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Letter to the Editors-in-Chief

Efficacy and safety of direct oral anticoagulant therapy for the treatment of venous thromboembolism in patients with chronic liver disease

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1. Introduction

The appropriate use of anticoagulation therapy in patients with liver disease poses a significant challenge to healthcare providers. Previously, patients diagnosed with chronic liver disease (CLD) were considered "auto-anticoagulated" as was evident by an elevation in the prothrombin time and thrombocytopenia secondary to hepatic dysfunction [1]. However more recent findings suggest that these patients are at an increased risk of developing venous thromboembolism (VTE) when compared to the general population [2]. As the severity of CLD progresses, the fibrotic deposition of scar tissue slowly replaces the presence of normal liver parenchyma. Consequently, the resulting lack of healthy hepatocytes leads to impaired synthesis of several clotting factors and an imbalance in hemostasis [3,4].

Current guidelines do not address the thromboembolic risk associated with CLD, and lack specific recommendations for the treatment of VTE. The 2016 CHEST guidelines for Antithrombotic Therapy for VTE Disease recommend direct oral anticoagulants (DOACs) over vitamin K antagonists (VKA) for treatment of DVT or PE in all patients without cancer [5]. The use of vitamin K antagonists, such as warfarin, can be problematic in the CLD patient population due to alterations in coagulation assays caused by liver disease itself. DOACs provide a potential alternative to warfarin therapy. However, initial approval trials omitted CLD patients resulting in subsequent package labeling recommending caution or complete omission in patients with liver disease. Despite the potential advantages of DOACs over warfarin, the efficacy and safety in patients with CLD has not been well established. The objective of this study was to evaluate the efficacy and safety of DOAC therapy in patients with CLD in the treatment of VTE.

2. Materials and methods

This was an Institutional Review Board approved single center retrospective study performed at Wake Forest Baptist Medical Center. The study population was identified using a retrospective data extraction from the electronic medical record via International Classification of Disease (ICD) 9/10 codes of patients admitted to from January 1, 2013 through June 2018. Patients at least 18 years of age diagnosed with an acute pulmonary embolism (PE), deep vein thrombosis (DVT), or portal vein thrombosis (PVT) treated with dabigatran, apixaban, rivaroxaban, edoxaban, or warfarin, with a concomitant diagnosis of liver disease were included for analysis. A diagnosis of CLD was confirmed via radiographic imaging (abdominal ultrasound, computed tomography of the abdomen). Patients were stratified based on the receipt of DOAC or warfarin. Patients receiving anticoagulation prior to the index VTE or receiving anticoagulation for an indication other than VTE were excluded.

Baseline demographics, laboratory values and pertinent characteristics were collected for all patients. Additionally, the use of parenteral therapies and medications effecting the risk of VTE and hemorrhage were also reviewed. The primary outcome was the rate of recurrent VTE at 3 months. Secondary outcomes included major bleeding and non-major bleeding requiring hospitalization. Major bleeding was defined as fatal bleeding, bleeding into a critical organ, bleeding requiring a transfusion of at least 2 units of packed red blood cells, or a fall in hemoglobin of at least 2 g/deciliter. Bleeding was further categorized as gastrointestinal or intracranial hemorrhage where appropriate. Outcomes were assessed and adjudicated by the authors via manual chart review evaluating provider notes, pertinent imaging and laboratory values.

Statistical analysis was performed using SPSS v.25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were assessed using the chi square or Fisher's exact test where appropriate. Continuous variables were analyzed using the Mann-Whitney test. All tests of significance were two-tailed and a p value ≤ 0.05 was considered statistically significant. A stepwise multivariate logistic regression was performed to identify predictors of DOAC utilization. Missing data was excluded from analysis.

3. Results

One hundred nine patients with a history of CLD receiving treatment with oral anticoagulation for an acute VTE were included for analysis. Eighty-two patients received treatment with warfarin therapy while 27 patients received treatment with a DOAC. Rivaroxaban (n = 12) and apixaban (n = 12) were the most commonly prescribed DOAC followed by dabigatran (n = 3).

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Table 1
Baseline patient characteristics.

	Warfarin n = 82	DOAC n = 27	*p*-Value
Age	55 (50–64)	60 (53–62)	0.12
Male	54 (65.9)	15 (55.6)	0.34
BMI	26.5 (23.5–32.9)	31.1 (24.3–37.3)	0.06
Race			
Caucasian	64 (78)	20 (74.1)	0.79
African American	11 (13.4)	7 (25.9)	0.14
Other	7 (8.5)	0	0.19
Heart failure	23 (28)	2 (7.4)	0.03
CKD	20 (24.4)	2 (7.4)	0.09
History of VTE	39 (47.6)	9 (33.3)	0.2
DM (%)	35 (42.7)	9 (33.3)	0.39
Malignancy	22 (26.8)	7 (25.9)	0.93
Hypercoagulable state	39 (47.6)	12 (44.4)	0.78
Ascites	46 (56.1)	11 (40.7)	0.17
Esophageal varices	17 (20.7)	3 (11.1)	0.39
Etiology of cirrhosis			
Alcohol	18 (22)	5 (18.5)	0.79
Viral	26 (31.7)	8 (29.6)	1
NASH	10 (12.2)	5 (18.5)	0.52
Autoimmune	1 (1.2)	0	1
Other	27 (32.9)	9 (33.3)	0.81
Platelet count	167 (96–219)	152 (84–252)	0.71
INR	1.3 (1.1–1.6)	1.2 (1.1–1.5)	0.68
Creatinine	0.94 (0.75–1.31)	0.72 (0.6–0.95)	0.003
AST	34 (25–58)	39 (22–53)	0.62
ALT	24 (15–40)	39 (12–56)	0.29
Total bilirubin	1 (0.5–1.8)	0.8 (0.5–1.2)	0.15
Albumin	2.9 (2.6–3.5)	3.4 (2.4–3.8)	0.21
Meld	16 (9–24)	10.5 (8–20)	0.16
Child Pugh			
A	18 (22)	11 (40.7)	0.06
B	49 (59.7)	16 (59.3)	0.96
C	15 (18.3)	0	0.02
Index VTE DVT	41 (50)	9 (33.3)	0.13
Index VTE PE	21 (25.6)	10 (37)	0.25
Index VTE PVT	20 (24.4)	8 (29.6)	0.59
Parenteral anticoagulation	74 (90.2)	14 (51.9)	< 0.001
Antiplatelet at discharge	18 (22)	6 (22.2)	0.98
Acid suppression at discharge	49 (59.8)	12 (44.4)	0.17

Values are expressed as median (interquartile range).

Baseline patient characteristics are shown in Table 1. Alcohol and viral infection were the most common etiologies of liver disease. More patients receiving warfarin therapy had a history of heart failure (28% vs 7.4% $p = 0.034$) and a higher serum creatinine (0.94 vs 0.72 $p = 0.003$) at initiation of therapy than patients on DOAC therapy. Patients receiving DOACs had significantly better liver function based on Child Pugh classification, however no significant difference in MELD score was identified between the two groups. There was no significant difference in index VTE category between groups. Lastly, more patients receiving warfarin therapy were treated with parenteral anticoagulation (90.2% vs 51.9% $p < 0.001$).

Recurrent VTE occurred in 10 (12.2%) patients receiving treatment with warfarin and 3 (11.1%) of patients treated with DOAC therapy at 3 months ($p = 1$). Additionally, no difference was identified in the rate of individual VTE endpoints between groups (Table 2). Eleven (13.4%) patients in the warfarin group experienced a major bleed compared to 2 (7.4%) of patients receiving DOAC therapy ($p = 0.51$). Within the warfarin group two patients experienced an intracranial hemorrhage. A significant difference was not identified in the rate of hospital admission for non-major bleeding events (8.1% vs. 2.3% $p = 0.3$). Only a history of heart failure was identified as an independent predictor of warfarin use (OR 0.211 CI: 0.045–0.983).

4. Discussion

The safe and effective use of DOACs could serve as a panacea for thrombotic complications in patients with CLD. However, initial reports

Table 2
Patient outcomes.

	Warfarin n = 82	DOAC n = 27	*p*-Value
Recurrent VTE at 3 months	10 (12.2)	3 (11.1)	1
Recurrent DVT	4 (40)	1 (33.3)	1
Recurrent PE	4 (40)	2 (66.7)	0.64
Recurrent PVT	2 (20)	0	1
Major bleeding	11 (13.4)	2 (7.4)	0.51
Fatal bleeding	0	0	NA
Transfusion ≥2 units	2 (18.2)	1 (33.3)	1
Drop in hgb ≥2 units	2 (18.2)	2 (66.7)	0.26
Gastrointestinal bleeding	8 (73)	1 (33.3)	1
Intracranial hemorrhage	2 (18.2)	0	1
Admission for non-major bleeding event	5 (6.1)	1 (3.7)	1

Values are expressed as median (interquartile range).

of rivaroxaban induced hepatotoxicity impeded early adaptation of DOAC therapy in this population [6]. Recently, small trials and individual case reports have showcased the potential of DOAC therapy in patients with CLD. To date, all published trials have been comprised of mixed patient populations, with populations of VTE treatment and stroke prevention in atrial fibrillation included. Interestingly, the majority of patients studied utilized rivaroxaban or apixaban, with very few using dabigatran and no patient receiving edoxaban or betrixaban [1,7–10]. Of the two retrospective analyses available for review, one focused entirely on bleeding events and reported no difference in bleeding rates between the traditional anticoagulation and DOAC groups (16% and 20%, respectively, $p = 0.9$) [1]. The remaining trial monitored for safety and efficacy over 3 years; however, only 1 thrombotic event was reported. As such, a large gap remains in understanding the role for DOACs in preventing recurrent thrombotic events in this complicated patient population [10].

Here, we report the largest single center analysis to solely include CLD patients with a known thrombotic event requiring therapeutic anticoagulation. This focused analysis revealed no statistical difference in recurrent VTE or major bleeding events, substantiating the aforementioned research. Patients with heart failure were more likely to receive warfarin, suggesting provider comfort with warfarin in patients with organ dysfunction. Likewise, the lack of an FDA approved targeted Xa reversal agent during the study period may have also contributed to prescriber hesitation in patients at an increased risk for bleeding complications.

Cautionary use of DOAC therapy in patients with chronic organ dysfunction is not a novel concept and prescribing patterns were recently elucidated by data published from the Vascular Liver Disease Interest Group (VALDIG) Consortium. The VALDIG Consortium surveyed 50 member centers to garner prescribing patters seen with DOAC therapy in cirrhosis or splanchnic vein thrombosis. Data was provided from 45 centers and compared DOAC use in patients with and without cirrhosis. Not surprisingly, providers reported switching patients from VKA to DOAC therapy due to INR instability, improved patient comfort, and elimination of routine monitoring. Patients prescribed anticoagulation in this consortium had no difference in baseline hepatic or renal function. Importantly cirrhotic patients receiving DOAC therapy were prescribed a reduced dose, underscoring prescriber hesitation in utilization of DOACs in CLD. In addition to receipt of a reduced dose, patients experiencing complications during DOAC therapy are less likely to have a DOAC resumed, as shown by a recent 2017 retrospective analysis [9].

Similar to the current report, Hum et al. demonstrated no statistically significant difference in safety or treatment failure when comparing DOAC to traditional anticoagulation (LMWH or VKA) in patients with chronic liver disease. However, the authors did report longer average days of anticoagulation in patients receiving traditional anticoagulation (574 ± 498 vs 319 ± 289, $p = 0.04$). The authors

speculate this finding may be due to permanent discontinuation of DOAC therapy following a bleeding event, whereas those receiving traditional anticoagulation were more likely to have therapy resumed [10].

This analysis carries with it inherent limitations common with a retrospective chart review. The sample of patients treated with DOACs was small; likely reflecting provider concern over the safety of such therapy in this population. Additionally, no patients with severe liver disease (Child Pugh C) were included in the DOAC group. As with any retrospective study, patient follow-up was limited to chart review. Therefore, clinical outcomes of patients presenting to outside facilities could not be captured.

In conclusion, the use of DOAC therapy in patients with CLD for the treatment of acute VTE resulted in similar rates of recurrent VTE and major bleeding when compared to warfarin. Further studies, especially in patients with severe liver disease are warranted to confirm these findings.

Addendum

Charles Puleo contributed to the study design, analysis, data interpretation and management, manuscript development and final review/approval.

Alexander Kovalic contributed to the analysis, data interpretation and management, manuscript development and final review/approval.

Sarah Nisly contributed to the study design, institutional review board approval, analysis, data interpretation and management, manuscript development and final review/approval.

Kyle Davis contributed to the study design, institutional review board approval, analysis, data interpretation and management, manuscript development and final review/approval/submission.

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