Long-term outcomes of endovascular aneurysm repair according to instructions for use adherence status

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ABSTRACT

Objective: Endovascular aneurysm repair (EVAR) has become the standard treatment for abdominal aortic aneurysms (AAAs). Endovascular device manufacturers have defined specific anatomic criteria for the aneurysm characteristics that should be observed as instructions for use (IFU) for specific grafts. In clinical practice, the prevalence of performing EVAR outside the IFU has been high. In the present study, we aimed to determine the effects of nonadherence to the IFU on the outcomes.

Methods: Patients who had undergone EVAR for an infrarenal AAA between 2005 and 2013 were included. IFU nonadherence was defined as any violation of device-specific IFU criteria and was compared with IFU adherence. The primary outcomes were all-cause mortality, aneurysm-related mortality, AAA rupture, graft-related adverse events (GRAEs), including limb-related adverse events, and type Ia endoleaks. A second aim was to study whether the prevalence of EVAR performed outside the IFU has increased over time.

Results: A total of 258 patients were included, 144 (55.8%) of whom had been treated according to the IFU and 114 (44.2%) outside the IFU. In the IFU nonadherence group, all-cause mortality (hazard ratio [HR], 1.39; 95% confidence interval [CI], 1.02-1.89; $P = .037$) and aneurysm-related mortality (HR, 5.1; 95% CI, 1.4-18.6; $P = .015$), and the incidence of AAA rupture (HR, 5.4; 95% CI, 1.1-26.6; $P = .036$) and GRAEs (HR, 1.7; 95% CI, 1.1-2.8; $P = .025$). No significant association was found between the incidence of type Ia endoleaks and neck-related IFU or limb-related adverse events and iliac-related IFU. However, neck length was a risk factor for type Ia endoleaks (HR, 18.2, 95% CI, 6.3-52.2; $P < .001$), aneurysm-related mortality (HR, 8.7; 95% CI, 1.8-41.6; $P = .007$), AAA rupture (HR, 21.7; 95% CI, 2.8-166; $P = .003$), and GRAEs (HR, 4.4; 95% CI, 2.0-9.7; $P < .001$). An IFU violation regarding neck angulation was also a risk factor for all-cause mortality (HR, 2.0; 95% CI, 1.1-3.7; $P = .032$), aneurysm-related mortality (HR, 7.6; 95% CI, 1.4-42.8; $P = .021$), AAA rupture (HR, 79.4; 95% CI, 6.3-999; $P = .001$), and GRAEs (HR, 4.3; 95% CI, 1.9-9.5; $P < .001$). The prevalence of EVAR performed outside the IFU did not increase over time.

Conclusions: Performing EVAR outside the IFU had a negative effect on outcomes, including all-cause mortality, aneurysm-related mortality, AAA rupture, and GRAEs. Neck angulation and neck length seemed to be the most crucial aneurysm characteristics. (J Vasc Surg 2022;■:1-8.)

Keywords: Abdominal aortic aneurysm; Endovascular aortic repair; Instructions for use; Morbidity; Mortality

Endovascular aneurysm repair (EVAR) has demonstrated superior results in terms of morbidity and mortality compared with open surgical treatment in the short term.[1-3] However, late outcomes have exhibited higher reintervention rates and aneurysm-related mortality for patients who have undergone EVAR.[1,3]

Endovascular device manufacturers have defined specific anatomic requirements for aneurysm characteristics to be observed as instructions for use (IFU). Randomized controlled trials comparing open surgery and EVAR have included only those patients who had met the device-specific IFUs. However, in clinical practice, IFU nonadherence rates have been high, ranging from 40% to 44%.[4-6] The application of EVAR to aneurysms with a more complex anatomy has enabled the treatment of patients who would be considered at high risk for open surgery. The prevalence of EVAR performed outside the IFU has also been shown to have increased over time.[4]

The relationship between adherence to the IFU and outcomes has remained controversial. Some studies have demonstrated a greater incidence of graft-related

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adverse events (GRAEs)[5,7] and endoleaks,[8-10] higher reintervention rates,[9,11,12] and poorer survival[4,11,13] after an IFU violation. However, some studies have shown no differences in the outcomes.[6,12,14-17]

In the present study, we evaluated whether IFU nonadherence was associated with overall and AAA-related mortality and GRAEs, such as type I endoleak, and whether nonadherence to the IFU has become more common over time.

METHODS

Patients who had undergone EVAR for an infrarenal AAA between January 2005 and December 2013 at a single academic institution were identified from a prospectively maintained database. The follow-up data were collected retrospectively from the electronic medical records until December 31, 2019. We performed a retrospective study of prospectively collected registry data; thus, institutional review board approval was not required.

Patients were eligible for EVAR if they had had an AAA diameter of >5.5 cm for the men or >5.0 cm for the women or an AAA with a rapidly increasing sac (>1 cm/y or >5 mm within 6 months). Ruptured aneurysm cases were excluded; however, urgently managed patients with symptomatic or massive aneurysms were included. Patients with missing or low-quality preoperative computed tomography (CT) angiography (CTA) scans were also excluded.

The decision regarding the possibility of endovascular treatment and the decision regarding treatment with a standard endograft would be feasible were made by a multidisciplinary team. All procedures were performed by the same group of vascular surgeons and interventional radiologists in a fully equipped operating room with fluoroscopic guidance, with the patient under spinal, local, or general anesthesia.

The baseline demographic data were recorded, including sex, age, and smoking history. In addition, the comorbidities, including diabetes, hypertension, dyslipidemia, cerebrovascular disease, coronary artery disease, peripheral artery disease, heart failure, renal insufficiency, and obstructive pulmonary disease, were obtained. The device type and configuration (bifurcated or aorto-uniiliac) used were recorded. The endografts used were the Zenith (Cook Medical Inc, Bloomington, IN), Endurant (Medtronic, Minneapolis, MN), and Excluder (W.L. Gore & Associates, Flagstaff, AZ).

To define the IFU adherence status, the patients' preoperative CTA scans were reviewed retrospectively by an interventional radiologist unaware of the clinical characteristics or outcomes. The anatomic measurements were obtained from the axial, sagittal, and coronal views and multiplanar reformation reconstructions. The measurements included the neck diameter (too narrow or too wide), neck length, sagittal and coronal neck angulation, neck thrombus, neck calcification, neck conicity, maximum sac diameter, common iliac diameter and length, and femoral access. Aneurysm morphology was classified as either within or outside the device-specific IFU determined by each manufacturer. A conical neck shape was defined as an >3-mm increase in neck diameter for each 1 cm in length. The proximal neck thrombus was defined as ≤50% circumferential thrombus, and proximal neck calcification was defined as ≥50% calcification. IFU nonadherence was defined as a violation of any criterion of the device-specific IFU. The device-specific IFU parameters are listed in Table I.

The imaging protocol for radiographic follow-up consisted of a CT scan at 30 days postoperatively, duplex ultrasound at 1 year, CTA at 2 years, and duplex ultrasound annually thereafter. In addition to duplex ultrasound, CT was obtained if evidence of an endoleak or sac enlargement was present. The follow-up data included the presence of a type I to IV endoleak, the need for aneurysm-related reintervention, and the occurrence of stent graft migration, limb occlusion, kinking, rupture, and mortality.

The primary study outcomes included all-cause mortality and aneurysm-related mortality after the primary EVAR procedure, a secondary aneurysm-related intervention, or death from aneurysm rupture at any point during the study period. Rupture-free survival was also analyzed. GRAEs—defined as the presence of a type I, III, or IV endoleak; reintervention for a type II endoleak; any other graft-related reintervention; aneurysm rupture; and/or aneurysm-related mortality—were also included in the study outcomes. Reinterventions to treat access site complications were not included in the graft-related interventions. The study outcomes were stratified by adherence to the IFU. The relationship between the

ARTICLE HIGHLIGHTS

- **Type of Research:** A single-center, retrospective, observational study
- **Key Findings:** In our study, nonadherence to the instructions for use was associated with higher all-cause and aneurysm-related mortality and a greater incidence of abdominal aortic aneurysm rupture and graft-related adverse events for 258 patients who had undergone endovascular aneurysm repair (EVAR). Neck length and neck angulation were the most crucial anatomic characteristics predicting the outcome.
- **Take Home Message:** Performing EVAR outside of the instructions for use had negative effects on the results. Special caution is required regarding the aneurysm neck length and angulation when evaluating a patient's anatomic suitability for standard EVAR.

Table I. Device-specific instructions for use (IFU) criteria

Anatomic parameter	Zenith	Endurant	Excluder
Neck diameter, mm	18-32	19-32	19-29
Neck length, mm	≥15	≥10	≥15
Neck angulation, °	<60	≤60	≤60
Iliac fixation site length, mm	>10	≥15	≥10
Iliac fixation site diameter, mm	7.5-20	8-25	8-25

presence of a type Ia endoleak and adherence to neck-related IFU (any IFU violation) and specific neck characteristic–related criteria violations were analyzed. The relationship between the iliac-related IFU and limb-related adverse events, defined as a type Ib endoleak, kinking, or thrombosis, was also analyzed. As a secondary outcome, we evaluated whether the prevalence of EVAR performed outside the IFU had increased over time.

Statistical analysis. Data are presented expressed as the median and quartiles. Categorical variables were compared using the χ^2 test or the Fisher exact test. Comparisons between the two groups were performed using the Mann-Whitney *U* test for continuous variables. Time-based clinical outcomes were evaluated using Kaplan-Meier analysis with the log-rank test. The Cox proportional hazards model was used to estimate the hazard ratio (HR) and identify the risk factors for worse outcomes. All *P* values were two-sided, with $P < .05$ regarded as indicative of statistical significance. All statistical analyses were conducted using SPSS software, version 26 (IBM Corp, Armonk, NY).

RESULTS

During the study period, a total of 544 patients had undergone surgery for a nonruptured AAA; 182 patients had undergone open repair and 362 had undergone EVAR. Of the 362 patients in the EVAR group, 104 had had low-quality or missing CTA scans and were excluded from the present study, leaving 258 patients who had met the inclusion criteria and were included in the present study. All individual device-specific IFU criteria had been met by 144 patients (55.8%) and at least one IFU parameter had been violated in the treatment of 114 patients (44.2%). Of these 114 patients, one IFU criterion and at least two IFU criteria had been violated for 87 and 27 patients, respectively. The patients who had received treatment outside the IFU had more often received a Zenith or Endurant endoprosthesis and were more likely to have had hypertension. Otherwise, no significant differences were found in the baseline characteristics between the groups (Table II).

Neck calcification was the most frequently violated IFU criterion. The violation rates for the specific IFU criteria are listed in Table III. Patients who had received an Endurant or a Zenith endograft had more often received treatment outside the IFU (55.8% and 47.0%) compared with those treated with the Excluder endograft (30.6%; $P = .012$).

The median follow-up time for the IFU adherence and nonadherence groups was 6.8 years and 6.2 years, respectively. During follow-up, the overall mortality was 60.4% (n = 87) in the IFU adherence group and 74.6% (n = 85) in the IFU nonadherence group. The Kaplan-Meier survival analysis revealed significantly increased survival for patients treated within the IFU ($P = .012$; Fig, *A*). After adjustment for hypertension and graft type, mortality remained higher for the patients treated outside the IFU (HR, 1.39; 95% confidence interval [CI], 1.02-1.89; $P = .037$) in the Cox model. Specific IFU criteria were analyzed separately, and Cox modeling revealed that a violation of the neck angulation IFU and iliac-related IFU was significantly associated with all-cause mortality (HR, 2.0; 95% CI, 1.1-3.7; $P = .032$; and HR, 2.3; 95% CI, 1.4-3.9; $P = .002$; respectively; Table IV). The IFU nonadherence group was further subdivided into those with only one violated IFU criterion and those with two or more violated IFU criteria. Survival was worse for those with two or more violated IFU criteria than for the IFU adherence group and those with only one violated criterion ($P = .024$).

A total of 10 AAA ruptures were identified: 2 in the IFU adherence group (1.4%) and 8 in the IFU nonadherence group (7.0%; $P = .025$). Of the eight ruptures identified in the patients treated outside the IFU, seven had had one violated IFU criterion and one had had three violated criteria. The violations included three necks that were too short, two that were too angulated, one that was too wide, one that was too narrow, one that was too calcified, and one that was too conical and one non-IFU limb. The ruptures had occurred at a median of 4.6 years (range, 3.0-10.1 years) postoperatively. Rupture-free survival was significantly higher for the IFU adherence group ($P = .014$; Fig, *B*). After adjustment for hypertension and graft type, the association remained significant (HR, 5.4; 95% CI, 1.1-26.6; $P = .036$). The association of nonadherence to specific anatomic parameters and aneurysm rupture was analyzed separately in the Cox proportional hazards models. Violations of both neck length and neck angulation IFU were associated with an increased risk of rupture (HR, 21.7; 95% CI, 2.8-166; $P = .003$; and HR, 79.4; 95% CI, 6.3-999; $P = .001$; respectively; Table IV). No neck thrombus violations were found in the patients who had experienced rupture; therefore, neck thrombus was not included in the Cox model.

Aneurysm-related mortality was greater in the IFU nonadherence group than in the IFU adherence group (9.6% vs 2.1%; $P = .011$). Furthermore, the Kaplan-Meier

Table II. Baseline patient characteristics stratified by instructions for use (IFU) adherence

Characteristic	IFU adherence		*P* value
	Yes (n = 144)	No (n = 114)	
Age, years			.484
Median	77.0	76.4	
Q1; Q3	71.3; 81.6	71.7; 83.0	
Male sex	88.2	81.6	.158
Urgent procedure	6.9	2.6	.155
Diabetes	16.0	21.9	.260
Dyslipidemia	43.8	48.2	.530
Hypertension	61.8	73.7	.047
Coronary artery disease	50.0	48.2	.803
Cerebrovascular disease	11.8	17.5	.213
Pulmonary disease	24.3	19.3	.367
Renal insufficiency	26.4	25.4	.887
Peripheral artery disease	5.6	8.8	.335
Heart failure	9.7	6.1	.363
Smoking			.623
Never	16.0	13.3	
Current	20.1	16.8	
Ex-smoker	25.0	31.9	
Missing data	38.9	38.1	
Endograft used			.013
Zenith	49.3	55.3	
Endurant	16.0	25.4	
Excluder	34.7	19.3	

Q, Quartile.
Data presented as percentages, unless noted otherwise.

Table III. Violations of specific instructions for use (IFU) criteria (N = 258)

IFU violation	No. (%)
Any IFU violation	114 (44.2)
Neck length	14 (5.4)
Neck diameter too wide	12 (4.7)
Neck diameter too narrow	20 (7.8)
Neck angulation	13 (5.0)
Neck calcification	47 (18.2)
Neck thrombus	4 (1.6)
Neck conicity	23 (8.9)
Iliac diameter/length	18 (7.0)

estimates showed lower freedom from aneurysm-related mortality in the IFU nonadherence group than in the IFU adherence group ($P = .006$; Fig, *C*). After adjustment, freedom from aneurysm-related mortality remained inferior in the IFU nonadherence group (HR, 5.1; 95% CI, 1.4-18.6; $P = .015$). In the Cox model, violations of the IFU for neck length and neck angulation were both independent risk factors for aneurysm-related mortality (HR, 8.7; 95% CI, 1.8-41.6; $P = .007$; and HR, 7.6; 95% CI, 1.4-42.8; $P = .021$; respectively; Table IV).

The reintervention rates and the presence of type I or III endoleaks are listed in Supplementary Table I (online only). GRAEs were more frequent in the IFU nonadherence group than in the IFU adherence group (35.1% vs 22.9%; $P = .037$). IFU nonadherence was associated with lower freedom from GRAEs compared with IFU adherence ($P = .016$; Fig, *D*). In the adjusted Cox proportional hazards model, IFU nonadherence was a significant predictive factor for of GRAEs (HR, 1.7; 95% CI, 1.1-2.8; $P = .025$). Cox hazards regression analysis also revealed that violations of both neck length and neck angulation IFU criteria were risk factors for GRAEs (HR, 4.4; 95% CI, 2.0-9.7; $P < .001$; and HR, 4.3; 95% CI, 1.9-9.5; $P < .001$; respectively; Table V).

A type Ia endoleak had developed in 8 patients (5.1%) in the neck IFU adherence group and 10 patients (9.9%) in the neck IFU nonadherence group ($P = .209$). Kaplan-Meier analyses failed to show a significant difference in the freedom from type Ia endoleaks between the two groups ($P = .125$). Hypertension, graft type, and sex differed significantly between the neck-related IFU adherence and nonadherence groups and were included in Cox hazards model when violations of the specific neck-related IFU criteria were analyzed. A violation of the neck length IFU was associated with poorer type Ia endoleak-free survival (HR, 18.2; 95% CI, 6.3-52.2; $P < .001$; Table V).

Iliac-related adverse events were found in 29 patients (12.1%) in the iliac-related IFU adherence group and 3 patients (16.7%) in the iliac-related IFU nonadherence group ($P = .475$). Freedom from limb-related adverse events was similar between the groups on Kaplan-Meier analysis ($P = .207$).

Whether the prevalence of performing EVAR outside the IFU had increased annually during the study period was analyzed using Mantel-Haenszel statistics. However, no significant increase over time was observed ($P = .354$).

DISCUSSION

The results from the present study have shown that all-cause mortality and the incidence of AAA rupture, aneurysm-related mortality, and GRAEs were higher for the IFU nonadherence group. A neck length–related IFU violation was an independent risk factor for aneurysm-related mortality, rupture, GRAEs, and type Ia endoleaks. Also, a neck angulation–related IFU violation was an independent risk factor for mortality, aneurysm-related mortality, rupture, and GRAEs.

EVAR has enabled the treatment of patients who would be considered at high risk for open surgery. This has probably led physicians to treat AAAs with a more challenging anatomy using EVAR with standard endografts, although these AAAs do not meet the IFU criteria.

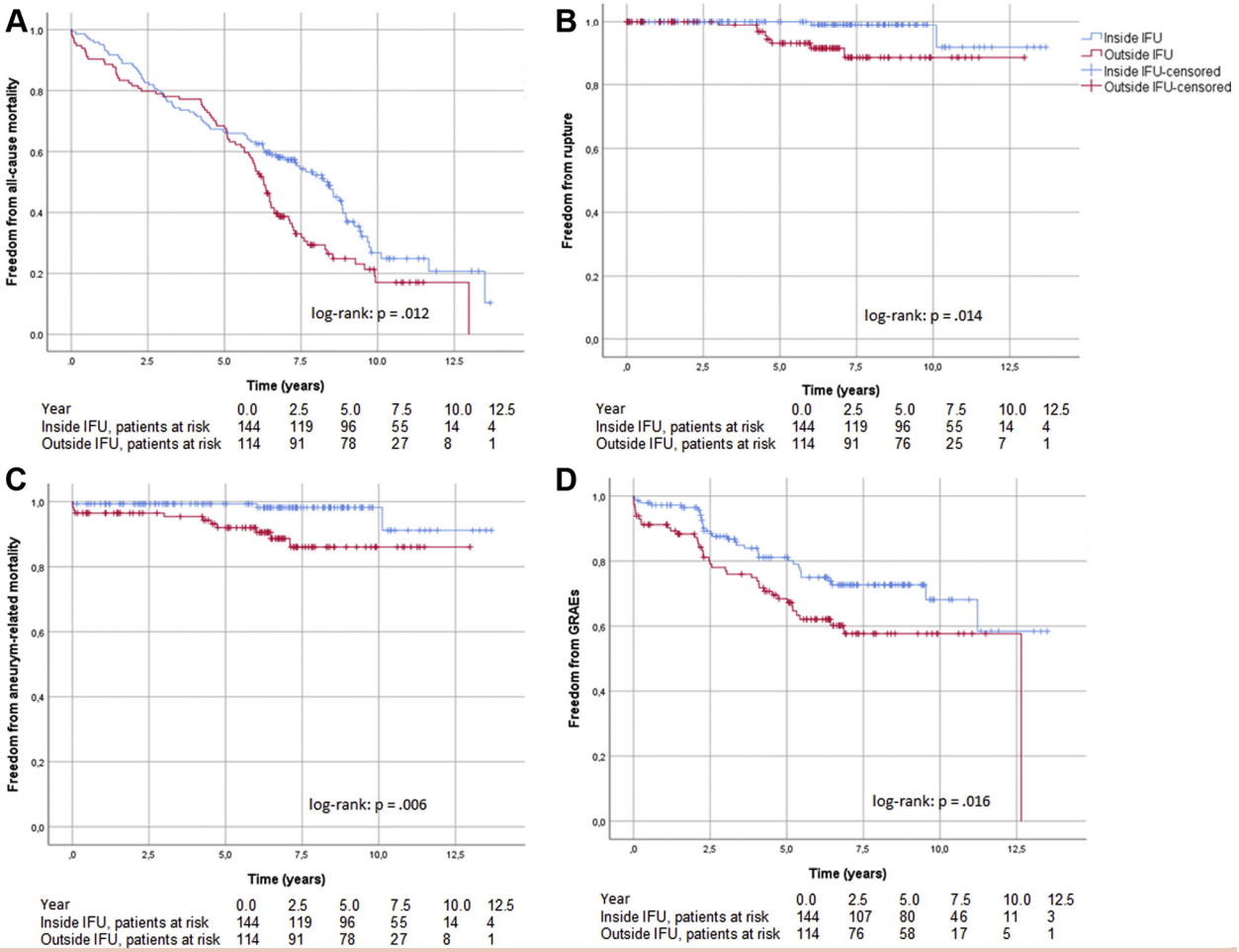

Fig. Freedom from all-cause mortality **(A)**, rupture **(B)**, aneurysm-related mortality **(C)**, and graft-related adverse events (GRAEs) for patients treated within (*blue line*) and outside (*red line*) the instructions for use *(IFU)*.

Table IV. Risk factors for mortality, rupture, and aneurysm-related mortality evaluated using Cox hazards modeling

	All-cause mortality			AAA rupture			ARM		
Risk factor	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Neck length	1.3	0.6-2.5	.485	21.7	2.8-166	**.003**	8.7	1.8-41.6	**.007**
Neck diameter too wide	1.3	0.7-2.7	.440	1.0	0.9-11.8	.974	1.6	0.3-8.4	.581
Neck diameter too narrow	0.8	0.4-1.4	.371	2.0	0.2-20.0	.540			NA
Neck angulation	2.0	1.1-3.7	**.032**	79.4	6.3-999	**.001**	7.6	1.4-42.8	**.021**
Neck calcification	1.3	0.9-1.9	.224	0.7	0.8-7.0	.786	2.1	0.6-7.3	.231
Neck thrombus	2.4	0.8-6.6	.100			NA			NA
Neck conicity	1.2	0.7-2.2	.464	0.4	0.3-5.6	.494	1.2	0.2-6.8	.873
Iliac IFU	2.3	1.4-3.9	**.002**	6.1	0.5-78.6	.164	5.2	1.0-28.6	.057
Hypertension	1.7	0.8-1.6	.369	1.0	0.0-100	.941	5.9	0.7-47.9	.095
Graft type									
Zenith	0.8	0.6-1.3	.503	0.1	0.0-1.8	.117	0.8	0.1-4-5	.815
Endurant	0.7	0.5-1.1	.096	1.7	0.3-10.3	.572	1.3	0.3-5.5	.700

AAA, Abdominal aortic aneurysm; *ARM*, aneurysm-related mortality; *CI*, confidence interval; *HR*, hazard ratio; *IFU*, instructions for use; *NA*, not applicable.
Boldface *P* values represent statistical significance.

Table V. Risk factors for graft-related adverse events (GRAEs) and type Ia endoleaks evaluated with Cox hazards modeling

	GRAEs			Type Ia endoleak		
Risk factor	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Neck length	4.4	2.0-9.7	**<.001**	18.2	6.3-52.2	**<.001**
Neck diameter too wide	0.5	0.2-1.8	.317	0.3	0.0-2.8	.299
Neck diameter too narrow	1.1	0.5-2.5	.743	0.3	0.0-3.0	.300
Neck angulation	4.3	1.9-9.5	**<.001**	3.2	0.7-14.8	.140
Neck calcification	1.3	0.7-2.3	.474	0.7	0.2-3.4	.678
Neck conicity	0.8	0.3-1.8	.525	1.4	0.3-6.6	.669
Iliac IFU	2.1	0.9-5.1	.094	–	–	–
Hypertension	0.8	0.4-1.3	.314	0.8	0.2-2.4	.638
Graft type						
Zenith	0.9	0.5-1.8	.838	0.5	0.1-1.9	.242
Endurant	1.3	0.7-2.3	.362	0.3	0.0-3.0	.300

CI, Confidence interval; *HR,* hazard ratio; *IFU,* instructions for use.
Boldface *P* values represent statistical significance.

The liberal use of standard stent grafts has raised concern regarding whether applying EVAR devices outside the IFU carries the risk of the development of a type I endoleak and AAA growth after the procedure, which could lead to reintervention or AAA rupture. Several studies have examined EVAR outcomes stratified by IFU adherence, with conflicting results.[6-12,14,17] In the present study, the rate of IFU nonadherence was 44.2%, similar to that reported by previous studies, with IFU violation rates of 32% to 52%.[4-7,10,13,18]

A meta-analysis reported in 2020, including 17 studies and 4498 patients, found greater overall mortality for patients treated outside the IFU (HR, 1.20; 95% CI, 1.02-1.42; $P < .03$).[4] Also, AbuRahma et al[13] reported poorer survival for patients treated outside the IFU. In the present study, overall mortality was also higher for the patients treated outside the IFU (HR, 1.39; 95% CI, 1.02-1.89; $P = .037$). Overall mortality was also higher for the patients with two or more violated IFU criteria than for the patients with one violated IFU criteria or those treated within the IFU. However, several studies found no differences in the outcomes for all-cause mortality.[6,14,17] These studies had mainly reported their mid-term results, with median follow-up time ranging from 2.4 to 3.5 years. In contrast, the median follow-up in the present study was >6 years.

During the follow-up period, a significant association was found between the occurrence of AAA rupture and IFU nonadherence (HR, 5.4; 95% CI, 1.1-26.6; $P = .036$). The incidence of AAA rupture was 1.4% among those treated within the IFU and 7.0% for those treated outside the IFU. However, recent studies have reported contrasting findings, with IFU adherence having no actual effect on the rate of aneurysm rupture and a much lower incidence of late aneurysm rupture in general (range, 0.6%-1.7%).[4,5,7,8,17] A possible reason for these conflicting findings is the length of follow-up. In our study, AAA ruptures had occurred at a median of 4.6 years postoperatively, with a minimum of 3.0 years. In contrast, other studies have reported a median follow-up time ranging from 1.9 to 3.5 years.[4,5,7,8,17] Zacharias et al[19] found that the mean interval between the initial procedure and rupture was 38 months for patients who had developed a type Ia endoleak. Few studies have reported the results for aneurysm-related mortality, and most found no significant association with IFU adherence.[4,6,17] In the present study, IFU nonadherence was related to greater aneurysm-related mortality (HR, 5.1; 95% CI, 1.4-18.6; $P = .015$).

Lower freedom from GRAEs after an IFU violation has been reported previously, as has an association between a neck criterion–related IFU violation and the occurrence of GRAEs, type I endoleak, and the need for reintervention.[5,7,13] However, these results have not been consistent in the literature.[6] In the present study, IFU nonadherence carried a significant risk of GRAEs (HR, 1.7; 95% CI, 1.1-2.8; $P = .025$).

A wide aneurysm neck has been reported to be associated with mortality, sac enlargement, neck-related adverse events, and type Ia endoleaks.[8,11,12,20] In the present study, a wide neck was not a risk factor for any of the reported adverse events. However, violations of the neck angulation and neck length criteria were strong predictors of adverse outcomes. A short proximal neck has previously been found to be a risk factor for adverse events, worse survival, and type Ia endoleaks.[12,21] Neck angulation of >60° has been reported to carry a risk of poorer survival, type Ia endoleaks, and the need for reintervention.[13,22] Appropriate neck angulation and neck length can be regarded as crucial for an adequate seal of the stent graft; therefore, the risk of failure during follow-up could be greater if they were compromised.

We did not find an association between an iliac-related IFU violation and iliac-related adverse events in the present study, although a violation of iliac-related IFU criteria

had had a negative effect on mortality (HR, 2.23; 95% CI, 1.4-3.9; $P = .002$). The iliac-related IFU criteria had been violated for only 18 patients, which might explain the nonsignificant association. A review of the literature showed that not all studies had included the iliac anatomy in the IFU adherence status,[7,10,13] and a separate analysis of iliac-related IFU violations is very rare. Schanzer et al[20] found that a wide common iliac artery is an independent predictor of AAA sac enlargement. Matsumoto et al[14] included device-limb occlusion and type Ib endoleak in their study outcomes. However, they had compared them by overall IFU adherence instead of adherence to iliac-related IFU criteria and found no significant differences.[14]

The most probable explanation for the differences in the results from the present study and those from previous studies is the length of follow-up. The median follow-up in our study was 6.8 years for the IFU adherence group and 6.2 years for the IFU nonadherence group. The available data showed that most studies on this subject had reported only mid-term results, ranging from 2 to 3.5 years.[5-7,12-14,16-18] EVAR-related complications can be expected to occur in the long term and the long-term durability of EVAR has been criticized. The results of studies with ≥3 years follow-up are listed in Supplementary Table II (online only).

The assumption was that the prevalence of EVAR performed outside the IFU had increased during the study period. However, the annual prevalence remained similar, and this assumption could not be confirmed. However, a meta-analysis of 4498 patients reported an increasing prevalence of EVAR performed outside the IFU during the study period.[4]

Patients treated outside the IFU might have been considered to too old or frail or to have comorbid conditions too serious to allow for an open procedure or to be offered technically more sophisticated endovascular solutions, such as fenestrated or branched endografts. It is also possible that not all IFU criteria were considered to be equally important, such as neck calcification, which was the most frequently violated criterion in the present study. Fenestrated grafts were not available until 2008 in our unit. Because scope of the present study was to evaluate the long-term outcomes of IFU nonadherence, we did not retrospectively evaluate how many patients in the IFU nonadherence group would have been suitable for fenestrated grafts. The different characteristics and availability of specific standard endografts and operator preference could also have influenced the specific endograft choice.

The present study had some limitations. First, our study was a nonrandomized, retrospective study using data from a prospectively maintained database, and the results might reflect a selection bias. The only difference in the baseline demographics when stratified by IFU status was in the prevalence of hypertension. However, this difference probably did not indicate that patients treated outside the IFU would have been at a higher surgical risk than those treated within the IFU. Still, the presence of more challenging aneurysm anatomy might indicate more rapid progression of the aortic pathology and, therefore, poorer outcomes. Suprarenal endografts (Zenith and Endurant) were used more often in the IFU nonadherence group than in the IFU adherence group. A more challenging neck anatomy could have affected the decision to use suprarenal fixation, which could explain the difference. However, the graft type was included in the analyses and did not affect the results.

The strengths of the present study included the long follow-up time. IFU status was determined by the device-specific IFU, and all anatomic parameters were observed. Furthermore, the specific anatomic characteristics, such as neck morphology, were all included in the analysis.

CONCLUSIONS

The results from the present study suggest that IFU nonadherence will be associated with greater mortality and morbidity after EVAR. Special caution should be taken regarding aneurysm neck length and angulation when evaluating a patient's anatomic suitability for standard EVAR. New endografts designed to accommodate severe neck angulation have already been introduced into the market. These technologies might provide an option for those patients who might otherwise be excluded from standard EVAR.

AUTHOR CONTRIBUTIONS

Conception and design: TH, SP, IU, VS
Analysis and interpretation: TH
Data collection: TH, SP, VJ, IU, SV, VS
Writing the article: TH
Critical revision of the article: TH, SP, VJ, IU, SV, VS
Final approval of the article: TH, SP, VJ, IU, SV, VS
Statistical analysis: TH
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Overall responsibility: TH

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

Supplementary Table I (online only). Types of graft-related adverse events (GRAEs)

Variable	IFU adherence (n = 144)	IFU nonadherence (n = 114)	*P* value
Type Ia endoleak	4.9	9.6	.147
Type Ib endoleak	9.0	9.6	.865
Reintervention for type II endoleak	11.8	8.8	.540
Type III endoleak	0.7	0.9	.868
Other reinterventions	3.5	5.3	.544
Rupture	1.7	7.0	.025
Aneurysm-related mortality	2.1	9.6	.011
All GRAEs	22.9	35.1	.037

IFU, Instructions for use.
Data presented as percentages.

Supplementary Table II (online only). Summary of studies with ≥3 years of follow-up

Investigator	Patients, No.	Outside of IFU, %	Follow-up period[a]	End points	Results
Beckerman et al[17]	566	68.9	3.54 ± 2.65 years	All-cause mortality; aneurysm-related mortality; rupture; reinterventions; endoleaks; sac enlargement	No difference
Gargiulo et al[11]	118	NA	3.79 ± 11.9 years	Type Ia endoleak; neck-related reinterventions; mortality; aneurysm-related mortality	Wide necks associated with type Ia endoleak; reinterventions
Hoshina et al[12]	38,008	47.6	2403 ± 15 days	Mortality; adverse events; sac dilatation; reinterventions	Risk factors for mortality included neck diameter, neck length, calcification; adverse events included neck diameter, neck length, angulation, calcification; sac dilatation determined by neck diameter, angulation; reinterventions included neck diameter, neck length, calcification
Oliveira et al[8]	427	NA	3.9 years (2.3-5.4)	Neck-related adverse events; type Ia endoleak; neck-related reinterventions	Wide necks associated with type Ia endoleak, adverse events, reinterventions
Walker et al[6]	489	41.9	3.1 years (1.6-5.0)	All-cause mortality; aneurysm-related mortality; endoleaks; adverse events; reinterventions; sac size change	No difference

IFU, Instructions for use; *NA*, not applicable.
[a]Data presented as mean ± standard deviation or median (interquartile range).