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EDITORIAL COMMENT

DOACs in Patients With Atrial Fibrillation and Liver Disease

Time to Expand the Safety Zone?*

Eue-Keun Choi, MD, PhD, So-Ryoung Lee, MD

Chronic liver disease (CLD) is one of the major causes of morbidity and mortality that increases public health burden worldwide (1). The underlying causes of CLD include hepatitis B or C viral infections, alcohol-related liver disease, and nonalcoholic fatty liver disease (2,3). CLD has been independently associated with an increased risk of atrial fibrillation (AF) (4). Liver disease is often accompanied by a combination of complex abnormalities of the coagulation pathways (5,6). The increased risk of clinical bleeding is related to decreased levels of procoagulant factors; however, anticoagulants, such as antithrombin and protein C, are also reduced, together with an increased level of factor VIII, which restores the balance of hemostasis and also increases the risk of thrombotic events in the arterial and venous systems. Although the thromboembolic risk increased in AF patients with liver disease, stroke prevention with oral anticoagulants is challenging because it causes a higher risk of bleeding. There is growing evidence that vitamin K antagonists might be associated with a lower risk of ischemic stroke and a positive net clinical benefit compared with nontreatment in AF patients with advanced liver disease (7). Direct oral anticoagulants (DOACs) have been demonstrated to have comparable efficacy and better safety compared to vitamin K antagonists (8). Although renal excretion is one of the essential mechanisms of elimination, DOACs have a wide range of hepatic elimination rates (apixaban 75%, rivaroxaban 65%, edoxaban 50%, dabigatran 20%). Thus, the impairment of liver function could influence pharmacokinetics, leading to an increased risk of bleeding.

After the withdrawal of ximelagatran, the first direct thrombin inhibitor, from the market due to severe hepatic injury, risk of liver injury was one of the main concerns in developing DOACs. Thus, strict criteria to exclude patients with significant active liver diseases or persistent elevation of liver enzymes or bilirubin were applied in the pivotal clinical trials of DOACs, considering the potential risk of liver injury and also major bleeding (**Table 1**) (9-12). Consensus guidelines recommended that 4 DOACs were contraindicated in patients with Child-Turcotte-Pugh class C liver cirrhosis (13). However, there have been no consensus statements for patients with relatively mild liver disease or abnormalities on liver function tests. Considering the growing number of patients with both AF and liver disease, there is an unmet need for evidence supporting the use of DOAC in these specific populations.

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Coincidentally in this issue of the *Journal*, Qamar et al. (14) report the clinical efficacy and safety of edoxaban compared to warfarin in patients with AF and a history of liver disease. The ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial excluded patients who had persistent elevation (confirmed by repeat assessment within 1 week) of liver enzymes >2-fold during the screening period (<30 days of randomization) (12). Thus, remained patients with elevated liver enzymes at randomization could be included in the trial, and these patients were regarded as having a history of liver disease in the study by Qamar et al.

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From the Division of Cardiology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea. Dr. Choi has received research grant support from Daiichi-Sankyo and Bristol-Myers Squibb/Pfizer. Dr. Lee has reported that she has no relationships relevant to the contents of this paper to disclose.

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TABLE 1 Summary of Exclusion Criteria of Liver Disease in Pivotal Trials of 4 Direct Oral Anticoagulants

	ENGAGE AF-TIMI 48 Trial (Edoxaban)	RE-LY Trial (Dabigatran)	ROCKET AF Trial (Rivaroxaban)	ARISTOTLE Trial (Apixaban)
Diagnosis	Active liver disease	Active liver disease, including active hepatitis C, active hepatitis B, or active hepatitis A	Significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis)	
Laboratory findings				
AST/ALT	≥2× ULN*	>2× ULN†		>2× ULN
ALP	≥2× ULN*	>2× ULN†	>3× ULN	
Total bilirubin	≥1.5× ULN*			≥1.5× ULN
Viral marker	History of positive hepatitis B antigen or hepatitis C antibody	HBsAg+, anti-HBc IgM+ positive HCV RNA		

*Persistent elevation confirmed by repeat assessment within a week. †Persistent elevation.

ALP = alkaline phosphatase; ALT = alanine transaminase; ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AST = aspartate transaminase; ENGAGE AF-TIMI 48 = Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction 48; HBc = hepatitis B core; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy; RNA = ribonucleic acid; ROCKET AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; ULN = upper limit of normal.

(14). Although patients with active liver disease and a history of hepatitis B or C infection were ineligible, those who had a prior history of liver disease could be enrolled at the discretion of the site investigator, and these patients were also included in the group with a history of liver disease. Almost all of the patients had a mild history of liver disease, but the risk of bleeding was significantly increased compared with those without liver disease. However, in line with the main results, the efficacy and safety of edoxaban compared to warfarin were mostly consistent irrespective of liver disease. Importantly, these clinical outcomes were supported by the unique data of pharmacokinetics and pharmacodynamics of edoxaban. The availability of blood levels of endogenous FXa activity and edoxaban concentrations is the main strength of this study, and the fact that these levels did not differ significantly according to the presence of liver disease strongly supports the consistent efficacy and safety data of edoxaban. Last, the incidence of drug-induced liver injury was not different between the edoxaban and warfarin groups. Liver injury was monitored by meticulous follow-up with liver function test and adjudicated by independent hepatologists. These data provide timely evidence to expand the safety zone of edoxaban in patients with liver disease.

There are several limitations to be mentioned. First, the number of patients with liver disease was small, and therefore, a strong conclusion cannot be made; however, it was still enough to generate a hypothesis. Second, the definition of "history of liver disease" was heterogeneous; hence, a more specific and objective definition of liver disease would be needed in future studies. Also, the cause of elevated liver enzymes at randomization is unclear. Third, considering that the grade of liver disease was mild and also that the elevation of liver enzymes at randomization may be transient, the data cannot be applied to patients with moderate or severe liver disease. In a recent observational study in Taiwan, DOACs showed a comparable risk of thromboembolism and a lower risk of major bleeding in patients with liver cirrhosis (15). To fill the gap between the randomized control trial and real-world practice, and expand these results to DOAC for stroke prevention in patients with AF and moderate or severe liver disease, further studies are needed. Last, an appropriate dose of DOACs in patients with liver disease would not be answered. Although the lower-dose edoxaban regimen (30/15 mg) showed comparable efficacy and better safety, the number of AF patients with liver disease in this group is too small.

In conclusion, stroke prevention in AF patients with liver disease is important, and the current study provides evidence for the use of edoxaban in this population, with better or at least comparable clinical efficacy and safety compared with warfarin. However, the study results were based on patients with "mild" liver disease; therefore, further studies are needed to expand the safety zone of DOACs to patients with more than "mild" liver disease.

ADDRESS FOR CORRESPONDENCE: Dr. Eue-Keun Choi, Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea. E-mail: choiek17@snu.ac.kr.

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