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ORIGINAL ARTICLE
VASCULAR SECTION

Improvements in patient outcomes with next generation endovascular aortic repair devices in the ENGAGE Global Registry and the EVAR-1 clinical trial

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ABSTRACT

BACKGROUND: The outcomes from the randomized controlled trials (RCTs) comparing endovascular aortic aneurysm repair (EVAR) to open surgical repair (OSR) may no longer be reflective of currently technology. Here the EVAR-1 trial and the ENGAGE registry are examined to assess potential improvements in outcomes with modern stent graft systems.
METHODS: EVAR-1 was a multicenter, prospective, randomized controlled trial in the UK and patients were enrolled between 1999 and 2004 and treated with first- and second-generation devices. ENGAGE is an observational, nonrandomized, prospective registry that completed enrollment between 2009 and 2011. All ENGAGE patients were treated with the Endurant AAA Stent Graft System. A descriptive comparison of the published four-year outcomes of all-cause mortality (ACM), aneurysm-related mortality (ARM), rupture after elective EVAR, and reinterventions are reported.
RESULTS: Through the four-year timepoint, freedom from ACM was 74.4% in the EVAR-1 Trial and 74.6% in the ENGAGE registry. ARM in the EVAR-1 trial was 4.2% and in the ENGAGE registry was 1.9%. Death due to rupture through four years was 1.6% (10/626) and 0.5% (6/1263) in the EVAR-1 and ENGAGE patients, respectively. In the EVAR-1 trial, the proportion of patients requiring at least one reintervention through the four-year timepoint was 19.3% (121/626) whereas in the ENGAGE registry, reinterventions occurred in 10.9% (138/1263) of patients.
CONCLUSIONS: EVAR patient outcomes have improved since the time of the original EVAR *vs*. OSR trials and data from real-world registries should be considered a primary resource for developing new guidelines for patient selection and management.

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KEY WORDS: Randomized controlled trial; Patient outcome assessment; Endovascular procedures.

The minimally invasive and perioperative benefits of endovascular abdominal aortic aneurysm repair (EVAR) have made it the preferred option in the treatment of patients with abdominal aortic aneurysms (AAA). The EVAR-1, ACE, OPEN, and DREAM studies were large randomized controlled trials (RCTs) that documented patient outcomes with EVAR compared to open surgical repair (OSR) for the treatment of AAA.[1-4] In these landmark trials, the short and intermediate-term outcomes with EVAR were as good as OSR but there were also higher rates of long-term complications for the EVAR patients. While these RCTs were instrumental in the acceptance of

EVAR, the enrollment periods were the early 2000s and only included older first and second generation devices; thus, the outcomes may no longer be reflective of currently available technology.

There have been many device improvements since the time of those landmark RCTs. For example, Type I endoleaks and graft migration were concerns for earlier generation endografts.[5-7] Changes to the devices have been made to enhance fixation and accuracy of deployment[8, 9] and modern grafts now have decreased rates of reintervention and late conversion.[10] As the patient population receiving EVAR has expanded, currently available devices are also more conformable to improve outcomes in patients with more complex anatomies.[9] The Endurant Stent Graft System (Medtronic, Santa Rosa, CA, USA) is one of these new generation stent grafts with a lower-profile delivery, greater radial strength, and a small amplitude M-shaped proximal stent for better sealing of the proximal neck. Recent literature suggests the newer-generation EVAR devices, like the Endurant stent graft, have better performance with fewer complications and reinterventions.[10-13]

With the clear evolution of EVAR devices, Donas *et al.* called for research designed to draw more robust conclusions about the performance of current technology[12] but a new RCT evaluating old *versus* new EVAR devices would be unethical. To our knowledge, there have been few previous studies on temporal changes in outcomes due to device improvements. One study examined the full evolution of EVAR devices from early physician made grafts through the current generation Endurant stent graft systems and found significant improvement in all-cause and aneurysm related mortality, perioperative complications, and reinterventions.[14] Matsumoto *et al.* used results from two similarly designed thoracic endograft clinical studies, Valor and Valor II, to show that the second generation graft studied in the Valor II trial had significantly higher freedom from secondary procedures which they attributed to device design, operator familiarity, and surrounding equipment improvements.[15]

This analysis compares outcomes from the largest RCT, the Comparison of Endovascular Aneurysm Repair with Open Repair in Patients with Abdominal Aortic Aneurysm (EVAR-1), with the the largest real-world registry for any single EVAR stent graft, Endurant Stent Graft Natural Selection Global Postmarket Registry (ENGAGE).[16] The objective is to report differences in patient outcomes that may be due to improvements in technology and patient management in the modern era of stent grafts.

Materials and methods

The trial design and methodology of the EVAR-1 trial has been previously reported[17] and the four-year results were released in 2005.[1] Briefly, EVAR-1 was a multicenter, prospective, randomized controlled trial RCT of 1,252 patients in the United Kingdom conducted between September 1, 1999 and August 31, 2004 with 41 participating centers. Written informed consent was obtained from all patients and the study was approved by the North-West Multicentre Research Ethics Committee. A total of 626 patients were assigned to EVAR and 626 were assigned to open repair (OR). EVAR-1 was the first RCT to compare EVAR with OSR for endpoints of mortality, quality of life, durability, and cost-effectiveness.[1, 5, 18, 19] Types of stent grafts used in EVAR-1 are shown in Figure 1 with the majority of devices implanted being the Cook Zenith (54%) and Medtronic Talent (32%).

Details of the ENGAGE registry and methodology of data collection have been published previously as well.[11, 20] ENGAGE is an observational, nonrandomized, prospective real-world "all comer" registry that began enrollment in March 2009. Inclusion and exclusion criteria were minimal compared to the extensive requirements of IDE trials. All patients signed consent for their data release and the trial was approved by the local institutional review boards. To date, the registry has enrolled 1263 patients at 79 centers in 30 countries. All patients were treated with the Endurant Stent Graft for elective repair of their AAAs.

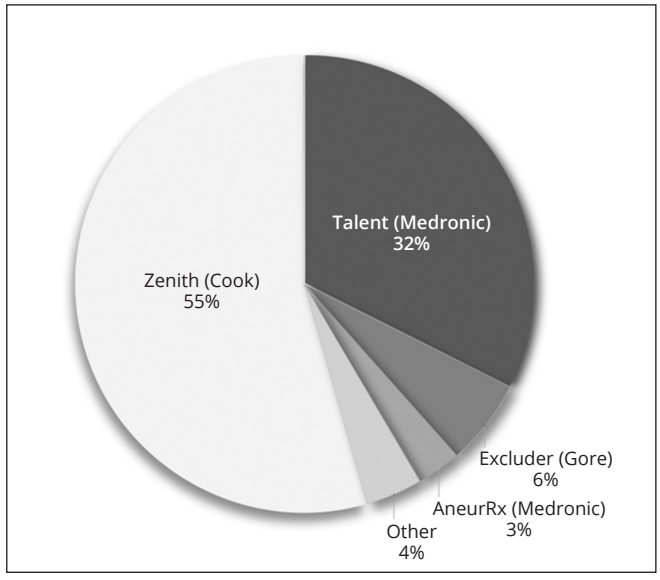

Figure 1.—Stent grafts used in the EVAR-1 Trial.

TABLE I.—*Study design, patients, and devices in both EVAR-1 and the ENGAGE global post market registry.*

	EVAR-1[17]	ENGAGE[11]
Design	Prospective RCT (investigational)	Real world "all comer" registry; intent-to-treat (observational)
Centers	41	79
Countries	1 (UK)	30 countries across 6 continents
Key inclusion/exclusion criteria	Inclusion criteria: • ≥60 years of age • Must be fit for OR as determined by the surgeon • AAA>5.5 cm Exclusion criteria: • AAA 5.5 cm by CT scan • Otherwise unsuitable for EVAR	Inclusion criteria: • 18 years of age • Indication for elective AAA repair Exclusion criteria: • Probability of nonadherence to follow-up requirements and • Concurrent participation in another trial that might confound results
Years of enrollment	September 1999 to August 2004	March 2009 to April 2011
Planned follow-up	5 to 10 years (median 6 years)	30-day and annual visits up to 10 years
Number of patients enrolled	1252 patients (626 patients randomized in each arm)	1263 patients consecutively enrolled
Devices studied	Multiple first-generation AAA devices	A single third-generation AAA device (Endurant)

Both the EVAR-1 trial and ENGAGE registry were conducted following good clinical practice and the principles outlined in the Declaration of Helsinki.

Major elements of research design, patient enrollment, and devices in EVAR-1 and the ENGAGE registry are summarized in Table I.[11, 17] Differences in the published four-year outcomes from the EVAR arm (626 patients) of the EVAR-1 trial and the four-year data of the ENGAGE registry are reported descriptively. The patient baseline characteristics and death due to rupture are presented as a mean±standard deviation for continuous variables or a percentage of patients for categorical variables. All-cause mortality, aneurysm related mortality, and reinterventions are reported.

Results

Of the baseline characteristics that were reported in both studies, 19.0% of ENGAGE and 9.0% of EVAR-1 patients had diabetes. The prevalence of cardiac disease in ENGAGE and EVAR-1 was 53.7% and 43.1%, respectively. In addition, ASA class IV patients comprised 10.6% of the ENGAGE cohort whereas this sicker class of patient was excluded from participating in the EVAR-1 Trial (Table II).[11, 17]

Through the four-year timepoint, freedom from all-cause mortality (ACM) was 74.4% (466/626) and 74.6% (942/1263) in the EVAR arm of the EVAR-1 Trial and the ENGAGE registry, respectively (Figure 2A). Through four years, aneurysm-related mortality (ARM) in the EVAR-1 trial it was 4.2% (26/626) and 38.5% (10/26) of the deaths were attributed to graft rupture after EVAR deployment.

TABLE II.—*Select baseline and anatomic characteristics from both randomized groups in the EVAR-1 trial and ENGAGE.*

	EVAR-1[17] N.=543	ENGAGE[11] N.=1263
Age (years±SD)	74.2±6.0	73.1±8.1
N. of males	90.9% (494)	89.5% (1130/1263)
AAA diameter (cm± SD)	6.5±0.9	6.0±1.2
Diabetes	9.0% (49)	19.0% (237/1245)
Cardiac disease[a]	43.1% (234)	53.7% (678/1262)
Tobacco use [a]	-	49.3% (608/1233)
Current smokers[b]	21.2% (115)	N/A
Past smokers[b]	67.6% (367)	N/A
Never smoked[b]	11.2% (61)	N/A
ASA[c,d] Classification (%)		
Class I	-	6.0% (76/1262)
Class II	-	41.8% (528/1262)
Class III	-	41.5% (524/1262)
Class IV	Excluded from EVAR-1	10.6% (134/1262)

[a]Cardiac disease classified in EVAR-1 as history of any of the following: myocardial infarction (MI), cardiac revascularization, angina, cardiac valve disease, significant arrhythmia, and uncontrolled congestive cardiac failure; in ENGAGE, cardiac disease classified as MI, arrhythmia, coronary artery disease, and cardiac revascularization; [b]baseline variable not reported in ENGAGE; [c]baseline variable not reported in the EVAR-1 Trial; [d]American Society of Anesthesiologists.

In the ENGAGE registry, ARM through four years was 1.9% (24/1263) with 25.0% (6/24) deaths due to rupture (Figure 2B).

In the EVAR-1 Trial, the proportion of patients requiring at least one reintervention through the four-year timepoint was 19.3% (121/626). The proportion of patients having at least one reintervention through the four-year timepoint in ENGAGE was 10.9% (138/1263) with the main causes being type I endoleaks (21.7%), stent graft occlusions (21.2%), and type II endoleaks (20.1%). The freedom

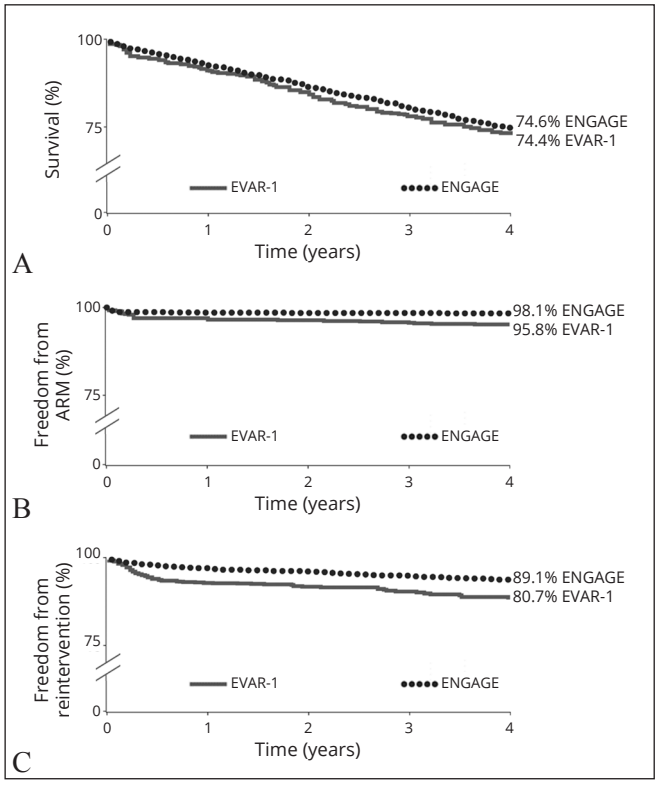

Figure 2.—Freedom from all-cause mortality (A), aneurysm related mortality (B), and reinterventions (C) through four years in the EVAR-1 Trial and the ENGAGE Registry.

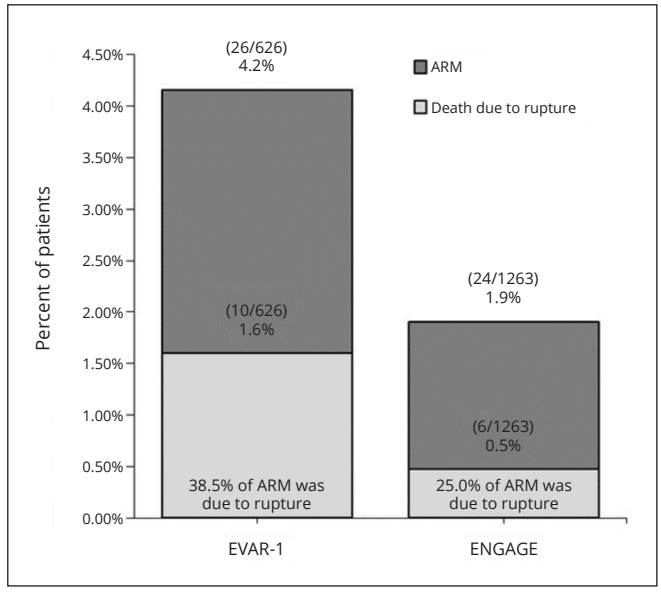

Figure 3.—Aneurysm related mortality and deaths due to rupture through four years in the EVAR-1 Trial and the ENGAGE Registry.

from reinterventions through four years in EVAR-1 and ENGAGE are in Figure 2C.

Overall, death attributable to rupture through four years was 1.6% (10/626) and 0.5% (6/1263) in the EVAR-1 and ENGAGE patients, respectively (Figure 3). There were a total of 25 graft rupture complications in the EVAR-1 trial and there were 11 ruptures through four years in the ENGAGE registry.

Discussion

In this descriptive comparison of the EVAR-1 RCT and ENGAGE data registry, there were notable differences showing modern endograft devices have improved outcomes compared to the older generation stent grafts. Patients treated with the Endurant stent graft had a low rates of aneurysm related mortality, complications, and need for reintervention which is aligned with findings from previous literature.[10-14] There is a large multicenter registry of 1763 patients from northern California in which enrollment occurred between the RCTs and the ENGAGE registry (2000-2010).[21] The freedom from ACM, ARM, and reinterventions in this California registry fell in between the rates reported in EVAR-1 and the ENGAGE registry. Further supporting the idea of improved EVAR outcomes over time, the Swedish Vascular Registry also reports a linear improvement in EVAR outcomes over time for the four time periods in their analysis.[22]

The role of other temporal improvements must also be acknowledged as nearly a decade has elapsed from the beginning of enrollment of EVAR-1 (September 1999) to the start of the ENGAGE registry (March 2009). Physicians have become more proficient in EVAR and studies have concluded that patient outcomes are improved with more experienced operators.[23, 24] The increasing use of imaging methods such as intravascular ultrasound during EVAR is also reported to improve patient outcomes through reduced contrast load and fluoroscopy time.[25, 26] Finally, other paired technologies, such as Endoanchors for which the pivotal clinical trial began in 2007, have been reported to have an effect in reducing endoleaks and migration complications.[27, 28] Temporal changes in device design, operator familiarity, and surrounding equipment improvement were noted to have contributed to the improvements in outcomes in a similar field of thoracic endografts in their Valor and Valor II clinical studies.[15]

While the overall proportion of patients requiring a

reintervention was 19.3% in EVAR-1 and 10.9% in ENGAGE, the freedom from event curves diverge the most in the immediate postoperative period. This difference in the curves suggest modern EVAR devices effectively reduce early complications and then maintained a consistent slope and relative advantage throughout the 4-year period when compared to the older generation stent grafts. The difference in need for reinterventions could be attributed to the better fixation provided by the improved design of the proximal end of the Endurant stent graft.[11, 13]

In the ENGAGE registry, 82% of patients were treated within the instructions for use. This number is higher than earlier studies where on label usage ranged from 61-68% for their respective devices implanted.[29, 30] The increased off label usage in the earlier studies was surprising but possibly due to modern devices having expanded indications, more patients are likely to be within the instructions for use. Despite the enrollment of a much broader range of patients including those that were sicker (*i.e.* ASA class IV, history of diabetes, heart disease) in the ENGAGE registry, the lower rates of ARM and reinterventions indicate the better performance of newer generation devices even in a more challenging population.

Clinical equipoise would not be possible in a study of current and previous generation endografts and so these retrospective comparisons are the only suitable method to assess temporal changes in outcomes. Comparable risk characteristics and outcomes between the DREAM Trial and the EUROSTAR registry led the authors to believe the EUROSTAR data offered a reliable source of real-world practice and justified future research comparisons using registry data.[31] Other reports have concluded well designed observational studies do not overestimate the magnitude of effect of treatments and can provide comparable data as RCTs.[32, 33] With the inclusion of a broad range of patients, real-world registries offer insights into patient selection, customized patient follow-up, and increased cost-effectiveness. With the acceptance of global registries as reliable measures of the real-world experience with modern EVAR devices, the outcomes of the landmark RCTs are becoming dated. As long-term outcomes from modern device registries become available, those should serve as the new benchmark studies for the assessment of EVAR.

Limitations of the study

While there are inherent limitations with comparing a RCT to a patient registry, differences in patient outcomes and device performance between the old and new stent grafts are still meaningful in the assessment of modern day EVAR systems. Limitations of this analysis include the population in the ENGAGE registry was a diverse real-world patient population while the EVAR-1 Trial had a relatively limited sample of patients in the UK which likely suggests baseline demographics were different. In addition, follow up compliance is inherently not as strictly adhered to in a registry as compared to a RCT and as a result, events missed in follow up could be higher in a registry than a RCT. However, the reliability of registry data was previously reported by Leurs *et al.* where they found similar outcomes from the DREAM trial and EUROSTAR registry despite the difference in experimental design.[31] ENGAGE has robust monitoring as previously reported.[20] Finally, while the EVAR-1 trial was used as the comparator with the ENGAGE global registry in this analysis, other RCTs, such as the DREAM, ACE, and OVER trials could have also qualified as a landmark dataset.

Conclusions

Patients in the ENGAGE global registry are having low reintervention rates and few graft related adverse events through four years postindex procedure. With significant changes in stent graft technology and patient management practices since the period of landmark RCTs like EVAR-1, the outcomes of the ENGAGE registry are more reflective of current technology. Moving forward, the data from large contemporary EVAR registries like ENGAGE will be vital to the continued improvement of EVAR technology, patient selection, patient management, and cost effectiveness. While longer-term data is still necessary to evaluate the durability of modern EVAR devices, current real-world EVAR registries like ENGAGE should replace the RCTs as the new benchmark for EVAR device performance.

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Conflicts of interest.—Dittmar Böckler: consultant for Medtronic, W.L. Gore & Associates, Cook, Siemens, Endologix, and Arsenal AAA and receives research grant support from Medtronic; Adam H. Power: research grant support from Medtronic and consultant for W.L. Gore and Associates; Hence J. Verhagen: Consultant for Medtronic, W.L. Gore & Associates, Abbott, Endologix, and Arsenal AAA; Joep A. Teijink: Research grant support from Medtronic, W.L. Gore & Associates, and Cook. All other authors have no conflicts of interest related to this research to disclose.

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