Circulation

ORIGINAL RESEARCH ARTICLE

Aspirin Plus Rivaroxaban Versus Rivaroxaban Alone for the Prevention of Venous Stent Thrombosis Among Patients With Post-Thrombotic Syndrome: The Multicenter, Multinational, Randomized, Open-Label ARIVA Trial

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BACKGROUND: In patients with post-thrombotic syndrome, stent recanalization of iliofemoral veins or the inferior vena cava can restore venous patency and improve functional outcomes. The risk of stent thrombosis is particularly increased during the first 6 months after intervention. The ARIVA trial (Aspirin Plus Rivaroxaban Versus Rivaroxaban Alone for the Prevention of Venous Stent Thrombosis in Patients With PTS) tested whether 100 mg of daily aspirin plus 20 mg of rivaroxaban is superior to 20 mg of rivaroxaban alone to prevent stent thrombosis within 6 months after stent placement for post-thrombotic syndrome.

METHODS: In this multinational, academic, open-label, independently adjudicated trial, patients with a Villalta score >4 points and a stenosis or occlusion of the inferior vena cava, iliac veins, or common femoral vein successfully treated with venous stent placement were randomized in a 1:1 fashion to the study groups. Key exclusion criteria included <18 or >75 years of age, contraindications to anticoagulant use, or acute venous thrombosis <3 months. The primary efficacy outcome was the composite of no occlusion in the treated segment assessed at serial duplex ultrasound examinations or no reintervention needed to maintain patency within 6 months. Secondary outcomes, including Villalta score, quality of life, and safety outcomes, were also assessed. The study was registered at ClinicalTrials.gov (NCT04128956).

RESULTS: From 2020 through 2022, 172 patients were screened, 169 were randomized, and 162 were included in the full analysis set, receiving either aspirin plus rivaroxaban (n=80) or rivaroxaban alone (n=82) for 6 months. Mean±SD age was 42.8±14.7 years; 103 patients (60.9%) were women; 154 patients (97.5%) were White; and leg ulcers were present in 7% of patients. The primary patency rate at 6 months was 94.8% versus 92.4% (absolute risk difference, 2.4% [95% CI, −13.6 to 18.0]), respectively. The mean±SD decrease in the Villalta score for the affected leg (without ulcer) from baseline to 6 months was −6.7±4.4 and −7.0±5.2 points (*P*=0.36), respectively. There were no differences in other outcomes or quality of life at 6 months. No major bleeding occurred.

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CONCLUSIONS: The overall primary patency rate during the first 6 months after endovascular intervention for post-thrombotic syndrome was higher than expected and comparable between patients receiving aspirin combined with rivaroxaban and those receiving rivaroxaban alone.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04128956.

Key Words: aspirin ■ endovascular procedures ■ post-thrombotic syndrome ■ rivaroxaban ■ thrombosis

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Clinical Perspective

What Is New?

- The ARIVA trial (Aspirin® Plus Rivaroxaban Versus Rivaroxaban Alone for the Prevention of Venous Stent Thrombosis in Patients With PTS) is the first randomized, multicenter study to evaluate the efficacy and safety of adding aspirin to rivaroxaban for preventing venous stent thrombosis in patients with post-thrombotic syndrome.
- The trial demonstrated similarly high 6-month stent patency rates (>90%) for both aspirin plus rivaroxaban and rivaroxaban alone, suggesting no significant benefit of dual therapy in this context.

What Are the Clinical Implications?

- Rivaroxaban alone, without additional antiplatelet therapy, appeared sufficient for maintaining stent patency within 6 months of venous stent placement for post-thrombotic syndrome.
- These findings highlight the importance of optimizing patient selection and exploring alternative antithrombotic strategies, especially for high-risk individuals receiving endovascular recanalization for post-thrombotic syndrome.

Nonstandard Abbreviations and Acronyms

ARIVA	Aspirin Plus Rivaroxaban Versus Rivaroxaban Alone for the Prevention of Venous Stent Thrombosis in Patients With PTS
CIVIQ-20	Chronic Venous Insufficiency Quality of Life Questionnaire
DSMB	Data and Safety Monitoring Board
PTS	post-thrombotic syndrome
TEAE	treatment-emergent adverse event

Deep vein thrombosis is the most common clinical manifestation of venous thromboembolism, affecting ≈2 per 1000 individuals per year.[1] Deep vein thrombosis causes significant morbidity during its acute phase and leads to functional complications months after the initial diagnosis. Post-thrombotic syndrome (PTS) is the most frequent long-term complication of proximal deep vein thrombosis, occurring in up to 50% of patients with iliofemoral deep vein thrombosis treated with standard anticoagulation and compression stockings.[1–3] PTS contributes to substantial individual burden, leading to long-term morbidity, persistent discomfort, and impaired quality of life for affected patients, often resulting in a reduced ability to perform daily activities.[4–6]

Compression stockings, exercise and physical therapy, wound care, and long-term anticoagulant treatment may relieve the symptoms related to the presence PTS and stabilize the disease.[7–10] However, no medical treatment was proven effective to reverse PTS, leading to a regression of subjective limitations and symptoms. Recanalization of chronically occluded iliac veins with stent placement has been shown in a randomized trial and multiple single-arm studies to restore blood flow and to alleviate functional limitations associated with PTS.[11–14] Several aspects of venous stent placement require further investigation, including the optimal antithrombotic strategy.

Currently, there is no agreement on the optimal antithrombotic strategy to prevent venous stent thrombosis. As a result, existing guidelines, consensus documents, and surveys provide varied and inconsistent recommendations on antithrombotic treatment after venous stent placement, particularly concerning the use of antiplatelet agents.[15,16] Most previous studies used vitamin K antagonists or direct oral anticoagulants after stent placement, and some studies used low-molecular-weight heparins for several weeks before the initiation of oral anticoagulation therapy.[12,17–22] In the Swiss venous stent registry,[12] rivaroxaban was the most frequently used oral anticoagulant. An observational study suggested that antiplatelet treatment as an add-on therapy may improve patency rate compared with anticoagulation alone.[23]

The ARIVA trial (Aspirin Plus Rivaroxaban Versus Rivaroxaban Alone for the Prevention of Venous Stent Thrombosis in Patients With PTS; EudraCT 2019-001723-12, ClinicalTrials.gov NCT04128956) investigated whether combining aspirin with the direct oral anticoagulant rivaroxaban was superior to anticoagulation with rivaroxaban alone in preventing stent thrombosis within the first 6 months after stent placement in patients with PTS.

METHODS

Trial Design and Oversight

The ARIVA trial was an open-label, multicenter, randomized trial with independently adjudicated clinical outcomes of patients with PTS undergoing stent placement. The primary efficacy objective was to assess whether the use of 100 mg of aspirin once daily on top of 20 mg of therapeutic-dosed rivaroxaban once daily was superior to rivaroxaban alone to reduce venous stent thrombosis in patients with PTS within the first 6 months after endovascular therapy. The secondary objective was to demonstrate the safety of aspirin on top of therapeutic-dosed rivaroxaban. The trial was conducted at 6 centers in 3 countries (Austria, Switzerland, and Germany) and was sponsored by the University of Zurich. Data analysis was performed independently by an external biostatistician. Institutional review committees approved the study, and all subjects gave informed consent before enrollment.

Trial Patients

Eligible patients were between 18 and 75 years of age; had a confirmed diagnosis of PTS (Villalta score >4) secondary to a confirmed stenosis or occlusion of the inferior vena cava, iliac vein, or common femoral vein; underwent successful venous stent intervention; were on treatment or planned for treatment with rivaroxaban; and provided informed consent for study participation. Key exclusion criteria included contraindications to antithrombotic therapy, need for anticoagulants other than rivaroxaban, and an acute venous thrombosis. A complete list of inclusion and exclusion criteria is available in the Supplemental Material.

Study Outcomes

The primary efficacy outcome was the composite of freedom from occlusion in the treated segment and reintervention needed to maintain patency (primary patency rate) within 6 months. A duplex ultrasound of the affected leg was conducted according to a standardized protocol during all follow-up visits after 3 and 6 months to evaluate the presence or absence of thrombosis in the treated segment, as described in Figure S1.[24] In case of reintervention, final confirmation of occlusion was obtained by digital subtraction venography of the stent segment.

Secondary efficacy outcomes included the following: (1) primary patency rate at 3 months; (2) secondary patency rates at 6 months; (3) primary sustained clinical success at 3 and 6 months; (4) incidence of patients with open stents but residual stenosis >50%; (5) limb circumference difference between legs; (6) quality of life (Chronic Venous Insufficiency Quality of Life Questionnaire [CIVIQ-20] score); (7) changes in Villalta and revised venous clinical severity scores at 3 and 6 months; and (8) investigator and patient global efficacy judgments after 6 months, a subjective assessment on treatment effectiveness using a 5-point rating scale ranging from 0 (very good) to 4 (worse than baseline).

The secondary patency rate was defined as the percentage of patients with a patent stent at 6 months follow-up regardless of any reintervention for stent occlusion. Primary sustained clinical success was defined as the absence of PTS (Villalta score ≤4) and no reintervention. The CIVIQ-20 is a patient-reported assessment scale consisting of 20 items across 4 dimensions: psychological (9 items), physical (4 items), social (3 items), and pain (4 items). Patients completed the questionnaire themselves, without assistance from the clinical team. Each item was rated on a 5-point scale from 1 (best possible) to 5 (worst). The Villalta score for the affected leg consists of 5 patient-rated venous symptoms and 6 clinician-rated physical signs, which were each rated on a 4-point scale (from 0=none to 3=severe). The revised venous clinical severity score for the affected leg consists of 10 venous symptoms, which were each rated on a 4-point scale from 0 (none) to 3 (severe) and summed.

Safety outcomes included the incidence of adverse events, encompassing bleeding events and cause-specific death. Major, clinically relevant nonmajor, and minor bleeding events were defined according to the International Society on Thrombosis and Haemostasis criteria.[25]

Study Arms

Eligible patients were randomly assigned after successful stent placement to receive either 100 mg of aspirin once daily plus 20 mg of rivaroxaban once daily or 20 mg of rivaroxaban once daily as a stand-alone treatment in a 1:1 ratio. Screening and inclusion in the study were performed by trained study personnel. During an initial treatment adjustment period of up to 2 weeks after intervention and randomization, therapeutic-dosed enoxaparin (1 mg/kg SC twice daily) could be administered instead of rivaroxaban at the investigator's discretion.

Study Procedures

In this clinical trial, patients followed a structured schedule consisting of 3 visits and 2 phone calls over a 6-month period. The trial began with visit 1 (day 1 -up to day 3- after the intervention), during which patients were enrolled in the study and allocated by an online randomization tool. Patients underwent block-stratified randomization (by study center) with a randomization ratio of 1:1. At day 45±15, phone call 1 was made to perform a safety check on the patient's condition. The following approved venous stents were used in ARIVA: sinus-Obliquus (optimed GmbH), Venovo Venous Stent (Becton Dickenson), BeYond Venous (Bentley), Abre Venous Stent System (Medtronic), and blueflow Venous Stent (Plusmedica). At day 91±15, patients attended visit 2, an interim follow-up visit to assess progress. Phone call 2 was scheduled at day 137±15 for safety check. Finally, patients returned for visit 3 on day 183±30, marking the end of treatment and the conclusion of their participation in the trial. Because most stent occlusions occur within the first 6 months after implantation, this time frame was chosen to evaluate the primary efficacy outcome.[26] The study physicians and sonographers performing follow-up visits were not blinded to the treatment arm allocation.

The following ultrasound parameters were recorded during all of the postintervention clinical visits: (1) presence or absence of color flow within each stented segment, (2) in-stent and stent-inlet peak flow velocities and flow pattern (eg, spontaneously modulated by respiration or other) as measured by pulsed-wave Doppler, and (3) presence or absence of post-thrombotic changes distal to the stent (inflow vessel quality). Further details on the diagnostic procedures for stent stenosis and occlusions can be found in the Protocol section of the Supplemental Material and Figure S1.

Suspected primary outcome events were adjudicated independently by an external clinical event committee composed of 3 independent vascular physicians who were blinded to group assignment. Bleeding events have not been externally adjudicated; they were documented with the use of adverse event forms, and the information recorded by the investigators was subjected to monitoring. The Data and Safety Monitoring Board (DSMB) reviewed bleeding events once every 50 included patients and after the completion of the trial; the DSMB was consulted for decisions about the conduction of the trial and on major protocol amendments. A DSMB charter is available as Supplemental Material.

Sample Size Calculation

In the literature, primary patency rates ranged between 68.0% and 93.1% at 3 to 36 months of follow-up. This rate was 78% at 6 months in the Swiss venous stent registry of patients with iliofemoral PTS.[26] Therefore, we assumed a primary patency rate of 78% in the control group (rivaroxaban alone) and 90% in the test group (aspirin in addition to rivaroxaban), the latter being a conservative estimate based on the data from observational studies.[23] A total of 292 patients (146 per group) were required to demonstrate statistically significant superiority of the test group over the control group. This calculation was based on a power of 80% and a 1-sided type I error rate of α=0.025.

Because of the slow recruitment rate, the DSMB recommended a single interim analysis for the primary efficacy end point at an information rate of ≈40% (126 patients, plus dropouts, having completed the 6-month visit). The interim analysis aimed to provide: (1) an estimate of the risk difference between the treatment groups, along with a 95% CI, at 40% information rate; and (2) the conditional power of the trial to be positive. The conditional power approach assessed the probability of achieving a statistically significant final result based on the interim findings.

Statistical Analysis

The safety population included all patients randomized and with at least one documented application of aspirin (applicable only for the test group) and a safety data point after visit 1. The full analysis set served for efficacy analyses and included all randomized patients with at least one documented application of aspirin (applicable only for the test group) and documented application of the basic medication rivaroxaban and efficacy data after visit 1. Patients not assessable for stenosis or occlusion by duplex ultrasound were excluded. The per-protocol population served for the efficacy analyses and included all patients from the full analysis set who did not show any relevant protocol deviation and were classified as clinically evaluable.

The superiority analysis for the primary efficacy outcome was tested by applying the Fisher's exact test and estimating the risk differences. The 2-sided 95% CI of the treatment difference in patency rates (absolute risk difference) was displayed. Superiority was tested in the full analysis set as a confirmatory test and in the per-protocol population as a further sensitivity analysis to prove the robustness of results concerning deviations from the clinical trial protocol. These analyses were to be performed only on adjudicated patency rates and after exclusion of patients with missing data at follow-up. To account for missing data if visit 3 was performed as the premature termination visit, clinical data up to visit 3 were used for evaluation the same as these data were "regular visit 3" data for the full analysis set cohort evaluation. For the primary end points defining rates, the cumulative incidence is presented using the Kaplan-Meier method accompanied by a log-rank *P* value.

The inferential analysis of the secondary end points was primarily of exploratory nature. The 2-sided 95% CI of the treatment difference in rates (absolute risk difference) was displayed. The treatment effect for scores was calculated with a linear mixed model for repeated measurements. Analysis was implemented with SAS PROC MIXED. All authors had full access to all the data in the study and take responsibility for its integrity and the data analysis.

RESULTS

From March 2020 through November 2023, a total of 172 patients were screened for randomization at 6 centers. Ultimately, 169 patients were randomized to receive either aspirin plus rivaroxaban (n=85) or rivaroxaban alone (n=84) and were included in the safety evaluable set. A total of 162 patients were included in the full analysis set (n=80 and n=82, respectively), whereas 138 patients with no major protocol violations, notably drug compliance >80%, were included in the per-protocol set (n=67 and n=71, respectively; Figure 1). After the exclusion of 6 patients (3 from each group) because of missing data at visit 3, a total of 156 patients were included in the primary efficacy analysis.

The baseline characteristics of the study population are presented in Table 1. The mean±SD age of participants was 42.8±14.7 years, and 103 (60.9%) were women. The majority of patients (97.5%) were White. The median Villalta score at baseline was 10 (interquartile range, 7–14), with 11 patients (6.8%) presenting with leg ulcerations. The left leg was mainly affected by PTS (67.9%), with a total of 76 patients (47.2%) presenting a May-Thurner anatomy (compression of the left common iliac vein by the right common iliac artery). A median of 2 (quartiles 1 and 3 and 1 and 2) dedicated venous self-expanding nitinol stents with diameters ranging from 12 to 18 mm were implanted in the left (137; 84.6%) and right (42; 25.9%) iliofemoral veins. The inferior vena cava was treated in 31 patients (19.1%) with stents having a diameter of 20 mm; of these, 12 patients required a total of 2 stents, and 19 patients required one stent.

The average intake of aspirin was 165.2 (SD, 61.3) tablets for a compliance exceeding 80% recorded in 88.7% of patients. Rivaroxaban was taken for an average of 177.0 days (SD, 36.7 days) in the intervention group and 175.8 days (SD, 40.9 days) in the control group, for a compliance exceeding 80% recorded in 93.7% and 92.7% of patients, respectively.

Primary Efficacy Outcome

From the results of the interim analysis, which included ≈40% of trial patients with 6-month follow-up, the

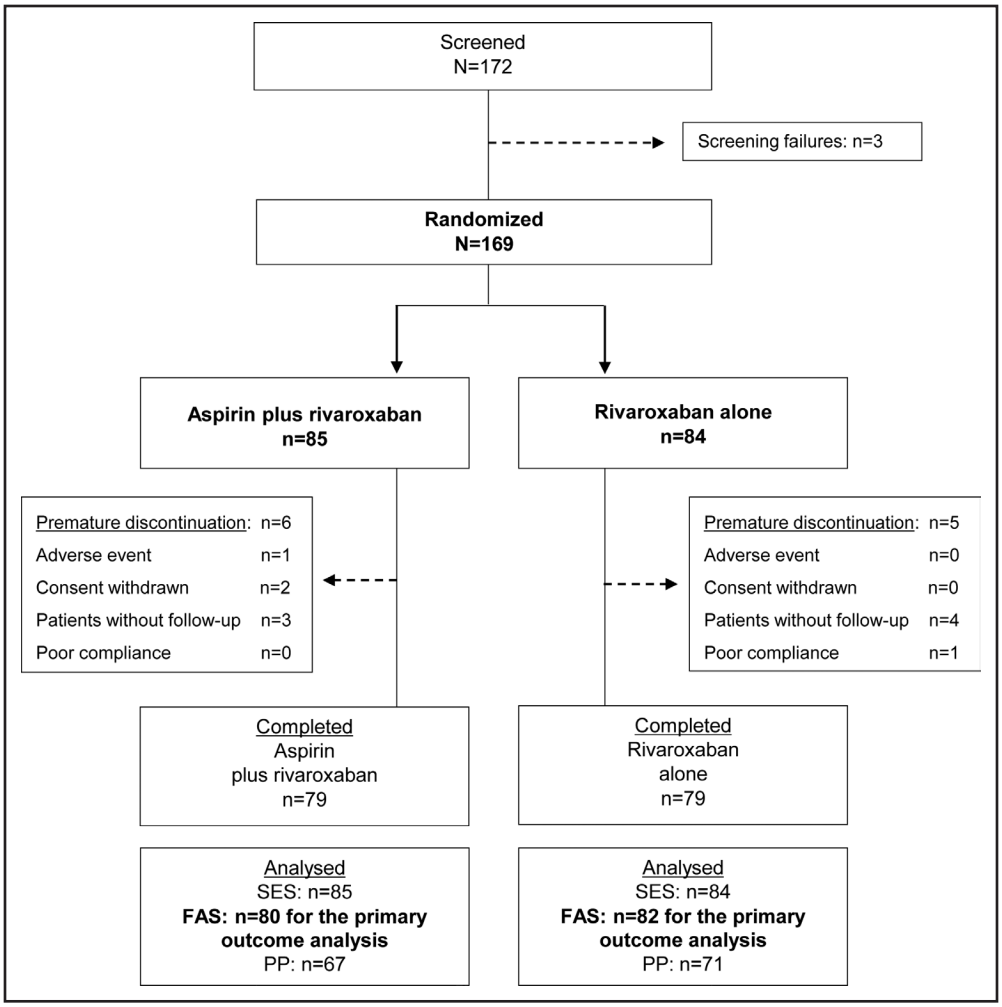

Figure 1. Flowchart depicting the study population.
FAS indicates full analysis set; PP, per protocol population; and SES, safety evaluable set.

DSMB concluded that achieving the necessary conditional power of 80% was highly unlikely without increasing the originally planned sample size and that low recruitment rates rendered the continuation of the trial impractical, even with the current sample size. Consequently, the DSMB recommended that the sponsor terminate the study. At that point, 169 patients had been enrolled; 126 patients were included in the interim analysis, and additional patients were enrolled by the time the 6-month follow-up was completed for the last patient in the interim analysis.

The primary patency rate at 6 months was 94.8% in the intervention group and 92.4% in the control group. The superiority testing using the Fisher's exact test resulted in an absolute risk difference of 2.4% (95% CI, −13.6 to 18.0; 1-sided *P*=0.37; Figure 2). Similar results were obtained for the primary efficacy outcome assessed in the per-protocol population, as depicted in Table 2. An interaction analysis is reported in Table S1.

As part of a prespecified analysis to account for missing values for the primary efficacy outcome, we analyzed the primary outcome rate in the full analysis set also including patients with visit 3 performed as premature termination visit, resulting in a primary patency rate of 95.0% in the intervention group and 92.7% in the control group.

Secondary Efficacy Outcomes

The results of secondary outcome analysis are given in Table 2. After 3 months, the primary patency rate was 94.7% in the intervention group versus 94.9% in the control group (2-sided *P*=1.00). The secondary patency rate at 6 months was 100% in the intervention group versus 96.2% in the control group (*P*=0.08). The incidence of open stents with >50% residual stenosis after 3 months based on ultrasound assessment was 2.7% in the intervention group versus 1.3% in the control group, leading to an absolute risk difference of 1.40 % (95% CI, −14.45 to 17.29; 2-sided *P*=0.61). Reinterventions were needed in 2 patients (2.5%) in the intervention group versus 5 (6.4%) in the control group: one patient in the

Table 1. Baseline Characteristics

	Aspirin plus rivaroxaban	Rivaroxaban alone	Total
Safety evaluable set			
n	85	84	169
Age, y	43.4 (15.3)	42.1 (14.2)	42.8 (14.7)
Women, n (%)	50 (58.8)	53 (63.1)	103 (60.9)
Body mass index, kg/m^2	26.7 (6.0)	26.9 (6.2)	26.8 (6.1)
Full analysis set			
n	80	82	162
Race and ethnicity, n (%)			
White	78 (97.5)	76 (97.4)	154 (97.5)
Black	0 (0.0)	2 (2.6)	2 (1.3)
Asian	2 (2.5)	0 (0.0)	2 (1.3)
Active smokers, n (%)	22 (26.2)	20 (23.8)	42 (25.0)
Comorbidities, n (%)			
Ulcerative colitis	2 (2.5)	1 (1.2)	3 (1.9)
Obesity	4 (5.0)	5 (6.1)	9 (5.6)
Rheumatoid arthritis	0 (0.0)	1 (1.2)	1 (0.6)
Hypothyroidism	10 (12.5)	4 (4.9)	14 (8.6)
Antiphospholipid syndrome	1 (1.3)	0 (0)	1 (0.6)
Antithrombin deficiency	0 (0.0)	1 (1.2)	1 (0.6)
Factor V Leiden (G1691A variant)	9 (11.3)	6 (7.3)	15 (9.3)
Venous malformations	4 (5.0)	1 (1.2)	6 (3.1)
Characteristics of venous lesions and PTS, n (%)			
Affected leg			
Left leg	52 (65.0)	58 (70.7)	110 (67.9)
Right leg	8 (10.0)	9 (11.0)	17 (10.5)
Inferior vena cava	5 (6.3)	2 (2.4)	7 (4.3)
Left and right leg	1 (1.3)	3 (3.7)	4 (2.5)
Other	14 (17.6)	13 (12.2)	28 (14.8)
May-Thurner compression	36 (45.0)	40 (49.4)	76 (47.2)
Side of index intervention, n (%)			
Bilateral	16 (20)	13 (15.9)	29 (17.9)
Right side only	9 (11.3)	9 (11)	18 (11.1)
Left side only	54 (67.5)	59 (72)	113 (69.8)
Endovascular inferior vena cava reconstruction, n (%)	19 (23.8)	12 (14.6)	31 (19.1)
No. of stents used	2 (2, 3)	2 (1, 2)	2 (1, 2)
Stent length, mm	250 (150, 310)	235 (120, 270)	250 (140, 300)
Stent extension to the common femoral vein, femoral vein or deep femoral vein, n (%)	50 (62.5)	50 (61.0)	100 (61.7)
Jalaie anatomic classification of PTS extension, n (%)			
I	10 (12.5)	10 (12.2)	20 (12.3)
II	11 (13.8)	9 (11.0)	20 (12.3)
III	16 (20)	11 (13.4)	27 (16.7)
IVa	16 (20)	21 (25.6)	37 (22.8)
IVb	1 (1.3)	0	1 (0.6)
VI	13 (16.3)	14 (17.1)	27 (16.7)
Villalta score at baseline, median (IQR)	9 (6, 14)	11 (7, 16)	10 (7, 14)
Active low-molecular-weight heparin run-in, n (%)	42 (52.5)	47 (57.3)	89 (54.9)
Duration, median (IQR), mean (SD)	7 (0, 13)	7 (0, 12)	6 (0, 13)
Medication with antacid/proton pump inhibitors, n (%)	17 (21)	15 (18)	32 (20)

IQR indicates interquartile range; and PTS, post-thrombotic syndrome.

Data are number (percentage of available data), mean (SD), or median (quartiles 1–3) unless otherwise specified. Anatomic classification of PTS extension according to Jalaie et al.[35]

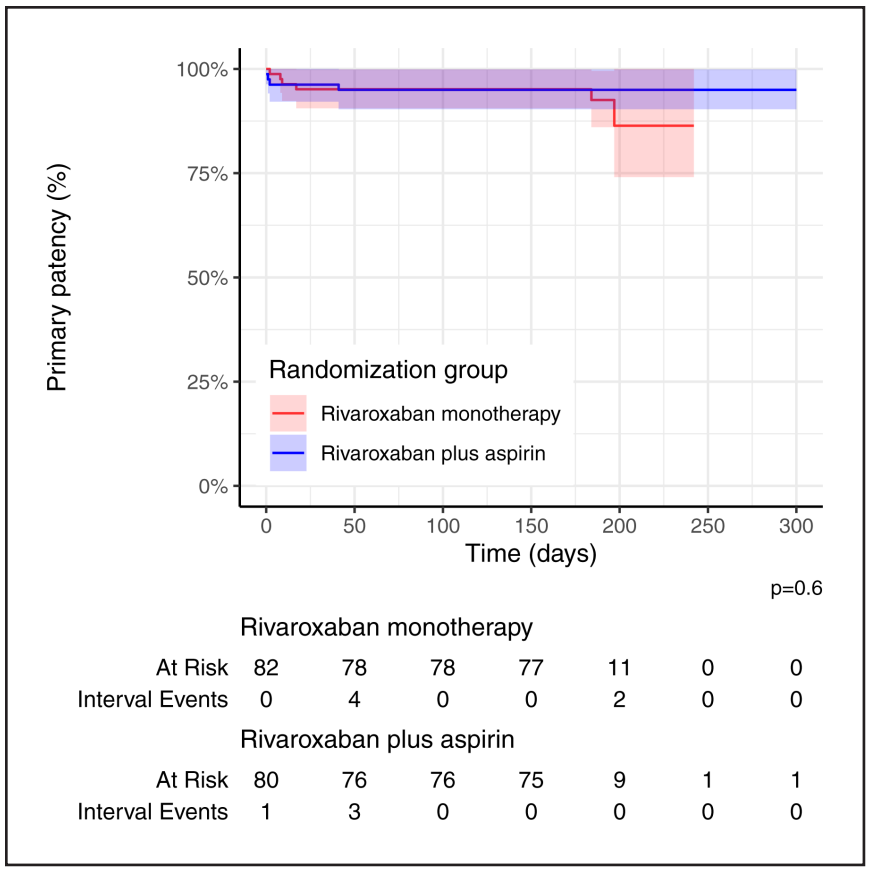

Figure 2. Kaplan-Meier curve estimator for the primary efficacy outcome.
The curve depicts the time free from occlusion in the treated segment or reintervention needed to maintain patency, defining primary patency. The *P* value was calculated with a log-rank test.

intervention group needed 2 reinterventions, whereas no patients in the control group needed >1 reintervention.

Primary sustained clinical success after 3 months was 63.2% in the intervention group compared with 50.7% in the control group, for an absolute risk difference of 12.6 (95% CI, −4.0 to 28.8; 2-sided *P*= 0.17). After 6 months, the results for primary sustained clinical success were similar to those at 3 months, with 62.2% of patients with a Villalta score ≤4 in the intervention group and 52.0% in the control group, for an absolute risk difference of 10.2 (95% CI, −6.0 to 26.3; 2-sided *P*=0.25; Table 2).

The mean±SD decrease in Villalta score for the affected leg (without ulcer) from baseline to month 3 was −6.9±4.7 points in the intervention group and −7.1±4.8 points in the control group (2-sided *P*=0.54). Comparable results were obtained at month 6 and for patients with ulcers (Table 2). At 3 months, the mean±SD revised venous clinical severity score decreased −3.9±3.4 points in the intervention group and −4.6±3.3 points in the control group (2-sided *P*=0.25). Comparable results were seen at month 6 and for patients with ulcers.

Quality of life, measured by the CIVIQ-20, improved in both groups through months 3 and 6. A descriptive overview of CIVIQ-20 for each dimension and the overall score is given in Table 3. The global efficacy was rated as very good or good in >90% of patients at 3 and 6 months by both the patients and the investigators (Table S2).

Adverse and Bleeding Events

Overall, no major bleeding was recorded. Clinically relevant nonmajor bleeding events occurred in 7 patients (8.2%) in the intervention group and in 2 patients (2.4%) in the control group (Table 4). Minor bleeding events occurred in 6 patients (7.1%) in the intervention group and in 5 patients (6.0%) in the control group.

During the trial, a total of 120 adverse events occurred in 69 of 169 patients (40.8%). Two adverse events occurred before treatment in 2 patients. A total of 118 treatment-emergent adverse events (TEAEs) were reported in 40.2% of patients: 45.9% in the intervention group and 34.5% in the control group. Most TEAEs were mild to moderate, with 9 severe TEAEs reported in 4.1% of patients. The majority of TEAEs (95 in 33.7% of patients) resolved by the end of the trial. The 3 most frequently reported TEAEs were: (1) device occlusion, occurring in 10 TEAEs among 9 of 169 patients (5.3%); (2) pain in extremity, reported in 5 of 169 patients (3.0%); and (3) menorrhagia, reported in 5 of 169 patients (3.0%). Additional information is reported in Table 4 and Table S3.

Potential Predictors of Occlusion in the Treated Segment

We studied potential predictors of occlusion in the treated segment based on previous literature. Stent extension to

Table 2. Primary and Secondary Efficacy Outcomes

	Aspirin plus rivaroxaban (n=80)	Rivaroxaban alone (n=82)	Group difference (95% CI or SE)	*P* value
Primary efficacy outcome				
Primary patency rate after 6 mo (full analysis set)	73/77 (94.8)	73/79 (92.4)	2.4 (−13.6 to 18.0)	0.37
Primary patency rate after 6 mo (per-protocol set)	62/64 (96.9)	66/70 (94.3)	2.6 (−14.5 to 19.4)	0.34
Patients with premature termination visit excluded from primary analysis	3	3		
Primary patency rate after 6 mo accounting for premature termination*	76/80 (95.0)	76/82 (92.7)		
Secondary efficacy outcomes				
Primary patency rate after 3 mo	71/75 (94.7)	75/79 (94.9)	−0.3 (−16.2 to 15.4)	1.0
Secondary patency rate after 6 mo	76/76 (100)	75/78 (96.2)	−3.8 (−0.4 to 8.1)	0.08
Incidence of patients with open stents but >50 % residual stenosis at 3 mo	2/75 (2.7)	1/79 (1.3)	1.40 (−14.5 to 17.3)	0.61
Primary sustained clinical success after 3 mo	43/68 (63.2)	37/73 (50.7)	12.6 (−4.0 to 28.8)	0.17
Primary sustained clinical success after 6 mo	46/74 (62.2)	39/75 (52.0)	10.2 (−6.0 to 26.3)	0.25
Change in Villalta score without ulcus after 3 mo, points	−6.9 (4.7)	−7.1 (4.8)	−0.4 (0.6)	0.54
Change in Villalta score without ulcus after 6 mo, points	−6.7 (4.4)	−7.0 (5.2)	−0.5 (0.6)	0.36
Change in Villalta score with ulcus after 3 mo, points	−7.6 (6.1)	−8.3 (5.5)	0.1 (0.7)	0.93
Change in Villalta score with ulcus after 6 mo, points	−6.9 (5.5)	−8.2 (6.4)	0.3 (0.8)	0.75
Change in rVCSS after 3 mo, points	−3.9 (3.4)	−4.6 (3.3)	0.6 (0.5)	0.25
Change in rVCSS after 6 mo, points	−3.5 (3.7)	−4.7 (3.9)	0.8 (0.6)	0.15

rVCSS indicates revised venous clinical severity score.

Data are number (percentage of available data), mean (SD), or median (quartile 1–3) unless otherwise specified. Primary outcome events are taken from the Critical Event Committee evaluation.

P values are 1-sided for the primary efficacy outcome and 2-sided for the secondary outcomes.

*Full analysis set including 6 patients with premature termination visit (visit 3).

the common femoral vein (or more distal), the presence of post-thrombotic leg inflow veins, and a Jalaie anatomic classification of ≥III were associated with the occurrence of stent occlusion at univariate analysis (Table S1).

DISCUSSION

The randomized, multinational, independently adjudicated, open-label ARIVA trial was the first randomized trial evaluating the efficacy and safety of antithrombotic strategies in preventing venous stent thrombosis in patients with PTS undergoing endovascular treatment of iliofemoral veins or the inferior vena cava. The trial was halted prematurely after an interim analysis because the likelihood of reaching the necessary conditional power was too low to be able to show the superiority of aspirin on top of therapeutic-dosed rivaroxaban compared with therapeutic-dosed rivaroxaban alone. A reason for this can be found in the overall primary patency rate, which was much higher than expected and estimated from historical data available before study initiation.[22,26–28] On the other hand, the very low rate of stent occlusions confirms the feasibility and effectiveness of endovascular procedures for post-thrombotic obstructions in the iliofemoral veins or inferior vena cava. The overall patency rate in ARIVA was particularly high, considering that 61% of patients had post-thrombotic inflow veins and therefore received venous stent extension below the inguinal ligament (ie, stents placed in the common femoral, femoral, or deep femoral veins).

The primary patency rate at 6 months was not different between the intervention group (aspirin plus rivaroxaban) and the control group (rivaroxaban alone). The observed absolute risk difference of 2.4% (95% CI, −13.6 to 18.0) indicates that the addition of aspirin did not confer a clinically meaningful benefit in preventing stent occlusion within the first 6 months after intervention. Despite the lack of statistical significance, both groups demonstrated high patency rates of >90%, suggesting that rivaroxaban alone is effective in maintaining stent patency in this population.

The lack of a significant difference between the 2 groups may be attributed to 2 main factors. First, the sample size was smaller than initially planned, reducing the power of the study to detect a meaningful difference. Second, primary patency rates were higher than expected. Historically, primary patency rates after stent placement were low, in part because of suboptimal stent designs, less precise imaging techniques, inadequate postprocedural care, and suboptimal patient selection.[29] The ARIVA trial reflects these advancements, as evidenced by the high primary patency rates observed in both the intervention and control groups at 6 months: 94.8% and 92.4%, respectively. These results are in line with a recent clinical trial on iliac vein stenting for chronic venous disease.[14] In contrast, primary patency rates at 6

Table 3. Quality of Life by CIVIQ-20

Change from baseline	Aspirin plus rivaroxaban (n=80)	Rivaroxaban alone (n=82)	Total (N=162)
Pain dimension score			
After 3 mo/visit 2			
n_{valid}	78	79	157
Median	25.0	31.3	25.0
Q1/Q3	12.50/37.50	12.50/43.75	12.50/37.50
After 6 mo/visit 3			
n_{valid}	77	78	155
Median	25.0	25.0	25.0
Q1/Q3	12.50/37.50	12.50/43.75	12.50/43.75
Physical dimension score			
After 3 mo/visit 2			
n_{valid}	76	77	153
Median	18.8	25.0	18.8
Q1/Q3	6.25/37.50	6.25/43.75	6.25/37.50
After 6 mo/visit 3			
n_{valid}	72	76	148
Median	21.9	25.0	25.0
Q1/Q3	6.25/31.25	6.25/43.75	6.25/37.50
Social dimension score			
After 3 mo/visit 2			
n_{valid}	77	75	152
Median	25.0	25.0	25.0
Q1/Q3	8.33/33.33	8.33/33.33	8.33/33.33
After 6 mo/visit 3			
n_{valid}	77	74	151
Median	25.0	25.0	25.0
Q1/Q3	8.33/33.33	0.00/33.33	0.00/33.33
Social psychological score			
After 3 mo/visit 2			
n_{valid}	76	75	151
Median	8.3	13.9	11.1
Q1/Q3	2.78/18.06	2.78/27.78	2.78/22.22
After 6 mo/visit 3			
n_{valid}	75	76	151
Median	8.3	12.5	11.1
Q1/Q3	0.00/19.44	0.00/26.39	0.00/25.00
Total score			
After 3 mo/visit 2			
n_{valid}	78	78	156
Median	16.9	20.6	19.4
Q1/Q3	7.50/27.50	6.25/32.50	6.88/28.75
After 6 mo/visit 3			
n_{valid}	78	78	156
Median	15.6	17.5	17.5
Q1/Q3	8.75/27.50	7.50/32.50	7.50/30.00

CIVIQ-20 indicates Chronic Venous Insufficiency Quality of Life Questionnaire; n_{valid}, number of valid observations, and Q1/Q3, quartile 1/quartile 3.

months from controlled studies ranged between 85% and 88% (Table S4),[21,30–33] and they were lower in observational registries.[12] In this context, the marginal additional benefit of adding antiplatelet therapy such as aspirin may be less impactful. Another contributing factor to the high patency rates seen in the ARIVA trial is likely the result of improved patient selection in choosing candidates for endovascular treatment for PTS. Patients with good inflow vessels are more likely to benefit from stent placement and to achieve better long-term patency.[29,34] In this trial, we performed an exploratory analysis of potential factors associated with stent occlusions. We found poor inflow characterized by post-thrombotic femoral or deep femoral veins, longer post-thrombotic venous segments according to the Jalaie anatomic classification of PTS,[35] and stent extension to the common femoral vein or more distal appeared to be the main predictors.

Another promising therapeutic approach for preventing stent thrombosis that warrants further investigation is the use of novel factor XI inhibitors, which specifically target the contact pathway of coagulation, a key mechanism in stent-related thrombus formation.[36] Compounds such as abelacimab, which can be administered once monthly,[37] may also offer improved patient compliance. Such new strategies are currently being studied for patients with cancer-associated acute venous thromboembolism and may be beneficial as alternative or add-on therapies particularly for patients with PTS at high risk for stent occlusion. Identifying these high-risk patients and the validation of risk assessment models for patients with PTS undergoing venous stent placement will be essential to optimizing treatment and improving long-term outcomes.

Secondary efficacy outcomes showed no significant differences between the 2 treatment arms primarily because of the small sample size and possibly an effect size of aspirin that was not large enough. Of note, both groups experienced substantial reductions in functional Villalta scores and revised venous clinical severity scores, corresponding to a functional improvement, as well as improvements in quality of life as measured by the CIVIQ-20 scale. The safety profile of the 2 treatment regimens was consistent with previous studies involving antiplatelet and anticoagulant therapies.[28,32] No major bleeding events were observed in either group. Clinically relevant nonmajor bleeding, notably menorrhagia, occurred more frequently in the intervention group (8.2% versus 2.4%). The overall incidence of adverse events was comparable between groups.

There has been ongoing discussion about whether studies on endovascular interventions for PTS should prioritize primary patency rates over patient-reported outcomes as the primary measure of efficacy.[38,39] The severity of PTS, as assessed by the Villalta score, is closely associated with patient-reported outcomes, including quality of life.[4,40] This trial has shown a parallel

Table 4. Adverse Events and Safety Outcomes

	Aspirin plus rivaroxaban (n=85)			Rivaroxaban alone (n=84)			
	Events, n	Patients, n (%)	95% CI	Events, n	Patients, n (%)	95% CI	*P* value
All AEs	73	40 (47.1)	36.4–57.7	47	29 (34.5)	24.4–44.7	0.12
Pretreatment AEs	2	2 (2.4)	0–5.6	0	NA	0–0	0.50
TEAEs	71	39 (45.9)	35.3–56.5	47	29 (34.5)	24.4–44.7	0.16
Trial procedure-nonrelated TEAEs	49	28 (32.9)	22.9–42.9	36	24 (28.6)	18.9–38.2	0.62
Trial procedure-related TEAEs	22	18 (21.2)	12.5–29.9	11	9 (10.7)	4.1–17.3	0.09
Major bleeding events	0	0 (0.0)	NA	0	0 (0.0)	NA	1.00
Clinically relevant nonmajor bleedings	9	7 (8.2)	2.4–14.1	2	2 (2.4)	0–5.6	0.17
Minor bleeding events	7	6 (7.1)	1.6–12.5	5	5 (6.0)	0.9–11	1.00
Fatal TEAEs	0	0 (0.0)	NA	0	0 (0.0)	NA	1.00
VTE-related TEAEs leading to death	0	0 (0.0)	NA	0	0 (0.0)	NA	1.00
Bleeding-related TEAEs leading to death	0	0 (0.0)	NA	0	0 (0.0)	NA	1.00
Other TEAEs leading to death	0	0 (0.0)	NA	0	0 (0.0)	NA	1.00

AE indicates adverse event; NA, not applicable; TEAE, treatment-emergent adverse event; and VTE venous thromboembolism.
Number (percentage) presents number (percentage) of patients with at least one event. Comparisons were done with the Fisher exact test.

improvement in PTS severity and quality of life after endovascular treatment, with the degree of improvement in both measures comparable to that reported in previous studies.[32,41] Conversely, reports indicate that patients with patent veins tend to report worse quality of life scores compared with those who experience stent occlusion.[6,42] We advocate for the use of a composite primary outcome in future studies, integrating patient-reported outcomes and primary patency in a hierarchical framework.

The study has several limitations that may affect the interpretation and generalizability of the findings. A key limitation was the smaller-than-planned sample size, with only 169 patients enrolled, reducing the statistical power to detect significant differences between arms. The trial was terminated prematurely because of slow recruitment, which was attributable primarily to the COVID-19 pandemic. In addition, the open-label design of the study may have introduced bias. Furthermore, the per-protocol analysis included only ≈80% of the randomized patients, namely those with a drug compliance exceeding 80%. In the latter group, the primary patency rate appeared to be higher in both treatment arms. The 6-month follow-up period, although sufficient for short-term outcomes such as stent patency, may not have captured the long-term efficacy and safety of the interventions. Previous studies showed that the primary patency at 12 months was between 80% and 84%, whereas it was higher (85% to 88%) at 6 months (Table S4).[21,30–33] Moreover, the study was conducted at experienced centers across Austria, Switzerland, and Germany, which may limit the generalizability of the results to different populations and health care settings. Finally, the exclusion of high-risk patients with contraindications to antithrombotic therapy or those with cancer narrows the applicability of the findings.

Conclusions

The overall primary patency rate during the first 6 months after endovascular intervention for PTS was higher than expected and comparable between patients receiving aspirin combined with rivaroxaban and those receiving rivaroxaban alone. Future research should focus on refining patient selection and exploring the potential benefits of adjunctive or alternative antithrombotic therapies, particular in patients with PTS at higher risk of stent occlusion.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4

Figure S1

Reporting checklist

APPENDIX

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