RESEARCH LETTER

Reduced-dose apixaban and dabigatran in patients with advanced liver cirrhosis and venous thromboembolism: a case series

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Introduction Liver cirrhosis, or advanced liver disease, with the annual incidence of 15 to 132 per 100 000 people in Europe[1] is associated with an increased risk of both bleeding and thrombosis. Therefore, anticoagulant treatment in patients with this disease is challenging. The risk of venous thromboembolism (VTE) in patients with cirrhosis is nearly twice as high compared with the general population.[2] Selection and appropriate dosing of anticoagulants is hampered by often intrinsically elevated international normalized ratio (INR), reduced platelet count, and the presence of esophageal varices. It has been shown that low albumin concentrations and increased Child-Pugh Scores (CPS) predict VTE in cirrhotic patients.[2]

Non–vitamin K antagonist oral anticoagulants (NOACs) have comparable efficacy and lower bleeding risk in patients with VTE compared with vitamin K antagonists; however, those with liver cirrhosis were excluded from randomized controlled trials on NOACs.[2] In patients with CPS class B, both apixaban or dabigatran could be used with caution, while in class C, NOACs are not recommended.[2] Limited evidence for the efficacy and safety of NOACs in this patient group is derived from observational studies, including those performed in patients with atrial fibrillation (AF) that demonstrated similar efficacy and better safety of reduced-dose NOACs compared with warfarin.[3]

Regarding studies on VTE, Davis et al[4] observed similar rates of recurrent VTE (11% vs 12%, respectively) at 3-month follow-up of 27 patients receiving apixaban, rivaroxaban, or dabigatran (59% in CPS class B) as compared with 82 patients on a vitamin K antagonist. In 16 cirrhotic patients with VTE or splanchnic vein thrombosis on apixaban or rivaroxaban (55% in CPS class B) and 18 on warfarin or low-molecular-weight heparin, Intagliata et al[5] reported a similar risk of major bleeding (6.7% vs 8.3% / year) and higher risk of any bleeding (26.9% vs 12.1%/year, respectively). Kunk et al[6] analyzed 69 patients with cirrhosis, including 47 patients with VTE, treated with apixaban, rivaroxaban, or dabigatran (26 patients with CPS class B) and observed major bleeding in 4 patients during a median follow-up of 6 months.

The aim of this case series was to evaluate the efficacy and safety of apixaban and dabigatran in VTE patients with CPS class B liver cirrhosis.

Patients and methods We enrolled 35 consecutive patients diagnosed with CPS class B cirrhosis (7–9 points), who experienced symptomatic unprovoked VTE and were referred to our clinic since January 2014. The diagnosis of cirrhosis was based on the presence of typical symptoms and laboratory investigations with imaging by ultrasonography, computed tomography, or magnetic resonance imaging. All patients were initially treated with low-molecular-weight heparin for 2 to 6 months, then according to the patient's preferences, to oral anticoagulation, apixaban 2.5 mg twice daily, or dabigatran 110 mg twice daily were initiated and the choice of a specific agent was left at the physician's discretion. We excluded patients with known malignancy, recent bleeding, thrombocytopenia below 50 × 10^3/μl, antiphospholipid syndrome, pregnancy, and chronic kidney disease stage 5. Patients with CPS class A or C were not eligible.

We collected data on risk factors and comorbidities defined as previously described[7] along with the medications used. Routine laboratory investigations were evaluated at the first visit. The study was part of the observational study

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on VTE approved by the Bioethical Commission of Regional Medical Chamber in Kraków (number 135/KBIL/OIL/2013) and patients gave informed consent.

Patients were followed on a 3-to-6-month basis (a visit at the center or telephone contact) until October 2020. The primary end point was symptomatic recurrent deep vein thrombosis (DVT), pulmonary embolism (PE), or thrombosis at atypical locations including the portal vein, all defined previously.[7] New documented major bleeding and clinically relevant non-major bleedings (CRNMB) defined according to the International Society on Thrombosis and Haemostasis criteria[8] were recorded. Interruptions in therapy were also analyzed.

Statistical analysis Statistical analysis was performed with Statistica 13 software (StatSoft, Tulsa, Oklahoma, United States) and package R, version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).[9] Continuous variables are expressed as medians (interquartile ranges), whereas qualitative variables are shown as numbers (percentages). Normal distribution was assessed with the Shapiro–Wilk test. The comparison of continuous variables was performed by the Mann–Whitney test. The Fisher exact test was used to compare qualitative variables between the 2 groups. A P value of less than 0.05 was considered statistically significant.

Results As shown in TABLE 1, the final analysis included 32 VTE patients with CPS class B liver cirrhosis (3 patients were lost to follow-up after the first visit). Most of the patients experienced DVT with concomitant PE (65.6%). Cirrhosis was caused most commonly by alcoholic liver disease (37.5%). At baseline, 22 patients (68.8%) had ascites, 19 (59.4%) had INR greater than 1.2 (including 3 [9.4%] with INR >1.7), and 22 (68.8%) had an albumin level below 35 g/l. No one had encephalopathy.

Eighteen patients (56.3%) received apixaban 2.5 mg twice daily and 14 (43.7%) dabigatran 110 mg twice daily. Patient characteristics in the 2 treatment groups were similar except for the causes of cirrhosis, that is, the patients on apixaban more commonly had viral hepatitis, while those on dabigatran, alcoholic liver disease (P = 0.04; TABLE 1).

During a median (interquartile range) follow-up of 50 (47–54.5) months, 3 thrombotic events were reported (2.2%/year), including 2 DVTs (1.5%/year) and single PE (0.75%/year), all with 7 points in CPS, INR greater than 1.2, and ascites. Two had positive family history of VTE.

The recurrent VTE episodes were observed in a 61-year-old woman receiving apixaban following COVID-19 treated at home, in a 75-year-old man following discontinuation of apixaban for 2 months while on prophylactic enoxaparin, and finally in a 63-year-old man who discontinued dabigatran and received enoxaparin 40 mg/d subcutaneously for 3 months; after recurrence, dabigatran 110 mg twice daily was reinitiated.

Two major bleeding (1.5% / year) and 3 (2.2% / year) CRNMB episodes were reported. None of the patients with any bleeding were treated with acetylsalicylic acid or had an INR greater than 1.7.

A major upper gastrointestinal bleeding was reported in a 55-year-old woman and 68-year-old man, both on apixaban, with prior invasive therapy of esophageal varices, after 7 and 13 months of anticoagulation, respectively. Two CRNMB, that is, large posttraumatic hematoma and massive epistaxis were reported in a 48-year-old and 65-year-old women, respectively, both on apixaban. The third CRNMB, gastrointestinal bleeding, occurred in a 56-year-old woman on dabigatran at month 21 of follow-up.

During follow-up, 10 (7.5% / year) patients died in no direct relation to VTE recurrence or bleeding.

Discussion The present case series is the first Polish study on VTE patients with liver cirrhosis on NOACs. We show that both apixaban 2.5 mg twice daily and dabigatran 110 mg twice daily could be used in the prevention of recurrent VTE in patients with CPS class B cirrhosis.

The risk of recurrent VTE and major bleeding was lower in the present study compared with previous reports on patients with VTE and liver cirrhosis treated with NOACs.[4,6] Of note, in most previous studies the number of patients with CPS class B cirrhosis was lower than in our study (from 11 to 26 vs 32, respectively) and the follow-up was shorter (from 3 to 9 months). The reasons for such a good prognosis in the present study are likely multiple. The dosing regimens of NOACs in previous studies[4,6] have not been specified, while in the current study, reduced-dose apixaban and dabigatran were administered. Obviously, standard-dose NOACs increase bleeding risk compared with reduced-dose anticoagulants,[3] therefore, better safety profile is not surprising. There were also differences in patient characteristics among the studies, for example Davis et al[4] enrolled patients with malignancy and those with other hypercoagulable states.

We showed similar efficacy and higher safety compared with a systematic review by Hoolwerf et al[10] that included as few as 5 small retrospective studies in which 108 patients the mean CPS score corresponded to class B. The risk of major bleeding in that study was higher (4% to 15% during follow-up from 6 to 9 months) compared with our group. Taken together, reduced-dose NOAC can be used in CPS class B to prevent recurrent VTE and there is no evident relation of major bleeds on NOAC to thrombocytopenia, high INR, aspirin use, or inhibitor proton nonuse. With appropriate clinical surveillance, we did not observe any bleeds caused by esophageal varices. Importantly, 2 of the 3 recurrent VTE occurred after NOAC withdrawal, which confirms

TABLE 1 Baseline characteristics of patients with liver cirrhosis following venous thromboembolism

Characteristic		All patients (n = 32)	Apixaban (n = 18)	Dabigatran (n = 14)	*P* value
Age, y		61.5 (55.5–68.0)	60 (55–68)	62.5 (60–69)	0.44
Male sex		17 (53.1)	10 (55.6)	7 (50)	0.99
Body mass index, kg/m^2		27.4 (24.7–29.5)	28 (25.7–31.2)	26.8 (24.6–28.4)	0.18
Current smoking		6 (18.8)	4 (22.2)	2 (14.3)	0.67
Time since cirrhosis diagnosis, mo		22.5 (17.–34.5)	23 (19–46)	21 (15–33)	0.46
Cause of cirrhosis	Viral hepatitis	10 (31.2)	8 (44.4)	2 (14.3)	0.04
	Alcoholic liver disease	12 (37.5)	3 (16.7)	9 (64.3)	
	Autoimmune hepatitis	6 (18.8)	4 (22.2)	2 (14.3)	
	Other	4 (12.5)	3 (16.7)	1 (7.1)	
Thrombotic manifestation	PE + DVT	21 (65.6)	11 (61.6)	10 (71.4)	0.76
	Isolated PE	4 (12.5)	2 (11.1)	2 (14.3)	
	SVT/iliofemoral DVT	7 (21.9)	5 (27.8)	2 (14.3)	
VTE family history		15 (46.9)	10 (55.6)	5 (35.7)	0.31
Child-Pugh Score class B	7 points	24 (75)	13 (72.2)	11 (78.6)	0.99
	8 points	8 (25)	5 (27.8)	3 (21.4)	
Comorbidities	Heart failure	12 (37.5)	9 (50)	3 (21.4)	0.15
	Hypertension	10 (31.2)	7 (38.9)	3 (21.4)	0.45
	Diabetes mellitus	2 (6.2)	1 (5.6)	1 (7.1)	0.99
	Ulcer disease	7 (21.9)	3 (16.7)	4 (28.6)	0.67
	Prior bleeding	5 (15.6)	5 (27.8)	0	0.052
Laboratory investigations	INR	1.23 (1.1–1.4)	1.21 (1.1–1.3)	1.27 (1.2–1.4)	0.42
	ALT, U/l	46.5 (32–59)	49 (30–59)	42.5 (33–55)	0.75
	AST, U/l	44 (34–51.5)	41.5 (33–55)	45.5 (35–50)	0.99
	Albumin, g/l	33.4 (31.6–37.0)	33.4 (31.6–36)	33.4 (31.6–37.3)	0.87
	Bilirubin, µmol/l	38.9 (29.7–43.9)	38.1 (29.6–42.3)	39.6 (33.7–44.8)	0.72
	Hemoglobin, g/dl	11.5 (10.7–12.8)	11.5 (10.8–12.8)	11.5 (10.2–12.8)	0.92
	Platelet count, × 10^3/µl	111 (91.5–151)	111 (91–144)	111.5 (93–161)	0.95
	eGFR, ml/min/1.73 m^2	64.5 (55–70.5)	64 (45–70)	65.5 (60–72)	0.22
Medications	Acetylsalicylic acid	4 (12.5)	3 (16.7)	1 (7.1)	0.61
	Statin	4 (12.5)	2 (11.1)	2 (14.3)	0.99
	Proton pump inhibitors	27 (84.4)	14 (77.8)	13 (92.9)	0.35
Follow-up	Duration, mo	50 (47–54.5)	50 (46–53)	52.5 (48–55)	0.49
	Recurrent VTE	3 (9.4)	2 (11.2)	1 (7.1)	0.99
	Clinically relevant bleeding	5 (15.6)	4 (22.2)	1 (7.1)	0.35
	Death	10 (31.2)	6 (33.3)	4 (28.6)	0.99

Data are shown as number (percentage) or median (interquartile range).

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; PE, pulmonary embolism; SVT, splanchnic vein thrombosis; VTE, venous thromboembolism

the relevance of appropriate secondary prevention of thrombosis.

Of note, apixaban (50% of full dose) was more commonly used than dabigatran (73% of full dose) despite easy access to a specific antidote, idarucizumab, which might have been considered the encouragement for the use of dabigatran in patients at high bleeding risk although its use has been associated with increased mortality within 30 days.[11]

The study has several limitations, including all inherent to its study design with lack of the control group. First, the case series was small but comparable or even larger than in other studies on the same clinical condition.[4,6] Secondly, we are aware that asymptomatic thromboembolic events, particularly DVT, may have gone unnoticed. Thirdly, the current findings could not be easily extrapolated to other VTE populations such as very elderly patients, those with cancer or CPS class C cirrhosis,[8] since they were not included in the present case series. Besides, though some patients were educated on VTE and anticoagulation to increase compliance,[12] we did not assess in a systematic manner adherence and persistence of NOACs use.

In conclusion, our study indicates that apixaban and dabigatran could be effective and safe

as secondary prophylaxis of VTE in patients with CPS class B cirrhosis. Further studies are needed to confirm the efficacy and safety of NOACs in advanced liver disease.

ARTICLE INFORMATION

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