Midterm results from a physician-sponsored investigational device exemption clinical trial evaluating physician-modified endovascular grafts for the treatment of juxtarenal aortic aneurysms

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ABSTRACT

Objective: The objective of this study was to report midterm results of an ongoing physician-sponsored investigational device exemption pivotal clinical trial using physician-modified endovascular grafts (PMEGs) for treatment of patients with juxtarenal aortic aneurysms who are deemed unfit for open repair.

Methods: Data from a nonrandomized, prospective, consecutively enrolling investigational device exemption clinical trial were used. Data collection began on April 1, 2011, and data lock occurred on May 31, 2015, with outcomes analysis through December 31, 2015. Primary safety and efficacy end points were used to measure treatment success. The primary safety end point was the proportion of subjects who experienced a major adverse event within 30 days of the procedure. The primary efficacy end point was the proportion of subjects who achieved treatment success. Treatment success required the following at 12 months: technical success, defined as successful delivery and deployment of a PMEG with preservation of those branch vessels intended to be preserved; and freedom from type I and III endoleak, stent graft migration >10 mm, aortic aneurysm neck enlargement >5 mm, and aortic aneurysm rupture or open conversion.

Results: During the 50-month study period, 64 patients were enrolled; 60 began the implant procedure and 59 received the PMEG implant. Aneurysm anatomy, operative details, and lengths of stay were recorded and included aneurysm diameter (mean, 65.9 mm; range, 49-104 mm), proximal seal zone length (mean, 40.8 mm; range, 18.9-72.2 mm), graft manufacture time (mean, 55.1 minutes), procedure time (mean, 156.8 minutes), fluoroscopy time (mean, 39.6 minutes), contrast material use (mean, 75.3 mL), estimated blood loss (mean, 213 mL), and length of hospital stay (mean, 4.1 days) with intensive care unit length of stay (mean, 2.2 days). There were 145 fenestrations made for 110 renal arteries and 38 superior mesenteric arteries (SMAs). One patient had an SMA stent placed before the procedure for severe stenosis, and one subject had the SMA stented during the procedure. Renal arteries were stented whenever possible (93%). There were 102 stented renal arteries in 58 patients. There were no open conversions or explantations. Thirty-day mortality was 5.1% (3/59). There were zero type Ia, one type Ib, and two type III endoleaks during follow-up treated with successful rein- tervention. The overall rate of major adverse events at 30 days was 11.9%. The primary efficacy end points were achieved in 94.1% of patients.

Conclusions: These midterm results are favorable and verify our early report that endovascular repair with PMEG is safe and effective for managing patients with juxtarenal aortic aneurysms. PMEG has exceptional midterm rates of morbidity, mortality, and endoleak and may outperform standard endovascular aneurysm repair with favorable anatomy. In patients who are poor open surgical candidates who present with symptomatic or ruptured juxtarenal aortic aneurysms, PMEG continues to be an extremely appealing option as reliable off-the-shelf solutions are not widely available. Preoperative planning remains the key ingredient for success with use of these techniques. (J Vasc Surg 2017;65:294-302.)
endograft is placed higher in the aorta compared with standard infrarenal repair to provide proximal seal and fixation in a longer segment of healthy parallel aorta above the aneurysm. Meanwhile, the fenestrations or “windows” in the endograft allow blood flow through the vital branch arteries, such as the renal arteries and superior mesenteric artery (SMA), which would otherwise be covered by the graft, and the goal of excluding the aneurysm from aortic pressure and flow is achieved. Several centers have published encouraging results using various commercially available devices and methods, such as the Cook Zenith Fenestrated (ZFEN) device (Cook Medical, Bloomington, Ind). However, there are increasing numbers of elderly and frail patients who fall outside of device sizing specifications or who need a more urgent repair with off-the-shelf technology that has yet to become widely available. We sought to report an update with our midterm results regarding off-the-shelf endograft modification for juxtarenal aneurysm repair with physician-modified endovascular grafts (PMEGs).

**METHODS**

This clinical trial is in compliance with all Food and Drug Administration (FDA) regulations, policies, and procedures governing investigational device exemptions (IDEs). The FDA granted approval to begin this pivotal trial on January 26, 2011, with up to 150 subjects to enroll. The study protocol was also approved by the University of Washington Institutional Review Board (Human Subjects Division), and all patients signed informed consent to participate. Anatomic inclusion criteria for those patients with a juxtarenal AAA were 1 month, 6 months, and 12 months following the index procedure. The follow-up events are as follows: procedural blood loss, duration of procedure, inten-

**Table I. Anatomic inclusion criteria**

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<th>Anatomic criterion Parameter</th>
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<tr>
<td>Proximal neck diameter, mm</td>
<td>20-32 (OD)</td>
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<tr>
<td>Proximal neck length, mm</td>
<td>≥2</td>
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<tr>
<td>Juxtarenal aortic angle, degrees</td>
<td>≤60</td>
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<tr>
<td>Iliac diameter, mm</td>
<td>8-20 (OD)</td>
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<tr>
<td>Iliac length (distal seal zone), mm</td>
<td>≥15</td>
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**Description and objectives.** We are now >4 years into this prospective, consecutively enrolling, nonrandomized, single-institution clinical evaluation. Our institution previously reported the early safety and efficacy of physician-modified FDA-approved off-the-shelf aortic endografts to preserve branch vessel patency when they are used in the treatment of patients with asymptomatic, symptomatic, or ruptured juxtarenal aortic aneurysms with no other options for repair. Patients in this study are considered not to be candidates for elective open repair and are American Society of Anesthesiologists class 3 or greater. In this series, eligible patients were offered PMEG initially and then later a choice between PMEG and the Cook ZFEN device once ZFEN became commercially available in 2012. This report serves as an interim description of midterm results.

**Study primary end points.** The primary safety end point is defined as the proportion of subjects who experience a major adverse event (MAE) within 30 days of the initial procedure. The primary efficacy end point is the proportion of subjects who achieve treatment success. Treatment success is a composite end point assessed at 12 months that requires the following criteria to be met: technical success, defined as successful delivery and deployment of the PMEG with preservation of those branch vessels intended to be preserved; and freedom from type I and III endoleaks at 12 months, stent graft migration >10 mm at 12 months, aortic aneurysm sac enlargement >5 mm at 12 months, and aortic aneurysm rupture or conversion to open repair through 12 months.

**Study secondary end points.** The following secondary safety end points were evaluated through 12 months: mortality rates at 30 days and 12 months, aneurysm-related mortality at 30 days and 12 months, MAE through 12 months, conversion to open repair, and aneurysm rupture. The secondary clinical utility end points evaluated were procedural blood loss, duration of procedure, intensive care unit stay, and length of hospital stay.

**Follow-up intervals and events.** Follow-up intervals were 1 month, 6 months, and 12 months following the initial implant procedure and annually through 5 years. We now have follow-up data for patients >4 years from the index procedure. The follow-up events are as follows: physical examination; ankle-brachial index at hospital discharge if there is history of peripheral artery disease; contrast-enhanced spiral abdominal/pelvic computed tomography (computed tomography angiography); abdominal radiography (kidney, ureter, and bladder), including anterior-posterior, lateral, left anterior oblique, and right anterior oblique projections; device/aneurysm assessment based on imaging analysis; laboratory assessment; and assessment of adverse events.

**MAEs.** MAEs included death, myocardial infarction, stroke, renal failure, respiratory failure, paralysis, bowel ischemia, and procedural blood loss of >1 liter. All MAEs were adjudicated by a Clinical Events Committee composed of three academic faculty members from various medical and surgical specialties at the University of Washington. The Clinical Events Committee determines which adverse events are considered MAEs for evaluation of the primary (30 days) and secondary (1 year) safety end points. Participation in this committee was voluntary.
Procedural details. Our early experience and procedural details with PMEG have been previously published. Three-dimensional reconstruction imaging software (Aquarius; TeraRecon, Foster City, Calif) was used routinely for preoperative planning to ensure precise placement of aortic fenestrations in “clock face” positions for branch vessel preservation. We performed back-table graft modification of an off-the-shelf device (Cook Zenith Flex) using three-dimensional imaging of the aorta and branch arteries to determine the precise location of each fenestration. We created unique fenestrations for the renal arteries, the SMA, and occasionally the celiac artery at the time of the index procedure. As a part of our protocol, after main body deployment, we selected each renal artery and placed balloon-expandable iCast covered stents (Atrium Medical, Hudson, NH) with varying degrees of proximal flare into the artery for adequate seal (Fig 1). Proximal seal zone length was defined as the distance from proximal fabric edge to the lower border of the lowest renal artery plus the infrarenal aortic neck length in millimeters. Our technique has evolved and is now based on many new improvements in preoperative planning: manual centerline adjustment to mimic the course of a stiff wire, constraining ties, arc length measurements, and rapid and efficient operative technique using a dedicated team.

Statistical analysis. This study is designed to estimate the rate of MAEs following juxtarenal AAA repair with PMEG. The proportion of patients receiving a PMEG who experience one or more MAEs within 30 days of the procedure is the rate of interest. A target performance goal of 56% is based on the rate of MAEs at 30 days reported for open surgical control patients from the Society for Vascular Surgery Lifeline Registry of Endovascular Repair. Treatment success is the primary efficacy end point for the study. The proportion of patients who experienced treatment success at 12 months is the rate of interest. PMEG is considered to be effective if this study’s result verifies that the lower limit of the one-sided 95% confidence interval is above 80%. All data are presented as percentages, means ± standard deviation, and range where appropriate.

RESULTS
During the 50-month study period, 64 patients were enrolled; 60 patients began the PMEG procedure and 59 were implanted. The first patient (subject 001) in our study was enrolled in March 2011 and the last (subject 067) was enrolled on May 15, 2015. Data lock for this interim analysis occurred on May 31, 2015, with outcomes analysis through December 31, 2015. By comparison, during the study period, there were an additional 370 procedures for aortic aneurysmal disease including 12 elective open repairs for juxtarenal aortic aneurysms, 51 for open repair of ruptured AAA with short necks, and 44 ZFEN cases. Four enrolled patients did not undergo the PMEG procedure. One patient ruptured and died 1 day before the procedure, one had insurance denial, one withdrew consent, and one was awaiting treatment at the time of this report. One patient who began the procedure did not receive the modified endograft because of difficulty in advancing the delivery system through tortuous iliac anatomy with subsequent rupture of the iliac artery.

Time from presentation to treatment averaged 21 days (range, 0 [rupture] to 104 days). Fifty-nine patients had 30-day follow-up, 49 had 6-month follow-up, 44 had 1-year follow-up, 29 had 2-year follow-up, 21 had 3-year follow-up, and 15 had 4-year follow-up. Mean follow-up for the cohort was 831 days (2.3 years). 76.3% of patients were male (45/59). Demographics are shown in Table II.
PMEG procedure details are listed in Table III, anatomic details of repair are listed in Table IV, and lengths of hospital stay are reported in Table V. As these are interim results, not all patients in this cohort had made it to each follow-up time point at the time of data lock and analysis.

There were 145 fenestrations made for 110 renal arteries and 38 SMAs. One patient had an SMA stent placed, and renal arteries were stented whenever possible (93%). There were 102 stented renal arteries in 58 patients. There were no open conversions or explantations. Thirty-day mortality was 5.1% (3/59). One patient died on postoperative day 1 of idiopathic massive thromboembolization. One patient died on postoperative day 11 of respiratory failure due to severe chronic obstructive pulmonary disease and ischemic embolic stroke, and the third patient died on postoperative day 23 of respiratory failure. Mortality and lengths of stay are shown in Table V. Table VI highlights the primary effectiveness end point and treatment success. The MAE rate at 30 days was 11.9% and is depicted in Table VII.

Overall, there was one type Ib and two type III endoleaks treated with successful reintervention during the study period. At 30 days, there were no type I or type III endoleaks and 10 type II endoleaks (16.9%). At 6 months, there were six type II endoleaks and one type IIIb endoleak. The type IIIb endoleak was from the separation of a left renal stent from the main body and was described in an earlier report. At 1 year, there was one new type Ib endoleak and four type II endoleaks. At 2 years, there were two type II endoleaks and one new type IIIa endoleak. This type IIIa endoleak was from bilateral iliac limb separation with no migration of the proximal fenestrated graft. At 3 years, there was only one type II endoleak. At 4 years, there were no endoleaks reported. There were no type Ia
endoleaks at any follow-up time point. The rate of endoleak during the study period is depicted in Fig 2.

The primary efficacy end points were achieved in 94.1% of patients (95% technical success) and 93.2% of subjects experiencing freedom from migration, rupture or conversion, type I or III endoleaks, or sac enlargement (100%, 100%, 95.5%, 97.7%). Three subjects did not experience technical success. Subject 010 had his renal arteries stented 4 days after the index procedure. In subject 017, we were unable to cannulate the left renal artery; and in subject 045, we were unable to pass the graft through tortuous iliac anatomy, and the device was therefore not implanted. Of the 44 patients with 1-year follow-up, 43 (97.7%) had evidence of sac stability or shrinkage, and 1 (2.3%) had sac enlargement of >5 mm (Fig 3). Of the 21 patients with 3-year follow-up, 20 (95.2%) had evidence of sac stability or shrinkage, and 1 (4.8%) had sac enlargement. Freedom from all-cause and aneurysm-related mortality is shown in Fig 4 and compares favorably with prior reports in well-designed studies.5,6 Freedom from reintervention is reported in Fig 5. More than two-thirds of patients did not require reintervention in this series. The most common reasons for reintervention during the study period were pseudoaneurysm in the access vessels (n = 3), type II endoleak (n = 2), type Ib endoleak (n = 2 separate interventions for the same endoleak), and renal stent separation (n = 2).

**DISCUSSION**

In the United States, as we prepare for the “silver tsunami” of elderly patients presenting with complex vascular disease and inability to tolerate an open operation, endovascular options must continue to evolve to effectively treat these patients with durable outcomes. The volume of fenestrated endovascular repairs of AAAs is rapidly increasing to meet this demand; however, there are no reliable devices available for immediate use in the case of rupture, symptomatic AAA, or unusual aneurysm or patient anatomy.

Our experience has revealed to us that patients undergoing fenestrated repair using devices specifically customized to fit their unique anatomy have extraordinarily better results than patients undergoing standard EVAR to treat short-neck aneurysms or even standard EVAR alone. Concerns surrounding wide application of fenestrated technology to more patients revolve around fear of initial or eventual visceral artery stenosis or occlusion. Some authorities also question the wisdom of inserting stents into healthy renal arteries. Indeed, if these two issues can be overcome and proven to be durable, safe, and cost-effective, it is our opinion that
customized devices for all patients with aortic aneurysms should become the preferred method of treatment. This includes conventional-risk patients and those eligible for standard EVAR. A 95% rate of sac stability or regression and low rate of endoleak is a phenomenal result and worthy of wide attention. There was a single instance of mesenteric ischemia treated with a celiac stent 4 years after implantation and one case of suspected bowel ischemia on postoperative day 1 that resolved with medical management. There were no SMA occlusions. Renal stent patency was 100%. When a 41-mm seal zone length can be accomplished ($r = 19-73$ mm) in a majority of patients, the results eclipse every other device currently available (Fig 6). Indeed, customized fenestrated devices have become our preferred method for treating any aneurysm patient with the slightest hint of a diseased infrarenal aortic neck.

The only commercially available fenestrated endograft available in the United States is the ZFEN device. Another fenestrated device has been tested in a clinical trial in the United States and abroad (Ventana; Endologix, Irvine, Calif), but this trial was abruptly halted because of a high incidence of renal events, and reports from this trial have yet to be published. Our experience with the ZFEN device has been positive; however, nearly 90% of the patients enrolled into the current IDE trial were not candidates for the ZFEN device on the basis of anatomic restrictions (clock-face positions of fenestrations being too close, lengths between fenestrations too long, or infrarenal neck lengths $<4$ mm). Fig 7 depicts a typical example of a ZFEN device that cannot be manufactured or sold within the United States but is easily available with PMEG under our IDE clinical trial. The ZFEN device requires an absolute minimum of 4 weeks to be manufactured, sterilized, and shipped to the United States from Brisbane, Australia, which does no good in the case of a symptomatic or ruptured aortic aneurysm. In our collective experience, three patients ruptured their...
aneurysms and died before undergoing repair with a preordered ZFEN device. Thus, there is a call for an easier and faster method of repair with customized devices. Our 30-day mortality remains comparable to current results of fenestrated endograft repair.\(^1\)\(^,\)\(^7\) In our early series, we had a single death, or 3.8% 30-day mortality, and with increased number of patients, it is now 5.1% (3/59), as we experienced two more deaths within the 30-day window. One death was highly unusual. Despite a brief and technically efficient operation using three fenestrations, the patient awakened with mottling from the umbilicus caudally, paralysis, and strongly palpable pedal pulses on physical examination. This symptomatic patient died 12 hours later from autopsy-proven massive thromboembolization to the pelvis, colon, and spinal cord. On retrospective review of his preoperative computed tomography scan, it was evident that his 8-cm aneurysm had a large degree of stranding around it and irregular thrombus within the aneurysm sac. The other two deaths were due to the patient’s underlying comorbidity.

In comparing our results to other trials of standard EVAR with anatomically suitable subjects, our results compare favorably. In the Open vs Endovascular Repair (OVER) trial, there was a 30% risk of reintervention and 18% risk of death at 4 years.\(^5\) In the EVAR 1 trial, nearly half the patients were dead at 4 years, and 72% of subjects survived without reintervention to 8 years. Endovascular aneurysm-related survival was 93% at 8 years.\(^6\) However, we need to recall that these were all subjects who were anatomically suitable for EVAR. In our series, the patients were not anatomically suitable for standard EVAR. The mean neck length was 5.4 mm, and we had an aneurysm-related survival of an amazing 94% at 4 years. Perhaps the more relevant study to compare our own to would be the EVAR 2 trial, in which the subjects were unfit for open repair.\(^8\) The 30-day mortality in that study was twice ours at 9%, and a staggering 21% had aneurysm-related mortality at 4 years. Recall again that these were unfit patients but were anatomically suitable for standard EVAR.

In our midterm results of PMEGs, we show that individually tailored devices are a safe, efficient, and effective way to treat the increasing number of poor open surgical candidates with juxtarenal aortic aneurysms. We hope to show that adoption of such technology will accelerate our collective ability to address complex aneurysms and that PMEG could be a widely acceptable therapeutic method in the future. Even though there will continue to be a place for PMEG within IDE protocols, an even broader applicability of this technology will likely come from software automation of the planning process and simplification of the procedure. Both of these aspects are currently under development and destined for clinical study. Ultimately, versions of the planning and modification techniques used in this IDE study, along with streamlining of the manufacturing process, could be incorporated into the rapid delivery of commercially available, patient-specific fenestrated endografts.

With regard to chimney and snorkel procedures to treat similar but not identical anatomy, we believe well-planned and accurately delivered fenestrated endografts will be superior in several ways. The present interim results exceed those in a recent comprehensive report on chimneys and snorkels in terms of length of seal zone (41 mm vs 21 mm), rate of type Ia endoleaks (0% vs 5.8% at latest follow-up), branch stent occlusion (0% vs 13% at 3 years), and procedure times (157 vs 233 minutes), among others.\(^9\)

There are some limitations worth mentioning. The only graft available for modification in this study cohort was the Cook Zenith Flex. To ensure strut-free renal fenestrations, which were always stented whenever possible, the
A typical example of a physician-modified endovascular graft (PMEG) device that cannot be manufactured or sold within the United States as a ZFEN device but is easily available under our investigational device exemption (IDE) clinical trial.

A, Intraoperative photograph of the actual graft created for a patient with a solitary right kidney and a superior mesenteric artery (SMA) origin that is close to the origin of the right renal artery.

B, Preoperative computed tomography angiography axial image.

C, Intraoperative angiogram showing successful implantation.

D, Axial image at 1 year demonstrating a widely patent SMA and right renal artery.
large SMA fenestration typically had struts spanning the fenestration based on the stent design inherent to the Cook device. Nevertheless, with patient data out to 4 years, we have seen one case of mesenteric ischemia unrelated to the implant or procedure and one suspected case of transient bowel ischemia on postoperative day 1 that resolved with medical management, no SMA occlusions, and only one secondary intervention for an SMA stenosis in a patient who had a pre-existing SMA stenosis before the PMEG procedure. In our experience, good alignment between the SMA fenestration and SMA ostium, without stenting, has led to excellent patency. Reports of SMA “shuttering” in the literature may be due to poorly planned or inaccurately placed endografts.

Our results and practice of this technology continue to be under an IDE, and wide dissemination is not easily achieved. Also, the precise methods by which we create the device require a somewhat gradual learning curve; we are currently studying exactly how long it takes to become proficient at PMEG creation and ways to simplify graft modification. Our future directions are focused on development and dissemination of proper fenestrated EVAR technique including simplified preoperative planning and graft preparation. For example, physician modification of a blank ZFEN device would be useful as graft modification time would be minimal.

CONCLUSIONS

These midterm data are favorable and continue to verify our early report that endovascular repair with PMEG is safe and effective for managing patients with juxtarenal aortic aneurysms. PMEG is efficient and has acceptable midterm rates of morbidity, mortality, and endoleak and appears durable. In patients who are poor open surgical candidates who present with symptomatic or ruptured aneurysms, PMEG continues to be an extremely appealing option as reliable off-the-shelf solutions are not widely available.

AUTHOR CONTRIBUTIONS

Conception and design: BS
Analysis and interpretation: BS, RH
Data collection: BS, RH, BT
Writing the article: BS, BT
Critical revision of the article: BS, BT
Final approval of the article: BS, RH, BT
Statistical analysis: BS
Obtained funding: BS
Overall responsibility: BS

REFERENCES


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