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332.THROMBOSIS AND ANTICOAGULATION: CLINICAL AND EPIDEMIOLOGICAL

Safety and Efficacy of Direct Oral Anticoagulants in Patients with Liver Cirrhosis: A Systematic Review and Meta-Analysis

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Introduction

Direct oral anticoagulants (DOACs) are widely used for treatment of venous thromboembolism (VTE) and stroke prophylaxis in patients with atrial fibrillation. Liver cirrhosis increases the risk of conditions necessitating anticoagulation, but also increases the risk of bleeding, complicating anticoagulation use. Traditionally, low molecular weight heparin (LMWH) or Vitamin K Antagonists (VKA) have been used in this patient population. However, VKA use can be complicated due to difficulty monitoring in the context of synthetic dysfunction and baseline INR abnormalities.

DOACs have emerged as alternative agents, with less proposed reliance on hepatic elimination. Apixaban, rivaroxaban, edoxaban and dabigatran are eliminated by the liver at 75%, 65%, 50% and 20% respectively. However, safety data on DOACs in cirrhosis patients is limited due to historic exclusion from larger trials. Patients with severe Child-Pugh (CP) classes are notably underrepresented in major trials. Various guidelines currently classify CP class C (and sometimes B) as contraindications to DOACs.

Methods

A literature search of MEDLINE and Embase from inception to Jan 2023 identified randomized controlled trials (RCTs) and cohort studies comparing DOACs to LMWH/VKA in cirrhosis patients. Two independent reviewers screened and extracted data at title, abstract, and full-text. Patient characteristics, CP class, and anticoagulation regimens were extracted.

The primary outcome was major bleeding per ISTH criteria. Secondary outcomes include clinically relevant non-major bleeding (CRNMB) and minor bleeding per ISTH criteria as a composite outcome, VTE incidence, and arterial thromboembolism (ATE) incidence. Results were stratified into two subgroups: CP B&C Exclusive, and CP Unspecified (primary study did not report or stratify by CP class). A meta-analysis was conducted using the Mantel-Haenszel random-effects model and presented as odds ratios (OR) with corresponding 95% confidence intervals (CI).

Results

Of 794 articles screened, 21 articles (2 RCTs, 1 prospective cohort, 13 retrospective cohorts, 5 abstracts) were included for analysis (n = 5738). Overall, DOACs were associated with a lower risk of major bleeding compared to controls (OR=0.63 [0.45, 0.89], p<0.01). This result was consistent in the CP B&C Exclusive subgroup (OR=0.42 [0.29, 0.62], p<0.01, 5 studies) but not in the CP Unspecified subgroup (OR=0.71 [0.48, 1.08], p=0.11, 13 studies). One large study (n=3213), Lawal 2023, weighed 20.1% in the CP B&C Exclusive group, favoured DOACs in reduction of major bleeding (OR=0.37, 95%CI [0.24,0.57]). Removal of this study in a post-hoc sensitivity analysis led to no differences in major bleeding in the CP B&C subgroup (OR=0.79, 95%CI [0.31,1.97]), CP Unspecified subgroup (OR=0.71, 95%CI [0.48,1.08]), or overall bleeding (OR=0.75, 95%CI [0.55,1.03]).

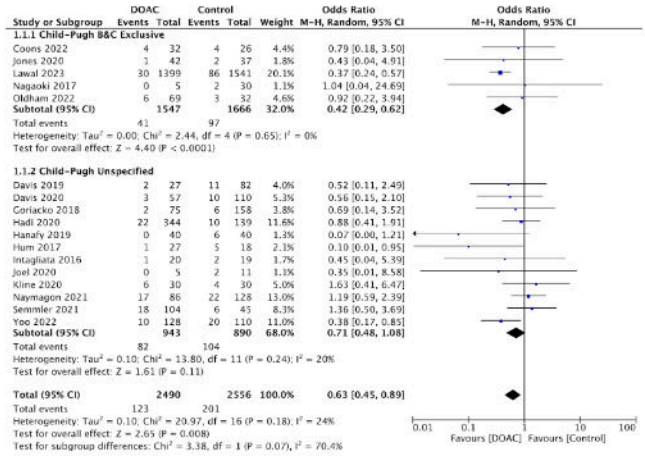
For CRNMB and minor bleeding, DOACs did not differ from control overall or in any subgroups. DOACs significantly reduced the risk of VTE in the CP Unspecified subgroup and overall. The difference in VTE incidence was non-significant in the CP B&C Exclusive subgroup, however the analysis only had two studies. The difference in ATE incidence in the overall sample and all subgroups was non-significant.

Conclusion

In this analysis comparing DOACs to LMWH/VKAs in patients with liver cirrhosis, DOACs were associated with a statistically significant reduction in the risk of major bleeding overall and in the more advanced subgroups (CP B&C). The association

between DOACs and the risk of CRNMB and minor bleeding was non-significant. Patients using DOACs had lower VTE incidence compared to those using LMWH/VKA, with no difference in ATE incidence.
Limitations include the inability to stratify CP class B and C due to limited CP class C evidence, reducing confidence in our ability to differentiate a differing effect in these two groups. Furthermore, a single large study (Lawal 2023), heavily influenced the major bleeding outcome; its removal shifted the conclusion from favouring DOACs to non-significant differences.
Nevertheless, these results provide reassurance on the safety profile of DOACs in comparison to LMWH/VKA in patients with cirrhosis, particularly in those with moderate to severe liver cirrhosis, a population of clinical uncertainty. There is no concerning evidence for future trials, which are much needed, to include this population.

Disclosures Crowther: *CSL Behring:* Honoraria; *Pfizer:* Honoraria; *Treasurer, American Society of Hematology:* Membership on an entity's Board of Directors or advisory committees; *Bayer:* Honoraria; *Eversana:* Consultancy; *Syneos Health:* Consultancy; *Hemostasis Reference Laboratory:* Consultancy; *Precision Biologics:* Consultancy; *Astra-Zeneca:* Consultancy.



Panel 1. Major bleeding in Child-Pugh B&C and Child-Pugh Unspecified groups with DOAC vs VKA

Outcome	CP Class B & C	Control	Effect Size	Number of Studies in Meta-Analysis
Major Bleeding (events/total sample)	41/1547	97/1666	OR = 0.42 (95% CI: 0.29 to 0.62; p=<0.0001; I^2=0%)	5
Venous Thromboembolism (events/total sample)	6/109	4/72	OR = 1.02 (95% CI: 0.25 to 4.07; p=0.98; I^2=0%)	2
Arterial Thromboembolism (events/total sample)	12/1399	24/1541	OR = 0.55 (95% CI: 0.27 to 1.10; p=0.09; I^2=NA)	1
CRNMB & Minor Bleeding (events/total sample)	24/117	10/93	OR = 2.21 (95% CI: 0.88 to 5.51; p=0.09; I^2=0%)	3
Outcome	**CP Unspecified**	**Control**	**Effect Size**	**Number of Studies in Meta-Analysis**
Major Bleeding (events/total sample)	82/943	104/890	OR = 0.71 (95% CI: 0.48 to 1.08; p=0.11; I^2=20%)	12
Venous Thromboembolism (events/total sample)	39/764	65/636	OR = 0.55 (95% CI: 0.32 to 0.95; p=0.03; I^2=0%)	10
Arterial Thromboembolism (events/total sample)	3/188	8/239	OR = 0.72 (95% CI: 0.17 to 3.05; p=0.65; I^2=15%)	5
CRNMB & Minor Bleeding (events/total sample)	94/659	109/690	OR = 0.79 (95% CI: 0.57 to 1.10; p=0.16; I^2=0%)	11
Outcome	**Overall**	**Control**	**Effect Size**	**Number of Studies in Meta-Analysis**
Major Bleeding (events/total sample)	123/2490	201/2556	OR = 0.63 (95% CI: 0.45 to 0.89; p=0.008; I^2=24%)	17
Venous Thromboembolism (events/total sample)	45/873	69/708	OR = 0.60 (95% CI: 0.36 to 0.99; p=0.05; I^2=0%)	12
Arterial Thromboembolism (events/total sample)	15/1587	32/1780	OR = 0.58 (95% CI: 0.31 to 1.07; p=0.08; I^2=0%)	6
CRNMB & Minor Bleeding (events/total sample)	118/776	119/783	OR = 0.89 (95% CI: 0.65 to 1.21; p=0.45; I^2=0%)	14

Panel 2. Summary of the Effect Sizes of All Outcomes

Abbreviations (from left to right, top-down): CP, Child-Pugh; OR, odds ratio; CI, confidence interval; NA, not applicable; CRNMB, clinically relevant non-major bleeding.

Figure 1

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