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The Efficacy and Safety of Anticoagulants in the Treatment of Cirrhotic Portal Vein Thrombosis: A Systematic Review and Meta-Analysis

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Abstract

Objective: To evaluate the efficacy and safety of anticoagulant therapy in patients with cirrhotic PVT, and compare differences in efficacy and safety among different anticoagulants.

Methods: We comprehensively searched Pubmed, Cochrane Library, EMBASE, and ClinicalTrials.gov from inception to April 2022 for studies using anticoagulants for cirrhotic PVT. Meta-analysis was performed to calculate odds ratios (ORs) with 95% confidence intervals (CIs).

Results: 3 RCTs and 14 cohort studies involving 1270 patients were included. Anticoagulant therapy can increase the recanalization rate compared with non-anticoagulation therapy (OR 4.44, 95% CI 3.11-6.32, $I^2 = 2.5\%$) and can decrease the extension rate of cirrhotic PVT (OR 0.33, 95% CI 0.18-0.62, $I^2 = 41.0\%$), without increasing the incidence of total bleeding (OR 1.21, 95% CI 0.75-1.97, $I^2 = 9.8\%$), major bleeding (OR 0.98, 95% CI 0.49-1.95, $I^2 = 19.7\%$), and variceal bleeding (OR 0.35, 95% CI 0.12-1.01, $I^2 = 39.9\%$). Subgroup analysis showed that VKA, LMWH, and DOACs could increase the recanalization rate of PVT and were not associated with the risk of bleeding. Studies that compared direct oral anticoagulants (DOACs) with warfarin directly showed that the recanalization rate of PVT in the DOACs group might be higher than that in the warfarin group (OR 30.99, 95% CI 7.39-129.87, $I^2 = 0.0\%$), and there was no difference in the rate of total bleeding (OR 0.30, 95% CI 0.01-8.65, $I^2 = 79.6\%$).

Conclusions: Anticoagulants are safe and effective in patients with cirrhotic PVT. The rate of PVT recanalization associated with DOACs may be higher than warfarin.

Keywords

liver cirrhosis, portal vein thrombosis, PVT, anticoagulants, meta-analysis

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Portal vein thrombosis (PVT) is a common complication of liver cirrhosis, and the incidence is about 5%~20%.[1,2] The pathogenesis of cirrhotic PVT is related to decreased portal blood flow and hypercoagulability. The existence of PVT increases mortality and graft failure after liver transplantation and is life-threatening when extended to the mesenteric vein.[3] Recent studies have shown that recanalization of PVT is associated with better survival.[4] Therefore, it is necessary to treat PVT for patients with liver cirrhosis.

Concerns about anticoagulant therapy of PVT are portal hypertension and esophageal varices are common complications in patients with liver cirrhosis, which can lead to variceal bleeding,[5] and anticoagulant therapy may have the risk of increasing the incidence of bleeding. Besides, since patients with liver cirrhosis are in a state of "rebalance", the spontaneous

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recanalization of PVT was observed and the pooled rate was 39.8%.[6] Thus, it is still controversial whether to conduct anticoagulant therapy for patients with cirrhotic PVT because of the unclear bleeding risk and prognosis of anticoagulant therapy.[7] As the safety and efficacy of anticoagulants for cirrhotic PVT are still insufficient, the American College of Gastroenterology (ACG) clinical guideline[8] did not recommend anticoagulant therapy for all cirrhotic PVT patients and suggested weighting the risk of bleeding against benefits. In addition, the guidelines only suggested heparin or low molecular weight heparin (LMWH) for PVT to initiate anticoagulation and did not mention other anticoagulants. The optimal anticoagulant regimen is still uncertain. In this study, we conducted a systematic review and meta-analysis to compare the efficacy and safety of anticoagulants and the differences among different anticoagulants.

Methods

This systematic review and meta-analysis were reported by the PRISMA statement.[9] The protocol was registered in the PROSPERO (Number CRD42021251163).

Literature Search

We performed an extensive search for all available studies in English indexed in PubMed, Cochrane Library, and EMBASE from inception to April 2022. We used MeSH terms and free texts on cirrhotic PVT and anticoagulants to collect RCTs and observational studies that evaluated the efficacy and/or safety of anticoagulants for patients with cirrhotic PVT. The search strategies was shown in Appendix 1. In addition, we performed a manual search for relevant studies through ClinicalTrial.gov and the reference lists of all included studies.

Study Selection

Two authors (Zhang Z, Zhao Y) independently reviewed the titles and abstracts according to the following inclusion criteria: (1) studies using anticoagulants including LMWHs, vitamin K antagonists (VKA), direct oral anticoagulants (DOACs), for patients with cirrhotic PVT; and (2) patient's age $\geq$ 18. Then three authors (Zhang Z, Zhao Y, Han B) screened the full texts for the final inclusion. We resolved discrepancies through discussion or consultation with another reviewer (Dr Cui X). The exclusion criteria included: (1) studies using anticoagulants for preventing PVT; (2) non-drug anticoagulation of cirrhotic PVT such as transjugular intrahepatic portosystemic shunt (TIPs); (3) malignant PVT; (4) splanchnic vein thrombosis without portal vein involvement; and (5) studies with duplicate data, abstracts only or non-English studies.

Data Extraction

Three authors (Zhang Z, Zhao Y, Han B) extracted data into predesigned tables. The following information was collected: (1) Characteristics of the studies, including the name of the first author, year of the publication, type of study; (2) baseline characteristics of included patients. Such as age, gender, INR, creatinine, platelet count, and hemoglobin; (3) Anticoagulants used in the studies, including dosage, duration of treatment and follow-up; and (4) Outcomes of the anticoagulants, including the recanalization and extension of PVT, and bleeding events. The recanalization of PVT included partial and complete recanalization of the thrombus in the main portal vein and its branches. The partial recanalization was defined as at least a 30% reduction in the long diameter and/or 50% reduction in the cross-sectional area of the main thrombus, without evidence of thrombus extension. Bleeding events included variceal bleeding and major bleeding. The major bleeding events were determined according to the International Society on Thrombosis and Haemostasis criteria or as reported.

Risk of Bias Assessment

We used Cochrane risk-of-bias tool to assess the risk of bias in RCTs. The Newcastle-Ottava Scale (NOS)[10] was used for the risk of bias in observational studies, and the quality was high when studies got more than 7 stars.

Statistical Analysis

We performed a meta-analysis to compare PVT recanalization and bleeding events between the anticoagulant group and the non-anticoagulant group, and among the different anticoagulant groups. We pooled and compared the data by random-effect model and used the inverse-variance method to calculate the odds ratios (OR) with 95% confidence intervals (CIs). The I^2 statistic was used to assess the heterogeneity, with substantial heterogeneity defined when I^2 is greater than 50%.[11]

We performed subgroup analysis and meta-regression to evaluate the safety and efficacy of different anticoagulants and explore the source of heterogeneity. We performed sensitivity analysis on the results, and funnel plot to assess the presence of publication bias. The publication bias was solved by the "trim and fill" test. A P-value of <0.05 suggests a statistical significance. All analyses were performed with the software Stata (version 15.1, USA).

Results

We retrieved 579 studies by our search strategies. Among these, 149 were removed because of the duplication, and then 430 studies were identified. After abstracts and full texts screening, 17 studies involving 1270 patients were included, which included 3 RCTs and 14 cohort studies (Appendix 2). These studies were published from 2005 to 2022 with sample sizes ranging from 11 to 214. Baseline characteristics of included patients was shown in Table 1. Most patients were male, average age ranged from 41.3 to 69. The quality of the included study is shown in Appendix 3, 4.

Table 1. Baseline Characteristics of the Studies included in this Meta-Analysis.

Study	Type	Anticoagulants	n	Age	Gender (M/F)	Child-Pugh Class A/B/C (n)	PT (INR)	Creatinine (mmol/L)*	Platelet count (10^9/L)*	Hemoglobin (g/dL)	Follow-up time (months)*	Anticoagulation duration (months)*
Francoz 2005[12]	Retrospective cohort study	Nadroparin, 5700 U/d, 5 days + ??acenocmarol INR goal 2-3	19	48.7 ± 7.5	13/6	2/13/4	NR	75.8 ± 19.9	74.4 ± 40.5	NR	NR	8.1
		Control	10	52 ± 5.7	7/3	2/6/2	NR	81.6 ± 22.8	79.3 ± 33	NR	NR	NA
Senzolo 2012[13]	Prospective cohort study	Nadroparin (95 U/Kg/d)	33	55.5 ± 5	25/10	11/16/8	NR	75.4 ± 26.2	78.3 ± 36.5	NR	21.6 ± 8.5	6
		Control	21	52.3 ± 4	13/8	5/9/7	NR	82 ± 30.3	78.3 ± 36.5	NR	24.5 ± 8.2	NA
Cai 2013[14]	Retrospective cohort study	Nadroparin 85 U/kg, q12 h, 3days + warfarin INR goal 1.5-2	5	52.8 ± 9.2	5/0	2/4/0	NR	NR	107 ± 20	NR	37.2 ± 21.2	3
		Control	6		5/1	4/1/1	NR	NR	114.7 ± 15.9	NR	38.0 ± 9.3	NA
Chung 2014[15]	Retrospective cohort study	Warfarin 2.7 mg/d (mean)	14	59.4 ± 12.0	10/4	6/8/0	1.38 ± 0.28	NR	NR	NR	3.8 ± 3.1	3.7 ± 2.1
		Control	14	58.7 ± 13.2	11/3	7/6/1	1.43 ± 0.18	NR	NR	NR	3.6 ± 3	NA
Chen 2016[16]	Retrospective cohort study	Warfarin INR goal 2-3	30	44.97 ± 12.3	NR	7.68 ± 1.7	1.49 ± 0.66	73.5 ± 13.9	112.6 ± 32.78	11.5 ± 2.9	33.2 ± 29.2	median 7.6 (range 0.2-52)
		Control	36	47.86 ± 10.6	NR	7.71 ± 1.8	1.26 ± 0.18	75.8 ± 18.8	142.8 ± 99.8	11.3 ± 3.3	25.9 ± 23	NA
Pettinari 2018[17]	Retrospective cohort study	56 received LMWH; 15 received fondaparinux; 10 received VKAs	81	57.9 ± 11.1	56/25	43/33/5	1.1 ± 0.3	NR	84.8 ± 57.2	NR	Median 19 (range 3-94)	13.4 ± 14
		Control	101	57.7 ± 11.3	74/27	37/45/19	1.5 ± 0.5	NR	99.3 ± 81.8	NR		NA
Ferreira 2019[18]	Retrospective cohort study	15 received LMWH; 22 received VKA, INR goal 2-3	37	60 ± 10	28/9	12/16/9	1.4 ± 0.3	1.0 ± 0.5 mg/dl	106.9 ± 92.1	10.2 ± 2.0	25.5 (1-146)	1-12
		Control	43	59 ± 8	25/18	9/18/16	1.4 ± 0.2	1.0 ± 0.7 mg/dl	111.0 ± 65.1	11.0 ± 2.4		NA
Ai 2020[19]	Prospective cohort study	26 received rivaroxaban, 20 mg, qd; 14 received dabigatran, 150 mg bid	40	56.1 ± 16.1	26/14	7.2 ± 1.52	0.9 ± 1.1	NR	96.9 ± 24.6	NR	6	6
		Control	40	52.3 ± 19.4	24/16	7.4 ± 1.67	0.9 ± 0.8	NR	102 ± 20.7	NR		NA
Naymagon 2020[20]	Retrospective cohort study	Warfarin, INR goal 2-3; enoxaparin, 1 mg/kg, bid; rivaroxaban, 20 mg/d; apixaban, 5 mg, bid; dabigatran, 150 mg, bid	86	median 60 (IQR 54-67)	52/34	21/42/23	median 1.3 (IQR 1.2-1.4)	median 0.9 (IQR 0.7-1.2) mg/dl	median 90 (IQR 69-134)	NR	median 27 (IQR 12-48)	median 18.8 (IQR 10.8-52.8)

(continued)

Table 1. (continued)

Study	Type	Anticoagulants	n	Age	Gender (M/F)	Child-Pugh Class A/B/C (n)	PT (INR)	Creatinine (mmol/L)*	Platelet count (10^9/L)*	Hemoglobin (g/dL)	Follow-up time (months)*	Anticoagulation duration (months)*
		Control	128	median 60 (IQR 54-66)	90/38	31/57/40	median 1.3 (IQR 1.2-1.4)	median 0.9 (IQR 0.8-1.2) mg/dl	median 82 (IQR 57-130)	NR		NA
Zhou 2020[21]	Single blinded RCT	Nadroparin, 1month + warfarin, INR goal 2-3	32	55 ± 9	21/11	6.51 ± 1.27	1.3 ± 0.2	60.9 ± 16.0	126.2 ± 170.9	NR	6	6
		Control	32	53 ± 10	21/11	6.81 ± 1.44	1.4 ± 0.2	65.8 ± 16.1	134.6 ± 137.5	NR		NA
Bert 2020[22]	Retrospective cohort study	LMWH	7	60.86 ± 6.31	6/1	NR	1.25 (0.77)	1.05 (0.61) mg/dl	114.86 ± 33.29	11.7 (4.2)	NR	NR
		Control	9	60.56 ± 8.31	6/3	NR	1.63 (1.93)	0.89 (1.16) mg/dl	81.22 ± 27.88	12.9 (3.4)	NR	NR
Lv 2021[23]	Prospective cohort study	heparin 8000-12,000 U/d 5 days + warfarin INR goal 2-3; heparin 8000-12,000 U/d 5 days + warfarin + enoxaparin 4000-8000 IU/d or Rivaroxaban 10 mg/d	63	47.2 ± 11.3	36/27	33/27/3	NR	0.89 ± 0.18 mg/dl	221.1 ± 167.1	11.1 ± 2.8	31.7 (IQR 18.1-49.5)	12
		Control	48	53.9 ± 12.2	31/17	13/25/10	NR	0.96 ± 0.26 mg/dl	141.6 ± 117.8	9.9 ± 2.6		NA
Florescu 2021[24]	Retrospective cohort study	Enoxaparin 200 U/kg + Enoxaparin or VKA INR goal 2-2.5	54	53 (range 23-73)	29/25	13/40/1	NR	NR	NR	NR	32 (range 3-109)	NR
		Control	53	55.65 (range 25-75)	25/28	14/37/2	NR	NR	NR	NR		NR
Cui 2015[25]	RCT	Enoxaparin 1 mg/kg, q12h	31	53.1 ± 10.1	19/12	median 7.0 (IQR 6.0-8.0)	median 1.5 (IQR 1.4-1.7)	67.7 ± 15.6	83.3 ± 18.5	NR	NR	6
		Enoxaparin 1.5 mg/kg, qd	34	52.3 ± 10.1	24/10	median 7.0 (IQR 6.0-8.0)	median 1.5 (IQR 1.4-1.7)	71.8 ± 16.1	83.9 ± 19.5	NR		6
Nagaoki 2017[26]	Retrospective cohort study	Danaparoid, 2500 U/d for 2 weeks + 16 received edoxaban, 30 mg, qd; 4 received edoxaban, 60 mg, qd	20	median 69 (range 53-74)	13/7	15/5/0	NR	NR	median 117 (range 46-238)	NR	6	6
		Danaparoid, 2500 U/d for 2 weeks + warfarin, INR goal 1.5-2.0	30	median 67 (range 24-83)	17/13	15/10/5	NR	NR	median 98 (range 31-416)	NR		7

(continued)

Table 1. (continued)

Study	Type	Anticoagulants	n	Age	Gender (M/F)	Child-Pugh Class A/B/C (n)	PT (INR)	Creatinine (mmol/L)*	Platelet count (10^9/L)*	Hemoglobin (g/dL)	Follow-up time (months)*	Anticoagulation duration (months)*
Hanafy 2018[27]	RCT	Enoxaparin, 1 mg/kg q12 h, 3 days + rivaroxaban, 10 mg, q12 h	40	46 ± 5	32/8	6.4 ± 0.4	1.2 ± 0.04	1.1 ± 0.34 mg/dl	46.25 ± 3.7	NR	12	6
		Enoxaparin, 1 mg/kg q12 h, 3 days + warfarin, INR goal 2-2.5	40	41.3 ± 2.3	35/5	6.2 ± 0.3	1.1 ± 0.2	1 ± 0.4 mg/dl	48.0 ± 7.5	NR		6m
Ilcewicza 2021[28]	Retrospective cohort study	5 Rivaroxaban 20 mg daily; 1 Rivaroxaban 15 mg daily; 3 Apixaban 2.5 mg bid; 4 Apixaban 5 mg bid	13	60 ± 18	9/4	median 6 (range 5-11)	1.15 ± 0.6	NR	216 ± 193	NR	1.5	NR
		Warfarin bridged with heparin or LMWH	20	51 ± 12	15/5	median 8 (range 6-9)	1.1 ± 0.2	NR	247 ± 157	NR	1.5	NR

*The units of platelet count are converted into 10^9/L; time units are converted into months, 30 days = 1 month, 12 month = 1 year. Data are mean ± SD.
Abbreviations: M, male; F, female; INR, international normalized ratio; m, months; U, units; IQR, interquartile range; NA, not available; NR, no report.

Efficacy and Safety of Anticoagulant Group Versus non-Anticoagulant Group

13 studies had compared the anticoagulant group with the non-anticoagulant group, 12 of them were observational studies and one was a single-blind RCT study. In terms of efficacy, the meta-analysis showed the recanalization rate of PVT in the anticoagulant group was higher than that in the non-anticoagulant group (OR 4.44, 95% CI 3.11-6.32, $I^2 = 2.5\%$) (Figure 1). Anticoagulants can increase both the rate of complete recanalization (OR 3.49, 95% CI 2.40-5.06, $I^2 = 0.0\%$) and partial recanalization (OR 2.69, 95% CI 1.27-5.57, $I^2 = 26.3\%$). In addition, the anticoagulant group was associated with a lower rate of PVT extension (OR 0.33, 95% CI 0.18-0.62, $I^2 = 41.0\%$). Subgroup analysis showed that VKA, LMWH, and DOACs could increase the recanalization rate of PVT. Meta-regression analysis showed that gender, age, INR, hemoglobin, creatinine, platelet count, follow-up time, and anticoagulation duration were not the sources of heterogeneity in recanalization and extension rate of the anticoagulants (Appendix 5).

In terms of safety, there was no significant difference in the rate of total bleeding (OR 1.21, 95% CI 0.75-1.97, $I^2 = 9.8\%$), major bleeding (OR 0.98, 95% CI 0.49-1.95, $I^2 = 19.7\%$), and variceal bleeding (OR 0.35, 95% CI 0.12-1.01, $I^2 = 39.9\%$) between the anticoagulant group and non-anticoagulant group (Figure 2). And different anticoagulants were not the source of heterogeneity in bleeding rate (Appendix 5).

Efficacy and Safety of DOACs Versus Warfarin

According to the studies that compared DOACs with warfarin directly, the recanalization rate of PVT in the DOACs group might be higher than that in the warfarin group (OR 30.99, 95% CI 7.39-129.87, $I^2 = 0.0\%$). The extension rate of PVT in the DOACs group might be lower than that in the warfarin group (OR 0.08, 95% CI 0.01-0.45, $I^2 = 0.0\%$). There was no difference in the rate of total bleeding (OR 0.30, 95% CI 0.01-8.65, $I^2 = 79.6\%$), major bleeding (OR 0.16, 95% CI 0.02-1.39, $I^2 = 0.0\%$), and variceal bleeding (OR 0.12, 95% CI 0.00-6.06, $I^2 = 77.1\%$) between the DOACs group and warfarin group (Figure 3).

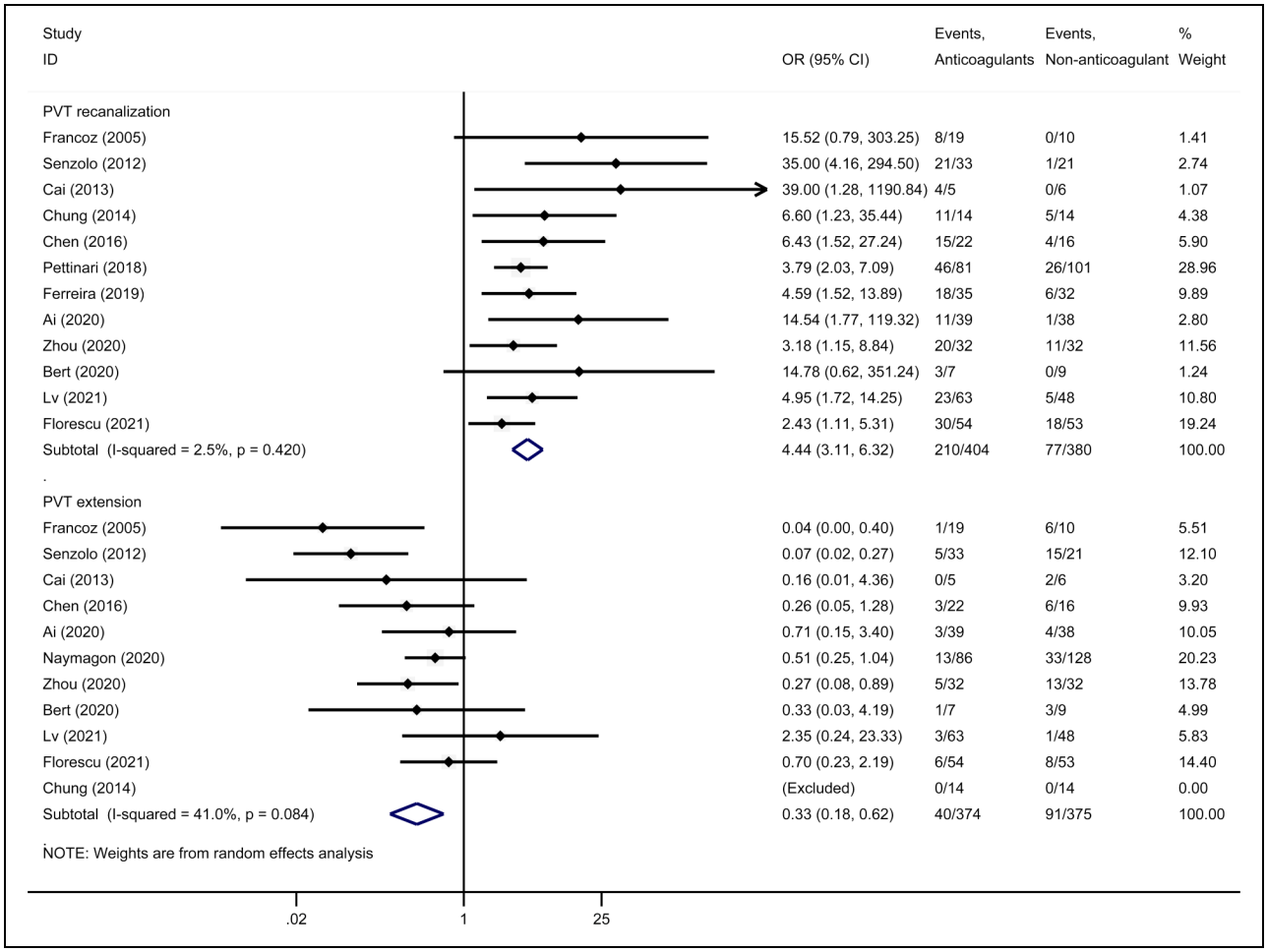

Figure 1. PVT recanalization and extension of anticoagulants versus non-anticoagulant group.

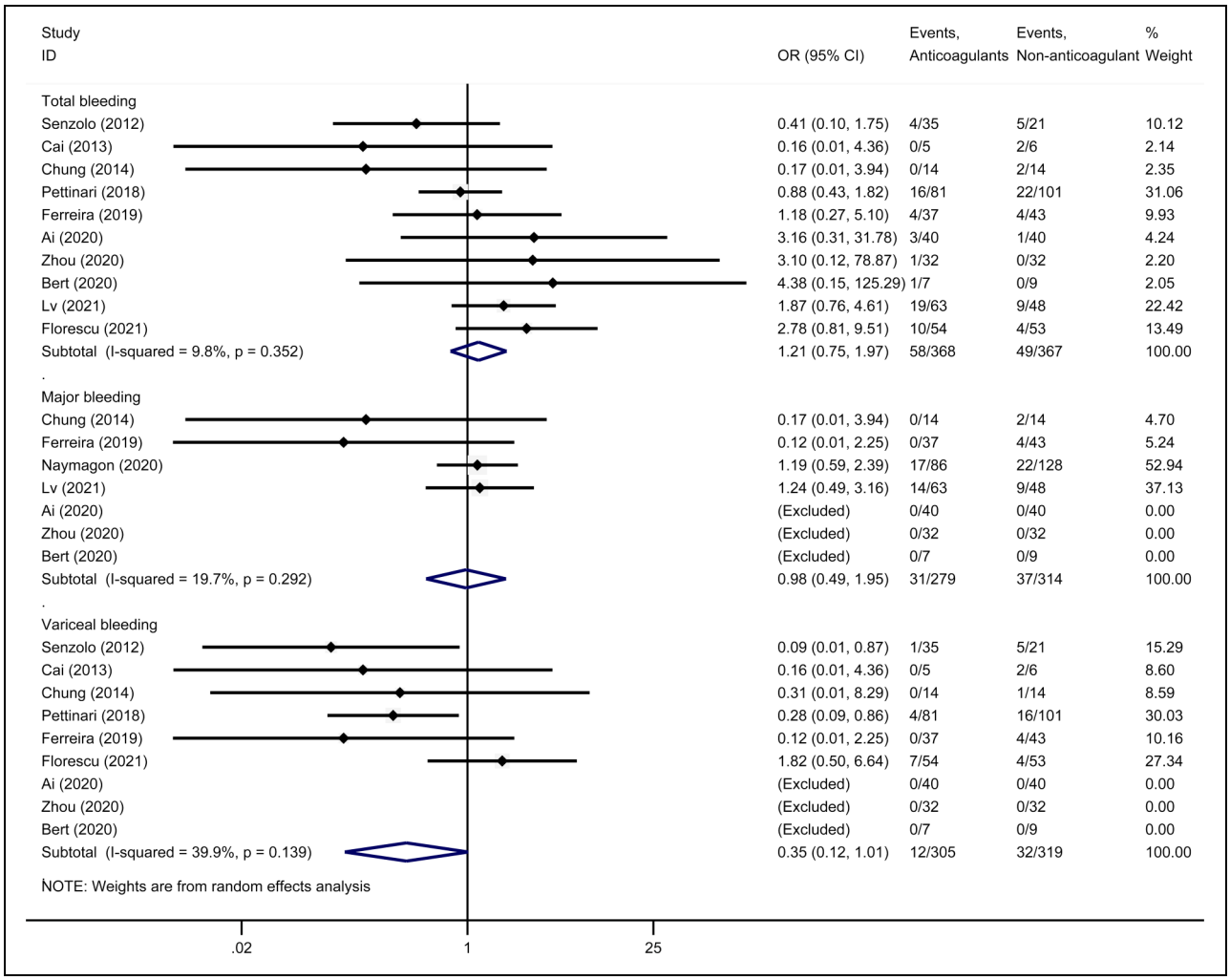

Figure 2. Bleeding events of anticoagulant group versus non-anticoagulant group.

Sensitivity Analysis and Publication Bias

We excluded one study at a time, and when Florescu's study was excluded, the anticoagulant group had a lower rate of variceal bleeding than the non-anticoagulant group (OR 0.21, 95% CI 0.09-0.51, $I^2 = 0.0\%$). None of the studies had a significant impact on other results. The figure of sensitivity analysis can be seen in Appendix 6. There was visible gross asymmetry observed in the funnel blot, suggesting publication bias (Appendix 7. Supplementary Figure 6). We used the "trim and fill" test to adjust the funnel chart without significantly changing the results.

Discussion

In this meta-analysis, we found that anticoagulants were associated with an increased rate of PVT recanalization and a reduced rate of PVT extension. Anticoagulants did not increase the rate of total bleeding, major bleeding, and variceal bleeding. Besides, the meta-analysis of different anticoagulants showed the PVT recanalization rate of DOACs might be higher than VKA.

Consistent with previous meta-analyses,[29,30] we found the efficacy of anticoagulation treatment for cirrhotic PVT can promote the PVT recanalization without increased risk of bleeding. American Gastroenterological Association (AGA)[31] Clinical Practice pointed out that the use of warfarin or heparin-derived medications was associated with increased rates of recanalization. This was confirmed in our study along with the fact that DOACs may have a similar effect.

For a long time, there is insufficient information on the efficacy of DOACs for cirrhosis. Current guidelines[8] do not recommend the use of DOACs to treat PVT in patients with cirrhosis. In this study, we found that DOACs was non-inferior to warfarin in safety and efficacy. Warfarin is the most commonly used oral anticoagulant, but the food-drug interaction and INR monitoring increase the misgiving of doctors prescribing anticoagulants and hinder patient compliance. Besides, the baseline prothrombin time was prolonged and baseline INR was increased in patients with cirrhosis and PVT, which may

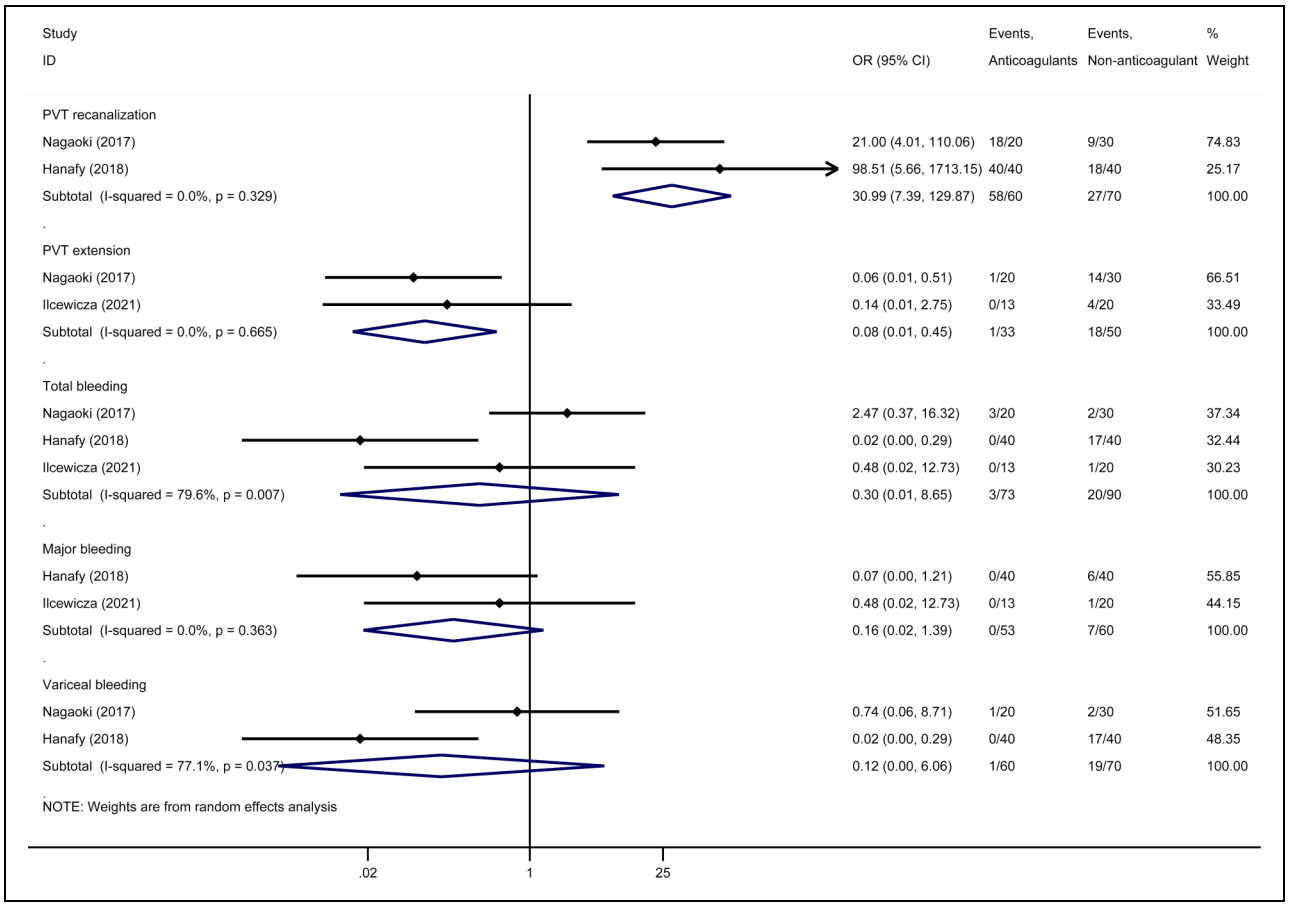

Figure 3. Efficacy and safety of DOACs versus Warfarin.

make warfarin based on the regular prothrombin time-INR underdosed in cirrhosis.[32] But in terms of DOACs, they are not needed to adjust the dosage based on INR. This may be the reason why DOACs have a higher rate of recanalization and a lower rate of PVT extension than warfarin. DOACs have the advantage of not requiring dose adjustment by laboratory testing which brings better compliance and cost-effectiveness. Therefore, DOACs have the potential to become one of the alternatives for anticoagulant therapy for cirrhotic PVT. But more studies comparing different anticoagulants are still needed to confirm our conclusions.

The risk of bleeding was the concern for the clinical application of anticoagulants in the treatment of cirrhotic PVT. Neither our study nor previous meta-analysis found using anticoagulants can increases the risk of bleeding. Our study also found that anticoagulants did not increase the rate of major bleeding. These findings supported using anticoagulants in patients with cirrhotic PVT. During the clinical practice, patients should be closely monitored for signs of bleeding, and reversal agents[33] should be used to terminate the anticoagulant effect in time when major bleeding occurred.

The ACG clinical guideline[8] suggested that anticoagulation is not associated with an increased risk of variceal bleeding in patients with cirrhotic PVT and the presence of gastroesophageal varices is not a contraindication to anticoagulation. A previous meta-analysis concluded that anticoagulants could reduce the incidence of variceal bleeding (0.1% vs 18.5%; RR 0.15, 95%CI 0.04-0.55; $P = 0.004$).[29] Recanalization of PVT has been reported to reduce esophageal variceal pressure,[34] which may lead to the reduction of variceal bleeding. Our study suggested that there was no significant difference in variceal bleeding between the anticoagulant group and non-anticoagulant group after including more studies. However, the results had changed after Florescu's study was excluded in the sensitivity analysis. The weight of Florescu's study accounts for 27.34% of the results, so we should be paid attention to its result. This suggests that more studies on the effect of anticoagulants on the variceal bleeding rate are needed to confirm this conclusion.

Several meta-analyses[29,30,35] have been published recently on anticoagulant therapy for portal PVT in cirrhosis. We included more studies and patients than Ghazaleh's study. Compared with the study conducted by Chen and Koh et al, we had stricter inclusion criteria as the population of our study was strictly defined as patients with cirrhosis and portal vein thrombosis. And we excluded the abstract-only studies because the populations and outcomes of those studies were difficult to define. Besides, we not only compared both the

anticoagulant group versus the non-anticoagulant group and also different anticoagulants.

Our study has several limitations. First of all, most of the studies we included were observational studies, which may decrease the level of evidence. However, RCTs present a higher level of evidence, but the strict inclusion and exclusion criteria make the research populations different from the clinical practice. Secondly, the baseline characteristics of included studies varied greatly. We collected the baseline characteristic that was risk factors of PVT and conducted a meta-regression analysis including gender, age, INR, hemoglobin, creatinine, platelet count, follow-up time, and anticoagulation duration. But no modification effects were found. The heterogeneity of the outcomes of our meta-analysis was acceptable (I^2<50%). Of course, there were also risk factors that were not included in the meta-regression. For example, one study tested[20] the JAK2V617F gene, while others did not. However, only one of the 214 patients was positive, suggesting the low incidence of JAK2V617F, which may have little effect on the overall results. Furtherly, some studies excluded patients with underlying thrombogenic hematologic, pregnancy, or other situations that might affect the outcomes, while others did not mention. Further studies with strict exclusion criteria to eliminate risk factors of PVT were needed for cirrhosis patients.

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Supplemental Material

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References

1. Tsochatzis EA, Senzolo M, Germani G, et al. Systematic review: portal vein thrombosis in cirrhosis. *Aliment Pharmacol Ther*. 2010;31(3):366-374.
2. Chen H, Trilok G, Wang F, et al. A single hospital study on portal vein thrombosis in cirrhotic patients - clinical characteristics & risk factors. *Indian J Med Res*. 2014;139(2):260-266.
3. Basili S, Pastori D, Raparelli V, et al. Anticoagulant therapy in patients with liver cirrhosis and portal vein thrombosis: insights for the clinician. *Therap Adv Gastroenterol*. 2018;11:1-10.
4. Senzolo M, Riva N, Dentali F, et al. Long-term outcome of splanchnic vein thrombosis in cirrhosis. *Clin Transl Gastroenterol*. 2018;9(8):176.
5. Sogaard KK, Astrup LB, Vilstrup H, et al. Portal vein thrombosis; risk factors, clinical presentation and treatment. *BMC Gastroenterol*. 2007;7(1):34.
6. Qi X, Guo X, Yoshida EM, et al. Transient portal vein thrombosis in liver cirrhosis. *BMC Med*. 2018;16(1):83.
7. Mancuso A. Anticoagulation for portal vein thrombosis in cirrhosis. *Am J Gastroenterol*. 2019;114(6):1000-1001.
8. Simonetto DA, Singal AK, Garcia-Tsao G, et al. ACG Clinical guideline: disorders of the hepatic and mesenteric circulation. *Am J Gastroenterol*. 2020;115(1):18-40.
9. Moher D, Liberati A, Tetzlaff J, et al. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62(10):1006-1012.
10. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
11. Haidich AB. Meta-analysis in medical research. *Hippokratia*. 2010;14(suppl 1):29-37.
12. Senzolo M, Sartori T M, Rossetto V, et al. Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. *Liver Int*. 2012;32(6):919-927.
13. Francoz C, Belghiti J, Vilgrain V, et al. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. *Gut*. 2005;54(5):691-697.
14. Cai M, Zhu K, Huang W, et al. Portal vein thrombosis after partial splenic embolization in liver cirrhosis: efficacy of anticoagulation and long-term follow-up. *J Vasc Interv Radiol*. 2013;24(12):1808-1816.
15. Chung JW, Kim GH, Lee JH, et al. Safety, efficacy, and response predictors of anticoagulation for the treatment of nonmalignant portal-vein thrombosis in patients with cirrhosis: a propensity score matching analysis. *Clin Mol Hepatol*. 2014;20(4):384-391.
16. Chen H, Liu L, Qi X, et al. Efficacy and safety of anticoagulation in more advanced portal vein thrombosis in patients with liver cirrhosis. *Eur J Gastroenterol Hepatol*. 2016;28(1):82-89.
17. Pettinari I, Vukotic R, Stefanescu H, et al. Clinical impact and safety of anticoagulants for portal vein thrombosis in cirrhosis. *Am J Gastroenterol*. 2019;114(2):258-266.
18. Ferreira C N, Reis D, Cortez-Pinto H, et al. Anticoagulation in cirrhosis and portal vein thrombosis is safe and improves prognosis in advanced cirrhosis. *Dig Dis Sci*. 2019;64(9):2671-2683.
19. Ai MH, Dong WG, Tan XP, et al. Efficacy and safety study of direct-acting oral anticoagulants for the treatment of chronic portal vein thrombosis in patients with liver cirrhosis. *Eur J Gastroenterol Hepatol*. 2020;32(10):1395-1400.
20. Naymagon L, Tremblay D, Zubizarreta N, et al. Safety, efficacy, and long-term outcomes of anticoagulation in cirrhotic portal vein thrombosis. *Dig Dis Sci*. 2021;66(10):3619-3629.
21. Zhou T, Sun X, Zhou T, et al. Efficacy and safety of nadroparin calcium-warfarin sequential anticoagulation in portal vein thrombosis in cirrhotic patients: a randomized controlled trial. *Clin Transl Gastroenterol*. 2020;11(9):e00228.

22. Bert J, Geerts A, Vanlander A, et al. Up to 50% of portal vein thrombosis remains undiagnosed until liver transplantation. *Clin Transplant*. 2020;34(12):e14107.
23. Lv Y, Bai W, Li K, et al. Anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis: a prospective observational study. *Am J Gastroenterol*. 2021;116(7):1447-11464.
24. Florescu MM, Costache A, Iacob SM, et al. Anticoagulation therapy for portal vein thrombosis in patients with cirrhosis in a tertiary center experience. *J Gastrointestin Liver Dis*. 2021;30-(3):374-379.
25. Cui SB, Shu RH, Yan SP, et al. Efficacy and safety of anticoagulation therapy with different doses of enoxaparin for portal vein thrombosis in cirrhotic patients with hepatitis B. *Eur J Gastroenterol Hepatol*. 2015;27(8):914-919.
26. Nagaoki Y, Aikata H, Daijyo K, et al. Efficacy and safety of edoxaban for treatment of portal vein thrombosis following danaparoid sodium in patients with liver cirrhosis. *Hepatol Res*. 2018;48(1): 51-58.
27. Hanafy AS, Abd-Elsalam S, Dawoud MM. Randomized controlled trial of rivaroxaban versus warfarin in the management of acute non-neoplastic portal vein thrombosis. *Vascul Pharmacol*. 2019;113:86-91.
28. Ilcewicz HN, Martello JL, Piechowski K. Evaluation of the efficacy and safety of direct oral anticoagulants in the treatment of portal vein thrombosis. *Eur J Gastroenterol Hepatol*. 2021;33-(6):911-916.
29. Ghazaleh S, Beran A, Aburayyan K, et al. Efficacy and safety of anticoagulation in non-malignant portal vein thrombosis in patients with liver cirrhosis: a systematic review and meta-analysis. *Ann Gastroenterol.* 2021;34(1):104-110.
30. Chen H, Lei J, Liang S, et al. Safety and efficacy of anticoagulation in patients with cirrhosis: a meta-analysis. *Can J Gastroenterol Hepatol*. 2021;2021:8859602.
31. O'Leary JG, Greenberg CS, Patton HM, et al. AGA Clinical practice update: coagulation in cirrhosis. *Gastroenterology*. 2019;157(1):34-43. e1.
32. Intagliata NM, Caldwell SH, Tripodi A. Diagnosis, development, and treatment of portal vein thrombosis in patients with and without cirrhosis. *Gastroenterology*. 2019;156(6):1582-1599.e1.
33. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: guidance from the anticoagulation forum. *Am J Hematol*. 2019;94(6):697-709.
34. Sarin SK, Philips CA, Kamath PS, et al. Toward a comprehensive new classification of portal vein thrombosis in patients with cirrhosis. *Gastroenterology*. 2016;151(4):574-577. e3.
35. Koh JH, Liew ZH, Ng GK, et al. Efficacy and safety of direct oral anticoagulants versus vitamin K antagonist for portal vein thrombosis in cirrhosis: a systematic review and meta-analysis. *Dig Liver Dis*. 2022;54(1):56-62.