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COMMENTARY

Accumulating evidence for direct oral anticoagulants in liver disease

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As readers of this journal are fully aware, venous thromboembolism (VTE) is a common disease, preferentially—but of course not exclusively—affecting individuals with comorbidity. This means that it is a routine clinical situation that patients with chronic liver disease need to be started on oral anticoagulation for a deep vein thrombosis (DVT) or pulmonary embolism (PE). In such a case, can we give direct oral anticoagulants (DOACs), or do we need to give low-molecular-weight heparin followed by vitamin K antagonists (VKA)?

While DOAC are now preferred over VKA (ie, warfarin, in large parts of the world) in the majority of cases, there is a gap in evidence for patients with chronic liver disease [1]. These patients were excluded from large phase 3 registration trials [2–5]. There has been published interest in the use of DOACs in liver disease-specific VTE, ie, splanchnic or portal vein thrombosis, but less so in DVT and PE [6].

The risk-to-benefit ratio for DOAC vs warfarin might be different in individuals with chronic liver disease. As DOAC are partly cleared by the liver, it is possible that patients with chronic liver disease have higher levels of DOAC, putting them at increased risk of bleeding. If this were the case, the choice of DOAC is important, as the degree to which they are cleared hepatically varies (75% for apixaban, 65% for rivaroxaban, 50% for edoxaban, and 20% for dabigatran [7]). On the other hand, warfarin management might be hampered by preexisting abnormal international normalized ratio leading to insufficient intensity of anticoagulation. It should also be weighted that, independent of the use or choice of anticoagulation, the risk of bleeding and thrombosis is increased in chronic liver disease [8,9]. It is not known whether this is also the case for recurrent VTE.

The study by Lawal et al. [7] gives us important data to inform the choice between DOAC and warfarin in patients with chronic liver disease who are started on anticoagulation for DVT or PE. They make use of an administrative claims database covering more than 20 million individuals with private health insurance in the United States. Eight thousand four hundred seventy-seven individuals were identified who were started on either a DOAC or VKA, with a previous encounter with chronic liver disease (defined by a broad spectrum of diagnostic codes for liver dysfunction) and a recent claim for DVT or PE. Warfarin was started in the majority (n = 5337) of individuals. The large majority of DOAC prescriptions were for rivaroxaban (n = 2161) or apixaban (n = 895); hardly any patients were prescribed dabigatran or edoxaban. Propensity matching was used to create 4 cohorts of matched pairs: DOAC vs warfarin (n = 2361), rivaroxaban vs warfarin (n = 2161), apixaban vs warfarin (n = 895), and rivaroxaban vs apixaban (n = 895).

The primary outcome of net clinical benefit, the composite of hospitalization for recurrent VTE and major bleeding, had a hazard ratio (HR) of 0.72 (95% CI, 0.61-0.85) in DOAC vs warfarin. This was driven by a lower rate of bleeding on DOAC. Rates of recurrent VTE and death were not different. It needs to be noted, however, that recurrent VTE had fewer events than major bleeding (90 vs 279), and the CI (point estimate, 0.81; 95% CI, 0.59-1.12) did not exclude a clinically relevant difference.

The comparisons between rivaroxaban and warfarin and apixaban and warfarin were similar, and these were similar to the comparison between DOAC and warfarin for the primary outcome.

In the analysis comparing rivaroxaban with apixaban, there was no statistically significant difference in the primary outcome, although the point estimate favored apixaban (HR, 0.68; 95% CI, 0.43-1.08). The same was seen for major bleeding (HR, 0.60; 95% CI, 0.35-1.06). For recurrent VTE and mortality, point estimates were close to 1.

Despite lower risk of hospitalization for major bleeding in DOAC compared to warfarin, the absolute risk was still high (see Figure 2 in the study by Lawal et al. [7]). These rates are far higher than those reported in the phase 3 studies, which is partly explained by study vs real life, but it is plausible that this also reflects the higher risk of bleeding in this patient group.

Subgroup analysis limited to individuals with either cirrhosis or decompensated cirrhosis showed the same results, with an HR of 0.64 (95% CI, 0.43-0.96) for the primary outcome.

The study has the inherent limitations of (1) using data that was collected for other purposes and (2) making comparisons within observational data. Regarding the use of administrative data, the authors state that previous work showed that the positive predictive value of exposure and outcome data was good for in-hospital but not for outpatient diagnosis [10,11]. This means that outpatient bleeding and recurrent thrombosis were not captured. However, it seems improbable that this would affect DOAC differently from VKA. It will have caused an underestimation—of unknown size—of the absolute risk of bleeding and recurrent VTE.

The authors did a thorough job exploring the risk of any confounding that might have remained after propensity matching. Two of the techniques that they used are very intuitive. The first is the calculation that the risk ratio of an unmeasured confounder should have been ≥1.63 to explain the difference between DOAC and VKA. The second is one that I find very elegant: they calculated the risk of hospitalization for pneumonia. If this were different for DOAC and VKA, it would indicate that one group was more vulnerable than the other. The HR here was 0.96 (95% CI, 0.77-1.19). Of course, none of the techniques is perfect in itself; the strength lies in the fact that none of them indicates that there was important residual confounding.

A number of limitations remain: the majority of patients have relatively mild liver disease, data on Child–Pugh classification are not available, and the quality of warfarin treatment (time in therapeutic range) is unknown.

The authors are conservative with their recommendations: they recommend that "patients with chronic liver disease should be included in future randomized trials to confirm these findings." I think that it is unlikely that such trials will be done and that we need to base our recommendations on data from real-world sources. This paper is a very good example of how such sources should be used: carefully and with methodological rigor.

For now, faced with patients with chronic liver disease and DVT or PE, this study adds confidence that apixaban and rivaroxaban are good treatment options.

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AUTHOR CONTRIBUTIONS

K.M. wrote the paper.

RELATIONSHIP DISCLOSURE

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