의학석사 학위논문

간경변 환자의 양성 문맥혈전증에 대해 직접 경구 항응고제와 비타민 K 저해제의 치료효과 비교

Direct Oral Anticoagulants and Vitamin K Antagonist for Benign Portal Vein Thrombosis in Patients with Liver Cirrhosis

울산대학교 대학원

의 학 과

이 여 진

간경변 환자의 양성 문맥혈전증에 대해 직접 경구 항응고제와 비타민 K 저해제의 치료효과 비교

지도교수 최종기

이 논문을 의학석사 학위 논문으로 제출함

2024년 2월

울산대학교 대학원

의 학 과

이 여 진

이여진의 의학석사 학위 논문을 인준함

심사위원 임 영 석 인

심사위원 이 단 비 인

심사위원 최 종 기 인

울 산 대 학 교 대 학 원

2024 년 2 월

국문요약

연구배경: 양성 문맥혈전증은 간경화 환자에게 잦은 빈도로 발생하는 합병증으로, 간경화로 인해 단백합성이 저하되며 이로 인해 응고물질과 항응고물질의 비가 불균형 해지며 발생한다. 문맥혈전이 존재할 시 문맥 혈류의 감소로 인해 간기능저하가 동반되기 때문에 항응고제를 이용한 치료를 시행함이 간경화 환자의 생존율을 향상시키는 것으로 알려져 있다. 최근 항응고치료제로 각광받는 직접 경구 항응고제는 심실세동, 폐동맥 혈전 등 여러 항응고제 투약이 필요한 환자군에서 기존에 투약하던 헤파린, 비타민 K 저해제와 생존율 및 부작용 발생비율에서 비등한 효과를 보이고 있다. 그러나 약물 대사가 간기능에 영향을 받기 때문에 간경화 환자군에서 그 효과에 대해 연구된 바가 적어 본 연구에서 이에 대해 알아보고자 하였다.

연구 방법: 2011 년부터 2021 년 사이 양성 문맥혈전증을 진단받고 항응고치료를 한 91 명의 환자군을 후향적으로 분석하였다. 91 명 중 23 명은 직접 경구 항응고제로 치료받았고 68 명은 비타민 K 저해제로 치료받았다. 항응고제 치료 중 출혈 부작용의 발생 여부, 생존율과 문맥혈전의 감소 여부를 확인하였다.

연구결과: 환자군의 중위 연령은 58.7 세였으며, 56 명(61.5%)이 남성이었다. B 형 간염 바이러스 감염이 간경화의 가장 흔한 원인이었고 Child-Pugh 점수의 중위 값은 6.7 점이다. 총 36 명(39.6%)의 환자에서 주 간문맥을 침범한 문맥혈전이 발견되었다. 치료기간동안 문맥혈전증이 일부 감소한 환자는 49 명(53.8%)이며 완전히 호전된 환자군은 30 명(33.0%)이었다. 출혈의 연간 발생률은 100PY 당 3.26 이다. Kaplan-Meier 분석으로 확인된 1 년, 2 년, 3 년 누적 주요 출혈 발생률은 각각 7.3%, 8.6%, 8.6% 였다. 전체 환자 중 10 명에서 출혈이 발생했고 직접 경구 항응고제 그룹에서 2 명, 비타민 K 저해제에서 8 명이 확인되었다. 위장 출혈(90%)이 주된 출혈 원인이었다. 치료군 간에 출혈 발생률, 문맥혈전 감소 여부, 출혈을 제외한 사망률은 유의한 차이가 없었고, 성향점수 매칭한 그룹들 간 에서도 출혈 발생률, 문맥혈전 감소여부, 사망률에서 유의한 차이를 보이지 않았다.

연구결론: 직접 경구 항응고제는 이전 혈전증의 치료효과가 증명되었던 비타민 K 저해제와 부작용 발생률 및 치료 효과, 사망률에 대해 큰 차이를 보이지 않았다.

Contents

List of tables and figures

INTRODUCTION

Benign portal vein thrombosis (PVT) is often developed in patients with liver cirrhosis (LC), with reported incidence of 0.6% to 5.0% in compensated cirrhosis and over 26% in decompensated cirrhosis (1). The pathophysiology underlying the development of PVT in patients with LC is tied to the disruption of liver architecture. This leads to a slowed portal blood flow and an imbalance between procoagulant and anticoagulant systems due to reduced protein synthesis stemming from LC (2, 3). The onset of PVT can further deteriorate liver function by exacerbating portal hypertension, which may result in complications such as variceal bleeding, ascites, and increased mortality (4, 5). This decline in liver function may differ based on the location and extent of the PVT and the condition of the remaining liver function. As a result, treatment guidelines generally recommended anticoagulation for PVT unless there are contraindications in patients with compensated LC (6, 7). However, in those with decompensated LC, treatment decisions must be approached with greater caution, weighting the risks and benefits of anticoagulation.

Traditionally, Vitamin K antagonist (VKA) has been used to treat various forms of venous thromboembolism, including PVT. However, challenges in the therapeutic monitoring of VKA in patients with LC have limited its widespread adoption. This unpredictable monitoring may lead to severe bleeding events during treatment, making physicians hesitant about treating PVT with VKA in patients with LC.

Over the past few decades, direct oral anticoagulants (DOAC) have gained popularity for anticoagulation in various contexts, due to their proven efficacy, safety, and ease of monitoring in comparison to traditional VKA in multiple randomized trials (17-19). Nevertheless, the benefits of this shift have not been fully realized by patients with LC, as those with advanced liver disease were excluded from most randomized DOAC trials. There are no randomized or prospective studies specifically for patients with LC treating benign PVT. However, there has been a trend towards using DOACs in selected patients with LC for anticoagulation. Various observational studies, including our own research on atrial fibrillation (8), have highlighted the efficacy and safety of DOACs in patients with LC (9-12). Prior studies examining DOAC uses in patients with PVT are quite limited. Notably, studies comparing DOACs to VKAs for PVT treatment are few, with most including fewer than 20 patients (13-15).

In light of this, we aimed to assess the effectiveness and safety of DOACs compared to VKAs in treating PVT in patients with LC, drawing data from a large hospital electronic database.

METHODS

Study participants

This study was approved by the Institutional Review Board of Asan Medical Center, Seoul, Republic of Korea (IRB No. 2022-1619), and the need for informed consent was waived by the IRB.
A total of 3,583 patients who were diagnosed with LC and with "thrombosis" on radiologic report between January 2011 and December 2022 were initially abstracted from the electronic medical records database of Asan Medical Center using International Classification of Disease, Tenth Revision (ICD-10) codes. We excluded patients if any of the following met: history of hepatocellular carcinoma (HCC) within 2 years of the development of PVT (n=2,821), no anticoagulation for benign PVT (n=420), follow-up period <3 months (n=83), receiving liver transplantation before the development of PVT (n=50), non-HCC malignancy (n=46), previously existing chronic PVT before 2011 (n=33), no definite delineated PVT on radiologic image despite of existing the description of PVT on the report (n=16), acute post-operative PVT (n=9), insufficient medical record (n=16). Finally, a total of 91 patients treated for PVT with either DOAC (n=21) or VKA (n=68) were analysed in the present study (Figure 1).

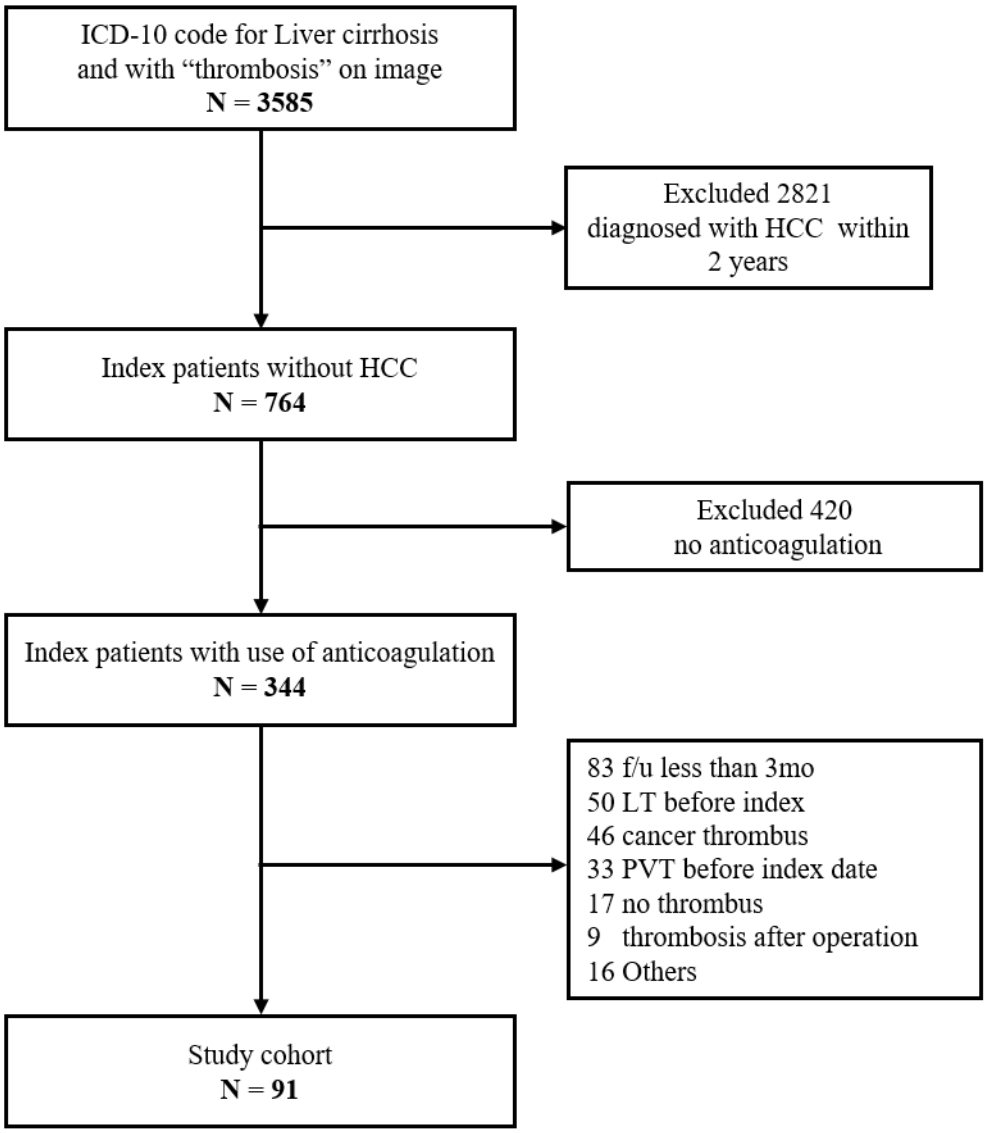

Figure 1. Flowchart of the screening and selection of the study population

Abbreviations: HCC, Hepatocellular carcinoma; LT, Liver transplantation; PVT, Portal vein thrombosis

Clinical variables and treatment

Data on patient characteristics and outcomes were obtained from electronic medical records. All patients had undergone standard clinical examinations, liver function tests, and imaging tests every 1–3 months during follow-up. LC was defined as the presence of any of the following: a coarse liver echotexture and nodular liver surface on ultrasonography or computed tomography (CT), or clinical features of portal hypertension (e.g., ascites, splenomegaly, or esophageal varices).

PVT was defined as the absence of portal blood flow in part of or in the entire lumen of any site of the portal vascular system caused by the presence of solid material within the vein, as documented on abdominal CT. Location of PVT was classified into three groups: PVT with or without intrahepatic branch PV, and PVT with mesenteric vein thrombosis. Severity of PVT was classified into complete if no blood flow exists in the portal vein lumen and partial if blood flow exists in the portal vein lumen despite it being partially occluded. Location of PVT and recanalization is described at Table 1.

Treatment regimen decision was made at each attending physician's discretion. VKA was used for targeting the INR between 1.5 and 2.5. Among DOACs approved in Korea during the study period, rivaroxaban, dabigatran, and apixaban were used in the included patients.

Table 1. Main classification system for portal vein thrombosis

Location	
Main portal vein	PVT only located in main portal vein
Portal vein branch	PVT involved main portal vein and above portal vein branch
Portal vein + splanchnic vein	PVT involved included main portal vein or portal vein branch with splanchnic vein
Recanalization	
Complete	Completely disappeared thrombus in follow up radiologic exam
Partial	Decreased > 50% of the thrombus in follow up radiologic exam

Study outcomes

The primary safety outcome was the cumulative incidence of major bleeding during the treatment. Major bleeding was defined as an overt bleeding accompanied with a decrease in hemoglobin levels of 2 g/dl or more, the transfusion of two or more units of packed red blood cells, or bleeding that occurs in the intracranial, intraspinal, intraocular, retroperitoneal, pericardial areas, or that is fatal, as defined by the International Society on Thrombosis and Hemostasis criteria (16). Other bleeding events that stopped anticoagulation except major bleeding was also counted. The secondary outcome was the recanalization rate of PVT established on follow-up imaging and bleeding-free survivals. In the context of PVT treatment, if subsequent imaging shows an improvement in portal vein flow, it is defined as 'partial recanalization'. If PVT has completely disappeared, it is referred to as 'complete recanalization'. The index date for this study was the first date of VKA or DOAC treatment following identification of PVT on radiologic examination. Patients were followed up until the earliest of the following events: diagnosis of any type of cancer, death of any cause, liver transplantation, or the last follow-up date or March 31, 2023. The median follow-up duration of the study population was 2.8 years (interquartile range [IQR], 1.5–4.4).

Statistical analysis

Data were summarized as median values and IQR for continuous variables and numbers with percentages for categorical variables. The t-test or Mann-Whitney test for continuous variable was used for continuous variables, and the chi-square or Fisher's exact tests for categorical variables, as appropriate. The cumulative incidences of major bleeding between the two treatments were estimated using the Kaplan-Meier method and compared with the log-rank test. Cox proportional hazard models were used to identify risk factors for bleeding in our study patients. Propensity score (PS)-matched analysis was used to minimize potential confounding between patients treated with DOACs and those treated with VKA. PS was computed using the following 15 variables: age, sex, white blood cell, hemoglobin, platelet, serum albumin, aspartate aminotransferase, alanine aminotransferase, total bilirubin, creatinine, prothrombin time, location of PVT, and Child-Pugh score. For PS matching, a nearest-neighbour 1:1 matching scheme with the caliper size of 0.2 was employed. None of the standardized differences for any baseline covariates in the matched exceeded 0.2. P values <0.05 were considered statistically significant. Statistical analyses were conducted using R software, version 4.2.3 (https://www.r-project.org).

RESULTS

Baseline characteristics of the study population

Of the 91 included patients, 23 (25.2%) were treated with DOACs and 68 (74.7%) were administered VKA for treating PVT (Table 2). The median age was 58.7 years and 56 (61.5%) were male. Hepatitis B virus infection was the most common etiology of underlying liver disease. Median Child-Pugh score was 6.7. The number of patients in Child-Pugh class A, B, and C was 50 (54.9%), 32 (35.2%), and 9 (9.9%), respectively. Esophageal varices were identified on pre-treatment endoscopy in 73 (82.0%) patients among 85 patients who performed endoscopy prior to anticoagulation. Main PVT was found in 36 (39.6%) patients and main PVT extension to mesenteric vein was observed in 27 (39.7%) patients.

When compared to patients with VKA, patients with DOAC were older, and had a significantly higher platelet count. However, no statistical significance was observed in serum albumin, total bilirubin, Child-Pugh score, and prevalence of esophageal varices on pre-treatment endoscopy. Rivaroxaban was most used DOAC in this study (14, 60.8%).

Additionally, during the observational period, patients were categorized based on the occurrence of bleeding (Table 3). The group with bleeding did not exhibit significant differences when compared to the other groups. However, due to the small sample size of this group (n = 10), an additional table was created to provide a comprehensive view of all patients who experienced major bleeding (Table 4).

Table 2. Baseline characteristics of Study population

Characteristics	Total cohort			
	Total (n = 91)	DOAC (n = 23)	Warfarin (n = 68)	P-value
Demographic characteristics				
Age, years	58.7 ± 11.0	62.3 ± 8.2	57.4 ± 11.6	0.103
Male sex, n (%)	56 (61.5)	17 (73.9)	39 (57.4)	0.245
Etiology of liver cirrhosis				0.103
HBV	43 (47.3)	7 (30.4)	36 (52.9)	
HCV	4 (4.4)	0 (0.0)	4 (5.9)	
Alcoholic	14 (15.4)	5 (21.7)	9 (13.2)	
Others	30 (32.9)	11 (47.8)	19 (27.9)	
Laboratory findings				
Platelets, 1,000/mm^3	98.1 ± 84.4	149.5 ±133.9	80.7 ± 49.7	0.024
Prothrombin time, %	67.6 ± 17.6	71.3 ± 20.7	66.4 ± 16.4	0.248
Albumin, g/dL	3.2 ± 0.6	3.2 ± 0.6	3.2 ± 0.6	0.651
Total bilirubin, mg/dL	1.7 ± 1.4	1.6 ± 0.9	1.8 ± 1.5	0.491
Creatinine, mg/dL	1.1 ± 1.1	1.0 ± 0.4	1.1 ± 1.2	0.601
Imaging findings				
PVT location				0.087
Main portal vein	36 (39.6)	7 (30.4)	29 (42.6)	
Branch portal vein	28 (30.8)	5 (21.7)	23 (33.8)	
Main portal vein + splanchnic vein	27 (29.7)	11 (47.8)	16 (23.5)	
History of liver-related complication				
Spontaneous bacterial peritonitis	2 (2.2)	0 (0.0)	2 (2.9)	0.993
Hepatic encephalopathy	4 (4.4)	0 (0.0)	4 (5.9)	0.548
Ascites				0.238
Mild to moderate	26 (28.6)	7 (30.4)	19 (27.9)	
Severe	19 (20.9)	2 (8.7)	17 (25.0)	
CP score	6.7 ± 2.0	6.7 ± 1.6	6.7 ± 2.1	0.959
CP class				0.804
Class A	50 (54.9)	14 (60.9)	36 (52.9)	
Class B	32 (35.2)	7 (30.4)	25 (36.8)	
Class C	9 (9.9)	2 (8.7)	7 (10.3)	
Varix				0.111
Identified on endoscopy	73 (82.0)	16 (69.6)	58 (85.3)	
Endoscopy not performed	6 (6.7)	4 (17.4)	3 (4.4)	
Treatment regimen				
Rivaroxaban		14 (60.8)		
Dabigatran		1 (4.3)		
Apixaban		8 (34.8)		
VKA			68 (100.0)	

Note: Data are presented as a mean value with SD or count with proportions.
Abbreviations: DOAC, direct oral anticoagulant; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; SD, standard deviation; PVT, portal vein thrombosis; CP, child-pugh; VKA, vitamin K antagonist

Table 3. Baseline characteristics between patients with bleeding and without bleeding

Characteristics	Total cohort			
	Total (n = 91)	Bleeding (n = 10)	No bleeding (n = 81)	P-value
Demographic characteristics				
Age, years	58.7 ± 11.0	58.4 ± 8.7	58.4 ± 11.3	0.927
Male sex, n (%)	56 (61.5)	6 (60.0)	50 (61.7)	1.0
Etiology				0.473
HBV	43 (47.3)	4 (40.0)	39 (48.1)	
HCV	4 (4.4)	1 (10.0)	3 (3.7)	
Alcoholic	14 (15.4)	1 (10.0)	13 (16.0)	
Others	30 (32.9)	4 (40.0)	26 (32.1)	
Laboratory findings				
Platelets, 1000/mm^3	98.1 ± 84.4	74.7 ± 36.2	101.0 ±88.3	0.093
Prothrombin time, %	67.6 ± 17.6	68.8 ± 17.1	67.5 ± 17.8	0.829
Albumin, g/dL	3.2 ± 0.6	3.2 ± 0.6	3.2 ± 0.6	0.751
Total bilirubin, mg/dL	1.7 ± 1.4	1.3 ± 0.7	1.8 ± 1.4	0.088
Creatinine, mg/dL	1.1 ± 1.1	1.2 ± 0.7	1.0 ± 1.1	0.598
Imaging findings				
PVT location				0.251
Main portal vein	36 (39.6)	6 (60.0)	30 (37.0)	
Portal vein branch	28 (30.8)	1 (10.0)	7 (33.3)	
Portal vein + splanchnic vein	27 (29.7)	3 (30.0)	24 (29.6)	
Complete recanalization	30 (33.0)	2 (20.0)	28 (34.6)	0.596
Partial recanalization	49 (53.8)	4 (40.0)	45 (55.6)	0.583
History of liver-related complication				
SBP	2 (2.2)	0 (0.0)	2 (2.5)	1.000
Hepatic encephalopathy	4 (4.4)	0 (0.0)	4 (4.9)	1.000
Ascites				0.704
Mild to moderate	26 (28.6)	3 (30.0)	23 (38.4)	
Severe	19 (20.9)	3 (30.0)	16 (19.8)	
CP score	6.7 ± 2.0	6.8 ± 1.5	6.7 ± 2.1	0.887
CP class				0.560
Class A	50 (54.9)	4 (40.0)	46 (56.8)	
Class B	32 (35.2)	5 (50.0)	27 (33.3)	
Class C	9 (9.9)	1 (10.0)	8 (9.9)	
Varix				0.526
Identified on endoscopy	73 (82.0)	9 (90.0)	65 (80.2)	0.613
Endoscopy not performed	6 (6.7)	0 (0.0)	7 (8.6)	

Note: Data are presented as a mean value with SD or count with proportions.
Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; SD, standard deviation; PVT, portal vein thrombosis; SBP, spontaneous bacterial peritonitis; CP, child-pugh

Table 4. Summary of patients with major bleeding event

No.	Sex	Age	Bleeding event	**Lab data at baseline**			CP score	Location of PVT	Recanalization date	Anticoagulation type
				PLT(1000/mm$^{3)}$	PT (%)	Cr(mg/dL)				
1	M	53.6	GI bleeding	94	91.8	1.1	5	Main PV	2015-10-17	Warfarin
2	M	44.8	GI bleeding	34	59.5	1.33	7	Main PV	2016-05-07	Warfarin
3	F	61.7	GI bleeding	105	100.7	0.52	6	Main PV	2017-10-17	Warfarin
4	M	61.8	GI bleeding	53	74.3	0.73	6	Main PV + splanchnic	2021-01-13	DOAC(rivaroxaban)
5	M	68.3	GI bleeding	135	73	0.86	7	Main PV + splanchnic	(-)	Warfarin
6	F	48.7	GI bleeding	152	47.7	2.54	10	Main PV	(-)	DOAC(rivaroxaban)
7	F	73.0	Hemoptysis	34	64.6	0.91	5	PV branch	(-)	Warfarin
8	F	61.0	GI bleeding	106	69	2.34	7	Main PV	(-)	Warfarin
9	M	52.0	GI bleeding	40	51.5	0.59	7	Main PV	(-)	Warfarin
10	M	25.7	GI bleeding	94	55.5	1.3	8	Main PV + splanchnic	(-)	Warfarin

Table 5. Baseline characteristics of the propensity score-matched cohorts

Characteristics	Total cohort		
	DOAC (n = 14)	Warfarin (n = 21)	P-value
Age, years	62.8 [60.0-65.1]	59.1 [53.4-66.0]	0.490
Male sex, n ()	9 (64.3)	13 (61.9)	1.0
Platelets, 1000/mm^3	78.0 [58.0-148.0]	89.0 [68.0;137.0]	0.827
Prothrombin time, %	72.5 [57.6-75.0]	69.0 [60.0-77.4]	0.960
Albumin, g/dL	3.1 [2.9-3.4]	3.3[2.8-3.6]	0.661
Total bilirubin, mg/dL	1.4 [1.1-2.4]	1.0 [0.9-1.7]	0.128
Creatinine, mg/dL	0.9 [0.7-1.0]	0.8 [0.7-0.8]	0.157
PVT location			0.320
Main portal vein	4 (28.6)	9 (42.9)	
Portal vein branch	4 (28.6)	2 (9.5)	
Portal vein + splanchnic vein	6 (42.9)	10 (47.6)	
CP score	6.0 [6.0-8.0]	6.0 [5.0-8.0]	0.648
Statue of liver cirrhosis			1.0
Compensated	8 (57.1)	11 (52.4)	
Decompensated	6 (42.9)	10 (47.6)	

Note: Data are presented as the mean ± standard deviation, median (interquartile range), or frequency (proportion).
Abbreviations: DOAC, Direct oral anticoagulant; PVT, portal vein thrombosis; CP, child-pugh

Clinical outcomes in the entire study population

Among 91 included patients, involving 306 person-years (PYs) of observation, 10 patients developed major bleeding events with an annual incidence of 3.26 per 100 PYs. The 1-, 2-, and 3-year cumulative major bleeding incidence determined by Kaplan-Meier analysis were 7.3%, 8.6%, and 8.6%, respectively. Major bleeding events occurred in 2 patients in the DOAC group and 8 patients in the VKA group. GI bleeding (n=2) was the major bleeding events in the DOAC group. GI bleeding (n=7), Hemoptysis (n=1) was the major bleeding causes in the VKA group (Table 4).

The cumulative incidence of major bleeding events at 1-, 2-, and 3-years were 9.1%, 9.1%, and 9.1% in the DOAC group and 6.6%, 8.5%, and 8.5%, in the warfarin group, respectively. No significant difference was observed in the risk of major bleeding event between the two treatments. (Figure 2A, P=0.8). Bleeding free survival also had no significance (Figure 2B. P=0.94)

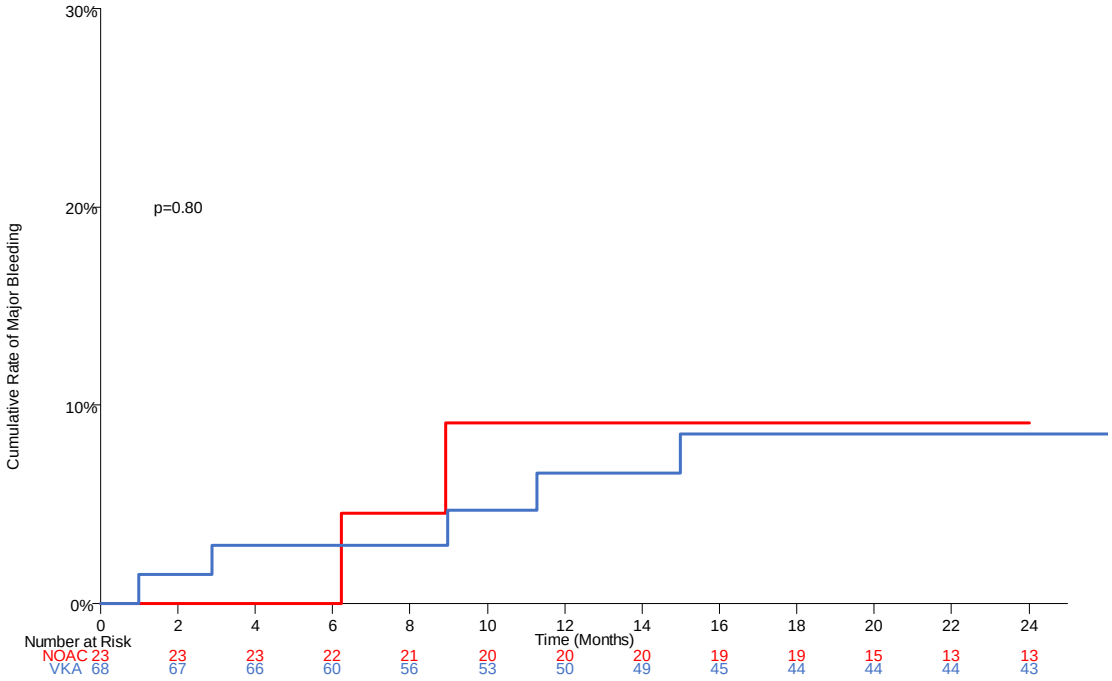

Figure 2A. Kaplan–Meier plot of the cumulative incidence of major bleeding according to the treatment types of anticoagulation for PVT in patients with LC

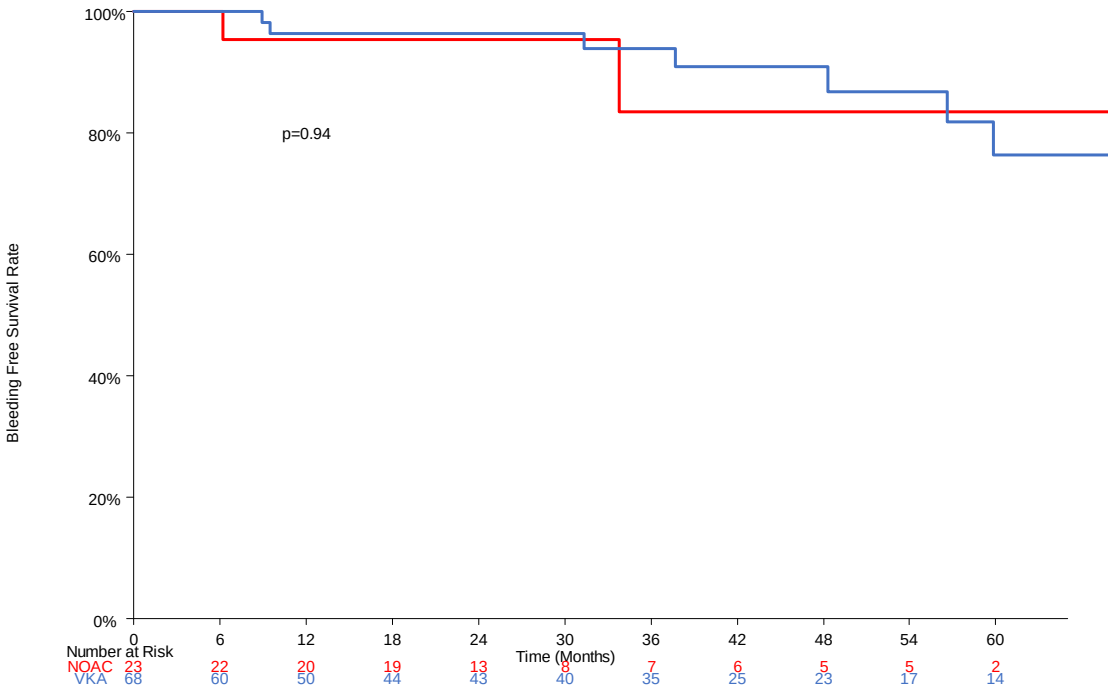

Figure 3B. Kaplan–Meier plot of bleeding free survival according to the treatment types of anticoagulation for PVT in patients with LC

Recanalization

During anticoagulation, partial recanalization occurred in 49 (53.8%) patients and complete recanalization was achieved in 30 (33.0%) of all patients. The 1-, 2-, and 3-year cumulative partial recanalization determined by Kaplan-Meier analysis were 41.1%, 60.2%, and 62.1%, respectively. The cumulative partial recanalization over a period of 1, 2, and 3 years, as determined by Kaplan-Meier analysis, was 41.1%, 60.2%, and 62.1% respectively (Figure 3A, P=0.15).

When examining the cumulative incidence of complete recanalization at intervals of 1, 2, and 3 years, the DOAC group exhibited rates of 50.0%, 65.7%, and 71.4% respectively, while the VKA group showed rates of 39.0%, 59.0%, and 59.0% respectively. Despite these differences, no significant disparity was detected in the risk of recanalization events between the two treatment modalities (Figure 3B, P=0.31).

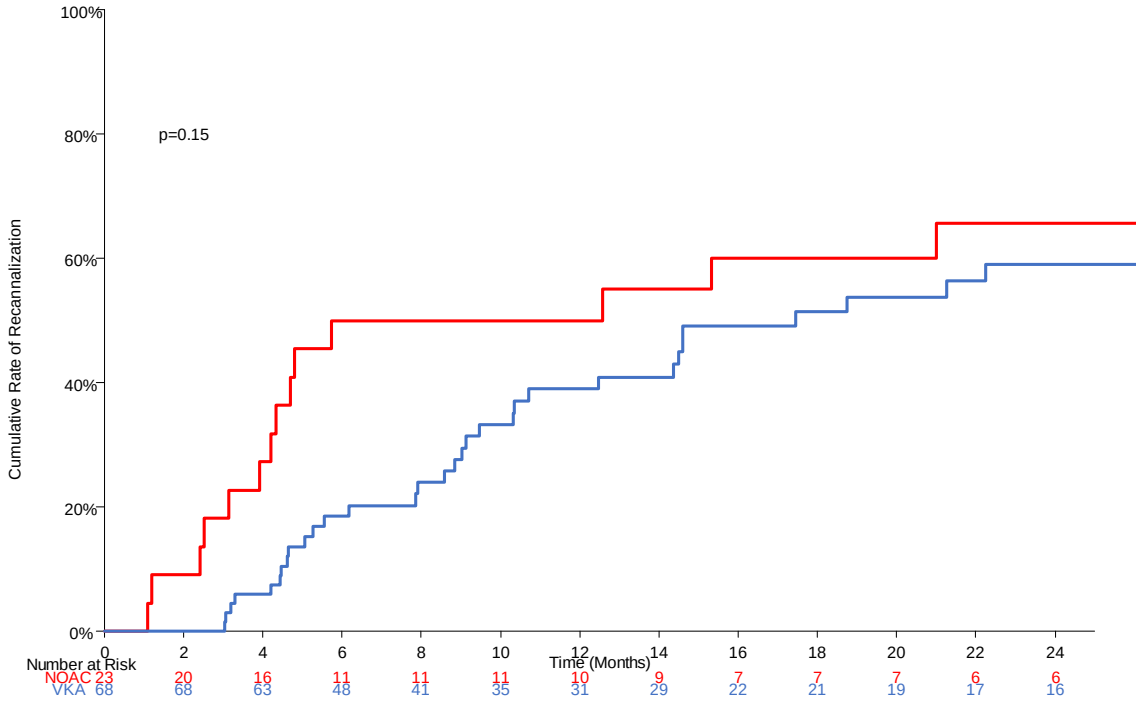

Figure 4A. Kaplan–Meier plot of the cumulative incidence of partial recanalization according to the treatment types of anticoagulation for PVT in patients with LC

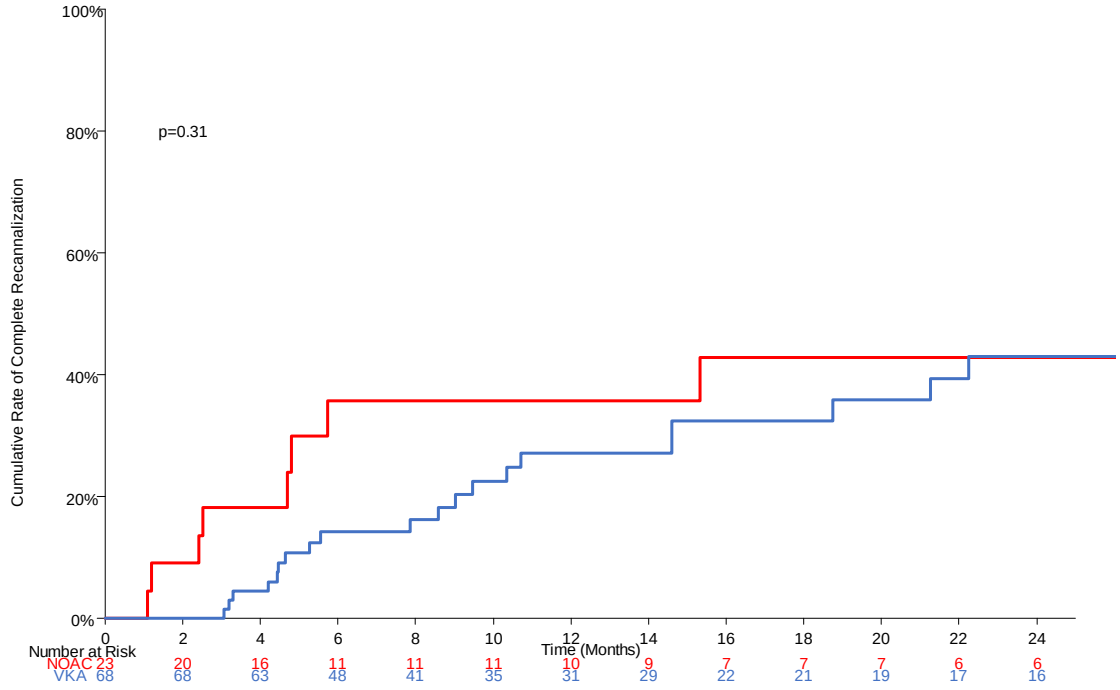

Figure 5B. Kaplan–Meier plot of the cumulative incidence of complete recanalization according to the treatment types of anticoagulation for PVT in patients with LC

Clinical outcomes in the propensity-score matched cohort

We generated 15 PS-matched pairs from the entire cohort for fair comparison between the two treatments. The baseline characteristics in the PS-matched cohort are presented in Table 5. After PS matching, all baseline covariates were found to be well balanced and did not exceed 0.2 of the standardized mean difference. In these 15 PS-matched pairs, the risk of a major bleeding, complete recanalization, and bleeding free survival did not significantly differ between the DOAC and VKA (Figure 4A,4B,4C).

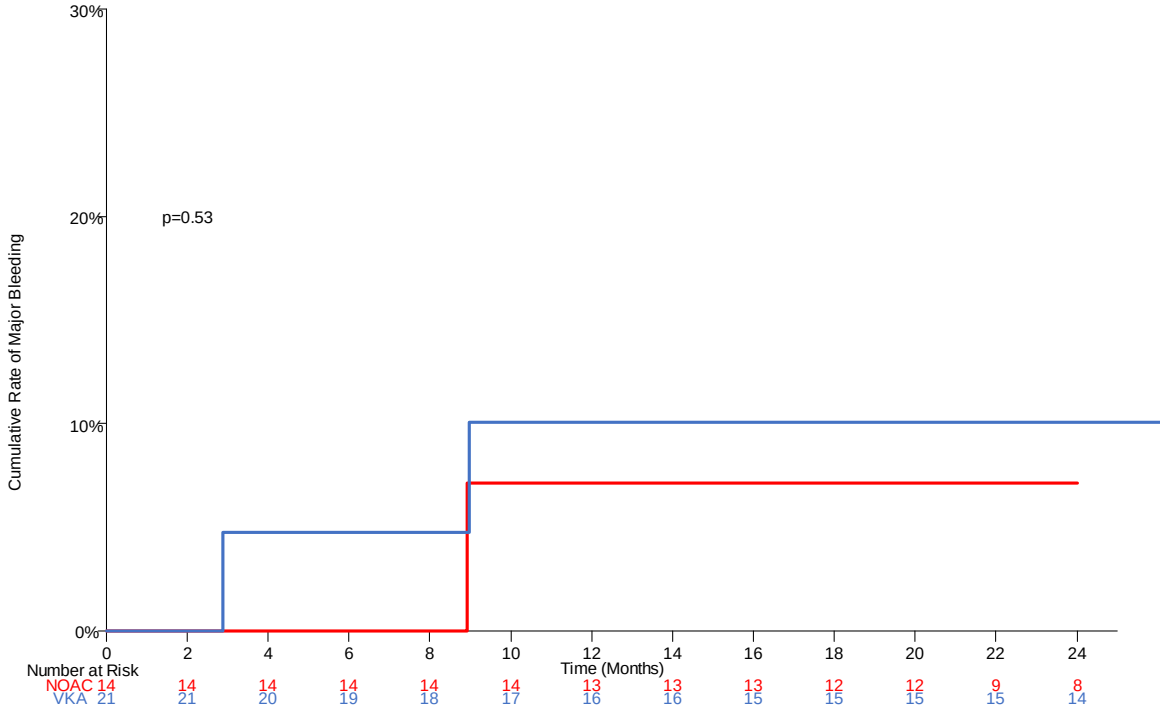

Figure 6A. Kaplan–Meier plot of the cumulative incidence of major bleeding according to the treatment types of anticoagulation for PVT in PS matched cohort with LC

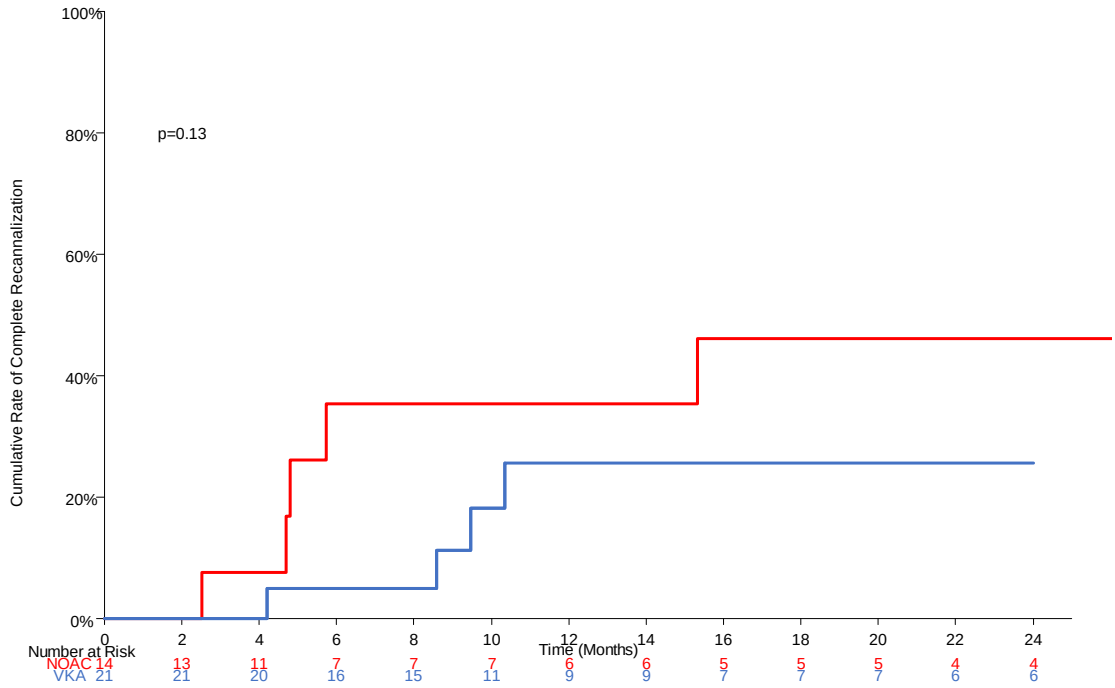

Figure 7B. Kaplan–Meier plot of the cumulative incidence of complete recanalization according to the treatment types of anticoagulation for PVT in PS matched cohort with LC

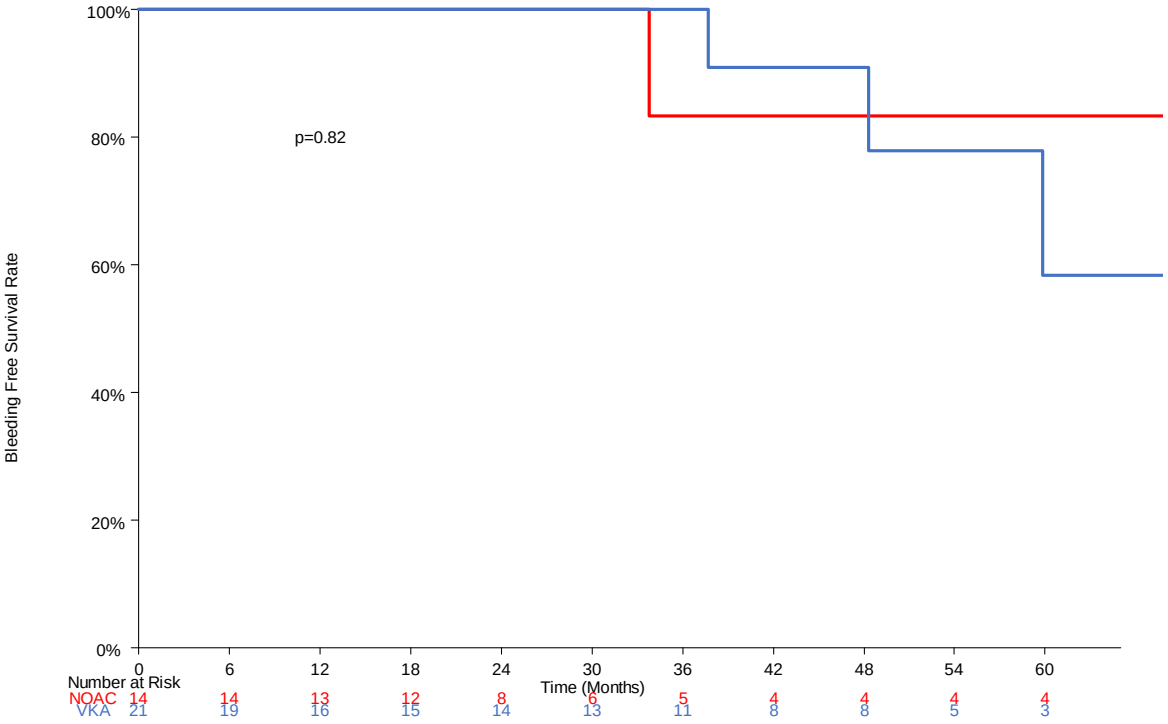

Figure 8C. Kaplan–Meier plot of bleeding free survival according to the treatment types of anticoagulation for PVT in PS matched cohort with LC

DISCUSSION

In this study, we found that the recanalization rate of each treatment group has no difference between each treatment. Both groups also had similar count of bleeding event in treatment of PVT, and bleeding-free survival rate in propensity matched patient groups. More than half of patients achieved at least 50% of reduction of lumen size during the use of anticoagulant. Along the treatment group, 10 patients had event of major bleeding with GI bleeding.

Before this study, most studied recognized the use of anticoagulation usage in other diseases that required anticoagulation, such as atrial fibrillation and pulmonary thromboembolism in patients with liver cirrhosis. Major bleeding events and recanalization rates also had no changes between NOAC and warfarin, corresponding with this study. Davis et al performed a retrospective observational analysis of 167 adult patients with a diagnosis of cirrhosis for whom needed therapy of anticoagulation (17). Of these patients, 110 received warfarin and 57 received a DOAC (apixaban: 52.6%, rivaroxaban: 45.6%, dabigatran: 1.8%). The results showed that the incidence of major bleeding was similar between the warfarin and DOAC groups (9.1% vs. 5.2%, $p = 0.381$). No difference in the rate of stroke or recurrent embolic event at 90 days was also identified between the two groups. Since administration of DOAC in atrial fibrillation proved to be no significant difference when comparing warfarin with the incidence of side effects such as bleeding and cerebral infarction, studies have begun to show how effective the introduction of DOAC was in benign PVT that also requiring anticoagulant therapy. Before this study, several studies have evaluated the effectiveness of DOAC in treating benign PVT in patients with LC. Ai et al studied patients with benign PVT and compared the outcomes of bleeding and recanalization in those who were prescribed DOAC as anticoagulants with control groups that did not receive any anticoagulation treatment (18). This study aligns with previous research that explored the management of PVT and its impact on improving survival rates (19). Additionally, a combination therapy of Low Molecular Weight Heparin (LMWH) followed by DOAC has been suggested as a potential treatment option for thrombosis (15). This approach demonstrated superior results in reducing PVT volume and progression of PVT compared to the therapy of LMWH followed by VKA.

The use of DOAC is not advised for patients diagnosed with Child-Pugh class B or C cirrhosis, or for any patients suffering from a liver disease that is accompanied by a coagulopathy (20). While each DOAC exhibits a distinct rate of hepatic excretion, there are currently no precise guidelines for the administration of DOACs in patients with LC in clinical practice. As such, each DOAC had a variable degree of hepatic metabolism, and the type of DOAC could be an important point in analysing their respective effects (21). The DOAC that was most used in this study was rivaroxaban (60.8%) and rivaroxaban proved its variability of effect in patients with LC. The minor pharmacodynamic study

that assessed the impact of a single 10 mg dose of rivaroxaban on patients with diverse levels of hepatic impairment, as well as on healthy controls has been represented as evidence for the use of rivaroxaban (22). However, the treatment outcomes have varied across different studies. For instance, an in vitro study conducted by Potze et al. found no significant difference in the anticoagulation effect between healthy controls and patients with CTP A or B cirrhosis (23). Interestingly, rivaroxaban exhibited a diminished anticoagulant effect in CTP C patients when compared to controls, and patients with CTP A and B (23). In the population of this study, the mean CP score was about 6.7 ± 2.0 and most patients were in scoring group of class A. Then, the usage of DOACs could be considered safer for the treatment of DVT, possibly supported by the evidence of the use of rivaroxaban.

The practice of balancing between coagulopathy and hypercoagulability in patients with liver cirrhosis had been proved before. To compensate for each coagulation status, prophylactic use of anticoagulation could help to prevent PVT. Even though the prophylaxis of venous thromboembolism had been studied, the evidence of treatment was insufficient to advise for or against the use of prophylaxis, due to the lack of quality and homogeneity of available data (24, 25). But the opposite findings have also been reported previously. For patients with liver cirrhosis and portal hypertension who underwent splenectomy to treat thrombocytopenia and prevent immune reactions following liver transplantation, a decrease in antithrombin III activity was anticipated. Prophylaxis with LMWH significantly reduced the incidence of PVT (25).

The limitations of this study include its confinement to a single medical center, which could introduce selection bias. Additionally, the study was unable to match the baseline characteristics of each treatment group respectively, due to the small number of DOAC users, which limited the ability to measure the effects of each DOAC medication. The study also excluded LMWH due to a lack of sufficient samples. Furthermore, as this is a retrospective study, it is challenging to accurately determine the real effects of DOAC and VKA on patients with LC.

CONCLUSION

In patients with liver cirrhosis suffering from PVT, DOAC demonstrated a comparable effect to VKA. This similarity was observed in terms of bleeding events, recanalization, and mortality rates. For patients with mild to moderate cirrhosis, DOACs have been shown to be a safe and effective alternative to warfarin. However, further research is needed to confirm these findings and to determine the relative safety of DOACs in patients with severe cirrhosis.

RERERENCES

[1] Gaiani S, Bolondi L, Li Bassi S, Zironi G, Siringo S, Barbara L. Prevalence of spontaneous hepatofugal portal flow in liver cirrhosis. Clinical and endoscopic correlation in 228 patients. Gastroenterology 1991;100(1):160-7.

[2] Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med 2011;365(2):147-56.

[3] Nery F, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, Plessier A, Roulot D, Chaffaut C, Bourcier V, Trinchet JC, Valla DC. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. Hepatology 2015;61(2):660-7.

[4] Janssen HL, Wijnhoud A, Haagsma EB, van Uum SH, van Nieuwkerk CM, Adang RP, Chamuleau RA, van Hattum J, Vleggaar FP, Hansen BE, Rosendaal FR, van Hoek B. Extrahepatic portal vein thrombosis: aetiology and determinants of survival. Gut 2001;49(5):720-4.

[5] Condat B, Pessione F, Hillaire S, Denninger MH, Guillin MC, Poliquin M, Hadengue A, Erlinger S, Valla D. Current outcome of portal vein thrombosis in adults: risk and benefit of anticoagulant therapy. Gastroenterology 2001;120(2):490-7.

[6] Northup PG, Garcia-Pagan JC, Garcia-Tsao G, Intagliata NM, Superina RA, Roberts LN, Lisman T, Valla DC. Vascular Liver Disorders, Portal Vein Thrombosis, and Procedural Bleeding in Patients With Liver Disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2021;73(1):366-413.

[7] European Association for the Study of the Liver. Electronic address eee. EASL Clinical Practice Guidelines: Vascular diseases of the liver. J Hepatol 2016;64(1):179-202.

[8] Yoo SY, Kim E, Nam GB, Lee D, Shim JH, Kim KM, Lim YS, Lee HC, Chung YH, Lee YS, Choi J. Safety of direct oral anticoagulants compared to warfarin in cirrhotic patients with atrial fibrillation. Korean J Intern Med 2022;37(3):555-66.

[9] Intagliata NM, Maitland H, Caldwell SH. Direct Oral Anticoagulants in Cirrhosis. Curr Treat Options Gastroenterol 2016;14(2):247-56.

[10] Koh JH, Liew ZH, Ng GK, Liu HT, Tam YC, De Gottardi A, Wong YJ. 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.

[11] 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):911-6.

[12] Priyanka P, Kupec JT, Krafft M, Shah NA, Reynolds GJ. Newer Oral Anticoagulants in the Treatment of Acute Portal Vein Thrombosis in Patients with and without Cirrhosis. Int J Hepatol 2018;2018:8432781.

[13] Naymagon L, Tremblay D, Zubizarreta N, Moshier E, Mascarenhas J, Schiano T. Safety, Efficacy, and Long-Term Outcomes of Anticoagulation in Cirrhotic Portal Vein Thrombosis. Dig Dis Sci 2021;66(10):3619-29.

[14] Ai B, Zhang L, Huang D, Chen J, Liu Z, Hu X, Zhou S, Hu Y, Zhao J, Yang F. Efficacy and safety of bevacizumab in advanced lung adenocarcinoma patients with stable disease after two cycles of first-line chemotherapy: A multicenter prospective cohort study. Thorac Cancer 2020;11(12):3641-4.

[15] Nagaoki Y, Aikata H, Daijyo K, Teraoka Y, Shinohara F, Nakamura Y, Hatooka M, Morio K, Nakahara T, Kawaoka T, Tsuge M, Hiramatsu A, Imamura M, Kawakami Y, Ochi H, Chayama K. Efficacy and safety of edoxaban for treatment of portal vein thrombosis following danaparoid sodium in patients with liver cirrhosis. Hepatol Res 2018;48(1):51-8.

[16] Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Journal of Thrombosis and Haemostasis 2005;3(4):692-4.

[17] Davis KA, Joseph J, Nisly SA. Direct oral anticoagulants and warfarin in patients with cirrhosis: a comparison of outcomes. J Thromb Thrombolysis 2020;50(2):457-61.

[18] Ai MH, Dong WG, Tan XP, Xu L, Xu C, Zhang Q, Zhang Y, Li J. 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):1395-400.
[19] Guerrero A, Campo Ld, Piscaglia F, Scheiner B, Han G, Violi F, Ferreira C-N, Téllez L, Reiberger T, Basili S, Zamora J, Albillos A, Valla D, Durand F, Artaza T, García-Pagán JC, Magaz M, La Mura V, Primignani M, Luca A, Stanciu C, Senzolo M, Amitrano L, Stefanescu H, Nery F, Chevret S, Girleanu I. Anticoagulation improves survival in patients with cirrhosis and portal vein thrombosis: The IMPORTAL competing-risk meta-analysis. Journal of Hepatology 2023;79(1):69-78.
[20] Graff J, Harder S. Anticoagulant therapy with the oral direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban and the thrombin inhibitor dabigatran etexilate in patients with hepatic impairment. Clin Pharmacokinet 2013;52(4):243-54.
[21] Qamar A, Vaduganathan M, Greenberger NJ, Giugliano RP. Oral Anticoagulation in Patients With Liver Disease. Journal of the American College of Cardiology 2018;71(19):2162-75.
[22] Kubitza D, Roth A, Becka M, Alatrach A, Halabi A, Hinrichsen H, Mueck W. Effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of a single dose of rivaroxaban, an oral, direct Factor Xa inhibitor. Br J Clin Pharmacol 2013;76(1):89-98.
[23] Potze W, Arshad F, Adelmeijer J, Blokzijl H, van den Berg AP, Meijers JC, Porte RJ, Lisman T. Differential in vitro inhibition of thrombin generation by anticoagulant drugs in plasma from patients with cirrhosis. PLoS One 2014;9(2):e88390.
[24] Pasta A, Calabrese F, Labanca S, Marenco S, Pieri G, Plaz Torres MC, Intagliata NM, Caldwell SH, Giannini EG. Safety and efficacy of venous thromboembolism prophylaxis in patients with cirrhosis: A systematic review and meta-analysis. Liver Int 2023;43(7):1399-406.
[25] Villa E, Cammà C, Marietta M, Luongo M, Critelli R, Colopi S, Tata C, Zecchini R, Gitto S, Petta S, Lei B, Bernabucci V, Vukotic R, De Maria N, Schepis F, Karampatou A, Caporali C, Simoni L, Del Buono M, Zambotto B, Turola E, Fornaciari G, Schianchi S, Ferrari A, Valla D. Enoxaparin Prevents Portal Vein Thrombosis and Liver Decompensation in Patients With Advanced Cirrhosis. Gastroenterology 2012;143(5):1253-60.e4.

Abstract

Background: Benign portal vein thrombosis (PVT) is frequently observed in patients with liver cirrhosis. It is primarily disrupted liver architecture by repeated exposure to toxic substances or hepatitis. This disruption leads to an imbalance between procoagulant and anticoagulant factors, resulting in reduced protein synthesis associated with liver cirrhosis. Because PVT deteriorated liver function as its presence, many guidelines suggested treat of PVT with vitamin k antagonist (VKA) as traditional treatment. Direct oral anticoagulants (DOAC) have emerged as a preferred choice of its safety to treat thrombosis, but its efficacy has not proved in patients with liver dysfunction before. This study aims to prove effect of DOAC comparable to VKA.

Methods: A retrospective analysis was conducted on 91 patients who received anticoagulation therapy for PVT between 2011 and 2021 at a tertiary referral center in South Korea. Of these patients, 23 treated with DOAC and 68 treated with VKA. The primary outcome was major bleeding events during the follow-up period. The secondary outcome was recanalization rate of PVT during the follow-up imaging and bleeding-free survivals.

Results: The median treatment age was 58.7 years and 56 (61.5%) were male. Hepatitis B virus infections was the most common etiology of underlying liver disease. Median child-pugh score was 6.7. Main PVT was found in 36 (39.6%) patients. Partial recanalization occurred in 49 (53.8%) patients; 30 (33.0%) patients got complete recanalization during treatment. Annual incidence of major bleeding is 3.26 per 100PYs. The 1-,2-,3-year cumulative major bleeding incidence determined by Kaplan-Meier analysis were 7.3%, 8.6% and 8.6% respectively. Major bleeding events occurred in 2 patients in the DOAC group, and 8 patients in the VKA groups. GI bleeding (9, 90%) was the major bleeding causes. Incidence of major bleeding, complete recanalization, bleeding between treatment groups had no marked variance between treatment groups. Even in propensity-matched cohort groups there is no difference between types of anticoagulation.

Conclusion: DOAC had similar effect with VKA in patient with portal vein thrombosis in liver cirrhosis, with bleeding event and recanalization with mortality