

## RATES OF HEMORRHAGIC EVENTS AND HEMODIALYSIS CIRCUIT THROMBOSIS IN PATIENTS WITH END-STAGE RENAL DISEASE ON HEMODIALYTIC TREATMENT RECEIVING A FACTOR-XI INHIBITOR: A SYSTEMATIC REVIEW AND META-ANALYSIS.

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**Background and aims:** In patients undergoing hemodialysis, anticoagulants are commonly used to reduce thromboembolic events and circuit thrombosis. However, patients affected by end-stage renal disease (ESRD) are considered at higher risk of hemorrhagic events. Inhibiting coagulation Factor XI (FXI) is shown to be safer in terms of bleeding events, given its peripheral role in the coagulation cascade. Therefore, new anti-FXI therapies, such as monoclonal antibodies and antisense oligonucleotides, which are not kidney-dependent, offer a promising option for patients undergoing hemodialysis. This review aims to explore the best available evidence about the safety of FXI inhibitors in patients affected by ESRD requiring hemodialysis.

**Methods:** We performed a systematic review screening three online databases (Pubmed, EMBASE, WebOfScience) including all Randomized controlled trials (RCTs) of at least phase II, comparing FXI inhibitors with placebo in patients with ESRD requiring hemodialysis. Our primary outcome was the rate of major bleeding (MB) and clinically relevant nonmajor bleeding (CRNMB) defined by ISTH definitions. Hemodialysis circuit associated thrombosis was defined according to local investigator through visual assessment of the hemodialysis circuit chamber. Study quality was assessed with the RoB2 tool. Sensitivity analyses have been carried out to

minimize the risk of bias excluding high risk of bias studies.

**Results:** This systematic review included five phase II randomized controlled trials (RCTs), of which four were eligible for meta-analysis, encompassing a total of 969 randomized patients. Using a random-effects model, the pooled relative risk (RR) for the primary outcome including all doses of FXI inhibitors studied was 0.79 (95% CI: 0.48-1.31), showing a not increased bleeding risk for the intervention (Figure 1). When the analysis was limited to the highest tested doses, the RR remained similar at 0.76 (95% CI: 0.41-1.42). No statistical heterogeneity was observed ( $I^2 = 0\%$ ).

Two of the four trials that reported on circuit thrombosis demonstrated a significant reduction in such events. Specifically, IONIS-FXIRx at 300 mg achieved an RR of 0.37 (95% CI: 0.24-0.58), while Osocimab showed a reduced risk at both low (RR 0.71, 95% CI: 0.54-0.93) and high doses (RR 0.66, 95% CI: 0.49-0.87). Overall, FXI inhibitors significantly reduced circuit thrombosis compared to placebo, with a pooled RR of 0.72 (95% CI: 0.62-0.84) and no observed heterogeneity ( $I^2 = 0\%$ ).

**Conclusions:** FXI inhibitors did not statistically increase the number of CRNMB and MB in the study population reducing the circuit thrombotic events rates. Larger phase III trials are still needed to confirm the presented results.

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