

Clinical outcomes of Endurant II stent-graft for infrarenal aortic aneurysm repair: comparison of on-label versus off-label use

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PURPOSE

We aimed to compare the outcomes of the Endurant II (Medtronic) stent-graft used under instructions for use versus off-label in high-risk patients considered unfit for conventional surgery.

METHODS

Data from patients treated with the Endurant II stent-graft between December 2012 and March 2015 were retrospectively analyzed. Sixty-four patients were included. Patients were assigned to group A if treated under instructions for use (n=34, 53%) and to group B if treated off-label (n=30, 47%). Outcome measures included perioperative mortality and morbidity, survival, freedom from reintervention, endoleak incidence, in-hospital length of stay, and mean stent-graft component used. Mean follow-up was 22.61±12 months (median, 21.06 months; range, 0–43 months).

RESULTS

One perioperative mortality (1.6%) and one perioperative complication (1.6%) occurred in group B. At two months follow-up, one iliac limb occlusion (1.6%) occurred in group A. No type I/III endoleaks were recorded. A type II endoleak was identified in three cases (4.7%). Overall survival at three years was 89% (97% for group A, 82% for group B; $P = 0.428$). Reintervention-free survival at three years was 97% for both groups ($P = 0.991$). A longer in-hospital stay was observed in group B ($P = 0.012$).

CONCLUSION

The Endurant II (Medtronic) new generation device was safe in off-label setting at mid-term follow-up. The off-label use of the Endurant II (Medtronic) is justified in patients considered unfit for conventional surgery. Larger studies are required in this subgroup of patients.

The introduction of endovascular aneurysm repair (EVAR) (1) has revolutionized the treatment of the abdominal aortic aneurysm (AAA), becoming the first-line approach in most centers. Since the initial experience with EVAR, the need to improve endovascular materials has arisen in order to increase the EVAR feasibility and to expand its indications (2). Moreover, the increased ability with the endovascular approach pushed many vascular specialists to use EVAR off-label, outside the instructions for use (IFU), especially in high-risk patients who are ineligible for conventional surgery (3, 4). Herein we report our experience with the Endurant II (Medtronic) stent-graft used under IFU and off-label in high-risk patients considered unsuitable for conventional surgery.

Methods

Single-center data of patients who underwent EVAR from December 2012 to March 2015 were analyzed retrospectively. All data, including demographics, clinical and diagnostic preoperative assessments, intraoperative features, early (30-day) and late follow-up results, were prospectively collected and inserted into standardized piloted forms. Informed consent was obtained from all patients for the procedure itself, anonymous data collection, and analysis.

Patients treated by standard EVAR with the Endurant II (Medtronic) stent-graft were screened and included in the study. Inclusion criteria consisted of infrarenal aorto-iliac pathology treated by a standard combination of Endurant II (Medtronic) stent-graft implantation (including a bifurcated main body, a contralateral limb, and eventually limb extensions).

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Exclusion criteria consisted of additional tools to preserve renal and/or visceral patency; combined use of thoracic and abdominal devices; combined use of Endurant II (Medtronic) component with other fabric stent-graft; and nonelective repair using EVAR (for symptomatic or ruptured AAA).

A total of 64 patients with a mean age of 75.5 ± 8 years (range, 60–93 years) were included. Patients were divided into two groups according to Endurant II (Medtronic) manufacturer's IFU (on-label vs off-label). Group A included 34 patients (53%) treated by on-label EVAR according to IFU (adequate iliac/femoral access that is compatible with vascular access techniques, devices and/or accessories; proximal neck length of ≥ 10 mm; infrarenal neck angulation of $\leq 60^\circ$; distal fixation length of ≥ 15 mm; aortic neck diameters with a range of 19 to 32 mm; iliac diameters with a range of 8 to 25 mm; and morphology suitable for aneurysm repair). Group B included 30 patients (47%) presenting at least one characteristic outside the IFU. Only patients considered at high-risk for conventional surgery were treated by off-label EVAR (5). The minimum anatomical requirements for off-label EVAR in group B were aor-



Figure 1. a, b. Intraoperative angiogram of an 80-year-old man treated with off-label use. Angiogram (a) shows a 7 mm neck length and a positioned (undeployed) stent-graft. The left renal artery is lower than the right. The arrow shows the stent-graft positioned just below the left renal artery. Final angiogram (b) shows complete proximal sealing and regular patency of the lowest renal artery (left). The stent-graft is deployed just below the left renal artery (arrow).

Main points

- Endovascular aneurysm repair (EVAR) is the first line approach in abdominal aortic aneurysm (AAA) treatment and the need to improve endovascular materials has arisen in order to increase the EVAR feasibility and to expand its indications.
- Anatomic limitations of EVAR have been historically identified as hostile neck, iliac tortuosity, and access.
- The increased ability with this tool have pushed many vascular specialists to use EVAR off-label, outside the instructions for use, especially in high-risk patients with AAA considered unfit for conventional surgery.
- In this study, patients treated off-label presented a significantly larger aneurysm neck diameter and aneurysm sac diameter; a significantly shorter neck length, a higher proximal infrarenal neck angulation and a higher incidence of conical neck.
- No differences were detected in mortality, morbidity, adjunctive intraoperative maneuvers, type Ia endoleak, three-year survival, and three-year freedom from reintervention rates.
- The off-label use of the Endurant (Medtronic) stent-graft is an additional tool in the treatment of patients presenting with AAA that are considered unsuitable for conventional surgery.

tic neck length ≥ 7 mm; maximum neck diameter ≤ 36 mm; and neck angulation $\leq 90^\circ$ (Fig. 1). All the preoperative anatomic assessments were performed on computed tomography angiography (CTA). CTAs were analyzed manually and with Endosize software (Therenva); discrepancies were solved through discussion.

Primary outcomes analyzed were perioperative mortality and morbidity. Secondary outcomes were EVAR limb occlusion, survival, freedom from reintervention, endoleak incidence, in-hospital length of stay, and the mean number of stent-graft components used. Procedure duration, contrast medium usage, and fluoroscopy time were also analyzed.

The follow-up protocol consisted of CTA at 1, 6, 12 months and yearly thereafter for both groups. In case of CTA contraindication during the follow-up, unenhanced CT and duplex ultrasonography were combined (eventually with contrast enhancement).

Statistical analysis

Data analysis was performed using SPSS 16.0 (SSPS Inc.). Statistical significance was assigned at two-sided $P < 0.05$. Baseline characteristic differences between groups A and B were assessed with one-way analysis of variance. Differences between the groups were assessed using the t test for continuous variables and the chi-square test for categorical variables. Kaplan-Meier curves were used to estimate survival and freedom from reinterventions; standard error exceeding 10% was reported. Differences in curves were assessed using the Brelow test.

Results

At baseline, group B had a significantly higher prevalence of coronary artery disease (15% vs. 10%, $P = 0.042$) and chronic pulmonary obstructive disease (46% vs. 27%, $P = 0.050$) (Table 1).

Table 1. Comorbidities and risk factors of patients treated by on-label (group A) and off-label (group B) use of Endurant

	Group A	Group B	<i>P</i>
No. of patients	34 (53)	30 (47)	
Age (years), mean	75.1	76.1	0.613
Hypertension	28 (82)	28 (93)	0.254
Diabetes	7 (21)	4 (13)	0.518
Lipid disorder	13 (38)	11 (37)	0.993
CAD	10 (29)	15 (50)	0.042
CVD	5 (15)	9 (30)	0.224
PAD	4 (12)	1 (3)	0.357
COPD	9 (27)	14 (46)	0.050
Smoke	18 (53)	21 (70)	0.219
RFI	3 (9)	5 (17)	0.448
Malignancy	3 (9)	1 (3)	0.609

Data are presented as n (%) unless otherwise noted.
CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease; COPD, chronic obstructive pulmonary disease; RFI, renal function impairment.

Table 2. Preoperative anatomic findings of patients treated by on-label (group A) and off-label (group B) use of Endurant

	Group A n=34	Group B n=30	<i>P</i>
Neck diameter at lowest renal artery (mm)	23.8±3 (18–28)	24±5 (16–33)	0.121
Neck diameter at 10 mm below or above the aneurysm sac (mm)	29.6±4 (18–28)	30.9±6 (16–36)	0.024
Aneurysm sac maximal diameter (mm)	60.1±15 (50–120)	65.8±21 (52–110)	0.030
Aortic bifurcation diameter (mm)	32±9 (21–63)	33.3±10 (18–64)	0.550
Neck length (mm)	23.4±4 (12–26)	18±6 (7–22)	<0.001
Proximal infrarenal neck angulation (°)	28.4±12 (4–60)	38.8±20 (15–85)	0.006
Conical infrarenal neck, n (%)	16 (47.1)	23 (76.7)	0.054

Data are presented as mean±standard deviation (range) unless otherwise noted.

Preoperative anatomic findings showed a significantly larger aneurysm neck diameter at 10 mm below the lowest renal artery (or above aneurysm sac origin) in group B (30.6±6 mm vs. 29.6±4 mm, *P* = 0.024). Aneurysm sac diameter was significantly higher in group B (65.8±21 mm vs. 60.1±15 mm, *P* = 0.030). Neck length was significantly shorter in group B (18±6 mm vs. 23.4±4 mm, *P* < 0.001) and the proximal infrarenal neck angulation was significantly higher in group B (38.8°±20° vs. 28.4°±12°, *P* = 0.006). A higher percentage of patients in group B presented a conical neck (76.7% vs. 47.1%, *P* = 0.054) (Table 2).

Perioperative mortality was registered in one patient (1.6%) in group B. This patient was transferred to the ward after an uncomplicated EVAR procedure. After three hours he suffered from acute chest and abdomi-

nal pain and suddenly died. No autopsy was available for this patient.

No adjunctive intraoperative maneuvers were required in groups A or B. A perioperative complication requiring reintervention occurred in one patient (1.6%) in group B. In this case, a right access surgical revision was required for a lymphatic fistula. Iliac limb occlusion occurred at two months in a patient from group A due to iliac stent-graft kinking; this was managed with femoro-femoral crossover.

At a mean follow-up of 22.61±12 months (median, 21.06 months; range, 0–43 months), neither type I nor type III endoleaks were recorded postoperatively or during the follow-up. A type II endoleak occurred in three patients (4.7%): one patient in group A and two patients in group B (*P* = 0.486).

The three-year overall survival was 89% with no statistically significant difference between the two groups (97% for group A vs. 83% for group B; *P* = 0.428) (Fig. 2). Overall, the estimated intervention-free survival was 97% with no statistically significant differences between the groups (*P* = 0.991) (Fig. 3). During the follow-up, four deaths occurred. The cause of death was not related to the aortic pathology in these patients (malignancy in three patients and cerebral stroke in one).

Mean length of stay in the hospital was 6±5 days (median 6 days; range, 3–24 days). Length of stay was significantly longer in group B compared with group A (8±6 days, median 7 days, range 3–18 days vs. 5±4 days, median 6 days, range 3–13 days; *P* = 0.012).

Mean number of component graft used per patient was 2.5±2 (range, 2–4) in group A and 2.9±3 (range, 2–5) in group B (*P* = 0.118). No cuff extensions were employed in either group.

Mean procedure duration for groups A and B was 163±37 min and 189±69 min, respectively (*P* = 0.033); mean contrast medium usage was 95±18 mL and 118±24 mL, respectively (*P* = 0.169); fluoroscopy time was 21±7 min and 27±9 min, respectively (*P* = 0.044).

Discussion

In our experience with the Endurant II (Medtronic) stent-graft used to treat AAAs under IFU vs. off-label, no difference was observed in perioperative mortality and morbidity. During the follow-up, no type I/III endoleaks were registered in either group. At three-year follow-up, no significant differences in terms of survival and intervention-free survival were recorded. A significantly longer in-hospital length of stay, mean procedure duration and fluoroscopy time were reported for patients treated off-label.

The Endurant (Medtronic) stent-graft was introduced in 2008 with the aim to overcome anatomic limitations of concurrent devices and expand EVAR indications (6), since patients presenting with unfavorable anatomy had more-comorbidity and thus were at higher risk for conventional surgery (7, 8).

Anatomic limitations of EVAR have been historically identified as hostile neck, iliac tortuosity, and difficult access. While the iliac tortuosity and access can be overcome using special techniques (e.g., iliac conduit), hostile neck still remains as the most relevant issue with 20% of AAA presenting with inadequate neck for EVAR procedures (9, 10).

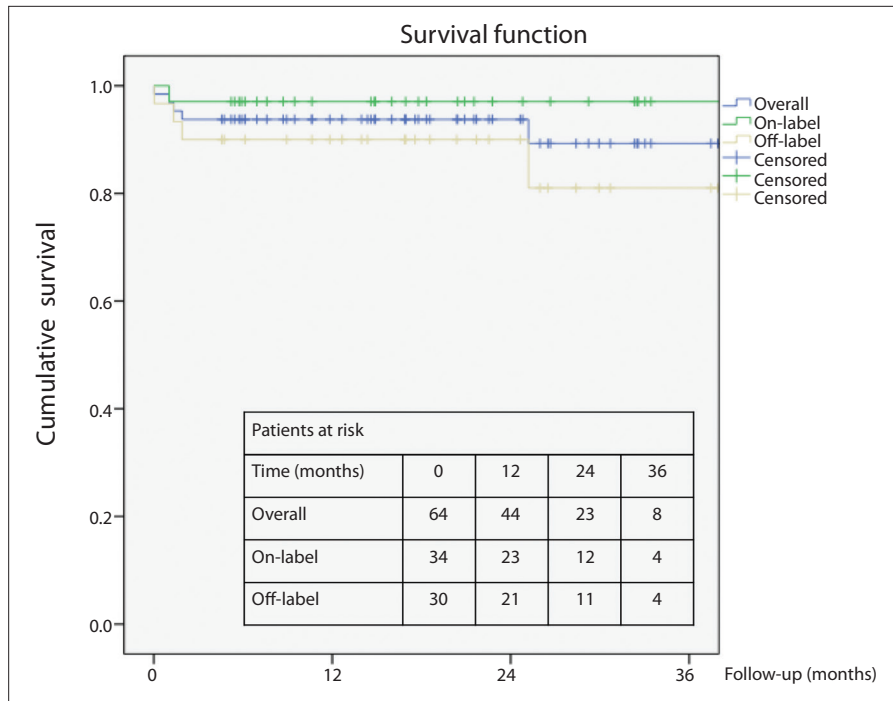


Figure 2. Estimated survival function. Standard error (SE) exceeds 10% at 24 months for overall curve; SE does not exceed 10% at 36 months for on-label treatment; SE exceeds 10% at 2 months for off-label use. No significant differences were observed between the curves ($P = 0.428$).

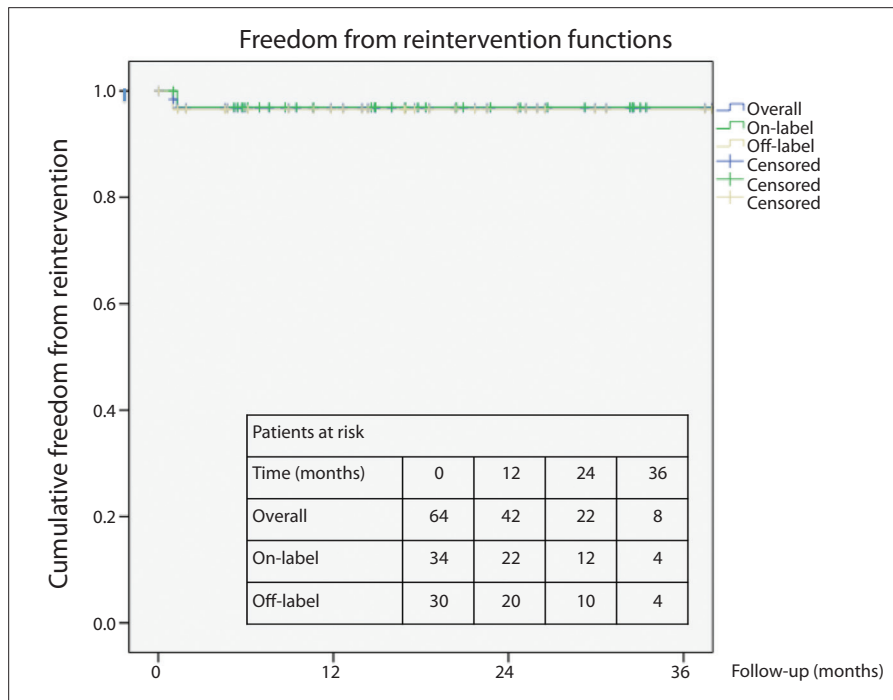


Figure 3. Estimated freedom from reintervention. SE does not exceed 10% at 36 months for all curves. No significant differences were observed between the curves ($P = 0.991$).

EVAR outcomes in patients presenting with hostile neck show higher complication rates such as type Ia endoleak. Thus, most authors suggest cautious off-label use of stent-graft, only in high-risk surgical patients (4). Despite the advocated caution

in treating patients outside the manufacturer's IFU, almost one-third of patients are currently treated off-label (11). Results from the Endurant Stent Graft Natural Selection Global Postmarket Registry, showed that intra-operative hostile neck (length and

thrombus/calcification) was related to a higher incidence of adverse events compared with adequate neck (12).

In a recent meta-analysis of 1559 patients, Antoniou et al. (3) reported that there is no high-level evidence to demonstrate the off-label use of stent-graft as safe. Thus they recommended a cautious use of off-label EVAR and only in high-risk patients. The study outcomes showed a significantly higher incidence of adjunctive maneuvers, perioperative morbidity, endoleak incidence and mortality at one-year in patients treated with off-label EVAR. No significant differences were reported in technical success, perioperative mortality, perioperative reinterventions, perioperative endoleaks, and one-year reintervention rate. As argued by the same authors, the higher incidence of type Ia endoleak was not followed by a reintervention and this could explain the higher one-year mortality. However, this meta-analysis included studies with old generation devices and different fabrics.

Recent studies focused on the feasibility and the outcomes of Endurant II (Medtronic) used off-label. These studies also reported a higher incidence of type Ia endoleak and iliac limb occlusion for off-label stent use compared with patients treated under IFU (13–15).

Fenestrated and branched EVAR (F/BEVAR) (16, 17) and chimney and periscope EVAR (ch-EVAR) (18, 19) have been introduced to overcome these anatomic limitations with good results even in emergent settings (20). Moreover, ch-EVAR can be employed with good results in the treatment of type Ia endoleak after standard EVAR (21). However, these tools require high endovascular skills and have a higher cost. In our experience, we registered one case of perioperative mortality among patients treated with off-label EVAR; in this case no amenable cause of death was recognized and autopsy was not available. In our study we did not encounter any type Ia endoleaks, but type II endoleak occurred in three cases. It can be proposed that the absence of type I endoleak (especially in group B) can be justified by the limited patient sample. However, the new generation device that we employed could also play a role in the reduced type Ia endoleak incidence in patients treated with off-label EVAR. A longer mean procedure duration and fluoroscopy time was reported in patients treated off-label. We can speculate that the need for a more accurate projection before the

stent-graft deployment (shorter neck and higher neck angulation) could be related to these outcomes. Despite this, contrast medium usage was not significantly greater in patients treated off-label.

Retrospective analysis, small sample size and lack of randomization represent major limitations of this study. However, the use of new generation device yields supportive evidence for off-label use in patients considered unfit for conventional surgery.

In conclusion, the Endurant II (Medtronic) new generation device was safe in our single-center experience even when employed in an off-label setting at mid-term follow-up. No differences in outcomes were evident between the group treated under IFU and the group treated off-label. The off-label use the Endurant (Medtronic) stent-graft represents an additional tool in the treatment of patients presenting with AAA that are considered unfit for conventional surgery. More extensive experience is required in this subgroup of patients.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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