Scientific Research Publishing

International Journal of Clinical Medicine, 2025, 16(3), 209-223
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

# Efficacy and Safety of Urokinase versus Alteplase in VIABAHN Stent-Graft Thrombolysis

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**How to cite this paper:** Zwarts, S.A., van Wagenberg, J.M. and van Walraven, L.A. (2025) Efficacy and Safety of Urokinase versus Alteplase in VIABAHN Stent-Graft Thrombolysis. *International Journal of Clinical Medicine*, **16**, 209-223.
https://doi.org/10.4236/ijcm.2025.163013

**Received:** January 30, 2025
**Accepted:** March 7, 2025
**Published:** March 10, 2025



## Abstract

**Objectives:** Evaluation of efficacy and safety of urokinase and alteplase for intra-arterial thrombolysis therapy for thrombosed VIABAHN stent-graft (SG) endoprosthesis in the femoropopliteal tract. **Methods:** In this retrospective study, 96 target limbs were included and analyzed with thrombosed SGs in the femoropopliteal tract treated with intra-arterial thrombolysis between January 2016 and August 2023. Short- and long-term efficacy and safety were examined by comparing the use of alteplase and urokinase. **Results:** The cohort (N = 96, 78.1% male, median age 70 years (63 - 76)) included 26 (27.1%) limbs treated with urokinase and 70 (72.9%) with alteplase. The average time to occlusion was 15.5 months (3.0 - 36.3). Alteplase exhibited a shorter treatment time (26.13 ± 9.37 hours) compared to urokinase (30.58 ± 9.07 hours; P = 0.04). Success rates, after additional interventions were 93.3% for urokinase and 90.0% for alteplase (P = 0.73). Major complication and amputation rates were 9.2% and 7.3%, respectively. Urokinase had a lower one-year patency (13.9%) than alteplase (36.6%) (P = 0.06). One-year patency for the entire cohort was 29.8%. **Conclusion:** Both urokinase and alteplase proved equally effective and safe for treating thrombosed VIABAHN SGs, with a slight preference for alteplase based on treatment time. However, low patency rates and high complication and amputation rates highlight the need for additional interventions, proper indication, and strict follow-up.

## Keywords

Alteplase, Urokinase, Intra-Arterial Thrombolysis, In-Stent Thrombosis, Endoprosthesis

## 1. Introduction

Long and complex lesions in the superficial femoral artery (SFA) were tradition-

ally managed by open bypass surgery. The European Society for Vascular Surgery (ESVS) now recommends endovascular therapy as the primary choice for lesions shorter than 25 cm. According to these guidelines, primary stenting should be considered in intermediate to long SFA lesions [1]. An advantage of the use of VIABAHN SGs is the potential prevention of intimal hyperplasia, reducing the risk of in-stent restenosis [2]. However, the Achilles heel of the SG is a possible distal or proximal edge stenosis, which may undetected or untreated lead to in-stent thrombosis [3]. In-stent thrombosis is a common cause of stent-graft failure, and may lead to acute lower limb ischemia and possibly result in limb amputation [2] [4].

Standard lower extremity arterial thrombosis treatment involves surgical thrombectomy or intra-arterial thrombolysis (IAT). In studies conducted on native artery thrombosis, two trials concluded IAT showed superiority above surgical thrombectomy [5] [6], and two studies concluded equal efficacy for both treatments [7] [8]. One study investigated in-stent thrombosis and concluded that IAT is an effective treatment with low rates of complications and amputations [4]. In current Dutch guidelines, IAT is considered above surgical thrombectomy in the absence of critical limb threatening ischemia (CLTI). CLTI is defined as sensory loss more extensive than the toes, mild to moderate muscle weakness, and is associated with rest pain, corresponding to Rutherford stages four and above. When CLTI is present, both IAT and surgical thrombectomy can be considered [1] [9].

IAT can be conducted using either urokinase or alteplase. Thrombolysis is achieved by breaking down fibrin and fibrinogen through direct or indirect plasminogen activators [10]. Both urokinase and alteplase promote the conversion of plasminogen to plasmin, which breaks down fibrin and fibrinogen, leading to thrombus breakdown [11]. The mechanism by which plasminogen is converted to plasmin differentiates these two medications. Alteplase directly activates fibrin-bonded plasminogen, resulting in a more effective conversion to plasmin. Urokinase indirectly activates plasminogen by catalytically cracking this plasminogen into plasmin while simultaneously lowering concentrations of fibrinogen and blood coagulation factors V and VII in the bloodstream [12]. Due to a global shortage of urokinase in 2019, alteplase has become the standard medication used for IAT in most hospitals [13]. Multiple studies comparing urokinase and alteplase in native artery thrombosis concluded a higher affinity of alteplase to plasminogen than urokinase, resulting in accelerated thrombolysis [5] [11] [12]. However, thus far no research has been conducted comparing urokinase and alteplase specifically for VIABAHN SG thrombosis.

This study compares the efficacy and safety of urokinase (UK) and alteplase (AL) in treating VIABAHN SG thrombosis. Short- and long-term complications, treatment time, re-occlusion rate, amputation rate, one-year patency and one-year survival were collected and analyzed.

## 2. Methods

A non-WMO (Medical Research Involving Human Subjects Act) application was

submitted to the Medical Ethics Review Committee at the Medical Center Leeuwarden (MCL) and received approval in June 2023.

### 2.1. Study Design

This study evaluated the efficacy and safety of urokinase and alteplase used for intra-arterial thrombolysis for thrombosed SGs between January 2016 and August 2023. This timeframe aligns with the initiation of electronic patient records documentation for all regional vascular procedures. From 2016, all vascular surgery procedures in the region have been concentrated in one large hospital, facilitating an evaluation of outcomes of occluded SGs for all patients. Data were collected and retrospectively analyzed from electronic patient records from four different hospitals, in which follow-up took place. Patients meeting the following inclusion criteria were eligible: one or more VIABAHN SG in the superficial femoral artery or popliteal artery, and treatment with IAT using either UK or AL for in-stent thrombosis. Exclusion criteria included any intervention other than IAT, thrombosis of the femoropopliteal tract outside the SG, and objections against data use for research purposes as documented in patients' medical files. These inclusion criteria were selected to ensure a well-defined study group, allowing for clear and consistent conclusions to be drawn. The above exclusion criteria ensure that the results are not skewed by deviant stent location or multiple interventions at the same time. The decision to not distinguish between amounts of SG or indication was made to ensure a large enough study group to make significant statistical testing possible and reliable. From the included cases, we extracted patient characteristics (age, sex, comorbidities, time to occlusion), stent placement dates, stent characteristics, clinical symptoms, data on thrombolysis and any additional interventions, and follow-up data from patient records and anonymously coded the data in an SPSS database. A total of 96 target limbs were included and analyzed.

### 2.2. Outcome Measures

The primary outcome of this study is the difference in efficacy and safety between urokinase and alteplase. Efficacy was measured using treatment duration, presence of residual lesions, the need for additional interventions, complications, duration of ICU/CCU stay and patency, defined as the time between thrombolysis and re-occlusion diagnosed with duplex. Stents were not considered for follow-up if thrombolysis failed due to the absence of restored blood flow after treatment. Safety was measured using complication rates, amputation rates, and one-year survival. Patients who received thrombolysis within one year prior to analysis were excluded from the one-year patency and survival analysis.

### 2.3. Intra-Arterial Thrombolysis

Patients underwent a percutaneous puncture of the common femoral artery (CFA) under local anesthesia, with or without a crossover procedure, depending on their anatomy and vascular status. A sheet was inserted, through which the

thrombolysis catheter was positioned into the thrombosed SG or proximal to the occlusion [12]. Alteplase thrombolysis involved a 5 mg bolus with 5000 IU heparin, followed by continuous infusion at 1.0 mg/h for six to twelve hours. If the initial response was insufficient, thrombolysis persisted at 0.5 mg/h; if adequate, the infusion continued at 0.2 mg/h until the desired results were achieved. Responses were reassessed every six to twelve hours, and dosages were adjusted accordingly [1]. Urokinase administration varied over different time periods. From January 2016 to April 2018, patients received an initial dose of 50.000 IU urokinase and 5000 IU heparin. From June 2022 onwards, the initial dose comprised solely of 5000 IU heparin. Subsequently, urokinase was infused at 4000 IU/min for the first four hours and 2000 IU/min for the following twenty hours. Depending on the response after 24 hours, the infusion rate was either maintained or reduced to 1000 IU/min until satisfactory results were achieved. Responses were reassessed every six to twelve hours, and dosages were adjusted accordingly.

### 2.4. Statistical Analysis

Data were presented as mean ± standard deviation (SD) or median ± interquartile range (IQR) for continuous variables or as counts and percentages for discrete variables. A P-value of <0.05 was considered statistically significant, and 95% confidence intervals (CIs) were reported where needed. Baseline characteristics were analyzed with independent t-tests for continuous variables, and chi-square tests or Fisher's exact tests for categorical variables. Short-term and long-term efficacy outcomes (except patency) were tested for significant differences in both study groups using independent t-tests, chi-square tests, and Fisher's exact tests. The distribution of variables between study groups was tested with the Mann-Whitney U-test. Kaplan Meier's function of survival and the log-rank test were used to calculate patency and compare the two study groups. All analyses were performed with SPSS software (version 28.0; IBM Corporation, Somers, NY, USA).

## 3. Results

### 3.1. Baseline Characteristics

This study included 96 target legs (75 male (78.1%), median age 70 years (IQR 63 - 76)). The median time to occlusion was 15.5 months (IQR 3.0 - 36.3), with a significantly longer time for the UK-group compared to the AL-group (P = 0.04). Causes of occlusion were similar between study groups (P = 0.06), with only a significant difference in occlusion caused by improper antithrombotic agent (ATA) use (UK N = 3 versus AL N = 0, P = 0.02). The cause of occlusion was unknown in 39 cases (40.6%) and caused by edge stenosis in 32 cases (33.3%). Approximately half of the patients (N = 44, 45.9%) presented with CLTI, of which the majority was classified as Rutherford 4 (N = 34, 35.4%). There was no significant difference in the prevalence of comorbidities between study groups. Patients most commonly had two devices (N = 41, 42.7%) implanted, followed by one device (N = 35, 36.5%). The mean distal stent diameter was 6.53 ± 1.64 mm. Stent

diameters between study groups were significantly different (P = 0.04), with more 6 mm stents in the UK group (P = 0.03) and more 7 mm stents in the AL group (P = 0.03). The baseline characteristics for the study population are depicted in Table 1.

Table 1. Baseline characteristics.

| Characteristics | Urokinase (N = 26) | Alteplase (N = 70) | Total (N = 96) | P-value |
|---|---|---|---|---|
| Male | 21 (80.8%) | 54 (77.1%) | 75 (78.1%) | 0.70 |
| Age at occlusion (years) | 71 (65 - 77) | 70 (63 - 76) | 70 (63 - 76) | 0.69 |
| Time to occlusion (months) | 25.0 (16.5 - 42.5) | 8.5 (2.3 - 33.5) | 15.5 (3.0 - 36.3) | 0.04 |
| *Missing* | 0 (0.0%) | 2 (2.9%) | 2 (2.1%) | |
| ICU admission | 24 (92.3%) | 62 (88.6%) | 86 (89.6%) | 0.73 |
| Cause of occlusion | | | | 0.06 |
| *Edge stenosis* | 9 (34.6%) | 23 (32.9%) | 32 (33.3%) | 1.00 |
| *Suboptimal (out) flow* | 4 (15.4%) | 6 (8.5%) | 10 (10.4%) | 0.45 |
| *Improper ATA use* | 3 (10.5%) | 0 (0.0%) | 3 (3.1%) | 0.02 |
| *Suspicion of clotting disease* | 2 (7.7%) | 4 (5.7%) | 6 (6.3%) | 0.66 |
| *Anatomical cause* | 1 (3.8%) | 5 (7.1%) | 6 (6.3%) | 1.00 |
| *Cause unknown* | 7 (26.9%) | 32 (45.7%) | 39 (40.6%) | 0.11 |
| Rutherford classification | | | | 0.60 |
| *Category 0* | 0 (0.0%) | 1 (1.4%) | 1 (1.4%) | |
| *Category 1* | 2 (7.7%) | 6 (8.5%) | 8 (8.3%) | |
| *Category 2* | 4 (15.4%) | 7 (10.0%) | 11 (11.5%) | |
| *Category 3* | 5 (19.2%) | 21 (20.0%) | 26 (27.1%) | |
| *Category 4* | 11 (42.3%) | 23 (32.9%) | 34 (35.4%) | |
| *Category 5* | 0 (0.0%) | 6 (8.6%) | 6 (6.3%) | |
| *Category 6* | 2 (7.7%) | 2 (2.9%) | 4 (4.2%) | |
| *Missing* | 2 (7.7%) | 4 (5.7%) | 6 (6.3%) | |
| Comorbidities | | | | |
| *Diabetes mellitus* | 11 (42.3%) | 19 (27.1%) | 30 (31.3%) | 0.43 |
| *Missing* | 0 (0.0%) | 1 (1.4%) | 1 (1.0%) | |
| *Hypertension* | 23 (88.5%) | 54 (77.1%) | 77 (80.2%) | 0.55 |
| *Missing* | 0 (0.0%) | 1 (1.4%) | 1 (1.0%) | |
| *Hyperlipidemia* | 22 (84.6%) | 48 (68.8%) | 70 (72.9%) | 0.30 |
| *Missing* | 0 (0.0%) | 1 (1.4%) | 1 (1.0%) | |
| *Atrial fibrillation* | 2 (7.7%) | 15 (21.4%) | 17 (17.7%) | 0.23 |
| *Missing* | 0 (0.0%) | 2 (2.9%) | 2 (2.1%) | |
| *Coronary artery disease* | 7 (26.9%) | 22 (31.4%) | 29 (30.2%) | 0.90 |

**Continued**

| | | | | |
|---|---|---|---|---|
| *Missing* | 0 (0.0%) | 2 (2.9%) | 2 (2.1%) | |
| *Heart failure* | 0 (0.0%) | 2 (2.9%) | 2 (2.1%) | 1.00 |
| *Missing* | 0 (0.0%) | 2 (2.9%) | 2 (2.1%) | |
| Stent quantity | | | | 0.56 |
| *1* | 11 (42.3%) | 24 (34.3%) | 35 (36.5%) | |
| *2* | 11 (42.3%) | 30 (42.9%) | 41 (42.7%) | |
| *3* | 2 (7.7%) | 11 (15.7%) | 13 (13.5%) | |
| *4* | 1 (3.8%) | 1 (1.4%) | 2 (2.1%) | |
| *Missing* | 1 (3.8%) | 4 (5.7%) | 5 (5.2%) | |
| Distal stent diameter mean (mm) | 6.48 ± 1.81 | 6.56 ± 1.56 | 6.53 ± 1.64 | 0.83 |
| Distal stent diameter (mm) | | | | 0.04 |
| *5* | 5 (19.2%) | 16 (22.8%) | 21 (21.8%) | 0.78 |
| *6* | 16 (61.5%) | 24 (34.3%) | 40 (41.7%) | 0.03 |
| *7* | 0 (0.0%) | 11 (15.7%) | 11 (11.5%) | 0.03 |
| *8* | 1 (3.8%) | 6 (8.6%) | 7 (7.3%) | 0.67 |
| *9* | 0 (0.0%) | 1 (1.4%) | 1 (1.0%) | 1.00 |
| *10* | 0 (0.0%) | 4 (5.7%) | 4 (4.2%) | 0.57 |
| *11* | 3 (11.5%) | 2 (2.9%) | 5 (5.2%) | 0.13 |
| *Missing* | 1 (3.8%) | 6 (8.6%) | 7 (7.3%) | |
| Distal landing zone | | | | 0.84 |
| *P1 or above* | 7 (26.9%) | 22 (31.4%) | 29 (30.2%) | |
| *P2* | 5 (19.2%) | 15 (21.4%) | 20 (20.8%) | |
| *P3* | 14 (53.8%) | 33 (47.1%) | 47 (49.0%) | |

Values are median (interquartile range), mean ± SD or N(%). ICU: intensive care unit, ATA: antithrombotic agent.

## 3.2. Outcomes

### 3.2.1. Short-Term Outcomes

Short- and long-term outcomes are depicted in Table 2. The duration of thrombolysis treatment was significantly longer for the UK group (30.58 ± 9.07 hours) compared to the AL group (26.13 ± 9.37 hours) (P = 0.04). Both groups had comparable complication rates (P = 0.76). Complications were seen in thirty patients (31.3%), of which nine cases (9.4%) were major complications (major bleeding (N = 5), fasciotomy (N = 4)). There was no significant difference regarding the patency of run-off vessels (P = 0.86). After thrombolysis treatment, 50 patients (52.1%) had significant residual lesions in the VIABAHN SG, with comparable amounts between groups (P = 0.72). In the UK group, 17 patients (65.4%) received additional treatment, of which three patients (11.5%) had no residual lesions. Three patients (11.5%) received no further treatment, even though they had residual lesions.

**Table 2.** Outcomes.

| | Urokinase (N = 26) | Alteplase (N = 70) | P-value |
|---|---|---|---|
| **Short-term outcomes** | | | |
| Thrombolysis duration (hours) | 30.58 ± 9.07 | 26.13 ± 9.37 | 0.04 |
| ICU-stay (days) | 1.73 ± 0.60 | 1.50 ± 0.61 | 0.10 |
| Complications | | | 0.76 |
| *None* | 19 (73.1%) | 49 (70.0%) | 0.81 |
| *Inguinal injuries* | 4 (15.4%) | 10 (14.3%) | 1.00 |
| *Bleeding elsewhere* | 1 (3.8%) | 4 (5.7%) | 1.00 |
| *Early discontinuation* | 0 (0.0%) | 4 (5.7%) | 0.57 |
| *Contrast allergy* | 0 (0.0%) | 1 (1.4%) | 1.00 |
| *Four-compartment fasciotomy* | 2 (7.7%) | 2 (2.9%) | 0.30 |
| Outflow vessels | | | 0.86 |
| *0* | 1 (3.8%) | 3 (4.3%) | 0.92 |
| *1* | 7 (26.9%) | 17 (24.3%) | 0.79 |
| *2* | 8 (30.8%) | 22 (31.4%) | 0.95 |
| *3* | 10 (38.5%) | 28 (40.0%) | 0.89 |
| Residual lesions | 17 (65.4%) | 43 (61.4%) | 0.72 |
| Additional treatment | 17 (65.4%) | 41 (58.6%) | 0.64 |
| *Additional PTA* | 13 (50.0%) | 29 (41.4%) | 0.45 |
| *Additional stent* | 8 (30.8%) | 23 (32.9%) | 0.85 |
| *Additional thrombosuction* | 0 (0.0%) | 2 (2.9%) | 1.00 |
| Successful treatment | 24 (93.3%) | 63 (90.0%) | 0.73 |
| **Long-term outcomes** | | | |
| Deaths (one year post-intervention) | 1 (5.3%) | 2 (3.1%) | 0.06 |
| *Missing data* | 7 (26.9%) | 6 (8.6%) | |
| *Treatment < one year ago* | 7 (26.9%) | 5 (7.1%) | |
| *Lost to follow-up* | 0 (0.0%) | 1 (1.4%) | |
| Amputations | | | 0.54 |
| *None* | 22 (84.6%) | 45 (64.3%) | 0.75 |
| *Minor* | 0 (0.0%) | 3 (4.3%) | 0.55 |
| *Major* | 3 (11.5%) | 7 (10.0%) | 1.00 |
| *Missing data* | 1 (3.8%) | 15 (21.4%) | |
| Time to re-occlusion (months) | 5.35 ± 0.85 | 7.48 ± 0.72 | 0.49 |

Values are mean ± SD, or N(%). ICU: intensive care unit, PTA: percutaneous transluminal angioplasty.

In the AL group, 41 patients (61.4%) received additional treatment. Seven patients (10.0%) received further treatment without residual lesions, and nine patients (12.9%) received no other treatment whilst having residual lesions. After

supplementary treatments, thrombolysis was successful in 24 out of 26 patients (93.3%) in the UK group and 63 out of 70 (90.0%) in the AL group (P = 0.73).

### 3.2.2. Long-Term Outcomes

No significant differences were found in long-term outcomes. All-cause mortality within the first-year post-thrombolysis was 3.1%, with one case in the UK group and two cases in the AL group (P = 0.06). One patient died four months post-treatment of cardiogenic shock. The cause of death for the other two patients (four- and 11-months post-treatment) was not reported in the patient records. Amputation rates were evenly distributed between groups (P = 0.54). A total of 13 patients (13.5%) had an amputation of the target limb, of which 10 patients (10.4%) underwent major amputation. Seven amputations (7.3%) were due to failed thrombolysis. Patency in both study groups was similarly low, with a one-year patency of 13.9% in the UK group and 36.6% in the AL group (P = 0.06). The three, six, and nine months of patency post-thrombolysis were found to be similar as well (P = 0.58, P = 0.85, and P = 0.20, respectively). Average time to re-occlusion for the study population was 4.21 ± 4.14 months. The primary patency, respective p-values, and corresponding survival plots are displayed in Figure 1.

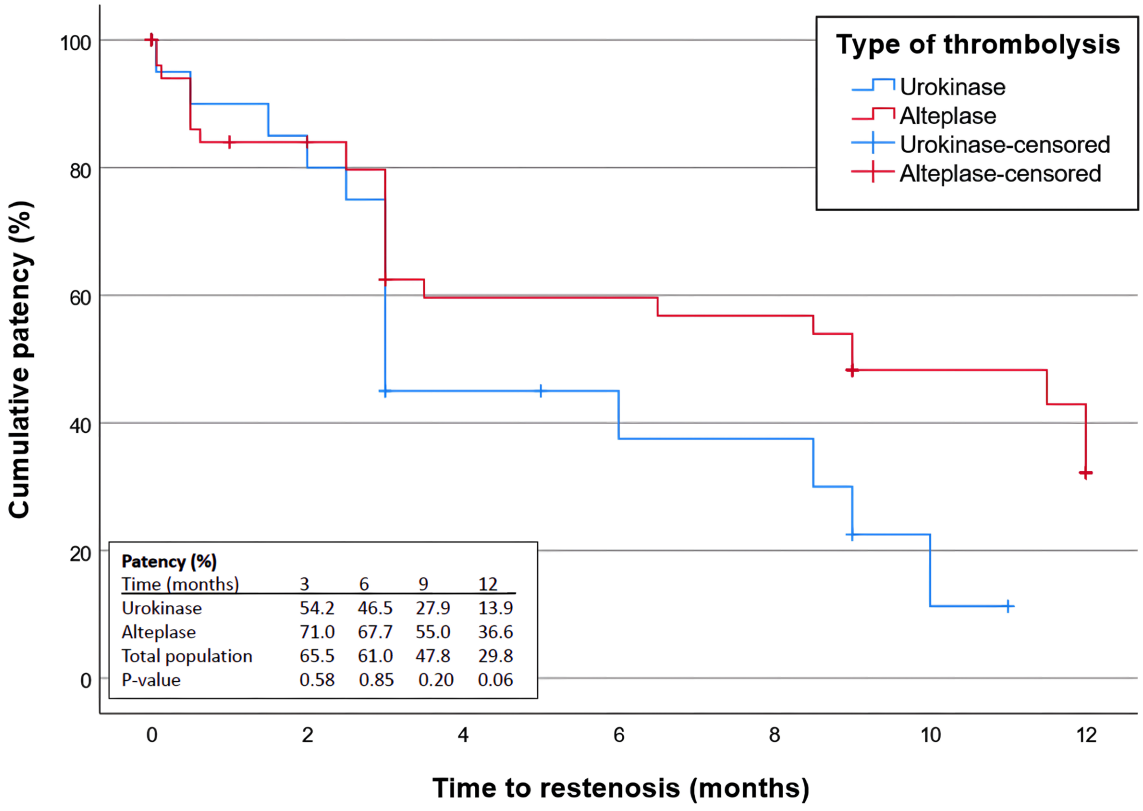


Figure 1. One-year stent-patency.

### 3.2.3. Antithrombotic Agent Use

Most patients were on a monotherapy ATA regimen pre-intervention (N = 63, 65.6%). The only significant difference in the baseline was more thrombocyte

aggregation inhibitor (TAI) use in the UK group (N = 10, 38.5%) compared to the AL group (N = 8, 11.4%) (P = 0.001). ATA uses pre- and post-thrombolysis is depicted in Table 3. Most patients were prescribed dual therapy (N = 77, 80.2%) versus monotherapy (N = 19, 19.8%), with no significant difference between groups (P = 0.51).

Table 3. Antithrombotic agents; changes and usage pre- and post-intervention.

| | Urokinase (N = 26) | Alteplase (N = 70) | Total (N = 96) | P-value |
|---|---|---|---|---|
| ATA use pre-intervention | | | | |
| Monotherapy | 21 (80.8%) | 42 (60.0%) | 63 (65.6%) | 0.06 |
| *TAI* | 10 (38.5%) | 8 (11.4%) | 18 (18.8%) | 0.001 |
| *P2Y12 inhibitor* | 6 (23.1%) | 18 (25.7%) | 24 (25.0%) | 1.00 |
| *VKA* | 1 (3.8%) | 10 (14.3%) | 11 (11.5%) | 0.28 |
| *DOAC* | 4 (15.4%) | 6 (8.6%) | 10 (10.4%) | 0.45 |
| Dual therapy | 5 (19.2%) | 28 (40.0%) | 33 (34.4%) | 0.06 |
| *DAPT* | 2 (7.7%) | 17 (24.3%) | 19 (19.8%) | 0.09 |
| *TAI + DOAC* | 1 (3.8%) | 6 (8.6%) | 7 (7.3%) | 0.67 |
| *TAI + VKA* | 2 (7.7%) | 4 (5.7%) | 6 (6.3%) | 0.66 |
| *P2Y12 inhibitor + DOAC* | 0 (0.0%) | 1 (1.4%) | 1 (1.0%) | 1.00 |
| ATA changes < 3 m pre-intervention | | | | 0.80 |
| *None* | 16 (61.5%) | 41 (58.6%) | 57 (59.4%) | |
| *Yes. addition* | 5 (19.2%) | 10 (14.3%) | 15 (15.6%) | |
| *Yes. change* | 1 (3.8%) | 3 (4.3%) | 4 (4.2%) | |
| *Yes. discontinuation* | 1 (3.8%) | 2 (2.9%) | 3 (3.1%) | |
| *Wrong use or wrong type* | 0 (0.0%) | 6 (8.6%) | 6 (6.3%) | |
| *Unknown* | 3 (11.5%) | 8 (11.4%) | 11 (11.5%) | |
| ATA use post-intervention | | | | |
| *Monotherapy* | 4 (15.4%) | 15 (21.4%) | 19 (19.8%) | 0.51 |
| *TAI* | 1 (3.8%) | 2 (2.9%) | 3 (3.1%) | |
| *P2Y12 inhibitor* | 0 (0.0%) | 3 (4.3%) | 3 (3.1%) | |
| *VKA* | 0 (0.0%) | 6 (8.6%) | 6 (6.3%) | |
| *DOAC* | 3 (11.5%) | 4 (5.7%) | 7 (7.3%) | |
| *Dual therapy* | 22 (84.6%) | 55 (78.6%) | 77 (80.2%) | 0.51 |
| *DAPT* | 12 (46.2%) | 29 (41.4%) | 41 (42.7%) | |
| *TAI + DOAC* | 5 (19.2%) | 13 (18.6%) | 18 (18.8%) | |
| *TAI + VKA* | 3 (11.5%) | 10 (14.3%) | 13 (13.5%) | |
| *P2Y12 inhibitor + DOAC* | 1 (3.8%) | 0 (0.0%) | 1 (1.0%) | |
| *P2Y12 inhibitor + LMWH* | 1 (3.8%) | 2 (2.9%) | 3 (3.1%) | |
| *P2Y12 inhibitor + VKA* | 0 (0.0%) | 1 (1.4%) | 1 (1.0%) | |

Values are N(%). ATA: antithrombotic agent, TAI: thrombocyte aggregation inhibitor, VKA: vitamin K antagonist, DOAC: direct oral anticoagulants, DAPT: dual antiplatelet therapy.

## 4. Discussion

Both urokinase and alteplase were proven effective modalities for treating thrombosed SGs. Alteplase exhibited slight superiority with significantly shorter treatment times (26.13 ± 9.37 hours versus 30.58 ± 9.07 hours, P = 0.04) and shorter average ICU stay (1.50 ± 0.61 days as opposed to 1.73 ± 0.60 days for urokinase, P = 0.10). These findings are consistent with prior studies investigating the working mechanisms of these thrombolytics [11] [12]. Tan *et al.* reported a quicker onset of action and superior thrombolysis rates with alteplase compared to urokinase [12]. Furthermore, despite a statistically insignificant difference, alteplase resulted in a more favorable one-year patency (36.6% versus 13.9%). However, the differences between alteplase and urokinase are small and may not be clinically significant in all scenarios, since shorter treatment time does not automatically correspond to shorter hospital stay or less (major) complications. Caution should be taken when choosing between alteplase and urokinase, considering broader clinical contexts such as patient characteristics and available hospital resources.

Intra-arterial thrombolysis with urokinase and alteplase showed equally high success rates of 93.3% and 90.0% (P = 0.73). However, IAT as a standalone treatment resulted in high rates of residual lesions and low success rates (34.6% in the UK group and 38.6% in the AL group), highlighting the importance of additional treatments to restore optimal blood flow. The need for additional treatments was demonstrated in previous research, stating that 50% of patients needed supplementary treatments post-thrombolysis for successful results [4]. The STILE trial concluded that the durability of the treatment mainly depends on secondary treatments [6]. As reflected in our results, secondary treatments after IAT are imperative. Additional treatments, for example, percutaneous transluminal angioplasty or deployment of additional stents, are necessary to achieve optimal and durable results. Further research is needed to identify the most effective interventions and the optimal timing for their implementation.

There is no significant difference in outcome between both thrombolytics regarding major complication and amputation rates, reflecting the safety of both treatments (P = 0.76, P = 0.87, respectively). In this study, 9.4% of the patients had a major complication and 7.3% needed an amputation, which is higher than mentioned in previous research [2] [4]-[6]. We hypothesize fewer complications and amputations when IAT is mainly used on patients presenting without CLTI, as recommended in the Dutch guidelines [1]. The treatment of patients with Rutherford 4 or higher with IAT is discouraged due to the limited time these patients have to achieve revascularization [1]. Average thrombolysis treatment takes longer than 24 hours, exposing patients to longer ischemic time and higher risk of compartment syndrome compared to surgical thrombectomy [1] [2]. The fourloge fasciotomies in this study (N = 4, 4.2%) were performed on patients who presented with CLTI and may have been preventable if these patients were treated with surgical thrombectomies. Besides fasciotomies, our study reported five cases (5.2%) of significant bleeding, a rate comparable to previous research [2] [5] [6];

three patients had significant bleeding from punction sites, and two patients suffered bleeding elsewhere in the body, necessitating blood transfusions. Amputation rates in both study groups were comparable (P = 0.87). Our study concluded a total of seven amputations (7.3%) that resulted from failed thrombolysis, similar to previous research [4]; five were performed shortly after discontinuation of thrombolysis, and two patients were treated conservatively, worsened clinically and eventually had amputations within thirty days after treatment. Again, it is remarkable that five of seven amputations were patients presenting with CLTI and, therefore, had an absolute indication for treatment but a to-be-argued indication for IAT [1]. It is critical to correctly indicate whether to use thrombolysis, surgical thrombectomy, or bypass surgery when dealing with patients with CLTI, with accurate decision-making possibly leading to lower complication and amputation rates. To assess amputation risk and revascularization benefit we recommend the use of the WIfI (wound, ischemia, foot infection) classification to compose treatment plans in patients with CLTI [1] [14] [15]. We recommend using IAT on patients presenting without CLTI and surgical thrombectomy or open bypass surgery for patients presenting with CLTI, as currently stated in Dutch and European guidelines [1].

Notably, post-intervention there was a high variability in ATA regimens. Currently, there is no guideline regarding the use of ATA after IAT for SG thrombosis. Previous research concluded that the use of 2 or more ATAs significantly reduces the risk of re-thrombosis in SGs, however, there is no consensus on what combination of medications is preferred [2]. We recommend conducting further research to identify the best post-thrombolysis ATA policy for thrombosed SGs and making evidence-based protocols accordingly.

As, in both study groups, high re-occlusion rates were noted and consequently low one-year patency (13.9% for UK and 36.6% for AL), without an anatomical substrate, proper ATA regimens might be crucial in this patient group. Statistically, we found no significant difference in primary patency at three- , six- , nine- , and twelve-month post-thrombolysis (P = 0.58; P = 0.85; P = 0.20; P = 0.06), however, our study did not control for ATA as a confounding factor in the one-year patency analysis. Since there is no previous research on this subject to compare our results, we recommend further research to determine if there is a difference in primary patency after treatment with alteplase or urokinase and if confounding factors like comorbidities, stent characteristics and variations in ATA regimens influence these results.

For the study population, we concluded a one-year patency rate post-thrombolysis of 29.5%, significantly lower than previously published patencies of 55% - 56% [2] [4]. We hypothesize that poor follow-up after thrombolysis could explain the low patency rates. The average time from implantation to primary occlusion was 15.5 months and drops after thrombolysis to 4.21 ± 4.14 months. From this data, we conclude that many SG reocclude within the first year post-thrombolysis. Currently, patients are only followed up at six weeks and yearly post-thrombo-

lysis. The vast majority of patients after thrombolysis reoccludes between the current two follow-up moments. Implication of an extra follow-up, for instance at three or six months, could decrease the rate of re-occlusion by screening specifically for residual or rebound lesions after treatments. Previous research that performed standardized follow-ups at six weeks and six, nine, and twelve months post-implantation concluded that continuous surveillance of patients led to fewer cases of thrombosis, explained by earlier recognition and treatment of less severe edge stenosis [3] [15]. Edge stenosis is the Achilles heel of the SG, with high rates of in-stent thrombosis (up to 66%) caused through this mechanism [4]. Edge stenosis, especially when recognized early on, is treated more quickly and effectively than occluded SGs [3]. We recommend conducting research on a more strict and longer follow-up schedule, hypothesizing that detecting and treating (edge) stenosis early on, could improve patency after implementation and after successful thrombolysis.

### 4.1. Limitations

This study includes a few limitations. The patient population is small and resides mainly in the same area, leading to a homogeneous population and limiting the generalization of our findings to broader populations. Additionally, results may be skewed by a gap in our inclusion criteria, resulting in patients with different indications for the endograft and, thus, different disease processes being included in the study. This study did not control for confounding factors, resulting in less accurate results which should be interpreted with caution. The study's retrospective design accompanies incomplete and missing data, impacting our results' overall accuracy and power. Furthermore, this study suffered a considerable loss in follow-up due to the retrospective design and the lack of a uniform follow-up protocol. Data collection was performed by one researcher, leading to possible observer bias. Lastly, the follow-up period from this study was short. More reliable results and insight can be gathered with extended follow-up periods. Recommendations for future research include adopting a multi-center, preferably prospective approach, with standardized follow-up protocols and longer follow-up time.

### 4.2. Conclusion

Urokinase and alteplase proved to be equally effective and safe modalities; however, alteplase has a slight preference based on treatment times. While success rates are comparable between groups, this study highlights the challenges of standalone intra-arterial thrombolysis and accentuates the need for additional interventions to achieve optimal and durable results. Complications, amputations, and patency show no significant difference between both study groups. Incidences of major complications and amputations were high, and administering thrombolytics should be approached with caution. It is imperative to establish guidelines stating for which patient categories intra-arterial thrombolysis is indicated and beneficial. Patency rates in both study groups were low, and we recommend strict

follow-up schedules to improve these outcomes. Finally, we recommend conducting further research to identify the best post-thrombolysis ATA policy.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

## Conflicts of Interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We declare that the submission is original work and is not under review at any other publication.

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## Abbreviations

- SG: stent-graft
- SFA: superficial femoral artery
- IAT: intra-arterial thrombolysis
- CLTI: critical limb threatening ischemia
- UK: urokinase
- AL: alteplase
- CFA: common femoral artery
- ATA: antithrombotic agent
- TAI: thrombocyte aggregation inhibitor