CLINICAL RESEARCH STUDY

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Comparison of Fondaparinux and Low-Molecular-Weight Heparin in the Treatment of Portal Vein Thrombosis in Cirrhosis

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ABSTRACT

BACKGROUND: Portal vein thrombosis is the most common thrombotic complication in cirrhosis. About 60% of anticoagulated patients can achieve recanalization. Despite fondaparinux (FPX) theoretical advantages, data are lacking about safety and efficacy for treatment of portal vein thrombosis in cirrhosis.

METHODS: Cirrhotic patients with portal vein thrombosis treated with FPX or low-molecular-weight heparin (LMWH) were retrospectively included. The extension of thrombosis at baseline and its evolution during anticoagulant treatment were evaluated. Patients were treated with LMWH or FPX at therapeutic dosage and reduction was considered in selected cases.

RESULTS: There were 124 patients included. Main portal vein branch, splenic, and superior mesenteric veins were involved in 84%, 13%, and 36% of cases, respectively. Forty-one patients (33%) were treated with FPX and 83 (67%) with LMWH. The probability of resolution of thrombosis at 36 months was significantly higher in patients treated with FPX than in those treated with LMWH (77% vs 51%; $P = .001$), particularly when prescribed at reduced dose. With multivariate analysis, the treatment with FPX (hazard ratio 2.38; $P = .002$) and use of a full dose (hazard ratio 1.78; $P = .035$) were independent predictors of portal vein full recanalization. Bleeding rate was higher in patients treated with FPX than in those treated with LMWH (27% vs 13%; $P = .06$).

CONCLUSIONS: FPX appears to be more effective than LMWH in the treatment of portal vein thrombosis when used at reduced dose, also in complete thrombosis. FPX should be considered among possible treatments for portal vein thrombosis in cirrhosis.

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INTRODUCTION

Nonmalignant portal vein thrombosis is the most common thrombotic complication in patients with cirrhosis with annual incidence of 4.6%-12.8%,[1-5] and prevalence of up to 26% in liver transplant candidates.[2,6-8]

The clinical impact of portal vein thrombosis is still unclear in compensated patients;[1] however, it has been independently correlated with increased risk of uncontrolled variceal bleeding and, when complete or extended to the superior mesenteric vein, with higher mortality after liver transplantation.[9-11] Spontaneous recanalization occurs in approximately one-third of patients; however, those who receive anticoagulation show higher recanalization rate and reduced progression of thrombosis, without increased risk of bleeding.[12,13] Per current guidelines, treatment in cirrhosis is based on low-molecular-weight heparin (LMWH) or vitamin K antagonists.[14] However, both these drugs have limitations and potential side effects that include twice-daily subcutaneous administration for LWMH, increased risk of bleeding in patients with platelet count $<50 \times 10^9$/L,[15,16] and excessive risk of anticoagulation for vitamin K antagonists.[17]

CLINICAL SIGNIFICANCE

- Fondaparinux and low-molecular-weight heparin are both effective drugs for the treatment of portal vein thrombosis in patients with cirrhosis.
- Fondaparinux seems to be more effective when administered at reduced dose, independent of the presence of complete portal vein thrombosis.
- However, fondaparinux has to be used with caution due to the possible higher rate of bleeding in cirrhotic patients.

In patients with deep vein thrombosis and pulmonary embolism, previous evidence has demonstrated that fondaparinux (FPX) has comparable efficacy and safety compared with unfractionated heparin and LMWH.[18,19] Further potential advantages of FPX include once-daily administration[20] and lack of immune-induced thrombocytopenia.[21]

The use of FPX for the treatment of portal vein thrombosis in cirrhosis could have important clinical implications and may allow simplification of antithrombotic treatment in these patients.

Our aim in this retrospective study was to compare safety and efficacy of FPX vs LMWH in the treatment of portal vein thrombosis in patients with cirrhosis.

PATIENTS AND METHODS

Patients

A retrospective analysis was performed of all consecutive cirrhotic patients treated for portal vein thrombosis at the Gastroenterology/Multivisceral Transplant Unit and at the Unit of Internal Medicine and Hepatology, Padua University Hospital from January 2013 to December 2017. Inclusion criteria were: 1) diagnosis of cirrhosis according to clinical, biochemical, ultrasonographic, endoscopic, or histological findings; 2) age ≥18 years old; 3) portal vein thrombosis confirmed by computed tomography (CT) scan, magnetic resonance (MRI), or angiography. Exclusion criteria were: 1) use of antiplatelet agents during the 2 weeks prior to initial evaluation; 2) hepatocellular carcinoma; 3) extrahepatic malignancy; 4) previous liver transplant; 5) isolated thrombosis of the superior mesenteric vein or the splenic vein; 6) treatment with oral anticoagulants during the study period. This study was approved by Padua University Hospital Ethical Committee (Prot. AOP/0564).

Baseline Assessment

At first evaluation, all patients underwent CT or MRI scanning to define the extent of portal vein thrombosis according to the Yerdel classification, with specification of the occlusion for every venous segment (portal vein, superior mesenteric splenic veins).[6] Thrombus characteristics were assessed as previously reported.[22] Thrombosis was defined as partial or total, when thrombotic material occupied < or ≥90% of the vessel lumen, respectively. Thrombus age was estimated based on past medical history, previous radiological studies, and thrombus characteristics at diagnosis.

At diagnosis of thrombosis, demographic clinical and laboratory characteristics were collected, including the thrombophilic screening when available.

Anticoagulation Protocol

Prior to starting anticoagulation, all patients underwent laboratory tests including full blood counts, and endoscopic screening for esophageal varices. Prophylaxis for variceal bleeding was performed according to Baveno guidelines.[23]

Patients were treated with LMWH or FPX according to physician's choice. Per the local protocol, anticoagulation consisted of the administration of body weight dose-adjusted LMWH or FPX at therapeutic dosage. Dose reduction was considered in the case of: platelet count $<50 \times 10^9$/L, estimated glomerular filtration rate was <30 mL/min, LMWH <50 mL/min (FPX), body weight <50 kg (FPX), patients considered to be at high risk of bleeding due to clinical conditions, associated comorbidities, or previous history of bleeding. Glomerular filtration rate was estimated by the Modification in Renal Diet (MDRD)-6 equation.[24] Anticoagulation was either continued or discontinued according to physician's choice (based on achievement of complete recanalization, onset of side effects, patient tolerance, etc.). For each patient, the number of days between the estimated thrombus onset and start of anticoagulation was recorded and classified as an interval and as a binary classification according to the 6-month interval, which was previously demonstrated to correlate with response to anticoagulation.[22]

Follow-Up Imaging

After the onset of anticoagulation therapy, splanchnic veins permeability was evaluated with abdominal Doppler ultrasound at least every 3 months. CT scan was performed on all patients at 6 ± 1 and at 12 ± 1 months. Abdominal imaging was also performed whenever hospital admissions for complications of cirrhosis were required or when Doppler ultrasound was not diagnostic.

Endpoints

Primary endpoint was complete recanalization of the portal vein trunk or its main branches, and of superior mesenteric or splenic veins. Secondary endpoints were: 1) partial (>50%) recanalization of the portal vein trunk or its main branches; 2) survival; 3) bleedings.

Patient status (dead, alive, or transplanted), patency of splanchnic veins (confirmed by MRI or CT scan), were recorded after the start of anticoagulation treatment until last follow-up. Anticoagulation safety was assessed comparing bleedings between the 2 groups. Severity of bleeding was assessed according to the International Society of Thrombosis and Haemostasis guidelines.[25]

Statistical Analysis

Values for continuous variables were presented as mean ± standard deviation or medians (interquartile ranges [IQR]) according to distribution. Categorical-nominal variables were presented as frequencies. For subgroup comparisons, quantitative variables were compared using Student's *t* test or Mann-Whitney test, and categorical variables using chi-squared or Fisher's exact tests, as appropriate. Survival curves were estimated with the Kaplan-Meier method and compared with the log-rank test. The reaching of the primary end-point was evaluated only when the patient was receiving anticoagulation, whereas patients with anticoagulation withdrawn were omitted. The curves were cut at 36 months for 2 reasons: 1) no complete re-permeation was observed thereafter; 2) very few patients were given anticoagulant treatment for more than 36 months. Variables found to be significantly associated with portal vein thrombosis complete re-permeation were included in a multivariate Cox regression analysis with stepwise backward elimination (entry $P = .05$/drop $P = .05$). Results were expressed as hazard ratios (HR) and 95% confidence interval (95% CI). All tests were 2-tailed, and a P value of $< .05$ was considered statistically significant. Statistical analysis was performed using SPSS (version 25.0; IBM, Armonk, NY).

RESULTS

Study Population

There were 124 patients with cirrhosis and portal vein thrombosis included (mean age 60 ± 12 years, 69% male). Mean Model for End Stage Liver Disease (MELD) score was 12 ± 4, and 95 patients (77%) had esophageal varices at enrollment. Most patients had thrombocytopenia (median 56 × 10^9/L, IQR 41-80 × 10^9/L) and grade I thrombosis (41%). Approximately 30% of patients had complete portal vein thrombosis; superior mesenteric and splenic vein were involved in 14 (11%) and 41 (33%) patients, respectively.

Forty-one patients (33%) were treated with FPX and 83 (67%) with LMWH (Table 1 shows the comparison of baseline characteristics). Patients treated with FPX had significantly higher MELD-Na score and bilirubin. Characteristics of thrombosis and use of full dose of anticoagulant were comparable between groups. The majority of patients received a reduced anticoagulant dose (71% in FPX and 60% in LMWH groups). Thrombocytopenia was the most frequent reason for prescribing a reduced dose, followed by severe renal dysfunction and previous history of gastrointestinal bleeding. The remaining patients were treated with reduced dose due to severe portal hypertensive gastropathy, gastric antral vascular ectasia, history of bleedings, or tense ascites requiring frequent paracentesis. The time from diagnosis of thrombosis and start of anticoagulation was longer in patients treated with LMWH, however, the percentage receiving anticoagulation within 6 months from diagnosis was comparable between groups. Among 75 patients who had thrombophilic screening, 10 had heterozygous mutation of either prothrombin gene G20210A or Leiden Factor, with no difference between groups (Supplementary Table 1, available online).

Portal Vein Recanalization

Median duration of the anticoagulant treatment was relatively shorter in the FPX vs the LMWH group (8 [IQR 5-30] vs 12 [IQR 6-18] months; $P = .799$). Full re-permeation of the portal vein was achieved in 56 patients, and the probability of full recanalization was 51%, 57%, and 61% at 12, 24, and 36 months, respectively. Table 2 shows the comparison of baseline characteristics in patients who achieved complete recanalization of the portal vein or not. Platelet count was higher in patients achieving full recanalization.

Complete recanalization was more common in FPX vs LMWH groups (59% vs 39%; $P = .035$). Probability of portal vein recanalization at 36 months was 77% and 51% ($P = .001$) in the FPX and LMWH groups, respectively (Figure 1). Patients treated with full anticoagulant dose had a significantly higher crude rate of complete recanalization than those treated with reduced dose (60% [27/45 patients] vs 37% [29/79 patients]; $P = .012$). The probability of full recanalization was 86% and 49% ($P = .048$) at full dose and reduced dose, respectively. Patients anticoagulated ≥6 months after diagnosis of portal vein thrombosis had lower recanalization rate than those treated within 6 months (23 vs 51%; $P = .011$). At multivariate Cox regression analysis, treatment with FPX (HR 2.38; 95% CI, 1.39-4.09; $P = .002$) and use of full anticoagulant dose (HR 1.78; 95% CI, 1.04-3.02; $P = .035$) were independent predictors of portal vein complete recanalization (Supplementary Table 2, available online). As shown in Figure 2, when comparing patients treated with reduced dose of anticoagulant, FPX

Table 1 Demographic, Clinical, and Laboratory Characteristics of Patients Treated with Fondaparinux or Low-Molecular-Weight Heparin

Variable	Fondaparinux (n = 41)	LMWH (n = 83)	*P* Value
Age (years), mean (SD)	60 (12)	59 (11)	.933
Sex (male), n (%)	27 (66)	59 (71)	.699
Etiology of cirrhosis, n (%)			.870
Alcohol	14 (34)	31 (37)	
HCV	13 (32)	31 (37)	
HBV	6 (15)	8 (10)	
NASH	3 (7)	4 (5)	
Other	5 (12)	9 (11)	
Esophageal varices — F1/F2/F3, n (%)	25/7/1 (61/17/5)	49/12/1 (59/14/1)	.885
Prophylactic endoscopic variceal band ligation, n (%)	6 (15)	9 (11)	.740
MELD-Na score, mean (SD)	13 (4)	11 (3)	.014
Child Pugh score, mean (SD)	8 (2)	7 (2)	.200
Child class A/B/C (%)	34/55/11	48/44/8	.4
INR — median (IQR)	1.3 (1.2-1.4)	1.2 (1.4-1.4)	.791
Bilirubin (μmol/L), median (IQR)	28 (19-40)	21 (16-33)	.021
Albumin (g/L), median (IQR)	36 (7)	34 (8)	.329
Serum creatinine (μmol/dL), median (IQR)	75 (63-96)	75 (65-96)	.696
Sodium (mmol/L), mean (SD)	139 (4)	138 (3)	.349
Platelet ($\times 10^9$/L), median (IQR)	57 (42-77)	56 (40-84)	.162
Platelet <50 $\times 10^9$/L, %	19	37	.85
Estimated glomerular filtration rate <50 mL/min, %	4	1	.02
Yerdel classification, n (%)			.284
Grade I	14 (34)	37 (45)	
Grade II	16 (39)	19 (23)	
Grade III	8 (20)	22 (27)	
Grade IV	3 (7)	5 (6)	
Complete thrombosis, n (%)	15 (37)	23 (28)	.423
Full dose anticoagulant treatment, n (%)	12 (29)	33 (40)	.345
Time from diagnosis to treatment (days), median (IQR)	30 (9-90)	60 (30-150)	.010
Time from diagnosis to treatment ≥6 months, n (%)	6 (15)	20 (24)	.325

HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; IQR = interquartile range; MELD-Na = Model of End-stage Liver Disease sodium; NASH = nonalcoholic steatohepatitis.

was more effective than LMWH (66% vs 40%; $P = .004$; panel B), while no difference was found in patients treated with full dose (100% vs 61%, $P = .141$; panel A).

No difference was found in permeation rate in partial and complete portal vein thrombosis between the 2 drugs, however, FPX showed a trend toward higher effectiveness also in patients with complete thrombosis (Supplementary Figure, available online).

Recurrence Rate

Among 56 patients who achieved complete recanalization, 18 had anticoagulation suspended, and 4 of these (22%) had thrombosis recurrence. When including also those with partial response, 28/79 discontinued anticoagulant therapy, and 9 of these (32%) had recurrence/progression of thrombosis. No difference was found between LMWH and FPX in terms of recurrence rate.

Survival

During follow-up, 30 patients died, 12 underwent liver transplant (4 were on FPX and 8 on LMWH), and 22 were lost to follow-up. Probability of survival was 91%, 84%, and 65% at 12, 24, and 48 months, respectively, and, despite higher MELD-Na in the FPX group, it did not differ between patients receiving FPX and LMWH (56% vs 71%; $P = .095$). Probability of survival did not differ between patients who achieved complete recanalization and those who did not (75% vs 58%; $P = .217$). At multivariate analysis, age (HR 1.02; 95% CI, 1.01-1.10; $P = .021$) and MELD-Na (HR 1.10; 95% CI, 1.03-1.18; $P = .007$) were independent predictors of survival at 48 months.

Bleeding and Other Complications

Overall, 22 bleeding episodes (18%) were observed in 22 patients (Table 3). Bleeding rate was higher in patients treated with FPX than LMWH (27% vs 13%), although it was not statistically significant ($P = .06$). Life-threatening bleedings occurred in 1 patient on FPX (post-paracentesis hemoperitoneum resulting in patient's death) and in 5 patients on LMWH (3 with variceal bleeding and 2 with intracranial hemorrhage). Variceal bleeding occurred despite previous endoscopic (n = 2) and pharmacological prophylaxis (n = 1). No specific risk factor for bleeding, other than anticoagulant treatment, was found in patients who had intracranial bleeding (both aged <65 years, with normal renal function, no previous history of intracranial bleeding). Rates of bleedings depending on administered dose (data not shown) and discontinuation of drug due to bleeding episodes did not differ between the 2 groups. Among LMWH-treated patients, 3 (3.6%) developed heparin-induced thrombocytopenia and anticoagulant treatment was discontinued.

Table 2 Characteristics of Patients Who Achieved or Not a Full Re-Permeation Within 36 Months

Variable	No Complete Re-Permeation (n = 68)	Complete Re-Permeation (n = 56)	*P* Value
Age (years), mean (SD)	60 (10)	59 (11)	.745
Sex (male), n (%)	45 (66)	41 (73)	.398
Etiology of cirrhosis, n (%)			.741
Alcohol	23 (34)	22 (39)	
HCV	23 (34)	21 (38)	
HBV	8 (12)	6 (11)	
NASH	4 (6)	3 (5)	
Other	10 (15)	4 (7)	
Esophageal varices, n (%)	53 (79)	42 (78)	.860
MELD-Na score, mean (SD)	13 (4)	11 (3)	.151
Child Pugh score, mean (SD)	7 (2)	7 (2)	.126
INR, median (IQR)	1.3 (1.2-1.4)	1.2 (1.2-1.4)	.486
Bilirubin (μmol/L), median (IQR)	26 (18-41)	24 (16-30)	.120
Albumin (g/L), median (IQR)	36 (6)	35 (5)	.314
sCr (μmol/dL), median (IQR)	75 (65-99)	75 (64-94)	.790
Sodium (mmol/L), mean (SD)	139 (3)	138 (3)	.110
Platelet ($\times 10^9$/L), median (IQR)	54 (42-76)	73 (51-87)	.018
Yerdel classification, n (%)			.545
Grade I	24 (35)	27 (48)	
Grade II	21 (31)	14 (25)	
Grade III	18 (27)	12 (21)	
Grade IV	5 (7)	3 (5)	
Complete thrombosis, n (%)	22 (32)	16 (29)	.649
Anticoagulant treatment (fondaparinux), n (%)	17 (25)	24 (43)	.035
Full dose anticoagulant treatment, n (%)	18 (27)	27 (48)	.012
Time from diagnosis to treatment (days), median (IQR)	75 (30-180)	45 (16-90)	.074
Time from diagnosis to treatment ≥6 months, n (%)	20 (29)	6 (11)	.011

HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; IQR = interquartile range; MELD-Na = Model for End-stage Liver Disease sodium; NASH = nonalcoholic steatohepatitis; sCr = serum creatinine.

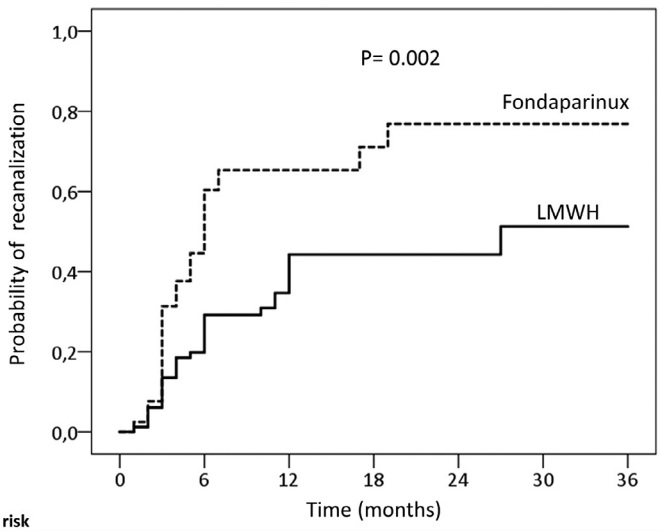

Figure 1 Probability of portal vein recanalization in patients treated with fondaparinux or low-molecular-weight heparin (LMWH).

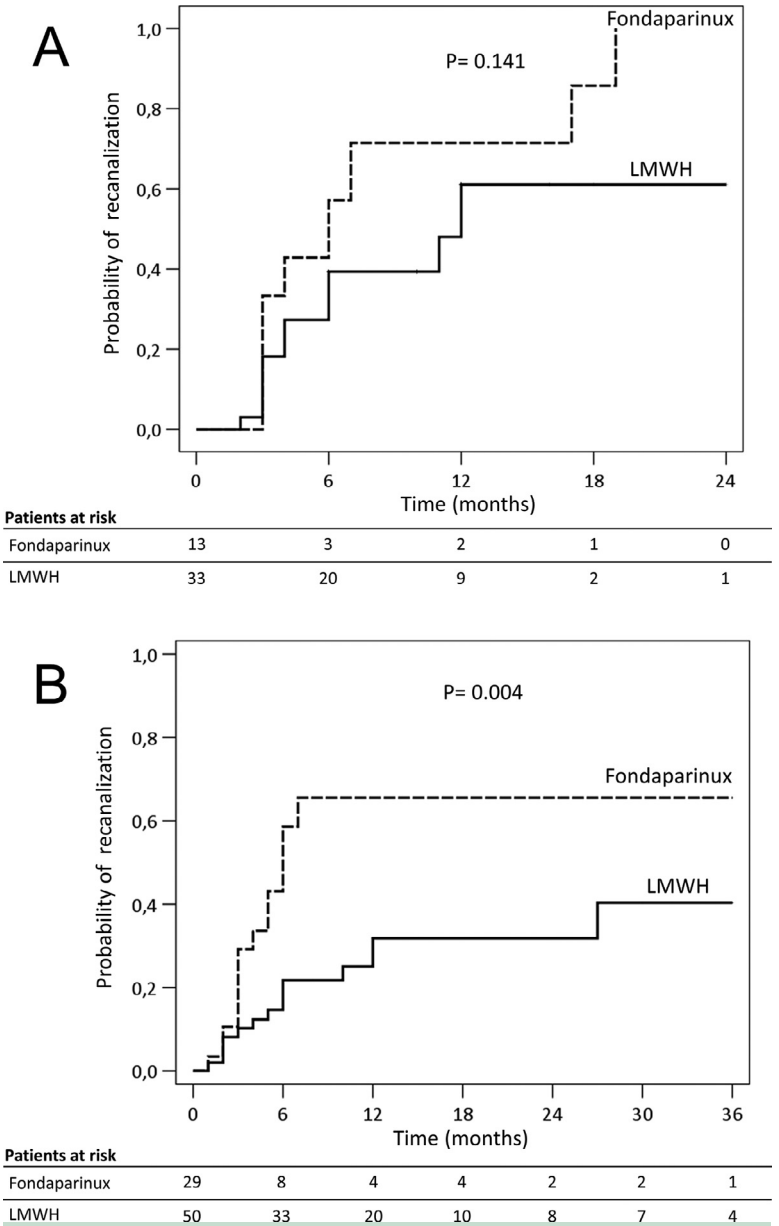

Figure 2 Probability of portal vein recanalization in patients treated with fondaparinux or low-molecular-weight heparin (LMWH) in patients treated at full dose (panel A) or at reduced dose (panel B).

DISCUSSION

Portal vein thrombosis is a common indication for anticoagulation in cirrhosis. No optimal anticoagulation regimen has yet been determined and no clear recommendations exist in recent guidelines and consensus publications.[14,26]

FPX exhibits complete bioavailability by the subcutaneous route and is rapidly absorbed, requiring only a single daily dose. It also has a reproducible linear pharmacokinetic profile, with minimal intra- and intersubject variability, and no need for individual dose adjustment or laboratory monitoring. Furthermore, cases of heparin-induced thrombocytopenia have not been previously reported. In addition, unlike heparins, FPX is synthesized chemically, leading to batch-to-batch consistency and absence of potential contaminations.[20]

This is the first study that specifically compares efficacy and safety of LMWH vs FPX in a large cohort of patients with cirrhosis treated for portal vein thrombosis.

In line with previous cohorts,[2,9,15,22,27,28] most patients had partial thrombosis, and overall probability of full recanalization was 51%, 57%, and 61% at 12, 24, and 36 months, respectively. Also, patients treated ≤6 months after the diagnosis had a higher rate of recanalization, confirming the importance of early start.[22]

Table 3 Bleeding Episodes During Anticoagulation Treatment

Variable	Fondaparinux (n = 41)	LMWH (n = 83)	*P* Value
Overall bleeding episodes, n (%)	11 (27)	11 (13)	.06
Grade of bleeding, n			.455
Grade 1*	7	6	
Grade 2†	3	5	
Grade 3‡	1	0	
Life-threatening bleeding, n (%)	1 (3)	5 (8)	.282
Discontinuation of treatment due to bleeding, n (%)	8 (21)	11 (17)	.823

FPX = fondaparinux; GI = gastrointestinal; LMWH = low-molecular-weight heparin.

*1 variceal hemorrhage, 1 post-paracentesis hemoperitoneum, 2 upper GI bleeding (non-PH-related), and 3 lower GI bleeding (non-PH-related) in patients treated with FPX, and 2 variceal hemorrhage, 2 intracranial bleeding, 1 lower GI (non-PH-related), and 1 upper GI (non-PH-related) in patients treated with LMWH.

†2 episodes of lower GI bleeding (non-PH-related) and 1 episode of epistaxis in patients treated with FPX, and 2 episodes of lower GI bleeding (non-PH-related), 1 episode of upper GI bleeding (non-PH-related), 1 epistaxis, and 1 bleeding gums in patients treated with LMWH.

‡1 leg hematoma in patients treated with FPX.

Potze et al[29] recently observed a modestly increased in vitro response to LMWH and a reduced response to FPX of plasma from cirrhotic patients with respect to healthy controls, however, pharmacokinetics may be altered in decompensated patients. In patients with non-splanchnic venous thrombosis, FPX showed similar efficacy to LWMH and unfractionated heparin.[18,19] Nevertheless, only one case-series study investigated the efficacy of FPX in acute portal vein thrombosis in 7 patients with decompensated cirrhosis.[30] In this study, treatment with FPX was an independent predictor of portal vein full recanalization, and showed a trend toward higher effectiveness in cases of complete thrombosis.[22] The higher efficacy of FPX could be due to its longer half-life and stronger inhibition of Factor Xa, demonstrated in noncirrhotic patients. In addition, at therapeutic concentration, 94% of FPX molecules bind to their target protein with no aspecific binding to plasmatic proteins, indicating low potential for drug−drug interactions.[20] These results should encourage further studies to confirm the efficacy of FPX for both treatment and prophylaxis of portal vein thrombosis in cirrhotic patients awaiting liver transplantation.[31]

As expected, patients treated with the full dose showed a higher rate of complete recanalization, however, in clinical practice, most decompensated patients require dose adjustments, as in this cohort. Despite the fact that plasmatic hypercoagulability has been shown to be higher in decompensated patients,[32,33] the pharmacokinetics of anticoagulant drugs in patients with ascites and compromised renal function are still not fully defined, therefore, anticoagulant dose adjustments are mainly guided by other special population studies.[34]

Buller et al[19] demonstrated that, in patients with deep vein thrombosis, those with mild renal insufficiency treated with either LMWH or FPX had the same risk of bleeding, whereas in the case of a creatinine clearance <30 mL/min, major bleeding occurred in 8% of patients treated with FPX vs 5.6% of patients treated with LMWH. Because of the high risk of bleeding, FPX is contraindicated in patients with creatinine clearance <30 mL/min. For patients with moderate renal function impairment we chose to administer both drugs at reduced dosages and, interestingly, in these cases, FXP was more efficient in re-permeation of the portal vein than LMWH (66% vs 40%; $P = .004$). The reason for these findings could lie in the fact that this pentasaccharide selectively binds to antithrombin, causing rapid inhibition of Factor-Xa.[35] Therefore, FPX effectively reduces thrombin generation without directly affecting thrombin function, and this could imply that it may maintain its effectiveness even at lower doses. Indeed, a less variable anticoagulant effect was observed in patients treated with 2.5 mg of FPX than in those treated at a full dose of enoxaparin.[35]

On the other hand, we found a relatively increased bleeding tendency in patients treated with FPX compared with those treated with LMWH, reaching statistical significance when portal-hypertensive bleedings were excluded. Although the retrospective design and relatively small number of subjects who experienced clinically significant bleeding do not allow any definitive conclusion to be drawn, our findings would suggest caution in the use of FPX in this setting. Conflicting data exist about the risk of bleeding in patients with non-splanchnic thrombosis treated with FPX,[36,37] and this, together with our findings, indicates the need for large prospective studies to evaluate the actual safety of this drug in cirrhotic patients.

Probability of survival was not significantly different between patients who achieved complete recanalization vs those who did not. However, this study was not empowered to determine the clinical impact of portal vein re-permeation, and its retrospective nature did not allow treatment randomization, leading to potential selection bias. Although the 2 groups were homogeneous and results were consistent after adjusting for multiple confounders, the role of other potential factors cannot be excluded. Finally, this is a single-center study requiring external validation. Still, it is the largest monocentric cohort of cirrhotic patients with portal vein thrombosis treated with anticoagulant drugs in the current literature.

In conclusion, both LMWH and FPX are effective and can be considered for the treatment of portal vein thrombosis in cirrhotic patients. Remarkably, FPX also remained effective when prescribed at reduced dose, independent of the presence of complete thrombosis. On the other hand, the relatively higher bleeding rates observed in FPX-treated patients suggest caution in the use of this drug in patients with cirrhosis. In clinical practice, the choice of FPX vs LMWH should take into consideration the pros and cons of each anticoagulant and individual patient characteristics.

Further prospective studies are required on the use of FPX for the treatment of splanchnic vein thrombosis in patients with cirrhosis.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2021.05.013.

SUPPLEMENTARY MATERIAL

PubMed

#1 (Agaricales[mh] OR agaricales[tw] OR agaricus[tw] OR agarics[tw] OR agaricaceae[tw] OR bispora[tw] OR bisporus[tw] OR mushroom[tw] OR mushrooms[tw]) NOT ("mushroom shaped"[tw] OR "mushroom shape"[tw] OR "mushroom like" OR "mushroom cloud" OR occluder*[tw] OR "mushroom poisoning"[mh] OR "mushroom poisoning"[tw])

#2 "Cardiovascular Diseases"[mh] OR arrhythmia*[tw] OR "Atrial Fibrillation"[tw] OR "Atrial Flutter"[tw] OR "Bradycardia"[tw] OR "Tachycardia"[tw] OR "Ventricular Fibrillation"[tw] OR "heart failure"[tw] OR "cardiac failure"[tw] OR "myocardial failure"[tw] OR "cardiac insufficiency"[tw] OR cardiomyopath*[tw] OR myocarditis[tw] OR stroke*[tw] OR "cardiac arrest"[tw] OR "Cardiopulmonary Arrest"[tw] OR asystole*[tw] OR "sudden cardiac death"[tw] OR "cardiovascular disease"[tw] OR "Cardiovascular Diseases"[tw] OR "Heart Diseases"[tw] OR "Heart Disease"[tw] OR "coronary heart disease"[tw] OR "coronary heart diseases"[tw] OR "coronary disease"[tw] OR "coronary diseases"[tw] OR "coronary artery disease"[tw] OR "ischemic heart disease"[tw] OR "ischaemic heart disease"[tw] OR "Myocardial Ischemia"[tw] OR "Myocardial Ischemias"[tw] OR "Myocardial Ischaemia"[tw] OR "Myocardial Ischaemias"[tw] OR "acute coronary syndrome"[tw] OR "myocardial infarction"[tw] OR "myocardial infarct"[tw] OR "heart attack"[tw] OR "heart attacks"[tw] OR "cardiovascular events"[tw] OR "cardiovascular event"[tw]

#1 AND #2

Ovid MEDLINE

#S1 exp Cardiovascular Diseases/

#S2 (arrhythmia* or "Atrial Fibrillation" or "Atrial Flutter" or "Bradycardia" or "Tachycardia" or "Ventricular Fibrillation" or "heart failure" or "cardiac failure" or "myocardial failure" or "cardiac insufficiency" or cardiomyopath* or myocarditis or stroke* or "cardiac arrest" or "Cardiopulmonary Arrest" or asystole* or "sudden cardiac death" or "cardiovascular disease" or "Cardiovascular Diseases" or "Heart Diseases" or "Heart Disease" or "coronary heart disease" or "coronary heart diseases" or "coronary disease" or "coronary diseases" or "coronary artery disease" or "ischemic heart disease" or "ischaemic heart disease" or "Myocardial Ischemia" or "Myocardial Ischemias" or "Myocardial Ischaemia" or "Myocardial Ischaemias" or "acute coronary syndrome" or "myocardial infarction" or "myocardial infarct" or "heart attack" or "heart attacks" or "cardiovascular events" or "cardiovascular event").mp.

#S3 S1 or S2

#S4 exp Agaricales/

#S5 ((agaricales or agaricus or agarics or agaricaceae or bispora or bisporus or mushroom or mushrooms) not ("mushroom shaped" or "mushroom shape" or "mushroom like" or "mushroom cloud" or occluder* or "mushroom poisoning")).mp.

#S6 S4 or S5

#S7 S3 and S6

Embase

#S1 'cardiovascular disease'/exp

#S2 arrhythmia*:ab,ti,kw OR 'atrial fibrillation':ab,ti,kw OR 'atrial flutter':ab,ti,kw OR 'bradycardia':ab,ti,kw OR 'tachycardia':ab,ti,kw OR 'ventricular fibrillation':ab,ti,kw OR 'heart failure':ab,ti,kw OR 'cardiac failure':ab,ti,kw OR 'myocardial failure':ab,ti,kw OR 'cardiac insufficiency':ab,ti,kw OR cardiomyopath*:ab,ti,kw OR myocarditis:ab,ti,kw OR stroke*:ab,ti,kw OR 'cardiac arrest':ab,ti,kw OR 'heart arrest':ab,ti,kw OR 'cardiopulmonary arrest':ab,ti,kw OR asystole*:ab,ti,kw OR 'sudden cardiac death':ab,ti,kw OR 'cardiovascular disease':ab,ti,kw OR 'cardiovascular diseases':ab,ti,kw OR 'heart diseases':ab,ti,kw OR 'heart disease':ab,ti,kw OR 'coronary disease':ab,ti,kw OR 'coronary diseases':ab,ti,kw OR 'coronary artery disease':ab,ti,kw OR 'myocardial ischemia':ab,ti,kw OR 'myocardial ischemias':ab,ti,kw OR 'myocardial ischaemia':ab,ti,kw OR 'myocardial ischaemias':ab,ti,kw OR 'acute coronary syndrome':ab,ti,kw OR 'myocardial infarction':ab,ti,kw OR 'myocardial infarct':ab,ti,kw OR 'heart attack':ab,ti,kw OR 'heart attacks':ab,ti,kw OR 'heart infarction':ab,ti,kw OR 'heart infarct':ab,ti,kw OR 'cardiovascular events':ab,ti,kw OR 'cardiovascular event':ab,ti,kw

#S3 S1 or S2

#S4 ('edible mushroom'/de OR 'mushroom'/de OR 'agaricus bisporus'/de OR 'agaricus'/exp OR agaricus:ti,ab,kw OR mushroom:ti,ab,kw OR mushrooms:ti,ab,kw OR agaricales:ti,ab,kw OR bispora:ti,ab,kw) NOT ('mushroom shaped':ti,ab,kw OR 'mushroom cloud':ti,ab,kw OR 'mushroom like':ti,ab,kw OR 'amanita phalloides':ti,ab,kw OR 'mushroom poisoning'/de OR 'mushroom poisoning':ti,ab,kw OR occluder*:ti,ab,kw)

#S5 S3 and S4

Cochrane and CENTRAL

#1 MeSH descriptor: [Cardiovascular Diseases] explode all trees

#2 (arrhythmia* OR 'Atrial Fibrillation' OR 'Atrial Flutter' OR 'Bradycardia' OR 'Tachycardia' OR 'Ventricular Fibrillation' OR 'heart failure' OR 'cardiac failure' OR 'myocardial failure' OR 'cardiac insufficiency' OR cardiomyopath* OR myocarditis OR stroke* OR 'cardiac arrest' OR 'heart arrest' OR 'Cardiopulmonary Arrest' OR asystole* OR 'sudden cardiac death' OR 'cardiovascular disease' OR 'Cardiovascular Diseases' OR 'Heart Diseases' OR 'Heart Disease' OR 'coronary disease' OR 'coronary diseases' OR 'coronary artery disease' OR 'Myocardial Ischemia' OR 'Myocardial Ischemias' OR 'Myocardial Ischaemia' OR 'Myocardial Ischaemias' OR 'acute coronary syndrome' OR 'myocardial infarction' OR 'myocardial infarct' OR 'heart attack' OR 'heart attacks'

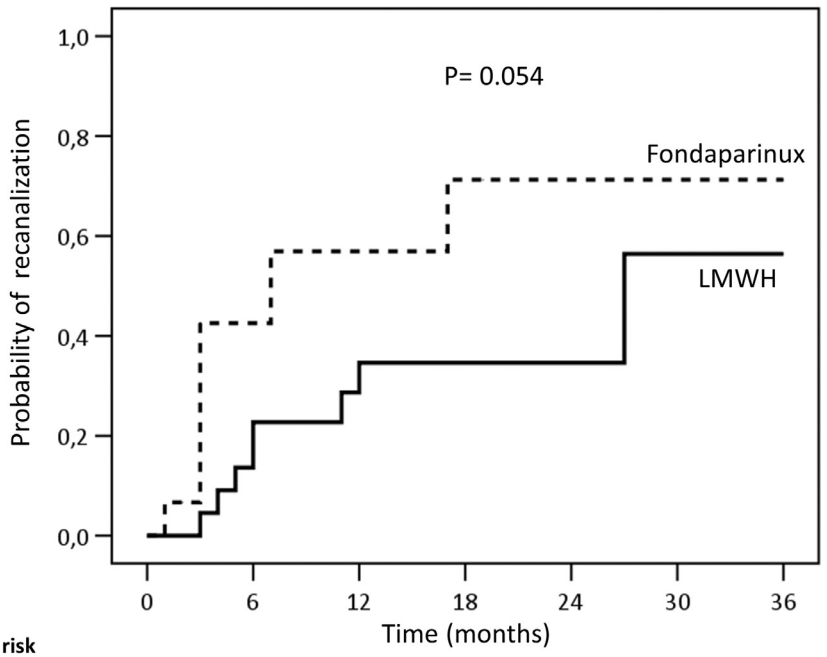
Supplementary Table 1 Thrombophilic Screening Results in Patients Treated with Fondaparinux or Low-Molecular-Weight Heparin (LMWH)

Variable	Fondaparinux (n = 22)	LMWH (n = 53)	*P* Value
Fibrinogen (mg/dL), mean (SD)	238 (94)	258 (125)	.538
Factor VIII activity (%), mean (SD)	167 (45)	167 (58)	.969
Factor IX activity (%), mean (SD)	79 (31)	86 (29)	.427
Factor XI activity (%), mean (SD)	59 (20)	69 (27)	.148
Antithrombin activity (%), mean (SD)	63 (13)	67 (19)	.400
Protein S activity (%), mean (SD)	77 (20)	81 (21)	.448
Protein C activity (%), mean (SD)	50 (16)	53 (18)	.424
Plasminogen activity (%), mean (SD)	67 (17)	79 (19)	.054
Heterozygous Factor V Leiden mutation, n (%)	1 (5)	4 (8)	1.000
Heterozygous prothrombin G20210A mutation, n (%)	1 (5)	4 (8)	1.000

Supplementary Table 2 Independent Predictors of Portal Vein Thrombosis Full Re-Permeation (Introduce)

Variable	Hazard Ratio	95% CI	*P* Value
Age (years)	1.01	0.98-1.03	.629
Sex (female)	0.81	0.44-1.51	.513
Treatment (fondaparinux)	2.18	1.26-3.79	.005
Yerdel classification (CD vs AB)	0.80	0.42-1.50	.479
Complete thrombosis	0.79	0.44-1.43	.433
Full dose anticoagulant treatment	1.80	1.04-3.10	.035
Time from diagnosis to treatment ≥ 6 months	0.45	0.19-1.08	.075
Stepwise backward (in 0.05; out 0.10)			
Treatment (fondaparinux)	2.17	1.26-3.73	.005
Full dose anticoagulant treatment	1.70	0.99-2.90	.053
Time from diagnosis to treatment ≥6 months	0.47	0.20-1.10	.081
Stepwise backward (in 0.05; out 0.05)			
Treatment (fondaparinux)	2.38	1.39-4.09	.002
Full dose anticoagulant treatment, n (%)	1.78	1.04-3.02	.035

CI = confidence interval.



Patients at risk							
Fondaparinux	15	5	3	2	1	1	1
LMWH	23	17	11	6	4	2	1

Supplementary Figure Probability of portal vein recanalization in patients with complete portal vein thrombosis treated with fondaparinux or low-molecular-weight heparin (LMWH).

OR 'heart infarction' OR 'heart infarct' OR 'cardiovascular events' OR 'cardiovascular event'):ti,ab,kw

#3 #1 OR #2

#4 MeSH descriptor: [Agaricales] explode all trees

#5 agaricus:ti,ab,kw OR mushroom:ti,ab,kw OR mushrooms:ti,ab,kw OR agaricales:ti,ab,kw OR bispora:ti,ab,kw

#6 #4 OR #5

#7 #3 AND #6