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# Outcomes of thoracic endovascular aortic repair in thoracic aortic aneurysm and penetrating aortic ulcer using the Conformable Gore TAG within and outside the instructions for use

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## Abstract

**Objective:** To describe the outcome of thoracic endovascular aortic repair (TEVAR) in thoracic aortic aneurysm and penetrating aortic ulcer with respect to instructions for use status.

**Methods:** Between October 2009 and September 2017, a total of 532 patients underwent TEVAR; of which 195 have been treated using the Conformable GORE® TAG® thoracic endoprosthesis (CTAG). Fifty-six patients of this cohort underwent TEVAR for thoracic aortic aneurysm/penetrating aortic ulcer using the CTAG. Depending on the preoperative computed tomography angiography findings, patients were classified as inside or outside the device's instructions for use. All inside instruction for use patients underwent postoperative reclassification regarding the instructions for use status. Study endpoints included TEVAR-related reintervention, exclusion of the pathology (endoleak type I/III), TEVAR-related mortality, and graft-related serious adverse events. The median duration of follow-up was 29.7 months (range: 0–109.4 months).

**Results:** Of the 56 patients, 17 were primarily classified as outside instruction for use, and in additional 13 patients, TEVAR was performed outside instruction for use, leading to 30 outside instruction for use patients (53.6%). Twenty-six patients (46.4%) were treated inside instruction for use. Reintervention-free survival was lower in outside instruction for use patients ($P = 0.016$) with a hazard ratio of 9.74 (confidence interval 1.2–80.2; $P = 0.034$) for TEVAR-related reintervention. With respect to endoleak type I/III, relevant difference was detected between inside/outside instruction for use status ($P = 0.012$). The serious adverse event rate was 30.4%, mainly in outside instruction for use patients ($P = 0.004$). Logistic regression analysis indicated an association between graft-related serious adverse event/instructions for use status (odds ratio 6.11; confidence interval 1.6–30.06; $P = 0.012$). In-hospital death was seen more frequently in outside instruction for use patients ($P = 0.12$) as was procedure-related death (log-rank test: $P = 0.21$).

**Conclusion:** TEVAR for thoracic aortic aneurysm/penetrating aortic ulcer is frequently performed outside instruction for use despite preoperative inside instruction for use eligibility, leading to important consequences for technical/clinical outcome. Instructions for use adherence in TEVAR should be of interest for further large-scale studies.

**Keywords**

TEVAR, instructions for use, thoracic aortic aneurysm, penetrating aortic ulcer, reintervention, outcome

## Introduction

The anatomical and clinical conditions in which an aortic stent graft may be used are summarized in the device's instruction for use (IFU). The IFU is the product of extensive engineering studies and long-term

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preclinical and clinical trials, serving as an interface between the endograft and the treating physician to facilitate planning, sizing, and implantation. Adherence to the IFU maximizes stent graft performance in order to achieve the greatest possible safety, reliability, and durability.

Over recent years, endovascular repair of abdominal aortic aneurysms (EVAR) has progressively expanded to more complex anatomies, often requiring implantation outside IFU (oIFU).[1] Whilst some researchers have reported no major differences between treatment oIFU and inside the IFU (iIFU) with respect to patient outcome,[2,3] others have described higher rates of type I endoleaks, representing treatment failure.[4–6] Furthermore, increased rates of reintervention (RI) have been described in oIFU–EVAR[7]. Therefore, most authors advocate cautious use of oIFU–EVAR and generally reserve it for high-risk patients.[8,9] In contrast to EVAR, the results of oIFU application of stent grafts in thoracic endovascular aortic repair (TEVAR) have hardly been investigated.[10,11] The aim of this study was therefore to investigate the outcomes of TEVAR in thoracic aortic aneurysm (TAA) and penetrating aortic ulcer (PAU) with respect to IFU status.

## Methods

### Study design

This is a retrospective single-center study investigating the outcomes of TEVAR in TAA/PAU with respect to IFU status (iIFU/oiFU). The patients were identified from a prospectively maintained departmental TEVAR database. The local ethics committee approved data collection (protocol no. S-158/2015).

### Study population

Between October 2009 and September 2017, 532 TEVAR procedures were performed for various pathologies. In 195 patients, the Conformable GORE® TAG® thoracic endoprosthesis (CTAG; W. L. Gore & Associates, Flagstaff, AZ, USA) was used. Of these, 56 patients (24 female/32 male) were treated for isolated TAA or PAU, representing the herein analyzed cohort. Patients treated with a combination of the CTAG and other devices and patients treated with any other devices were excluded to enhance comparability and to minimize potential confounders. Given the heterogeneous pathophysiological background, patients treated for any aortic pathology other than isolated TAA or PAU were also excluded from analysis. In 29 patients, a PAU was present, while in 27 patients, TEVAR indication was TAA. Sixteen patients (ruptured PAU (rPAU): $n = 6$, ruptured TAA (rTAA): $n = 10$) were treated as emergencies. Median age was 73 years (range: 52–91 years). The demographics and comorbidities are summarized in Table 1.

### Procedural data

TEVAR procedures up to September 2010 were performed using the Axiom-U imaging system (Siemens, Germany). From October 2010 onward, TEVAR took place in a hybrid-operating room (Artis-Zeego multiaxis-imaging system; Siemens, Germany). The implantation protocol has been published.[12] LSA revascularization was selectively undertaken following an institutional protocol. Indications comprise long segment aortic coverage $\geq$200 mm, prior/concomitant infrarenal aortic replacement, renal insufficiency, hypoplastic right vertebral artery, patent left internal mammary artery graft as well as functioning dialysis fistula in the left arm.[13] The procedure-related data are detailed in Table 2.

### Instructions for use

The CTAG became the preferred TEVAR device at the authors' institution in October 2009. The current generation of the CTAG, with active control system, has been used since July 2017, sharing the same IFU.[14] The IFU criteria are detailed in Table 3.

### Imaging and follow-up

The computed tomography angiography (CTA) protocol includes imaging before discharge at six months, one year, and annually thereafter.[15,16] The standardized aortic CTA protocol includes multiple detector electrocardiography-gated CTA with 1-mm slice thickness of the entire aorta (supraaortic branches to femoral arteries) acquired at 60% of the R–R interval correlating to late diastole. Based on the CTAG's IFU, a strictly defined measurement protocol was followed. IFU assessment comprised measurement of every IFU criterion (i.e. length/diameter of proximal/distal landing zone (PLZ, DLZ) as well as device overlap). Measurements were made on the preoperative and postoperative CTA as well as on the follow-up (FU) scan after 12 months using three-dimensional reconstruction software and centerline measurements (OsiriX PRO (aycan), Rochester, NY, USA). If FU exceeded 12 months, the last FU scan was also reviewed. All scans were evaluated by two experienced readers, blinded to all clinical information. For metric parameters, the mean of the readers' estimates was considered as final. In case of discrepancies, the investigators reached a consensus. The inter-observer variability is shown in Supplementary Table 1. A preoperative and at least one postoperative scan was available in all cases (imaging FU: 100%). Median FU was 29.7 months

**Table 1.** Patient demographics and comorbidities.

| | Total ($n = 56$) | iIFU ($n = 26$) | oIFU ($n = 30$) | *P* |
|---|---|---|---|---|
| Age, median (range) | 73 (52–91) | 76 (60–90) | 72 (52–91) | 0.74 |
| Gender (male/female) | 33/23 | 17/9 | 16/14 | 0.36 |
| ASA classification (median/range) | 3 (2–4) | 3 (2–4) | 3 (2–4) | 0.53 |
| Heart failure | 10 (17.9%) | 6 (23.1%) | 4 (13.3%) | 0.49 |
| Hypertension | 49 (87.5%) | 23 (88.5%) | 26 (86.7%) | 1.00 |
| History of myocardial infarction | 12 (21.4%) | 8 (30.8%) | 4 (13.3%) | 0.11 |
| CAD | 23 (41.1%) | 14 (53.8%) | 9 (30.0%) | 0.07 |
| Carotid stenosis | 12 (21.4%) | 3 (11.5%) | 9 (30.0%) | 0.09 |
| PAOD | 8 (14.3%) | 2 (7.7%) | 6 (20.0%) | 0.26 |
| History of stroke | 1 (1.8%) | 1 (3.8%) | 0 (0.0%) | 0.46 |
| COPD | 14 (25.0%) | 7 (26.9%) | 7 (23.3%) | 0.75 |
| Diabetes mellitus | 11 (19.6%) | 4 (15.4%) | 7 (23.3%) | 0.52 |
| BMI $> 30\,kg/m^2$ | 8 (14.3%) | 5 (19.2%) | 3 (10.0%) | 0.45 |
| Renal insufficiency (creatinine $>1.2$ mg/dl) | 11 (19.6%) | 6 (23.1%) | 5 (16.7%) | 0.55 |
| Need for hemodialysis | 1 (1.8%) | 1 (3.8%) | 0 (0.0%) | 0.46 |
| History of smoking | 24 (42.9%) | 15 (57.5%) | 9 (30.0%) | 0.04 |
| Previous aortic surgery/intervention | | | | 0.27 |
| Abdominal aorta | 13 (23.2%) | 7 (26.9%) | 6 (20.0%) | |
| Thoracic aorta | 6 (10.7%) | 4 (15.4%) | 2 (6.7%) | |
| TAA/PAU | 27(48.2%)/29 (51.8%) | 17 (30.4%)/9 (16.1%) | 10 (33.3%)/20 (66.6%) | 0.031 |
| Arch types | | | | 0.38 |
| Type 1 | 13 (23.2%) | 4 (15.4%) | 9 (30.0%) | |
| Type 2 | 27 (48.2%) | 13 (50.0%) | 14 (46.7%) | |
| Type 3 | 16 (28.6%) | 9 (34.6%) | 7 (23.3%) | |

ASA: American Society of Anesthesiologists; BMI: body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; IFU: instructions for use; iIFU: inside IFU; oIFU: outside IFU; PAOD: peripheral artery occlusive disease; PAU: penetrating aortic ulcer; TAA: thoracic aortic aneurysm.

(range: 0–109.4 months). Following an institutional FU protocol, TEVAR–FU included medical history and CTA at admission, before TEVAR, before discharge, one year after TEVAR, and annually thereafter. Clinical–FU was 91.1% complete. Five patients were lost to FU.

## *Study endpoints and definitions*

The primary study endpoint was the outcome of TEVAR with respect to the IFU status, including freedom from TEVAR-related RI, successful exclusion of the pathology, TEVAR-related mortality, and graft-related serious adverse events (grSAE). The presence of type I/III endoleak (EL-I/EL-III) as well as type II EL fed by the LSA (EL-II–LSA) was defined as technical failure in the context of this study.

IFU assessment was performed retrospectively with respect to morphological data only, not considering any potential clinical or individual surgeon-related factors. Based on the preoperative CTA, cases were retrospectively classified as suitable for TEVAR meeting the IFU criteria (primary iIFU) or not (primary oIFU). A case was defined as oIFU if at least one IFU parameter was violated. In patients eligible for iIFU repair, the first postoperative CTA was evaluated equally. In cases where the device(s) had not been implanted according to the IFU despite morphological IFU eligibility, the patient was classified as secondary oIFU (Table 3). For analysis of the study endpoints, primary and secondary oIFU patients were subsumed to oIFU, as TEVAR had not been performed within the IFU criteria.

RI was defined as any secondary endovascular, open, or hybrid procedure related to primary TEVAR or progression of the aortic disease, including early/late conversion.grSAE were defined as: EL-I/III and EL-II–LSA, graft migration $> 10$ mm, aortic diameter expansion within the treated segment $> 5$ mm, retrograde aortic dissection (RTAD), stent graft-induced new entry (SINE), or open conversion.

The definitions for migration, aortic diameter expansion, primary technical success, and death used in this study meet the reporting standards for TEVAR published in 2010.[17] EL types were defined according to White et al.[18]

## *Statistical analysis*

Patient and disease characteristics are described as absolute/relative frequencies for categorical

**Table 2.** Procedural details.

| | Total ($n = 56$) | iIFU ($n = 26$) | oIFU ($n = 30$) | *P* |
|---|---|---|---|---|
| Elective/emergency procedures | 40 (71.4%)/16 (28.6%) | 21/5 | 19/11 | 0.15 |
| Duration of procedure (min; median/range) | 96.0 (35–465) | 92.5 (35–360) | 98.5 (57–465) | 0.20 |
| Radiation time (min; median/range) | 11.0 (3–62.7) | 10.6 (4.1–30.2) | 12.5 (3–62.7) | 0.36 |
| Contrast agent volume (ml; median/range) | 110 (30–470) | 110 (30–450) | 112.5 (60–470) | 0.37 |
| Dose area product (mGy/cm$^2$; median/range) | 23,381.2 (511.1–717,522) | 24,970.0 (511.1–455,382.0) | 21,362.2 (1644.1–717522.0) | 0.34 |
| Maximum aortic diameter | 57.6 (29.7–110.9) | 62.4 (41.1–81.2) | 53.0 (29.7–110.9) | 0.217 |
| Lesion length (mm; median/range) | 44.7 (10.6–181.8) | 69.2 (20.0–181.8) | 29.6 (10.6–117.3) | 0.003 |
| No. of implanted devices (median/range) | 1 (1–4) | 1 (1–3) | 1 (1–4) | 0.15 |
| 1 | 35 (62.5%) | 14 (53.8%) | 21 (70.0%) | |
| 2 | 14 (25.0%) | 7 (26.9%) | 7 (23.3%) | |
| 3 | 6 (10.7%) | 5 (19.2%) | 1 (3.3%) | |
| 4 | 1 (1.8%) | 0 (0.0%) | 1 (3.3%) | |
| Access | | | | 0.40 |
| Transfemoral | 49 (87.5%) | 21 (80.8%) | 28 (93.3%) | |
| Transfemoral/transbrachial | 3 (5.4%) | 2 (7.7%) | 1 (3.3%) | |
| Iliac conduit | 4 (7.1%) | 3 (11.5%) | 1 (3.3%) | |
| Proximal landing zone | | | | 0.013 |
| 0 | 1 (1.8%) | 0 (0.0%) | 1 (3.3%) | |
| 1 | 8 (14.3%) | 1 (3.8%) | 7 (23.3%) | |
| 2 | 17 (30.4%) | 6 (23.1%) | 11 (36.7%) | |
| 3 | 18 (32.1%) | 14 (53.8%) | 4 (13.3%) | |
| 4 | 12 (21.4%) | 5 (19.2%) | 7 (23.3%) | |
| Proximal landing zones/grouped | | | | 0.006 |
| 0–2 | 26 (46.4%) | 7 (26.9%) | 19 (63.3%) | |
| 3–4 | 30 (53.6%) | 19 (73.1%) | 11 (36.7%) | |
| Rapid pacing | 27 (48.2%) | 9 (34.6%) | 18 (60%) | 0.051 |
| LSA coverage | 26 (46.4%) | 7 (26.9%) | 19 (63.3%) | 0.006 |
| Primary LSA revascularization | 11 (19.6%) | 4 (15.4%) | 7 (23.3%) | 0.313 |
| Primary LSA occlusion | 5 (8.9%) | 2 (7.7%) | 3 (10%) | 0.57 |
| Length of hospital stay (d; median/range) | 12 (1–51) | 11 (5–29) | 12 (1–51) | 0.98 |
| Length of ICU stay (d; median/range) | 3 (0–51) | 3 (0–14) | 3 (0–51) | 1.00 |

d: days; ICU: intensive care unit; IFU: instructions for use; iIFU: inside IFU; oIFU: outside IFU; LSA: left subclavian artery, min: minutes; ml: milliliter; *n*: number.

variables or median/range for continuous variables. Student t-test, $\chi^2$ test, and Fisher exact test are used for univariate comparisons of continuous and categorical variables as appropriate. Survival and freedom from RI are compared using the log-rank test. The Kaplan–Meier method is employed to estimate the overall survival, TEVAR-related survival, and freedom from TEVAR-related RI with respect to the IFU status. Multivariable Cox-proportional hazard models for overall survival/RI are used to provide hazard ratios (HR) and the corresponding 95% confidence intervals (CI). Odds ratios (OR) and the corresponding 95% CIs are calculated by logistic regression models for binary endpoints. All regression models were adjusted for gender, age, and emergency status. Due to the exploratory nature of the analysis, no adjustment for multiple testing was done. All *P*-values are of descriptive nature. For descriptive analysis, PASW Statistics (version 18.0; IBM Corp, Somers, NY) was used. All other analyses were realized using the software R (version 3.3.2 https://www.R-project.org/).

## Results

### *IFU status and procedural details*

Of 56 patients, 30 were classified as oIFU (53.6%) and 26 as iIFU. Based on preoperative imaging, a total of 17 of 56 patients (30.3%) were retrospectively classified as primary oIFU, hence not treatable within the IFU criteria due to the underlying aortic morphology (Table 3). In these 17 patients, 21 IFU violations were observed. Evaluation of the postoperative scan revealed another 13 patients in whom stentgrafting was performed oIFU despite IFU eligibility (secondary oIFU: 13/39; 33.3%), resulting in a total of 30/56 (53.6%) oIFU cases. IFU violations leading to primary and secondary oIFU status are displayed in Table 3. Analysis showed an association between PLZ and IFU status ($P = 0.006$; Table 2). Equally, LSA coverage was more frequently seen in oIFU patients ($P = 0.006$). In these, primary LSA revascularization has been performed 11/26, more often observed iIFU (57.1% iIFU vs. 36.8% oIFU, $P = 0.313$; Table 2).

**Table 3.** IFU parameter recommendations and violations.

| IFU parameter | IFU CTAG recommendation | Primary oIFU $N = 17/56$ (30.3%) Total oIFU: 30/56 (53.6%) IFU violation preoperative scan $N = 17$ | Secondary oIFU $N = 13/39$ (33.3%) IFU violation postoperative scan $N = 13$ |
|---|---|---|---|
| PLZ length[a] | ≥20 mm | 14/17 (82.4%) | 5/13 (38.5%) |
| DLZ length | ≥20 mm | 3/17 (17.6%) | 6/13 (46.2%) |
| PLZ diameter | 16–42 mm | 1/17 (5.9%) | |
| DLZ diameter | 16–42 mm | 3/17 (17.6%) | |
| Overlap[b] | 30/50 mm | | 2/13 (15.4%) |

CTAG: Gore Conformable TAG; DLZ: distal landing zone; IFU: instructions for use; iIFU: inside IFU; oIFU: outside IFU; LSA: left subclavian artery; mm: millimeter; PLZ: proximal landing zone.

[a]In cases where LSA coverage was needed for sufficient PLZ creation, PLZ length is measured from the ACC orifice to the most proximal part of the pathology. These cases were classified as iIFU. Cases in which the extended PLZ was still < 20 mm or cases where the extended PLZ was not fully exploited were classified as oIFU.

[b]Using multiple devices, CTAGs IFU suggests the use of one to two sizes different in diameter with an overlap of at least 30 mm; if overlapping devices of the same diameter, overlap should be at least 50 mm.[14]

Of the 56 patients analyzed, 40 (71.4%) were electively treated. Twenty-nine of these 40 cases were primary treatable iIFU, but evaluation of the postoperative scan revealed oIFU implantation in eight cases, leading to a secondary oIFU rate in elective cases of 27.6% (8/29). The remaining 16 patients (28.6%) were emergently treated, including 10 primary iIFU cases. In this latter group, IFU violations led to a secondary oIFU rate of 50% (5/10). With respect to IFU status, a bivariate analysis showed no difference regarding the emergency cases in the iIFU/oIFU groups ($P = 0.15$). Bivariate analysis of patient demographic/clinical information showed no difference between the groups (Table 1). In-hospital results are summarized in Table 4. Primary technical success was achieved in 92.9% (52/56) without difference between iIFU/oIFU patients (26/26 vs. 26/30; $P = 0.12$). There were no intraoperative conversions/no deaths within 24 h.

## Outcomes with respect to IFU status

*TEVAR-related RI.* A total of 19 unintentional RI were performed in 14/56 patients, yielding an overall RI rate of 25% (iIFU $N = 3$ vs. oIFU $N = 11$; $P = 0.003$). In nine patients, the RI was TEVAR-related, leading to a TEVAR-related RI rate of 16.1%. TEVAR-related RIs were performed in one iIFU patient, while the remaining eight patients were oIFU ($P = 0.029$). The median time between TEVAR and (first) RI in oIFU patients was 35 days (range: 1–1290 days). oIFU patients requiring RI showed IFU violations concerning the DLZ in $N = 1$, the PLZ in $N = 4$, and a combination of PLZ/DLZ in $N = 3$ cases. In all cases but one, the IFU violation related directly to the performed RI. All RIs are displayed in Table 5.

Freedom from TEVAR-related RI was significantly lower in oIFU patients (log-rank test: $P = 0.016$; Figure 1(a)). Kaplan–Meier analysis did not indicate any difference regarding freedom from TEVAR-related RI when stratified by elective/emergency (log-rank test: $P = 0.41$) (Figure 1(b)). Cox-proportional hazards model revealed an HR of 9.74 (CI 1.2–80.2; $P = 0.034$) for a TEVAR-related RI in oIFU patients.

*Endoleaks.* Twenty EL were detected in 19 patients (19/56; 33.9%) (Table 6). The accumulated rate of EL-I/III was 12.5% (7/56), occurring in oIFU patients only ($P = 0.012$); four of whom underwent RI. The one EL-Ia (IFU violation: PLZ) was successfully repaired by proximal endograft extension. Of the four patients with EL-Ib (all oIFU due to insufficient DLZ length), one underwent RI but died on-table (rupture), while another patient refused RI. The remaining two patients were successfully treated with distal extension. One of the two patients with EL-III (both oIFU for rTAA despite IFU eligibility with insufficient device overlap) died of cardiac failure on the second postoperative day. The second patient with EL-III declined further RI and died 2.4 years after the index procedure (multiorgan failure).

Seven of 14 EL-II were fed by the LSA, yielding an EL-II–LSA rate of 12.5% (7/56). All but one of EL-II–LSA occurred in oIFU patients ($P = 0.11$). In all, IFU violation was due to an insufficient PLZ despite LSA coverage. In three patients, primary LSA revascularization was performed during TEVAR (carotid–subclavian bypass $n = 2$; right carotid–LSA crossover bypass with reinsertion of the left carotid artery $n = 1$), one patient received carotid–carotid bypass for LZ creation and in one patient additional LSA occlusion with a

**Table 4.** In-hospital outcomes.

| | Total ($n = 56$) | iIFU ($n = 26$) | oIFU ($n = 30$) | *P* |
|---|---|---|---|---|
| In-hospital mortality | 4/56 (7.1%) | 0/26 | 4/30 (13.3%) | 0.12 |
| Thirty-day mortality | 5/56 (8.9%) | 0/26 | 5/30 (16.7%) | 0.055 |
| Primary technical success[a] | 52/56 (92.9%) | 26/26 (100%) | 26/30 (86.7%) | 0.12 |
| Reasons for technical nonsuccess | | | | |
| EL type I b | 2/56 (3.6%) | 0/26 | 2/30 (6.7%) | 0.49 |
| EL type III | 2/56 (3.6%) | 0/26 | 2/30 (6.7 %) | 0.49 |
| Intraoperative conversion | 0/56 | | | |
| Death $\leq 24$ h | 0/56 | | | |

Categorical data are *n* (number)/%.

EL: endoleak; IFU: instructions for use; iIFU: inside IFU; oIFU: outside IFU.

[a]In accordance with the Society for Vascular Surgery Reporting Standards from 2010, primary technical success was defined as absence of the following: surgical conversion to open repair, death within 24 h, type I or III endoleaks as evidenced by procedural angiography.[32]

vascular plug was performed during the index procedure. EL-II–LSA required RI in five cases: secondary LSA occlusion was performed in three, while one patient received secondary PLZ ballooning, resulting in RTAD and conversion. The last RI was performed in the patient already treated with a vascular plug during primary TEVAR. FU–CTA showed insufficient occlusion with EL-II–LSA, for which he received additional secondary LSA coiling. The remaining two patients died for non-aortic reasons before the planned RI.

In summary, 14 EL-I/III and EL-II–LSA occurred in 13 patients (13/56; 23.2%), of whom 12 were oIFU ($P = 0.001$). Logistic regression analysis found an association between oIFU-status/occurrence of EL-I/III and EL-II–LSA (OR: 15.09, CI 2.6–289.5; $P = 0.0129$). Regarding the effect of primary/secondary LSA occlusion in PLZ 0–2 TEVAR: after elimination of RIs performed for LSA occlusion, analysis showed a similar effect with regards to oIFU ($P = 0.037$). Kaplan–Meier analysis indicated a lower RI-free survival of oIFU cases after elimination of the aforementioned RI (log-rank test: $P = 0.02$; Supplementary Figure 1). All EL and the associated RI are displayed in Tables 5 and 6.

*Mortality.* oIFU patients showed higher procedure-related in-hospital mortality (4/56; iIFU $N = 0$ vs. oIFU $N = 4$; $P = 0.12$) and higher 30-day mortality (5/56; iIFU $N = 0$ vs. oIFU $N = 5$; $P = 0.055$) (Table 4). All four in-hospital deaths were procedure-related (two emergency cases/two elective cases). Of the two emergency cases, one patient died (rTAA/oIFU) on postoperative day 2 (heart failure), while the other died (rTAA, oIFU) 15 days after TEVAR (multiorgan failure). One elective patient (PAU/oIFU) died of hemorrhage (aortoesophageal fistula) on postoperative day 6. The last patient (elective TEVAR for PAU/oIFU) suffered from RTAD proven by postoperative CTA and underwent emergency conversion. He died six days after primary TEVAR (cardiac failure). The reason for one additional death within 30 days (oIFU/rPAU) remained unclear. Over a median FU of 29.7 months (range: 0–109.4 months), overall mortality was 42.9% (24/56) (Figure 2). With respect to IFU status, overall mortality was 7/26 (iIFU) vs. 17/30 (oIFU; $P = 0.025$). Kaplan–Meier analysis showed reduced survival probability in oIFU patients (log-rank test: $P = 0.026$) as well as in emergency patients (log-rank test: $P = 0.0024$). The procedure-related death rate was 14.3% (8/56 cases). There was no difference in procedure-related death with respect to IFU status (iIFU $N = 2$ vs. oIFU $N = 6$; $P = 0.16$; log-rank test: $P = 0.21$) (Figure 3(a)), but with respect to emergency status (elective $N = 4$ vs. emergency $n = 4$; log-rank test: $P = 0.038$) (Figure 3(b)). No pathology-related deaths occurred during FU (Supplementary Table 2). Mortality from RI was 22.2% (2/9). Both patients were treated oIFU: one patient died intraoperatively during distal extension for EL-Ib (rupture). The other patient died after conversion for RTAD (cardiac failure), caused by ballooning for EL-II–LSA.

*grSAE.* Overall, 21 grSAE were observed in 17 patients, yielding a grSAE rate of 30.4% (Table 7). There was no SINE and no late conversion. Three grSAE occurred in three iIFU patients (3/26; 11.5%) and 18 in 14 oIFU patients (14/56; 46.7%; $P = 0.004$). Stratified to landing zones, graft-related SAE (grSAE) was 19.6% in PLZ 0–2 (3.8% iIFU vs. 33.3% oIFU) vs. 10.7% in PLZ 3–4 (7.7% iIFU vs. 13.3% oIFU; $P = 0.272$). Twelve of the 14 grSAE in the oIFU group showed a direct causal relation with the IFU violation (Supplementary Table 3). Logistic regression analysis showed an association between oIFU status and occurrence of grSAEs (OR: 6.11, CI: 1.6–30.06; $P = 0.012$).

**Table 5.** TEVAR-related reinterventions.

| # | IFU status | Pathology | PLZ | IFU violation | Urgency | RI indication | Interval | RI | Success RI | FU |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | iIFU | TAA | 2 | – | Elective | 1. ELII/LSA | 10 days | 1. LSA occlusion | Yes | Death/laryngeal cancer |
| | | | | | | 2. Persistent EL/ Ø expansion | 30 days | 2. Endolining | Yes<br>Yes | |
| 2 | oIFU | TAA | 3 | DLZ length | Elective | EL I b | 3.5 years | Distal extension + chimney SMA in rupture | No | Death in table[a] |
| 3 | oIFU | rTAA | 2 | PLZ length | Emergency | EL II | 11 days | LSA occlusion | Yes | Death/unknown |
| 4 | oIFU | rTAA | 4 | PLZ length | Emergency | EL I a | 37 days | Prox. Extension | Yes | alive |
| 5 | oIFU | iPAU | 2 | PLZ length | Elective | EL II /LSA | 2 days<br>2 days | Balloon-dilatation<br>PLZ leading to RTAD → conversion | Yes | Death/myocardial infarction + organ failure after conversion[a] |
| 6 | oIFU | iPAU | 1 | PLZ length | Elective | EL II | 25 days | LSA occlusion | Yes | Death/malnutrition |
| 7 | oIFU | iPAU | 2 | PLZ length | Elective | SSS | 390 days | LCA–LSA bypass | Yes | alive |
| 8 | oIFU | iPAU | 2 | PLZ length<br>DLZ length | Elective | 1.Left brachial ischemia<br>2. EL I b | 34 days<br>3.5 years | 1. LCA–LSA bypass<br>2. Dist. extension | Yes<br>Yes | LOF |
| 9 | oIFU | rPAU | 2 | Ø PLZ<br>Ø DLZ | Emergency | 1. EL II LSA<br>2. EL I b | 34 days<br>230 days | 1. LSA occlusion<br>2. Dist. extension | Yes<br>yes | alive |

dist.: distal; DLZ: distal landing zone; EL: endoleak; iIFU: inside IFU; LCA: left carotid artery; LOF: lost of follow-up; LSA: left subclavian artery; oIFU: outside IFU; r: ruptured; RI: reintervention; RTAD: retrograde aortic dissection; s: symptomatic, sec.: secondary; SSS: subclavian steal syndrome; PAU: penetrating aortic ulcer; PLZ: proximal landing zone; prox.: proximal; TAA: thoracic aortic aneurysm; Ø: diameter.

[a]Death classified as mortality from RI (2/9; 22.2%).

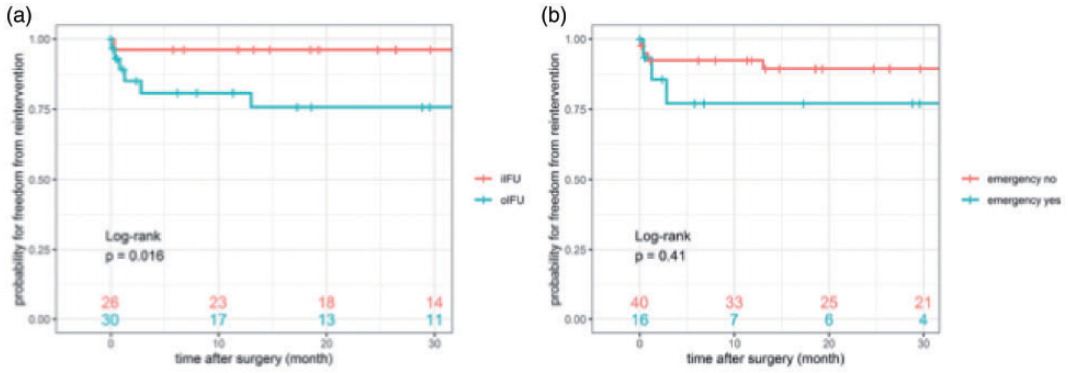


**Figure 1.** Freedom from TEVAR-related reintervention stratified to IFU status: (a) red line: inside IFU, blue line outside IFU and stratified to emergency status; (b) red line: elective cases, blue line: emergency cases).

**Table 6.** Endoleaks with respect to IFU status.

| Endoleak | All ($n = 56$) 20 in 19 cases | iIFU ($n = 26$) 5 cases | oIFU ($n = 30$) 14 cases | *P* 0.031 | IFU violation | RI 9 |
|---|---|---|---|---|---|---|
| Primary endoleak (*N*) | 16 | 4 | 12 | 0.042 | | |
| Secondary endoleak (*N*) | 4 | 1 | 3 | 0.62 | | |
| EL type | | | | | | |
| Ia | 1 | 0 | 1 | | PLZ $N = 1$ | 1 |
| Ib | 4 | 0 | 4 | | DLZ $N = 4$ | 3 |
| III | 2 | 0 | 0 | | Overlap $N = 2$ | 0 |
| II | 13 | 5 | 8 | | | |
| *LSA* | *7* | *1* | *6* | | PLZ $N = 6$ | 5 |
| *ICA* | *4* | *3* | *1* | | DLZ | 0 |
| *BA* | *2* | *1* | *1* | | PLZ | 0 |
| EL rate type I/III | 7 (12.5%) | 0 | 7 (23.2%) | 0.012 | | |
| EL rate type II – LSA | 7 (12.5%) | 1 | 6 (20.0%) | 0.11 | | |
| EL rate type I/III/II – LSA | 13 (23.2%) | 1 (3.8%) | 12 (40.0%) | 0.001 | | |
| EL I/III + RI | 12 (21.4%) | 1 (3.8%) | 11 (36.7%) | 0.003 | | |
| EL I/III/II LSA + RI | 14 (25.0%) | 1 (3.8 %) | 13 (43.3%) | 0.0007 | | |

BA: bronchial artery; DLZ: distal landing zone; EL: endoleak; IFU: instructions for use; iIFU: inside IFU; IC: intercostal artery; LSA: left subclavian artery; N: number, oIFU: outside IFU; PLZ: proximal landing zone; RI: reintervention.

## Discussion

These real-world data show that TEVAR for TAA/PAU is frequently performed oIFU despite preoperative iIFU eligibility. Individuals treated oIFU showed a clearly elevated risk for TEVAR-related RI. Furthermore, oIFU patients showed a sixfold risk for grSAE, underlining the potential postoperative burden of oIFU–TEVAR.

In contrast to EVAR, in which treatment oIFU has been intensively discussed,[1] the literature on oIFU–TEVAR is still limited. Guidelines recommend a suitable "landing zone" above/below aortic pathologies $\geq$20 mm.[19,20] This meets the IFU criteria of most available devices, including the CTAG.[14] Ranney et al.[21] showed that TEVAR results for TAA performed iIFU are satisfying. In their 192 patients, the overall and aorta-specific survival rates at 141 months were 45.7 and 96.2%, respectively, with a low RI rate of 7% for EL in 7% of the cases.[21] However, the results of oIFU–TEVAR, are, given the lack of specific studies, still not well reported.[22] In our study, more than half of the analyzed patients were treated oIFU (53.6%). IFU violation for LZ was the most common aberration observed. A total of 28 patients showed LZ outside the IFU criteria. More interestingly, about one-third (33.3%) showed insufficient exploitation of the PLZ/DLZ despite preoperative IFU eligibility, emphasizing the pertinence of precise perioperative imaging analysis, procedural planning, and meticulous device deployment.

A few groups have evaluated the influence of PLZ length, specifically with respect to EL-Ia formation.[23] Gottardi et al.[24] reported that a PLZ length of $\geq$20 mm prevents EL, while Czerny et al.,[25] in a TAA cohort

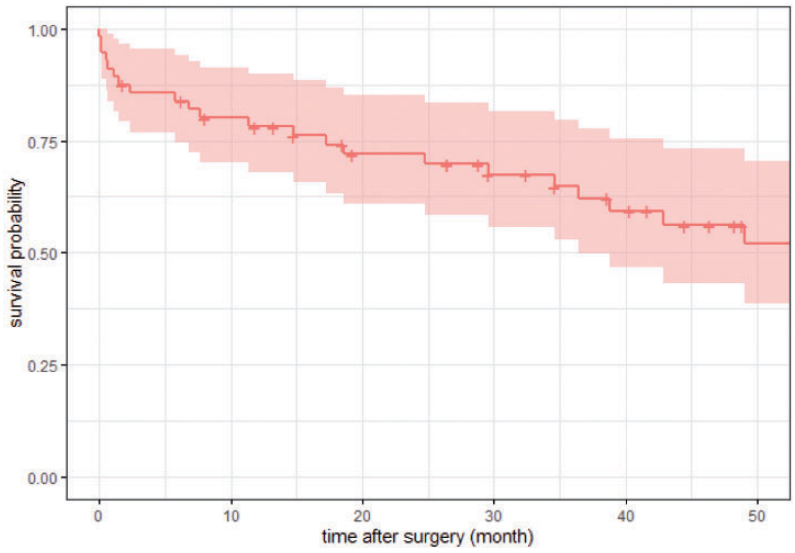


**Figure 2.** Overall survival (all-cause mortality) in 56 patients treated with TEVAR for thoracic aortic aneurysm and penetrating aortic ulcer.

| Time (months) | 0 | 10 | 20 | 30 | 40 | 50 |
|---|---|---|---|---|---|---|
| Number at risk | 56 | 42 | 33 | 27 | 21 | 13 |

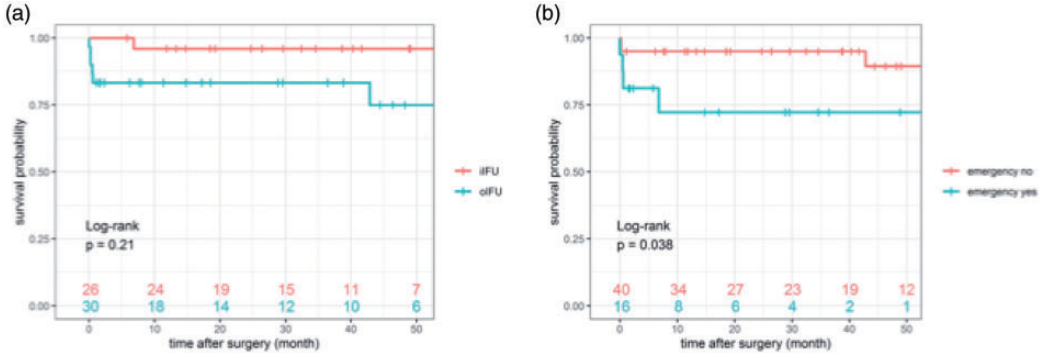


**Figure 3.** Procedure-related survival in 56 patients treated with TEVAR for thoracic aortic aneurysm and penetrating aortic ulcer, stratified to IFU status: (a) red line: inside IFU, blue line outside IFU) and to emergency status; (b) red line: elective cases, blue line: emergency cases.

**Table 7.** Outcomes with respect to IFU status.

| | All ($n = 56$) | iIFU ($n = 26$) | oIFU ($n = 30$) | *P* |
|---|---|---|---|---|
| TEVAR-related RI | 9 (16.1%) | 1 (3.8%) | 8 (26.7) | 0.029 |
| EL rate type I/III | 7 (12.5%) | 0 | 7 (23.2%) | 0.012 |
| EL rate type II LSA | 7 (12.5%) | 1 (3.8%) | 6 (20.0%) | 0.11 |
| RTAD | 1 | 0 | 1 | |
| Late conversion | 0 | | | |
| SINE | 0 | | | |
| Graft migration | 3 | 1 | 2 | |
| Aortic diameter expansion | 3 | 2 | 1 | |
| Overall graft-related SAE | 17 (30.4%) | 3 (11.5%) | 14 (46.7%) | 0.004 |

EL: endoleak; IFU: instructions for use; LSA: left subclavian artery; RI: reintervention; RTAD: retrograde type A dissection; SAE: serious adverse event; SINE: stent graft-induced new entry.

with landing zones of 5–50 mm, identified a short PLZ as independent risk factor for early (HR: 6.5; $P = 0.011$) and late EL (HR: 4.4; $P = 0.029$). Further insights were provided by Boufi et al.,[11] who depicted a short PLZ as independent predictor of EL-Ia (HR: 0.89; $P = 0.032$). In their analysis, a PLZ length of $\leq$24 mm holds a risk of 18.6% for EL formation.

Herein, there was one case of EL-Ia, in which the PLZ length did not meet the IFU criterion. Notably, this was the only EL-Ia observed despite detection of 20 PLZ deviations. On the one hand, this may be the result of the ongoing progress in stent graft design, offering superior alignment/conformability compared to former devices, especially for pathologies involving the arch.[26,27] This has been reported to reduce rates of EL-Ia, at least in "suitable" TAA with sufficient PLZ.[28,29] On the other hand, justified doubt remains regarding the durability of oIFU–LZ as FU is usually limited, especially in real-world studies.

In this context, the occurrence of EL-II has to be discussed. Although not primarily regarded as treatment failure, there is evidence that EL-II in TEVAR is associated with RI, particularly in cases involving the LSA.[15,23,30] In this study, seven EL-II–LSA occurred, six of them in oIFU patients, often leading to RI. Although the severity of EL-II in contrast to EL-I/III should not be overrated, the LSA orifice is involved in PLZ length in up to 40% in TEVAR collectives in terms of LZ creation,[15] especially in TEVAR cohorts comprising high rates of type 2/3 arches (76.8% in the presented cohort). Therefore, this subgroup of EL should be considered separately.[23,25] In the context of our results, all RI for EL-II occurred early (at 10–34 days). This demonstrates the relevance of LSA-fed leakage, contributing to an impaired circumferential sealing. Thus, it may cautiously be proposed that EL-II–LSA can equally be described as treatment failure. Preemptive LSA occlusion should liberally performed in cases involving the LSA orifice in order to reduce the need for RI and create most durable landing zones. This adjunctive procedure can be performed with low complication rates.[31]

The reporting standards for TEVAR define primary EL-Ib as a treatment failure.[32] Overall, literature on its occurrence is limited. A recent meta-analysis reports the incidence of EL-Ib as up to 8%.[33] Interestingly, none of the evaluated articles reported on the influence of DLZ length. Furthermore, no study mentioned evaluated IFU adherence. Berezowski et al.,[34] in a non-dissected pathology cohort, differentiated between accurate/inaccurate TEVAR landing with respect to the celiac trunk in DLZ length $< 40$ mm. Although no exact measurements were given, inaccurate landing may, liberally, be defined as oIFU. The incidence of primary EL-Ib was significantly higher in the inaccurate group (0 vs. 13 patients; $P = 0.049$). Two of the patients with EL-Ib suffered from rupture and eight underwent distal RI, highlighting the importance of proper distal sealing.[34] Herein, we observed EL-Ib in four patients. All were treated oIFU with respect to their DLZ ($\leq$20 mm). Focusing on EL-I/III, the probability of occurrence was considerably higher in oIFU patients ($P = 0.012$) as was that of additional EL-II–LSA as "liberal" treatment failure ($P = 0.001$). Owing to the limited numbers of patients/events, regression analysis failed to show a statistically reliable association between oIFU–TEVAR, EL-I/III EL, and EL-II–LSA. Nevertheless, considering the data published by others, it seems accurate to state that oIFU landing carries the risk of considerable immediate and future problems. Physicians performing TEVAR should aim for sufficient PLZ/DLZ whenever possible and strive for meticulous FU. This is supported by the results of this study, which revealed that patients treated oIFU have a ninefold risk for TEVAR-related RI.

The RI rates in TEVAR collectives are reported to be around 10%.[35–38] As shown by Fairman et al.[35] in 7006 TEVAR patients, the need for RI is associated with increased in-hospital mortality ($P = 0.075$). This indicates the relevant impact of RI on TEVAR outcome.

Of the nine patients requiring RI, eight were treated oIFU. Analysis of the performed RI shows that IFU adherence was actually possible in some of these patients, particularly in cases involving the LSA. Equally, both cases of EL-III resulting from an insufficient overlap seem avoidable in retrospect. Adherence to the IFU requirements should be intended whenever possible. A multidisciplinary approach to challenging aortic surgery and close FU in oIFU cases is strongly recommended.

The procedure-related mortality observed herein did not differ significantly between iIFU/oIFU patients ($P = 0.21$), but did differ between elective/emergency status ($P = 0.038$). However, two-thirds of the emergency cases were oIFU, possibly interfering with this result given the limited number of events. Undoubtedly, emergency TEVAR requires special consideration. Since its introduction in the mid-1990s, TEVAR has been rapidly adopted for a variety of thoracic aortic diseases, including a substantial proportion of emergency procedures. At the authors' institution, about one-third of TAA- and almost half of PAU patients are treated non-electively. In our study, 29% were emergently treated, with no apparent difference with respect to IFU status ($P = 0.15$). Of note, 11 of these patients were treated oIFU, five of them despite preoperative iIFU eligibility. Clearly, the treatment goal in patients with a ruptured aorta is to prevent death, so some patients were treated despite being

oIFU or under (intentional or unintentional) acceptance of IFU deviation. The in-hospital mortality among patients who undergo emergency TEVAR for rTAA is considerable: the medium-/long-term survival rates range from 20 to 60%.[22,39,40] In complicated PAU, the mortality rates are lower, but still considerable compared to elective cases.[41] To date, IFU adherence has not been at the focus of attention in these subsets of patients, for obvious reasons. Therefore, accurate estimation of the impact of IFU adherence/deviation on survival in real-world cohorts including emergency cases is not possible.

Against this background, the level of urgency may still bias the strong association between RI and oIFU treatment, as three of the nine patients with RI underwent emergency repair. However, this means that oIFU patients face both lower survival and increased risk of grSAE with potential subsequent RI. Therefore, it seems mandatory to create a most durable result in elective scenarios, even if this means "going the extra mile," i.e. LZ creation.[24] In emergency cases, the treatment goal is to save the patient's life. However, in the light of our findings, we advocate keeping the risk for subsequent RI as low as possible because the need for RI potentially exposes the patient to further harm.

### *Limitations*

Our study features several limitations. First, it is a retrospective study analyzing a limited number of patients. Equally, the number of events, specifically EL-I/III, is low. Therefore, the presented statistical analysis is of limited informative value. As discussed, the level of urgency may interfere with the IFU status with respect to survival/need for RI. Owing to the limited case number, regression analysis could not be performed for all endpoints.

## Conclusion

This study shows that TEVAR is frequently performed oIFU, leading to relevant consequences for technical/clinical outcome. Given the potentially considerable consequences of unsuccessful TEVAR, such as subsequent endovascular or open reintervention, requiring hospitalization and confrontation with morbidity and mortality, IFU requirements should be taken into account whenever possible, at least in elective settings. In particular, IFU compliance with respect to landing zones should be aimed for.

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