

## Endovascular Aneurysm Repair Current Status

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Since first described by Parodi in 1991, endovascular aortic repair (EVAR) has progressively and dramatically changed the approach to treating abdominal aortic aneurysm (AAA) disease.<sup>1</sup> Whereas historically developed to treat patients unfit for open repair, EVAR now represents the primary paradigm by which most infrarenal AAAs are managed. This paradigm shift has occurred in the setting of long-term clinical uncertainty and increased expense, largely secondary to the costs of the endograft itself.

EVAR is currently performed by multiple interventional and surgical specialties. Outcomes are associated with lower in-hospital mortality rates compared with open repair, often permitting successful discharge of patients within 24 hours. Because the market share of EVAR has increased, the endograft industry has also seen tremendous growth and development. Cross-sectional imaging with 3-dimensional reconstructions has become paramount to the appropriate and timely management of aortic aneurysms. At present, even in the setting of aortic rupture, EVAR is preferred because it has been associated with lower mortality rates compared with open repair.

Despite the rampant increase in EVAR, not all patients are anatomic candidates for EVAR as defined by industry-issued instructions for use. Therefore, alternative treatment strategies, such as altering endografts with fenestrations or sidearm grafts, snorkeling stent grafts alongside endografts, or performing hybrid debranching procedures with open bypasses to the viscerals and renals followed by endografting have been developed. Although the data supporting EVAR as the primary treatment option for infrarenal AAA is robust, its superiority over open repair can be questioned until the long-term outcomes (>10 years) from landmark randomized controlled trials begin to surface. Parenthetically, the indications for EVAR seem to be increasing because clinical equipoise remains ambiguous and fewer trainees are required to perform open AAA repair. Although early use of EVAR was primarily at centers of excellence, currently it has become the most common manner for AAA repair.<sup>2</sup>

This review will reflect on the landmark trials which have validated the use of EVAR. Data supporting the use of aortic endografts from the 4 primary manufacturers [Medtronic Inc (Minneapolis, MN), W.L Gore and Associates (Flagstaff, AZ), Cook Medical Inc (Bloomington, IN), and Endologix (Irvine,

CA)] who have obtained Food and Drug Administration (FDA) approval will be summarized. The literature supporting the use of branched or fenestrated endografts for use in the management of pararenal and thoracoabdominal aortic aneurysms (TAAA) will be reviewed. Finally, we will discuss products in the endograft pipeline, as well as the expanding indications for EVAR.

### Clinical Trials Supporting the Use of EVAR

#### EVAR-1 Trial

EVAR-1 trial offers the longest follow-up of any of the randomized controlled trials comparing EVAR with open repair (Table 1). Early 30-day results were reported in 2004, mid-term results in 2005, and long-term follow-up out to 8 years in 2010.<sup>3-6</sup> Patient demographics were not significantly different between treatment groups.

During 6904 person-years of follow-up, 524 deaths occurred, 76 of which were aneurysm related. Kaplan-Meier survival curves for all-cause mortality among the 2 cohorts converge at 2 years demonstrating that the survival advantage favoring EVAR is lost. With regard to aneurysm-related mortality, Kaplan-Meier curves converged at 6 years, because endograft failure leading to late rupture-related mortality increased substantially in the EVAR group.

Secondary outcomes including graft complications, reinterventions, and costs favored open repair over the long term. The decision for reintervention for a graft-related complication was left to the local clinician. Although there was a health-related quality of life benefit with EVAR at 3 months, this benefit was lost at 1 year, because both the EVAR and open repair groups had returned to their baseline quality of life scores.

Based on these findings, EVAR-1 investigators concluded that whereas EVAR offered lower operative mortality, there was no difference in total or aneurysm mortality. Further, EVAR was associated with increased rates of complications, reinterventions, and costs.

#### DREAM Trial

One year after the start of the EVAR-1 trial, the Dutch randomized endovascular aneurysm management (DREAM) trial

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**Table 1. EVAR-1 Trial**

Enrollment period	September 1999–August 2004
Patients enrolled	1252 (626 patients in each arm)
Country of study	United Kingdom
Type of study	Multicenter prospective randomized controlled trial
Analysis	Intention to treat
Inclusion criteria	1. At least 60 y of age (male or female) 2. Aneurysm at least 5.5 cm in any plane on CT scan 3. Aortic anatomy suitable for EVAR 4. Medically and anesthesiologically fit to undergo an open repair
Follow-up (min-max)	5–10 y (median 6 y)
Primary outcome	All-cause mortality
Secondary outcome	Aneurysm-related mortality, health-related quality of life, postoperative complications, reinterventions, and hospital costs
Endografts used	51% Zenith (Cook, Copenhagen, Denmark) 33% Talent (Medtronic, Minneapolis, MN) 7% Excluder (Gore, Flagstaff, AZ) 4% AneuRx (Medtronic) 5% Other
Results (EVAR vs Open)	
30-day mortality	1.8% vs 4.3%; AOR, 0.39; 95% CI, 0.18–0.87; $P=0.02$
In-hospital mortality	2.3% vs 6.0%; AOR, 0.39; 95% CI, 0.2–0.76; $P=0.006$
Overall mortality*	7.5 vs 7.7; AHR, 1.03; 95% CI, 0.86–1.23; $P=0.72$
Overall aneurysm mortality*	1.0 vs 1.2; AHR, 0.92; 95% CI, 0.57–1.49; $P=0.73$
Complications*†	12.6 vs 2.5; AHR, 4.39; 95% CI, 3.38–5.7; $P<0.001$
Reinterventions*	5.7 vs 1.7; AHR, 2.86; 95% CI, 2.07–3.94; $P<0.001$
Costs‡	\$23 153–\$18 586

CT indicates computed tomography; EVAR, endovascular aortic repair; AOR, adjusted odds ratio; and AHR, adjusted hazard ratio.

\*As measured in 100 person years.

†Type 1–3 endoleak, graft rupture, kink, migration, thrombosis, stenosis, infection, or embolization, aortic perforation or dissection, dilation of proximal or distal landing zones, renal infarction, continued sac growth, anastomotic aneurysm.

‡Primary admission as well as aneurysm-related readmissions.

began enrolling patients. (Table 2). Operative mortality was reported in 2004, while 2-year and long-term follow-up were reported in 2005 and 2010, respectively.<sup>7–10</sup> Preoperative randomization produced 2 equally matched cohorts.

Unlike the EVAR-1 trial, complications were classified and graded according to the Ad Hoc Committee for Standardized Reporting Practices in Vascular Surgery developed by the Society for Vascular Surgery/International Society for Cardiovascular Surgery.<sup>11,12</sup> Although there was an initial trend toward a survival advantage with EVAR, at 2-year and long-term follow-up cumulative survival rates were similar. Based on these results, authors of the DREAM trial, like the authors of the EVAR-1 trial, concluded that in long-term follow-up EVAR and open repair are similar with respect to survival, although there was a higher rate of secondary intervention in the EVAR group.

### OVER Trial

The outcomes after endovascular versus open repair of abdominal aortic aneurysms (OVER) study was the first randomized controlled trial in the United States comparing EVAR with open repair.<sup>13</sup> Short-term follow-up was reported in 2009 (Table 3). At 2 years, there was no significant difference in secondary procedures, quality of life, or erectile

dysfunction. These results led the study authors to conclude that EVAR offers significantly lower postoperative mortality rates compared with open repair. Furthermore, the authors concluded that this early advantage was not offset at 2 years because there was no late increase in mortality or morbidity in the EVAR group at 2 years.

### ACE Trial

The most recent trial to come to publication is the French trial, Aneurysme de l'aorte abdominale: Chirurgie versus Endoprothese (ACE).<sup>14–16</sup> Short-term follow-up was recently published in 2011 (Table 4). Unlike the 3 previous trials, 30-day perioperative mortality was similar between EVAR and open repair. These results led the study authors to conclude that in patients with low-to-intermediate risk, there is no difference in perioperative or midterm survival or in major and minor complications in patients undergoing EVAR or open repair.

### Lesson Learned from Clinical Trials

The early success cited by the majority of the aforementioned randomized controlled trials impacted clinical practice and introduced EVAR as a new treatment option in patients with infrarenal AAAs. However, mid- and long-term results became

**Table 2. DREAM Trial**

Enrollment period	November 2000–December 2003
Patients enrolled	351 (173 in EVAR arm vs 178 in open repair arm)
Country of study	The Netherlands and Belgium
Type of study	Multicenter prospective randomized controlled trial
Analysis	Intention to treat
Inclusion criteria	1. Aneurysm at least 5.0 cm 2. Aortic anatomy suitable for EVAR 3. Medically suitable for open repair as determined by an internist
Follow-up (min-max)	5.1–8.2 y (median 6.4 y)
Primary outcome	Composite of operative mortality and moderate or severe complications
Endografts used	33.3% Zenith 26.9% Talent 21.6% Excluder 17.5% Other
Results (EVAR vs Open)	
Operative mortality*	1.2% vs 4.6%; RR, 3.9; 95% CI, 0.9 to 32.9; $P=0.10$
Operative mortality+SC	4.7% vs 9.8%; RR, 2.1; 95% CI, 0.9 to 5.4; $P=0.10$
Operative mortality+MC or SC	18.1% vs 23.6%; RR, 1.3; 95% CI, 0.9 to 2.0; $P=0.23$
MC or SC	11.7% vs 26.4%; RR, 2.3; 95% CI, 1.4 to 3.8; $P<0.001$
Two-year cumulative survival	89.7% vs 89.6%; 95% CI, –6.8 to 6.7; $P=0.86$
Long-term cumulative survival†	68.9% vs 69.9%; 95% CI, –8.8 to 10.8; $P=0.97$
Freedom from intervention‡	70.4% vs 81.9%; 95% CI, 2.0 to 21.0; $P=0.03$

DREAM indicates the Dutch randomized endovascular aneurysm management trial; EVAR, endovascular aortic repair; RR, risk ratio; MC, moderate complication; and SC, severe complication.

\*Defined as death within 30-days or death within the same hospitalization.

†Median follow-up at 6.4 y.

‡Six y after randomization.

available, the role of EVAR became subject to some criticism. Even after the publication of EVAR-1 and DREAM, a survey of 1400 Dutch surgeons with regard to operative management of AAA suggested that these European randomized trials did not induce major changes in the decision making for AAA patients suitable for both EVAR and open repair.<sup>17</sup> However, whereas there was no mid- or long-term survival advantage of EVAR at a cost of an increased number of reinterventions, there is an element of practicality that is easily overlooked. EVAR likely offers an upfront survival advantage secondary to decreased procedural mortality. In addition, EVAR uniformly is associated with decreased transfusion rates, decreased intensive care unit, and hospital lengths of stay, as well as an earlier return to daily activities.

One also must consider the immature nature of graft design when the first European trials were being performed. Endografts used in these early trials were only second or third generation devices. Current manufactures are in their fifth and sixth generation of endograft development, having gone through years of problem identification and resolution. Early generation endografts were made of thinner fabric and had higher rates of fabric tears, stent fatigue, and stent fracture.<sup>18</sup> EVAR-1 began enrolling patients for randomization only 8 years after use of the first homemade endograft was reported. The EVAR-1 trial allowed noncommercialized or homemade grafts. Furthermore, 3% of the grafts in EVAR-1 and 10% of the grafts used in DREAM are no longer even

manufactured. Graft failure and migration propagating types 1 and 3 endoleaks have the potential to contribute directly to aneurysm-related mortality. The AneuRx graft (Medtronic, Inc, Minneapolis, MN), which has been shown to have migration rates ranging from 27% to 42% at 3 years, was implanted in 20%, 7%, and 4% of patients in OVER, DREAM, and EVAR-1, respectively.<sup>19,20</sup>

Advances in technology aside, clinical acumen and experience in treating AAAs have increased in the past decade. Patient and endograft selection have been refined. Reintervention techniques have been perfected, while the natural history of endoleaks is better understood. For example, in EVAR-1 several endograft migrations or disconnections were knowingly left untreated ultimately leading to aortic aneurysm rupture. In fact, 17 out of the 22 patients who experienced late rupture had known graft complications that were not corrected. Moreover, 15 of these patients had recognized aneurysm expansion and yet were still left untreated.<sup>21</sup> Had these graft failures been managed based on current recommendations for treating endoleaks in the setting of aneurysm expansion, aneurysm-related mortality may have been different.

Both the DREAM and EVAR-1 trials regarded type 2 endoleaks as complications, a factor that gave a statistical advantage to open repair. There was no comment on which type 2 endoleaks were treated, because this was left to the discretion of the treating surgeon. Not only did type 2 endoleaks contribute to increased complication rates, but potentially they

**Table 3. OVER Trial**

Enrollment Period	October 2002–October 2008
Patients enrolled	881 (444 in EVAR arm vs 437 in open repair arm)
Country of study	United States of America
Type of study	Multicenter prospective randomized controlled trial
Analysis	Intention to treat
Inclusion criteria	1. Abdominal aortic aneurysm at least 5.0 cm 2. Associated iliac artery aneurysm of 3.0 cm 3. Aortic aneurysm of at least 4.5 cm with rapid growth or saccular morphology 4. Anatomically and medically eligible for either EVAR or open repair
Follow-up (mean)	1.8 y
Primary outcome	Long-term all-cause mortality
Secondary outcome	Reinterventions, short- and long-term morbidity, quality of life, and erectile dysfunction
Endografts used	39.6% Excluder 37.4% Zenith 19.8% AneuRx 2.9% Other
Results (EVAR vs Open)	
Operative mortality*	0.5% vs 3.0%; $P=0.004$
All-cause mortality†	7.0% vs 9.8%; HR, 0.7; 95% CI, 0.4–1.1; $P=0.13$

OVER indicates the Outcomes Following Endovascular Versus Open Repair of Abdominal Aortic Aneurysms; EVAR, endovascular aortic repair; and HR, hazard ratio.

\* 30-days or during the same hospitalization.

† Interval follow-up at 2 y (mean 1.8 y).

also led to increased reintervention rates, because currently, in the absence of symptoms or growth, observation is the initial therapy for type 2 endoleaks. Because the management of type 2 endoleaks has become more selective, repetitive computed tomography scanning to detect type 2 endoleaks is being replaced with duplex ultrasound.<sup>22</sup>

To further illustrate how some of these initial randomized, controlled trials have biased clinical practice, it is important to point out that only the OVER trial considered reintervention for incisional hernias as a complication after open repair. Thus, only the OVER trial was able to demonstrate no difference in secondary interventions between the 2 cohorts.<sup>23</sup> In a similar fashion, because the EVAR-1 trial did not include incisional complications in follow-up, the cost analysis favoring open repair is likely inaccurate.

### Expanded Indication for EVAR

Although previous and ongoing randomized controlled trials comparing EVAR with open repair were suggesting clinical equipoise, the indications for EVAR continued to expand. The efficacy of EVAR for the surgically unfit, EVAR for rupture, and EVAR for small AAAs all became clinically relevant questions that were asked over the last decade in randomized, controlled trials.

### Trial for the Unfit for Open Repair (EVAR-2)

Whereas the 4 previously described major randomized, controlled trials enrolled patients who were physically fit enough to undergo either EVAR or open repair, the EVAR-1 trial investigators simultaneously enrolled patients who were too high risk for open surgical repair into a second controlled

trial, randomizing such unfit patients to EVAR or observation. This trial, known as EVAR-2, shared an identical enrollment protocol and data collection methods as EVAR-1.<sup>5</sup> Using an intention to treat protocol, 338 patients were enrolled and randomized between September 1999 and December 2003.<sup>24</sup> After midterm analysis on this cohort, an additional 66 patients were recruited for long-term follow-up for a total of 404 patients.<sup>25</sup> The study was designed to detect a 10% difference in all-cause mortality per year with 90% power at the 5% significance level. A total of 197 patients were randomized to EVAR while 207 received observation. However, of the 207 patients in the observation arm, 70 of them eventually underwent some form of aneurysm repair attributable to rupture, rapid growth, improved fitness, symptomatic AAA, or patient preference. There was no difference in baseline characteristics between the EVAR or observation group with respect to demographics or comorbidities. The 30-day operative mortality was 7.3% in the EVAR group. Within the first 6 months of randomization, there was an insignificant increase in aneurysm-related deaths in the EVAR group, presumably reflecting operative mortality (16.3 versus 9.0 deaths/100 person-years; adjusted hazard ratio, 1.78; 95% CI, 0.75–4.21;  $P=0.19$ ). After 6 months and out to 4 years after randomization, there was a significant increase in aneurysm-related mortality in the observation group. (2.3 versus 7.6 death/100 person-years; adjusted hazard ratio, 0.34; 95% CI, 0.16–0.72;  $P=0.005$ ). For the duration of the study, measured in rate of aneurysm-related deaths per 100 person-years, EVAR demonstrated a survival advantage over observation with 3.6 versus 7.3 (adjusted hazard ratio, 0.53; 95% CI, 0.32–0.89;  $P=0.02$ ). However, despite this, there was no significant difference by

**Table 4. ACE Trial**

Patients enrolled	299 (150 in EVAR arm vs 149 in open repair arm)
Country of study	France
Type of study	Multicenter prospective randomized controlled trial
Analysis	Intention to treat
Inclusion criteria	1. Abdominal aortic aneurysm greater than 5.0 cm in males 2. Abdominal aortic aneurysm greater than 4.5 cm in females 3. Common iliac artery aneurysm greater than 3.0 cm 4. Anatomically eligible for EVAR 5. Medically fit defined by the SVS/AAVS medical comorbidity grading system <sup>15</sup>
Follow-up (min-max)	0–4.8 y (median 3.0 y)
Primary outcome	All-cause mortality and major adverse events*
Secondary outcome	Vascular reinterventions, minor complications, sexual dysfunction, incisional complications, buttock claudication
Endografts used	51% Zenith 34.6% Talent 6% Excluder 2.6% Powerlink
Results (EVAR vs Open)	
30 day all-cause mortality	1.3% vs 0.6%; <i>P</i> =NS
30 day major adverse events*	2% vs 0.6%; <i>P</i> =NS
Cumulative Survival at 1 y	95.2%±1.8% vs 96.5%±1.5%; <i>P</i> =0.24
Cumulative Survival at 3 y	86.3%±3.4% vs 86.7%±4.4%; <i>P</i> =0.24
Vascular Reinterventions at 3 y	16% vs 2.7%; <i>P</i> <0.0001

ACE indicates Aneurysme de l'aorte abdominale: Chirurgie versus Endoprothese; EVAR, endovascular aortic repair; SVS/AAVS, Society for Vascular Surgery/American Association for Vascular Surgery; and NS, not significant.

\* Myocardial infarction, permanent stroke, permanent hemodialysis, major amputation, paraplegia, and bowel infarction.

the end of follow-up, or any time point in-between, in all-cause mortality between the EVAR and observational group (21.0 versus 22.1 deaths/100 person-years, adjusted hazard ratio, 0.99; 95% CI, 0.78–1.27; *P*=0.97).

### **Trials Comparing EVAR and Open Repair for Rupture**

In the setting of rupture, 2 separate meta-analyses published in 2008 and 2011 both demonstrated a pooled 30-day mortality rate of 24% with EVAR, whereas open repair carries a mortality rate of nearly 50%.<sup>26–28</sup> It stands to reason that if the physiological insult of laparotomy as well as increased blood loss and ischemia time associated with open repair can be avoided, then outcomes would be improved. Despite such speculation and retrospective data, a single randomized controlled trial comparing EVAR versus open repair for ruptured, but hemodynamically stable infrarenal AAAs demonstrated no survival benefit at 30 days (53% for EVAR versus 53% for open repair).<sup>29</sup> Although this study was limited by its small sample size (32 patients, of which 4 died preoperatively), it was the first to demonstrate that randomization is possible for ruptured AAA. Since this initial publication, 3 additional European randomized controlled trials have begun. The Endovascular versus Chirurgie dans les Aneurysmes Rompus (ECAR) trial began enrollment in 2008.<sup>30</sup> This trial aims to recruit 160 patients to compare 30-day mortality rates in hemodynamically stable ruptured AAAs with favorable anatomy for EVAR. As of late 2009, this trial had included 45

patients. Like the French ECAR trial, the Dutch AJAX trial will be designed to recruit only stable patients, all of whom will be anatomically suitable for endovascular repair. The larger Immediate Management of the Patient with Rupture: Open versus Endovascular (IMPROVE) trial plans to recruit 600 patients to show a 14% survival benefit at 30 days.<sup>31,32</sup> Unlike the ECAR trial, IMPROVE plans to include hemodynamically labile patients and randomization will occur before defining aortic anatomy with cross-sectional imaging. This trial began recruiting patients in 2009.

Emerging evidence would seem to indicate that specialized or tertiary centers capable of offering both open and EVAR options may achieve an improvement in overall mortality rates for ruptured AAA. A meta-analysis evaluating 19 centers that reported mortality rates for both EVAR and open repair in the setting of rupture demonstrated a pooled mortality rate after open repair of 44.4% (95% CI, 40.0%–48.8%), and the pooled overall mortality after EVAR or open repair was 35% (95% CI, 30%–41%). This latter observation represents a large improvement over the classically quoted 50% mortality rate for open repair in the setting of ruptured AAA.<sup>33</sup>

### **Trials of EVAR in the Setting of Small AAAs**

With midterm success of the first randomized controlled trials demonstrating an early mortality benefit, the indications for EVAR expanded to include low risk patients with small aneurysms. Although the UK Small Aneurysm trial (UKSAT) and US Aneurysm Detection and Management (ADAM) trial both

randomized patients to undergo open repair versus surveillance for aneurysms ranging in diameter from 4.1 to 5.5 cm, neither demonstrated a survival advantage of early surgery.<sup>34,35</sup> Both the UKSAT and ADAM trial offered long-term follow-up; 12 and 8 years, respectively.<sup>36</sup> However, with EVAR perceived as a less-invasive and safer alternative, there was a renewed interest in early intervention for small aneurysms to prevent rupture. Out of this interest came 2 randomized controlled trials.

### CAESAR Trial

The European comparison of surveillance versus aortic endografting for small aneurysm trial (CAESAR) began enrolling patients in 2004.<sup>37</sup> Patients were eligible for enrollment only if their aneurysm anatomy was appropriate for EVAR. Over 4 years, 360 patients were randomized to either early EVAR (182) or surveillance (178) with a primary end point of all-cause mortality.<sup>38</sup> With a maximum follow-up of 54 months (mean 32.4 months), there was no significant difference in all-cause mortality between EVAR (14.5%) and surveillance (10.1%) cohorts (hazard ratio 0.76; 95% CI, 0.30–1.93;  $P=0.6$ ). Aneurysm mortality was also similar between groups. However, because aneurysms in the surveillance cohort continued to grow, by 36 and 54 months, the estimated probability of needing aneurysm repair was 59.7% and 84.5%, respectively. Thus, at 36 months, 3 out of every 5 small aneurysms under observation would have required repair. During this period, it is estimated that 16.4%, or 1 out of every 6 aneurysms that required repair would have lost anatomic eligibility for EVAR. The CAESAR trial also evaluated health-related quality of life between EVAR and surveillance cohorts using the Short Form 36 Health Survey.<sup>39</sup> Although both groups demonstrated similar baseline scores, at 6 months the EVAR cohort demonstrated significantly higher total, physical, and mental domain scores, whereas the surveillance group demonstrated an insignificant decrease in all scores. However, this quality of life advantage in the EVAR group appeared to be short lived, because by 12 months there was no significant difference from baseline scores among the 2 groups. With these results, CAESAR study investigators concluded no advantage of early intervention for small AAAs, but recommended close surveillance for continued aneurysm growth.

### PIVOTAL Trial

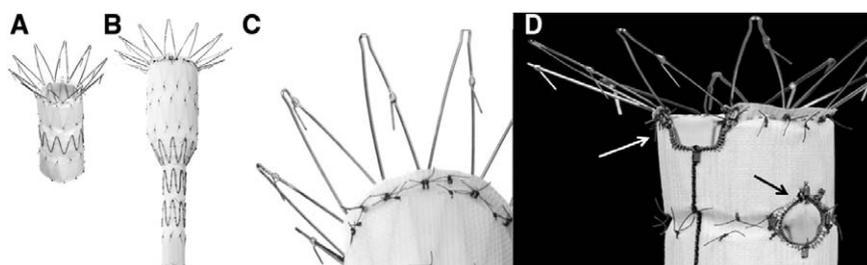
The Positive Impact of Endovascular Options for treating Aneurysms Early (PIVOTAL) Trial performed in the United States randomized 728 patients with aneurysms 4.0 to 5.0 cm to EVAR or surveillance.<sup>40</sup> Primary end points included

aneurysm-related death, as well as all-cause mortality. After a mean follow-up of 20 months, 15 deaths had occurred in each group (4.1%; unadjusted hazard ratio, 1.01; 95% CI, 0.49–2.07;  $P=0.98$ ), with 2 aneurysm-related deaths per group (0.6%; unadjusted hazard ratios, 0.99; 95% CI, 0.14–7.06;  $P=0.99$ ). Given the low mortality in both groups with midterm follow-up, PIVOTAL study investigators concluded that in the appropriate patient either early intervention or surveillance is a safe alternative. Both CAESAR and PIVOTAL investigators agreed that longer term follow-up is needed.

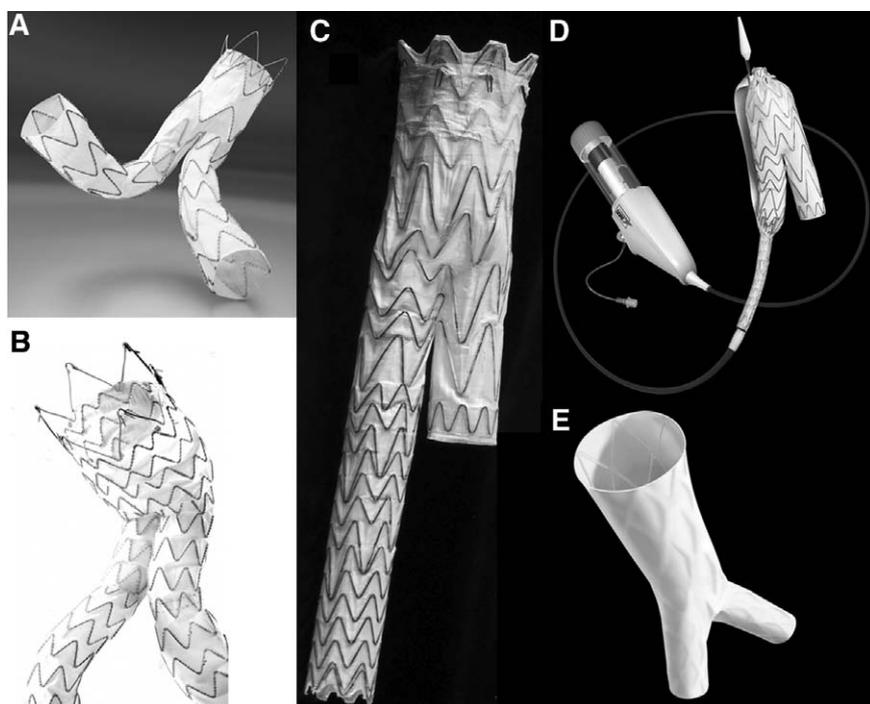
### Currently Available FDA-Approved Endografts

Currently, there are 6 FDA-approved abdominal aortic endografts available on the market: AneuRx, Talent, and Endurant (Medtronic Inc, Minneapolis, MN), Excluder (W.L. Gore and Associates, Flagstaff, AZ), Zenith (Cook Medical, Inc, Bloomington, IN), and Powerlink (Endologix, Irvine, CA). The AneuRx graft, currently in its 7th generation, gained its initial approval in 1996. Using only radial force and lacking either suprarenal or anatomic fixation, migration rates as high as 42% have been reported in follow-up for the AneuRx stent graft. However, when strict adherence to the instructions for use for the AneuRx device was followed, migration was only 6.1% at 4 years.<sup>19,20,41</sup> Whereas other grafts can accommodate challenging aortic necks, the inability of the AneuRx to perform in the setting of difficult aortic anatomy has made it the primary target for secondary intervention. Given these limitations, the FDA has issued multiple warnings, most recently in 2008, emphasizing strict observance of the AneuRx instructions for use and routine surveillance and follow-up.

The development of the Cook Zenith Renu AAA Ancillary Graft (Cook Medical, Inc, Bloomington, IN) was developed to provide active proximal suprarenal fixation for preexisting endovascular aortic grafts with failed or failing proximal fixation or seal. This graft comes in 2 forms, a main body extension and an aorto-uni-iliac converter (Figure 1A and B). Approved in June 2005, a 14-month postmarket registry was created with a plan for 5 years of follow-up.<sup>42</sup> Renu was used in 151 patients in 95 centers. Of these procedures, the AneuRx device accounted for 83% of all preexisting endovascular aortic grafts treated with Renu. Although there was a technical success rate at the time of implantation of 98%, over a median follow-up of 45 months, clinical success decreased to 79%. The most common cause for treatment failure included persistent type 1 of 3 endoleaks ( $n=18$ ), sac enlargement ( $n=9$ ), and death ( $n=5$ ). The Zenith Renu therefore provides a valuable endovascular option for previously placed failing grafts, especially in a population with comorbidities precluding open graft explantation.



**Figure 1.** The Cook Zenith Renu AAA Ancillary Graft (Cook Medical, Inc, Bloomington, IN) graft comes in 2 forms, (A) main body extension and (B) an aorto-uni-iliac converter. C, The Zenith Graft demonstrating suprarenal barbed fixation. D, Fenestration (black arrow) and scallop (white arrow) on the Zenith Fenestrated AAA Endovascular Graft (D).



**Figure 2.** **A**, The Talent Abdominal Stent Graft (Medtronic, Inc, Minneapolis, MN). **B**, The Endurant AAA Stent Graft System (Medtronic, Inc, Minneapolis, MN). Note the suprarenal stent with anchoring pins for secure fixation. **C**, The Gore Excluder AAA Endoprosthesis is made of a nitinol frame covered with expanded polytetrafluoroethylene. Note the scalloped ends with proximal nitinol anchoring pins. **D**, GORE Excluder (W.L. Gore and Associates, Flagstaff, AZ) with C3 Delivery System offers 360 degrees of rotational freedom and reconstrainable top. **E**, The Powerlink graft (Endologix, Irvine, CA) uses anatomic fixation distally, seating the graft atop the aortic bifurcation.

The second Medtronic endograft to receive FDA approval was the Talent graft (Figure 2B). Talent was FDA approved in 2008 after the result of its pivotal trial. Five-year follow-up of this initial US trial demonstrating early and long-term efficacy for the Talent enhanced low profile system was published in 2010.<sup>43</sup> Because of the recently approved and released Endurant Stent Graft System, marketing of the Talent graft has decreased substantially.

Even with the long-term success of the AneuRx and Talent endografts, Medtronic developed the Endurant Stent Graft System to accommodate aortic necks with up to 60 degrees of angulation with infrarenal aortic neck lengths of just 10 mm. Unlike Talent, but similar to Zenith (Cook Medical, Inc, Bloomington, IN) the Endurant endograft possess active, barbed suprarenal fixation. (Figure 2A). The Endurant is indicated for aortic neck diameters ranging from 19 to 32 mm and is packaged in an 18 or 20 French delivery system. Clinical trials began in Europe in 2007 and in the US in 2008.<sup>44,45</sup> Both trials were multicenter enrolling 80 and 149 patients, respectively, with a planned 1-year follow-up. Among the European and US trials, all-cause mortality at 1 year was 5% and 4%, respectively, with no aneurysm-related mortality in either group. There were no type 1 or 3 endoleaks noted in either trial, nor were there any open conversions or graft migration detected at 1 year. Based on this data, demonstrating early safety and efficacy, the Endurant Stent graft received FDA approval in December 2010.

Different from the polyester-covered Talent, Endurant, and Zenith endografts, the Gore Excluder (W.L. Gore and Associates, Flagstaff, AZ) is made of a nitinol stent frame covered by expanded polytetrafluoroethylene (Figure 2C). Originally released in Europe in 1997, the Excluder received FDA approval in 2002.<sup>46,47</sup> High permeability of the expanded

polytetrafluoroethylene in the original Excluder model was associated with transgraft migration of serum resulting in increased pressure and sac expansion. The modified low-permeability Gore product, released in June 2004, incorporated additional film layers to decrease filtration and resulting endotension. The graft itself has a scalloped proximal main body and no suprarenal fixation, but does make use of nitinol anchoring hooks. Current indications for the Excluder include aneurysm necks of 15 mm, ranging from 19 to 29 mm, all of which can be delivered via an 18 or 20 French sheath, making it one of the lowest profile endografts. The Excluder makes use of a rapid pull sting deployment mechanism, deploying the graft in a proximal to distal fashion.

The C3 Excluder stent-graft, approved in the United States in 2011, provides the ability to deploy Excluder endograft with the option to reconstrain and redeploy if necessary (Figure 2D). After reconstraining the device, the C3 design allows 360 degrees of rotational freedom, as well as cranial and caudal movement. Such freedom assists in precise placement at the proximal seal zone, as well as aligning the contralateral gate and thus eliminating the need for predeployment orientation. In the first 25 patients to receive the C3 delivery system, repositioning was done in 72% of cases to achieve a better proximal seal or to facilitate contralateral gate access.<sup>48</sup>

The Zenith (Cook Medical, Inc, Bloomington, IN) device is a modular bifurcated polyester graft supported by a stainless steel frame complete with a bare barbed suprarenal fixation stent. (Figure 1C) Main body diameters are available in 22 to 36 mm to accommodate aortic necks ranging from 18 to 32 mm with lengths as short as 15 mm and angulation up to 60 degrees. Delivery systems up to 22 French are used to accommodate the largest of main bodies. The Zenith graft was introduced in 1997 and received FDA approval in May

2003 after the US pivotal Zenith Multicenter Trial (ZMT).<sup>49</sup> Between 2000 and 2003, 352 patients were enrolled in the pivotal trial, of which patients were followed out for a total of 5 years.<sup>50</sup> At long-term follow-up, Kaplan-Meier survival estimates in the standard and high risk groups were 83% and 61%, respectively ( $P<0.001$ ). Cumulative risk of conversion, limb occlusion, migration  $>10$  mm, or component separation was  $\leq 3\%$  at 5 years. As noted in the original ZMT, long-term data continue to support the durability and safety of the Zenith endovascular graft.

The Powerlink (Endologix, Inc, Irvine, CA) is a unibody bifurcated graft composed of an endoskeleton made of a single wire of cobalt chromium and covered with expanded polytetrafluoroethylene fabric. The body of the graft is free of any suturing or welding, with the fabric attached to the endoskeleton only at the ends of the device (Figure 2E). The Powerlink graft relies on anatomic fixation, as the graft sits on the aortic bifurcation, unlike previous endografts that rely on supra or infrarenal fixation.<sup>51</sup> In this manner, the Powerlink graft does not have any hooks or barbs, but rather is built from the bottom up. The Powerlink is available in main body diameters of 22, 25, and 28 mm. Using large proximal extension cuffs (Powerlink XL), aortic necks ranging from 18 to 32 mm in diameter with at least 15 mm of length and up to 60 degrees of angulation can be treated.<sup>52</sup> Main body grafts are accommodated by a 17 or 19 French delivery system whereas the proximal aortic extensions require a 21 French sheath. However, the recently FDA-approved next generation graft technology, the AFX endovascular AAA system, is a low profile device which can deliver grafts up to 34 mm in diameter through a single 17 French sheath. Unique to the Powerlink device, the contralateral limb is delivered through a 9 French sheath.

Although commercially available in Europe since 1999, the Powerlink endograft did not receive FDA approval until 2004. A contemporary meta-analysis reviewing 3 prospective multicenter US trials published in 2010 provides long-term follow-up on the Powerlink device.<sup>53</sup> This meta-analysis contains 34 patients from the original pivotal trial, 79 patients from the Powerlink XL trial, and 44 patients from a trial examining the safety and efficacy of a suprarenal aortic extension cuff.<sup>51,52,54</sup> Only patients who had a graft placed using anatomic fixation were included for review. Technical success was achieved in 99% of cases and there were no reported deaths within the first 30 days after surgery. At 1-year follow-up, all-cause mortality was 7% (11 deaths) with no aneurysm-related mortality, no ruptures, and no conversions. There were only 6 type 1 endoleaks (2.2% incidence per year for the first 3 years) for the entire cohort over 5 years of follow-up and no type 3 endoleaks. Device migration, defined as graft movement of  $>10$  mm, was 0% over the follow-up period. Although small in sample size, these long-term favorable results highlight the durability of this graft which offers the lowest profile on the market.

### EVAR in the Setting of Unfavorable Anatomy

Although EVAR quickly became accepted as a less-invasive option for repair of infrarenal AAAs, unfavorable anatomy of the proximal aortic neck precludes up to 40% of patients from an endovascular option because most commercialized

endografts require at least 10 mm length of proximal neck below the renal arteries to achieve an adequate seal.<sup>55</sup> Targeting a segment of healthy, nonaneurysmal aorta and avoiding landing the proximal endograft in conical, short, or thrombus lined neck is not only necessary to avoid a type 1A endoleak, but also to prevent graft migration over time. By overcoming such anatomic limitations, it is estimated that up to 80% of infrarenal aneurysms could be treated with EVAR.<sup>56</sup> Incorporation of the renal and visceral arteries into the endograft repair using a variety of techniques including fenestrations, branches, snorkels, and chimneys have allowed for the expanding application of EVAR to include preserving pelvic flow in the setting of iliac aneurysm disease and repair of TAAA.

Park et al<sup>57</sup> described the first fenestrated aortic graft in 1996 whereas the use of a multi-branched stent-graft to repair a TAAA was described by Chuter et al<sup>58</sup> in 2001. Since these initial publications, the use of fenestrations and branches to treat unfavorable anatomy in pararenal AAA and TAAA has expanded worldwide with over 5000 cases being performed by 2010.<sup>59</sup> The largest series comparing open surgical repair with endovascular repair for TAAA was performed between 2001 and 2006. Using investigational endografts, this large series compared 372 open thoracic aortic aneurysm or TAAA repairs with 352 endovascular repairs. At 30 days, there was no significant difference in mortality between the 2 groups (8.3% in open repairs and 5.7% in endovascular repairs,  $P=0.2$ ).<sup>60</sup> No intraoperative deaths occurred in this series. One-year mortality rates were 15.9% and 15.6% for open and endovascular repair, respectively ( $P=0.9$ ).

The comparative low perioperative mortality in treating TAAA with an endovascular approach, as well as acceptable medium and long-term durability, has led to the development and commercialization of branched and fenestrated endografts. Currently, Cook Medical, Inc (Bloomington, IN), is the only manufacturer commercially producing custom-made fenestrated and branched endografts, which are available in Europe, Australia, and South America. Fenestrations are nitinol-reinforced holes in the fabric of the aortic stent-graft component. (Figure 1D) The radio-opaque nitinol rings are oriented under fluoroscopy to match the branch configuration of renal and if necessary, visceral vessels. To improve the seal of the fenestration against the vessel, especially in large diameter aortic necks, balloon expandable covered stents may be deployed through the fenestration into the target vessel. When total vessel occlusion is not necessary, a scallop in the graft can be created. Because each graft is custom made with fenestrations individualized for a specific aortic anatomy, the crux of these grafts is time and cost. Furthermore, a mastery of 3-dimensional reconstructive software is necessary to precisely size and design each endograft.

Another option for renal and visceral vessel preservation in the setting of juxtarenal AAA or TAAA is the use of a branched or cuffed endografts. Branches or cuffs are stent-supported fabric projections of the mainbody graft that come off at variable angles and lengths to accommodate cannulation of target vessels. The length of the cuff theoretically provides a better seal zone than a fenestration. However, cuffs add bulk, increasing the profile of the device. Additionally, cuffs also increase the length of aorta necessary to be covered during

endovascular TAAA repair because the distal end of the cuff is positioned 2 to 4 cm proximal to the intended target artery to allow for vessel cannulation and stenting. In short, cuffs may work best when there is adequate space between the main body stent graft and aortic wall and fenestrations may be best used when there is little or no perigraft space.<sup>61</sup> Combining both cuffs and fenestrations to create a graft for each individual aorta is paramount to achieving an adequate seal free of endoleak. However, such custom grafting limits an off the shelf approach to endograft repair for complex aortic anatomy.

One large prospective multicenter trial in the United States and 1 retrospective analysis from France using the Zenith Fenestrated AAA Endovascular Graft (Cook Medical, Inc, Bloomington, IN) have recently been published. The purpose of the US trial was to evaluate the safety and preliminary effectiveness of the device in treating juxtarenal AAA with short proximal necks as well as refine patient selection criteria. Between January 2005 and January 2006, 30 patients were enrolled from 5 centers.<sup>62</sup> Small, large, or scalloped fenestrations were used to preserve visceral and renal flow. Twenty patients received a main body with 1 superior mesenteric artery scallop and bilateral renal artery fenestrations. The remaining 10 patients received some variation of renal artery fenestration or scallop. No deaths occurred within 30 days of the procedure. Two late deaths occurred at 677 and 754 days, both of which were not aneurysm related. At 24 months, there were no ruptures and no conversions to open repair. Of 57 renal artery fenestrations or scallops, 54 with stenting, there were 4 patients diagnosed with late renal artery stenosis and 2 renal artery occlusions. There was no type 1 or type 3 endoleak detected at 24 months. Clinically significant graft migration occurred in 1 patient leading to a renal artery stenosis which was subsequently repaired. Aneurysm sac shrinkage of 5 mm or greater was noted in almost 70% of patients at 24 months.

The French retrospective experience with the Zenith fenestrated AAA endovascular graft includes 134 patients with juxtarenal, suprarenal, or Crawford extent IV TAAA from May 2004 through January 2009.<sup>63,64</sup> All patients were considered to be physiologically high risk for open repair. Mean aneurysm size was 5.5 cm and mean number of fenestrated vessels per patient was 3. In total, 403 visceral or renal vessels were fenestrated or scalloped with a technical success rate of 99% (398/403). Discharge computed tomography revealed 99% patency on the target vessels (394/398). The 30-day mortality rate was 2% (3/134), with 2 of these patients having intraoperative complications requiring additional procedures. Mean follow-up was 15 months (range was 2–53 months). Twelve patients died in follow-up, none of which were aneurysm related. The majority of late deaths were either related to cancer (42%) or myocardial infarction (25%). Twelve reinterventions were performed in follow-up, 6 for endoleaks. There was 1 type 1A endoleak discovered 18 months postoperatively and 1 type 1B at 2 months follow-up. Two type 3 and two type 2 endoleaks were intervened on. All were treated endovascularly. Renal artery stent fractures were noted in 4 vessels at follow-up and were restented appropriately. Renal artery occlusion occurred in 4 vessels with follow-up out to 36 months. In comparison with the morbidity

and mortality of open repair for aneurysms involving the visceral vessels, both the US prospective study and French retrospective study have demonstrated safety and efficacy in midterm follow-up.<sup>62–64</sup>

### Non-FDA-Approved Endografts in Development

In addition to fenestrated and branched endografts, the endograft pipeline is full of new devices to deal with hostile necks, small delivery vessels, type 2 endoleaks, and other challenging anatomy. The advent of suprarenal and anatomic fixation decreased the incidence of graft migration and potential type 1 endoleaks. However, not all aortic anatomy is conducive to achieving fixation, and it is thought that highly angulated necks have the greatest potential for fixation failure. Similarly, tortuous iliac anatomy increases the complexity of EVAR. As such, most commercialized endografts are indicated for aortic necks of 60 degrees angulation or less. The AorFix (Lombard Medical Technologies, Tempe, AZ) is an endograft with indications for angulated aortic necks of up to 90 degrees. It has unique ringed inner scaffolding that allows the device to be flexed axially without kinking or collapsing. Eight proximal hooks assist in preventing graft migration. Midterm results from Greece and the United Kingdom are promising, however, samples sizes in both of these studies were small.<sup>65–67</sup> The ongoing large prospective US trial known as the Prospective Aneurysm Trial: High Angle Aortic Bifurcated Stent-graft (PYTHAGORAS) trial should help to better define the indications and limitations of this endograft.

Similar to the Aorfix, the Anaconda (Vascutek, Renfrewshire, Scotland) has been used to achieve a seal in tortuous aortic necks >60 degrees. Although not available in the United States, the Anaconda has been used in Europe for over a decade. Unique to the Anaconda is the ability to reposition the proximal stent for precise positioning. Midterm clinical results from a multicenter prospective trial evaluating 61 patients reported no type 3 endoleak at 24 months and no instances of migration.<sup>68</sup> One type 1 endoleak was recognized at the time of operation and was repaired with a proximal extension cuff. At 2 years, all-cause mortality was 9.8% and aneurysm-related mortality was 0%. A large Italian registry published results in 2011 after 2 years of enrollment.<sup>69</sup> A total of 787 cases were included with a 30-day mortality rate of 0.9% when the endograft was successfully implanted and 27.2% when a conversion to open repair was necessary. Type 1 and 3 endoleaks were reported 0.6% and 0.1% of the time, respectively. This registry is ongoing. At this time, it is unknown if the Anaconda will obtain an indication for aneurysm repair in the United States.

In cases where challenging neck anatomy is of concern, the HeliFix Aortic Securement System (Aptus Endosystems, Inc, Sunnyvale, CA) is intended to provide fixation and augment sealing between endovascular aortic grafts and the aorta.<sup>70</sup> The system is indicated for use in patients whose endovascular grafts have exhibited migration or endoleak, or are at risk of such complications, as in the case of a reverse tapered neck. The HeliFix is a helical staple which is delivered through a 16 French sheath and deployed through the graft into the aortic wall using a motorized control unit. The

FDA approved this device in November 2011. The HeliFx can be used with the Zenith, Excluder, AneuRx, Talent, or Endurant endografts. Already approved in Europe, HeliFx is designed to be used with the Fortevo endograft system. The Fortevo endograft is a low profile (18F) device which relies on the transmural fixation of the HeliFx staple to achieve a proximal seal.

Perhaps one of the most unique innovations in EVAR is the Nellix sac-anchoring endoprosthesis (Endologix, Irvine, CA).<sup>71</sup> The Nellix system is described as 2 balloon expandable endoframes (stents) surrounded by an endobag which is filled in situ with self-curing polymer. The endoframes provide inline flow from the infrarenal aorta to the iliac arteries. The polymer containing endobags fill the flow lumen, occluding retrograde flow and potential endoleaks as well as anchoring the unit within the sac. The initial report of 34 patients, 50% with unfavorable anatomy, revealed 100% technical success rate with 1 perioperative death (1/34; 2.9%). This patient was considered high risk with multiple medical comorbidities and was subjected to a prolonged infrarenal aortic occlusion time during device deployment. One other patient died at 10 months from congestive heart failure. Two type 1 endoleaks were noted during a mean follow-up of 15 months. A type 1A endoleak was seen on follow-up computed tomography scan at 30 days, but had resolved by day 60. Another patient had a type 1B endoleak and was observed closely with no expansion of aneurysm sac size for 12 months before the leak was electively treated. At a mean follow-up of 15 months, there have been no ruptures, no conversions to surgery, no migration and no additional endoleaks.

## Conclusion

Endovascular repair of aortic aneurysms has revolutionized the treatment and management strategy of aortic pathology. In the 20 years since initially described, EVAR has become the preferred method of infrarenal AAA repair. Although long-term follow-up from the initial EVAR trials failed to show a mortality benefit of EVAR past 2 years, it goes without debate that EVAR results in less operative time, less blood loss, quicker time to discharge, less morbidity, and decreased short-term mortality when compared with open repair. Early trials were conducted at a time when the EVAR learning curve was still being defined and the devices used in the trials were third or fourth generation at best. Furthermore a number of patients were treated with grafts that are currently no longer in use, were used outside the instructions for use, or have been associated with migration. It remains unknown if a repeat of the EVAR trials using the best available graft technology would lead to different outcomes.

## Disclosures

None.

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