NEJM Evidence

Published November 22, 2022
NEJM Evid 2022; 1 (12)
DOI: 10.1056/EVIDoa2200104

ORIGINAL ARTICLE

Rivaroxaban Prophylaxis in Noncirrhotic Portal Vein Thrombosis

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Abstract

BACKGROUND In patients with noncirrhotic chronic portal vein thrombosis (PVT), the benefit of long-term anticoagulation is unknown. We assessed the effects of rivaroxaban on the risk of venous thromboembolism and portal hypertension-related bleeding in such patients.

METHODS In this multicenter, controlled trial, we randomly assigned patients with noncirrhotic chronic PVT without major risk factors for thrombosis to receive either rivaroxaban 15 mg/day or no anticoagulation. The primary end point was 2-year thrombosis-free survival. Secondary end points included the occurrence of site-specific thromboses and major bleeding events.

RESULTS A total of 111 participants were enrolled in the trial, with a mean age of 50.4±13.2 years; 58% of participants were men. An unplanned interim analysis was requested by the independent data safety monitoring board (DSMB) after 10 thrombotic events occurred. The thrombosis incidence rate was 0 per 100 person-years in the rivaroxaban group and 19.71 per 100 person-years (95% confidence interval, 7.49 to 31.92) in the no anticoagulation group (log-rank P=0.0008) after a median follow-up of 11.8 months. Based on the interim analysis, the DSMB recommended switching patients from the no anticoagulation group to anticoagulation. After a median follow-up of 30.3 months (intraquartile range, 24.3 to 47.8), major bleeding occurred in two patients receiving rivaroxaban and in one patient not receiving anticoagulation. No deaths occurred.

CONCLUSIONS After a median follow-up of 11.8 months, among patients with noncirrhotic chronic PVT without major risk factors for thrombosis, daily rivaroxaban reduced the incidence of venous thromboembolism and did not increase major bleeding events.

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(Funded by grants from the French Ministry of Health and the Association de Malades des Vaisseaux du foie; ClinicalTrials.gov number, NCT02555111.)

Introduction

Nonmalignant extrahepatic portal vein obstruction in adults is predominantly related to thrombosis and referred to as portal vein thrombosis (PVT).[1,2] The development of PVT is associated with one or more underlying risk factors for thrombosis in 60 to 70% of cases.[1,3-5] Several conditions are considered to be major (e.g., myeloproliferative neoplasms, antiphospholipid syndrome, or homozygous factor V Leiden) or mild-to-moderate (e.g., heterozygous G20210A factor II or G1691A factor V mutations or low-titer antiphospholipid antibodies) risk factors for PVT.[1,6-9] Protein C and protein S deficiency can be difficult to interpret in the spectrum of liver disease, especially in the absence of a personal or family history of unprovoked venous thrombosis.[10-12]

The two major complications of long-term PVT are gastrointestinal bleeding related to portal hypertension and recurrent thrombosis. Intestinal infarction is the most severe outcome of recurrent thrombosis and is associated with a mortality rate of 20 to 60% and severe disability due to extended resection or postischemic intestinal stenosis.[1,2]

Retrospective studies in patients with a history of PVT suggest that permanent anticoagulation therapy may significantly decrease the incidence of recurrent thrombosis without increasing the occurrence or severity of gastrointestinal bleeding and may independently improve survival.[13-17] However, the scope and strength of existing recommendations from scientific societies are limited by these retrospective studies' heterogenous populations and an absence of randomized therapeutic trials.[1,2,18,19] Clarifying the benefit-risk ratio of anticoagulation therapy, especially direct oral anticoagulants (DOACs), in patients with a history of PVT and without major risk factors for recurrent thrombosis is an important issue and has not been determined.[20]

The goal of this trial was to assess the efficacy of rivaroxaban 15 mg/day to prevent the recurrence of thromboembolic events or death in patients with noncirrhotic chronic PVT and without major risk factors for thrombosis.

Methods

TRIAL DESIGN AND ETHICS

This randomized, open-label, controlled trial was performed between September 2015 and January 2020 (NCT02555111) at eight centers in France with experience in the management of vascular liver disease. The institutional review board (Ile-de-France IV no. 53-15, September 2, 2015) and the French Medicine Agency (July 28, 2015) approved the protocol provided with the full text of this article at evidence.nejm.org. All participants provided written informed consent.

POPULATION

Adult patients with a history of either chronic, including portal cavernoma, or recent PVT diagnosed more than 6 months before enrollment and without major prothrombic risk factors as defined below were eligible to participate. Recent PVTs were documented by a contrast-enhanced multiphasic computed tomography (CT) scan or magnetic resonance imaging (MRI), followed by recanalization or persistence of obstruction, and found to affect the trunk or the right or left branches of the portal vein, with or without splenic or mesenteric vein involvement and with or without intestinal ischemia. Diagnosis of PVT was based on previously defined guidelines,[1,2] and patients may or may not have been treated with anticoagulants. PVT was classified in accordance with the recent American Association for the Study of Liver Diseases practice guidance document.[2] Case definitions of chronic PVT and recent (acute) PVT are available in the Supplementary Appendix (p. 4) with the full text of this article at evidence.nejm.org.

Patients were included whether or not they had a provoked thrombosis, defined as the presence of a local cause or use of recent estrogen-containing oral contraceptives at diagnosis. A history of prior noncirrhotic PVT or a previous diagnosis of cavernoma were considered as previous thromboembolic episodes in the assessment of thrombotic risk; patients with two or more episodes of acute PVT were excluded.

All patients were screened for the following major prothrombotic risk factors: myeloproliferative neoplasms

(including Janus kinase 2 V617F gene mutation), antiphospholipid syndrome, homozygous or composite heterozygous G20210A factor II or G1691A factor V mutations, and a personal or first-degree family history of unprovoked venous thrombosis.[9,19,21,22] Patients found to have low-risk thrombophilia, defined as heterozygous mutation G1691A factor V Leiden or G20210A factor II, interpretable decreased activity of antithrombin, protein C or protein S in the absence of personal or first-degree family history of deep vein thrombosis (DVT), or hyperhomocysteinemia, were eligible to be included. Patients with a history of intestinal resection (due to past mesenteric infarction), cirrhosis, hepatocellular carcinoma, or childhood cavernoma were not eligible. The Supplementary Appendix (p. 4-5) provides a full list of inclusion and exclusion criteria. Patient eligibility was reviewed by a central eligibility committee that included three hepatologists and three hematologists. Complete screening file and study protocol are provided in Table S1 and the Supplementary Appendix text.

OUTCOMES

The primary end point was the occurrence of a symptomatic or asymptomatic venous thromboembolic event at any site or death within 2 years of randomization. According to the Prospective Randomized Open Blinded End-Point (PROBE) methodology,[23] an independent committee, including a hepatologist and a radiologist blinded to the treatment group, assessed all thoracoabdominal CT scans and clinical data for recurrent thrombosis.

Secondary end points included death, pulmonary embolism (PE), DVT, major bleeding (according to the International Society on Thrombosis and Haemostasis guidelines definition),[24] portal hypertension-related bleeding (as defined by Baveno VI guidelines[18]), nonbleeding complications of portal hypertension (i.e., ascites, portal cholangiopathy), minor bleeding, liver toxicity (as defined by an otherwise unexplained increase in serum aminotransferase levels), and any other adverse events.

RANDOMIZATION AND TREATMENT

A randomization sequence was used for treatment assignments, with stratification according to anticoagulant therapy at inclusion and treatment center. Patients were randomly allocated (1:1 ratio) to either oral rivaroxaban 15 mg once daily for the duration of follow-up or no anticoagulant medication. The dose of 15 mg/day was chosen because anticoagulation may have a beneficial effect on portal hypertension-related bleeding by reducing portal pressure, as previously suggested,[13,15] and using a reduced dose of 15 mg/day compared with the standard dose of 20 mg/day was deemed beneficial for the benefit-risk balance in those patients also at higher bleeding risk due to portal hypertension, thrombocytopenia, or invasive procedures. At the time the study started, the dose of 15 mg/day had been tested in studies on patients with atrial fibrillation and those with renal failure.[25]

FOLLOW-UP VISITS

Visits occurred at the time of randomization (baseline) and at 1, 3, and 6 months, and every 6 months thereafter for 24 to 48 months. Clinical and laboratory data were obtained at each follow-up visit. Abdominal Doppler ultrasounds were obtained every 6 months starting at month 3, injected abdominal CT scans or MRIs were obtained annually starting at inclusion, and D-dimers were obtained annually starting at 1 month. In symptomatic patients, additional investigations (thoracoabdominal CT scan and lower-limb Doppler ultrasound) were performed according to usual practice at the discretion of the supervising physician.

STUDY TIMELINE, SAMPLE SIZE, AND STATISTICAL ANALYSES

We assumed an annual rate of thrombosis recurrence of 3.5% in the nontreated group versus 0.8% in the rivaroxaban group, and an estimated 6% of patients would be lost to follow-up. Based on these assumptions, a sample size of 296 was planned to achieve 80% power at a two-sided type I error rate of 0.05. We estimated that 24 months were needed to recruit patients, with a minimum follow-up of 24 months. After temporary suspension of inclusions due to five thrombotic events in the nontreated group within 21 weeks of study initiation (first interim analysis), the independent data safety monitoring board (DSMB) recommended that the study continue. The study protocol was therefore amended with an additional interim analysis planned after a total of 10 thrombotic events.

Analyses of the primary and secondary outcomes included all patients who underwent randomization (intent-to-treat population). Analysis of the primary outcome was based on a group-sequential design with two interim analyses with O'Brien–Fleming stopping boundaries (i.e., 0.0005 and 0.014, respectively). This analysis was performed using a two-sided log-rank test stratified by anticoagulation therapy at the time of randomization. Every effort

was made to obtain the required data at each scheduled evaluation from all enrolled participants. There were no missing data for the primary end point.

Patient enrollment was discontinued after 28 months on the recommendation of the independent DSMB on January 19, 2018, after the second interim analysis. Thereafter, all patients from the no anticoagulation group were offered the opportunity to switch to rivaroxaban 15 mg/day and were observed for at least 24 months after randomization and up to 48 months. The DSMB recommendations supported the use of rivaroxaban 15 mg/day, but the choice of anticoagulation was ultimately left to the treating physician. Thus, there were two distinct periods to the trial: period 1 (randomized period) from randomization to January 19, 2018, the time of the last inclusion, when rivaroxaban 15 mg/day was prescribed to all patients in the treatment group versus no anticoagulation (Fig. 1A); and period 2 (follow-up period) from January 19, 2018, to the end of study on January 30, 2020 (Fig. 1B and Fig. S1), when rivaroxaban 15 mg/day was recommended, but not required, for all patients. Throughout the entire study, in patients developing a thrombotic event, anticoagulation with either rivaroxaban or other routine therapy was prescribed for all acute DVTs in accordance with clinical practice guidelines.

Major and minor bleeding events, as well as nonbleeding outcomes, were analyzed according to the treatment received throughout the entire study (both period 1 and period 2). We estimated person-time on treatment with rivaroxaban, on treatment with other anticoagulant therapies, and on no treatment using the start and stop dates of each type of treatment. The incidence rates of bleeding events and nonbleeding outcomes were calculated by dividing the number of incident events by the number of person-years during the corresponding period. Incidence rate ratios were estimated by Poisson regression models with 95% confidence intervals (CI). This method enabled the study of recurrent events.

Univariable Cox proportional-hazard models were used to assess whether known risk factors for thrombosis were associated with recurrent thrombosis among patients randomly assigned to the no anticoagulation group. In this analysis, patients were observed from random assignment until January 19, 2018 (period 1).

A P value of 0.05 or less was considered to be statistically significant. The CIs for end points other than the primary end point have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects. Data handling and analysis were performed with SAS statistical software (version 9.4; SAS Institute, Cary, NC).

Results

STUDY POPULATION AND CHARACTERISTICS

Overall, 111 patients with PVT were included across 8 participating hospitals (Table S2), including 55 patients in the rivaroxaban group and 56 in the no anticoagulation group (Fig. 1A). Baseline characteristics are summarized in Table 1 and Tables S3-S5. Median follow-up time for the entire study was 30.3 months (interquartile range, 24.3 to 47.8 months). Three patients (2.7%) were lost to follow-up. Median time from PVT diagnosis to inclusion was 1.7 years, (interquartile range, 0.9 to 5.3 years). The population was broadly representative of the patient population with noncirrhotic PVT, with the exception of age; trial participants were slightly younger than the reported median age for patients with noncirrhotic PVT (Table S5).

Baseline characteristics were comparable in the two arms (Table 1 and Tables S3-S5). Low-risk thrombophilia was identified in 48 patients (50%) on baseline screening. When PVT had been diagnosed, a local cause had been found in 17 patients (15%); all had been cured at time of inclusion. Clinical manifestations of PVT at inclusion are presented Table 1 and Table S1 and most commonly related to portal hypertension or cholangiopathy. Portosystemic collaterals were present in 56 patients (53%), esophageal varices in 32 patients (29%), and gastric varices in 10 patients (9%). Median elasticity in 93 patients was 5.5 kPa (intraquartile range, 4.3 to 6.7 kPa); 93 patients (100%) had liver stiffness less than 13 kPa and 91 (98%) had liver stiffness less than 10 kPa.

A total of 87 patients (90%) had received anticoagulation beyond 6 months after initial PVT diagnosis to prevent thromboembolism recurrence. At the time of inclusion, 82 patients (74%) were still on anticoagulation therapy. Of these patients, 73 (92%) were on vitamin K antagonists. Median time on anticoagulation was 15.8 months (intraquartile range, 8.9 to 38.1) before inclusion, and median international normalized ratio was 2.3 (intraquartile range, 1.7 to 2.8) at inclusion. Sixteen of the 29 patients not on anticoagulants at the time of inclusion were randomly assigned to the rivaroxaban group and 13 to the no anticoagulation group.

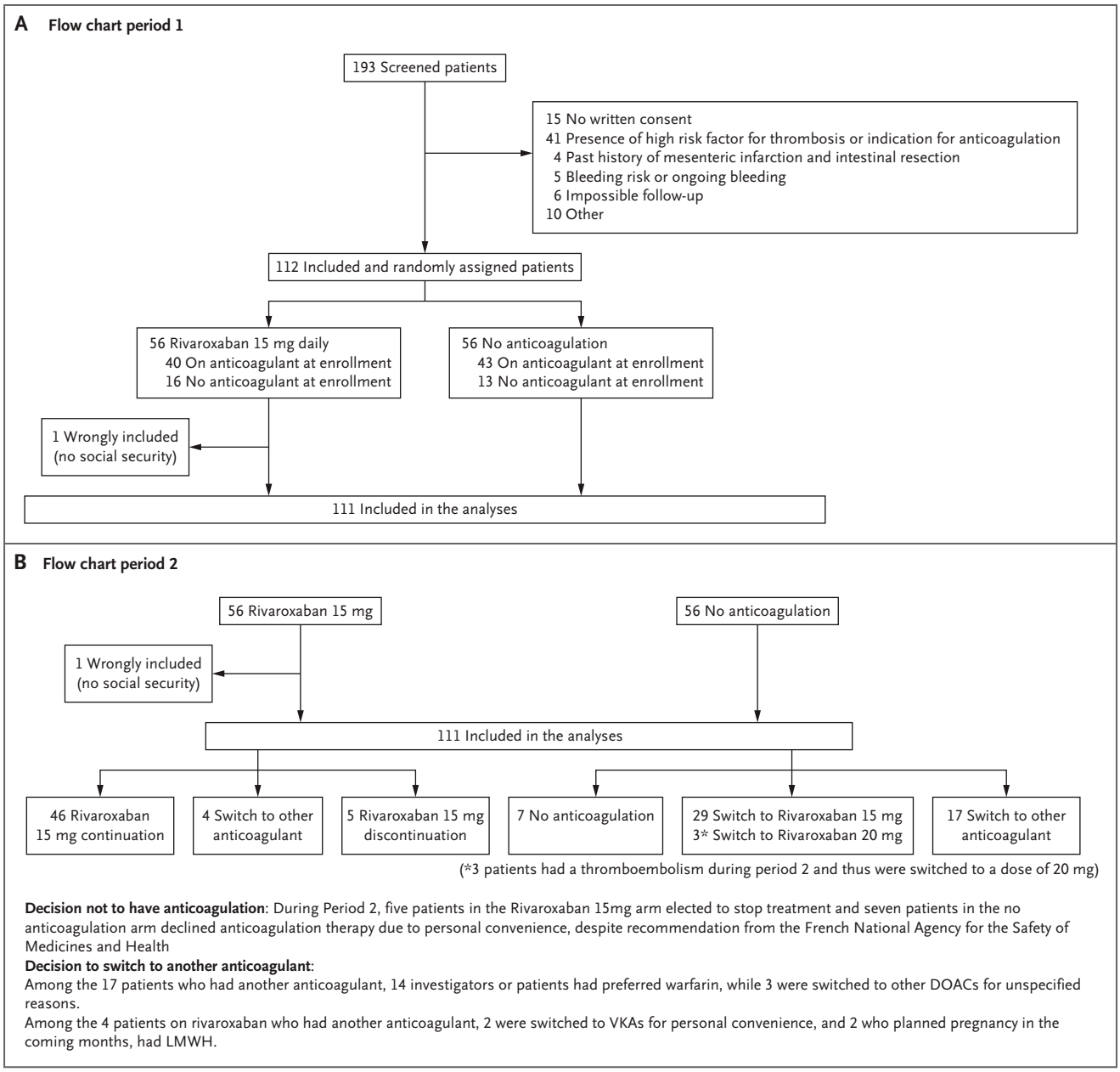

Figure 1. Flowchart for Periods 1 and 2.

(Panel A) Randomization phase — period 1 (randomized period) from randomization to January 19, 2018, the time of the last inclusion, when rivaroxaban 15 mg/day was prescribed to all patients in the treatment group, versus no anticoagulation. (Panel B) Follow-up phase — period 2 (follow-up period) from January 19, 2018, to the end of study on January 30, 2020, when rivaroxaban 15 mg/day was recommended, but not required, for all patients. DOAC denotes direct oral anticoagulant; LMWH, low-molecular-weight heparin; and VKA, vitamin K antagonist.

PRIMARY OUTCOME

The incidence rate of thrombotic events was 19.71 per 100 person-years (95% CI, 7.49 to 31.92) in the no anticoagulation group, whereas no thrombotic events occurred in the rivaroxaban group. All but one were symptomatic. Venous thromboembolic event-free survival significantly differed between treatment groups (log-rank test P=0.0008; Fig. 2). No deaths occurred. Five patients needed to be treated by rivaroxaban to avoid one recurrent thrombosis (95% CI, 3.1 to 13.3). Among 10 patients

Table 1. Characteristics of Patients at Inclusion.*

Characteristic	Total (N=111)	Rivaroxaban (n=55)	No Anticoagulation (n=56)	P Value
Mean age (SD) — yr	50.4 (13.2)	50.3 (12.6)	50.5 (14.0)	0.92
Male sex — no. (%)	64 (58)	31 (56)	33 (59)	0.78
Recent PVT at diagnosis — no. (%)	94 (85)	45 (82)	49 (87)	0.41
Ongoing anticoagulation at inclusion — no. (%)	82 (74)	39 (71)	43 (77)	0.48
Low-risk thrombophilia† — no. (%)	48 (50)	28 (60)	20 (42)	0.08
Patients with provoked risk factors for thrombosis at the time of PVT diagnosis — no. (%)				
Estroprogestative or pregnancy 3 months prior to PVT among 47 women	14 (30)	7 (29)	7 (30)	0.92
Abdominal or pelvic surgery within 3 months prior to PVT	13 (12)	8 (15)	5 (9)	0.36
Local inflammation or infection at the time of thrombosis diagnosis‡	17 (15)	8 (15)	9 (16)	0.82
Patients with other risk factors for thrombosis at the time of PVT diagnosis — no. (%)				
Body-mass index >30	29 (26)	13 (24)	16 (29)	0.59
Patients with at least one low-risk factor§ — no. (%)	102 (94)	47 (90)	55 (98)	0.06
Manifestations — no. (%)				
Esophageal varices	32 (29)	18 (33)	14 (25)	0.34
Portosystemic collaterals on imaging	56 (53)	28 (52)	28 (55)	0.75
Laboratory data — mean (SD)				
Platelets — 10^9/l	205.4 (84.4)	198.2 (88.0)	212.4 (80.8)	0.16
Serum creatinine — µmol/l	75.7 (15.4)	75.4 (16.2)	76.1 (14.7)	0.64
Splanchnic vein obstruction — no. (%)				0.65
Intrahepatic¶	25 (25)	11 (22)	14 (29)	
Intrahepatic and extrahepatic¶	62 (63)	34 (67)	28 (58)	
Extrahepatic¶	12 (12)	6 (12)	6 (12)	
Portal cavernoma	78 (70)	42 (76)	36 (64)	0.16
Recanalized portal tract	10 (9)	4 (7)	6 (11)	0.51

* PVT denotes portal vein thrombosis. The body-mass index is the weight in kilograms divided by the square of the height in meters.

† Low-risk thrombophilia at inclusion is heterozygous G1691A factor V mutation, heterozygous G20210A factor II mutation, protein S deficiency (PS; >50% nonmenopausal women, <55% menopausal women, or <60 men), protein C deficiency (PC; <70), antithrombin (AT) deficiency (AT <70), in the absence of familial or personal unprovoked first-degree thrombosis, or hyperhomocysteinemia.

‡ This includes two liver abscesses, six infectious colitis, three acute pancreatitis, and six other splanchnic or systemic infections.

§ Combined persisting low-risk factors at inclusion were male sex, body-mass index >30, >60 years of age, non-O blood group, heterozygous G1691A factor V mutation, heterozygous G20210A factor II mutation, PS deficiency (<50 nonmenopausal women, <55 menopausal women, or <60 men), PC deficiency (PC <70), AT deficiency (AT <70), in the absence of familial or personal unprovoked first-degree thrombosis, hyperhomocysteinemia, systemic disease, porto-sinusoidal vascular liver disease, induced first-degree family history ≥2, unprovoked second-degree family history ≥1, or factor VIII >15.

¶ There were missing data in 12 patients (i.e., 4 in the rivaroxaban group and 8 in the no anticoagulation group).

who experienced a thrombotic event, 9 (90%) had been treated with anticoagulation therapy before inclusion for a median time of 49.5 months (intraquartile range, 19.6 to 88.0 months). Among 46 patients who did not experience a thrombotic event, 34 (74%) had been treated with anticoagulation therapy before inclusion for a median time of 13.7 months (intraquartile range, 8.0 to 44.9 months).

Follow-up Period (Period 2)

During period 2, all randomly assigned patients were observed for a median of 21.5 months (intraquartile range, 20.1 to 22.4 months). Anticoagulation therapy was proposed to all patients. Forty-six of the 55 patients from the rivaroxaban arm continued rivaroxaban, whereas 4 switched to another anticoagulant, and 5 discontinued anticoagulants altogether. Thirty-two of the 56 patients

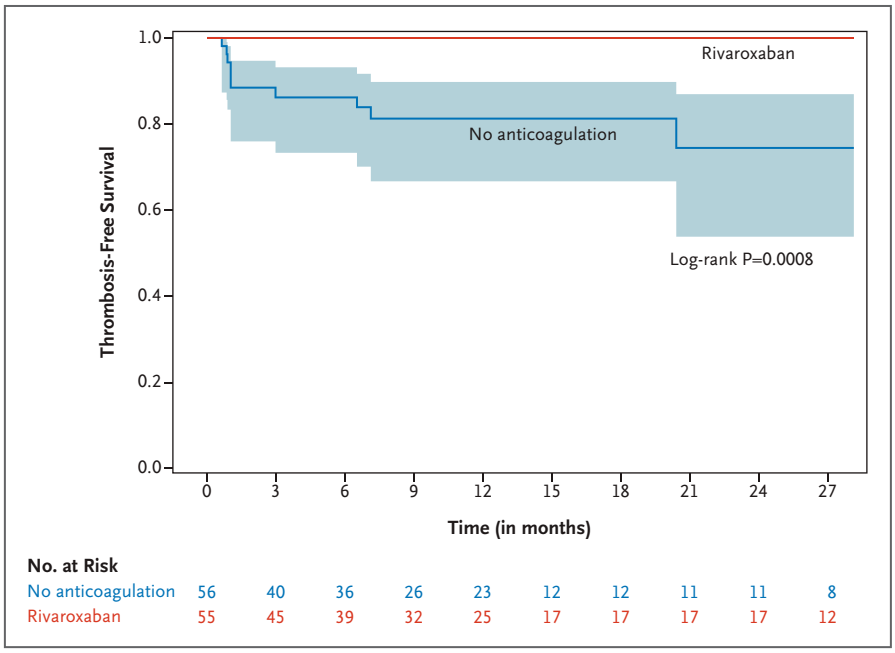

Figure 2. Kaplan–Meier Curves of Thrombosis-Free Survival with 95% Confidence Interval Limits.

from the no anticoagulation arm received rivaroxaban, including 29 at a dose of 15 mg/day and 3 at a dose of 20 mg/day, whereas 17 patients received another anticoagulant, and 7 received no anticoagulants (Fig. 1B).

During period 2, three patients who did not receive anticoagulation as part of period 2 of the trial had a single new thrombotic event. One patient treated with warfarin had recurrent PVT associated with a liver abscess. A detailed description of patients with recurrent venous obstruction is provided in Table S6.

Over the entire study period (periods 1 and 2), recurrent thrombotic events occurred more frequently during the time period without anticoagulation than during periods exposed to anticoagulant treatment (16.0 per 100 person-years vs. 0.4 per 100 person-years; incidence rate ratio, 37.3; 95% CI, 4.9 to 285.0).

SECONDARY END POINTS

During period 1, venous thrombosis occurred in 10 patients, splanchnic vein thrombosis in four patients, DVT in three, and PE in three (Table S6).

Throughout the entire study period (periods 1 and 2), major bleeding occurred in three patients — two in patients receiving rivaroxaban and one in a patient not receiving an anticoagulant (Table 2).

Fifty-seven minor bleeding episodes occurred. There were 16 events with gingivorrhagia (12 events in the rivaroxaban group in 9 patients and 4 in the no anticoagulation group in 4 patients), 13 events with epistaxis (12 events in the rivaroxaban group in 11 patients and 1 in the no anticoagulation group in 1 patient), 11 with rectal bleeding (7 events in the rivaroxaban group in 6 patients and 4 in the no anticoagulation group in 4 patients), 9 with uterine bleeding (6 events in the rivaroxaban group in 5 patients and 3 in the no anticoagulation group in 3 patients), and 6 other minor bleedings (3 events in the rivaroxaban group in 2 patients and 3 in the no anticoagulation group in 2 patients). Minor bleeding occurred more frequently during exposure to DOACs than during the period without treatment (incidence rate ratio, 4.86; 95% CI, 1.75 to 13.50). In one patient, recurrent minor rectal bleeding led to permanent anticoagulation discontinuation.

POST HOC ANALYSES

Kaplan–Meier subanalysis (Fig. S3) showed that there is a tendency for more recurrence when having received a PVT diagnosis a long time ago compared with a recent diagnosis.

Table 2. Incidence Rates and Incidence Rate Ratios for Secondary End Points.*				
Secondary End Point	No. of Events	Person-Years	Incidence Rate per 100 Person-Years (95% CI)	Incidence Rate Ratio (95% CI)
Severe bleeding				
No anticoagulant	1	81.3	1.2 (0–3.6)	1
DOACs	2	196.4	1.0 (0–2.4)	0.8 (0.1–9.1)
VKA or heparins	0	36.7	0	—
Minor bleeding				
No anticoagulant	4	81.3	4.9 (0.1–9.8)	1
DOACs	47	196.4	23.9 (17.1–30.8)	4.9 (1.8–13.5)
VKA or heparins	6	36.7	16.33 (3.3–29.4)	3.3 (0.9–11.8)
Portal hypertension bleeding				
No anticoagulant	1	81.3	1.2 (0–3.6)	1
DOACs	3	196.4	1.5 (0–3.3)	1.2 (0.1–11.9)
VKA or heparins	1	36.7	2.7 (0–8.1)	2.2 (0.1–35.4)
Ascites or symptomatic cholangiopathy				
No anticoagulant	1	81.3	1.2 (0–3.6)	1
DOACs	6	196.4	3.1 (0.6–5.5)	2.5 (0.3–20.6)
VKA or heparins	0	36.7	0	—

* The widths of the 95% confidence intervals (CIs) have not been adjusted for multiplicity; thus, 95% CI should be used to reject or not reject treatment consumption effects. DOAC denotes direct oral anticoagulant; and VKA, vitamin K antagonist.

Risk Factors for Recurrent Thrombosis

During period 1, none of the factors measured at baseline, including thrombophilia factors, was associated with recurrent thrombosis. Among the factors measured at 1 month, D-dimer 500 ng/ml or higher was associated with recurrent thrombosis (hazard ratio, 7.78; 95% CI, 1.49 to 40.67; Fig. 3) with a positive predictive value of 37.5% (95% CI, 13.8 to 61.2) and a negative predictive value of 93.8% (95%

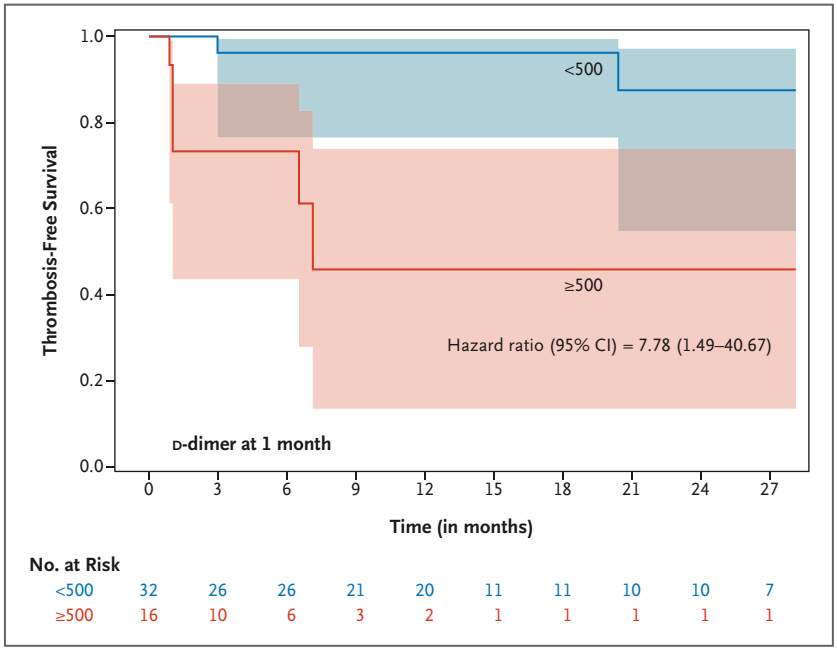

Figure 3. Kaplan–Meier Curves of Thrombosis-Free Survival According to D-Dimer Level at 1 Month with 95% Confidence Interval (CI) Limits.

Table 3. Factors Associated with Occurring Thromboembolism among Patients Randomly Assigned in the Nontreated Group.*

Factor	Occurring Thromboembolism (n=10)	No Occurring Thromboembolism (n=46)	Hazard Ratio (95% CI)
Age — yr	44.6 (36.2–50.7)	49.3 (43–64)	0.97 (0.92–1.02)
Male — no. (%)	6 (60)	27 (58.7)	0.81 (0.20–3.29)
Platelets — 10^9/l	232.5 (206–266)	205.5 (163–247)	1.01 (0.99–1.02)
Factor V — %	111.0 (98.0–128.0)	101.5 (84.0–116.0)	1.04 (1.00–1.07)
Leukocytes — 10^9/l	5.5 (4.6–7.1)	5.3 (4.4–6.1)	1.27 (0.92–1.75)
Hemoglobin — g/dl	14.9 (13.7–15.3)	14.3 (13.1–15.6)	1.24 (0.76–2.02)
Aspartate aminotransferase — IU/l	29.5 (22–43)	27.0 (22–31)	1.01 (0.98–1.03)
Alanine aminotransferase — IU/l	32.0 (20–42)	26.0 (20–35)	1 (0.99–1.02)
Alkaline phosphatase — IU/l	62.5 (57–82)	61 (54–72)	1 (0.98–1.02)
Albumin — g/l	38.2 (38–40)	39.4 (38–41)	0.85 (0.68–1.07)
Body-mass index >30 — no. (%)	3 (30)	13 (28.3)	1.00 (0.25–3.98)
Thrombophilia — no. (%)			
Protein S deficiency†	1 (10)	5 (11.1)	0.6 (0.07–4.84)
Protein C deficiency <70	1 (10)	7 (15.2)	0.5 (0.06–40)
Hyperhomocysteinemia	1 (11.1)	11 (28.2)	0.48 (0.06–3.97)
Provoked risk factors‡ — no. (%)	0	19 (41.3)	—
Portal vein thrombosis diagnosis delay	6.3 (2.4–7.9)	1.3 (0.8–5.3)	1.08 (0.94–1.25)
Complete recanalization of portal vein at inclusion	0	6 (13.3)	—
D-dimers at 1 month ≥500 ng/ml — no. (%)	6 (75)	10 (25)	7.78 (1.49–40.67)
Factor VIII at 1 month >150 — no. (%)	4 (50)	16 (40)	1.47 (0.32–6.71)

* Data are median (interquartile range), unless otherwise specified. The widths of the 95% confidence intervals (CIs) have not been adjusted for multiplicity; thus, 95% CI should be used to reject or not reject treatment consumption effects. The body-mass index is the weight in kilograms divided by the square of the height in meters.

† This is defined as <50 in women of child-bearing age, <55 in menopausal women, or <60 in men.

‡ This is defined as infectious local causes, surgery, or estroprogestative treatment within 3 months of the initial thrombosis.

CI, 85.4 to 100). Provoked causes for PVT were less likely to be associated recurrent thrombosis (Table 3).

ADVERSE EVENTS

Twenty-two other adverse events were reported in 17 patients, including four episodes of ascites and three episodes of portal cholangiopathy-related symptoms (Table S7). Four episodes of acute pancreatitis occurred in three patients treated with rivaroxaban, two of whom had taken codeine. There was no evidence for liver toxicity from rivaroxaban (Fig. S2).

Discussion

Our study is a multicenter, randomized controlled trial examining the risk of recurrent thrombosis in patients with noncirrhotic chronic PVT. Despite a careful exclusion of patients with major risk factors for recurrent venous thrombosis, the incidence of thrombotic episodes among those assigned to no anticoagulation in period 1 was close to 20 per 100 person-years, including unusual multisite thrombosis or PE. It is important to note that the results in period 2 confirm the high risk of thromboembolism without anticoagulation treatment found in the randomized phase (period 1). Thus, our trial provides data that a past history of PVT is a major risk factor for recurrent thrombosis even in the absence of recognizable major prothrombotic conditions. Our data do not address the issue of whether patients with porto-sinusoidal vascular liver disease, but without high risk factors for venous thrombosis, should be treated routinely with anticoagulation.[26] Overall, 50% of our patients had an identified low-to-moderate risk of thrombophilia, and none of the common underlying causes of thrombosis was significantly related to the risk of recurrence. Obesity and advanced age were also not identified as additional risk factors for recurrence. Furthermore, none of the patients who had provoked PVT at diagnosis had recurrent thrombosis. It is important to note that, similar to patients with DVT,[7,27,28] D-dimer levels less than 500 ng/ml 1 month after anticoagulant

discontinuation were strongly associated with a lower risk of recurrence.

In our trial, the incidence of recurrent thrombosis in the no anticoagulation group was higher than reported in retrospective PVT studies; those studies included patients both with and without prior anticoagulation therapy[13-16] or patients with DVT.[7,27,29,30] Our results support those of DVT[31-35] in a very specific population with rare disease in unusual site of thrombosis. The population we studied included approximately half of the patients with portal hypertension features and approximately one third with significant esophageal or gastric varices at high bleeding risk at inclusion. These patients have been systematically excluded in pivotal phase III trials evaluating the efficacy and safety of DOACs. Among the 55 patients allocated to the anticoagulant group that received rivaroxaban 15 mg/day, none had a new episode of thrombosis. Our prospective findings validate conclusions from retrospective data showing that anticoagulation plays an independent role in preventing recurrent thrombosis in patients with noncirrhotic chronic PVT.[13-17,36]

The benefit of preventing recurrent thrombosis with rivaroxaban should be balanced with the risk of bleeding during therapy. The incidence of major bleeding and portal hypertension-related bleeding we observed is much lower than previously reported in PVT or other vascular liver diseases in patients treated with vitamin K antagonists.[3,37] The incidence we observed is comparable to the 1% incidence when using 15 mg twice daily for 21 days, followed by 20 mg daily thereafter in pooled EINSTEIN studies for DVT or PE, but higher than the 0.4% and 0.5% incidences in the EINSTEIN CHOICE study, which compared two doses of rivaroxaban (10 mg/day and 20 mg/day) with acetylsalicylic acid.[38-42] Whether gastrointestinal bleeding is increased with DOACs compared with warfarin is still unclear. Nevertheless, the severity of these episodes does not seem to be increased.[43-45] Furthermore, although based on limited data, the risk of bleeding in patients with cirrhosis and portal hypertension seems to be lower with DOACs than with vitamin K antagonists.[46-48] Up to now, evidence for the safety and efficacy of DOACs in PVT in the absence of cirrhosis has been limited.[20]

The main strengths of this study were the use of a randomized controlled trial in a rare disease to address the benefit of prophylactic rivaroxaban in patients with noncirrhotic chronic PVT; however, some limitations exist. First, funding therapeutic trials in rare diseases is still challenging. In this publicly funded trial, we faced funding limitations that precluded the use of a placebo and led us to conduct an open-blinded trial. To limit the risk of misclassification due to the open-blinded design, an independent committee blinded to the treatment group assessed the major end point b reviewing imaging and clinical data to confirm the occurrence of thrombosis (PROBE methodology). Second, the early termination due to efficacy could have led to additional overestimation of the benefits of the intervention.[49] Third, results on D-dimer are interesting and in line with data on venous thromboembolism in general, but should be interpreted with caution considering the small sample size of the no anticoagulation group and the limits because of sex heterogeneity in previous studies.[32] Fourth, it is difficult to come to a conclusion on the major bleeding risk due to the small number of events and possible bias induced by anticoagulation administration at enrollment.

In patients with noncirrhotic chronic PVT without major prothrombotic risk factors, long-term rivaroxaban 15 mg once daily reduced thromboembolism without increased major bleeding incidence. In post hoc analyses, circulating D-dimer levels less than 500 ng/ml 1 month after anticoagulation discontinuation were associated with a low risk of recurrence at 2 years. These data should be validated in additional studies.

Disclosures

Supported by a grant Programme Hospitalier de Recherche Clinique (PHRC no. P110150) from the French Ministry of Health and a grant from the Association de Malades des Vaisseaux du Foie.

Author disclosures and other supplementary materials are available at evidence.nejm.org.

We thank Djalila Seghier, Kamal Zekrini, and the French National network for vascular liver diseases for their collaboration in data acquisition; the Association des Malades des Vaisseaux du Foie; the independent DSMB, Ariane Mallat, Philippe Sogni, and Michaela Fontenay for their scientific support; URC Paris Nord and Estelle Marcault for regulatory and logistic support; and Dr. Didier Lebrec, Sarwa Darwish Murad, and Dale Lebrec for their critical English revision of the manuscript.

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