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Oral anticoagulants and liver injury: the threat of uncontrolled confounding

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We value the comments from Drs. De Ponti and Raschi about our manuscript reporting the association of oral anticoagulation initiation with the risk of hospitalization for liver injury [1]. As they summarize in their letter, we showed that among patients with non-valvular atrial fibrillation (AF) initiating oral anticoagulation, the risk of liver injury hospitalization was highest among those starting warfarin and lowest for dabigatran. Our findings are consistent with those from the large phase 3 randomized trials supporting the approval of the new direct oral anticoagulants (DOACs), complement prior pharmacovigilance studies that suggested no increased hepatotoxicity in DOAC users compared to warfarin users, and should contribute to allaying concerns regarding the comparative liver toxicity of DOACs versus warfarin [2].

One important consideration raised by Drs. De Ponti and Raschi is the potential for uncontrolled confounding due to bias by indication. Since specific oral anticoagulants were not assigned randomly, patients initiating warfarin or any of the DOACs are likely to be different in characteristics that are also associated with their overall risk of liver injury. For example, the mean CHA₂DS₂-VASc score in warfarin initiators was 3.6, while the score was between 2.9 and 3.2 for DOAC initiators. We used standard approaches, such as multivariable adjustment and propensity score matching, to control for those differences [3]. These methods, however, rely on the unrealistic and untestable assumption that all factors

affecting the decision to prescribe a particular anticoagulant and also potentially related to the risk of liver injury were perfectly measured and included in the statistical models. Though we cannot demonstrate that confounding was completely controlled, the extensive list of clinical variables available and adjusted for in the analysis as well as the similar results when we used two different approaches for confounding control (multivariable analysis and propensity score matching) increase our confidence in the validity of our findings.

Finally, we wholeheartedly agree with Drs. De Ponti and Raschi's statement that additional studies in other settings and in different patient subgroups, such as those with venous thromboembolism, are urgently needed to characterize in full the effectiveness and safety of DOACs.

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