# Rivaroxaban or vitamin-K antagonists following early endovascular thrombus removal and stent placement for acute iliofemoral deep vein thrombosis

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Abstract: Background The optimal anticoagulant following catheter-based therapy of acute iliofemoral deep vein thrombosis (IFDVT) is unknown. Methods From the Swiss Venous Stent registry, an ongoing prospective cohort study, we performed a subgroup analysis of patients with acute IFDVT who underwent catheter-based early thrombus removal followed by nitinol stent placement. Duplex ultrasound and Villalta scores were used to determine patency rates and incidence of the post-thrombotic syndrome (PTS) in patients treated with either rivaroxaban (n = 73) or a vitamin K-antagonist (VKA; n = 38) for a minimum duration of 3 months. Results Mean follow-up duration was 24 ± 19 months (range 3 to 77 months). Anticoagulation therapy was time-limited (3 to 12 months) in 56% of patients (47% in the rivaroxaban group and 58% in the VKA group, p = 0.26), with shorter mean duration of anticoagulation in the rivaroxaban group (180 ± 98 days versus 284 ± 199 days, p = 0.01). Overall, primary and secondary patency rates at 24 months were 82% (95%CI, 71–89%) and 95% (95%CI, 87–98%), respectively, with no difference between the rivaroxaban (87% [95%CI, 76–94%] and 95% [95%CI, 85–98%]) and the VKA group (72% [95%CI, 52–86%] and 94% [95%CI, 78–99%]; p > 0.10 for both). Overall, 86 (86%) patients were free from PTS at latest follow-up, with no difference between the rivaroxaban and the VKA groups (57 [85%] versus 29 [88%]; p = 0.76). Two major bleeding complications (1 in each group) occurred in the peri-interventional period, without any major bleeding thereafter. Conclusions In patients with acute IFDVT treated with catheter-based early thrombus removal and venous stent placement, the effectiveness and safety of rivaroxaban and VKA appear to be similar.

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# Rivaroxaban or vitamin-K antagonists following early endovascular thrombus removal and stent placement for acute iliofemoral deep vein thrombosis

Short title: Anticoagulation after endovascular therapy of acute IFDVT

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**Abstract**

*Background:* The optimal anticoagulant following catheter-based therapy of acute iliofemoral deep vein thrombosis (IFDVT) is unknown.

Methods: From the Swiss Venous Stent registry, an ongoing prospective cohort study, we performed a subgroup analysis of patients with acute IFDVT who underwent catheter-based early thrombus removal followed by nitinol stent placement. Duplex ultrasound and Villalta scores were used to determine patency rates and incidence of the post-thrombotic syndrome (PTS) in patients treated with either rivaroxaban (n=73) or a vitamin K-antagonist (VKA; n=38) for a minimum duration of 3 months.

*Results:* Mean follow-up duration was 24±19 months (range 3 to 77 months). Anticoagulation therapy was time-limited (3 to 12 months) in 56% of patients (47% in the rivaroxaban group and 58% in the VKA group, p=0.26), with shorter mean duration of anticoagulation in the rivaroxaban group (180±98 days versus 284±199 days, p=0.01). Overall, primary and secondary patency rates at 24 months were 82% (95%CI, 71-89%) and 95% (95%CI, 87-98%), respectively, with no difference between the rivaroxaban (87% [95%CI, 76-94%] and 95% [95%CI, 85-98%]) and the VKA group (72% [95%CI, 52-86%] and 94% [95%CI, 78-99%]; p>0.10 for both). Overall, 86 (86%) patients were free from PTS at latest follow-up, with no difference between the rivaroxaban and the VKA groups (57 [85%] versus 29 [88%]; p=0.76). Two major bleeding complications (1 in each group) occurred in the peri-interventional period, without any major bleeding thereafter.

*Conclusions:* In patients with acute IFDVT treated with catheter-based early thrombus removal and venous stent placement, the effectiveness and safety of rivaroxaban and VKA appear to be similar.

Clinical Trial Registration: The study is registered on the National Institutes of Health website (ClinicalTrials.gov; identifier NCT02433054).

*Keywords:* Anticoagulation; catheter-directed thrombolysis; deep vein thrombosis; post-thrombotic syndrome; rivaroxaban

## Introduction

Deep vein thrombosis (DVT) is associated with severe morbidity and mortality. It is the most frequent type of venous thromboembolism (VTE) and responsible for approximately 800.000 deaths per year in the European Union and the United States combined.[1, 2] The most important long term complications of DVT are the post-thrombotic syndrome (PTS) and recurrent VTE. Patients with iliofemoral DVT (IFDVT) are at particularly high risk, with up to 50% of these patients suffering from the PTS,[3-5] most likely due to the strategic anatomic location with low recanalization rates of these veins.[6] Furthermore, patients with IFDVT have a twofold higher risk for recurrent VTE under therapeutic anticoagulation therapy than patients with more distal DVT.[7]

Early endovascular thrombus removal therapy, i.e. catheter-directed thrombolysis (CDT) or pharmacomechanical thrombectomy (PMT), reduces the risk of moderate or severe PTS by removing the occluding thrombus and by preventing secondary venous valve damage.[8-10] Up to 80% of patients with IFDVT have an underlying obstructive iliac vein lesion,[11, 12] which can be treated by stent placement once the acute thrombus has been removed.[13] Venous patency rates 6-24 months after catheter-based thrombus removal with or without stent placement in patients with IFDVT ranged between 72% and 100%.[14-16] Based on the results of small randomized-controlled trials and prospective cohort studies, clinical practice guidelines suggest the use of early thrombus removal strategies and adjunctive use of venous stents for residual obstructive vein lesions as first-line therapy in selected patients with acute IFDVT and low bleeding risk.[17-20]

Anticoagulation therapy remains the cornerstone for patients with DVT. Recently, direct oral anticoagulants (DOAC), including rivaroxaban, have replaced vitamin K-

antagonists (VKA) as first-line therapy in most DVT patients, due to reduced risk of major bleeding [21-24] and increased patient comfort. DOACs may become an alternative to low-molecular-weight heparins (LMWH) in patients with cancer-associated thrombosis and low risk of bleeding.[25, 26] However, the optimal type and duration of anticoagulant therapy after early thrombus removal for acute IFDVT, particularly in the presence of venous stents, is still unclear. Several studies have investigated the efficacy and safety of early thrombus removal and venous stent placement, but little attention has been paid to exploration and verification of antithrombotic therapy.[3, 9, 13, 15, 27-32] The majority of available studies reported time-limited anticoagulation with VKA after catheter-based therapy, but stent placement rates varied significantly between the studies (7% – 100%). Although there is a consensus that anticoagulation therapy is preferable to antiplatelet therapy, it remains unclear whether DOAC are equally effective as VKA in this setting. Unfortunately, recent large randomized controlled trials comparing the different DOACs with LMWH/VKA systematically excluded patients undergoing early thrombus removal or stent placement.[22, 24, 33, 34]. At present, consensus statement guidelines do not specifically address anticoagulant therapy in patients undergoing endovascular treatment of DVT.[19, 35]

The aim of our study was to report the effectiveness and safety of rivaroxaban and VKA in patients with early endovascular thrombus removal and stent placement for acute IFDVT.

## Methods

*Study design*

We performed a subgroup analysis derived from the Swiss Venous Stent registry, an ongoing prospective study enrolling consecutive patients who received venous nitinol stents at the University Clinic of Angiology in Bern since July 2011. We included all patients with acute IFDVT who underwent endovascular thrombus removal therapy (CDT and/or PMT) followed by stent placement. All patients had at least one clinical visit and duplex ultrasound study. Exclusion criteria were the inability to provide informed consent, age below 18 years, estimated life expectancy <3 months, endovascular therapy without stent placement, and post-interventional anticoagulation therapy other than rivaroxaban or VKA. For the current analysis, 11 patients who underwent endovascular therapy for IFDVT but received parenteral anticoagulation therapy only due to cancer associated IFDVT were excluded. During the study period, the stent placement rate in patients with IFDVT treated with early thrombus removal was 80%.[13, 16] The registry and participant consent form were approved by the Swiss Ethics Committee on research involving humans. The study is registered on the National Institutes of Health website (ClinicalTrials.gov; identifier NCT02433054). All authors had full access to all the data in the study.

*Data and subgroup definitions*

For all enrolled patients, baseline demographic information, disease-specific information (thrombosis localization, involved venous segments, symptom onset, recurrence), comorbid conditions, risk factors, and anticoagulation therapy (anticoagulant type, treatment duration, bleeding complications) were recorded using

a standardized case report form. Procedural data included type of catheter intervention (CDT/PMT), duration, dose and success of thrombolysis, and type and number of implanted stents.

For the purpose of the present analysis, we predefined two patient subgroups:

1. Patients treated with rivaroxaban for a minimum of 3 months.
2. Patients treated with VKA (targeting INR of 2.0 – 3.0) for a minimum of 3 months.

*Diagnosis and anticoagulation therapy*

IFDVT was objectively confirmed by duplex ultrasound or contrast-enhanced computed tomography. Acute DVT was defined as symptom duration ≤14 days; subacute DVT as thrombosis for which symptoms were present for 15 to 28 days. DVT was defined as provoked in the presence of recent immobilization (bed ridden for >72 h, plaster cast, or long-distance travel of >6 h), postoperative, trauma, hormone therapy (oral contraceptives, postmenopausal hormonal replacement, tamoxifen use), active cancer, pregnancy or postpartal period, or after acute medical illness (e.g. pneumonia, congestive heart failure).[36]

On admission, an intravenous bolus of heparin of 80 units per kg body weight was administered. If the patient was already on full anticoagulation therapy, the initial bolus was omitted. In case of CDT, patients were treated with intravenous heparin administered through the venous access sheath throughout the thrombolysis until time of second look venography, adjusted to target a factor Xa inhibition activity of 0.3 to 0.7 IU/ml. Within 24 h after full completion of the endovascular therapy, heparin was converted to either VKA (with overlapping LMWH for at least 5 days) or rivaroxaban. The choice of anticoagulation therapy was up to the treating vascular specialist, and there was no predefined algorithm for the allocation of the anticoagulation therapy.

VKA dosage was adapted by the general practitioner and we did not collect data on the time in the therapeutic range in the VKA group. We did not prescribe antiplatelet therapy after venous stenting by default, unless otherwise indicated.

*Catheter-based therapy*

Details on the CDT and PMT procedures have been published previously.[13, 37] In patients with thrombus extension into the popliteal veins or into the inferior vena cava, initial CDT was performed with a standard multi-sidehole catheter (e.g. Craigg-McNamara®, ev3 Endovascular, Plymouth, MN, USA) or an ultrasound-assisted catheter system (EkoSonic MACH4 Endovascular System®, EKOS Corporation, Bothell, WA, USA) according a standardized catheter thrombolysis protocol (20 mg recombinant tissue plasminogen activator [Actilyse; Boehringer Ingelheim, Ingelheim am Rhein, Germany] over 15 h ).[13, 16] In case of residual thrombi, either prolonged CDT or additional PMT using an AngioJet device (Boston Scientific, Minneapolis, MN, USA) was performed. If the thrombus burden was less extensive, single session PMT with an AngioJet device without prior CDT was an option.[37] Significant residual vein stenosis (visualized by digital subtraction venography in two orthogonal views, or by intravascular ultrasound if venography was equivocal), defined as luminal narrowing >50%, absent antegrade flow, or presence of collateral flow at the site of suspected stenosis, were treated by balloon angioplasty and stent implantation as previously described.[37]

*Clinical follow-up*

Clinical follow-up visits were routinely performed at our outpatient clinic by vascular specialists at 3, 6, 12 months, followed by yearly visits. At each visit, symptoms and

clinical signs of PTS were recorded using the Villalta score and revised venous clinical severity scores (rVCSS).[38, 39] Current anticoagulation therapy and recent VTE complications were assessed. Patients received a standardized duplex sonography examination at each follow-up visit, scanning for thrombotic and post-thrombotic changes of both the treated stent segments and the inflow vessels.

*Definition of outcomes*

*Technical success* was defined as antegrade flow and maximal luminal stenosis of ≤30% at termination of the procedure by venography, and evidence of spontaneous flow in the treated vein segment by duplex sonography.[13] *Primary patency rate* was defined as the percentage of patients with primary treatment success and without the occurrence of either thrombosis of the treated segment or re-intervention to maintain patency of the treated segment. *Primary assisted patency rate* was defined as the percentage of patients with primary treatment success and without the occurrence of thrombosis of the treated segment, irrespectively of any interval therapy. *Secondary patency rate* was defined as the percentage of patients with primary treatment success and without the occurrence of permanent loss of flow in the treated segment, irrespective of any interval therapy.[40]

In order to distinguish between the bleeding complications due to the endovascular intervention and those due to the anticoagulation therapy thereafter, we defined *peri-interventional bleeding complications* as bleeding complications within the first 72 h and *post-interventional bleeding complications* as bleeding complications ≥72 h after the end of the catheter-based treatment. Bleeding complications were classified according to the International Society on Thrombosis and Haemostasis, where major bleedings are either 1) fatal bleeding, 2) symptomatic bleeding in a critical area or

organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or 3) bleeding causing a drop in hemoglobin level of 20g/L, or leading to transfusion of ≥2 units of packed red blood cells. Minor bleedings are less severe bleedings not included in the definition of major bleedings.[41]

Presence of PTS was defined as a total Villalta score of ≥5 points, or the presence of a venous ulcer. PTS was classified as mild (Villalta score of 5 to 9 points), moderate (10 to 14 points), or severe (≥15 points, or presence of venous ulcers).

*Statistical analysis*

Data are presented as means ± standard deviations or absolute numbers and percentages for continuous and categorical variables, respectively. Categorical outcomes are presented as percentage with 95% confidence intervals (95%CI).

P-values for differences between the groups were calculated from unpaired t-tests or Wilcoxon rank test where appropriate for continuous variables, and chi-square test for categorical variables. The cumulative risks of patency rates were estimated with the Kaplan–Meier method, and compared by use of a univariate Cox-regression analysis. In addition, we compared time to events for primary and secondary patency rates between the groups using the log-rank test. A p-value $<0.05$ was considered statistically significant. Data were analyzed using STATA 14.1 software (STATACorp LP, College Station, TX, USA).

## Results

*Baseline characteristics and thrombosis extension*

A total of 111 patients with a mean age of 46 ± 20 years were included. Baseline characteristics were similar in both groups except for age, immobilization, hormone therapy and duration of symptoms (Table 1). All patients had thrombotic occlusion of the common or the external iliac veins, with thrombus extension to the common femoral, femoral, popliteal veins or the inferior vena cava in 79 (71%), 51 (46%), 38 (34%) and 22 (20%) patients, respectively, without difference between both study groups (Table 1).

*Procedural data*

Primary treatment success was achieved in all patients. CDT alone or in combination with PMT was performed in 102 (92%) patients, with no difference between the two study groups (Table 2). Procedural details including treatment duration, dose, thrombolysis success and number of stents were similar in both groups (Table 2).

*Anticoagulation therapy*

All patients received anticoagulation therapy for a minimum duration of three months, with 73 (66%) patients being treated with rivaroxaban and 38 (34%) patients with VKA (Table 2). Anticoagulation was prescribed for a limited duration in 56 (50%) of patients, and for extended duration in 44 (40%) of patients. In 11 (10%) patients, the duration (limited or extended) of anticoagulation therapy was not yet determined at the last follow-up visit. In patients with anticoagulation of limited duration, mean duration of anticoagulation therapy was shorter in the rivaroxaban group than in the VKA group

(180±98 days versus 284±199 days, p=0.01). At baseline, a total of 11 (10%) patients were on antiplatelet therapy, 7 (9.7%) in the rivaroxaban group and 4 (10.5%) in the VKA group (p=0.89). In the post-interventional period, 17 (15.5%) patients were treated with antiplatelet therapy in addition to anticoagulation, with more patients treated in the VKA group than in the rivaroxaban group (11 [28.9%] versus 6 [8.3%]; p=0.004), for a median duration of 152 days (range 87 to 1123 days). A total of 5 (4.5%) patients received antiplatelet therapy during follow-up (3 [4.2%] in the rivaroxaban group versus 2 [5.3%] in the VKA group; p=0.79).

*Patency rates*

The mean follow-up duration was 24±19 months (range 3 to 77 months), with a shorter follow-up duration in the rivaroxaban group (22±16 months) than in the VKA group (31±23 months, p=0.02). Overall, primary patency rates at 12 and 24 months were 88% (95%CI, 80-93%) and 82% (95%CI, 71-89%), respectively, with no difference between the rivaroxaban group (90% [95%CI, 80-95%] and 87% [95%CI, 76-94%]) and the VKA group (85% [95%CI, 68-94%] and 72% [95%CI, 52-86%], p=0.12, Figure 1), with a non-significant hazard ratio of 0.49 (95%CI; 0.20-1.20) in favour of rivaroxaban in univariate Cox regression analysis. Among the baseline characteristics from Table 1, only active malignancy (hazard ratio of 10.2; 95%CI 2.9-36.4) was significantly associated with reduced primary patency.

Overall, primary assisted patency rates at 12 and 24 months group were 90% (95%CI, 82-95%) and 88% (95%CI, 80-94%), respectively, with no difference between the rivaroxaban group (91% [95%CI, 82-96%] and 89% [95%CI, 79-95%]) and the VKA group (88% [95%CI, 71-95%] and 88% [95%CI, 71-95%], p=0.34). Overall, secondary patency rates at 12 and 24 months were 96% (95%CI, 89-98%) and 95% (95%CI, 87-

98%), respectively, with no difference between the rivaroxaban group (97% [95%CI, 89-99%] and 95% [95%CI, 85-98%]) and the VKA group (94% [95%CI, 78-98%] and 94% [95%CI, 78-99%], p=0.83, Figure 2).

*Clinical outcomes and complications during follow-up*

Clinical follow-up data were available for 100 (90%) patients. In 11 (10%) patients with available duplex ultrasound examinations, the Villalta score could not be calculated because of missing data for individual score items. Overall, 86 (86%) patients were free from PTS at latest follow-up, with no difference between the rivaroxaban and the VKA groups (57 [85%] versus 29 [88%]; p=0.76; Table 3): 13 (13%) patients (9 [13%] in the rivaroxaban versus 4 [12%] in the VKA group; p=0.85) developed a mild PTS, and 1 (1%) patient in the rivaroxaban group developed a moderate PTS. None developed severe PTS or leg ulcers. Overall, the final mean Villalta score was 1.6 ± 2.1 (1.8 ± 2.3 in the rivaroxaban versus 1.5 ± 2.0 in the VKA group; p=0.55) and the mean rVCSS was 2.4 ± 2.4 (2.6 ± 2.6 in the rivaroxaban versus 2.0 ± 2.1 in the VKA group; p=0.30) at latest follow-up (Table 3).

Overall, 15 (14%) patients developed a recurrent VTE during follow-up: 13 (12%) had thrombotic stent reocclusion, with 5 (5%; 3 [4%] in the rivaroxaban and 2 [5%] in the VKA group; p=0.78) patients having an early stent thrombosis (within 30 days), and 8 (4 [5%] in the rivaroxaban and 4 [11%] in the VKA group; p=0.33) patients had late stent thrombosis (after 30 days). One (1%) patient in the rivaroxaban group had a symptomatic non-fatal pulmonary embolism, and 1 (1%) patient in the VKA group had a contralateral DVT.

Bleeding complications occurred in 11 (10%) patients, with 6 (8%) in the rivaroxaban and 5 (13%) in the VKA group (p=0.41). Major bleeding complications occurred in 2 (2%) patients, both in the peri-interventional period, with 1 (1%; retroperitoneal hemorrhage requiring 4 U of packed blood cells) in the rivaroxaban and 1 (3%, bleeding complication at the inguinal puncture site requiring re-intervention with delayed wound healing) in the VKA group (p=0.64). Minor bleeding complications occurred in 9 (8%) patients, with 5 (7%) in the rivaroxaban and 4 (11%) in the VKA group (p=0.50). Four (44%) of them occurred in the peri-interventional period (all minor bleeding complications at the venous puncture site), and 5 (56%) in the post-interventional period (increased menstrual bleedings, epistaxis, bleeding after venous blood sampling).

## Discussion

We report the first larger, prospective cohort study on post-intervention anticoagulation therapy following catheter-based early thrombus removal and stent placement in patients with acute IFDVT. We found that the effectiveness and safety of rivaroxaban appeared to be at least as good as VKA to preserve stent patency without an increased risk for bleeding complications or VTE recurrence.

Currently, anticoagulation therapy remains standard of care for the treatment of DVT, and there is an ongoing debate whether an additional early thrombus removal strategy is superior to conservative therapy, at least in selected patients at high risk of PTS. Several studies have linked early thrombus removal therapy to decreased occurrence of PTS.[3, 13, 15, 27-29] The randomized controlled *TORPEDO* (Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion) and *CaVenT* (Catheter-directed Venous Thrombolysis) trials showed a 23% and 28% absolute risk reduction in PTS occurrence after 30 and 60 months, respectively.[15, 27] In contrast, the largest, most recent *ATTRACT* (Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis Randomized Trial) study failed to confirm these findings, as catheter-based therapy only prevented moderate-to-severe PTS.[10] None of these trials specifically reported on patency or clinical outcomes according to different anticoagulation treatment regimens. To our knowledge, there are no other studies available comparing the efficacy and safety of various anticoagulation therapy regimens in the setting of early thrombus removal for acute IFDVT.

The average age in our study population (46 years) was somewhat lower than in the three previous trials (53-61 years).[10, 15, 28] In the *CaVenT*, *TORPEDO*, and *ATTRACT* trials, VKA were the most frequently prescribed anticoagulants. The mean duration of anticoagulation therapy in patients with limited duration anticoagulation in

the *ATTRACT* trial (211 days) was similar compared to our study (219 days), the two other trials did not report on the duration of anticoagulation therapy. In contrast to our cohort of IFDVT patients, of whom all received a venous stent, only 17%, 30%, and 24% of patients included in the aforementioned trials received venous stents, respectively. Unfortunately, the ATTRACT trial did not investigate venous patency. While the presence of a stent as foreign body in the venous system might be considered a risk factor for early re-thrombosis on one hand, the elimination of the obstructing vein lesion is likely to reduce the long-term risk of ipsilateral recurrent DVT on the other. It remains unknown if venous stent placement in this setting has an effect on VTE recurrence and as a consequence on the required duration of anticoagulation therapy.

Currently, there is a great inconsistency in the use of antithrombotic agents after endovascular therapy of IFDVT. According to a recent international survey completed by 106 experts, half of them reported to use LMWH then VKA for 6 to 12 months for a presented case scenario of an acute IFDVT treated with CDT and venous stent placement, and one third of the experts reported the use of DOACs. Antiplatelet agents were used in combination with either DOACs or VKA by 27% and long-term anticoagulation with either DOACs or VKA was used by 12% of the experts.[42]

The standard of care for decades with VKA (with concomitant LMWH for the first few days) for the management of acute DVT has recently been replaced by DOACs, either directly after the diagnosis (e.g. rivaroxaban and apixaban) or preceded by LMWH for 5-10 days (e.g. dabigatran and edoxaban).[35] However, none of the DOACs has been tested in patients treated with early thrombus removal or venous stenting.[22, 24, 33, 34] Our study results add to the current knowledge that rivaroxaban, started within 24 hours after the end of the endovascular procedure, appears to be at least as effective and safe as the combination LMWH/VKA without an increase in bleeding complications.

Most bleeding complications occurred in the peri-procedural period and are certainly due to the endovascular intervention itself, while in the post-interventional period only few minor bleedings occurred in both study groups.

The clinical outcomes were favourable in both study groups, with only 14% of patients having a PTS after a mean follow-up of 24 months. Our results confirm the previous report from the pooled data of the randomized controlled *BERNUTIFUL* (BERN Ultrasound-assisted Thrombolysis for Ilio-Femoral deep vein thrombosis versUs standard catheter directed thromboLysis) trial, which reported an overall incidence of PTS at 12 months follow-up of 11%.[16] These results are in contrast with the relatively high incidence of PTS at 24 months in the interventional study arms of the *CaVenT* (41%) and *ATTRACT* (31%) trials, [3, 10] which might be due to the much higher stent placement rate in the BERNUTIFUL trial (80%) and the present study.[16]

Our study has several limitations. First, it was not randomized, and selection bias may have been present since anticoagulation choice was left to the treating physician. Second, patients in the VKA group had longer symptom duration, and INR levels and time in therapeutic range were not assessed. This may have influenced patency rates and the incidence of the PTS. Third, sample size was moderate, and group sizes were unequal. In a post-hoc analysis, the power to detect meaningful differences between the study groups based on our sample size and the observed primary patency rates was only 50%. Therefore, our results are hypothesize generating only and do not allow statements regarding the superiority of the various treatments. Fourth, patients with early thrombus removal without venous stent placement were not included in the Swiss Venous Stent registry. Last, the study was conducted in a single Swiss tertiary hospital, therefore limiting the generalizability of our findings.

In conclusion, rivaroxaban initiated after early thrombus removal and venous stent placement for acute IFDVT appeared to have similar effectiveness and rates of bleeding compared to standard therapy with LMWH as a bridge to VKA.

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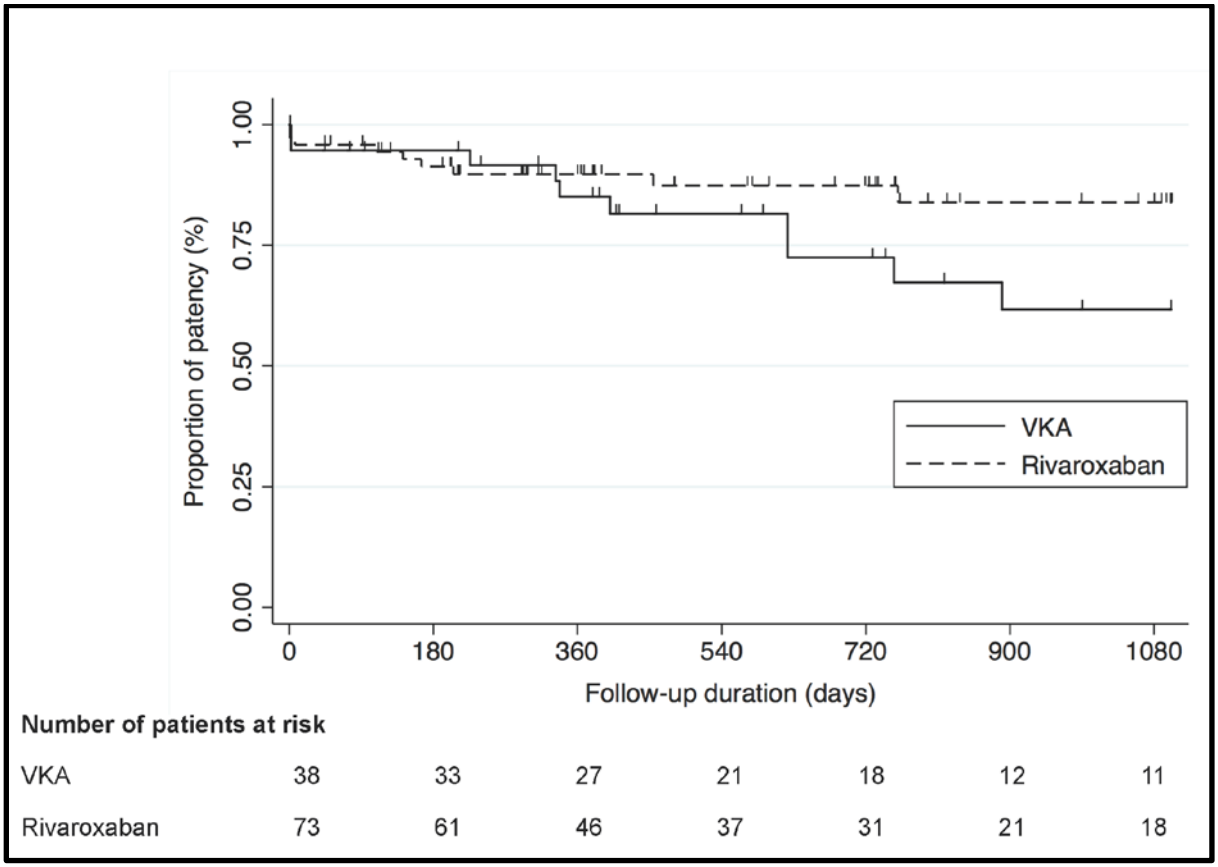
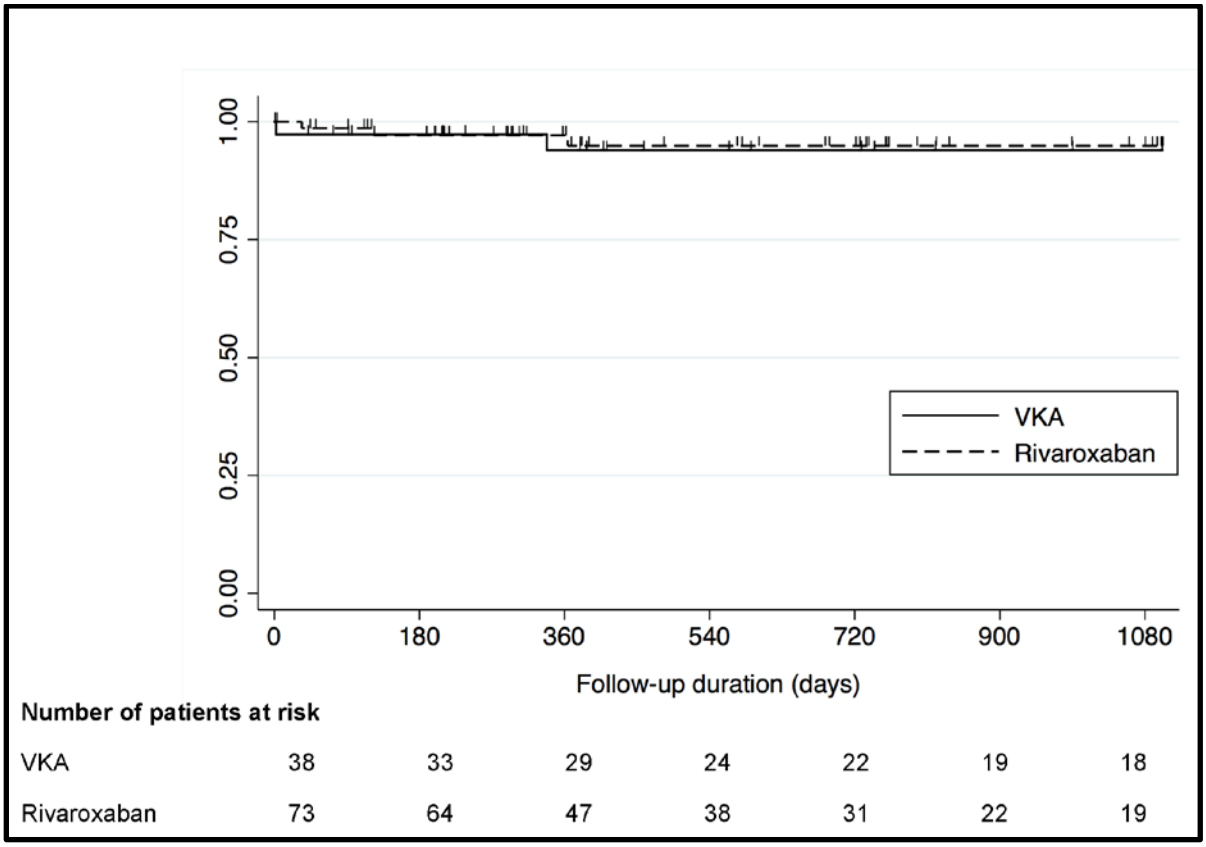
## Figures

### Figure 1: Primary patency in the VKA and DOAC group




Kaplan-Meier curves with primary patency rates for the VKA and rivaroxaban groups [log-rank, p=0.11]. The reported standard error was 8.6% for the VKA group and 4.3% for the rivaroxaban group at 2 years follow up. Standard error for VKA group exceeds 10% at 3 years follow up (10.1%).

**Figure 2**: **Secondary patency in the VKA and DOAC group**




Kaplan-Meier curves with secondary patency rates for the VKA and the rivaroxaban groups [log-rank, p=0.83]. The reported standard error was 4.2% for VKA group and 3.0% for the rivaroxaban group at 3 years follow up.

**Table 1.** Baseline characteristics

| | **Total (n = 111)** | **Rivaroxaban (n = 73)** | **VKA (n = 38)** | *P* Value |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age (years) | 46 ± 20 | 49 ± 21 | 40 ± 18 | 0.02 |
| Women | 70 (63) | 42 (58) | 28 (74) | 0.09 |
| Body mass index (kg/m2) | 26.3 ± 5.6 | 26.6 ± 5.9 | 25.0 ± 3.9 | 0.26 |
| **Risk factors and comorbidities** | | | | |
| Immobilization* (< 3 months) | 42 (38) | 33 (45) | 9 (24) | 0.02 |
| Current smoking | 12 (11) | 8 (11) | 4 (11) | 0.86 |
| Hormone therapy † | 35 (32) | 19 (26) | 16 (42) | 0.07 |
| Obesity | 23 (21) | 16 (22) | 7 (18) | 0.69 |
| Arterial hypertension | 24 (22) | 19 (26) | 5 (13) | 0.15 |
| Recent hospitalization (< 3 months) | 22 (20) | 17 (23) | 5 (13) | 0.21 |
| Varicose veins or previous surgery for varicose veins | 17 (15) | 13 (18) | 4 (11) | 0.31 |
| Known previous VTE | 26 (23) | 19 (26) | 7 (18) | 0.41 |
| Known thrombophilia | 17 (15) | 9 (12) | 8 (21) | 0.24 |
| Dyslipidemia | 8 (7) | 6 (8) | 2 (5) | 0.33 |
| Chronic pulmonary disease | 7 (6) | 4 (5) | 3 (8) | 0.62 |
| Severe infection or sepsis (< 3 months) | 9 (8) | 4 (5) | 5 (13) | 0.16 |
| Peripheral artery disease | 5 (5) | 3 (4) | 2 (5) | 0.78 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Active cancer or treatment (< 6 months) | 4 | (4) | 3 | (4) | 1 | (3) | 0.69 |
| Recent trauma (< 4 weeks) | 7 | (6) | 6 | (8) | 1 | (3) | 0.26 |
| Coronary artery disease | 3 | (3) | 3 | (4) | 0 | (0) | 0.20 |
| Diabetes | 9 | (8) | 7 | (10) | 2 | (5) | 0.45 |
| Acute rheumatic disease (< 3 months) | 3 | (3) | 3 | (4) | 0 | (0) | 0.21 |
| Recent surgery (< 4 weeks) | 10 | (9) | 9 | (12) | 1 | (3) | 0.10 |
| Provoked DVT | 78 | (70) | 50 | (68) | 28 | (74) | 0.57 |
| **Affected leg** | | | | | | | |
| Left leg DVT | 79 | (71) | 51 | (70) | 28 | (74) | 0.67 |
| Right leg DVT | 24 | (22) | 17 | (23) | 7 | (18) | 0.55 |
| Bilateral DVT | 8 | (7) | 5 | (7) | 3 | (8) | 0.84 |
| **Symptoms duration** | | | | | | | |
| Acute (≤14 days) | 97 | (87) | 68 | (93) | 29 | (76) | 0.01 |
| Subacute (15 to 28 days) | 14 | (13) | 5 | (7) | 9 | (24) | |
| **Thrombus, involved vein segments** | | | | | | | |
| Inferior vena cava | 22 | (20) | 16 | (22) | 6 | (16) | 0.44 |
| Common iliac vein | 82 | (74) | 54 | (74) | 28 | (74) | 0.97 |
| External iliac vein | 91 | (82) | 62 | (85) | 29 | (76) | 0.26 |
| Common femoral vein | 79 | (71) | 54 | (74) | 25 | (66) | 0.37 |
| Femoral vein | 51 | (46) | 37 | (51) | 14 | (37) | 0.17 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Popliteal vein | 38 | (34) | 25 | (34) | 13 | (34) | 0.99 |
| Lower leg veins | 12 | (11) | 8 | (11) | 4 | (11) | 0.94 |

*Note:* data presented as mean ± SD or number (%). * defined as bed ridden for > 72h, plaster cast, or long-distance travel of > 6h; † oral contraceptive pill, hormone replacement therapy or Tamoxifen use; DVT, deep vein thrombosis; VKA vitamin K-antagonist; VTE, venous thromboembolism

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**Table 2.** Procedural data and anticoagulation therapy

| | Total (n = 111) | Rivaroxaban (n = 73) | VKA (n = 38) | *P* Value |
|---|---|---|---|---|
| **Type of catheter intervention** | | | | 0.20 |
| CDT* alone | 54 (49) | 40 (55) | 14 (37) | |
| PMT alone | 9 (8) | 5 (7) | 4 (11) | |
| Combination of CDT and PMT | 48 (43) | 28 (38) | 20 (53) | |
| **Catheter thrombolysis details** | | | | |
| Thrombolysis duration (h) | 17.5 ± 6.9 | 17.9 ± 7.3 | 16.9 ± 6.0 | 0.49 |
| Thrombolysis dose (mg of r-tPA) | 21.9 ± 7.6 | 22.7 ± 8.0 | 20.4 ± 6.9 | 0.17 |
| **Thrombolysis success (% of thrombus load reduction)** | | | | |
| Complete (>90%) | 45 (41) | 30 (41) | 15 (39) | 0.97 |
| > 50% | 40 (36) | 27 (37) | 13 (34) | |
| < 50% | 15 (14) | 10 (14) | 5 (13) | |
| None | 2 (2) | 1 (1) | 1 (3) | |
| **Angioplasty and Venous stenting**† | | | | |
| - Mean number of stents | 1.7 ± 1.1 | 1.6 ± 0.9 | 2.0 ± 1.4 | 0.09 |
| **Anticoagulation, duration** | | | | |
| ***Limited duration*** | 56 (50) | 34 (47) | 22 (58) | 0.26 |
| - 3 months | 22 (20) | 17 (23) | 5 (13) | |
| - 6 months | 20 (18) | 11 (15) | 9 (24) | |
| - 12 months | 14 (13) | 6 (8) | 8 (21) | |
| - Mean duration of therapy (days) | 219 ± 151 | 180 ± 98 | 284 ± 199 | 0.01 |
| ***Extended duration*** | 44 (40) | 33 (45) | 11 (29) | 0.10 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Duration not determined yet*** | 11 | (10) | 6 | (8) | 5 | (13) | 0.41 |

*Note:* data presented as mean ± SD or number (%). *including ultrasound-assisted CDT; † Angioplasty without stenting was not performed. CDT, catheter-directed thrombolysis; LMWH, low-molecular-weight heparin; PMT, pharmacomechanical thrombectomy; r-tPA, recombinant tissue plasminogen activator; VKA, vitamin K-antagonist

**Table 3.** Clinical outcomes at 6, 12, and 24 months follow-up

| | **Total (n = 111)** | **Rivaroxaban (n = 73)** | **VKA (n = 38)** | *P* Value |
|---|---|---|---|---|
| **At 6 month follow-up** | **n=86** | **n=60** | **n=26** | |
| Mean Villalta score | 1.6 ± 2.0 | 1.8 ± 2.1 | 1.3 ± 1.7 | 0.27 |
| No PTS | 78 (91) | 53 (88) | 25 (96) | 0.50 |
| Mild PTS | 7 (8) | 6 (10) | 1 (4) | |
| Moderate PTS | 1 (1) | 1 (2) | 0 (0) | |
| Severe PTS | 0 (0) | 0 (0) | 0 (0) | |
| Mean rVCSS | 2.5 ± 2.2 | 2.6 ± 2.3 | 2.2 ± 1.8 | 0.39 |
| **At 12 month follow-up** | **n=80** | **n=49** | **n=31** | |
| Mean Villalta score | 1.5 ± 1.7 | 1.5 ± 1.7 | 1.5 ± 1.6 | 0.84 |
| No PTS | 75 (94) | 46 (94) | 29 (94) | 0.95 |
| Mild PTS | 5 (6) | 3 (6) | 2 (6) | |
| Moderate PTS | 0 (0) | 0 (0) | 0 (0) | |
| Severe PTS | 0 (0) | 0 (0) | 0 (0) | |
| Mean rVCSS | 2.1 ± 2.1 | 2.2 ± 2.5 | 2.0 ± 1.6 | 0.73 |
| **At 24 month follow-up** | **n=56** | **n=36** | **n=20** | |
| Mean Villalta score | 1.6 ± 2.2 | 1.6 ± 2.5 | 1.8 ± 1.8 | 0.86 |
| No PTS | 50 (89) | 31 (86) | 19 (95) | 0.55 |
| Mild PTS | 5 (9) | 4 (11) | 1 (5) | |
| Moderate PTS | 1 (2) | 1 (3) | 0 (0) | |
| Severe PTS | 0 (0) | 0 (0) | 0 (0) | |

| | | | |
|---|---|---|---|
| Mean rVCSS | 2.2 ± 2.7 | 2.2 ± 3.0 | 2.5 ± 2.4 | 0.78 |

*Note:* data presented as mean ± SD or number (%). PTS, post-thrombotic syndrome; rVCSS, revised venous clinical severity score; VKA, vitamin-K antagonist