Empowering EVAR Clinical Performance

Endurant II Stent Graft Durable Outcomes in the ENGAGE Real-World Registry

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During the last 20 years, endovascular repair of abdominal aortic aneurysms (AAAs) has evolved and is now generally accepted as a preferred option to conventional open surgical repair. A recently published meta-analysis of 25,078 patients undergoing endovascular aneurysm repair (EVAR) and 27,142 patients undergoing open surgical repair for AAAs showed significant reduction in 30-day mortality in the EVAR arm, but no difference was seen after 2 years.[1] A significantly higher proportion of reintervention procedures after EVAR was also noted.

Medtronic, Inc. (Minneapolis, MN) designed the market-leading Endurant® Stent Graft system to address the limitations of previous stent graft designs. A small-amplitude M-shaped proximal stent was designed to improve sealing at the proximal neck while potentially allowing for greater sizing flexibility. Radial strength was also improved while allowing a lower-profile delivery system. Active suprarenal fixation was added to prevent endograft migration. The Endurant Stent Graft system received CE Mark approval in July 2008 and US Food and Drug Administration approval in December 2010. Subsequently, the Endurant® II Stent Graft received FDA and CE Mark approval, with additional enhancements such as a lower-profile delivery system with extended hydrophilic coating, additional limb lengths, and enhanced radiopacity of the contralateral gate.

After a safety assessment trial in Europe,[2] the Endurant Stent Graft Natural Selection Global Postmarket Registry (ENGAGE) was undertaken to quantify the performance of Endurant within the context of contemporary, real-world use. ENGAGE is a multicenter, nonrandomized, single-arm prospective registry.

Procedural details and the early results from the ENGAGE registry have previously been published, showing high rates of clinical and technical success.[3] These results were very promising for the use of the Endurant Stent Graft system in a real-world study population, but longer follow-up was needed to assess the endograft's durability and effectiveness. Herein, we present the 1- and 2-year results of the ongoing ENGAGE registry.

ENGAGE REGISTRY STUDY DESIGN

Unprecedented in size, scope, and geographic representation, the ENGAGE Registry represents the combined experience of 79 high-volume sites in 30 countries across six continents. Enrollment started in March 2009 and was completed in April 2011; ENGAGE recruited 1,263 patients who were primarily implanted with the Endurant device. The eligibility criteria for ENGAGE were minimal in order to reflect real-world clinical practice.[4] To avoid selection bias, participating sites were requested to enroll patients consecutively. Ruptured AAAs were not considered for enrollment into ENGAGE. Data collected on each patient were recorded on a web-based electronic case report form to ensure reliable data collection, data management, secure authentication, and traceability; 100% of the data were reviewed, and more than 40% of patients' source documentation was monitored randomly.

RESULTS

Baseline

At the time of writing this article, 1-year data on all 1,263 patients and 2-year data on a cohort of 500 patients (39.6%) have been presented. The baseline char-

TABLE 1. PATIENT DEMOGRAPHICS AND RISK FACTORS

Variable		N = 1,263
Age (years), mean ± SD (range)	73.1 ± 8.1	(43–93)
Male sex	89.5%	(1130/1,263)
ASA classification		
Class I	6.1%	(77/1,262)
Class II	41.8%	(527/1,262)
Class III	41.5%	(524/1,262)
Class IV	10.6%	(134/1,262)
Symptoms		
Asymptomatic AAA	83.9%	(1,059/1,262)
Symptomatic AAA	16.1%	(203/1,262)
Mean AAA diameter (mm)	60.3 ± 11.7	(30–119)
Treated outside IFU	17.9%	(226/1,263)
Risk factors		
Tobacco use	49.3%	(607/1,232)
Hypertension	75.4%	(940/1,246)
Hyperlipidemia	60.5%	(719/1,189)
Diabetes	19%	(236/1,245)
Cardiac disease	53.5%	(675/1,262)
Cancer	20.5%	(254/1,242)
Family history of aneurysms	6.7%	(84/1,262)

acteristics are shown in Table 1. Patient demographics and risk factors were typical for abdominal aneurysms, comprising 90% men who were a mean age of 73.1 ± 8.1 years. Most of the patients were American Society of Anesthesiologists (ASA) class II or III, with a variety of cardiovascular risk factors and comorbidities. ENGAGE reflects a challenging, real-world population:

- 18% of patients were beyond the IFU;
- 16% of patients with symptomatic AAAs;
- 10.6% of patients were ASA risk class IV;
- 10.5% of patients were women.

No ruptured aneurysms were included. The mean AAA diameter was 60.3 ± 11.7 mm. Two hundred twenty-six endografts (17.9%) were implanted outside the IFU criteria. Stokmans et al described the procedural data and evaluation in a previous publication.[3]

Technical Outcomes and Secondary Procedures

The technical outcomes are presented in Table 2. Type I and III endoleaks were present at 1- and 2-year follow-up in 0.6% and 1.1% of patients, respectively. Migration of the main body was not reported. AAA shrinkage (> 5 mm) at 1 year continued from 41.1% to 56.1% at 2-year follow-up. Kaplan-Meier estimates a freedom from secondary endovascular procedures of 94.1% at 1 year and 93% at 2 years (Figure 1). The majority of secondary procedures were performed for iliac limb occlusion or stenosis.

Patient Outcomes

The patient outcomes are shown in Table 3. The conversion rates were reported in 0.6% of patients at 1 year and 0.8% of patients at 2 years. One or more major adverse events at 1- and 2-year follow-up were reported in 11.3% and 17.4% of patients, respectively. Myocardial infarction and renal failure were the most prevalent major adverse events after 2 years. In total, there were only three patients who had an abdominal aneurysm rupture within 2-year follow-up.

Mortality

The Kaplan-Meier estimate for 1-year overall survival was 91.7% and 86.4% for 2 years (Figure 2). The 2-year estimate for aneurysm-related survival was 98.1%. To date, only three cases of device-related mortality were reported.

DISCUSSION

The endovascular approach for the treatment of AAAs is a dynamic, ever-changing endeavor. For years, we were challenged to decrease complications and reinterventions while safely treating more complex anatomy, especially for cases unfit for open repair. With broader IFU criteria, the Endurant Stent Graft makes EVAR suitable for more AAA patients.

The ENGAGE registry was undertaken to quantify the performance of the Endurant Stent Graft system within the context of contemporary, real-world use. Eligibility for treatment with Endurant was left to the discretion of the investigator; ENGAGE represents a high-quality database of 1,263 AAA patients with high external validity. To guarantee and maintain the quality and completeness of data, site monitoring is routinely performed to ensure consistency and quality in the collected data. Protocol endpoints important in demonstrating the clinical performance of Endurant at 1 month and beyond are 100% monitored. The rigor behind the data collection in ENGAGE is unprecedented for a real-world postmarket study.

The necessity for secondary interventions at 2 years was 7%, which was remarkably lower compared to the 12% reported in the DREAM (Dutch Randomised Endovascular Aneurysm Management) trial and the 13.7% reported in the OVER (Open Versus Endovascular Repair) trial.[5] The difference in secondary intervention rates could be influenced by the more conservative approach to type

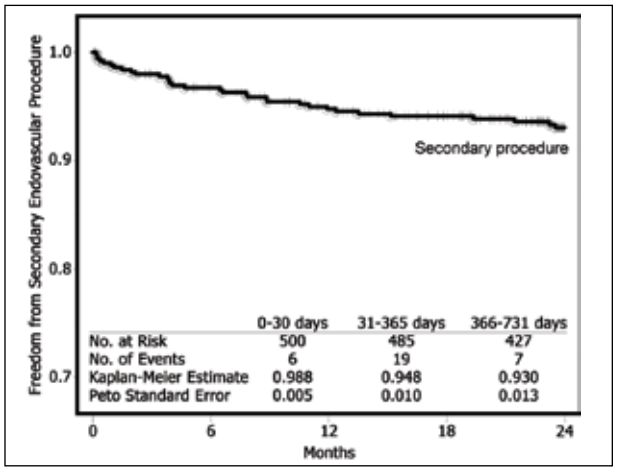

Figure 1. Kaplan-Meier estimates for secondary endovascular procedures.

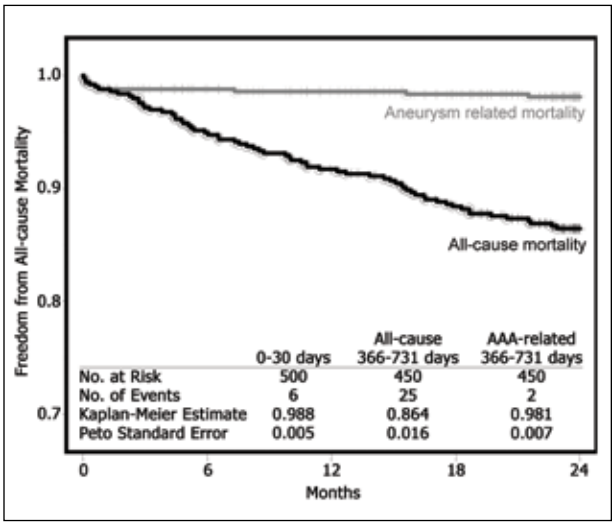

Figure 2. Kaplan-Meier estimates for all-cause mortality and AAA-related mortality.

II endoleaks in current practice. However, with 17.9% of patients treated outside the IFU, it should be taken into consideration that the eligibility criteria for ENGAGE were less strict than for DREAM and OVER.[6,7]

The majority of secondary interventions in ENGAGE were performed for iliac limb occlusion or stenosis. It is noted that a recently published independent analysis of the use of Endurant in 496 patients across three Dutch centers revealed that the incidence of limb occlusion after implantation of Endurant was 4% at 1.7 years (median follow-up), with most events occurring ≤ 2 months after implantation. In that analysis, "technical justification" (eg, extreme oversizing, positioning the graft at the kink of the iliac vessel, etc.) was the primary reason for occlusion in 60% of patients.[8]

Stent graft migration after EVAR is a serious complication and often results in emergency treatment. EUROSTAR (European Collaborators on Stent Graft Techniques for Abdominal Aortic Aneurysm Repair Registry) reported on several patients with endograft migration (4.3 cases per 100 patient years).[9] With the more contemporary stent graft, ENGAGE reports no endograft migration for Endurant, which is related to the improved fixation of the endograft to the aortic wall. Aneurysm rupture after EVAR is very rare, with a prevalence of 0.2% at 2 years in the 500-patient cohort.

At 1 and 2 years, freedom from AAA-related mortality in ENGAGE remained consistent at 98.6% and 98.1%, respectively. Compared with the landmark EVAR-1 and DREAM trials, the overall mortality rates in ENGAGE at 1 and 2 years were comparable. This is remarkable considering that ENGAGE did not exclude ASA class IV patients (10.6%) with a worse prognosis.

CONCLUSION

ENGAGE represents the largest contemporary EVAR registry with a single manufacturer's endograft. This study has raised the bar in terms of evidence-based medicine as it relates to EVAR. These data clearly set Endurant apart from other stent grafts in terms of both magnitude and quality of evidence. Not all registries are created equal in terms of breadth and quality. Because ENGAGE patients are enrolled consecutively and because all of the data from

TABLE 2. TECHNICAL PERFORMANCE AFTER 1- AND 2-YEAR FOLLOW-UP

Variable	1 Year (N = 1,263)		2 Years (N = 500)	
Type I/III endoleak	0.6%	(6/1,072)	1.1%	(4/375)
Migration main body	0%	(0/1,242)	0%	(0/490)
Significant decrease (> 5 mm) aneurysm sac	41.1%	(385/936)	56.1%	(185/330)
Significant increase (> 5 mm) aneurysm sac	3.4%	(32/936)	3.9%	(13/330)
Stent graft occlusion	3.5%	(44/1,242)	2.7%	(13/490)
Stent graft kinking	2%	(25/1,242)	2%	(10/490)

TABLE 3. PATIENT OUTCOMES AT 1- AND 2-YEAR FOLLOW-UP				
Variable	1 Year (N = 1,263)		2 Years (N = 500)	
One or more major adverse events	11.3%	(141/1,246)	17.4%	(84/483)
All-cause mortality	7.5%	(93/1,246)	13.7%	(66/483)
Bowel ischemia	0.2%	(3/1,246)	0.6%	(3/483)
Myocardial infarction	2%	(25/1,246)	2.7%	(13/483)
Paraplegia	0%	(0/1,246)	0%	(0/483)
Renal failure	1.1%	(14/1,246)	1.4%	(7/483)
Respiratory failure	0.1%	(1/1,246)	0.2%	(1/483)
Stroke	0.5%	(6/1,246)	0.6%	(3/483)
Secondary endovascular procedure (any type)	5.6%	(71/1,263)	6.4%	(32/500)
Conversion to surgery	0.6%	(7/1,263)	0.8%	(4/500)
Aneurysm rupture	0.2%	(2/1,263)	0.2%	(1/500)

ENGAGE are reviewed and verified by the investigators, medical practitioners can have confidence knowing that the ENGAGE results reflect the collective global experience with Endurant.

The 2-year results continue to demonstrate the durability, safety, and effectiveness of the Endurant Stent Graft. Despite numerous cases of challenging anatomy, rates of type I endoleak and migration are very low. Longer-term data are needed, but in this most recent analysis, the Endurant Stent Graft system demonstrates early markers for EVAR success. ENGAGE will continue follow-up for a total of 5 years. Two-year data of all 1,263 patients and 3-year data of the first 500 treated patients will be presented at the VEITH Symposium in November 2013. ■

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