

Editor's Choice — Five Year Outcomes of the Endurant Stent Graft for Endovascular Abdominal Aortic Aneurysm Repair in the ENGAGE Registry

Joep A.W. Teijink^{a,*}, Adam H. Power^b, Dittmar Böckler^c, Patrick Peeters^d, Steven van Sterkenburg^e, Lee H. Bouwman^f, Hence J. Verhagen^g, Marc Bosiers^h, Vincente Riambauⁱ, Jean-Pierre Becquemin^j, Philippe Cuypers^a, Marc van Sambeek^a

^a Catharina Hospital Eindhoven, Eindhoven, the Netherlands

^b Western University, London, Ontario, Canada

^c University Hospital Heidelberg, Heidelberg, Germany

^d Imelda Hospital Bonheiden, Bonheiden, Belgium

^e Rijnstate Hospital Arnhem, Arnhem, the Netherlands

^f Zuyderland Medisch Centrum Heerlen, Heerlen, the Netherlands

^g Erasmus University Medical Centre Rotterdam, Rotterdam, the Netherlands

^h AZ Sint-Blasius Campus Dendermonde, Dendermonde, Belgium

ⁱ Hospital Clinic Barcelona, Barcelona, Spain

^j Institut Vasculaire Paris Est, Hôpital Privé Paul d'Egine, Ramsay Group Champigny, Champigny, France

WHAT THIS PAPER ADDS

Analysis of the performance of modern stent grafts is necessary as earlier generation stent grafts are associated with an increased need for secondary interventions. Five year follow up of patients treated with the Endurant stent graft in the ENGAGE registry demonstrates better survival and lower rates of endoleaks, stent migration, and re-intervention. Longer term follow up to 10 years will be necessary to compare fully the advantages of endovascular aneurysm repair against open repair. However, these mid-term results show the Endurant stent graft was successful in treating a large cohort of patients with a wide range of anatomies.

Objective/background: Endovascular abdominal aortic aneurysm repair (EVAR) is commonly used to treat abdominal aortic aneurysm (AAA). However, the incidence of long-term complications and the need for re-interventions after EVAR remain a concern. Newer generation stent grafts have encouraging short and mid-term outcomes, but thorough analysis of their long-term performance is necessary.

Methods: The ENGAGE registry includes a total of 1263 patients with AAA enrolled from March 2009 to April 2011 at 79 centres across 30 countries. The aim of this study is to present standard EVAR outcomes in the registry after five years.

Results: A significant proportion of the ENGAGE patients presented with challenging features, such as 15.2% with an AAA diameter >7 cm, 12.0% with proximal neck lengths <15 mm, and 10.2% with infrarenal neck angles >60°. Of the 1263 enrolled subjects, 17.8% were implanted outside of the instructions for use for the device. At the five year follow up, the Kaplan–Meier overall survival rate was 67.4% and the freedom from aneurysm related mortality was 97.8%. Freedom from aneurysm rupture, secondary procedures, and conversion to open repair at five years were 98.6%, 84.3%, and 97.9% respectively. The five year freedom from type IA endoleaks was 95.2% and for type III endoleaks 97.4%. Aneurysm sac diameter at five years was observed to have either decreased ≥ 5 mm in diameter or remained stable in 89.4% of the patients.

Conclusion: Five year follow up of patients in the ENGAGE registry demonstrates sustained safety, effectiveness, and durability in an international cohort that is reflective of real world experience. Additional follow up is expected through to 10 years.

Keywords: ENGAGE, Endurant, EVAR, Long-term outcomes

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* Corresponding author. Department of Vascular Surgery, Catharina Hospital, Michelangelolaan 2, 5623 EJ Eindhoven, P.O. Box 1350, 5602 ZA Eindhoven, the Netherlands.

E-mail address: joep.teijink@cze.nl (Joep A.W. Teijink).
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INTRODUCTION

Endovascular abdominal aortic aneurysm repair (EVAR) has shown large improvements in clinical safety and effectiveness for the treatment of abdominal aortic aneurysms (AAA) since its initial introduction.^{1,2} Today EVAR is well established and in many cases the preferred option because both short and mid-term outcomes are as good as or better

than open surgical repair (OSR). However, the “Achilles heel” of EVAR is the incidence of mid and long-term complications resulting in the need for conversion to OSR or endovascular re-intervention.^{3–6} For example, long-term follow up in the EVAR 1 trial, as well as a 2017 meta-analysis,^{7–9} show earlier generation AAA stent grafts have a higher risk of migration. Other earlier studies have also suggested erosion of the short-term benefit of EVAR over OSR over time.^{3,4,10–13}

To address these concerns, there have been many technological advances in stent graft design to improve fixation, deployment, and applicability to more complex anatomies.¹⁴ Recent literature suggests that newer generation stent grafts have lower rates of complications and re-interventions.^{15–17} To truly assess the performance of newer generation stent grafts, it is necessary to use current registries, which include a wider patient population than the selective population in clinical trials. While registries may have some inherent data collection limitations, carefully designed observational studies can provide evidence comparable to randomised controlled trials (RCTs).^{18,19} The Endurant Stent Graft Natural Selection Global Postmarket Registry (ENGAGE) is a global, prospective multicentre registry evaluating the Endurant stent graft system (Medtronic, Santa Rosa, CA, USA) and is the largest registry for any single EVAR stent graft.²⁰ Stokmans *et al.* published the peri-operative, 30 day, and interim one year results,²¹ as well as a comparison between symptomatic and asymptomatic AAAs,²² from the ENGAGE registry. Other analyses of the ENGAGE registry have investigated outcomes for octogenarians, differences due to sex, and higher risk anatomies and conditions.^{23–30} The aim of the current study is to report the five year results of the ENGAGE registry and assess long-term outcomes.

METHODS

Full methodological details of the ENGAGE registry (NCT00870051) and data collection rationale have been published previously,^{21,31} as have the technical specifications of the Endurant stent graft system.²⁰ Briefly, ENGAGE is an observational, non-randomised, prospective “all comer” registry. Sites were encouraged to consecutively enrol patients, or at least blocks of five patients, to minimise selection bias. Inclusion criteria were minimal and accepted patients who fell outside of the instructions for use (IFU) guidance. Select exclusion criteria were probability of non-adherence to follow up requirements, or concurrent participation in another trial that might confound results (Table S1). To date, the registry has enrolled 1263 patients at 79 centres in 30 countries spanning six continents.

Initially annual follow up visits were planned for five years, now extended through to 10 years of follow up at most of the centres. The ENGAGE registry did not require specific tests or procedures that fall outside routine hospital practices, and computed tomography (CT) with contrast was the recommended imaging modality during follow up visits. Patients with impaired renal function or contrast

intolerance were recommended to have combinations of Doppler ultrasound, CT without contrast, or magnetic resonance imaging/angiography. Robust registry monitoring consists of 100% data management review, extensive data monitoring with all end points reviewed, and an independent clinical event committee adjudicating major adverse events within 30 days, and all deaths. Most participating ENGAGE registry sites received approval of the protocol and consent form by their appropriate local ethics committee. As this was a registry protocol that did not impose any additional interventions or changes to standard care practices, some sites did not require ethical committee approval or only required for a notification to their institutional review board. Informed consent for authorisation of data release was required as part of the trial participation and was obtained from all patients at the time of enrolment. The ENGAGE registry adheres to the Declaration of Helsinki and applicable local regulations. Furthermore, the registry was conducted with sections of ISO 14155, MEDDEV 2.12-2, and the International Conference on Harmonisation Good Clinical Practice as guidance.

Statistical analysis

This was a five year follow up analysis of the data in the ENGAGE registry database. Patient baseline characteristics, aneurysm characteristics, and risk factors are presented for the 1263 patients as a mean $\pm$ SD for continuous variables. Percentage of patients was used for categorical variables such as changes in aneurysm diameter. Outcomes such as all cause mortality, aneurysm mortality, freedom from endoleak, migration, AAA rupture, secondary endovascular interventions, and so on, through to five years were assessed with survival analyses. All variables are reported descriptively without hypothesis testing as this was a registry analysis and not a RCT. All analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

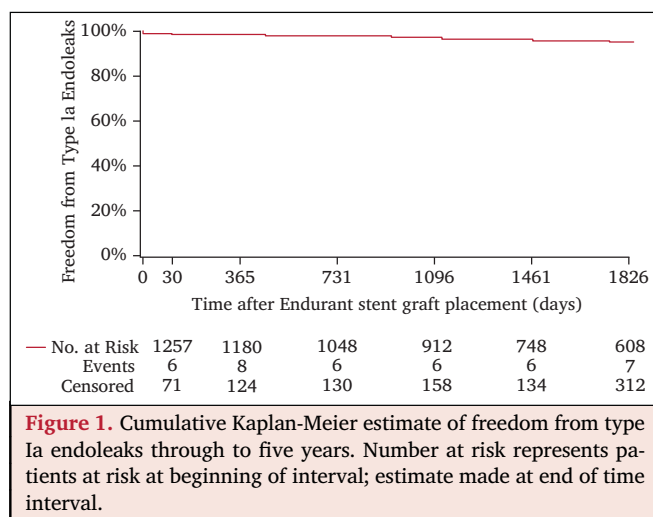
RESULTS

Baseline and procedural results

Of the 1263 patients enrolled, compliance with clinical and imaging follow up was 87.8% and 73.7% at five years, respectively. Baseline and procedural results are included in the supplementary material (Tables S2 and S3) and in the ENGAGE early results publication.²¹ To summarise, the cohort consisted of mostly elderly males with multiple risk factors and comorbidities. ENGAGE patients presented with challenging anatomical features, including 15.2% with an AAA diameter >7 cm, 12.0% with proximal neck lengths <15 mm, 10.2% with infrarenal neck angles $>60^\circ$, and 17.8% implanted outside the IFU. The technical and clinical success rates were 99.0% and 97.6%, respectively, with no deaths during the implantation procedure.

Five year outcomes: endoleaks and technical observations

Freedom from type IA endoleaks was 95.2% with a 95% confidence interval (CI) of 93.4–97.0% (Fig. 1). The five year freedom from any endoleak, type IB endoleaks, and type III



endoleaks was 68.6% (95% CI 65.3–71.9%), 95.9% (95% CI 94.5–97.3%), and 97.4% (95% CI 96.2–98.6%), respectively. There was one post-operative migration of the stent graft's main body occurring in year 4, resulting in 99.8% of patients being free from this event after five years. A second patient had an observed graft migration on day 1870, which was not included in the time to event curve because of the 1 826 day cut off. A summary of technical observations, as well as events such as conversions to open repair and rupture, is in Table 1.

All cause mortality and aneurysm related mortality within five years

The Kaplan–Meier estimate of overall survival through to five years was 67.4% with a 95% CI of 64.1–70.7% (Fig. 2). The Kaplan–Meier estimate of freedom from aneurysm related mortality through to five years was 97.8% (95% CI 96.8–98.8%), with six deaths occurring from years two to five. Of the 95 all cause deaths in the first year, 19 were aneurysm related. Of the 375 all cause deaths through to five years, 25 were aneurysm related.

Rupture, secondary endovascular procedures, and conversion to OSR

Freedom from secondary endovascular procedure was 84.3% (95% CI 81.4–87.2%) through to five years (Fig. 3). Indications for secondary endovascular procedures were type I endoleak (23%), type II endoleak (21%), stent graft occlusion (18%), stent graft stenosis (10%), AAA enlargement (8%), type III endoleak (6%), rupture (2%), and 12% other (migration, undetermined endoleak, kinking, etc.). Freedom from aneurysm rupture and conversion to OSR through to five years was 98.6% (95% CI 97.8–99.4%) and 97.9% (95% CI 96.7–99.1%), respectively.

Aneurysm sac diameter change through to five years

Fig. 4 shows the annual change in the aneurysm sac diameter over each year of follow up by either (i)

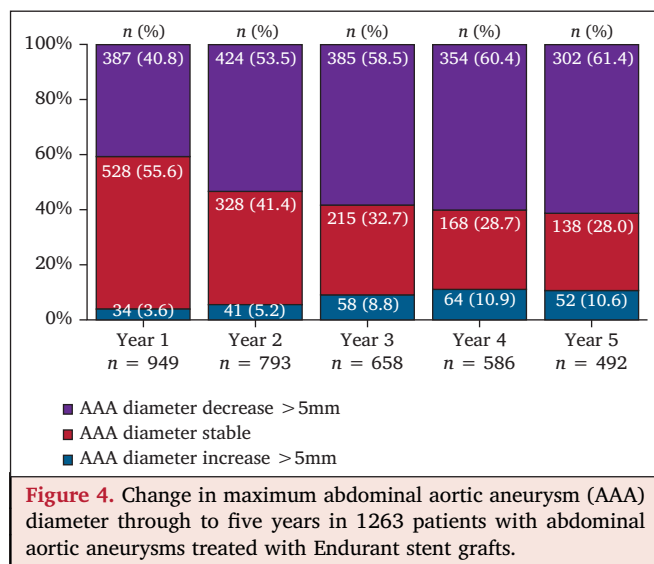
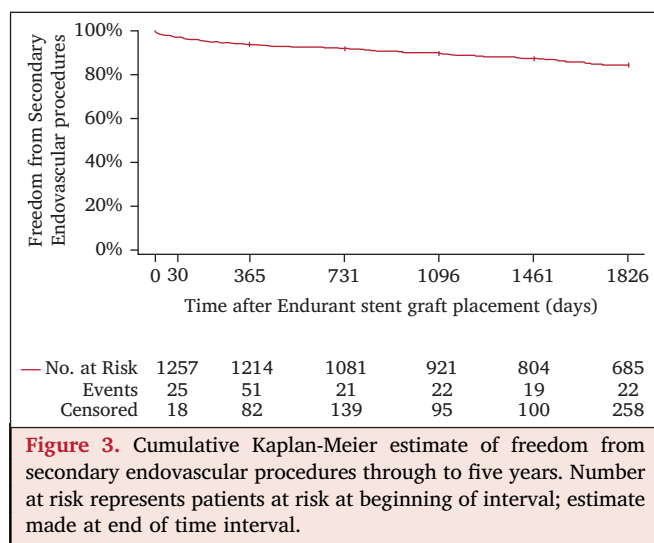
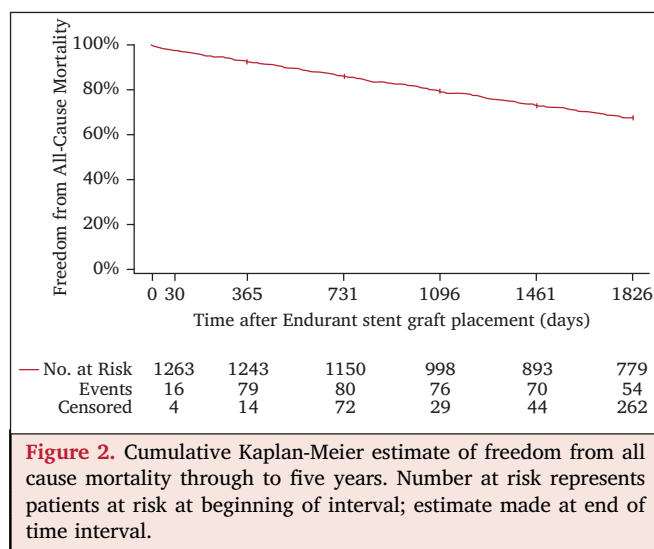
Table 1. Technical observations and major events during follow ups for ENGAGE Subjects					
Technical Observations (TOs) ¹	At 1 year % (m/n) ²	At 2 years % (m/n) ²	At 3 years % (m/n) ²	At 4 years % (m/n) ²	At 5 years % (m/n) ²
≥1 Technical observations	13.5% (146/1079)	13.0% (117/902)	12.2% (90/740)	12.5% (82/654)	11.3% (61/542)
Limb migration	0.1% (1/819)	0.9% (5/573)	0.2% (1/422)	0.0% (0/380)	0.0% (0/291)
Main body migration	0.0% (0/819)	0.0% (0/573)	0.0% (0/423)	0.3% (1/381)	0.3% (1/291)
Stent graft kinking	0.2% (2/805)	0.4% (2/560)	0.0% (0/415)	0.3% (1/371)	0.7% (2/284)
Suprarenal bare stent fracture	0.0% (0/819)	0.0% (0/573)	0.0% (0/423)	0.3% (1/381)	0.3% (1/292)
Stent graft occlusion	1.7% (17/1017)	0.4% (3/833)	0.4% (3/681)	0.3% (2/594)	0.2% (1/485)
Stent graft stenosis	1.1% (11/1017)	0.5% (4/834)	0.6% (4/678)	0.7% (4/590)	0.0% (0/476)
Endoleak	10.4% (108/1034)	11.0% (94/856)	10.6% (75/705)	10.3% (63/614)	9.4% (47/501)
Type I	0.5% (5/1034)	1.2% (10/856)	1.4% (10/705)	2.0% (12/614)	1.8% (9/501)
Type IA	0.3% (3/1034)	0.5% (4/856)	0.7% (5/705)	0.7% (4/614)	1.6% (8/501)
Type IB	0.2% (2/1034)	0.7% (6/856)	0.7% (5/705)	1.5% (9/614)	0.4% (2/501)
Type II	9.2% (95/1034)	8.4% (72/856)	8.5% (60/705)	7.7% (47/614)	7.2% (36/501)
Type III	0.2% (2/1034)	0.6% (5/856)	0.1% (1/705)	0.2% (1/614)	0.4% (2/501)
Type IV	0.1% (1/1034)	0.0% (0/856)	0.0% (0/705)	0.0% (0/614)	0.0% (0/501)
Major Events ³	0-365 Days % (m/n) ⁴	366-731 Days % (m/n) ⁴	732-1096 Days % (m/n) ⁴	1097-1461 Days % (m/n) ⁴	1462-1826 Days % (m/n) ⁴
Conversion to open surgery	0.6% (7/1263)	0.3% (3/1150)	0.1% (1/998)	0.2% (2/893)	0.8% (6/779)
Aneurysm Rupture	0.2% (2/1263)	0.2% (2/1150)	0.2% (2/998)	0.6% (5/893)	0.3% (2/779)

¹ Technical observations were assessed for Implanted Subjects

² m = number of implanted subjects who experienced the corresponding technical observation at the time point visit, n = number of implanted subjects who had valid images for each specific assessment of technical observations at the time point visit. For kinking, fracture, detachment, occlusion, stenosis, and migration (after 1 year) the subjects who experienced the specific event in the previous follow up visits would be excluded from both the denominator and numerator at the current visit.

³ Major events were assessed for the Intent to Treat Subjects.

⁴ m = number of subjects having corresponding event within given time period, n = number of ITT = intention to treat subjects at intra-operative or entered the given time period.



increase > 5 mm in diameter, (ii) stable/no change, and (iii) decrease > 5 mm in diameter. Patients were grouped based on their AAA diameter measurement at the yearly follow up as compared with their AAA diameter at their one month follow up. At five years, 89.4% ($n = 440/492$) AAAs were observed to have decreased in size or remained stable. At five years, 10.6% ($n = 52/492$) of the patients had an AAA diameter that was >5 mm larger than at their one month follow up.

DISCUSSION

The five year follow up analysis of the full cohort ($n = 1\,263$) of the ENGAGE registry showed several promising outcomes. The patients in this study had a freedom from all cause mortality through to five years of 67.4%. This is higher than a retrospective single centre review of patients receiving older generation grafts, where the all cause mortality was 52.1% at five years.³² While a meta-analysis of the early RCTs reported a five year estimated survival rate of 73.6%,⁸ this is expected given the patients in the RCTs were more carefully selected than those in the ENGAGE registry. The survival outcomes of the ENGAGE patients is very similar to other current stent grafts, which report five year survival rates ranging between 68.4% and 72.1%.^{33,34}

Previous reports show patients with older generation grafts had a five year freedom from rupture and freedom from aneurysm related mortality of 98% and 96%, respectively.³² The freedom from aneurysm rupture and aneurysm related mortality was similar in the ENGAGE cohort at 98.6% and 97.8%, respectively, after five years. De Bruin *et al.* point out that aneurysm rupture was not a frequent cause of death for either EVAR or open repair patients in the long term.⁴

The need for re-intervention is another concern for earlier generation stent grafts.⁸ Freedom from re-intervention at five years generally hovers around 80% for EVAR patients,^{7,32} and the six year freedom from secondary interventions was 81.9% and 70.4% for open repair and endovascular cohorts, respectively, in the Dutch Randomised Endovascular Aneurysm Management (DREAM) trial (with implants occurring between 2000 and 2003).⁴ The DREAM trial had strict inclusion criteria and patients with lower anatomical complexity. The ENGAGE registry consisted of older patients with higher American Society of Anaesthesiologists' (ASA) scores, which is associated with an increased need for secondary interventions.³⁵ Despite the more challenging cohort, the five year freedom from secondary endovascular procedures was 84.3% in the ENGAGE registry. There still remains room for improvement as open repair can have a freedom from re-intervention rate above 90%.¹²

Endoleak and migration are serious concerns because they can lead to further complications and so modern stent grafts have been designed to have better sealing and fixation. The five year freedom from any endoleaks and from type IA endoleaks in the ENGAGE registry was 68.6% and

95.2%, respectively. These rates are very similar to an estimated 74.6% of patients free from any endoleak through to five years and 93.2% free from type I endoleaks in a contemporary Australian cohort.³⁶ In the ENGAGE study, 89.4% of patients with follow up imaging had declining or stable (61.4% declining, 28.0% stable) sac diameters at five years. This percentage is comparable to early generation results, where 91% of patients had declining or stable (49% declining, 43% stable) sac diameters.³² However, more ENGAGE patients experienced sac diameter decline than those with the older stent grafts.

Main body graft migration was seen in one patient within the five year follow up in the ENGAGE registry compared with 25 cases (2.9% of patients) of clinically significant migration reported by Brewster *et al.* in their study of earlier generation stent grafts.³² Of the 173 patients that underwent endovascular repair in the DREAM Trial, seven (4.0%) had graft migration over a period of six years.⁴ Despite the ENGAGE registry having a larger fraction of patients with challenging anatomical features in their proximal neck, graft migration was minimal. The authors note that the imaging modality primarily used in the 30 day and one year follow ups was CT, but at the four and five year follow ups, duplex color Doppler ultrasound (CDUS) was more commonly used. Both techniques are considered comparable for aneurysm size, endoleaks, and graft patency assessment.³⁷ However, certain stent performance measures like graft migration, kinking, or fracture are difficult or even impossible to detect with CDUS, which could have resulted in an underestimation of these events.

There are several other registries with which to put the ENGAGE results in context, although direct comparisons are difficult given differences in stent graft device design, patient populations, and event definitions. Data from two centres in the European C3 of the Global Registry for Endovascular Aortic Treatment (GREAT) investigated long-term outcomes of another current stent graft in their 248 patients.³³ The overall survival and freedom from re-intervention at five years in this two-centre cohort are nearly identical to the five year ENGAGE results, despite the ENGAGE patients being older and consisting of more ASA class III and IV patients. Another large registry of patients with multiple types of EVAR grafts implanted from 2000 to 2010 in northern California had a similar all mortality survival through to five years.³⁸ The ENGAGE cohort had larger pre-operative aneurysm sizes and more complex anatomies than those in the Kaiser Permanente registry, so the similar survival rate is encouraging.

Although patients in the ENGAGE registry had similar freedom from secondary interventions and aneurysm related mortality to the US regulatory approval study,³⁹ the freedom from all cause mortality through five years was lower for the ENGAGE patients. These outcomes should be expected when comparing an investigation device clinical trial with strict inclusion/exclusion criteria with an all comer registry. Many patients in the ENGAGE registry would not have met the Investigational Device Exemption (IDE) clinical

trial screening requirements for neck length, angulation, and iliac sealing zones as they had more complex anatomies. This is a strength of registry data as the inclusion of patients who may not meet IFU standards allows for a better assessment of the real world graft performance. Treating off label patients, particularly those with challenging neck features, has been reported to be associated with increased risk of Type Ia endoleaks,^{40,41} or increased re-interventions.⁴² As a result, most advocate cautious use of off label EVAR and generally reserve it for high risk patients who still require treatment. Fenestrated grafts, chimney techniques,⁴³ or the use of other adjunctive devices like EndoAnchors⁴⁴ can offer alternatives so physicians can stay within IFU guidelines.

Limitations

Registries, by nature, are observational and are not designed to have the statistical power to draw robust comparisons as would a RCT. Also there can be more challenges with maintaining adherence to follow up in patient registries than in a RCT.³⁸ For example, the imaging follow up rate of 73.7% in the ENGAGE registry was lower than the 87% rate in the Endurant US regulatory trial.³⁹ The 87.8% compliance rate with clinical follow up in the ENGAGE registry was within the 87–98% rate that has been reported in other EVAR clinical trials.^{34,39,45}

CONCLUSIONS

In this five year analysis of the full cohort of the ENGAGE registry, the outcomes are positive. ENGAGE patients had better survival and lower re-intervention rates than previous generation stent grafts and the patients also experienced low rates of adverse events like endoleaks and main body migration. Longer term follow up out to 10 years will be necessary to compare fully the advantages of EVAR against open repair, but in the mid-term, this modern stent graft system has been successful in treating a large real world cohort of patients with a wide range of anatomies.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejvs.2019.01.008>.

CONFLICT OF INTEREST

J.A.T. receives unrestricted research grants from Medtronic, W.L. Gore & Associates, and Cook. A.P. receives ongoing reimbursement from Medtronic and receives speaker

honoraria from Cook and Medtronic. D.B. is a consultant for Medtronic, W.L. Gore & Associates, and Endologix, and receives research funding from Medtronic. H.V. is a consultant for Medtronic, W.L. Gore & Associates, Philips, Endologix, and Arsenal AAA. J.B. receives honoraria from Medtronic. P.C. and M.v.S. receive unrestricted research grants from Medtronic, W.L. Gore & Associates, and Cook. V.R. is a consultant for JOTEC, iVascular, and Bolton Medical, and receives speaker honoraria from Medtronic. None of the other authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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