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Prognosis review and time-to-event data meta-analysis of endovascular aneurysm repair outside versus within instructions for use of aortic endograft devices

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ABSTRACT

Background: Our objective was to investigate whether patients undergoing standard endovascular aneurysm repair (EVAR) outside the instructions for use (IFU) have worse outcomes than patients treated within IFU.

Methods: We conducted a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Electronic bibliographic sources were searched up to January 2019 using a combination of controlled vocabulary (thesaurus) and free-text terms to identify studies comparing outcomes of EVAR in patients treated outside versus within IFU. Pooled estimates of dichotomous outcomes were calculated using odds ratio (OR) or risk difference (RD) and 95% confidence interval (CI). We conducted a time-to-event data meta-analysis using the inverse-variance method and reported the results as summary hazard ratio (HR) and associated 95% CI. Random-effects methods of meta-analysis were applied. We formed meta-regression models to explore heterogeneity as a result of changes in practice over time.

Results: We identified 17 observational cohort studies published between 2011 and 2017, reporting a total of 4498 patients. The pooled prevalence of EVAR performed outside the IFU was 40% (95% CI, 33-48). Nonadherence to IFU was not associated with increased risk of perioperative mortality (RD, 0.01; 95% CI, -0.00 to 0.01; $P = .23$), aneurysm rupture (HR, 1.34; 95% CI, 0.30-5.93; $P = .70$), aneurysm-related mortality (HR, 0.88; 95% CI, 0.20-3.84; $P = .86$), technical failure (RD, 0.01; 95% CI, -0.03 to 0.05; $P = .56$), requirement for adjunctive procedures (OR, 1.48; 95% CI, 0.81-2.71; $P = .20$), type I endoleak (HR, 2.28; 95% CI, 0.58-8.91; $P = .24$), aneurysm sac expansion (HR, 0.86; 95% CI, 0.55-1.33; $P = .49$), or aneurysm-related reintervention (HR, 1.04; 95% CI, 0.81-1.34; $P = .74$). The overall mortality was significantly higher in patients treated outside the IFU (HR, 1.20; 95% CI, 1.02-1.42; $P = .03$). Meta-regression showed that the prevalence of EVAR performed outside the IFU has increased over time ($P = .019$).

Conclusions: Standard EVAR outside the IFU was not found to have worse aneurysm-related outcomes than treatment within the IFU. Standard EVAR outside the IFU could be considered in selected patients who are deemed high risk for complex open or endovascular surgery. (J Vasc Surg 2020;71:1415-31.)

Keywords: Aortic aneurysm; Endovascular aneurysm repair; EVAR; Instructions for use; IFU

Endovascular aneurysm repair (EVAR) has revolutionized the treatment of abdominal aortic aneurysm (AAA), offering an early survival advantage over open surgical repair. Even though a marked benefit in perioperative mortality has been demonstrated in randomized clinical trials,¹⁻³ such benefit decreases or is even lost over time. The rate of secondary intervention, aneurysm

rupture, and aneurysm-related mortality in the long term have been found to be higher with EVAR than with open surgical repair.^{4,5}

Adverse aortic morphology has been identified as the culprit for late failure of endovascular treatment. Endovascular device manufacturers publish instructions for use (IFU) recommendations based on preclinical engineering

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assessments and results of clinical studies that specify anatomic criteria for appropriate use of EVAR devices. Patients with hostile aortic neck anatomy undergoing standard EVAR have been found to have worse short-to medium-term outcomes compared with patients with favorable anatomy.⁶ Alternative treatment methods, such as fenestrated or chimney EVAR and open surgical repair, have been proposed when anatomic constraints are present. Because such techniques carry a higher perioperative morbidity and mortality risk, some endovascular specialists prefer to use standard EVAR outside the IFU in selected patients with adverse anatomic features who are deemed high risk for complex open or endovascular procedures. Such an approach might be justified in selected cases in light of improvements in endovascular techniques and aortic devices, technological advances, and the ever-increasing experience of endovascular specialists. On the other hand, violating the IFU is one of the reasons the long-term durability of EVAR is exposed to criticism.

In view of the ongoing controversy and scepticism regarding the use of standard EVAR outside IFU of aortic endograft devices,^{7,8} we aimed to compile, appraise, and analyze the pertinent evidence on the safety and efficacy of this practice in adverse aortic morphologies.

OBJECTIVE

Our objective was to investigate whether there are differences in outcomes between patients undergoing standard EVAR outside the IFU and those treated within the IFU of aortic endograft devices.

METHODS

Design

The objectives and methodology of our review were prespecified in a protocol that was registered with the number CRD42019121353 at the International Prospective Register of Systematic Reviews in Health and Social Care (PROSPERO). Our review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁹

Criteria for considering studies

Types of studies. We considered observational cohort studies comparing outcomes of EVAR in patients treated outside versus within the IFU.

Types of participants. Eligible participants were male or female patients of any age undergoing elective treatment for AAA with standard EVAR. Patients treated for symptomatic or ruptured AAA were not considered. We also excluded patients who underwent complex EVAR, such as fenestrated EVAR or EVAR with the chimney technique, patients treated with EVAR combined with planned EndoANCHOR placement, patients with aorto-iliac aneurysm treated with iliac bifurcation device, and those undergoing endovascular aneurysm sealing with the Nellix device.

Types of prognostic factor. The prognostic factor of interest was adherence to IFU of the aortic device used for the treatment of AAA with standard EVAR. IFU adherence was defined as compliance with all or some of the IFU recommendations as defined by the manufacturer's published criteria and was device specific. The definition of IFU may have varied across the studies, which may have used different criteria to define treatment outside or within IFU (eg, specific proximal aortic neck criteria such as neck length or diameter or a combination of such criteria). We used the definition of IFU used in the individual studies to categorize patients in those treated outside and within IFU. We considered any commercially available device.

Types of outcome measures.

Primary outcomes. Primary outcome measures were defined the following:

- perioperative (in-hospital or within 30 days of treatment) mortality
- freedom from aneurysm rupture
- freedom from aneurysm-related mortality

Secondary outcomes. Secondary outcome measures were defined the following:

- technical success
- requirement of adjunctive procedures
- early (within 30 days of treatment) type I endoleak and freedom from type I endoleak
- freedom from sac expansion
- early (within 30 days of treatment) reintervention and freedom from aneurysm-related reintervention
- overall survival

Search methods for identification of studies

The literature search strategy was developed by the review author team in collaboration with a clinical information specialist. Studies related to the subject were identified by searching electronic information sources. We used the Healthcare Databases Advanced Search interface developed by the National Institute for Health and Care Excellence. We interrogated the following electronic bibliographic databases: The National Library of Medicine's database (MEDLINE), Excerpta Medica Database (EMBASE), and the Cochrane Register of Studies (CENTRAL). A combination of controlled vocabulary (thesaurus) and free-text terms were used to search the databases. No language constraints were applied. The literature search was last run in January 2019. Our search strategy is presented in [Appendix 1](#) (online only).

Data collection and management

Two review authors conducted the prespecified literature searches and evaluated the eligibility of studies for inclusion independently. When disagreement arose, a third review author acted as an arbitrator.

Fig 1. Study flow diagram. AAA, Abdominal aortic aneurysm; EVAR, endovascular aneurysm repair.

One review author extracted data from selected studies. The collected data were then crosschecked by a second review author. Retrieved data were entered into a spreadsheet. Only published data were considered. We extracted study-related data, data related to risk of bias assessment, information on clinical characteristics of the study populations, data pertaining to the index procedure, aneurysm morphometric data, and outcome data.

Risk of bias assessment

The methodological quality of observational cohort studies was assessed with the Newcastle-Ottawa Scale (NOS).¹⁰ Using the tool, each study was judged on eight items, categorized into three groups: the selection of the study groups, the comparability of the groups, and the assessment of outcome. Stars awarded for each quality item served as a quick visual assessment. Stars were awarded such that the highest quality studies were awarded up to nine stars. We generated a summary of findings table and graded the quality of evidence using the system developed by the Grades of Recommendation, Assessment, Development and Evaluation working group applying an online platform (<https://gdt.gradepro.org/app/>).

Data synthesis

Measures of treatment effect. The prevalence of EVAR performed outside the IFU in the entire review population was pooled by meta-analyzing data from individual studies. The pooled proportion was calculated as the back transformation of the weighted mean of the transformed proportions.

Pooled estimates of dichotomous outcome data were calculated using the odds ratio (OR) or risk difference (RD) and associated 95% confidence interval (CI) to investigate differences between patients treated outside versus within the IFU. For late outcomes, a time-to-event data meta-analysis was conducted using the inverse-variance method and the result was reported as summary hazard ratio (HR) and associated 95% CI. We applied a mixture of direct (eg, from reported HRs with CI) or indirect methods (eg, when *P* value from log rank test and total events were provided or from survival curves incorporating numbers at risk) to calculate the individual study HR and standard error (SE) for specific outcome measures.¹¹ Data extracted from published Kaplan-Meier curves were digitalized using open-source software Plot Digitizer (<http://plotdigitizer.sourceforge.net>).

Table I. Study characteristics

Author, Year, Journal, Country	Single/ multicenter	Prospective/ retrospective	Recruitment period	Total no. patients (outside IFU/within IFU)
de Donato, ¹⁴ 2017, J Endovasc Ther, Italy	Multi	Registry	2010-2012	89 (32/57)
AbuRahma, ¹⁵ 2016, J Am Coll Surg, USA	Single	Retrospective	2003-2013	526 (275/251)
Pecoraro, ¹⁶ 2016, Diagn Interv Radiol, Italy	Single	Retrospective	2012-2015	64 (30/34)
Beckerman, ¹⁷ 2016, J Vasc Surg, USA	Single	Retrospective	2003-2014	566 (390/176)
Mahajan, ¹⁸ 2016, Ann Vasc Surg, USA	Single	NR	2002-2009	273 (163/110)
Walker, ¹⁹ 2015, J Vasc Surg, USA	Multi	Registry	2000-2010	489 (205/284)
Matsagkas, ²⁰ 2015, J Vasc Surg, Greece	Single	Retrospective	2008-2012	57 (19/38)
Hoshina, ²¹ 2014, Ann Vasc Dis, Japan	Single	NR	2006-2009	275 (82/193)
Matsumoto, ²² 2014, Surg Today, Japan	Single	Retrospective	2007-2010	150 (50/100)
Speziale, ²³ 2014, Ann Vasc Surg, Italy	Multi	Retrospective	2010-2011	196 (133/63)
Troisi, ²⁴ 2014, J Endovasc Ther, Italy	Multi	Retrospective	2007-2010	177 (56/121)
Igari, ²⁵ 2013, Ann Thorac Cardiovasc Surg, Japan	Single	NR	2008-2010	53 (20/33)
Lee, ²⁶ 2013, Eur J Vasc Endovasc Surg, USA	Single	Retrospective	2004-2007	218 (75/143)
Nakai, ²⁷ 2013, Jpn J Radiol, Japan	Single	NR	1999-2012	124 (38/86)
Bachoo, ²⁸ 2013, J Cardiovasc Surg, UK	Multi	Registry	2010-2012	399 (68/331)
Abbruzzese, ²⁹ 2013, J Vasc Surg, USA	Single	Retrospective	1999-2005	565 (222/343)
Handa, ³⁰ 2011, Circulation, ^a Japan	Multi	Retrospective	2007-2010	277 (92/185)
IFU, Instructions for use; NR, not reported.				
^a Published as a conference abstract.				

We performed a further meta-analysis of key clinical characteristics and anatomic and procedure-related data to evaluate if there was variability in patients treated outside versus within IFU. Pooled estimates of dichotomous data were calculated using the OR and associated 95% CI, whereas for continuous variables, we calculated the mean difference (MD) and associated 95% CI.

Assessment of heterogeneity. In-between study heterogeneity was examined with the Cochrane's Q (χ^2) test. We quantified inconsistency by calculating I^2 and interpreted it using the following guide: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% may represent considerable heterogeneity.¹²

Assessment of reporting bias. For each study, we plotted the effect (or proportion) by the inverse of its SE. Publication bias was assessed both visually evaluating the symmetry of the funnel plot and mathematically using the Egger regression intercept for outcomes reported by at least 10 studies.

Statistical models. In view of the anticipated variability in IFU of different aortic devices, type of IFU adherence (eg, any IFU, IFU pertaining to the proximal aortic neck) and the clinical or methodological diversity among the selected studies, we calculated the summary estimates using the random-effects models of DerSimonian and Laird.¹³ A forest plot was created for each treatment effect.

Sensitivity and subgroup analysis. We sequentially excluded studies of high risk of bias (indicated by achieving less than six stars in the NOS) and performed a pooled sensitivity analysis to assess whether the excluded studies, deemed to be biased, affected the final analysis. Sensitivity analysis was also conducted including studies that grouped their patient cohorts based on IFU for the proximal aortic neck. A separate sensitivity analysis excluded studies whose recruitment period expanded before 2007, hence representing treatments with older generation aortic devices. We had planned to conduct a subgroup analysis for the type of aortic device.

Meta-regression analysis. Meta-regression models were formed to explore potential heterogeneity as a result of changes in practice over time. As moderator, we used the year of publication. We investigated the association between the year of publication and the prevalence of EVAR performed outside the IFU across the studies. We also examined the impact of year of publication on the difference in overall survival between patients treated outside and within IFU. The slope coefficient and the P value were calculated for the covariate against the outcome of interest.

Statistical software. For data synthesis, we used the Review Manager (RevMan) computer program (version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and Comprehensive Meta-Analysis (CMA) software (Biostat, Englewood, NJ).

Table II. Study inclusion and exclusion criteria, instructions for use (IFU) adherence and duration of follow-up

Author	Inclusion criteria	Exclusion criteria	Type of IFU	Duration of follow-up
de Donato ¹⁴	Patients with a minimum CT follow-up of 24 months	NR	Proximal neck IFU ^a	32 months; range, 24-50 (mean)
AbuRahma ¹⁵	Patients who underwent EVAR for nonruptured infrarenal AAA at the authors' medical center during a 10-year period (2003-2013) using only FDA-approved devices	Patients who were operated on by physicians other than the 6 full-time academic vascular surgeons at the Vascular Center of Excellence at Charleston Area Medical Center; patients who lacked preoperative infrarenal aortic neck measurements due to lack of good quality CT scanning	Proximal neck IFU ^b	30 months; range, 1-140 (mean)
Pecoraro ¹⁶	Patients with infrarenal aortoiliac pathology treated by a standard combination of Medtronic Endurant II stent-graft implantation	Patients in whom additional tools to preserve renal and/or visceral patency were used; patients with combined use of thoracic and abdominal devices; patients with combined use of Medtronic Endurant II component with other stent-graft; patients who had nonelective EVAR (for symptomatic or ruptured AAA)	Any IFU	23 months; SD, 12 (mean)
Beckerman ¹⁷	Patients with a preoperative CT angiography scan with appropriate resolution for 3-dimensional reconstruction	Patients with ruptured aneurysm or aortic stent-grafts placed for indications other than AAA (eg, pseudoaneurysm, dissection, isolated iliac artery aneurysm); patients who had prior aneurysm repair; patients who had planned parallel stent grafts or physician-modified stent grafts placed	Any IFU	3.5 years; SD, 2.7 (mean)
Mahajan ¹⁸	Patients with adequate preoperative contrast-enhanced CT scan of the abdomen and pelvis stored in a digital format	Patients with a history of an open AAA repair; patients that received an endograft for reasons other than aneurysmal disease; patients with a history of endograft placement at another facility; patients with ruptured AAA or those who had an endograft placed at the authors' facility before the study dates; patients with a history of open AAA repair and/or history of endograft placement (including for reasons other than aneurysmal disease); patients who had ruptured AAA	Any IFU	NR
Walker ¹⁹	Patients whose initial EVAR procedures had relevant preoperative M2S (M2S Inc, imaging repository, West Lebanon, NH) analysis of CT imaging	NR	Any IFU	3.1 years; IQR, 1.6, 5.0 (median)
Matsagkas ²⁰	NR	NR	Proximal neck IFU ^c	24 months; SD, 12 (mean)
Hoshina ²¹	NR	NR	Proximal neck IFU ^d	33 months $\pm$ 18 vs 39 months $\pm$ 17 ^j
Matsumoto ²²	NR	NR	Any IFU	875 days (mean)
Speziale ²³	NR	Patients treated in urgent or emergency settings; patients with mycotic AAA or pseudoaneurysm	Proximal neck IFU ^e	All surviving patients completed a 2-year follow-up
Troisi ²⁴	NR	NR	Proximal neck IFU ^f	31 months; range, 1-65 (mean)

(Continued on next page)

Table II. Continued.

Author	Inclusion criteria	Exclusion criteria	Type of IFU	Duration of follow-up
Igari ²⁵	NR	NR	Any IFU ^g	25 months; range, 12-43 (mean)
Lee ²⁶	Patients treated with commercially available devices with complete and accessible anatomic and medical records	Patients treated with investigational devices or enrolled in other clinical trials	Proximal neck IFU	35 months; range, 12-72 (mean)
Nakai ²⁷	NR	Patients with proximal neck length <10 mm, proximal neck diameter <10 mm or >30 mm, suprarenal neck angulation >75 degrees, infrarenal neck angulation >90 degrees, and severely calcified iliac arteries	Proximal neck IFU ^h	24 months; range, 1-58 (mean)
Bachoo ²⁸	NR	NR	Proximal neck IFU ⁱ	30-day outcomes only
Abbruzzesse ²⁹	Patients treated with the three most frequently used stent-graft devices at the authors' center (Cook Zenith, Gore Excluder, Medtronic AnueRx)	Patients who underwent EVAR performed for repair of thoracic aortic aneurysm, isolated iliac artery aneurysm, subclavian artery aneurysm, vascular trauma, anastomotic pseudoaneurysm, or other vascular pathologies; patients treated with first-generation devices, defined as those that were used early in the authors' experience, which have subsequently been withdrawn from commercial use	Proximal neck IFU	30 months; SD, 21 (mean)
Handa ³⁰	NR	NR	Any IFU	NR

AAA, Abdominal aortic aneurysm; CT, computed tomography; EVAR, endovascular aneurysm repair; FDA, U.S. Food and Drug Administration; IQR, interquartile range; NR, not reported; SD, standard deviation.

^aNeck length <7 mm.

^bNeck length <10 mm, neck angulation >60 degrees, 50% circumferential proximal neck thrombus (2 mm thick), 50% calcified proximal neck, reverse taper neck, neck diameter >31 mm.

^cNeck length <10 mm.

^dNeck length <15 mm, neck angulation ≥60 degrees, "massive" atheromatous neck (thickness and length ≥5 mm and circumference ≥75%).

^eNoncylindrical neck considered as an hourglass neck, reverse conical neck (neck dilation >2 mm within 10 mm of the most caudal renal artery), or barrel neck (focal neck enlargement >3 mm within 15 mm of the most caudal renal artery); angulated neck: >65 angle between the juxta-renal aorta and the long axis of the aneurysm sac; short neck: neck length <15 mm; enlarged neck: proximal neck diameter >28 mm.

^fProximal aortic neck <15 mm in length with >75-degree infrarenal angulation or a proximal aortic neck <10 mm with >60 degree infrarenal angulation.

^gNeck length <15 mm, neck angulation >60 degrees, diameter of external iliac artery <7 mm, bilateral internal iliac artery embolization.

^hNeck length ≥15 mm, suprarenal neck angulation ≤45 degrees, infrarenal neck angulation ≤60 degrees, no significant thrombus in the sealing zone.

ⁱNeck length <15 mm, neck angle >60 degrees.

^jNot specified what ± indicates.

RESULTS

Results of the literature search

Search of electronic bibliographic sources retrieved a total of 473 reports. After discarding irrelevant items and excluding potentially eligible articles with reasons, 17 studies¹⁴⁻³⁰ met our eligibility criteria and were included in quantitative synthesis. One of the reasons for exclusion was comparisons of EVAR outcomes in patients with hostile versus friendly aortic anatomy. Studies reporting such comparisons were excluded because "outside IFU" is not similar to hostile aortic anatomy (eg, a 75-degree infrarenal neck angulation can be considered a hostile anatomic feature but within IFU for specific aortic devices). The PRISMA flow diagram is presented in Fig 1.

Description of studies

All 17 studies had an observational design and the vast majority were retrospective. Eleven studies were single-center studies,^{15-18,20-22,25-27,29} with the remainder being conducted in more than one institution. The corresponding author of six of the studies came from the United States,^{15,17-19,26,29} five corresponding authors came from Japan,^{21,22,25,27,30} four from Italy,^{14,16,23,24} and the remaining two each from the United Kingdom²⁸ and Greece.²⁰ The studies were published between 2011 and 2017, but the patient recruitment period spanned from 1999 to 2015.

The studies reported on a total of 4498 patients, of whom 1950 underwent standard EVAR outside the IFU of the aortic endograft devices and the remaining 2548 were treated within the IFU. The pooled prevalence of EVAR

Table III. Type of aortic device and procedural data (data presented as endovascular aneurysm repair [EVAR] outside instructions for use [IFU] versus EVAR within IFU)

Author	Type of aortic device	Aorto-uni-iliac device (%)	Embolization of internal iliac artery (%)
de Donato ¹⁴	All Trivascular Ovation	NR	NR
AbuRahma ¹⁵	Gore Excluder 55% vs 55%, Cook Zenith 20% vs 17%, Medtronic AneuRx 13% vs 16%, Endologix 5% vs 4%, Medtronic Endurant 1% vs 2%	NR	NR
Pecoraro ¹⁶	All Medtronic Endurant II	NR	NR
Beckerman ¹⁷	Gore Excluder 49% vs 24%, Medtronic Talent 28% vs 31%, Medtronic Endurant 12% vs 23%, Medtronic AneuRx 7% vs 18%, Cook Zenith 4% vs 3%, Endologix Powerlink 0.8% vs 0%, Trivascular Ovation 0% vs 0.6%	2 vs 5	NR
Mahajan ¹⁸	Gore Excluder 66%, Cook Zenith 26%, Medtronic AneuRx 5%, Guidant Ancure 2%, Endologix Powerlink 1%	NR	NR
Walker ¹⁹	Cook Zenith 50% vs 43%, Medtronic AneuRx 21% vs 36%, Gore Excluder 25% vs 19%, Medtronic Talent 3% vs 2%, Guidant Ancure 0.5% vs 0%, Terumo Anaconda 0% vs 0.4%	14 vs 17	NR
Matsagkas ²⁰	All Medtronic Endurant	NR	NR
Hoshina ²¹	Gore Excluder 51% vs 60%, Cook Zenith 49% vs 40%	NR	NR
Matsumoto ²²	Gore Excluder 64% vs 38%, Cook Zenith 34% vs 52%, Endologix Powerlink 2% vs 10%	NR	NR
Speziale ²³	Medtronic Endurant I 44%, Medtronic Endurant II 15%, Cook Zenith Low Profile 13%, Gore Excluder C3 12%, Cook Zenith 11%, Gore Excluder 6%	NR	NR
Troisi ²⁴	All Medtronic Endurant	NR	NR
Igari ²⁵	Gore Excluder 77%, Cook Zenith 13%, Endologix Powerlink 10%	NR	NR
Lee ²⁶	NR	NR	NR
Nakai ²⁷	Cook Zenith or Gore Excluder	NR	32 vs 41
Bachoo ²⁸	All Gore Excluder C3	NR	NR
Abbruzzesse ²⁹	Medtronic AneuRx 49%, Cook Zenith 31%, Gore Excluder 20%	NR	NR
Handa ³⁰	Cook Zenith 50%, Gore Excluder 43%, Endologix Powerlink 7%	NR	NR
Pooled estimate (95% CI)	NA	OR 0.67 (0.43-1.05); P = .08	OR 0.67 (0.30-1.51); P = .34

CI, Confidence interval; NA, not applicable; NR, not reported; OR, odds ratio.

performed outside the IFU was 40% (95% CI, 33%-48%). The statistical heterogeneity was significant ($P < .0001$, $I^2 = 96\%$), but the likelihood of publication bias was low ($P = .207$; [Supplementary Fig 1](#), online only). The baseline study characteristics are summarized in [Table I](#).

The inclusion and exclusion criteria for patient enrolment in the individual studies are presented in [Table II](#). Seven studies^{16-19,22,25,30} investigated outcomes with and without adherence to any IFU criteria of the aortic endograft devices used in standard EVAR, whereas the remaining studies focused on adherence to IFU concerning the proximal aortic neck. The specific IFU criteria in those studies are presented in [Table II](#). Most studies reported medium-term results with a follow-up ranging from 2 to 3.5 years.

The baseline demographics and clinical characteristics of the study populations are summarized in [Supplementary Table I](#) (online only). We noted great variability in reporting of such data among the studies.

Meta-analysis showed that patients treated outside the IFU were more likely to be female and be suffering from hypertension and chronic kidney disease.

Procedural data, including the type of aortic endograft device, are presented in [Table III](#). As expected, there were significant differences in aneurysm morphological characteristics between patients treated outside and within IFU, with patients in the investigated group (patients treated outside the IFU) having a larger and shorter proximal aortic neck, a greater infrarenal neck angulation, a higher rate of conical neck and iliac tortuosity, and a larger maximum aneurysm diameter than those in the control group ([Supplementary Table II](#), online only).

Risk of bias in included studies

The results of the risk of bias assessment are presented graphically in [Supplementary Fig 2](#) (online only). The median score in the NOS was 6 (range, 3-9). The main methodological constraints were lack of comparability

Table IV. Newcastle-Ottawa scale

Author	Selection			
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study
De Donato ¹⁴	—	*	*	*
AbuRahma ¹⁵	—	*	*	*
Pecoraro ¹⁶	*	*	*	*
Beckerman ¹⁷	*	*	*	*
Mahajan ¹⁸	—	*	*	*
Walker ¹⁹	—	*	*	*
Matsagkas ²⁰	*	*	*	*
Hoshina ²¹	—	*	—	*
Matsumoto ²²	*	*	*	*
Speziale ²³	*	*	*	*
Troisi ²⁴	*	*	*	*
Igari ²⁵	*	*	—	*
Lee ²⁶	*	*	*	*
Nakai ²⁷	*	*	*	*
Bachoo ²⁸	*	*	*	*
Abbruzzese ²⁹	—	*	*	*
Handa ³⁰	NA	NA	NA	NA

NA, Not available.
*Primary outcomes.

between the study cohorts, insufficient information on outcome assessment, and inadequacy of follow-up of cohorts (subjects lost to follow-up; Table IV). Our judgments and supports for judgment of risk of bias are presented in Appendix 2 (online only).

Effects of interventions. A summary of findings is presented in Table V. The forest plots of primary and secondary outcomes in patients treated outside versus within IFU are presented in Fig 2. The methods of calculation of HRs and their SEs in each study are presented in Appendix 3 (online only).

Primary outcomes.

Perioperative mortality. Nine studies^{15,16,22,23,25,26,28-30} (2457 patients) reported perioperative mortality. We found no significant difference in perioperative mortality between patients treated outside and within IFU (RD, 0.01; 95% CI, -0.00 to 0.01; $P = .23$). The statistical heterogeneity was low ($P = .61$, $I^2 = 0\%$).

Freedom from aneurysm rupture. One study¹⁷ (566 patients) reported data on freedom from aneurysm rupture. The hazard of aneurysm rupture was not significantly different between the two groups (HR, 1.34; 95% CI, 0.30-5.93; $P = .70$).

Freedom from aneurysm-related mortality. Four studies^{17,19,26,29} (1838 patients) reported data on freedom from aneurysm-related mortality. The difference between patients treated outside and within IFU was insignificant (HR, 0.88; 95% CI, 0.20-3.84; $P = .86$), but the statistical heterogeneity was substantial ($P = .002$, $I^2 = 80\%$).

Secondary outcomes.

Technical success. Data on technical success were reported by four studies^{14,20,23,28} (741 patients). The definition of technical success varied among the studies and is provided in a footnote in Fig 2. We found no significant difference in technical success between patients treated outside and within IFU (RD, 0.01; 95% CI, -0.03 to 0.05; $P = .56$). The between-study statistical heterogeneity was low ($P = .15$, $I^2 = 44\%$).

Adjunctive procedures. Six studies^{17,19,20,23,25,28} (reporting a total of 1760 patients) provided information on unplanned adjunctive procedures. Two studies^{20,28} reported only unplanned aortic cuff implantation. The requirement for adjunctive procedures was not significantly different between the groups (OR, 1.48; 95% CI, 0.81-2.71; $P = .20$), and the statistical heterogeneity was also low ($P = .05$, $I^2 = 56\%$).

Type I endoleak. Four studies^{15,16,23,25} (839 patients) reported data on early type I endoleak. One study¹⁵ reported endoleak detected intraoperatively or within 30 days of treatment, whereas the remaining three studies did not specify whether they reported intraoperative type I endoleak as well. The difference in early type I endoleak between patients treated outside and within IFU was not significant (RD, 0.04; 95% CI, -0.07 to 0.14; $P = .50$). The statistical heterogeneity was considerable ($P < .0001$, $I^2 = 93\%$). Freedom from type I endoleak was reported by four studies^{14,15,17,24} (1358 patients). One of those studies¹⁴ reported data on type Ia endoleak, whereas the remaining

Table IV. Continued.

Comparability		Outcome		
Comparability of cohorts on the basis of the design or analysis	Assessment of outcome ^a	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total
—	—	*	—	4
*	*	*	—	6
**	*	*	—	8
**	*	*	—	8
—	*	—	—	4
—	*	*	*	6
**	*	*	—	8
—	—	*	—	3
*	—	*	—	6
**	—	*	—	7
**	*	*	*	9
—	—	*	—	4
**	—	*	—	7
—	—	*	—	5
*	*	—	—	6
—	—	*	—	4
NA	NA	NA	NA	NA

three reported any type I endoleak. The hazard of type I endoleak was not significantly different between patients treated outside and within IFU (HR, 2.28; 95% CI, 0.58-8.91; $P = .24$), and the between-study statistical heterogeneity was moderate ($P = .010$, $I^2 = 74\%$).

Freedom from sac expansion. Two studies^{15,17} (1092 patients) reported data on freedom from sac expansion. Both defined sac expansion as >5 mm increase in sac size. The hazard of sac expansion was not significantly different between the two groups (HR, 0.86; 95% CI 0.55-1.33; $P = .49$). The statistical heterogeneity was low ($P = .41$, $I^2 = 0\%$).

Reintervention. Early (within 30 days) reintervention was reported by three studies^{15,16,23} (786 patients). The rate of early reintervention was not significantly different between the groups (RD, 0.06; 95% CI, -0.13 to 0.24 ; $P = .55$). The statistical heterogeneity was significant ($P < .0001$, $I^2 = 97\%$). Data on freedom from aneurysm-related reintervention were reported by nine studies^{14,15,17,20,21,23,24,26,29} (2669 patients). The hazard of aneurysm-related reintervention was not significantly different between patients treated outside and within IFU (HR, 1.04; 95% CI, 0.81-1.34; $P = .75$) and the statistical heterogeneity was low ($P = .41$, $I^2 = 3\%$).

Freedom from all-cause mortality. Data on overall survival were provided by 12 studies^{15-19,21-24,26,27,30} (3335 patients). The hazard of all-cause mortality was significantly higher in patients treated outside the IFU (HR, 1.20; 95%

CI, 1.02-1.42; $P = .03$). The statistical heterogeneity was low ($P = .58$, $I^2 = 0\%$), but the likelihood of publication bias was significant ($P = .015$; [Supplementary Fig 3](#), online only).

Sensitivity and subgroup analysis

Meta-analysis of studies that were judged to be of low risk of bias (excluding studies that scored less than six stars in the NOS) found that the significant difference in all-cause mortality in favor of treatment within IFU disappeared (HR, 1.10; 95% CI, 0.91-1.33; $P = .34$), whereas for the rest of the outcomes the effect estimates remained unchanged.

Sensitivity analysis including only studies that applied proximal aortic neck IFU criteria showed a difference from meta-analysis of the overall review population in the frequency of adjunctive procedures, which was marginally significant in favor of treatment within IFU (OR, 2.60; 95% CI, 1.01-6.65; $P = .05$; [Supplementary Fig 4](#), online only), whereas for the rest of the outcomes, the pooled effect estimate remained unchanged.

Further sensitivity analysis excluding studies whose recruitment period expanded before 2007 showed a significant difference in the requirement for adjunctive procedures in favor of treatment within IFU (OR, 2.22; 95% CI, 1.06-4.64; $P = .03$) and a borderline significant difference in overall survival in favor of treatment within IFU (HR, 1.48; 95% CI, 0.98-2.25; $P = .06$).

Table V. Summary of findings of endovascular aneurysm repair (EVAR) outside instructions for use (IFU) vs EVAR within IFU (intervention: EVAR outside IFU, comparison: EVAR within IFU)

Outcomes	Anticipated absolute effects ^a (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE) ^b	Comments
	Risk with EVAR within IFU	Risk with EVAR outside IFU				
Perioperative mortality	9 per 1000	0 per 1000 (0-0)	RD 0.01 (0.00-0.01)	2457 (9 observational studies)	⊕⊕○○ LOW	EVAR outside IFU appears to result in little to no difference in perioperative mortality
Freedom from aneurysm rupture	NA	NA	HR 1.34 (0.30-5.93)	(1 observational study)	⊕○○○ VERY LOW	We are uncertain about the effect of EVAR outside IFU on freedom from aneurysm rupture
Freedom from aneurysm-related mortality	NA	NA	HR 0.88 (0.20-3.84)	(4 observational studies)	⊕○○○ VERY LOW	We are uncertain about the effect of EVAR outside IFU on freedom from aneurysm-related mortality
Technical failure	16 per 1000	0 per 1000 (0-1)	RD 0.01 (−0.03 to 0.05)	741 (4 observational studies)	⊕○○○ VERY LOW	We are uncertain about the effect of EVAR outside IFU on technical failure
Adjunctive procedures	105 per 1000	148 per 1000 (87-241)	OR 1.48 (0.81-2.71)	1760 (6 observational studies)	⊕○○○ VERY LOW	We are uncertain about the effect of EVAR outside IFU on adjunctive procedures
Early type I endoleak	114 per 1000	5 per 1000 (−8 to 16)	RD 0.04 (−0.07 to 0.14)	839 (4 observational studies)	⊕○○○ VERY LOW	We are uncertain about the effect of EVAR outside IFU on early type I endoleak
Freedom from type I endoleak	NA	NA	HR 2.28 (0.58-8.91)	(4 observational studies)	⊕○○○ VERY LOW	We are uncertain about the effect of EVAR outside IFU on freedom from type I endoleak
Freedom from sac expansion	NA	NA	HR 0.85 (0.55-1.33)	(2 observational studies)	⊕⊕○○ LOW	EVAR outside IFU appears to not reduce freedom from sac expansion
Early reintervention	153 per 1000	9 per 1000 (−20 to 37)	RD 0.06 (−0.13 to 0.24)	786 (3 observational studies)	⊕○○○ VERY LOW	We are uncertain about the effect of EVAR outside IFU on early reintervention

Table V. Continued.

Outcomes	Anticipated absolute effects ^a (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE) ^b	Comments
	Risk with EVAR within IFU	Risk with EVAR outside IFU				
Freedom from aneurysm-related reintervention	NA	NA	HR 1.04 (0.81-1.34)	(9 observational studies)	⊕⊕○○ LOW	EVAR outside IFU appears to not reduce freedom from aneurysm-related reintervention
Freedom from all-cause mortality	NA	NA	HR 1.20 (1.02 to 1.42)	(12 observational studies)	⊕○○○ VERY LOW	We are uncertain about the effect of EVAR outside IFU on freedom from all-cause mortality.

CI, Confidence interval; GRADE, Grades of Recommendation, Assessment, Development and Evaluation; HR, hazard ratio; NA, not available.
 High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
^aThe risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
^bGRADE Working Group grades of evidence.

Meta-regression analysis

Meta-regression showed that the prevalence of EVAR performed outside the IFU increased over time ($P = .019$; [Supplementary Fig 1](#), online only). Meta-regression analysis found no significant association between the HR for all-cause mortality and the year of publication ($P = .288$; [Supplementary Fig 5](#), online only).

DISCUSSION

Summary of main results. We conducted a systematic review of the literature and meta-analysis of outcomes of standard EVAR performed outside versus within IFU. The pooled prevalence of EVAR performed outside the IFU was 40% and was found to be increasing over the years. We found no significant association between non-adherence to IFU and most of the defined outcomes. The overall mortality during follow-up was significantly higher in patients treated outside the IFU, but the effect size was rather small. Several studies did not report methods of assessment of outcomes of interest, which may explain the discrepancy in findings between aneurysm-related and all-cause mortality.

Overall completeness and applicability of evidence.

The observational study cohorts selected for qualitative and quantitative synthesis represent real-world clinical experiences across different continents. The studies applied wide inclusion criteria. The populations of most studies were not judged to be selected, reflecting representativeness of the exposed individuals undergoing EVAR, whereas the nonexposed cohorts were drawn from the same population as the exposed cohort. The

studies used a full range of different commercially available aortic devices, a small proportion of which are not in current use. Most patients were treated with second- or third-generation stent-graft devices, representing contemporary clinical practices. Sensitivity analysis excluding studies that included patients treated with older generation devices showed a higher rate of adjunctive intraoperative procedures in patients treated outside the IFU, but the rest of the meta-analysis outcomes remained unchanged.

An interesting finding was the increasing prevalence of EVAR performed outside the IFU over the years, which may reflect the increasing confidence of endovascular specialists in modern (third-generation) aortic devices for the treatment of adverse aortic morphologies. Another interpretation of this finding is that sicker and less fit patients may have been offered treatment with standard EVAR in more contemporary reports. These patients, who may have been considered high risk for complex open or endovascular procedures, would have been managed nonoperatively in earlier reports.

The experience of the operator in planning and performing the procedure may have had a substantial impact on our findings. Some of the authors explicitly stated that they carefully selected patients for treatment outside the IFU, they partially and not completely violated IFU, and the procedures were performed by experienced operators; thus the results of our analysis should be interpreted within this context. The absence of statistical difference for most outcomes may also be explained by the fact that most authors may have not gone far beyond the IFU criteria or that not all IFU criteria

a Perioperative mortality

b Freedom from aneurysm rupture

c Freedom from aneurysm-related mortality

d Technical failure^a

Fig 2. Forest plots of primary and secondary outcomes in patients treated outside versus within instructions for use (IFU). The *solid squares* denote the odds ratios (ORs), risk differences (RDs), or hazard ratios (HRs); the *horizontal lines* represent the 95% confidence intervals (CIs), and the *diamond* denotes the pooled HR. IV, Inverse variance; M-H, Mantel-Haenszel; SE, standard error. ^aDonato et al defined technical success as successful introduction and deployment of the device in the absence of surgical conversion, death, type I or III endoleaks, or graft limb obstruction; Matsagkas et al defined technical success as successful deployment of the endograft in the intended anatomic position and completion of the procedure with no type I or III endoleaks and without the need for a secondary intervention within the first 24 hours; Speziale et al defined technical success as successful passage of the delivery system through the iliac vessels, correct deployment of the device, appropriate positioning of the contralateral limb, and complete withdrawal of the delivery system in the absence of surgical conversion, mortality, type IA, IB, or III endoleaks, and migration or stent graft occlusion in the first 24 hours after surgery; Bachoo et al defined technical success as graft deployment at or within 5 mm of the intended position without technical error.

e Adjunctive procedures

f Early type I endoleak

g Freedom from type I endoleak

h Freedom from sac expansion

Fig 2. Continued.

are equally important. Another explanation for our findings is type II statistical error resulting from underpowered analyses. This is reflected in the study of Matsagkas et al,²⁰ which included the smallest number of patients and seemed to be an outlier for the outcomes freedom from aneurysm-related reintervention and adjunctive procedures.

Another constraint of the current data is that the vast majority of studies reported medium-term results (2 to

3 years; [Supplementary Table 1](#), online only). None of the studies reported results in the long term, when EVAR-related complications are expected to be encountered.

Even though the external validity of our review based on the aforementioned observations is adequate, a parameter that limits the applicability of our results and direct transfer into clinical practice is the variability in IFU criteria used in different studies. Some studies

i Early reintervention

j Freedom from aneurysm-related reintervention

k Freedom from all-cause mortality

Fig 2. Continued.

applied criteria concerning the proximal aortic neck, whereas some other studies used a wider spectrum of IFU criteria. Interestingly, sensitivity analysis including only studies that applied proximal aortic neck IFU criteria showed a difference from meta-analysis of the overall review population in the frequency of adjunctive procedures, which was marginally significant in favor of treatment within IFU (OR, 2.60; 95% CI, 1.01-6.65; $P = .05$), which demonstrates the differential effect of adherence to specific IFU criteria on treatment outcome. We also noted variability in proximal neck IFU parameters, with some studies investigating the impact of a

single anatomic constraint (eg, short proximal aortic neck) and others a combination of adverse proximal aortic neck anatomic features. Such heterogeneity does not allow the evaluation of impact of specific anatomic parameters on clinical outcomes and also explains the wide range in prevalence of patients treated outside the IFU in different studies. Because of lack of available data, no analysis could be performed to investigate a potential association between the number of violations in IFU and outcome parameters, and possibly define a maximum number of IFU criteria and type of IFU criterion that can be "safely" violated. Another source of

heterogeneity was that different aortic devices were used within and across different studies, and not all devices have the same IFU criteria. Such conceptual heterogeneity is reflected in the >50% inconsistency (I^2) in several outcomes, which makes it difficult to interpret the pooled estimate of HR, OR, or RD.

Quality of the evidence. We identified a considerable body of evidence consisting of 17 observational cohort studies investigating the review question, reporting a total of 1950 patients that underwent standard EVAR outside the IFU and another 2548 patients treated within IFU. The quality of evidence is downgraded mainly by the retrospective design of the studies. Furthermore, exposed and nonexposed individuals were not matched in the design in most studies and potential clinical and anatomic confounders were not adjusted for in our analysis. Several studies provided no data for several of our defined outcomes or the data provided were not suitable for meta-analysis, resulting in a relatively small number of studies being included in meta-analysis for most outcomes. A sufficient number of studies to investigate potential publication bias was available for all-cause mortality only. Such analysis showed significant evidence of reporting bias, indicating the possibility of preferential publication of positive results. Despite the aforementioned limitations in the quality of the body of evidence, most studies consistently reported no significant difference between the outside and within IFU groups for most primary and secondary outcomes, which is reflected in the low statistical heterogeneity.

Agreements and disagreements with other studies or reviews. Even though there is a considerable number of observational studies investigating the effect of specific adverse anatomic features, mostly concerning the proximal aortic neck, on outcomes after EVAR, there is no published review and meta-analysis investigating comparative outcomes of standard EVAR in patients treated outside versus within IFU. A couple of meta-analyses examining clinical outcomes of standard EVAR in patients with hostile versus those with friendly proximal aortic neck anatomy demonstrated increased risk in type I endoleak and aneurysm-related mortality in the former group in the short term.^{6,31} Furthermore, recent studies have identified anatomic neck constraints associated with poor clinical outcomes, such as wide proximal aortic neck, but the reported patients were largely treated within IFU of contemporary devices.³² A recently published nationwide survey in Japan reporting on 38,008 patients treated with EVAR between 2006 and 2015 found that iliac access constraints and severe neck calcification were strong risk factors for mortality, reintervention, and adverse events (stent graft migration or stenosis/occlusion or infection, acute ischemic events in the lower limbs, or aneurysm rupture).³³ Similar to the

figure found in our analysis, 46.6% of patients violated the IFU of aortic devices. This study did not examine comparative outcomes in patients undergoing EVAR outside versus within IFU; thus, it did not qualify for inclusion in our review.

CONCLUSIONS

Implications for practice. There was no difference in most outcomes between patients undergoing EVAR outside and those treated within IFU, which may be explained by the fact that most authors may have not gone far beyond the IFU criteria or that not all IFU criteria are equally important. IFU is a marketing (not clinical) document that has to satisfy legal requirements for safety, quality, and performance of the medical device. Therefore, it provides a degree of legal protection for the manufacturer and the physician when using the medical device, but it does not mean that clinicians must not use it outside the IFU.³⁴ Whether EVAR will provide a durable repair is for the endovascular specialist to decide based on collective clinical experience. To enhance clinical practice, IFU should be replaced with Clinical Indications for Use, which in some aspects might expand and in some others might constrain manufacturers' IFU. We recommend that every effort should be made to adhere to the IFU whenever possible. Although physicians are not directly regulated in their use of aortic devices in day-to-day practice, they are expected to practice in a manner that ensures the well-being of the patient. It is therefore recommended that practices of use of medical devices outside the IFU be recorded and outcome data monitored within institutional or national clinical research settings.

Standard EVAR outside the IFU can be considered in carefully selected patients who are deemed high risk for complex open or endovascular surgery. The review findings may be pertinent to the most frail and poor operative candidates with short life expectancy, in whom off-IFU EVAR could be considered instead of complex EVAR or open surgical repair. However, there need to be certain limitations defined as to how far beyond IFU criteria endovascular specialists can go (eg, a 14-mm proximal aortic neck has a different prognostic significance from a 5-mm severely angulated neck).

Implications for research. The long-term results of EVAR performed outside the IFU remain to be investigated. Further research would define the comparative prognostic significance of specific aortoiliac anatomic features. Because it can be assumed that the more violations of IFU, the worse the outcome, future research needs to define a maximum of IFU criteria that can be violated in selected patients and investigate the prognostic significance of specific IFU criteria. High-quality

evidence is required to demonstrate the comparative efficiency of standard EVAR performed outside the IFU, open surgical repair, and complex endovascular treatment, such as fenestrated or chimney EVAR.

AUTHOR CONTRIBUTIONS

Conception and design: GA, MJ

Analysis and interpretation: GA, MJ, HN, RN, SA, MM, KD, JV

Data collection: GA, SA

Writing the article: GA, MJ

Critical revision of the article: GA, MJ, HN, RN, SA, MM, KD, JV

Final approval of the article: GA, MJ, HN, RN, SA, MM, KD, JV

Statistical analysis: GA

Obtained funding: Not applicable

Overall responsibility: GA

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Additional material for this article may be found online at www.jvascsurg.org.

APPENDIX 1 (online only).

**Bibliographic search strategy (terms in capital letters
and within inverted comas represent thesaurus terms)**

Bibliographic source	Search term	No. of reports
MEDLINE	((abdominal aortic aneurysm).ti,ab OR "AORTIC ANEURYSM, ABDOMINAL"/OR (AAA).ti,ab) AND ((endovascular aneurysm repair).ti,ab OR (EVAR).ti,ab OR "ENDOVASCULAR PROCEDURES"/)) AND ((instructions for use).ti,ab OR (indications for use).ti,ab OR (IFU).ti,ab OR (on label).ti,ab OR (on-label).ti,ab OR (off label).ti,ab OR (off-label).ti,ab OR "OFF-LABEL USE"/OR (hostile anatomy).ti,ab OR (unfavourable anatomy).ti,ab OR (unfriendly anatomy).ti,ab OR (friendly anatomy).ti,ab OR (favourable anatomy).ti,ab)	264
EMBASE	((abdominal aortic aneurysm).ti,ab OR "ABDOMINAL AORTIC ANEURYSM"/OR (AAA).ti,ab) AND ((endovascular aneurysm repair).ti,ab OR (EVAR).ti,ab OR "ENDOVASCULAR ANEURYSM REPAIR"/)) AND ((instructions for use).ti,ab OR (indications for use).ti,ab OR (IFU).ti,ab OR (on label).ti,ab OR (on-label).ti,ab OR (off label).ti,ab OR (off-label).ti,ab OR (hostile anatomy).ti,ab OR (unfavourable anatomy).ti,ab OR (unfriendly anatomy).ti,ab OR (friendly anatomy).ti,ab OR (favourable anatomy).ti,ab)	165
CENTRAL	((abdominal aortic aneurysm).ti,ab OR "AORTIC ANEURYSM, ABDOMINAL"/OR (AAA).ti,ab) AND ((endovascular aneurysm repair).ti,ab OR (EVAR).ti,ab OR "ENDOVASCULAR PROCEDURES"/)) AND ((instructions for use).ti,ab OR (indications for use).ti,ab OR (IFU).ti,ab OR (on label).ti,ab OR (on-label).ti,ab OR (off label).ti,ab OR (off-label).ti,ab OR "OFF-LABEL USE"/OR (hostile anatomy).ti,ab OR (unfavourable anatomy).ti,ab OR (unfriendly anatomy).ti,ab OR (friendly anatomy).ti,ab OR (favourable anatomy).ti,ab)	44
The search in MEDLINE was run on 26 Dec 2018, in EMBASE on 5 Jan 2019, and in CENTRAL on 6 Jan 2019.		

APPENDIX 2 (online only).

Authors' judgments and support for judgments of risk of bias using the Newcastle-Ottawa scale

Abbruzzese²⁹ risk of bias table

Item	Authors' judgment	Support for judgment
Selection - Representativeness of the exposed cohort	High risk	The study population was selected: "Since the study was designed to compare device-specific outcomes after successful device deployment, we limited the analysis to successful EVAR procedures in which a device was successfully deployed."
Selection - Selection of the nonexposed cohort	Low risk	The nonexposed cohort was drawn from the same community as the exposed cohort.
Selection - Ascertainment of exposure	Low risk	Ascertainment of exposure via secure medical records.
Selection - Demonstration that outcome of interest was not present at start of study	Low risk	Evidently the outcomes were not present at the start of the study.
Comparability - Comparability of cohorts on the basis of the design or analysis	High risk	No information on comparability.
Outcome - Assessment of outcome	High risk	No description.
Outcome - Was follow-up long enough for outcomes to occur	Low risk	Follow-up was long enough for outcomes to occur.
Outcome - Adequacy of follow-up of cohorts	High risk	No statement.

AbuRahma¹⁵ risk of bias table

Item	Authors' judgment	Support for judgment
Selection - Representativeness of the exposed cohort	High risk	The study population was selected: "This study included only patients operated on by our 6 full-time academic vascular surgeons at the Vascular Center of Excellence at Charleston Area Medical Center/ West Virginia University, Charleston, WV." and "It also excluded patients who lacked preoperative infrarenal aortic neck measurements due to lack of good quality CT scanning."
Selection - Selection of the nonexposed cohort	Low risk	The nonexposed cohort was drawn from the same community as the exposed cohort.
Selection - Ascertainment of exposure	Low risk	Ascertainment of exposure via secure surgical records: "All patients' electronic medical records were retrospectively reviewed to supplement prospectively collected data."
Selection - Demonstration that outcome of interest was not present at start of study	Low risk	Evidently the outcomes were not present at the start of the study.
Comparability - Comparability of cohorts on the basis of the design or analysis	High risk	The cohorts were different in some clinical characteristics.
Outcome - Assessment of outcome	Low risk	Assessment of outcomes via record linkage: "All deaths were verified using the Social Security Death Index."
Outcome - Was follow-up long enough for outcomes to occur	Low risk	The follow-up was long enough to assess outcomes.
Outcome - Adequacy of follow up of cohorts	High risk	No statement.

Bachoo²⁸ risk of bias table

Item	Authors' judgment	Support for judgment
Selection - Representativeness of the exposed cohort	Low risk	The study population does not seem to be selected: "...confirm that the data within GREAT accurately reflect real world practice, are based on a large sample size accumulated over a short time period and represent diversity in practice, population and surgeon profiles."
Selection - Selection of the nonexposed cohort	Low risk	The nonexposed cohort was drawn from the same community as the exposed cohort.
Selection - Ascertainment of exposure	Low risk	Ascertainment of exposure via secure records: "All data are entered electronically, through a web-based interface...."
Selection - Demonstration that outcome of interest was not present at start of study	Low risk	Evidently the outcomes were not present at the start of study.
Comparability - Comparability of cohorts on the basis of the design or analysis	High risk	The cohorts were different in some clinical characteristics.
Outcome - Assessment of outcome	Low risk	Assessment of outcomes via record linkage: "All data are entered electronically, through a web-based interface...."
Outcome - Was follow-up long enough for outcomes to occur	High risk	"For the purpose of this study, we will present only 30-day outcomes."
Outcome - Adequacy of follow-up of cohorts	High risk	No statement.

Beckerman¹⁷ risk of bias table

Item	Authors' judgment	Support for judgment
Selection - Representativeness of the exposed cohort	Low risk	The study population does not seem to be selected: "...consecutive patients underwent aortic stent graft placement and were included in a prospectively maintained institutional database."
Selection - Selection of the nonexposed cohort	Low risk	The nonexposed cohort was drawn from the same community as the exposed cohort.
Selection - Ascertainment of exposure	Low risk	Ascertainment of exposure via secure records: "The prospectively maintained institutional database recorded patient background and demographic data including age, gender, comorbidities, procedure date, device used, and length of stay after EVAR. Comorbid conditions were collected from the electronic medical record."
Selection - Demonstration that outcome of interest was not present at start of study	Low risk	Evidently outcome of interest was not present at start of study.
Comparability - Comparability of cohorts on the basis of the design or analysis	Low risk	The study cohorts were comparable.
Outcome - Assessment of outcome	Low risk	Assessment of outcome via record linkage: "Mortality data were gathered from a combination of health system-wide electronic medical records as well as from the Social Security Death Index."
Outcome - Was follow-up long enough for outcomes to occur	Low risk	The follow-up was long enough to assess outcomes.
Outcome - Adequacy of follow-up of cohorts	High risk	No statement.

de Donato¹⁴ risk of bias table

Item	Authors' judgment	Support for judgment
Selection - Representativeness of the exposed cohort	High risk	No description of the derivation of the cohort.
Selection - Selection of the nonexposed cohort	Low risk	The nonexposed cohort was drawn from the same community as the exposed cohort.
Selection - Ascertainment of exposure	Low risk	Ascertainment of exposure via secure records: "A multicenter registry (TriVascular Ovation Italian Study) database was established to retrospectively gather data on all patients who underwent EVAR with an Endologix Ovation endograft at 13 centers in Italy...."
Selection - Demonstration that outcome of interest was not present at start of study	Low risk	Evidently outcome of interest was not present at start of study.
Comparability - Comparability of cohorts on the basis of the design or analysis	High risk	No description of comparability of cohorts.
Outcome - Assessment of outcome	High risk	No description.
Outcome - Was follow-up long enough for outcomes to occur	Low risk	Follow-up was long enough for outcomes to occur.
Outcome - Adequacy of follow-up of cohorts	High risk	No statement.

Handa³⁰ risk of bias table

Item	Authors' judgment	Support for judgment
Selection - Representativeness of the exposed cohort	Unclear risk	No data available.
Selection - Selection of the nonexposed cohort	Unclear risk	No data available.
Selection - Ascertainment of exposure	Unclear risk	No data available.
Selection - Demonstration that outcome of interest was not present at start of study	Unclear risk	No data available.
Comparability - Comparability of cohorts on the basis of the design or analysis	Unclear risk	No data available.
Outcome - Assessment of outcome	Unclear risk	No data available.
Outcome - Was follow-up long enough for outcomes to occur	Unclear risk	No data available.
Outcome - Adequacy of follow-up of cohorts	Unclear risk	No data available.

Hoshina²¹ risk of bias table

Item	Authors' judgment	Support for judgment
Selection - Representativeness of the exposed cohort	High risk	No description of the derivation of the cohort.
Selection - Selection of the nonexposed cohort	Low risk	The nonexposed cohort was drawn from the same community as the exposed cohort.
Selection - Ascertainment of exposure	High risk	No description.
Selection - Demonstration that outcome of interest was not present at start of study	Low risk	Evidently outcome of interest was not present at start of study.
Comparability - Comparability of cohorts on the basis of the design or analysis	High risk	The outside IFU cohort had a significantly higher age than the within IFU cohort.
Outcome - Assessment of outcome	High risk	No description.
Outcome - Was follow-up long enough for outcomes to occur	Low risk	Follow-up was long enough for outcomes to occur.
Outcome - Adequacy of follow-up of cohorts	High risk	No statement.

Igari²⁵ risk of bias table

Item	Authors' judgement	Support for judgement
Selection - Representativeness of the exposed cohort	Low risk	The study population was not selected.
Selection - Selection of the nonexposed cohort	Low risk	The nonexposed cohort was drawn from the same community as the exposed cohort.
Selection - Ascertainment of exposure	High risk	No description.
Selection - Demonstration that outcome of interest was not present at start of study	Low risk	Evidently outcome of interest was not present at start of study.
Comparability - Comparability of cohorts on the basis of the design or analysis	High risk	No description of comparability.
Outcome - Assessment of outcome	High risk	No description.
Outcome - Was follow-up long enough for outcomes to occur	Low risk	Follow-up long enough for outcomes to occur.
Outcome - Adequacy of follow-up of cohorts	High risk	"Follow-up data were available for 40 patients (75%)" and no description of the lost.

Lee²⁶ risk of bias table

Item	Authors' judgment	Support for judgment
Selection - Representativeness of the exposed cohort	Low risk	The study population does not appear to be selected: "All patients treated electively for EVAR from January 2004 to December 2007 at a single academic center were retrospectively identified from a prospectively maintained clinical database."
Selection - Selection of the no-exposed cohort	Low risk	The non-exposed cohort was drawn from the same community as the exposed cohort.
Selection - Ascertainment of exposure	Low risk	Ascertainment of exposure via secure records: "Only patients treated with commercially available stent-grafts with complete and accessible anatomic and medical records were included in this analysis." and "One surgeon (JTL) who was blinded to all clinical outcomes and endograft choice on pre-op films independently reviewed and re-measured all radiologic data for anatomic classification."
Selection - Demonstration that outcome of interest was not present at start of study	Low risk	Evidently outcome of interest was not present at start of study.
Comparability - Comparability of cohorts on the basis of the design or analysis	Low risk	No differences in demographics and clinical characteristics between the study cohorts.
Outcome - Assessment of outcome	High risk	No description.
Outcome - Was follow-up long enough for outcomes to occur	Low risk	Follow-up long enough for outcomes to occur.
Outcome - Adequacy of follow-up of cohorts	High risk	No statement.

Mahajan¹⁸ risk of bias table

Item	Authors' judgment	Support for judgment
Selection - Representativeness of the exposed cohort	High risk	The study population seems to be selected: "The study cohort was limited to subjects who had an adequate preoperative contrast enhanced CT scan of the abdomen and pelvis stored in a digital format."
Selection - Selection of the nonexposed cohort	Low risk	The nonexposed cohort was drawn from the same community as the exposed cohort.
Selection - Ascertainment of exposure	Low risk	Ascertainment of exposure via secure records: "The available preoperative CT scans were then analyzed using M2S, Inc. (West Lebanon, NH) Patient Evaluation and Management Services (PEMS) software to obtain the anatomic data...."
Selection - Demonstration that outcome of interest was not present at start of study	Low risk	Evidently outcome of interest was not present at start of study.
Comparability - Comparability of cohorts on the basis of the design or analysis	High risk	No description of comparability of study cohorts.
Outcome - Assessment of outcome	Low risk	Assessment of outcome via record linkage: "Vital status was assessed using the Social Security Death Master File (DMF)...."
Outcome - Was follow-up long enough for outcomes to occur	High risk	No information on length of follow-up.
Outcome - Adequacy of follow-up of cohorts	High risk	No statement.

Matsagkas²⁰ risk of bias table

Item	Authors' judgment	Support for judgment
Selection - Representativeness of the exposed cohort	Low risk	The exposed cohort looks truly representative of the EVAR population.
Selection - Selection of the non-exposed cohort	Low risk	The non-exposed cohort was drawn from the same community as the exposed cohort.
Selection - Ascertainment of exposure	Low risk	Ascertainment of exposure via secure records: "A dedicated database was established to prospectively collect patient data...."
Selection - Demonstration that outcome of interest was not present at start of study	Low risk	Evidently outcome of interest was not present at start of study.
Comparability - Comparability of cohorts on the basis of the design or analysis	Low risk	No differences in demographics and clinical characteristics between the study cohorts.
Outcome - Assessment of outcome	Low risk	Assessment of outcome via record linkage: "A dedicated database was established to prospectively collect patient data that included demographics, preoperative risk factors, operative time, blood loss, contrast media use, patient outcomes, length of stay, and complications."
Outcome - Was follow-up long enough for outcomes to occur	Low risk	Follow-up was long enough for outcomes to occur.
Outcome - Adequacy of follow-up of cohorts	High risk	No statement.

Matsumoto²² risk of bias table

Item	Authors' judgment	Support for judgment
Selection - Representativeness of the exposed cohort	Low risk	The study population does not seem to be selected.
Selection - Selection of the nonexposed cohort	Low risk	The nonexposed cohorts were drawn from the same community as the exposed cohort.
Selection - Ascertainment of exposure	Low risk	Ascertainment of exposure via medical records: "For the data analysis, the patients' medical records were reviewed retrospectively to determine...."
Selection - Demonstration that outcome of interest was not present at start of study	Low risk	Evidently outcome of interest was not present at start of study.
Comparability - Comparability of cohorts on the basis of the design or analysis	High risk	There was no difference in age and gender between the study cohorts, but no information on other clinical characteristics is provided.
Outcome - Assessment of outcome	High risk	No description.
Outcome - Was follow-up long enough for outcomes to occur	Low risk	Follow-up was long enough for outcomes to occur.
Outcome - Adequacy of follow-up of cohorts	High risk	A significant proportion of patients were lost to follow up and there was no description of those lost: "44 patients were lost to follow-up because they died or did not return for follow-up visits."

Nakai²⁷ risk of bias table

Item	Authors' judgment	Support for judgment
Selection - Representativeness of the exposed cohort	Low risk	The exposed cohort looks truly representative of the EVAR population.
Selection - Selection of the nonexposed cohort	Low risk	The nonexposed cohort was drawn from the same community as the exposed cohort.
Selection - Ascertainment of exposure	Low risk	Ascertainment of exposure via secure medical records.
Selection - Demonstration that outcome of interest was not present at start of study	Low risk	Evidently outcome of interest was not present at start of study.
Comparability - Comparability of cohorts on the basis of the design or analysis	High risk	The difference in male/female patients in the study cohorts was significant. No information on other clinical characteristics is provided.
Outcome - Assessment of outcome	High risk	No description.
Outcome - Was follow-up long enough for outcomes to occur	Low risk	Follow-up was long enough for outcomes to occur.
Outcome - Adequacy of follow-up of cohorts	High risk	No statement.

Pecoraro¹⁶ risk of bias table

Item	Authors' judgment	Support for judgment
Selection - Representativeness of the exposed cohort	Low risk	The study population does not seem to be selected.
Selection - Selection of the nonexposed cohort	Low risk	The nonexposed cohort was drawn from the same community as the exposed cohort.
Selection - Ascertainment of exposure	Low risk	Ascertainment of exposure via prospectively collected medical records.
Selection - Demonstration that outcome of interest was not present at start of study	Low risk	Evidently outcome of interest was not present at start of study.
Comparability - Comparability of cohorts on the basis of the design or analysis	Low risk	The study cohorts were largely comparable.
Outcome - Assessment of outcome	Low risk	Assessment of outcomes via record linkage.
Outcome - Was follow-up long enough for outcomes to occur	Low risk	Follow-up was long enough for outcomes to occur.
Outcome - Adequacy of follow-up of cohorts	High risk	No statement.

Speziale²³ risk of bias table

Item	Authors' judgment	Support for judgment
Selection - Representativeness of the exposed cohort	Low risk	The study population does not seem to be selected.
Selection - Selection of the nonexposed cohort	Low risk	The nonexposed cohort was drawn from the same community as the exposed cohort.
Selection - Ascertainment of exposure	Low risk	Ascertainment of exposure via prospectively collected medical records: "A double-center study was conducted on a prospectively compiled computerized database...."
Selection - Demonstration that outcome of interest was not present at start of study	Low risk	Evidently outcome of interest was not present at start of study.
Comparability - Comparability of cohorts on the basis of the design or analysis	Low risk	The study cohorts were comparable in terms of demographics and clinical characteristics.
Outcome - Assessment of outcome	High risk	No description.
Outcome - Was follow-up long enough for outcomes to occur	Low risk	Follow-up was long enough for the outcomes to occur.
Outcome - Adequacy of follow-up of cohorts	High risk	No statement.

Troisi²⁴ risk of bias table

Item	Authors' judgment	Support for judgment
Selection - Representativeness of the exposed cohort	Low risk	The study population does not seem to be selected.
Selection - Selection of the nonexposed cohort	Low risk	The nonexposed cohort was drawn from the same community as the exposed cohort.
Selection - Ascertainment of exposure	Low risk	Ascertainment of exposure via prospectively collected medical records: "All data concerning these interventions were prospectively collected in a dedicated database...."
Selection - Demonstration that outcome of interest was not present at start of study	Low risk	Evidently outcome of interest was not present at start of study.
Comparability - Comparability of cohorts on the basis of the design or analysis	Low risk	The study cohorts were comparable in terms of demographics and clinical characteristics.
Outcome - Assessment of outcome	Low risk	Assessment of outcome via record linkage: "All data concerning these interventions were prospectively collected in a dedicated database; the information included demographics, preoperative risk factors, clinical and diagnostic preoperative assessments, intraoperative features, and early (30-day) and late follow-up results."
Outcome - Was follow-up long enough for outcomes to occur	Low risk	Follow-up was long enough for outcomes to occur.
Outcome - Adequacy of follow-up of cohorts	Low risk	The follow-up was adequate: "...follow-up was available in 175 (98.9%) of the 177 patients...."

Walker¹⁹ risk of bias table

Item	Authors' judgment	Support for judgment
Selection - Representativeness of the exposed cohort	High risk	The study population seems to be selected: "...489 patients in the cohort of 1736 (28.2%) had anatomic data available from before the initial EVAR procedure, including 284 (58.1%) in the IFU-adherent group and 205 (41.9%) in the IFU non-adherent group."
Selection - Selection of the nonexposed cohort	Low risk	The nonexposed cohort was drawn from the same community as the exposed cohort.
Selection - Ascertainment of exposure	Low risk	Ascertainment of exposure via secure medical records: "Data collected from electronic medical records...."
Selection - Demonstration that outcome of interest was not present at start of study	Low risk	Evidently outcome of interest was not present at start of study.
Comparability - Comparability of cohorts on the basis of the design or analysis	High risk	The study cohorts were not comparable as there were differences in some demographic and clinical characteristics.
Outcome - Assessment of outcome	Low risk	Assessment of outcome via record linkage: "Data recorded in our registry during the follow-up period were also collected and included aneurysm rupture, major adverse event (ie, conversion to open repair, major embolic event, graft infection requiring explantation, device migration, loss of device patency requiring reintervention, and other miscellaneous complications that substantially affected clinical outcome), types of reintervention, AAA sac size, endoleak, leaving KPNC membership, moving outside the region, and mortality."
Outcome - Was follow-up long enough for outcomes to occur	Low risk	Follow-up was long enough for outcomes to occur.
Outcome - Adequacy of follow-up of cohorts	Low risk	Follow-up of cohorts was adequate: "Of these 489 patients, 49 (10.0%) were lost to follow-up, including 28 who left KPNC, 10 who moved outside the region, and 11 who discontinued imaging surveillance."
CT, computed tomography; EVAR, endovascular aneurysm repair.		

APPENDIX 3 (online only).

Method of hazard ratio and its standard error calculation

Author	Method of HR calculation
de Donato ¹⁴	HRs and CIs provided in the paper (direct method)
AbuRahma ¹⁵	HRs calculated from survival curves and numbers at risk (indirect method)
Pecoraro ¹⁶	HRs calculated from survival curves and numbers at risk (indirect method)
Beckerman ¹⁷	HRs calculated from log-rank test <i>P</i> values and numbers of events and numbers of patients in each group (indirect method)
Mahajan ¹⁸	HRs calculated from survival curves and numbers at risk (indirect method)
Walker ¹⁹	HRs calculated from survival curves and numbers at risk (indirect method)
Matsagkas ²⁰	HRs calculated from survival curves and numbers at risk (indirect method)
Hoshina ²¹	HRs calculated from log-rank test <i>P</i> values and numbers of events and numbers of patients in each group (indirect method)
Matsumoto ²²	HRs calculated from log-rank test <i>P</i> values and numbers of events and numbers of patients in each group (indirect method)
Speziale ²³	HR for all-cause mortality calculated from survival curves and numbers at risk; HR for aneurysm-related reintervention calculated from log-rank test <i>P</i> value and numbers of events and numbers of patients in each group (indirect method)
Troisi ²⁴	HRs calculated from survival curves and numbers at risk (indirect method)
Igari ²⁵	NA
Lee ²⁶	HR for freedom from aneurysm-related mortality calculated from survival curves and numbers at risk; rest of HRs calculated from curve data (indirect method)
Nakai ²⁷	HR calculated from curve data (indirect method)
Bachoo ²⁸	NA
Abbruzzese ²⁹	HRs calculated from log-rank test <i>P</i> values and numbers of events and numbers of patients in each group (indirect method)
Handa ³⁰	HRs calculated from log-rank test <i>P</i> values and numbers of events and numbers of patients in each group (indirect method)

CI, Confidence interval; HR, hazard ratio; NA, not applicable.

Meta Analysis

a

b

c

Supplementary Fig 1 (online only). Forest plot (a), funnel plot (P value for publication bias: 0.207) (b), and scatter plot (with year of publication used as moderator, $P = .019$) (c) of the pooled prevalence of endovascular aneurysm repair performed outside instructions for use. CI, Confidence interval.

Supplementary Fig 2 (online only). Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies (top); risk of bias summary: review authors' judgments about each risk of bias item for each included study (bottom).

Supplementary Fig 3 (online only). Funnel plot of comparison outside vs within instructions for use (IFU) for freedom from all-cause mortality (Egger regression intercept, $P = .015$).

Supplementary Fig 4 (online only). Sensitivity analysis including studies applying proximal aortic neck instructions for use (IFU) criteria. Forest plot of adjunctive intraoperative procedures in patients treated outside versus within IFU. The *solid squares* denote the odds ratios (ORs), the *horizontal lines* represent the 95% confidence intervals (CIs), and the *diamond* denotes the pooled OR. *M-H*, Mantel-Haenszel.

Supplementary Fig 5 (online only). Scatter plot of the hazard ratio for freedom from all-cause mortality with the year of publication as the moderator ($P = .288$).

Supplementary Table I (online only). Baseline demographics and clinical characteristics of the study populations (data presented as endovascular aneurysm repair [EVAR] outside instructions for use [IFU] versus EVAR within IFU)

Author	Male, %	Age, mean	Smoking, %	Diabetes, %	Coronary artery disease, %	Hypertension, %	COPD, %	Chronic kidney disease, %
de Donato ¹⁴	NR	NR	NR	NR	NR	NR	NR	NR
AbuRahma ¹⁵	80 vs 85	74 vs 73	26 vs 28 ^c	NR	58 vs 62	86 vs 85	35 vs 29	NR
Pecoraro ¹⁶	NR	76 vs 75	70 vs 53	13 vs 21	50 vs 29	93 vs 82	46 vs 27	17 vs 9
Beckerman ¹⁷	57 vs 25	75 (SD, 9) vs 75 (SD, 9)	NR	22 vs 19	82 vs 84 ^d	92 vs 88	43 vs 43 ^e	NR
Mahajan ¹⁸	NR	NR	NR	NR	NR	NR	NR	NR
Walker ¹⁹	85 vs 93	75 (SD, 7) vs 74.8 (SD, 8)	20 vs 19	23 vs 27	84 vs 74	88 vs 83	NR	NR
Matsagkas ²⁰	84 vs 90	72 (SD, 9) vs 72 (SD, 7)	58 vs 63	21 vs 21	63 vs 50	95 vs 95	47 vs 61	NR
Hoshina ²¹	73 vs 83	77 ± 8 vs 75 ± 8 ^a	NR	12 vs 11	27 vs 15	84 vs 52	32 vs 24 ^f	30 vs 18
Matsumoto ²²	88 vs 91	77 vs 76	NR	NR	NR	NR	NR	NR
Speziale ²³	80 vs 78	NR	66 vs 62	23 vs 18	49 vs 52	71 vs 71	28 vs 37	23 vs 14
Troisi ²⁴	86 vs 93	75 vs 73	84 vs 85	14 vs 14	52 vs 57	88 vs 88	46 vs 47	18 vs 12
Igari ²⁵	NR	NR	NR	NR	NR	NR	NR	NR
Lee ²⁶	89 vs 95	75 (range, 52-91) vs 73 (range, 52-91)	NR	15 vs 19	57 vs 53	75 vs 72	20 vs 24 ^e	16 vs 17
Nakai ²⁷	66 vs 92	77 vs 76	NR	NR	NR	NR	NR	NR
Bachoo ²⁸	NR	NR	61 vs 41	18 vs 13	37 vs 38	79 vs 76	12 vs 17	15 vs 11
Abbruzzesse ²⁹	NR	NR	NR	NR	NR	NR	NR	NR
Handa ³⁰	NR	77 ± 7 vs 78 ± 7 ^b	NR	NR	NR	NR	NR	NR
Pooled estimate (95% CI)	OR 0.61 (0.44-0.84); <i>P</i> = .003	MD 0.28 (−1.04 to 1.59); <i>P</i> = .68	OR 1.19 (0.89-1.60); <i>P</i> = .24	OR 0.97 (0.77-1.22); <i>P</i> = .77	OR 1.10 (0.88-1.37); <i>P</i> = .42	OR 1.42 (1.04-1.95); <i>P</i> = .03	OR 0.99 (0.78-1.25); <i>P</i> = .93	OR 1.55 (1.12-2.15); <i>P</i> = .008

CI, Confidence interval; *COPD*, chronic obstructive pulmonary disease; *MD*, mean difference; *NR*, not reported; *OR*, odds ratio; *SD*, standard deviation.

^aNot specified whether mean or median and what ± indicates.

^bNot specified what ± indicates.

^cCurrent smoker.

^dCardiac disease.

^ePulmonary disease.

^fRespiratory failure.

Supplementary Table II (online only). Aneurysm morphometric characteristics (data presented as endovascular aneurysm repair [EVAR] outside instructions for use [IFU] versus EVAR within IFU)

Author	Neck diameter, mm, mean	Neck, mm, mean	Infrarenal angulation, degrees, mean	Suprarenal angulation, degrees, mean	Severe thrombus, %	Severe calcification, %	Conical neck, %	Max AAA diameter, mm, mean	Concomitant iliac aneurysm, %	Tortuous iliac arteries, %
de Donato ¹⁴	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
AbuRahma ¹⁵	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pecoraro ¹⁶	24 (SD, 5) vs 24 (SD, 3)	18 (SD, 6) vs 23 (SD, 4)	39 (SD, 20) vs 28 (SD, 12)	NR	NR	NR	77 vs 47	66 (SD, 21) vs 60 (SD, 15)	NR	NR
Beckerman ¹⁷	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mahajan ¹⁸	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Walker ¹⁹	NR	NR	NR	NR	NR	NR	NR	60 (SD, 12) vs 57 (SD, 9)	NR	NR
Matsagkas ²⁰	27 (SD, 4) vs 26 (SD, 3)	6 (SD, 1) vs 16 (SD, 3)	10 (IQR, 5-27) vs 15 (IQR, 10-40) ^a	8 (IQR, 3-18) vs 6 (IQR, 2-15) ^a	16 vs 13 ^e	11 vs 13 ^e	NR	57 (SD, 0.6) vs 58 (SD, 0.8)	NR	NR
Hoshina ²¹	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Matsumoto ²²	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Speziale ²³	23 (SD, 3) vs 23 (SD, 3)	14 (SD, 7) vs 25 (SD, 8)	32 (SD, 20) vs 22 (SD, 15)	NR	NR	NR	NR	62 (SD, 11) vs 60 (SD, 13)	NR	NR
Troisi ²⁴	25 ± 4 vs 25 ± 3 ^{b,c}	13 ± 8 vs 24 ± 10 ^b	60 ± 23 vs 35 ± 17 ^{b,d}	NR	NR	NR	NR	59 ± 11 vs 56 ± 10 ^b	NR	NR
Igari ²⁵	21 (SD, 3) vs 20 (SD, 3)	32 (SD, 17) vs 37 (SD, 20)	NR	NR	NR	NR	NR	50 (SD, 8) vs 47 (SD, 8)	NR	NR
Lee ²⁶	NR	13 vs 25	68 vs 0.7 ^d	NR	11 vs 0 ^f	NR	49 vs 25	62 (SE, 1.3) vs 57 (SE, 0.8)	23 vs 26	21 vs 6 ^g
Nakai ²⁷	20 vs 20	26 vs 31	67 vs 41	40 vs 20	NR	NR	NR	56 vs 51	NR	NR
Bachoo ²⁸	24 (range, 17-31) vs 24 (range, 17-31) ^a	15 (range, 0-50) vs 27 (range, 15-95) ^a	59 (SD, 27) vs 23 (SD, 18)	NR	12 vs 11	21 vs 16	NR	66 (SD, 7) vs 59 (SD, 11)	NR	NR
Abbruzzesse ²⁹	24 (SD, 3) vs 23 (SD, 2)	22 (SD, 12) vs 27 (SD, 11)	29 (SD, 22) vs 16 (SD, 15) ^d	NR	NR	NR	NR	57 (SD, 12) vs 55 (SD, 9)	NR	NR
Handa ³⁰	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pooled estimate (95% CI)	MD 0.90 (0.56-1.24); <i>P</i> < .0001	MD -7.49 (-10.39 to 4.69); <i>P</i> < .0001	MD 19.01 (9.81-28.20); <i>P</i> < .0001	NR	OR 2.25 (0.46-11.05); <i>P</i> = .32	OR 1.27 (0.69-2.35); <i>P</i> = .45	OR 3.06 (1.82-5.14); <i>P</i> < .0001	MD 2.93 (0.26-5.60); <i>P</i> = .03	OR 0.72 (0.36-1.41); <i>P</i> = .33	OR 4.04 (1.69-9.66); <i>P</i> = .002

AAA, abdominal aortic aneurysm; CI, confidence interval; IQR, interquartile range; MD, mean difference; NR, not reported; OR, odds ratio; SD, standard deviation; SE, standard error.

^aMedian.

^bNot specified what ± indicates.

^cAt the level of the renal arteries.

^dNot specified whether infra- or suprarenal angulation.

^e>30%.

^f>50% (percentage based on the proportion of the volume taken up by thrombus in that segment in relation to the total volume of that aortic segment).

^giliac angle <90 degrees.