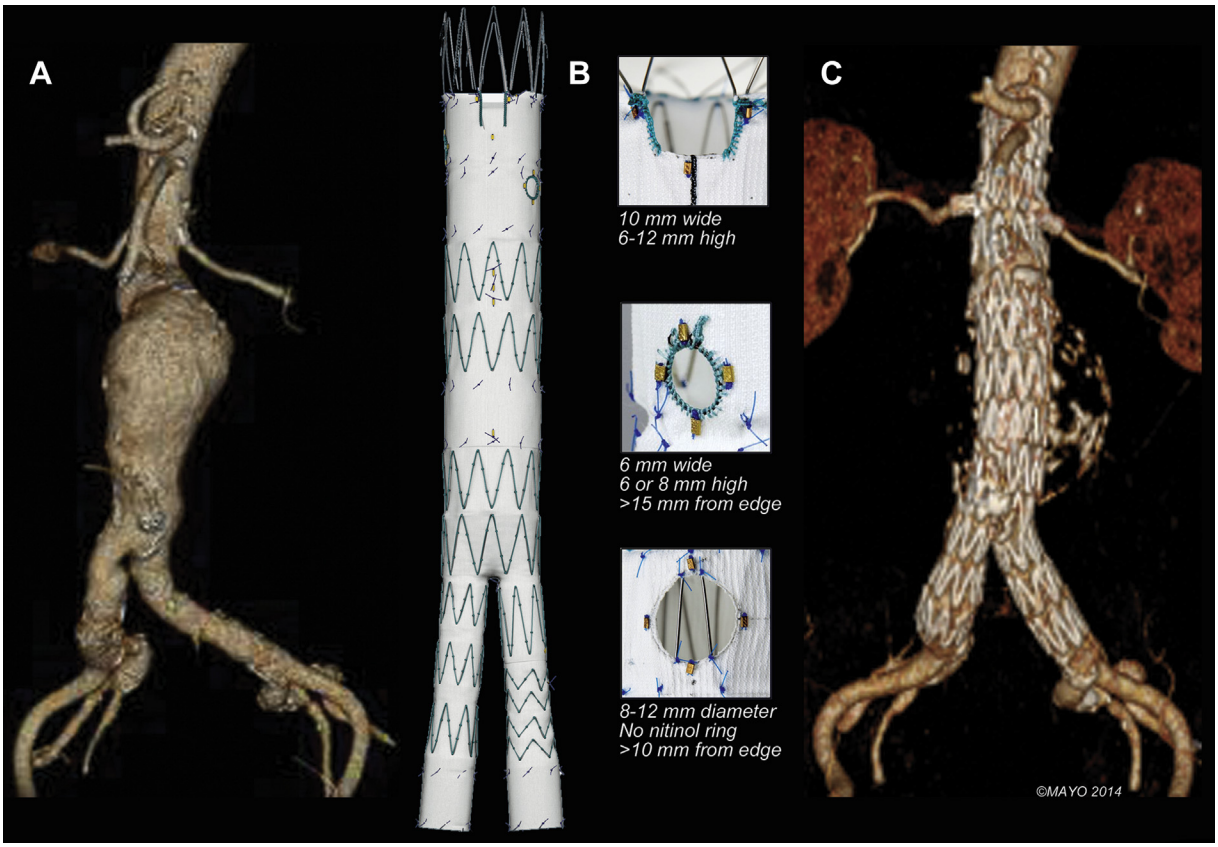
Exclusion criteria

General exclusion criteria
- Younger than 18 years
- Life expectancy less than 2 years
- Pregnant or breast-feeding
- Unwilling to comply with the follow-up schedule
- Inability or refusal to give informed consent

Medical exclusion criteria
- Baseline creatinine >2.0 mg/dL
- Cultural objection to receipt of blood or blood products
- Allergy to stainless steel, polyester, solder, gold, or nitinol
- Anaphylactic reaction to contrast material that cannot be adequately premedicated
- Leaking/ruptured or symptomatic aneurysm
- Uncorrectable coagulopathy
- Previous stent in any renal or visceral artery to be accommodated with a small fenestration

Anatomic exclusion criteria
- Significant occlusive disease, tortuosity, or calcification
- Proximal neck <4 mm or ≥15 mm in length unless otherwise compromised to preclude seal
- Proximal neck, measured outer wall to outer wall on a sectional image (CT), >31 mm in diameter or <19 mm in diameter
- Proximal neck angulated more than 45 degrees relative to the long axis of the aneurysm
- Immediate suprarenal neck angulated more than 45 degrees relative to the immediate infrarenal neck
- Proximal neck diameter change over the length of the proximal seal zone ≥4 mm
- Proximal seal site with circumferential thrombus/atheroma above the renal arteries
- Iliac artery diameter, measured inner wall to inner wall on a sectional image (CT), <7.5 mm at any point along access length (before deployment)
- Ipsilateral iliac artery fixation site diameter, measured inner wall to inner wall on a sectional image (CT), <9.0 mm (before deployment)
- Iliac artery diameter, measured outer wall to outer wall on a sectional image (CT), >21 mm at distal fixation site
- Iliac artery distal fixation site <30 mm in length
- Inability to maintain at least one patent hypogastric artery
- Renal artery stenosis >50%
- Nonbifurcated segment of any artery to be stented <15 mm in length
- Artery to be stented with a maximum diameter <3 mm or >8 mm at the vessel ostium
- Unsuitable arterial anatomy

CT, Computed tomography.



Supplementary Fig 1 (online only). A, Preoperative computed tomography angiography (CTA) of a patient with juxtarenal abdominal aortic aneurysm (AAA) treated by Zenith fenestrated stent graft **(B)**. **C,** Follow-up CTA with patent stent graft and no endoleak. Reproduced with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

Supplementary Table III (online only). Reasons for anatomic exclusion from participation in the Cook Zenith Fenestrated Abdominal Aortic Aneurysm (AAA) Endovascular Graft Trial

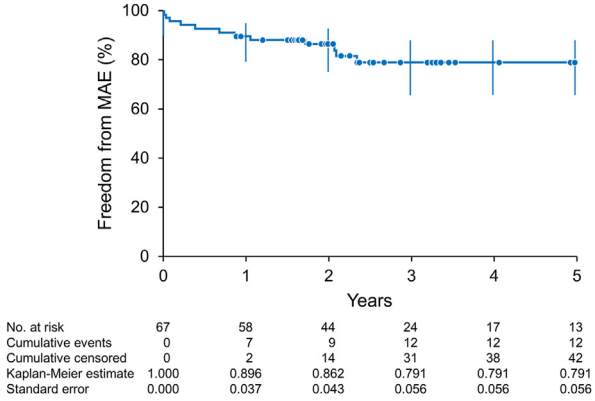
Criteria[a]	*No.*
Proximal neck <4 mm or >15 mm in length	60
Proximal neck diameter change over the length of the proximal seal zone >4 mm	37
Proximal neck >31 mm or <19 mm in diameter	34
Unsuitable arterial anatomy	33
Iliac artery diameter <0.5 mm at any point along access length	32
Proximal neck angulation >45 degrees relative to the long axis of the aneurysm	14
Significant occlusive disease, tortuosity, or calcification	12
Suprarenal neck angulation >45 degrees relative to the immediate infrarenal neck	9
Nonbifurcated segment of any artery to be stented <15 mm in length	9
Renal artery stenosis >50%	8
Ipsilateral iliac artery fixation site diameter <9.0 mm	7
Proximal seal site with circumferential thrombus/atheroma above the renal arteries	6
Inability to maintain at least one patent hypogastric artery	6
Iliac artery distal fixation site <30 mm in length	5
Aortic or aortoiliac aneurysm with diameter of ≤5 cm	4
Iliac artery diameter >21 mm at distal fixation site	4
Artery to be stented with a maximum diameter <3 mm or >8 mm at the vessel ostium	2
Total number of patients excluded	128

[a]A patient may meet more than one exclusion criterion.

Supplementary Table IV (online only). Early and late complications in patients participating in the Cook Zenith Fenestrated Abdominal Aortic Aneurysm (AAA) Endovascular Graft Trial

	Early (≤30 days) (n = 67)		*Late (>30 days) (n = 66)*	
Complications	*No.*	*%*	*No.*	*%*
Cardiac				
Arrhythmia requiring intervention or new treatment	2	3	4	6.1
Cardiac ischemia requiring intervention	0	0	2	3
Congestive heart failure	0	0	3	4.5
Q-wave myocardial infarction	0	0	1	1.5
Non-Q-wave myocardial infarction	0	0	1	1.5
Gastrointestinal				
Bowel/mesenteric ischemia	3	4.5	0	0
Bowel obstruction	0	0	1	1.5
Paralytic ileus > 4 days	1	1.5	0	0
Neurologic				
Stroke	0	0	1	1.5
TIA/RIND	0	0	0	0
Spinal cord ischemia/paralysis	0	0	0	0
Pulmonary				
Supplemental oxygen at discharge	2	3	1	1.5
Ventilation > 24 hours	1	1.5	0	0
Pneumonia requiring antibiotics	0	0	8	12
Renal				
Renal infarct	7	10	1	1.5
Renal artery stenosis	1	1.5	9	14
Renal artery occlusion	0	0	4	6.1
Serum creatinine rise to > 2 mg/dL and > 30%[a]	0	0	3	4.5
Vascular				
Embolization resulting in tissue loss or intervention	2	3	0	0
Limb thrombosis	0	0	0	0
Pseudoaneurysm	0	0	0	0
Vascular injury	1	1.5	0	0
Wound				
Incisional hernia	0	0	2	3
Seroma requiring treatment	0	0	1	1.5
Wound complication requiring return to operation room	1	1.5	0	0
Wound infection	2	3	2	3

RIND, Reversible ischemic neurologic deficit; *TIA,* transient ischemic attack.
[a]Measured in two or more tests.

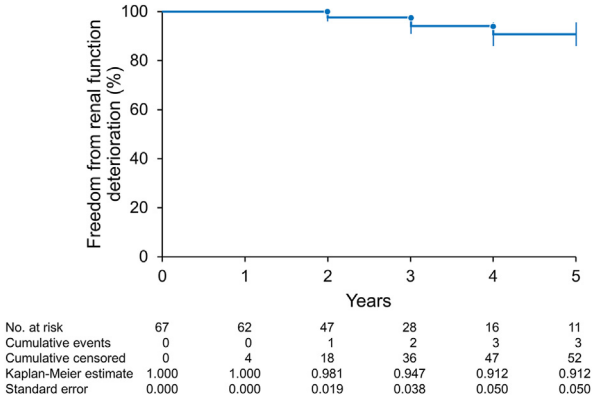


Supplementary Fig 2 (online only). Kaplan-Meier survival estimates of freedom from major adverse event (*MAE*) in the U.S. Zenith Fenestrated Abdominal Aortic Aneurysm (AAA) Endovascular Stent Graft Trial.

Supplementary Table V (online only). Kaplan-Meier estimates of freedom from renal adverse events in the Cook Zenith Fenestrated Abdominal Aortic Aneurysm (AAA) Endovascular Graft Trial

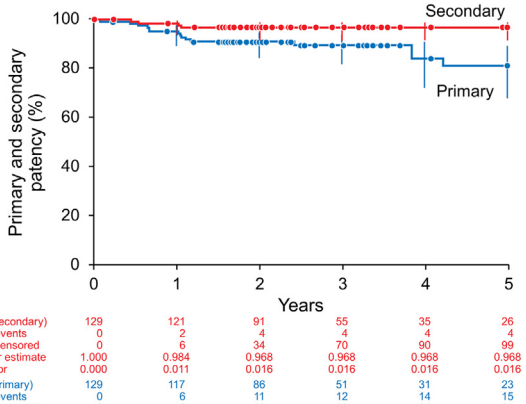
	Freedom from adverse event, Kaplan-Meier estimate (standard error)			
Examination period	*Renal infarct*[a]	*Renal function deterioration*[b]	*Dialysis*[c]	*Renal artery occlusion*
1-month	0.895 (0.037) (n = 59) (e = 7) (c = 0)	1.000 (0) (n = 66) (e = 0) (c = 0)	1.000 (0) (n = 66) (e = 0) (c = 0)	1.000 (0) (n = 66) (e = 0) (c = 0)
12-month	0.880 (0.040) (n = 56) (e = 8) (c = 2)	1.000 (0) (n = 62) (e = 0) (c = 4)	1.000 (0) (n = 62) (e = 0) (c = 4)	0.969 (0.022) (n = 61) (e = 2) (c = 3)
24-month	0.880 (0.040) (n = 43) (e = 8) (c = 15)	0.981 (0.019) (n = 47) (e = 1) (c = 18)	1.000 (0) (n = 48) (e = 0) (c = 18)	0.937 (0.031) (n = 45) (e = 4) (c = 17)
36-month	0.880 (0.040) (n = 28) (e = 8) (c = 30)	0.947 (0.038) (n = 28) (e = 2) (c = 36)	1.000 (0) (n = 30) (e = 0) (c = 36)	0.937 (0.031) (n = 27) (e = 4) (c = 35)
48-month	0.880 (0.040) (n = 18) (e = 8) (c = 40)	0.912 (0.050) (n = 16) (e = 3) (c = 47)	1.000 (0) (n = 19) (e = 0) (c = 47)	0.937 (0.031) (n = 18) (e = 4) (c = 44)
60-month	0.880 (0.040) (n = 14) (e = 8) (c = 44)	0.912 (0.050) (n = 11) (e = 3) (c = 52)	1.000 (0) (n = 14) (e = 0) (c = 52)	0.937 (0.031) (n = 14) (e = 4) (c = 48)

c, Cumulative censored; *e*, cumulative events; *n*, patients at risk.
[a]As reported by sites, regardless of whether confirmed by core laboratory.
[b]Increase in serum creatinine >2 mg/dL and >30% from baseline in two or more tests.
[c]Dialysis in patients with normal preoperative renal function.



No. at risk	67	62	47	28	16	11
Cumulative events	0	0	1	2	3	3
Cumulative censored	0	4	18	36	47	52
Kaplan-Meier estimate	1.000	1.000	0.981	0.947	0.912	0.912
Standard error	0.000	0.000	0.019	0.038	0.050	0.050

Supplementary Fig 3 (online only). Kaplan-Meier survival estimates of freedom from renal function deterioration in the U.S. Zenith Fenestrated Abdominal Aortic Aneurysm (AAA) Endovascular Stent Graft Trial.



No. at risk (secondary)	129	121	91	55	35	26
Cumulative events	0	2	4	4	4	4
Cumulative censored	0	6	34	70	90	99
Kaplan-Meier estimate	1.000	0.984	0.968	0.968	0.968	0.968
Standard error	0.000	0.011	0.016	0.016	0.016	0.016
No. at risk (primary)	129	117	86	51	31	23
Cumulative events	0	6	11	12	14	15
Cumulative censored	0	6	32	66	84	91
Kaplan-Meier estimate	1.000	0.952	0.911	0.896	0.842	0.813
Standard error	0.000	0.019	0.026	0.029	0.046	0.053

Supplementary Fig 4 (online only). Kaplan-Meier survival estimates of primary and secondary target renal stent patency in the U.S. Zenith Fenestrated Abdominal Aortic Aneurysm (AAA) Endovascular Stent Graft Trial.

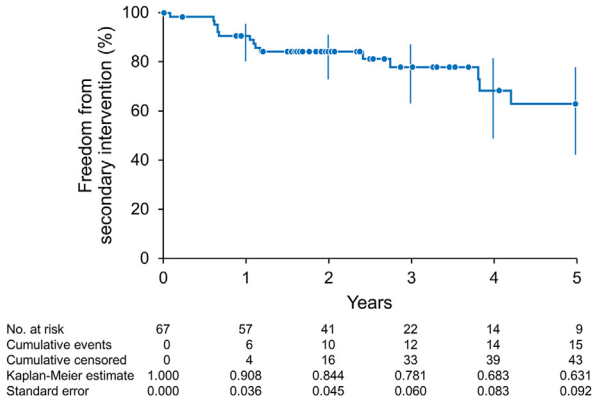
Supplementary Table VI (online only). Endoleak classification and incidence in the Cook Zenith Fenestrated Abdominal Aortic Aneurysm (AAA) Endovascular Graft Trial

	Time point,[a] *% (n/N)*							
Type of endoleak	*Predischarge*	*30 Days*	*6 Months*	*12 Months*	*24 Months*	*3 Years*	*4 Years*	*5 Years*
New endoleak	30 (17/56)	5.0 (3/60)	3.8 (2/53)	4.1 (2/49)	3 (1/32)	0 (0/17)	0 (0/12)	0 (0/9)
Any endoleak	30 (17/56)	23 (14/60)	21 (11/53)	27 (13/49)	19 (6/32)	18 (3/17)	17 (2/12)	0 (0/9)
Type I	0 (0/56)	0 (0/60)	0 (0/53)	0 (0/49)	0 (0/32)	0 (0/17)	0 (0/12)	0 (0/9)
Type II	29 (16/56)	23 (14/60)	20 (10/53)	20 (10/49)	19 (6/32)	18 (3/17)	17 (2/12)	0 (0/9)
Type III	0 (0/56)	0 (0/60)	0 (0/53)	0 (0/49)	0 (0/32)	0 (0/17)	0 (0/12)	0 (0/9)
Type IV	0 (0/56)	0 (0/60)	0 (0/53)	0 (0/49)	0 (0/32)	0 (0/17)	0 (0/12)	0 (0/9)
Unknown	1.8 (1/56)	0.0 (0/60)	1.9 (1/53)	6 (3/49)	0 (0/32)	0 (0/17)	0 (0/12)	0 (0/9)

[a]In some patients, the same endoleak was detected at multiple time points.

Supplementary Table VII (online only). Aneurysm sac changes in the Cook Zenith Fenestrated Abdominal Aortic Aneurysm (AAA) Endovascular Graft Trial

	Time point, % (n/N)						
Change in aneurysm size	*30 Days*	*6 Months*	*12 Months*	*24 Months*	*3 Years*	*4 Years*	*5 Years*
Increase (>5 mm)	0 (0/59)	0 (0/58)	0 (0/54)	0 (0/39)	11 (2/19)	6.3 (1/16)	0 (0/12)
No change	98 (58/59)	48 (28/58)	30 (16/54)	26 (10/39)	16 (3/19)	19 (3/16)	25 (3/12)
Decrease (>5 mm)	1.7 (1/59)	52 (30/58)	70 (38/54)	74 (29/39)	74 (14/19)	75 (12/16)	75 (9/12)



Supplementary Fig 5 (online only). Kaplan-Meier survival estimates of freedom from secondary intervention in the U.S. Zenith Fenestrated Abdominal Aortic Aneurysm (AAA) Endovascular Stent Graft Trial.