

# Utilization of Direct Acting Oral Anticoagulants in Patients with Liver Cirrhosis: Is It Safe?



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## Abstract

Patients with liver cirrhosis are known to have increased risk of bleeding particularly from gastrointestinal tract. However, recent literature has shown that patients with liver cirrhosis are also at increased risk of thrombotic complications. Therefore, it is important to consider anticoagulation in cirrhotic patients. The purpose of this article is to review the epidemiological studies available in scientific literature comparing the risk of bleeding in cirrhotic patients utilizing DOACs vs traditional anticoagulation.

**Abbreviations:** INR: International Normalized Ratio; VTE: Venous Thromboembolism; DVT: Deep Venous Thrombosis; PE: Pulmonary Embolism; PTT: Partial Thromboplastin Time; LMWH : Low-Molecular-Weight Heparin; NO: Nitric Oxide; PTT: Partial Thromboplastin Time; DOACs: Direct Oral Anticoagulants; AT: Antithrombin; ULN: Upper Limit Of Normal; AUC: Area Under The Plasma Concentration-Time Curve; PD pharmacodynamics; PK: pharmacokinetics

## Introduction

Liver plays central physiologic role in hemostasis as it synthesizes the majority of the procoagulant and anticoagulant factors. The levels of these factors are markedly affected by decrease function of liver associated with cirrhosis resulting in abnormal hemostatic mechanism. Generally, the impression in the clinical world is that liver cirrhosis is associated with decrease synthesis of procoagulant factors resulting in increased risk of bleeding. This phenomenon is known as auto-anticoagulation and is supported by elevated international normalized ratio (INR) and low platelet count usually observed in cirrhotic patients. In this regard, gastrointestinal bleeding and more specifically variceal bleed is of major concern since they contribute significantly to the mortality of patients with liver cirrhosis. At least, 30% mortality has been reported at the first episode with a 70% recurrence rate in this patient population and a one year survival estimate ranging from 32% to 80% [1]. However, decrease function of cirrhotic liver also results in reduce level of anticoagulant factors including anti thrombin III, protein S, and C which may result in increased tendency to form clots. Interestingly, recent data also indicates cases of venous thromboembolism (VTE) including both deep venous thrombosis (DVT) and pulmonary embolism (PE) in cirrhotic

patients ranging between 0.5% to 6.3% [2-10]. Dabbagh et al. [4] found that even an elevated INR > 2.2 was not protective against VTE in this patient population [4]. Gulley D et al. [10] noted that hospitalized cirrhotic patients without predisposing co-morbidities (e.g. neoplasm, congestive heart disease and chronic renal failure) had similar risks for VTE as compared to non cirrhotic patients [10]. Thus, the myth of auto-anticoagulation seems to be only partially true. Therefore, the abnormal routine blood tests (like elevated INR, Partial Thromboplastin Time [PTT], high MELD score and low platelet count) may indicate increased hemorrhage risk in this patient population which may not be completely protective against risk of VTE as these tests do not accurately reflect the activity of aforementioned anticoagulant factors in the serum. As a result, utilization of anticoagulation is now being increasingly encouraged in cirrhotic patient population to avoid thrombotic complications.

Direct oral anticoagulants (DOACs) are relatively newer class of anticoagulants which selectively inhibit factor Xa (for e.g. Apixaban, Rivaroxaban, and Edoxaban) and factor IIa (for e.g. Dabigatran) of the coagulation cascade. Being able to be administered orally, rapid onset of action, lack of heparin induced thrombocytopenia, fewer interactions, and non requirement of laboratory monitoring

are some of the advantages that DOACs carry over the traditional anticoagulant agents. DOACs may also be helpful in management of portal vein thrombosis (PVT) and portal hypertension (pHTN) in patient with cirrhosis as case reports have been reported about PVT controlled by Rivaroxaban treatment [11-13]. Vilaseca M et al. [14] investigated the effect of Rivaroxaban on various mediators of portal hypertension in CCl<sub>4</sub> and thio acetamide-cirrhotic rats. Rivaroxaban significantly decreased portal pressure in both models of cirrhosis by reducing oxidative stress, improving nitric oxide (NO) bioavailability, and ameliorating endothelial dysfunction. Rivaroxaban also markedly reduced intrahepatic microthrombosis by reduced fibrin deposition and deactivated hepatic stellate cells which plays major role in increasing intrahepatic vascular resistance by promoting fibrogenesis [14]. The purpose of this article is to review the epidemiological studies available in scientific literature comparing the risk of bleeding in cirrhotic patients utilizing DOACs vs traditional anticoagulation.

## Methods

An electronic Medline search was conducted using the key terms anticoagulation, oral anticoagulant, direct acting oral anticoagulant, novel oral anticoagulant, direct thrombin inhibitors, direct factor Xa inhibitors, Apixaban, Rivaroxaban, Dabigatran, Edoxaban, liver cirrhosis, chronic liver disease, and decompensated liver disease. Studies written in the English from January 2000 to March 2018 were considered for this review article. All search results were reviewed.

## Results

Hum J et al. [15] conducted a retrospective cohort study to compare the efficacy and safety of direct oral anticoagulants vs traditional anticoagulants in 45 patients with cirrhosis who were prescribed therapeutic anticoagulation over a 3-year period for thrombosis or prevention of stroke in patients with atrial fibrillation. 27 patients were prescribed one of the DOACs and 18 were prescribed vitamin K antagonist or low molecular weight heparin (LMWH). Similar total bleeding events (8 with DOACs vs 10 with other, P=0.12) were observed in the two groups but DOACs group had significantly less major bleeding events (1 [4%] vs 5 [28%], P = 0.03) [15]. In another retrospective study, Intagliata N et al. [16] compared the rates of bleeding in cirrhotic patients treated with DOACs (Rivaroxaban and Apixaban) to the cirrhotic patients treated with traditional anticoagulation (coumadin and LMWH) using a research database. The sample size consisted of 39 patients who received anticoagulation therapy over a 3-year period. 20 patients received DOACS and 19 received traditional anticoagulation. No significant difference in bleeding was observed in the two groups (three in the traditional anticoagulation group and four in the DOACS group, p = 0.9). Three major bleeding events were noted including two in the traditional anticoagulation group and one in the DOACS group [16]. Nagaoki Y et al. [17] also

conducted a retrospective cohort study in fifty cirrhotic patients comparing the efficacy and safety of Edoxaban and warfarin for treatment of portal vein thrombosis (PVT). After treating for two weeks with danaparoid sodium, patients were switched to either Edoxaban (n = 20) or coumadin (n = 30). The efficacy and safety of Edoxaban and warfarin was compared for up to 6 months. Clinically significant gastrointestinal bleeding was encountered in 3 of 20 (15%) patients of the Edoxaban group and 2 of 30 (7%) of the warfarin group but the difference was not statistically significant (P = 0.335) [17]. In a relatively larger retrospective cohort study, Goriacko P et al. [18] compared the rate of bleeding in chronic liver disease patients with atrial fibrillation treated with oral anticoagulants (coumadin vs DOACs). No significant difference in all-cause bleeding (HR 0.9, 95% CI 0.4-1.8) and major bleeding were observed between the two groups [18].

## Conclusion

The data on the safety of DOACs in patients with liver cirrhosis is in very initial stages. Based on our Medline literature search, we were able to find four studies comparing the risk of bleeding in cirrhotic patients utilizing DOACs vs traditional anticoagulation. All studies reported either decreased bleeding events in patients with liver disease treated with DOACs as compared to patients treated with traditional anticoagulation or no significant difference in bleeding risk. However, these studies were limited by retrospective nature, small sample size, and lack of randomization. Due to retrospective nature, underreporting of the bleeding events may have resulted in the underestimation of the risk of hemorrhage in these studies. Lack of randomization may have resulted in the underutilization of DOACs in cirrhotic patients at higher risk of bleeding such as those with high INR, low platelet count and presence of esophageal varices. This may have also confounded the results of these studies.

One of the major concerns regarding utilization of DOACs in cirrhotic patient population is the lack of specific antidotes in face of life-threatening gastrointestinal bleeding or urgent invasive procedure. Since DOACs have long half-life, drug discontinuation is insufficient in these circumstances. Recently, three agents including Idarucizumab, andexanet alfa, and ciraparantag have been introduced with promising antidotal effect against the DOACs [19]. Idarucizumab is the only agent to date which has been approved for use and is specific to Dabigatran [19]. Andexanet alfa is specific to factor Xa inhibitors and is still under investigation [19]. Ciraparantag is a universal antidote and is in earlier stages of development [19]. In a study on healthy volunteers, Prothrombin complex concentrate has been demonstrated to reverse the anticoagulant effect of Rivaroxaban and Dabigatran [20]. In another study, prothrombin concentrates and recombinant factor VIIA were added in vitro to plasma from healthy volunteers receiving Rivaroxaban and Dabigatran with (partial) reversal of these agents [21].

Another concern regarding the utilization of DOACs in patients with liver disease is that the abnormal functioning of liver may affect the pharmacodynamics (PD) and pharmacokinetics (PK) of DOACs resulting in unpredictable half-life and serum concentration of these agents in this patient population. As a result, caution and dose adjustment may be required when using DOACs in patients with abnormal liver function. Graff J et al. [22] observed that in patients with moderately impaired liver function (i.e. Child-Pugh classification B), the area under the plasma concentration-time curve (AUC) of Rivaroxaban after a single dose of 10 mg increased by 2.27-fold along with increase in factor Xa inhibition [22]. Since, Rivaroxaban is also excreted mainly by the kidneys (66%) and liver (34%), caution and dose adjustment of this agent is recommended in cirrhotic patients with cirrhosis with or without concomitant renal failure [22]. Rivaroxaban is also contraindicated in patients with liver cirrhosis associated with coagulopathy, increased bleeding risk, and patients classified as Child-Pugh B and C [22]. In contrast, the AUC of Dabigatran after a single dose of 150 mg decreased by 5.6 % in patients with moderately impaired liver function (i.e. Child-Pugh classification B) [22]. Also, Dabigatran is mainly (80%) eliminated via the kidneys and is likely the more safer choice in patients with liver cirrhosis [23]. Stangier J et al. [23] observed slower conversion of Dabigatran intermediate to active Dabigatran [24]. However, total drug exposure was comparable between healthy volunteers (n = 12) and patients with hepatic impairment (Child Pugh classification B, n = 12) [24]. Moreover, the parameters of coagulation, including activated partial thromboplastin time, clotting time, and thrombin time relationships were basically similar in both groups [24]. Therefore, Dabigatran can be used in patients with moderate hepatic impairment without the need for dose adjustment [24]. Dabigatran should be avoided in patients with elevated hepatic enzymes (>2× ULN) and is contraindicated in patients with hepatic impairment expected to have any impact on survival [22]. Increased AUC by 1.09-fold was observed for Apixaban after a single dose administration of 5 mg whereas AUC of Edoxaban decreased by 5.6 % after single dose administration of 15 mg [22]. In patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic dysfunction or transaminase levels >2× upper limit of normal (ULN), Apixaban can be used with caution. Apixaban should be avoided in patients with severe hepatic impairment and in those with increased bleeding risk [22].

It will be helpful to monitor activity of DOACs in cirrhotic patients particularly at increased risk of bleeding for example patients with esophageal varices, elevated INR, and low platelet count. Novel coagulation assays need to be developed to monitor the activity of DOACs in serum from patients with liver disease. In one study, Potze W et al. [25] noticed substantial reduction in anti-Xa levels when antithrombin (AT) dependent anticoagulant drugs (Unfractionated heparin, LMWH, and fondaparinux) were added to the plasma of patients with cirrhosis as compared to plasma from healthy controls. Therefore, they concluded that anti-Xa assay cannot be used to monitor AT-dependent anticoagulant drugs in

patients with cirrhosis, as it may result in underestimation of drug levels and increase risk of bleeding. However, this was not the case with Rivaroxaban and Dabigatran and they recommended that direct factor Xa and IIa inhibitors may be monitored through the respective anti-Xa and anti-IIa assays in patients with cirrhosis.

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