**Use of direct-acting oral anticoagulants in patients with atrial fibrillation and chronic liver disease**

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**Conflicts of interest**

TJH declares no conflicts of interest.

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Atrial fibrillation (AF) is the commonest sustained cardiac rhythm disorder, and is frequently associated with multimorbidity, including chronic liver disease (CLD). In the United States, the incidence rates of metabolic and alcohol-related liver disease, and their end-stage complications are continuing to rise. Alcohol consumption, obesity and non-alcoholic fatty liver disease (NAFLD) are associated with increased relative risk of incident AF, thus physicians are increasingly encountering patients with both AF and CLD.

The last two decades have bought about a shift in our understanding of the haemostatic system in patients with cirrhosis, whereby anti-haemostatic changes are balanced by an increase in pro-coagulant factors. Consequently, prothrombin time and activated partial thromboplastin clotting time are not reflective of the coagulation status in people with cirrhosis.1 The observed increased bleeding events in patients with cirrhosis are instead thought to be consequences of portal hypertension, and these individuals are not protected against thrombosis.

Thus, there is an important clinical need to understand the safety and efficacy of oral anticoagulants in patients with AF and CLD. This is problematic however as patients with liver disease (generally defined by the presence of elevated liver enzymes or cirrhosis), in addition to people with alcohol abuse were mostly excluded from the randomised controlled trials (RCT) which led to the approval of the DOACs,2–5 that are now recommended in treatment guidelines for stroke prevention in AF.6 DOACs are not reliant on the use of INR monitoring, a major benefit for patients with cirrhosis where this is uninterpretable and for people living with addiction who may struggle to attend for regular INR monitoring. Advanced liver disease can affect drug clearance and metabolism. While DOACs are metabolised in the liver to varying extents, they are less dependent on this mechanism of clearance compared to warfarin. There is therefore a compelling argument that DOACs may have more favourable safety profiles in patients with CLD and could be more widely prescribed.

Observational studies have attempted to bridge this evidence gap. A 2020 meta-analysis including 41,954 patients with AF and liver disease concluded that compared to warfarin use, DOACs were associated with comparable risks of stroke or systemic embolism (SSE) (relative risk (RR) 0.80, 95% confidence interval (CI) 0.57-1.12) and gastrointestinal bleeding (RR 0.90, 95% CI 0.61-1.34), with reduced risk of all-cause death (RR 0.78, 95% CI 0.66-0.93) and major bleeding (RR 0.68, 95% CI 0.53-0.88).7 In a subset of patients with cirrhosis, DOAC users experienced a significant reduction in the risk of major bleeding (RR 0.53, 95% CI 0.37, 0.76) and gastrointestinal bleeding (RR 0.57, 95% CI 0.38-0.84) compared with those prescribed warfarin. However, most participants were from Asia where there are higher prevalence rates of viral hepatitis and lower levels of alcohol and metabolic liver disease. This may be clinically relevant as NAFLD/diabetes is associated with reduced activity of CYP3A4,8 a key enzyme involved in the hepatic metabolism of apixaban and rivaroxaban.

Cohort studies comparing DOACs with warfarin from the United States and Europe have been small.7 Several observational studies have however compared the risk of oral anticoagulation (a DOAC or vitamin K antagonist) *versus* no anticoagulation in patients with AF and CLD. An analysis of 1238 Danish citizens with new onset AF and CLD reported that for patients with a CHA2DS2-VASc-score ≥2, five-year thromboembolism rates were significantly lower in patients receiving anticoagulation (16% versus 24%; average risk ratio 0.66, 95% CI 0.45-0.87).9 Bleeding risks were higher among patients with cirrhotic vs. non-cirrhotic disease, but this was not significantly affected by anticoagulant status (oral anticoagulation *versus* none: cirrhosis 0.72, 95% CI 0.28-1.15), no cirrhosis 1.28, 95% CI 0.67-1.90). Similarly, a retrospective analysis of 16,168 patients with AF and liver disease from Italy demonstrated that liver disease was associated with elevated risk of major bleeding, but oral anticoagulant use resulted in a reduction in risk of stroke (hazard ratio, HR 0.80, 95% CI 0.70-0.92) and major bleeding (HR 0.86, 95% CI 0.74-0.99).10

These findings are consistent with our understanding that there is an increased risk of bleeding in patients with cirrhosis, but this is driven by portal hypertension rather than coagulopathy. Of note, observational studies are subject to bias as individuals prescribed anticoagulation are likely to have less severe portal hypertension.

Finally, for patients with CLD, assessment of liver fibrosis may be a key component of the patient pathway for risk stratification of future clinical events. A post-hoc analysis of a prospective study of 2030 patients with AF, for example, identified that a high fibrosis-4 score (a non-invasive test for liver fibrosis) was associated with increased incidence of major bleeding in those receiving vitamin K antagonists, but not DOACs.11

In this issue of *Circulation*, Lawal et al present their findings of a large retrospective study of 10,209 participants with CLD and AF who were new users of oral anticoagulants identified via administrative claims.12 They report incidence rates per 100 person-years for SSE of 2.2 (all DOACs combined), 1.4 (apixaban), 2.6 (rivaroxaban), and 4.4 (warfarin). Analogous figures for major bleeding were 7.9 (all DOACs combined), 6.5 (apixaban), 9.1 (rivaroxaban), and 15.0 (warfarin). Following inverse probability treatment weights, the risk of hospitalization for SSE remained significantly lower with DOACs as a class (HR 0.64, 95% CI 0.46-0.90) and apixaban (HR 0.40, 95% CI 0.19-0.82), compared with warfarin, with no significant difference between rivaroxaban *versus* warfarin. The risk of hospitalization for major bleeding was also significantly lower for DOACs as a class (HR 0.69, 95% CI 0.58-0.82), apixaban (HR 0.60, 95% CI 0.46-0.78) and rivaroxaban (HR 0.79, 95% CI 0.62-1.00) compared to warfarin.

# However, patients with CLD were identified using ICD codes, which is open to coding inaccuracies. In addition, the severity of liver disease and likelihood of clinically significant portal hypertension is a vital consideration when weighing up the risk-benefit profile of prescribing anticoagulation in this group. Lawal and colleagues12 were unable to determine the Child-Pugh or Model for End stage Liver Disease (MELD) scores as laboratory results were not available for most participants. Instead validated algorithms based on diagnosis codes were used to identify patients with ‘compensated’ or ‘decompensated’ cirrhosis. Overall, 28.8% (n=2940) of the study population had cirrhosis, and 13.2% (n=1349) had decompensated cirrhosis. For patients with cirrhosis, the incidence of SSE was similar for DOACs compared to warfarin (HR 0.90, 95% CI 0.51-1.57). Encouragingly there was a significantly lower risk of all-cause death (HR 0.75, 95% CI 0.62-0.91) and major bleeding (HR 0.70, 95% CI 0.53-0.93) in DOAC users compared to warfarin users. While, this subgroup analysis was not powered to detect differences between DOACs and warfarin, it is the largest retrospective observational study published to date in this field. However, findings are likely to have been influenced by prescriber bias, as clinical scenarios will have dictated whether warfarin or a DOAC (including which DOAC and dose) was prescribed, impacting meaningful head-to head comparisons between the groups. This bias is also demonstrated by the fact that patients prescribed a reduced DOAC dose experienced more than a two-fold increase in incidence rates of hospitalization for major bleeding compared to those receiving a standard dose, presumably because of an elevated baseline risk of bleeding. Indeed, there will be a cohort of patients with CLD and AF in whom a conscious decision was made not to prescribe any anti-coagulation following an assessment of the risks and benefits, for whom the outcomes are unknown.

How should this paper inform current practice? This study provides the most robust ‘real-world’ evidence to date that DOACs are effective and safe in patients with CLD and AF. The European Association for the Study of the Liver (EASL),1 and the European Heart Rhythm Association (EHRA)13 recommend that DOACs should not be used in patients with Child-Pugh C cirrhosis (Table). This stage of liver disease is associated with increased incidence of variceal haemorrhage and low one-year survival rates in the absence of liver transplantation, so it seems reasonable to avoid prescription of oral anticoagulation in this group. The American Gastroenterology Association recommend anticoagulation in patients with cirrhosis and AF where indicated, but advise that patients with Child-Pugh C and/or low CHA2DS2-VASc scores, could choose no anticoagulation.1 EASL advise that there are no ‘formal contraindications’ to the use of DOACs in patients with Child-Pugh A cirrhosis and that real-world data supports this, albeit retrospective and underpowered.14 Findings from the current study support this guidance.12 There is concern regarding dose accumulation in patients with Child-Pugh B cirrhosis, following a small study which demonstrated a two-fold increase in drug exposure to rivaroxaban,15 therefore EASL advise that DOACs should be used with caution in this group. The EHRA practical guide13 recommends avoiding rivaroxaban in patients with Child-Pugh B cirrhosis entirely. As a result of been unable to define Child-Pugh stage, the present study is unable to further inform decision making for this group.12

Finally, while we lack RCT evidence on the clinical effectiveness and safety of oral anticoagulants (especially the DOACs) in patients with CLD and AF, in the absence of risk factors for significant portal hypertension, real-world studies suggest a favourable profile on both accounts.

**Table.** Recommendation for the use of direct-acting oral anticoagulants in patients with chronic liver disease and atrial fibrillation (adapted from the European Heart Rhythm Association guidelines)13

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Liver disease category** | **Dabigatran** | **Apixaban** | **Edoxaban** | **Rivaroxaban** |
| Chronic liver disease (no cirrhosis) | Standard dose | Standard dose | Standard dose | Standard dose |
| Child-Pugh A cirrhosis | Standard dose | Standard dose | Standard dose | Standard dose |
| Child-Pugh B cirrhosis | Use with caution | Use with caution | Use with caution | Do not use |
| Child-Pugh C cirrhosis | Do not use | Do not use | Do not use | Do not use |

The Child-Pugh score consists of the following components: international normalized ratio, bilirubin, albumin, grade of ascites and grade of encephalopathy.

**References**

1. O’Shea RS, Davitkov P, Ko CW, Rajasekhar A, Su GL, Sultan S, Allen AM, Falck-Ytter Y. AGA Clinical Practice Guideline on the Management of Coagulation Disorders in Patients With Cirrhosis. *Gastroenterology*. 2021;161:1615-1627.e1.

2. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, et al. Edoxaban versus Warfarin in Patients with Atrial Fibrillation. *New Eng J Med*. 2013;369:2093–2104.

3. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *New Eng J Med*. 2011;365:883–891.

4. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. *New Eng J Med*. 2011;365:981–992.

5. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *New Eng J Med*. 2009;361:1139–1151.

6. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2019;74:104–132.

7. Fu Y, Zhu W, Zhou Y, Chen H, Yan L, He W. Non-vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Patients with Atrial Fibrillation and Liver Disease: A Meta-Analysis and Systematic Review. *Amer J Cardiovasc Drugs*. 2020;20:139–147.

8. Jamwal R, de La Monte SM, Ogasawara K, Adusumalli S, Barlock BB, Akhlaghi F. Nonalcoholic fatty liver disease and diabetes is associated with decreased CYP3A4 protein expression and activity in human liver. *Mol Pharm*. 2018;15:2621.

9. Steensig K, Pareek M, Krarup AL, Sogaard P, Maeng M, Tayal B, Lee CJY, Torp-Pedersen C, Lip GY, Holland-Fischer P, et al. Thromboembolism and bleeding in patients with atrial fibrillation and liver disease - A nationwide register-based cohort study: Thromboembolism and bleeding in liver disease. *Clin Res Hepatol Gastroenterol*. 2022;46:101952.

10. Proietti M, Marzona I, Vannini T, Colacioppo P, Tettamanti M, Foresta A, Fortino I, Merlino L, Lip GYH, Roncaglioni MC. Impact of liver disease on oral anticoagulant prescription and major adverse events in patients with atrial fibrillation: analysis from a population-based cohort study. *Eur Heart J Cardiovasc Pharmacother*. 2021;7:F84–F92.

11. Pastori D, Lip GYH, Farcomeni A, del Sole F, Sciacqua A, Perticone F, Marcucci R, Grifoni E, Pignatelli P, Violi F, et al. Incidence of bleeding in patients with atrial fibrillation and advanced liver fibrosis on treatment with vitamin K or non-vitamin K antagonist oral anticoagulants. *Int J Cardiol*. 2018;264:58–63.

12. Oluwadolapo Lawal, Herbert Aronow, Fisayomi Shobayo, Anne Hume, Tracey Taveira, Kelly Matson, Yichi Zhang, Xuerong Wen. Comparative effectiveness and safety of direct oral anticoagulants and warfarin in patients with atrial fibrillation and chronic liver disease: A nationwide cohort study. *Circulation*. 2022;

13. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J*. 2018;39:1330–1393.

14. Villa E, Bianchini M, Blasi A, Denys A, Giannini EG, de Gottardi A, Lisman T, de Raucourt E, Ripoll C, Rautou PE. EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis. *J Hepatol*. 2022;76:1151–1184.

15. Kubitza D, Roth A, Becka M, Alatrach A, Halabi A, Hinrichsen H, Mueck W. Effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of a single dose of rivaroxaban, an oral, direct Factor Xa inhibitor. *Br J Clin Pharmacol*. 2013;76:89–98.