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to clot or not to clot

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Commentary

Antithrombotic therapy in chronic liver disease: to clot or not to clot

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Antithrombotic medications play a central role in the prevention of arterial and venous thromboembolism in several cardiovascular diseases, including in atherosclerotic disease and atrial fibrillation (AF). However, prescribing these medications is not risk free, particularly in patients with co-morbidities affecting bleeding risk, such as chronic liver disease (CLD). As such patients with CLD were omitted from landmark Phase 3 trials, the precise risk-benefit ratio in such populations remains poorly understood.

In this issue of *The Lancet Regional Health – Europe*, Chang et al provide a comprehensive review of prescribing practices in 4 million English patients with and without CLD between 1998 and 2020 [1]. They found that antithrombotic prescribing was lower amongst those with CLD compared to those without and was subject to significant geographical disparity, a previously recognised issue [2]. Adherence in both groups was suboptimal, though early discontinuation was marginally worse in the CLD group. Although anticoagulant prescribing for AF was lower in the CLD group, it was also suboptimal in the non-CLD group (33.5%); notably these figures were not stratified by CHA_2DS_2VASc score and so may underestimate the reality. Also, CLD is not a homogeneous diagnosis, although Chang et al provide some data on liver disease severity and different subgroups of liver disease.

Previous studies have demonstrated suboptimal prescribing of venous thromboembolism (VTE) prophylaxis in CLD patients [3]. The present study adds to the long-held suspicion that clinicians may be hesitant to prescribe antithrombotic medications (specifically, anticoagulants) to patients they perceive to have an increased bleeding risk. Such practice is frequently based on the misplaced notion that CLD patients with raised INR are "auto-anticoagulated". In fact, it has been shown that these patients may actually be at higher thrombotic risk, particularly in the setting of hypoalbuminaemia [4]. Given the complex haemostatic and clinical interactions in CLD (Table 1), it is perhaps unsurprising that a raised INR may promote hesitancy in prescribing antithrombotic drugs. However, the INR is poorly representative of their coagulation status. Indeed, there were acceptable safety profiles for anticoagulation in CLD patients, with no significant increase in bleeding risk [1], although there is heterogeneity between studies [3] and the full picture is unclear. Antithrombotic drugs may even be protective in CLD – the authors of the present study note that antiplatelets may slow the progression of liver fibrosis [1] – the same appears true of anticoagulants [5]. Other studies have demonstrated improved survival and reduced all-cause mortality in those with cirrhosis treated with anticoagulation [6,7], even in the absence of portal vein thrombosis [8].

Interestingly, the present study found no significant effect of anticoagulant non-adherence on strokes in the CLD group [1]. Previous studies in CLD have demonstrated a reduction in ischaemic stroke with anticoagulation in AF, especially with the Direct Oral Anticoagulants (DOACs) showing lower bleeding risk compared with warfarin [6,7]. Chang et al also noted improved adherence with DOACs [1] likely due to reduced monitoring requirements.

Nevertheless, the safety of DOACs is not well established in CLD as major trials excluded such patients [1,8]. A recent meta-analysis by Violi et al demonstrated similar safety and efficacy of DOACs compared with Warfarin in those with CLD [9]. Warfarin and Heparin are also not without their own complexities – particularly how to monitor INR in those with baseline INR derangements when standard target ranges do not apply to this patient group [8].

Hence, the decision to anticoagulate a CLD patient should be individualised and multidisciplinary involvement may be beneficial in complex cases. Management of the underlying CLD should be optimised – for example, non-selective beta-blockers reduce portal pressures and the risk of variceal bleeding. Prophylactic variceal banding can also be considered. Alternatives such as left atrial appendage closure in AF can be considered if the bleeding risk is deemed unacceptably high. Shared decision making with the patient is critical, aligned with the current approach to holistic care for AF and in keeping with the principles of the ABC (Atrial fibrillation Better Care) pathway that has been associated with improved clinical outcomes [10,11]. The availability of reversal agents for DOACs may also impact on the decision.

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Table 1
Factors affecting thrombotic and bleeding risk in patients with chronic liver disease.

Factors Affecting Bleeding Risk	Factors Affecting Thrombosis Risk	Clinical Factors
Impaired clotting factor synthesis	Impaired pro-coagulant factor production (protein C and S, antithrombin)	Oesophageal varices
Thrombocytopenia		Increased risk of portal and hepatic vein thrombosis
Impaired anticoagulant drug metabolism	Increased levels of Von Willebrand Factor and Factor VIII	Comorbidities (e.g. renal failure, atrial fibrillation, other pro-thrombotic states, etc)

In summary, although the haemostatics of liver failure are complex, the concept of "auto-anticoagulation" is incorrect and increasing evidence suggests anticoagulants may not only be safe in most CLD patients but may have an important treatment role. Further research is needed to fully define this. The suboptimal prescribing practices and factors relating to adherence and persistence described by Chang et al bear emphasis if we are to optimally manage this complex patient group.

Author Contributions

PC: wrote the first draft
DG and GYHL: concept and critical revisions

Declaration of Competing Interests

GYHL: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally.

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