Evolution of practice patterns and learning curve of aortic repair using the E-nside off-the-shelf inner branch thoracoabdominal endograft

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ABSTRACT

Objective: To report the impact of the learning curve on the outcomes of branched endovascular aortic repair using an off-the-shelf preloaded inner branch device (E-nside).

Methods: Data from a physician-initiated national multicenter registry, including patients treated with E-nside endograft (INBREED [ItaliaN Branch Registry of E-nside EnDograft]) were collected prospectively (2020-2024). End points were early (30-day) technical success, mortality, major adverse events (MAEs), and 2-year freedom from endograft instability and target vessel instability. Patients were divided into early and late cohorts based on the median date of the procedure in each center.

Results: There were 215 patients treated with the E-nside, 108 (393 target vessels) in the early and 107 (395 target vessels) in the late cohort. Most patients had a degenerative aneurysm (early, 82%; late, 75%; $P = .326$) or a chronic dissection (early, 6%; late, 15%; $P = .025$). Aneurysm extent was thoracoabdominal in 53% of patients and complex abdominal in 47%; and 23% were ruptured or symptomatic and 26% had an aneurysm size of more than 70 mm, without differences between groups. A narrow paravisceral aortic lumen of less than 25 mm was more frequent in the late cohort (late, 30%; early, 18%; $P = .037$). From the early to the late groups, there was an increase in the use of a total transfemoral approach (late, 29% vs early, 18%; $P = .042$), balloon-expandable bridging stents (late, 82% vs early, 76%; $P = .032$), and reinforcement bridging stents (late, 26%; early, 11%; $P < .001$). Operating time (late, 267 ± 131 minutes; early, 244 ± 130 minutes; $P = .230$), iodinated contrast volume (late, 181 ± 81 mL; early, 210 ± 141 mL; $P = 108$; $P = .302$), and dose area product (late, 272 ± 110 Gycm^2 early, 291 ± 118 Gycm^2; $P = .277$) were similar in the two groups. Intraprocedural complications decreased in the later stage of the learning curve (late, 11%; early, 23%; $P = .030$), whereas overall 30-day mortality (late, 8%; early, 6%; $P = .346$), technical success (late, 99%; early, 98%; $P = .286$), and MAEs (late, 27%; early, 29%; $P = .879$) remained substantially stable. There were no differences in 2-year freedom from endograft instability (late, 100 ± 0%; early, 96 ± 5%; $P = 1.00$), freedom from target vessel instability (late, 98 ± 3%; early, 94 ± 2%; $P = .090$), and target vessel primary patency (late, 97 ± 2%; early, 97 ± 2%; $P = .321$).

Conclusions: The increased experience with the E-nside endograft was associated with a more frequent use of a total transfemoral approach and use of balloon-expandable and reinforced bridging stents. From the early to the late stages, there was a significant decrease in intraoperative complications, although most centers were learning independent and achieved a consistent mortality, MAE, procedural metrics, and mid-term results from the start. (J Vasc Surg 2025;82:1168-78.)

Keywords: Branched endovascular aortic repair; Off-the-shelf; Aortic aneurysm; Aortic dissection; Learning curve; Practice patterns; physician

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Presented at the Vascular Annual Meeting of the Society for Vascular Surgery, New Orleans, Louisiana, June 4-7 2025.

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

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

https://doi.org/10.1016/j.jvs.2025.05.036

Branched endovascular aortic repair (BEVAR) is a complex procedure that is associated with a substantial learning curve, involving not only surgical skills, but also patient selection, endovascular planning, knowledge of the devices, and ability to rescue eventual complications.[1-3] Complex endovascular aortic repair has witnessed a great evolution since its first introduction, owing to the advances in endografts, techniques, and perioperative patient management. The progress in branched endografts has led to the availability of several custom made and off-the-shelf devices that may differ in important aspects, such as graft material, branches design, and available sizes, as well as procedural steps and anatomical feasibility.[4,5] Along with a general training in complex endovascular aortic repair, the introduction of a new product may require also a specific learning curve related to the particular device's characteristics.

The E-nside is an off-the-shelf branched endograft (E-nside, Artivion, Kennesaw, GA), characterized by four preloaded inner branches, that had been introduced in the European market in 2020. The clinical outcomes obtained by E-nside aortic repair had been previously reported, describing promising results in the elective and urgent setting,[6,7] in the treatment of both thoracoabdominal aortic aneurysm (TAAA) and juxta/pararenal aortic aneurysms.[8] However, the available literature provide aggregated results without a discrimination between the early vs late experience in E-nside use, and no prior studies evaluated the impact of the learning curve on the outcomes.

The aim of this study was to analyze the progression in patient selection, procedural data, technical choices, and outcomes from the early to late stages of the learning curve using the E-nside device. This information may help to understand the outcomes obtained with this device, and be useful to centers that initiate programs involving the use of E-nside for the treatment of TAAA and complex abdominal aortic pathologies.

ARTICLE HIGHLIGHTS

- **Type of Research:** Multicenter cohort study
- **Key Findings:** Of 215 patients treated in a multicenter registry of E-nside endograft, patients in the late cohort (n = 107) had more frequently a chronic dissection (early, 6%; late, 15%; $P = .025$) and a narrow paravisceral aortic lumen of less than 25 mm (late, 30%; early, 18%; $P = .037$) compared with the early cohort. There was also an increase in the use of a total transfemoral approach (late, 29% vs early, 18%; $P = .042$), balloon-expandable bridging stents (late, 82% vs early, 76%; $P = .032$), and reinforcement bridging stents (late, 26%; early, 11%; $P < .001$). Intraprocedural complications decreased in the later stage (late, 11%; early, 23%; $P = .030$), whereas overall 30-day mortality (late, 8%; early, 6%; $P = .346$), technical success (late, 99%; early, 98%; $P = .286$), and major adverse events (MAEs) (late, 27%; early, 29%; $P = .879$) remained substantially stable. Learning-dependent MAE rates were observed in four centers ($P = .027$). There were no differences in 2-year freedom from endograft instability (late, 100± 0%; early, 96 ± 5%; $P = 1.00$) and target vessel instability (late, 98 ± 3%).
- **Take Home Message:** Increased experience with the E-nside endograft led to a reduction in intraprocedural complications while maintaining stable early mortality and MAEs. Some centers showed learning-dependent MAE rates, stabilizing after the first five cases.

METHODS

Study design. Data were extracted from INBREED (ItaliaN Branch Registry of E-nside EnDograft), a physician-initiated, nonsponsored prospective multicenter cohort registry, including patients treated from June 2021 to December 2024[6] by the E-nside endograft in 35 participating centers. All centers using E-nside in Italy participate to the registry, which can thus regarded as a key indicator of the national trend in the use and outcomes of the device. All hospitals in the registry are tertiary referral hospitals, although there may be differences in the volume of complex endovascular procedures and E-nside repairs. Each center had a single physician, identified as the center's expert in complex endovascular procedures, who was present at all procedures conducted there. Decisions on indications, patient selection, surgical approach, and postoperative care were not standardized among centers, but based on each center's established practice and may have been subject to evolution during the study period. Institutional review board and ethics committee approval were obtained (Ethic Committee for Clinical Experimentation, Padova: study ID 211745).

Data collection and definitions. Anonymized data were entered by delegates from each participating center. One center (Vascular and Endovascular Surgery Division, Padova University, Padova, Italy) was responsible for the electronic data capture system (RedCap),[9] checking the quality of the imputed data, and performing the final analysis. A data quality control was performed with regular interval audits and queries were applied for specific errors, missing, incomplete or unclear data. Demographics, clinical characteristics operative data and 2-year outcomes were collected. Disease extent classification was based on preoperative computed tomography angiogram according to the Society for Vascular Surgery and European Society for Vascular Surgery guidelines.[10,11] Intraoperative adverse events (IAEs), technical success, and 30-days major adverse events (MAEs)

were reported. IAEs were defined as any intraoperative complication or technical problem occurring during initial arterial access, implantation of all the intended aortic and side branch components, and arterial closure, requiring any additional or unplanned intervention.[12] Additionally, intraoperative complication or technical problem that resulted in loss of the target artery (eg, dissection leading to target artery occlusion) were considered. IAEs were classified into three categories: access related, target vessel related, or graft related. Endograft-related technical success was defined as the successful introduction and deployment of the device in the absence of surgical conversion or mortality, type I or type III endoleak, branch occlusion, or graft limb obstruction.[10] Branch-related technical success consisted of successful catheterization and stent placement in all intended target vessels.[10] MAEs were defined as a composite end point consisting of any cause mortality, myocardial infarction, stroke, paraplegia, acute kidney injury[13] or new-onset dialysis, respiratory failure requiring prolonged (>24 hours past anticipated) mechanical ventilation or reintubation, and bowel ischemia requiring surgical resection. Mid-term (2-year) mortality, graft stability, and target vessel stability were assessed based on clinical and imaging assessment at 30 days, 6 months, 12 months, and yearly thereafter. Graft instability was defined as a composite end point including any E-nside-related event associated with patient death, aneurysm rupture, infection, or reintervention, excluding target vessel-related events, which are described under the definition of target vessel instability.[10] Target vessel instability was defined as a composite end point including any death or rupture related to side branch complication (endoleak, rupture) or any secondary intervention indicated to treat a branch-related complication, including endoleak, disconnection, kink, stenosis, occlusion, or rupture.[10]

Device and technique. Detailed device design and operative technique have been described elsewere.[6,14] Briefly, the E-nside is an off-the-shelf inner branched endograft with a 24F outer diameter delivery system, available in four different sizes, with a proximal diameter measuring 38 or 33 mm and a distal diameter of 30 or 26 mm. The four inner branches are preloaded and can be cannulated with a 0.018″ wire from the handle system; the wire is intended to be snared from above the top of the graft using an upper arm or contralateral femoral approach. The use of the preloaded system is optional and left to the discretion of the operating surgeon. By manufacturer's instructions for use, the device should land on a thoracic endograft, but in real-word clinical practice it has been safely used also without a proximal TEVAR.[6,8]

End points. Primary end points were IAE, early (30-day) technical success, mortality, MAE, and 2-year freedom from endograft instability and target vessel instability. Secondary end points were procedural metrics.

Exposure. Two groups of patients were compared, the early cohort and late cohort. Patients were divided into early and late cohorts based on the median date of the procedure in each center. Therefore, in each center, patients treated in the first one-half of the experience were included in the early cohort, and cases treated in the second one-half of the experience belonged to the late cohort. Patients treated in centers with a total case volume of fewer than three procedures were excluded from the analysis, owing to the impossibility to assess the impact of the learning curve properly. This cutoff was set to allow for a basic assessment of early trends in complications while preserving sufficient degrees of freedom for within-center comparisons (with comparison of at least two data segments). Additionally, it maximized the generalizability of the learning curve analysis to real-world practice, where procedural volumes may be limited.

Statistical analysis. Results were reported as number and percentage for categorical variables, mean ± standard deviation, or median (interquartile range) for continuous variables; these were compared with the Wilcoxon rank sum test or *t* test, as appropriate. The Pearson χ^2 and Fischer exact tests were used for analysis of categorical variables. Time-dependent outcomes were reported as Kaplan-Meier estimates, and compared using the log-rank test.

Cumulative rates of IAEs and MAEs were analyzed against the case number both on a center level (to evaluate specific center's learning curve) and a registry level (to investigate the overall national trend). A generalized linear regression model was used to fit the curve of cumulative proportion of IAE and MAE as a function of case order, to assess learning curve trends. The slope of the curve (β coefficient) at any given point indicates performance, where a positive slope signifies performance is worsening, a plateau signifies performance is stable, and a negative slope indicates performance is improving. The presence of any inflection point in the learning curve was assessed by polynomial regression. An adjusted multiple logistic regression model was also used to test whether the late cohort and case number (as indicator of centers' experience) were significant predictor of IAEs and MAEs. A *P* value of less than .050 was used to determine statistical significance. R 4.4 software (The R Foundation for Statistical Computing, Vienna Austria) was used for statistical analysis.

RESULTS

Patient population. Of the 227 patients included in the registry, 215 patients (831 target vessels) from 26 centers (mean, 8.3 per center) were included in the analysis, of which 108 were treated in the early cohort and 107 in

Table I. Demographics, risk factors, clinical and anatomical data of the 215 patients treated with E-nside endograft, stratified by early and late cohorts

	Early cohort (n = 108)	Late cohort (n = 107)	Total (n = 215)	*P* value
Age, years	73.3 ± 8.0	73.6 ± 8.3	73.5 ± 8.1	.819
Male sex	73 (67.6)	82 (76.6)	155 (72.1)	.139
BMI	26.4 ± 4.9	26.7 ± 4.8	26.6 ± 4.9	.725
Hypercholesterolemia	70 (64.8)	72 (68.6)	142 (66.7)	.561
Hypertension	99 (91.7)	96 (91.4)	195 (91.5)	.950
Coronary artery disease	31 (28.7)	32 (30.5)	63 (29.6)	.777
Chronic heart failure	9 (8.3)	20 (19.0)	29 (13.6)	.023
COPD	47 (43.5)	50 (47.6)	97 (45.5)	.548
Chronic kidney disease	22 (20.4)	32 (30.5)	54 (25.4)	.090
Genetically triggered aortic disease	3 (2.8)	4 (3.9)	7 (3.3)	.644
Any prior aortic repair	42 (38.9)	57 (53.2)	101 (46.9)	.040[a]
Prior open aortic repair	32 (29.6)	35 (33.7)	67 (31.6)	.529
Prior endovascular aortic repair	24 (22.2)	34 (33.0)	58 (27.5)	.079
Aortic pathology				.194
Acute or subacute dissection	3 (2.8)	2 (1.9)	5 (2.3)	
Chronic dissection	6 (5.6)	16 (15.2)	22 (10.3)	
Degenerative aneurysm	89 (82.4)	81 (75.2)	170 (78.9)	
Intramural hematoma	1 (0.9)	0 (0.0)	1 (0.5)	
Penetrating aortic ulcer	3 (2.8)	1 (1.0)	4 (1.9)	
Pseudoaneurysm	6 (5.6)	7 (6.7)	13 (6.1)	
Status of aortic pathology				.326
Contained rupture	2 (1.9)	6 (5.6)	8 (3.7)	
Nonruptured symptomatic	22 (20.4)	19 (17.8)	41 (19.1)	
Nonruptured asymptomatic	84 (77.8)	82 (76.6)	166 (77.2)	
Largest aortic diameter, mm	66.4 ± 16.2	65.4 ± 13.2	65.9 ± 14.8	.617
Aortic diameter >70 mm	25 (23.4)	28 (28.6)	53 (25.9)	.395
Anatomical classification				.453
Extent I	13 (12.0)	18 (16.8)	31 (14.4)	
Extent II	28 (25.9)	19 (17.8)	47 (21.9)	
Extent III	17 (15.7)	20 (18.7)	37 (17.2)	
Extent IV	21 (19.4)	21 (19.6)	42 (19.5)	
Juxtarenal	3 (2.8)	7 (6.5)	10 (4.7)	
Pararenal	26 (24.1)	22 (20.6)	48 (22.3)	
Minimum iliac artery diameter, mm	9.7 ± 10.0	10.4 ± 9.5	10.0 ± 9.8	.596
Narrow paravisceral aorta (<25 mm)	19 (17.6)	32 (29.9)	51 (23.7)	.037[a]

BMI, Body mass index; *COPD*, chronic obstructive pulmonary disease.
Values are mean ± standard deviation or number (%).
[a]Statistically significant.

the late cohort. Case volume was 5 or fewer patients in 9 centers, 6 to 10 in 9 centers, 11 to 15 in 3 centers, 16 to 20 in 3 centers, and more than 20 in 2 centers. The mean patient age was 74 ± 8 years, and most patients (n = 155 [72%]) were male. Demographics, risk factors, and clinical data, stratified by early and late cohorts, are provided in Table I. Compared with the early cohort, patients in the late cohort were more likely to have a prior open or endovascular aortic repair (late cohort, 53% vs early cohort, 39%; $P = .040$).

Most patients both in the early cohort and late cohort were treated for a degenerative aortic aneurysm (75% vs 82%; $P = .326$), but an increase in the treatment of chronic dissections (15% vs 6%; $P = .025$) was observed in the late cohort. Specific anatomical details are reported in Table I. Urgent treatment owing to contained rupture or symptomatic status was performed in 49 patients (23%), 25 (23%) in the late cohort and 24 (22%) in the early cohort ($P = .326$). Fifty-three patients (26%) underwent urgent treatment because of a

Table II. Procedural data of the 215 patients treated with E-nside endograft, stratified by early and late cohorts

	Early cohort (n = 108)	Late cohort (n = 107)	Total (n = 215)	*P* value
Femoral access				.023[a]
Percutaneous bilateral	60 (55.6)	47 (42.3)	107 (49.1)	
Percutaneous unilateral	15 (13.9)	30 (28.8)	45 (21.2)	
Surgical bilateral	33 (30.6)	30 (28.8)	63 (29.7)	
Upper arm access				.101
No	19 (17.5)	31 (28.9)	50 (24.3)	
Left side	68 (63.8)	54 (50)	122 (56.7)	
Right side	21 (23.1)	23 (21.2)	44 (20.4)	
Celiac artery				
Main bridging stent				
Balloon expandable	84 (77.8)	87 (81.3)	171 (79.5)	.070
Self-expandable	19 (17.6)	11 (10.3)	20 (9.3)	
Intentional occlusion	5 (4.6)	9 (8.4)	14 (6.5)	.408
Adjunctive bare metal stent	6 (5.8)	22 (20.5)	28 (13.0)	<.001[a]
Superior mesenteric artery				
Main bridging stent				.606
Balloon expandable	83 (76.8)	88 (82.2)	171 (79.5)	
Self-expandable	25 (23.1)	19 (17.8)	44 (20.4)	
Adjunctive bare metal stent	10 (9.2)	22 (20.5)	32 (14.9)	.015[a]
Right renal artery				
Main bridging stent				.748
Balloon expandable	78 (73.8)	81 (75.0)	160 (74.4)	
Self-expandable	28 (25.2)	24 (22.2)	51 (23.7)	
Intentional occlusion	1 (1.0)	3 (3.0)	4 (2.0)	.625
Adjunctive bare metal stent	15 (14.0)	26 (24.2)	41 (19.1)	.038[a]
Left renal artery				
Main bridging stent				.311
Balloon-expandable	75 (70.3)	83 (77.6)	159 (73.9)	
Self-expandable	27 (24.1)	19 (17.8)	45 (20.9)	
Intentional occlusion	6 (5.6)	5 (4.7)	11 (5.1)	1.00
Adjunctive bare metal stent	13 (13.7)	28 (29.5)	41 (21.6)	.008[a]
Prophylactic spinal drainage	39 (36.4)	27 (26.2)	66 (31.4)	.110
Staging				.252
Single-stage procedure	64 (59.8)	62 (62.6)	126 (61.2)	
Two-step procedure	44 (40.7)	45 (42.1)	89 (41.3)	
Adjunctive thoracic endograft	51 (48.1)	36 (36.0)	87 (42.2)	.051
Total thoracic aortic coverage, cm	18.3 ± 8.0	17.6 ± 9.2	17.7 ± 9.0	.822
Adjunctive distal EVAR	56 (51.8)	53 (49.5)	109 (50.7)	.973
Repair outside IFU	64 (59)	75 (70)	139 (64)	.024[a]
Total operating time, minutes	244 ± 130	267 ± 132	254 ± 131	.230
Total iodinated contrast volume, mL	201 ± 141	181 ± 81	191 ± 114	.302
Total fluoroscopy time, minutes	94 ± 53	157 ± 54	123 ± 36	.277
Dose area product, Gycm2	291 ± 118	272 ± 110	282 ± 107	.279

EVAR, Endovascular aortic repair; *IFU*, instructions for use.
Values are number (%) or mean ± standard deviation.
[a]Statistically significant.

Table III. Perioperative and early outcomes of the 215 patients treated with E-nside endograft, stratified by early and late cohorts

	Early cohort (n = 108)	Late cohort (n = 107)	Total (n = 215)	*P* value
Intraprocedural complications	25 (23.1)	12 (11.2)	37 (17.2)	.030[a]
Access related	10 (9.3)	5 (4.6)	15 (6.9)	
Device related	5 (4.6)	0 (0)	5 (2.3)	
Target artery related	10 (9.3)	7 (6.5)	17 (7.9)	
Technical success	106 (98.1)	106 (99.1)	213 (99.1)	1.00
Any MAE	31 (28.7)	29 (27.1)	60 (27.9)	.879
Death	6 (5.6)	9 (8.4)	15 (6.9)	.346
EBL>1000 mL	4 (3.8)	4 (3.7)	8 (3.7)	.940
Myocardial infarction	1 (0.9)	3 (2.8)	4 (1.9)	.289
Congestive heart failure	1 (0.9)	0 (0.0)	1 (0.5)	.323
Respiratory failure	5 (4.6)	8 (7.4)	13 (6.0)	.321
Stroke	5 (4.6)	1 (0.9)	6 (2.7)	.110
Spinal cord ischemia				.623
Motor able to ambulate	0 (0.0)	1 (0.9)	1 (0.5)	
Motor not able to ambulate	6 (5.6)	7 (6.5)	13 (6.0)	
Sensory deficit	4 (3.8)	2 (1.9)	6 (2.7)	
Acute kidney injury	12 (11.1)	7 (6.5)	19 (8.8)	.275
Early reintervention	12 (11.7)	9 (8.4)	21 (10.3)	.500
Access site complication	5 (4.6)	4 (3.7)	9 (4.2)	1.00
Branch complication	6 (5.6)	4 (3.7)	10 (4.7)	.748
Main graft complication	1 (0.9)	1 (0.9)	2 (0.9)	1.00

EBL, Estimated blood loss; *MAE*, major adverse event.
Values are number (%) or mean ± standard deviation.
Values are number (%).
[a]Statistically significant.

asymptomatic aneurysm measuring more than 70 mm (late cohort, 29% vs early cohort, 23%; $P = .395$). Aneurysm extent was thoracoabdominal in 53% of patients (late cohort, 53%vs early cohort, 54%) and complex abdominal in 47% (late cohort, 47%vs early cohort, 46%; $P = .453$). There were no differences between the two cohorts in aneurysm size (late cohort, 65.4 ± 13.2 mm vs early cohort, 66.4 ± 16.2 mm; $P = .617$), whereas presence of a narrow paraviceral aortic lumen of less than 25 mm[15] was more frequent in the late cohort (late cohort, 30%, early cohort, 18%; $P = .037$).

Procedural data. Procedural data are reported in Table II. From the early to the late cohorts, there was an increase in the use of a total transfemoral approach (late cohort, 29% vs early cohort, 18%; $P = .042$), balloon-expandable (late cohort, 82% vs early cohort, 76%; $P = .032$) rather than self-expandable (late cohort, 18% vs early cohort, 24%) bridging stents, and relining with reinforcement stents (late cohort, 24% vs early cohort, 11%; $P < .001$). An adjunctive proximal thoracic endograft was deployed in 42% (late cohort, 36% vs early cohort, 48%; $P = .051$); the lack of a proximal thoracic endograft was the most common cause (92%) of E-nside use outside instructions for use, that overall was performed in 139 patients (late cohort, 70% vs early cohort, 59%; $P = .024$). An infrarenal aortic bifurcated endograft was deployed in 51% (late cohort, 50% vs early cohort, 52%; $P = .973$).

Total operating time (late cohort, 267 ± 132 minutes vs early cohort, 244 ± 130 minutes; $P = .230$), iodinated contrast volume (late cohort, 181 ± 81 mL vs early cohort, 210 ± 141 mL; $P = .302$), and dose area product (late cohort, 272 ± 110 Gycm2 vs early cohort, 291 ± 118 Gycm2; $P = .2779$ were similar in the two groups.

Intraoperative and early outcomes. Intraprocedural complications occurred in 37 patients (17%), and were device related in 5 (2%), access related in 15 (7%), and target artery related in 17 (8%) (Table III). Device-related IAEs consisted in cranial migration of the endograft during deployment in four cases (leading to technical unsuccess in two cases) and loss of bridging stents during retrieve of the proximal cap in one case. Of the 17 target vessel complications, 8 resulted in impossibility to successfully bridge the target artery. Overall, patients in the late cohort had a lower rate of intraoperative complications (late cohort, 11% vs early cohort, 23%; $P = .030$).

Overall technical success was 99% (late cohort, 99% vs early cohort, 98%; $P = 1.00$) and was not achieved in

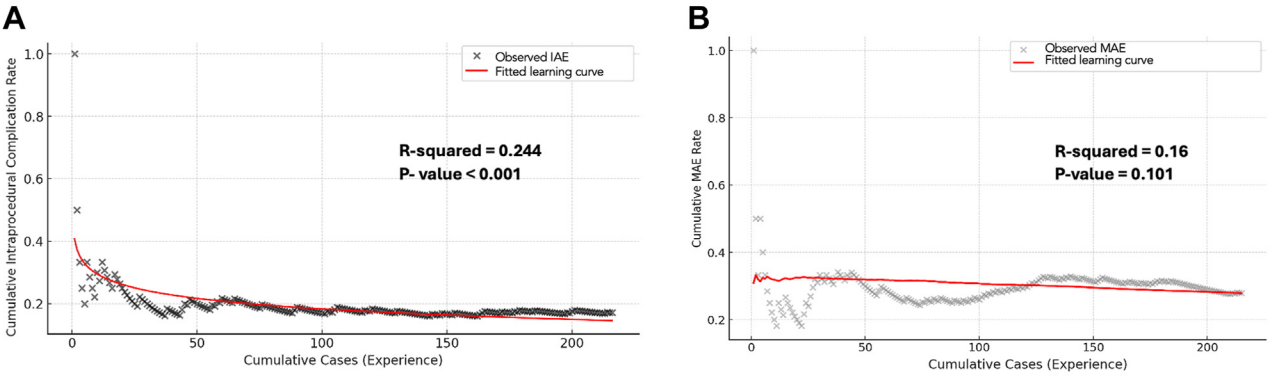

Fig 1. (A) Cumulative learning curve for IAEs in the E-nside registry. There was a significant ($P < .001$) trend toward an improvement since the start of the experience, that reached a plateau after the treatment of the first 48 cases. **(B)** Cumulative earning curve for MAEs in the E-nside registry. The rate of MAEs remained substantially ($P = .101$) stable since the start of the experience. *IAE,* Intraoperative adverse event; *MAE,* major adverse event.

thee cases owing to one intraoperative death and two cases of E-nside maldeployment. Target artery-related technical success was 99% (late cohort, 99.5% vs early cohort, 98.6%; $P = 286$). Overall 30-day mortality was 7% (late cohort, 8% vs early cohort, 6%; $P = .346$) and MAE rate was 28% (late cohort, 27% vs early cohort, 29%; $P = .879$). Specific MAEs are reported in Table III; the stroke rate decreased from 4.6% in the early cohort to 0.9% in the late cohort ($P = .110$). All postoperative strokes occurred in patients with upper extremity access. There were no differences in the two cohorts in the rate of early reinterventions (late cohort, 8% vs early cohort, 12%; $P = .500$).

In elective cases, the intraprocedural complication rate was 17% (late cohort, 9% vs early cohort, 24%; $P = .031$), the MAE rate was 27% (late cohort, 23% vs early cohort, 47%; $P < .001$), and mortality was 7% (late cohort, 7% vs early cohort, 6%; $P = .792$). In urgent cases, the intraprocedural complication rate was 18% (late cohort, 15% vs early cohort, 22%; $P = .592$), the MAE rate was 32% (late cohort, 29% vs early cohort, 48%; $P = .101$), and mortality was 7% (late cohort, 8% vs early cohort, 4%; $P = .366$). Complex AAAs had a 13% IAE rate (late cohort, 8% vs early cohort, 18%; $P = .158$) and 25% MAE rate (late cohort, 21% vs early cohort, 28%; $P = .158$); extent I, II, or III TAAA had a 22% IAE rate (late cohort, 16% vs early cohort, 28%; $P = .100$) and 31% MAE rate (late cohort, 26% vs early cohort, 34%; $P = .002$). There were no significant changes in IAE and MAE rates in patients with a narrow paravisceral aorta ($P = .098$ and $P = .369$, respectively) or aortic dissection ($P = .451$ and $P = .197$, respectively).

The multivariate analysis for IAE and MAE is detailed in Supplementary Table I (online only). After adjustment for other clinical and anatomical characteristics, the late cohort maintained a lower incidence of IAE (odds ratio [OR], 0.41; 95% confidence interval [CI], 0.18-0.87; $P = .020$). After adjustment for urgent setting (OR, 1.61; 95% CI, 0.44-6.22; $P = .469$), anatomical extent classification (OR, 2.19; 95% CI, 1.01-5.06; $P = .041$), and other clinical and anatomical factors, the late cohort had also a significantly lower rate of MAEs (OR, 0.03; 95% CI, 0.01-0.26; $P < .001$). The occurrence of IAEs was not significantly associated with MAEs (OR, 1.30; 95% CI, 0.13-1.63; $P = .814$) in the multivariate analysis.

National (registry) trends. The analysis for IAEs showed that overall in the registry there was a trend toward an improvement ($P < .001$) since the start of the experience, which plateaued after the treatment of the first 48 cases (Fig 1, *A*). The unadjusted cumulative rate of MAEs was substantially stable ($P = .101$) in the registry (Fig 1, *B*).

Learning curves. The unadjusted analysis of the learning curve per center highlighted that there were no significant effects of increased experience on IAEs (Fig 2, *A*). However, there were two possible patterns (Fig 2, *B*). Six centers had a negative slope, showing a significant effect of the learning curve in decreasing the incidence of IAEs ($P = .045$); these were categorized as learning-dependent centers. Learning-dependent centers had a plateau of the performance after the treatment of first five cases. These centers were responsible of the treatment of 60 patients (28%) in the registry (with a mean volume of 10 patients per center), and were characterized by an overall higher rate of urgent cases (50% vs 39%; $P = .022$), and TAAAs rather than complex abdominal aortic aneurysms (63% vs 50%; $P = .048$), compared with the remaining 20 centers (defined as learning independent). The learning-independent centers accounted for the treatment of 155 patients (with a mean volume of 8 patients per center), and exhibited a flat learning curve, with a stable incidence of intraoperative complications along with increased case load ($P = .929$). The multivariate analysis for IAE is displayed in Supplementary Table II (online only). After adjustment for other clinical and anatomical characteristics, the

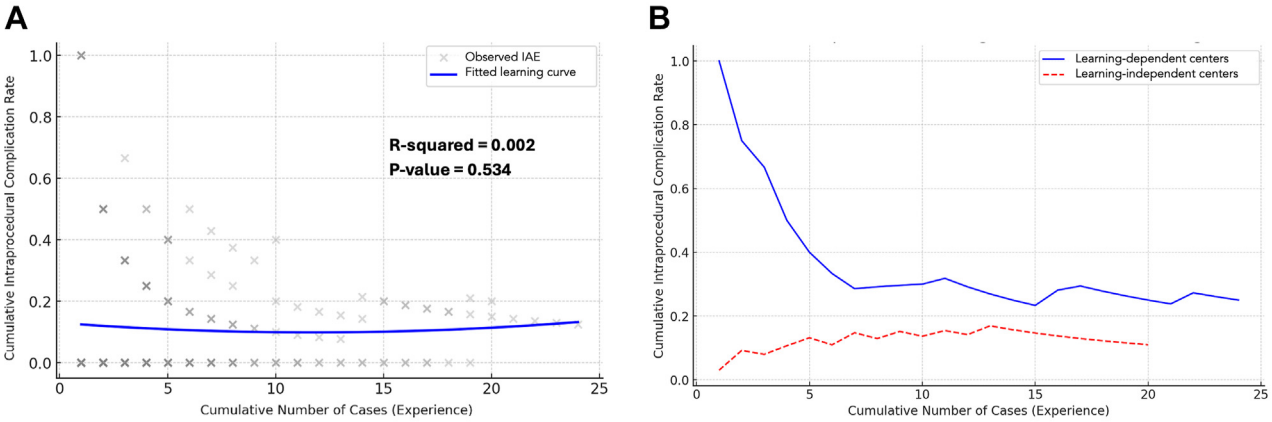

Fig 2. (A) Fitted (*blue line*) and observed (*gray crosses*) learning curve for intraoperative adverse events per each center using E-nside. Each cross indicates the observed IAE rate at each case number, for each center; the cross color (*from light grey to black*) reflects the number of centers overlapping under the same observed IAE rate. The center-specific rate of IAEs remained substantially ($P = .534$) stable since the start of the experience, but with a high variability across centers that was not explained by the model ($R^2 = .002$). **(B)** Learning curves for IAEs, stratified by learning-dependent centers (*blue line*) and learning-independent centers (*red line*). *IAE,* Intraoperative adverse event.

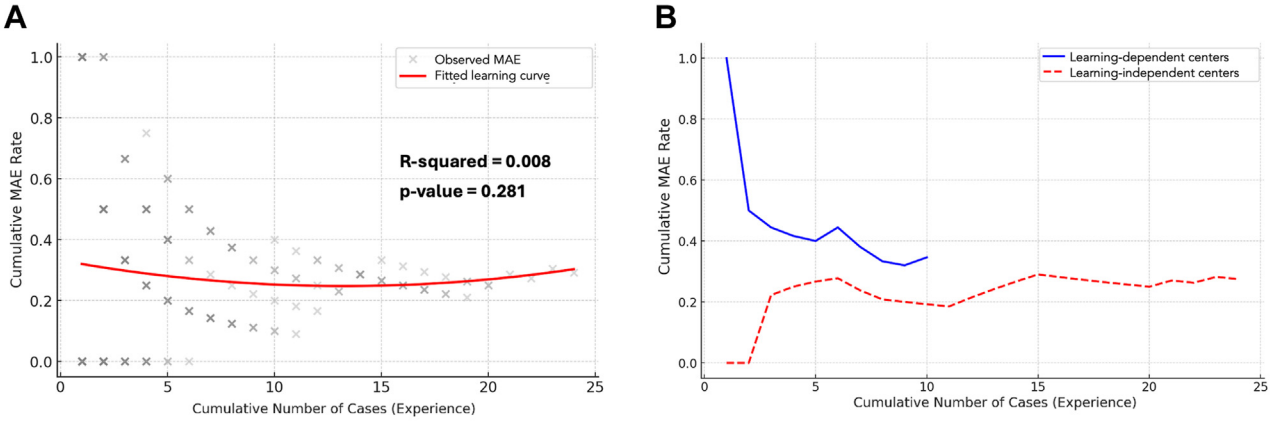

Fig 3. (A) Fitted (*red line*) and observed (*grey crosses*) learning curve for MAEs per each center using E-nside. Each cross indicates the observed MAE rate at each case number, for each center; the cross color (*from light gray to black*) reflects the number of centers overlapping under the same observed MAE rate. The center-specific rate of MAEs remained substantially ($P = .281$) stable since the start of the experience, but with a high variability across centers that was not explained by the model ($R^2 = .008$). **(B)** Learning curves for IAEs, stratified by learning-dependent centers (*blue line*) and learning-independent centers (*red line*). *IAE,* Intraoperative adverse event; *MAE,* major adverse event.

learning curve had a significant impact in reducing IAE (OR, 0.88; 95% CI, 0.21-0.99; $P = .040$).

Also for MAEs, there were learning dependent and learning independent centers (Fig 3). Four centers (accounting for the treatment of 34 patients) started from a high rate of MAEs and showed a significant effect of the learning curve ($P = .027$), with a plateau of the performance after the first five cases. These learning-dependent centers were characterized by a lower volume (mean, 7.5 vs 14.2; $P = .080$) compared with the learning-independent centers. The multivariate analysis for MAEs is detailed in Supplementary Table II (online only). After adjustment for relevant clinical and anatomical factors, the learning curve and center volume were not independently associated with MAEs (OR, 0.96; 95% CI, 0.99-3.86; $P = 538$).

Supplementary Table III (online only) provides detailed data on early cohort vs late cohort outcomes stratified by centers' case volume, classified into quartiles.

Two-year outcomes. The median follow-up duration was 28 months (late cohort, 30 months vs early cohort, 13 months; $P < .001$). Survival at 2 years was 85% (95% CI, 77-95) in the late cohort and 94% (95% CI, 89-99) in the

early cohort ($P = .030$), with a freedom from aortic-related mortality of 98% (95% CI, 95-100) in the late cohort and 99% (95% CI, 97-100) in the early cohort ($P = .200$). Freedom from graft instability was 97% (95% CI, 94-100) in the early cohort and 100% in the late cohort ($P = 1.00$), owing to two cases of proximal sealing failure within 1 year in the early cohort.

The 2-year freedom from target vessel instability was 98% (95% CI, 94-99) vs 94% (95% CI, 92-97; $P = .090$), and primary patency was 97% (95% CI, 95-100) vs 97% (95% CI, 95-98; $P = .321$) in the late cohort and early cohort respectively.

DISCUSSION

Our study used data from a multicenter national registry of the E-nside device to analyze the impact of the learning curve on patients' outcomes. The INBREED represents a unique collaboration, since it involves all centers using E-nside on a national level, and can be used to assess both national and specific centers trends in the use of E-nside. Trends in patient selection, procedural data, and outcomes were analyzed.

Regarding patient selection, an increased use of the E-nside was observed in the treatment of chronic dissections (late cohort, 15% vs early cohort, 6%; $P = .025$) and complex pathologies with a narrow paraviceral aortic lumen (late cohort, 30%, early cohort, 18%; $P = .037$). The increased use of E-nside in these anatomical setting represents the attempt to overcome the anatomical problem of a narrow (true) lumen, which may be a risk factors for target vessel instability in case an outer branches configuration is used.[15] It also reflects the effort to better select the patients that may benefit from the use of E-nside, compared with other patient-specific and off-the-shelf options. According to this trend, the presence of a narrow lumen/true lumen has become one of the main reasons for selecting this device, accounting for 30% of cases in the late cohort.

The changes in procedural data were mainly related to the access for bridging stent deployment and bridging stent choice. There was an increase in the use of a total transfemoral approach, following the general trend in BEVAR to limit upper extremity access to decrease the risk of perioperative stroke.[16-19] Notably, the rate of stroke decreased from 5% in the early cohort to 1% in the late cohort as a part of this process. However, the risk of stroke during E-nside deployment likely does not derive from the use of an arm approach by itself, but from possible technical pitfalls in obtaining the access and snaring the guidewires, with potential excessive manipulation of the aortic arch. A direct consequence of the transfemoral approach is the preferential use of a balloon-expandable stent, which can be deployed easily through a steerable sheath. Interestingly, the increased use of reinforcement stents does not derive from the observation of branches complication during the early phase, and should be interpreted as part of the overall evolution of the practice pattern in bridging stent use. In fact, flexible balloon-expandable stents are usually favored to take advantage of transfemoral access, at the cost of using a bridging stent with a limited resistance to compression that, therefore, is more often reinforced. Also, the more extended E-nside use in patients with a narrow paravisceral lumen is another reason for the more frequent bridging stent reinforcement. The shift in the bridging stent pattern did not influence target vessel instability, as previously reported, but longer follow-up is still needed to clarify this aspect.[19]

IAEs were strongly decreased by the increase in the experience, both on a national and a center level. This result is related to the improvement in the knowledge and confidence in the use of the specific device, as well as the learning of the adjustments and backups that may be useful in the operating room. Primary progress involved a decreased in device-related complications, which are due directly to initial unfamiliarity with the device. Vascular-related complications warrant special attention, because these are the most frequent severe adverse events associated with the use of E-nside.[6] The decrease in access-related complications was primarily achieved through improved patient selection, increased use of a surgical access, and the routine use of a 24F sheath to advance and deploy the endograft. This approach helps to prevent iliac access rupture and cranial migration of the device during deployment, which are potential adverse events particularly noted in the early cohort. The learning curve for preventing IAEs may be more challenging in complex cases, as centers with higher rates of TAAA and urgent treatments demonstrated significant impact of the level of experience on IAEs. In contrast, the number of cases needed to achieve a stabilization of the outcomes was low ($n = 5$), and the learning curve for IAEs was flat for most centers, showing that the device can be safely used from the beginning in centers with an average experience in complex endovascular aortic repair.

Despite the significant decrease in IAEs, the overall incidence of death and MAEs remained substantially stable. However, a strong impact of the learning curve on MAEs was observed in a minority of learning-dependent centers, represented by four low-volume hospitals. The strong learning-dependent outcomes reported in these centers led to the result of the multivariate analysis, describing a lower risk of MAEs (OR, 0.03; $P < .001$) in the late cohort, after adjustment for anatomical complexity, urgency, and patient comorbidities. Nevertheless, the learning curve for MAEs was flat for the large majority of centers, suggesting that other factors, such as patient comorbidity and the complexity of the procedure, are the most important determinants of MAEs. In fact, differently from IAEs, MAEs are less related to technical aspects of the procedure and are more associated with

the overall clinical and surgical management of the patient, as well as the baseline patients characteristics. Interestingly, IAEs were not significantly associated with MAEs (OR, 1.10; $P = .927$). This is likely because the ability to successfully rescue IAEs is crucial in preventing fatalities and major complications, a feature that has been documented as superior in high-volume centers.[20] Nevertheless, data on total volume of complex endovascular repairs were unavailable, and it is unclear whether these truly were low-volume centers or if the high initial MAE rates led to discontinuing E-nside use.

An important aspect in interpreting the study's results is that each center identified a local expert endovascular specialist who was present at all the procedures; for this reason, the learning curve and change in practice patter observed per center essentially reflects also the operators' experience. However, we believe that the center's experience, rather than the single operator's experience, might have a greater impact on the outcomes and practice patterns, because it involves a broader range of expertise, resources, and collaborative efforts of several specialists (eg, emergency physician, vascular surgeon, anesthesiology, scrub nurse, radiology technician) who contribute to procedural success and patient care.

Overall the results of this study underline that there has been a practice shift in the use of the E-nside, with an increase in the treatment of patients with aortic dissections and a narrow paravisceral aorta. From the technical standpoint, a more frequent use of a total transfemoral approach, together with balloon expandable bridging stents, was observed as a result of a more general practice change in BEVAR. A fast learning curve can lead to decrease of IAEs within the first five cases, and a target rate of mortality and MAEs can be achieve from the beginning in most centers with a standard level of complex endovascular practice. This information may help to explain the outcomes obtained with this device and be useful to centers that initiate programs involving the use of E-nside for the treatment of TAAA and complex abdominal aortic pathologies.

This study carried significant limitations. The number of patients treated per center was limited, and a higher case load per center would be necessary to assess the learning curve further. Consequently, the results provide an effective description of early and late experiences, but may not fully represent a comprehensive learning curve. The follow-up results from the two cohorts of patients had a different follow-up duration, that was inherent to the group definition, and might have biased the mid-term results. Also, the number of patients treated by the E-nside does not necessarily reflect the overall experience of the center in complex endovascular aortic repair, that may be a great determinant of the clinical outcome. At the same time, although there may be inevitable differences in baseline experience among centers, all included hospitals are vascular surgery referral centers with experience in complex endovascular aortic repair, where a BEVAR program was already initiated. A baseline complex endovascular experience in all procedures was guaranteed also by the presence of a local identified endovascular specialist in all surgeries. Therefore the results of the study more strongly reflects the specific learning curve with the device, rather than a general learning curve in BEVAR.

CONCLUSIONS

This study demonstrates that increased experience with the E-nside endograft in BEVAR led to a shift in patient selection, procedural techniques and materials, including extension of treatment to patients with a narrow paravisceral aorta, and a more frequent use of a total transfemoral approach with the use of balloon-expandable bridging stents. The study also shows that increased experience allowed a significant reduction in IAEs, in particular after the treatment of the first five cases. In contrast, the rates of mortality, MAEs, and mid-term complications were mainly independent of specific experience with E-nside, achieving consistent outcomes from the start in most centers.

AUTHOR CONTRIBUTIONS

Conception and design: FS, MP, MA
Analysis and interpretation: FS, MP, MA
Data collection: FS, MP, GP, EG, YT, MO, SR, AB, GP, AG, WM, MA, GS
Writing the article: FS
Critical revision of the article: FS, MP, GP, EG, YT, MO, SR, AB, GP, AG, WM, MA, GS
Final approval of the article: FS, MP, GP, EG, YT, MO, SR, AB, GP, AG, WM, MA, GS
Statistical analysis: FS
Obtained funding: Not applicable
Overall responsibility: FS

FUNDING

None.

DISCLOSURES

M.P. reports a consulting agreement with Artivion; all consulting fees are paid to the Department of Cardiac Thoracic Vascular Sciences and Public Health, University of Padua. G.S. reports a consulting agreement with Artivion. G.P. reports a consulting agreement with Artivion. M.A. reports a consulting agreement with Artivion; all consulting fees are paid to the Department of Cardiac Thoracic Vascular Sciences and Public Health, University of Padua.

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Submitted Apr 1, 2025; accepted May 20, 2025.

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

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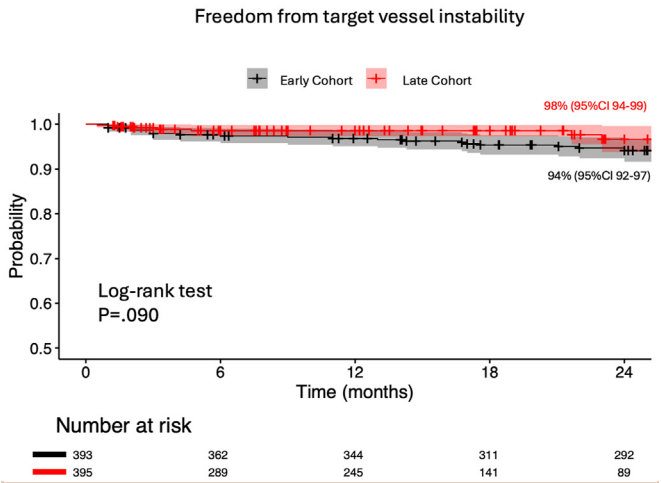

Supplementary Fig (online only). Kaplan-Meier estimates of freedom from target vessel instability in the early and late cohorts treated by E-nside endograft in the registry. Standard error of <10%. *CI*, Confidence interval.

Supplementary Table I (online only). Multivariate analysis evaluating the effect early vs late cohort treatment on intraprocedural adverse events (*IAEs*) and major adverse events (*MAEs*)

Variable	OR	95% CI	*P* value
IAE			
Late cohort	0.41	0.18-0.87	.020[a]
Center volume[b]	1.00	0.95-1.05	.815
Urgent setting	1.18	0.53-2.51	.693
TAAA	2.21	1.00-5.14	.046[a]
Narrow paravisceral lumen	1.27	0.53-2.89	.576
Chronic dissection	1.07	0.15-1.19	.946
Age	1.03	0.98-1.08	.181
Male sex	0.67	0.30-1.48	.319
MAE			
Late cohort	0.03	0.01-0.26	<.001[a]
Center volume[b]	1.08	0.98-1.20	.093
IAE	1.30	0.13-1.63	.814
Urgent setting	1.61	0.44-6.22	.469
TAAA	2.19	1.01-5.06	.041[a]
Narrow paravisceral lumen	3.04	0.47-3.49	.254
Chronic dissection	1.11	0.14-1.41	.876
Age	0.97	0.88-1.05	.489
Male sex	0.87	0.15-4.23	.869

CI, Confidence interval; *OR*, odds ratio; *TAAA*, thoracoabdominal aortic aneurysm.
[a]Statistically significant.
[b]Specific volume of E-nside repair.

Supplementary Table II (online only). Multivariate analysis evaluating the adjusted effect of the learning curve (case number) on intraprocedural adverse events (*IAEs*) and major adverse events (*MAEs*)

Variable	OR	95% CI	*P* value
IAE			
Case number	0.88	0.21-0.99	.040[a]
Urgent setting	1.16	0.55-2.46	.680
TAAA	1.80	0.86-3.87	.114
Narrow paravisceral lumen	1.21	0.51-2.67	.648
Chronic dissection	0.20	0.02-1.09	.092
Age	1.01	0.97-1.08	.456
Male sex	0.70	0.33-1.51	.299
MAE			
Case number	0.57	0.99-3.86	.538
IAE	1.10	0.19-1.29	.927
Urgent setting	0.98	0.31-3.14	.979
TAAA	0.47	0.13-1.55	.223
Narrow paravisceral lumen	2.48	0.47-24.8	.297
Chronic dissection	1.11	0.14-1.41	.361
Age	0.96	0.88-1.03	.308

CI, Confidence interval; *OR*, odds ratio; *TAAA*, thoracoabdominal aortic aneurysm.
[a]Statistically significant.

Supplementary Table III (online only). Comparison of the early cohort vs the late cohort stratified by centers' case volume, classified into quartiles

	Q1			Q2			Q3			Q4		
Variable	Early cohort (n = 33)	Late cohort (n = 21)	*P* value	Early cohort (n = 22)	Late cohort (n = 32)	*P* value	Early cohort (n = 29)	Late cohort (n = 25)	*P* value	Early cohort (n = 24)	Late cohort (n = 29)	*P* value
IAE	7 (21.9)	2 (9.5)	.342	3 (13.6)	4 (13.3)	.975	8 (27.6)	3 (12.0)	.156	7 (30.4)	3 (11.1)	.089
MAE	10 (30)	4 (19)	.023	8 (36)	11 (34)	.108	8 (28)	6 (24)	.170	5 (21)	8 (28)	.103
Death	2 (6.1)	0 (0.0)	.287	0 (0.0)	1 (3.3)	.409	1 (3.4)	4 (16.7)	.101	3 (12.5)	4 (14.8)	.811
EBL>1000 mL	3 (9.7)	1 (4.7)	.611	0 (0.0)	3 (10.0)	.145	1 (5.0)	0 (0.0)	.268	0 (0)	0 (0)	1.00
Myocardial infarction	0 (0)	0 (0)	1.00	0 (0.0)	1 (3.3)	.409	1 (3.4)	0 (0.0)	.369	0 (0.0)	2 (7.4)	.183
Respiratory failure	1 (3.2)	0 (0.0)	.441	2 (10.0)	2 (6.7)	.670	1 (3.4)	3 (13.6)	.180	1 (4.3)	3 (11.5)	.359
Postoperative stroke	2 (6.5)	0 (0.0)	.271	1 (5.0)	1 (3.3)	.768	2 (6.9)	0 (0.0)	.199	0 (0)	0 (0)	1.00
SCI			.257			.711			.199			.278
No	25 (80.6)	16 (88.9)		18 (90.0)	26 (86.7)		27 (93.1)	23 (100.0)		23 (100.0)	22 (84.6)	
Sensory deficit	4 (12.9)	0 (0.0)		0 (0.0)	1 (3.3)		0 (0)	0 (0)		0 (0.0)	1 (3.8)	
Motor not able to ambulate	2 (6.5)	2 (9.5)		2 (10.0)	3 (10.0)		2 (6.9)	0 (0.0)		0 (0.0)	2 (7.7)	
AKI	3 (9.7)	2 (9.5)	.873	4 (20.0)	3 (10.0)	.318	3 (10.3)	0 (0.0)	.112	2 (8.7)	2 (7.4)	.867
Early reintervention	2 (6.2)	4 (22.2)	.595	2 (9.1)	3 (10.0)	.046[a]	4 (13.8)	1 (4.3)	.251	1 (4.3)	4 (14.8)	
Main endograft complication	1 (3)	1 (4.7)	.921	0 (0.0)	0 (0)	1.00	0 (0)	0 (0)	1.00	0 (0.0)	0 (0)	1.00
Target vessel complication	(0.0)	1 (4.7)	.844	2 (9.1)	2 (6.2)	.685	1 (25.0)	0 (0.0)	.867	1 (4.3)	2 (7.4)	.451

AKI, Acute kidney injury; *EBL*, estimated blood loss; *IAE*, intraoperative adverse event; *MAE*, major adverse event; *SCI*, spinal cord ischemia; *TAAA*, thoracoabdominal aortic aneurysm.
Values are number (%).
[a]Statistically significant.