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The efficacy and safety of direct oral anticoagulants in noncirrhotic portal vein thrombosis

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Key Points

- DOACs are effective and safe for the treatment of acute ncPVT with or without concurrent involvement of other splanchnic vessels.
- Warfarin was associated with worse outcomes vs DOACs and enoxaparin for the treatment of ncPVT in this large, retrospective study.

Guidelines currently favor vitamin K antagonists or low-molecular-weight heparins for treatment of noncirrhotic portal vein thrombosis (ncPVT). Use of direct oral anticoagulants (DOACs) in PVT has been met with concern because of the lack of data. We conducted a retrospective study to investigate the efficacy and safety of DOACs for the treatment of ncPVT, and to compare them with standard therapies: 330 patients with ncPVT, followed-up for a mean 41.6 months, received warfarin (n = 108), enoxaparin (n = 70), rivaroxaban (n = 65), apixaban (n = 20), dabigatran (n = 8), fondaparinux (n = 2), or no anticoagulation (n = 57). The primary outcome was complete radiographic resolution (CRR) of PVT. Secondary outcomes included recanalization of occlusive PVT, cavernous transformation of the PV, development of chronic portal hypertensive symptoms (cPHS), and major bleeding. DOACs were associated with the highest CRR rates (dabigatran, 6/8 [75%]; apixaban, 13/20 [65%]; rivaroxaban, 42/65 [65%]). Enoxaparin was associated with a CRR rate similar to that of the DOACs (40/70 = 57%). Warfarin was associated with worse outcomes in this regard (CRR rate, 31% [33/108]; hazard ratio [HR] DOACs:warfarin, 2.91; 95% confidence interval [CI], 1.87-4.52; $P < .0001$). DOACs were associated with recanalization rates similar to enoxaparin and greater than warfarin (HR DOACs:warfarin, 3.45; 95% CI, 1.93-6.18; $P < .0001$). DOACs were associated with lower rates of cPHS, although this did not attain significance (DOACs, 8/93 [9%]; enoxaparin, 13/70 [19%]; warfarin, 31/108 [29%]). DOACs were associated with less major bleeding relative to warfarin (HR DOACs:warfarin, 0.20; 95% CI, 0.05-0.86; $P = .0307$). Patients harboring *JAK2V617F*, those with no evident predisposing factor for PVT, and those with occlusive thrombus demonstrated worse outcomes. DOACs appear effective and safe for the treatment of ncPVT.

Introduction

Although best described in the context of cirrhosis, portal vein thrombosis (PVT) may occur as a consequence of any proinflammatory intraabdominal process (such as infection, surgery, pancreatitis, or inflammatory bowel disease), or more rarely as a consequence of certain primary hematologic disorders (most notably *JAK2V617F*-positive myeloproliferative neoplasms or paroxysmal nocturnal hemaglobinuria).[1] Although optimal treatment of cirrhotic PVT remains a matter of some debate, anticoagulation (AC) is regarded as the standard therapy for acute noncirrhotic portal vein thrombosis (ncPVT).[1-3] Among cirrhotic patients, spontaneous resolution of PVT may be relatively common, thus lessening the potential benefit of AC, whereas factors such as coagulopathy of liver disease, thrombocytopenia, and the presence of varices, may all increase their risk for major bleeding on AC.[1-6] In contrast, among ncPVT patients spontaneous resolution is relatively rare, and bleeding risk typically not

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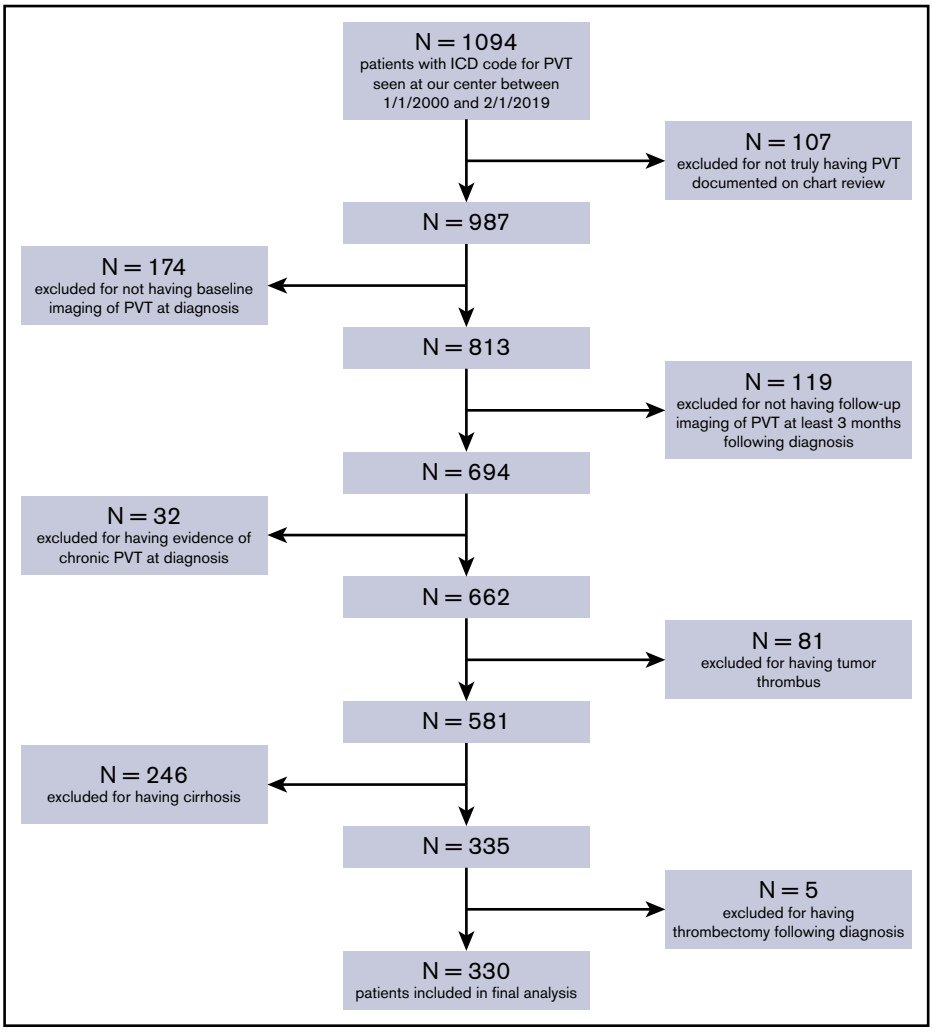

Figure 1. Inclusion and exclusion of study patients. A total of 1094 patients with an ICD code for PVT during the study period were identified. A total of 330 patients met all study criteria and were included in the analysis. The reasons for exclusion for the remaining patients are summarized in the text.

nearly so severe, thus generally shifting the risk-benefit analysis in favor of anticoagulation.[1] The primary aim of AC in acute ncPVT is to completely or partially recanalize the portal vein (PV) and prevent chronic thrombosis. Failure to do so may result in chronic noncirrhotic portal hypertension (ncPH) and its numerous attendant complications (including esophageal/gastric varices, ascites, and hepatic insufficiency).[1]

Professional society guidelines and expert opinions currently favor the use of vitamin K antagonists (VKAs) or low molecular weight heparins (LMWHs) for the treatment of PVT.[7-9] There is scant published data on the use of direct oral anticoagulants (DOACs) in PVT. Indeed, the initial prospective trials which established the use of DOACs for deep vein thrombosis (DVT) of the extremities and pulmonary embolism (PE) did not include patients with PV or other splanchnic vein thrombosis (SVT), and retrospective data are largely limited to case reports and small case series.[10-15] Additionally, the reported increased risk for gastrointestinal bleeding, at least with some DOACs, has been a matter of concern among this patient population.[9,16] Nevertheless, the use of DOACs for the treatment of ncPVT and other forms of SVT is becoming increasingly common among many practicing hematologists, particularly at centers which see high volumes of such patients. We sought to investigate the efficacy and safety of DOACs for the treatment of acute ncPVT, and compare them to standard therapies (VKAs and LMWHs). Herein we present our retrospective experience of 330 patients with ncPVT.

Methods

Patients and Outcomes

This retrospective study was approved by our institutional Program for the Protection of Human Subjects. We searched the medical records of our large urban tertiary care center to identify all patients carrying an International Classification of Diseases (ICD) code for PVT (I81) seen between 1 January 2000 and 1 February 2019. The identified medical records were then examined to verify the diagnosis of acute ncPVT, with or without concurrent thrombosis, in additional splanchnic vessels. The presence of PVT in each instance was confirmed by review of the radiology report at diagnosis, and the evolution of each PVT over time was assessed via review of subsequent radiology reports.

Patients were excluded if they had splanchnic vein thrombosis without portal vein involvement, had cirrhosis or tumor thrombus, received interventional thrombolysis/thrombectomy, lacked baseline imaging of PVT at diagnosis, lacked subsequent follow-up

Table 1. The baseline characteristics and treatments of 330 patients with noncirrhotic portal vein thrombosis

Characteristics and treatment	n (%)
Mean age (SD), y	49.0 (15.8)
Female	172 (52)
Predisposing factors for PVT	
Intraabdominal surgery	103 (32)*
Inflammatory bowel disease	63 (19)
Intraabdominal infection	48 (15)*
Non-HCC malignancy	42 (13)
JAK2 V617F mutation	37 (11)†
Pancreatitis	21 (6)*
Estrogen-containing OCP use	14 (4)
Pregnancy	5 (2)*
Other	8 (2)
2 or more factors	70 (21)
None	90 (27)
Imaging modality at diagnosis	
Contrast-enhanced CT	281 (85)
Contrast-enhanced MRI	28 (8)
Doppler ultrasound	21 (6)
Vessel involvement	
Main PV only	87 (26)
Left and/or right PV only	76 (23)
Main PV + additional vein	167 (51)‡
Occlusivity of thrombus	
Occlusive thrombus	188 (57)
Nonocclusive thrombus	142 (43)
Anticoagulant used	
Warfarin	108 (33)
Enoxaparin	70 (21)
Rivaroxaban	65 (20)
Apixaban	20 (6)
Dabigatran	8 (2)
Fondaparinux	2 (0.3)
No anticoagulation	57 (17)
Mean duration of follow-up (SD), mo	41.6 (44.3)¶

HCC, hepatocellular carcinoma; OCP, oral contraceptive pill; PV, portal vein; PVT, portal vein thrombosis; SD, standard deviation.

*All events occurred within 3 months before diagnosis of PVT.

†Includes patients with and without concurrent myeloproliferative neoplasm.

‡Additionally involved veins included the superior mesenteric vein, splenic vein, and hepatic vein.

¶All patients were followed for at least 3 months after initiation of anticoagulation.

imaging at least 3 months after diagnosis, or seemed to have chronic rather than acute PVT (eg, had known prior history of PVT or had evidence of cavernous transformation or other radiographic features to suggest chronic PVT at the time of initial diagnosis). Patients were deemed to have cirrhosis (and were therefore excluded) if they had any previously documented clinical history of cirrhosis, if their treating physician upon presentation documented suspicion of cirrhosis, if they had clinical or laboratory findings consistent with chronic liver disease and/or chronic portal hypertension (such as otherwise unexplained ascites, liver function test abnormalities, international normalized ratio elevation, thrombocytopenia, etc), or if they had any hepatic parenchymal findings consistent with cirrhosis on initial imaging (as noted in the radiology report).

The initial long-term AC used in each instance was recorded and formed the basis for comparison across patients. In many cases, intravenous heparin was used as initial short-term (or bridging) AC, and in these instances, the first long-term AC transitioned to thereafter was considered. Changes in AC after initiation of the first long-term AC were addressed via an intent-to-treat-style analysis, wherein patients were maintained in their initial AC group regardless of subsequent changes.

At the time of PVT diagnosis, patient's age, sex, etiology of PVT, location of PVT, and degree of PVT occlusion were assessed. PVT etiology was categorized into *JAK2V617F*-mediated, other known etiology, or unknown/idiopathic etiology. Location of PVT was defined as being located in the main PV only, in the left or right PV only, or involving any portion of the PV with concurrent involvement of additional splanchnic vessels. Degree of PVT occlusion was determined by the radiology report at diagnosis. Patients were followed from time of diagnosis until the end of the study period or until they were lost to follow-up within our health system.

The primary outcome was the rate of complete radiographic resolution (CRR) of PVT established on follow-up imaging. Secondary outcomes included recanalization (with or without complete resolution) of occlusive PVT, development of cavernous transformation of the PV, development of new chronic portal hypertensive symptoms (cPHS, defined as new varices demonstrated on EGD or new ascites requiring diuretic medications), and major (World Health Organization grade 3 or 4) bleeding. All radiologic outcomes (CRR, recanalization, cavernous transformation) were based on retrospective reviews of relevant imaging reports conducted by the study investigators. Radiology reports at our institution are standardized with respect to the reporting of patency and other characteristics of the portal vasculature. All reviewed radiology reports for included patients made explicit mention of the state of the portal vasculature, including patency of portal vessels, presence of residual thrombus, and presence/absence of cavernous transformation. In addition to comparing the above outcomes across ACs, outcomes were also compared across etiologies for PVT.

Statistical Methods

Continuous patient-, disease-, and treatment-related variables were summarized by the median and interquartile range, whereas categorical variables were summarized by n (%). Distributions of continuous and categorical variables were compared across type of AC, using the Fisher's exact test and Kruskal-Wallis test, respectively. DOACs were included in comparisons both as an aggregate group and individually. Comparisons were performed twice: first including patients who did not receive AC and then only including patients who received AC.

The Kaplan-Meier method was used to estimate the median times to event for the outcomes of CRR, recanalization, development of cavernous transformation, development of cPHS, and major bleeding events, with corresponding 95% confidence intervals (95% CIs) constructed based on the method of Brookmeyer and Crowley.[17]

Table 2. Baseline characteristics by anticoagulant used

Variable	No anticoagulant (n = 57)	Warfarin (n = 108)	Enoxaparin (n = 70)	DOAC (n = 93)	*P*
Age mean (SD), y	45.3 (16.8)	50.4 (14.8)	51.4 (16.9)	47.1 (15.2)	.5308
Sex, n (%)					.2816
Male	27 (47.4)	57 (52.8)	27 (38.6)	47 (50.5)	
Female	30 (52.6)	51 (47.2)	43 (61.4)	46 (49.5)	
Mean year of diagnosis (SD), y	2014 (4.9)	2013 (5.2)	2015 (4.1)	2017 (2.3)	<.0001
Time to start of AC from diagnosis, mean (SD), d	NA	2.4 (5.79)	1.6 (3.5)	4.0 (9.1)	.0611
Duration of follow-up, mean (SD), mo	47.9 (24.6)	55.8 (27.4)	33.0 (18.9)	28.1 (11.3)	<.0001
Imaging studies per year of follow-up mean (SD)	2.47 (1.2)	2.74 (0.8)	2.93 (1.3)	2.67 (1.1)	.1170
Etiology, n (%)					.0010
IBD	2 (3.5)	6 (5.6)	3 (4.3)	6 (6.5)	
IBD + surgery*	1 (1.8)	13 (12.0)	5 (7.1)	13 (14.0)	
Intraabdominal infection*	4 (7.0)	9 (8.3)	5 (7.1)	5 (5.4)	
JAK2V617 mutation	9 (15.8)	15 (13.9)	5 (7.1)	7 (7.5)	
Multiple	4 (7.0)	6 (5.6)	19 (27.1)	9 (9.7)	
Non-HCC malignancy	2 (3.5)	2 (1.9))	10 (14.3)	5 (5.4)	
OCP use	0 (0.0)	2 (1.9)	4 (5.7)	6 (6.5)	
Other	2 (3.5)	3 (2.8)	2 (2.9)	1 (1.1)	
Pancreatitis*	1 (1.8)	4 (3.7)	2 (2.9)	5 (5.4)	
Pregnancy*	0 (0.0)	0 (0.0)	2 (2.9)	2 (2.2)	
Surgery*	5 (8.8)	13 (12.0)	5 (7.1)	15 (16.1)	
Unknown/idiopathic	27 (47.4)	35 (32.4)	8 (11.4)	19 (20.4)	
Location of PVT, n (%)					.9064
Main PV only	22 (38.6)	28 (25.9)	15 (21.4)	22 (23.7)	
Left or right PV only	11 (19.3)	23 (21.3)	19 (27.1)	23 (24.7)	
Main PV + additional SVT	24 (42.1)	57 (52.8)	36 (51.4)	48 (51.6)	
Degree of PV occlusion, n (%)†					.3057
Occlusive	29 (50.9)	68 (63.0)	36 (51.4)	53 (57.0)	
Nonocclusive	28 (49.1)	40 (37.0)	34 (48.6)	40 (43.0)	

AC, anticoagulation; IBD, inflammatory bowel disease; NA, not available; SVT, splanchnic vein thrombosis.
*All events occurred within 3 months before diagnosis of PVT.
†Degree of occlusion determined via radiology report at diagnosis. Note that 2 patients were treated with fondaparinux and are not included in this table.

Comparisons of time-to-event distributions among the different ACs were made with the log-rank test. Multivariable Cox proportional hazards models were performed to estimate adjusted hazard ratios (HRs) with their corresponding 95% CIs. The multivariable models controlled for age, sex, etiology of PVT, location/extent of PVT, and occlusivity of PVT. To note, an HR >1 was deemed favorable for the desired outcomes of CRR and recanalization, whereas an HR >1 was deemed unfavorable for the adverse outcomes of cavernous transformation, cPHS, and major bleeding. Using the same models, we were able to perform pairwise comparisons among the different AC types, along with different etiologies of PVT for all the outcomes. Hypothesis testing was 2-sided and conducted at the 5% level of significance. All statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, NC).

Results

We identified 1094 patients carrying an ICD designation for PVT during the study period. A total of 764 of these patients were excluded for reasons outlined in Figure 1. The remaining 330 patients met all inclusion criteria. Their characteristics and treatments are described in Table 1. There were a variety of predisposing factors for PVT within this cohort. Of note, 27% of patients (n = 90) had no evident predisposing factor. Sixty-five percent of patients (n = 213) had some thrombophilia testing sent (before, at the time of, or after diagnosis of PVT). Thrombophilia testing was not standardized across patients. The most common positive test was *JAK2V617F*, which was present in 37 patients (23 of whom had evidence of a concurrent myeloproliferative neoplasm [MPN]). No patients with MPN lacking *JAK2V617F* were identified (there were no cases of *CALR*-mutated, *MPL*-mutated, or triple-negative MPN, nor were there any non-MPN patients harboring *CALR* or *MPL* mutations). Other relevant findings of thrombophilia testing included prothrombin gene mutation (n = 12), factor V Leiden (n = 11), protein S deficiency (n = 4), protein C deficiency (n = 3), paroxysmal nocturnal hemoglobinuria (n = 2), and consistently positive anti-phospholipid antibodies (n = 2). Sixty percent of patients (n = 198) were symptomatic of acute PVT at diagnosis, with the most common symptoms being abdominal pain.

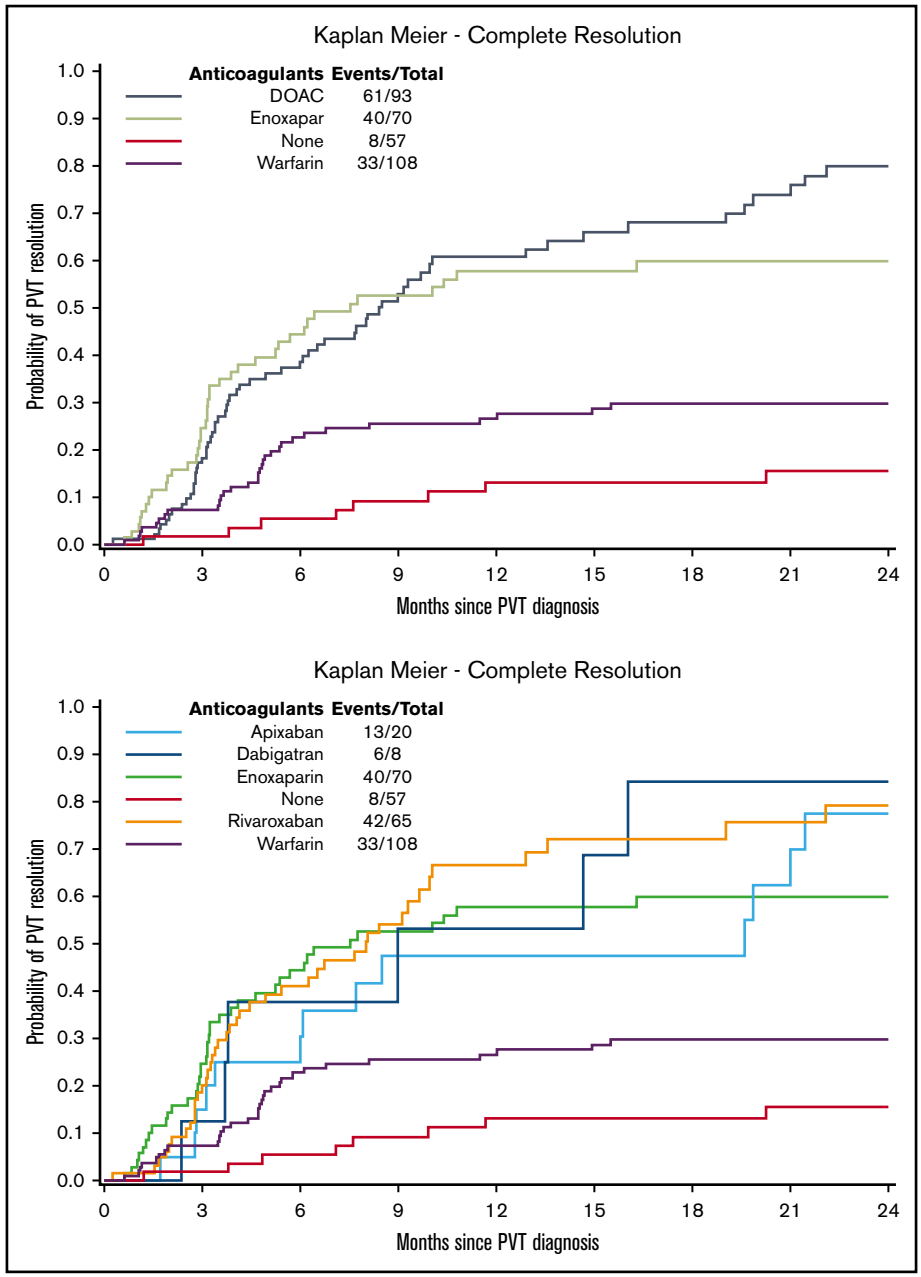

Figure 2. Complete radiographic resolution (CRR) of PVT compared across anticoagulants. The Kaplan-Meier curves depicted in the top panel demonstrate CRR rates across anticoagulants with all DOACs aggregated into a single group. The Kaplan-Meier curves depicted in the bottom panel demonstrate CRR rates across anticoagulants, with each DOAC shown individually.

A wide variety of ACs were used. Although the most commonly used ACs were the standard therapies of warfarin (n = 108) and enoxaparin (n = 70), many patients received DOACs (n = 93), most often rivaroxaban (n = 65). About 17% (n = 57) of patients received no AC. The baseline characteristics of all patients stratified by AC are shown in Table 2. Four percent of patients (n = 14) had a change in anticoagulation during follow-up, though only 2 of these changes occurred in the first 3 months of therapy and only 8 in the first year (all patients were maintained in their initial AC group for analysis, as described in the Methods). All patients completed at least 3 months of AC. Forty-four percent of anticoagulated patients (119/273) eventually discontinued AC during follow-up, with the most common reasons for discontinuation being resolution of PVT (n = 83) and bleeding (n = 21). Overall, the mean time to initiation of AC after diagnosis was 3.1 days (median, 0 days). Mean duration of follow-up was 41.6 months (SD, 44.3 months). Mean duration of follow-up did vary across groups, with the longest duration in the warfarin (55.8 months; SD, 27.4 months) group and the shortest in the DOAC group (28.1 months; SD, 11.3 months; Table 2). This difference in follow-up was likely in part a result of changes in AC prescribing patterns over the time frame of the study, with patients having been more likely to receive warfarin during the initial years and more likely to receive DOACs in recent years (Table 2). Among patients receiving warfarin, 62% of international normalized ratio assessments were in therapeutic range (between 2.0 and 3.0).

Figure 2 shows the primary outcome of CRR stratified by AC. CRR rates for DOACs are depicted both individually and as an aggregate group. The CRR rate was significantly higher among patients who

Table 3. Multivariable HRs relative to warfarin for CRR, recanalization, cavernous transformation, and cPHS

	Complete resolution		Recanalization		Cavernous transformation		Chronic portal hypertensive symptoms	
AC used	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Warfarin	Reference		Reference		Reference		Reference	
Apixaban	2.88 (1.50-5.54)	.0015	2.40 (1.00-5.77)	.0496	0.79 (0.28-2.23)	.6499	0.74 (0.17-3.16)	.6857
Dabigatran	4.17 (1.67-10.00)	.0022	3.03 (1.03-9.09)	.0445	0.54 (0.07-4.00)	.5496	1.05 (0.14-7.69)	.9600
DOACs (all)	2.91 (1.87-4.52)	<.0001	3.45 (1.93-6.18)	<.0001	0.68 (0.36-1.28)	.2298	0.67 (0.30-1.49)	.3284
Enoxaparin	2.23 (1.43-3.70)	.0006	1.92 (0.94-3.85)	.0714	1.05 (0.58-1.92)	.8585	1.06 (0.54-2.08)	.8572
Rivaroxaban	2.78 (1.75-4.55)	<.0001	4.35 (2.22-8.33)	<.0001	0.66 (0.31-1.39)	.2751	0.60 (0.23-1.59)	.3073
No AC	0.40 (0.18-0.89)	.0245	0.28 (0.07-1.23)	.0928	1.52 (0.89-2.56)	.1244	2.22 (1.25-3.99)	.0065

HRs (95% CIs) and *P* values from multivariable cox proportional hazards models. All HRs shown are in comparison with warfarin (ie, warfarin is the reference AC). DOACs are included both individually and combined in a single group. Note that for the outcomes CRR and recanalization, HRs >1 are favorable (as these are favorable outcomes). Note that for the outcomes cavernous transformation and cPHS, HRs >1 are unfavorable (as these are unfavorable outcomes). HRs for the secondary outcome major bleeding are not shown, as some could not be calculated because of no major bleeding events in the apixaban and dabigatran groups (all HRs that could be calculated were not statistically significant). Of note, however, when grouped in aggregate, DOACs were associated with a lower risk for major bleeding relative to warfarin (HR, 0.20, 95% CI, 0.05-0.86; $P = .0307$).

received AC (49%) than those who did not (14%; $P < .0001$). Among anticoagulated patients, those who received DOACs had the highest rates of CRR (61/93 = 66%). Enoxaparin had a CRR rate (40/70 = 57%) not significantly different than that of the DOACs ($P = .4248$). Compared with warfarin with a CRR of 31% (33/108), all other ACs were associated with a higher likelihood of CRR as reflected in their adjusted HRs; DOACs (HR 2.91, 95% CI 1.87, 4.52; $P < .0001$), enoxaparin (HR 2.23, 95% CI 1.43, 3.70; $P = .0006$). Each individual DOAC was also associated with higher CRR rates relative to warfarin (see Table 3). Among those patients with concurrent thrombosis of other splanchnic vessels, CRR of the PV always coincided with CRR of any other concurrent SVT.

Out of the 330 patients, 188 or 57.0% had an occlusive PVT at baseline, and thus could be evaluated for recanalization. Findings regarding recanalization across ACs were similar to those regarding CRR across ACs, as demonstrated in Figure 3. The recanalization rate of occlusive PVT was significantly higher among those patients who received AC (44%) than those who did not (7%; $P = .0004$). The DOACs were associated with recanalization rates similar to that of enoxaparin and greater than that of warfarin (HR DOACs: warfarin 3.45, 95% CI 1.93, 6.18; $P < .0001$). Warfarin was associated with lower recanalization rates relative to each individual DOAC (Table 3). Once again, among those patients with concurrent occlusive thrombosis of other splanchnic vessels, recanalization of the PV always coincided with recanalization of any other concurrent occlusive SVT.

Findings regarding cavernous transformation of the PV, a radiographic surrogate for transformation from acute to chronic PVT, are shown in Figure 4. Cavernous transformation rate was lower among those patients who received AC (27%) than among those who did not (54%) ($P = .0057$). Although the DOACs were associated with lower absolute rates of cavernous transformation relative to enoxaparin and warfarin, these HRs did not attain statistical significance (as cavernous transformation was a relatively rare outcome, particularly among patients on DOACs; Table 3).

Development of cPHS (defined as varices found on EGD or new ascites requiring diuretics) occurred in 19% of patients who received AC and 53% of patients who did not receive AC ($P < .0001$; Figure 5). Although there was a trend toward less cPHS among those receiving DOACs compared with those receiving enoxaparin or warfarin (DOACs 8/93 = 9%, enoxaparin 13/70 = 19%, warfarin 31/108 = 29%), these difference were not statistically significant on multivariable analysis (Table 3).

Recurrence of SVT was rare in this cohort, occurring in only 9/330 (2.7%) of patients. Recurrence was not found to be associated with any particular variable, including type of AC. As an aggregate group, DOACs were associated with a lower risk for major bleeding relative to warfarin (HR DOACs:warfarin 0.20, 95% CI, 0.05-0.86; $P = .0307$; Figure 6). However, when each DOAC was considered individually, there were no significant differences in major bleeding rates across anticoagulants. Twelve patients (3.6%) died during follow-up and mortality did not significantly differ across groups. Three of these deaths were related to PVT. In 1 of these instances recurrent portomesenteric thrombosis prompted subsequent gut ischemia resulting in fatal septic shock (this patient had been on enoxaparin). In the second, a patient who developed portal hypertension after unresolved PVT suffered a fatal variceal bleed (this patient had never been anticoagulated). The third died due to complications of liver failure, the result of noncirrhotic portal hypertension arising due to unresolved PVT (this patient had previously received warfarin). Of note, this study excluded all patients with less than 3 months follow-up, and thus patients who may have died of acute complications of their initial PVT would not have been included. Patients who received thrombectomy or thrombolysis were also excluded from this study, thus we have no data regarding this group. Twenty-four of the 104 patients (23%) who developed cPHS went on to receive a transjugular intrahepatic portosystemic shunt (TIPS). The frequency of TIPS did not differ significantly among groups.

Among the covariates taken into consideration during multivariable analysis, predisposing factor for PVT had the greatest impact on outcomes. Specifically, patients harboring *JAK2V617F*, and to a lesser extent those with no evident predisposing factor for PVT, had significantly worse outcomes than those with any other known predisposing factors for PVT. *JAK2V617F* positive patients demonstrated a CRR rate of 8% compared with 55% among those with any other evident predisposing factor ($P = .0016$), and they fared poorly with respect to secondary outcomes as well (recanalization 17% vs 49% $P = .0036$; development of cPHS

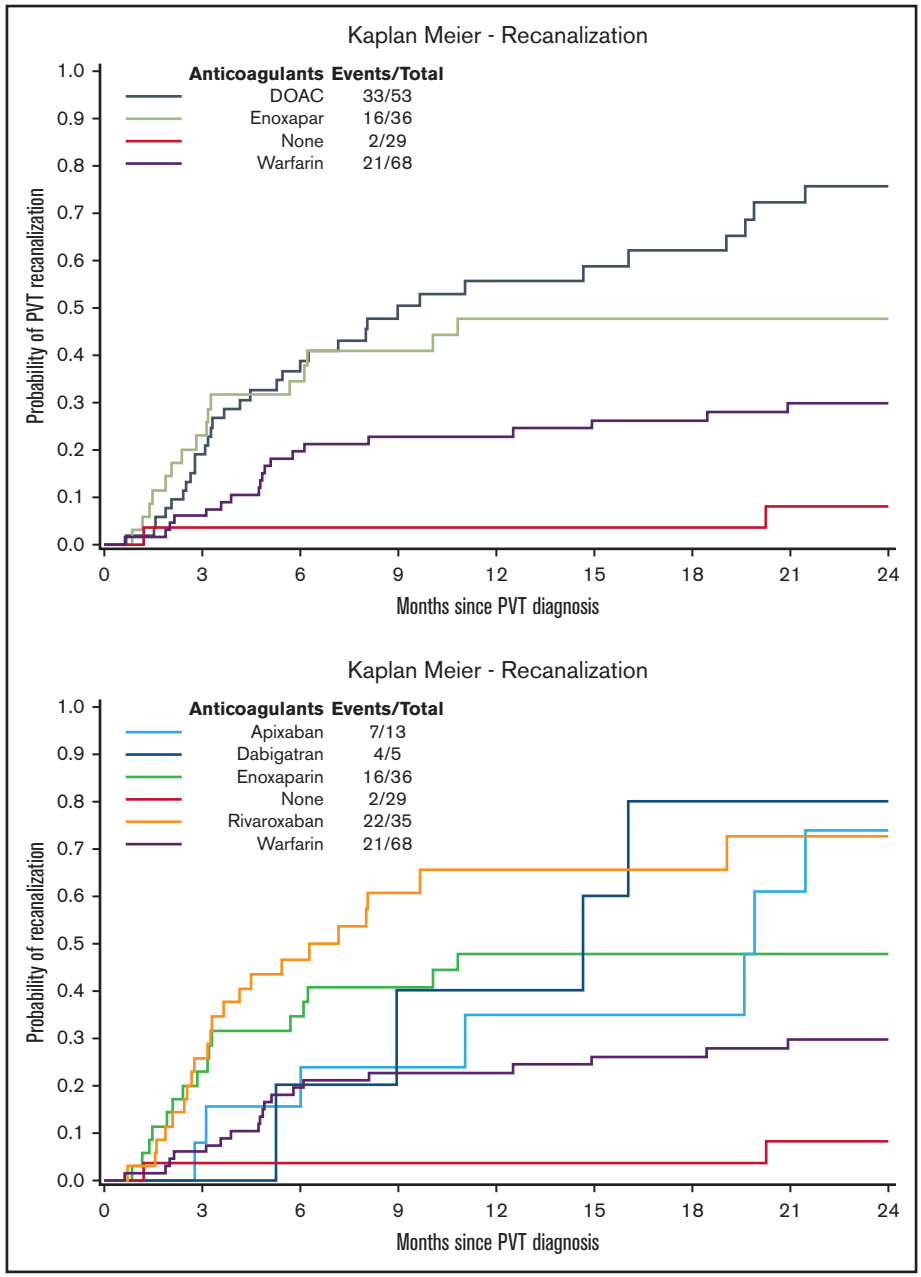

Figure 3. Recanalization of occlusive PVT compared across anticoagulants. The Kaplan-Meier curves depicted in the top panel demonstrate recanalization rates across anticoagulants, with all DOACs aggregated into a single group. The Kaplan-Meier curves depicted in the bottom panel demonstrate recanalization rates across anticoagulants, with each DOAC shown individually.

49% vs 17% $P = .5492$). The 90 patients with no evident predisposing factor also demonstrated worse outcomes compared with those with evident non-JAK2 predisposing factors (CRR 31% vs 55% ($P = .0152$); recanalization 32% vs 49% ($P = .0896$); development of cPHS 32% vs 17% ($P = .7406$)).

Among other notable covariates, patients whose PVTs were confined to branch portal veins only (without main PV involvement) tended toward better outcomes when compared with those with thrombosis of the main PV with regard to CRR (HR 1.83 95% CI 1.15, 2.91; $P = .0112$), recanalization (HR 2.58 95% CI 1.56, 5.76; $P = .0203$), cavernous transformation (HR, 0.18 95% CI, 0.06-0.50; $P = .0012$), and cPHS (HR, 0.72; 95% CI, 0.33, 1.58; $P = .4065$). Involvement of additional splanchnic vessels (besides only the PV itself) did not significantly influence outcomes. In the multivariable analysis, patients with fully occlusive PVT were more likely to have worse outcomes than patients with non-occlusive PVT for CRR, cavernous transformation, and cPHS; HR, 0.42; 95% CI, 0.29-0.61; $P < .0001$; HR 2.28 95% CI 1.43, 3.63; $P = .0005$, and HR 1.78 95% CI 1.08, 2.94; $P = .0248$, respectively.

Discussion

The use of DOACs for the treatment of PVT (and other SVT) remains contentious.[14] This controversy has its roots in the foundational clinical trials which established the use of DOACs for PE/DVT, as they included no patients with any type of SVT.[10-13] A decade after their publication data remain sparse and composed largely of individual case reports and limited case series.[14-16] As a result, professional society guidelines and published expert

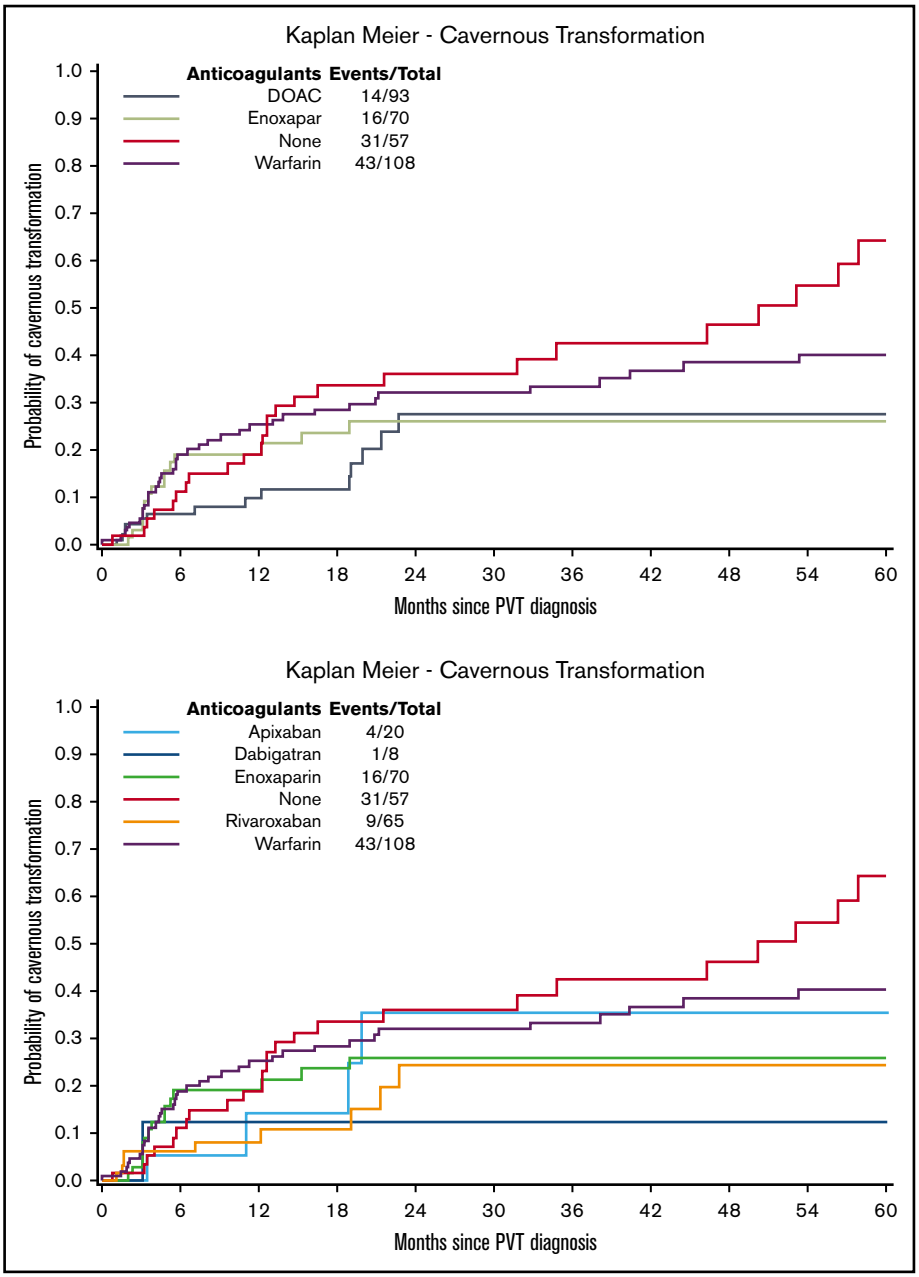

Figure 4. Cavernous transformation of the PV compared across anticoagulants. The Kaplan-Meier curves depicted in the top panel demonstrate cavernous transformation rates across anticoagulants with all DOACs aggregated into a single group. The Kaplan-Meier curves depicted in the bottom panel demonstrate cavernous transformation rates across anticoagulants, with each DOAC shown individually.

opinions have remained conservative regarding the use of DOACs in this setting, advising continued reliance on VKAs or LMWHs.[7-9]

This is by far the largest and most thorough study to assess the efficacy and safety of DOACs in PVT (or in any form of SVT), and the first to compare outcomes in PVT across anticoagulants. Among our retrospective cohort of 330 patients with acute ncPVT, each of the DOACs studied (apixaban, dabigatran, and rivaroxaban) were associated with similar results relative to enoxaparin, and associated with improved results relative to warfarin, with regard to the primary outcome of CRR of PVT. Each of the DOACs were also associated with improved results relative to warfarin with respect to the secondary outcome of recanalization of occlusive PVT (rivaroxaban was associated with higher recanalization rates relative to enoxaparin as well). Although the multivariable HRs across ACs were generally not significant with respect to our other secondary outcomes (including development of cavernous transformation of the PV and cPHS), the trends generally favored the DOACs. With regard to safety, there was no significant difference in major bleeding events across individual ACs (although as an aggregate group the DOACs were associated with less major bleeding than warfarin). Interestingly, each of the ACs trended toward a lower bleeding rate than no AC (with DOACs demonstrating the lowest bleeding rates of all). This was possibly due to lower rates of development of ncPH (and therefor a lower incidence of new varices and/or hepatic dysfunction) among anticoagulated patients.

Although the demonstrated efficacy and safety of DOACs in ncPVT are perhaps this study's most salient finding, just as striking are the relatively poor outcomes associated with warfarin (in comparison

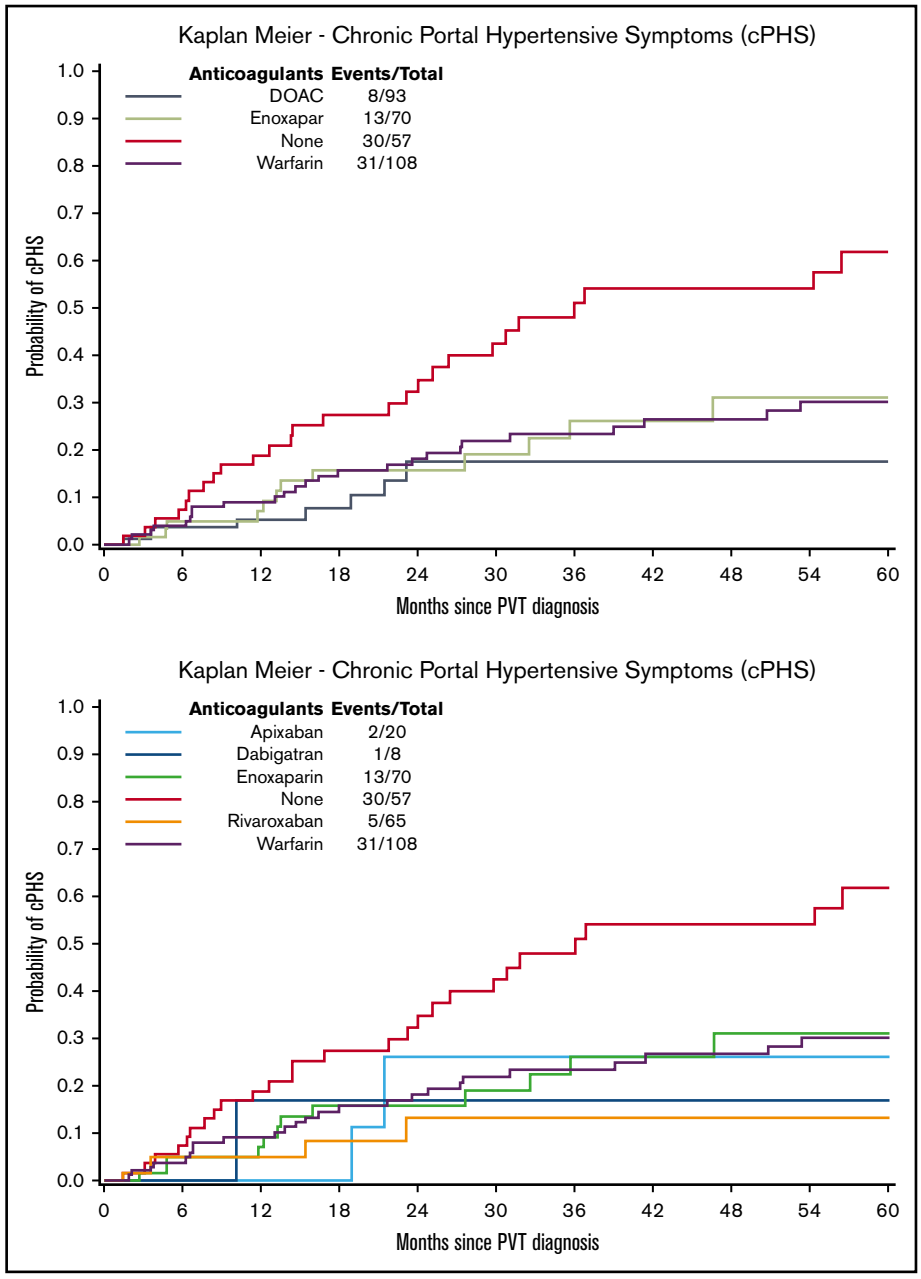

Figure 5. Development of cPHS compared across anticoagulants. The Kaplan-Meier curves depicted in the top panel demonstrate rates of development of cPHS across anticoagulants with all DOACs aggregated into a single group. The Kaplan-Meier curves depicted in the bottom panel demonstrate rates of development of cPHS across anticoagulants, with each DOAC shown individually.

with both DOACs and enoxaparin). It is not immediately clear why warfarin, long one of the standard therapies for SVT, should prove inferior to other ACs. Therapeutic drug monitoring of warfarin was neither standardized nor consistently documented among the patients in this cohort. However our finding that 62% of available international normalized ratio measurements were in a therapeutic range that is consistent with the findings in large prospective trials comparing warfarin and DOACs across a variety of indications.[18,19] There are a number of non-SVT studies, both retrospective and prospective, investigating both therapeutic and prophylactic AC, in which DOACs have demonstrated either frank superiority or a trend toward superiority, relative to warfarin.[12,20-27] It is conceivable that the relatively marginal differences in efficacy noted in these studies are magnified in the setting of PVT, in which the baseline AC failure rate is much higher than in other DVTs or in the prophylactic setting. Importantly, it is known from prior studies that that earlier initiation of therapeutic AC may improve outcomes in PVT.[28] Warfarin blood levels are often at their most labile during the initial weeks of therapy, when dosage is being frequently adjusted.[29] Thus, patients receiving warfarin may be suboptimally anticoagulated during the early phase of therapy, the phase that may be the most crucial in ensuring desirable long-term outcomes. In contrast, DOACs usually reach therapeutic blood levels early, reliably, and typically without need for dose adjustment.

Failure rates for resolution and recanalization of PVT are starkly high compared with rates of such outcomes in more common forms of venous thromboembolism.[30] In our study, even with AC, CRR of any PVT and recanalization of occlusive PVT were achieved in only 49% and 44% of patients, respectively (although somewhat higher when

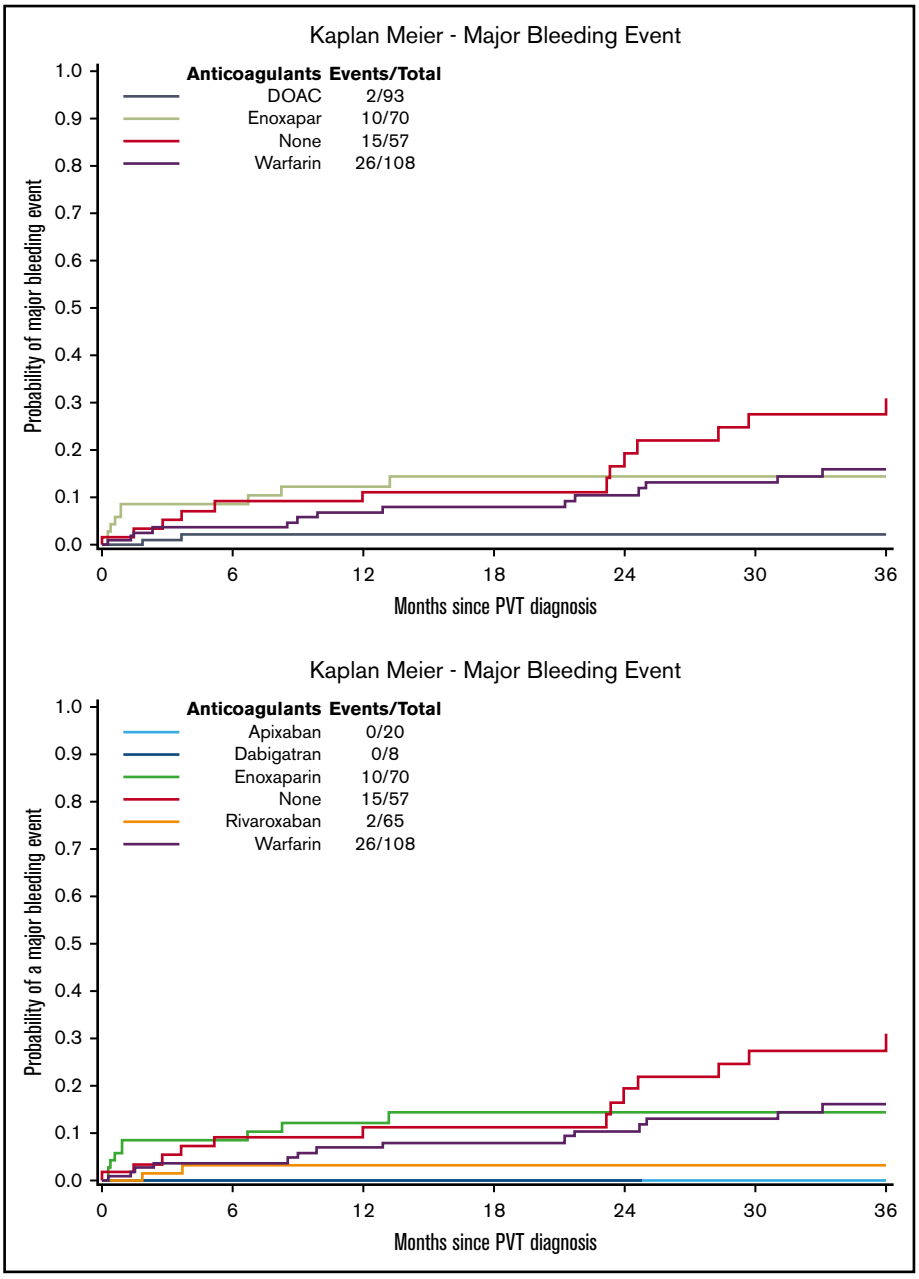

Figure 6. Major (World Health Organization grade 3 or 4) bleeding events compared across anticoagulants. The Kaplan-Meier curves depicted in the top panel demonstrate rates of major bleeding events across anticoagulants with all DOACs aggregated into a single group. The Kaplan-Meier curves depicted in the bottom panel demonstrate rates of major bleeding events across anticoagulants, with each DOAC shown individually.

excluding warfarin). These figures are comparable with outcomes reported in previous studies of PVT.[28,31,32] In addition, although AC was clearly effective in reducing the risk for chronic portal hypertension, nearly a fifth of anticoagulated patients still went on to develop cPHS during follow-up. Outcomes among certain subgroups, most notably those harboring *JAK2V617F* (CRR, 11%; recanalization, 21%; cPHS, 43% among those who received AC) were particularly poor. Given these underwhelming outcomes with AC alone, consideration should be given to early thrombolysis (in addition to AC) among those patients at greatest risk for recalcitrant PVT (specifically those with *JAK2V617F*, those with no evident predisposing factor for PVT, and those with occlusive thrombus).

This is of course not to discount the importance of AC, which although imperfect, was associated with significant benefit across outcomes (including triple the rate of CRR, a greater than 6-fold increase in recanalization rate, and a reduction of cPHS by nearly two-thirds). Professional society guidelines currently recommend using AC only for symptomatic SVT, and withholding AC for "incidentally detected SVT."[7] We note that a large proportion of patients in this cohort were asymptomatic at presentation (a characteristic common to other studies), and nearly all PVTs were detected "incidentally" (that is to say, SVT was rarely, if ever, atop the differential diagnosis before imaging).[33] With this in mind, and given the high likelihood of adverse long-term outcomes without AC, we would recommend AC (preferably with a DOAC or LMWH) for all patients with acute ncPVT deemed able to tolerate it, regardless of whether they were asymptomatic at diagnosis or whether their diagnosis was made "incidentally." AC was instituted early among this cohort (mean 3.1 days after diagnosis), as prior

studies have demonstrated that delays in AC may lead to inferior outcomes, and that resolution and recanalization with AC become highly unlikely in the chronic phase.[28]

Although compelling in its findings, this study does have some notable limitations. Certainly, its retrospective nature introduces a number of biases, most importantly that physician choice of AC may have been influenced by unknown and uncontrolled variables. Indeed, it is impossible to adjust for all possible confounding variables in such a study, and this sort of comparison has a great likelihood of selection bias. Given the observational nature of our data, we are limited in the definitive conclusions that can be drawn regarding the relative safety and efficacy across anticoagulants. Hopefully, however, the findings presented here may help motivate the performance of a randomized controlled trial. The nature and timing of follow-up imaging was not standardized across patients, with some patients receiving follow-up scans at frequent and regular interval, and others waiting long periods of time before their first follow-up imaging. This somewhat limits any conclusions that might be drawn about time to resolution of PVT. Indeed, many resolution and/or recanalization events noted more than a year after initiation of AC may have (and likely did) occur much earlier, but were documented in a delayed manner of because of the delayed follow-up imaging. In addition, we were unable to control for changes in AC prescribing patterns over the time frame of the study. Patients were more likely to receive warfarin during the initial years of the study, and more likely to receive DOACs in recent years. It is conceivable that this temporal bias may have affected our outcomes. Finally, given the retrospective nature of the study, it is possible that certain adverse events, most notably bleeding events, may have been missed, and therefore been underreported. Strengths of this study include the large number of patients included, strict inclusion criteria, long follow-up times, and robust statistical analysis.

This study should help establish the role of DOACs in the treatment of ncPVT. Given that more than half of the patients in this cohort had concurrent thrombosis of at least 1 other splanchnic vessel, our conclusions can likely be generalized to all ncSVT. These findings further the ongoing trend toward expanding the indications for DOACs across subtypes of venous thromboembolism, most recently exemplified by evidence favoring their use in cancer-associated thrombosis, cerebral venous thrombosis, and among morbidly obese patients.[34-38] Long-term outcomes among patients with ncPVT remain somewhat disappointing, and future studies should investigate the role of early thrombolysis and/or thrombectomy (in addition to AC), particularly among those patient groups most recalcitrant to AC alone (those with *JAK2V617F*, those with no evident predisposing factor for PVT, and those with occlusive thrombus at diagnosis).

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Authorship

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