Novel factor XI inhibitors for postoperative VTE prophylaxis: Breakthroughs and insights from the ROXI-VTE-I and ROXI-VTE-II trials

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The essence of postoperative venous thromboembolism (VTE) management is to balance antithrombotic efficacy against bleeding risk. Surgical trauma places patients in a paradoxical state of high risk for both thrombosis and hemorrhage. Consequently, the key clinical challenge is to provide sufficient anticoagulation while effectively mitigating the risk of bleeding. A major recent advance in anticoagulation is the extensive investigation of coagulation Factor XI (FXI). As a key component of the intrinsic coagulation pathway, FXI plays a crucial role in thrombosis but is not essential for physiological hemostasis, making it an ideal target for novel anticoagulants.[1] FXI can be activated by either activated factor XII (FXIIa) or thrombin. Previous studies have shown that FXIa inhibitors are associated with a lower risk of postoperative VTE compared to enoxaparin. However, the relative contributions of FXIIa-mediated activation of FXI to the development of postoperative VTE remain unclear.

In this context, the results of the ROXI-VTE-I and ROXI-VTE-II studies reported by Weitz et al. have garnered significant attention (Figure 1). These two Phase II clinical trials evaluated the efficacy and safety of two fully human monoclonal antibodies, REGN9933^{A2} and REGN7508Cat, for the prevention of VTE after knee replacement surgery.[2] The findings from these trials offer vital evidence for the clinical development of FXI inhibitors and enhance our understanding of postoperative thrombus formation. More importantly, this study innovatively selected two monoclonal antibodies with distinct mechanisms of action, and through an ingenious trial design, deeply investigated the specific contribution of FXIIa-mediated FXI activation to postoperative thrombogenesis.

The research results reveal an important association between the mecha-

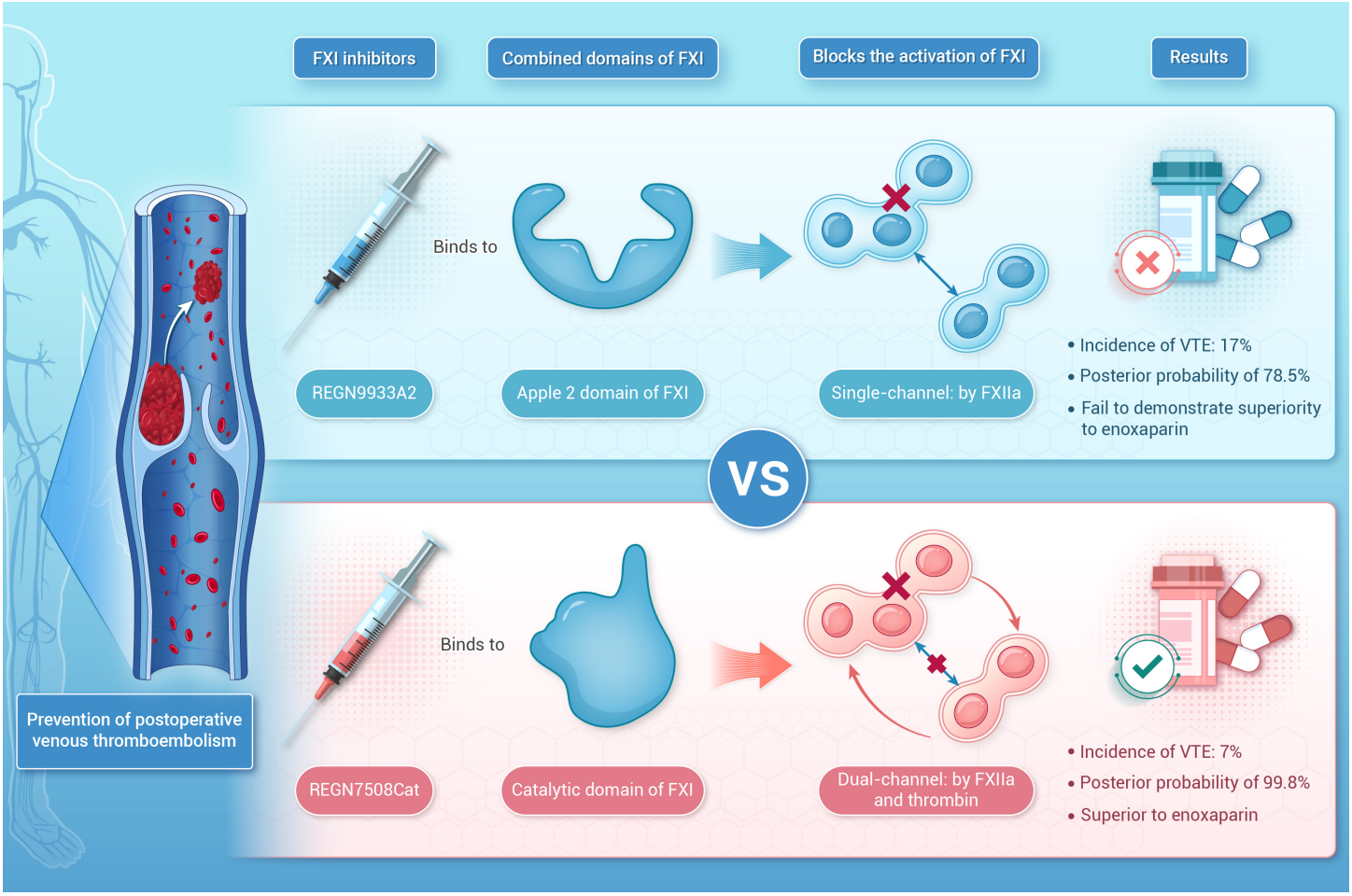

Figure 1. Mechanism of action and clinical efficacy of two novel factor XI inhibitors for postoperative venous thromboembolism prophylaxis. This figure illustrates the distinct mechanisms of action and corresponding clinical outcomes of REGN9933^{A2} and REGN7508Cat, two fully human monoclonal antibodies targeting FXI, in the prevention of postoperative VTE. REGN9933A2 binds to the Apple 2 domain of FXI and selectively inhibits FXIIa-mediated FXI activation (single-channel inhibition). In clinical trials, it resulted in a VTE incidence of 17% with a posterior probability of 78.5%, failing to demonstrate superiority over enoxaparin. In contrast, REGN7508Cat targets the catalytic domain of FXI, blocking both FXIIa- and thrombin-mediated FXI activation (dual-channel inhibition). This dual inhibition led to a markedly lower VTE incidence of 7% with a posterior probability of 99.8%, confirming its superior efficacy compared to enoxaparin for postoperative VTE prophylaxis.

nism of action of FXI inhibitors and their clinical efficacy. In these two trials, REGN7508Cat demonstrated superior efficacy to enoxaparin for the primary endpoint (VTE incidence: 7% vs. 17%, posterior probability: 99.8%), consistent with previous studies on other Factor XI inhibitors.[3] In contrast, REGN9933^{A2} did not show superiority (17% vs. 22%, posterior probability: 78.5%). This divergence primarily stems from their distinct mechanisms: REGN9933^{A2} targets the Apple 2 domain of FXI and only inhibits its activation mediated by FXIIa, whereas REGN7508Cat targets the catalytic domain, thereby blocking the activation of FXI mediated by both FXIIa and thrombin. The dual-blocking mechanism of REGN7508Cat provides a distinct advantage in inhibiting thrombosis. Conversely, the limited efficacy of REGN9933^{A2} indicates that targeting only the FXIIa-mediated FXI activation may not be enough to outperform enoxaparin. Nevertheless, despite REGN9933^{A2} failing to outperform enoxaparin, the results still suggest the involvement of FXIIa-mediated FXI activation in postoperative VTE formation.

This study confirms that REGN7508Cat is superior to enoxaparin in preventing postoperative VTE, but its potential advantages may extend beyond efficacy. The greatest theoretical advantage of FXI inhibitors lies in achieving a "decoupling" of antithrombotic efficacy from hemorrhagic risk. However, in the safety analysis of this study, no major or clinically relevant non-major bleeding events were reported in either trial. While this demonstrates the favorable safety profile of REGN7508Cat, it is insufficient to conclude that its safety is superior to that of current anticoagulant regimens. However, it should be noted that the subjects in this study were patients undergoing elective knee replacement surgery, whose bleeding risk is relatively controllable. Therefore, in populations at higher risk of bleeding, the advantage of REGN7508Cat in "not increasing bleeding risk" may become more pronounced. For instance, in elderly patients or those with comorbid gastrointestinal malignancies or renal insufficiency, FXI inhibitors could offer a safer alternative for such patients. Similarly, REGN9933^{A2} may also possess this potential advantage. However, this concept requires further validation in clinical trials.

Despite the promising advantages of REGN7508Cat, its unique pharmacokinetic profile is a double-edged sword. A single intravenous dose provides anticoagulation for several weeks, which greatly enhances patient adherence and is particularly suitable for prophylaxis during the short, high-risk postoperative period. However, the long half-life also presents a challenge: in the event of severe bleeding requiring emergency reversal or an urgent surgery, there is currently no specific antidote available, such as Idarucizumab or Andexanet alfa.[4] Although FXI inhibitors theoretically have a low bleeding risk, the inability to achieve rapid reversal remains a practical issue that clinicians must weigh.

Despite the rigorous design of the ROXI-VTE series of studies, several limitations remain. First, the potential bias introduced by the open-label design warrants close attention. Although endpoint events were adjudicated in a blinded manner, the open-label design may influence the clinical decision-making process. Healthcare personnel's awareness of treatment allocation could affect postoperative management strategies, potentially indirectly impacting the incidence of VTE. Second, the Bayesian analysis may lead to potential bias. The ROXI-VTE-II study incorporated data from the enoxaparin group of ROXI-VTE-I retrospectively; although this approach improved statistical efficiency, it introduced the risk of bias from historical data. The two studies were conducted at different time points, and there may be subtle but important differences in patient populations, surgical techniques, and postoperative care. The relative homogeneity of the study population limits the generalizability of the results. The inclusion criteria excluded patients with various high-risk characteristics, such as active cancer and a history of VTE - precisely those patient groups who most require individualized anticoagulation strategies in clinical practice. Furthermore, the study centers were predominantly located in Eastern European countries. Therefore, extrapolating the study findings to broader populations requires caution. In the future, more rigorous, randomized, double-blind, phase 3 studies, such as the ongoing ROXI-APEX and ROXI-ASPEN trials, are expected to provide definitive evidence for the use of FXI inhibitors in postoperative VTE prophylaxis. Furthermore, exploring the applications of REGN7508Cat and REGN9933^{A2} in other thrombotic diseases is also crucial. For instance, if studies of REGN7508Cat in stroke prevention for atrial fibrillation prove successful, it could reshape the anticoagulation therapy landscape.

In summary, the ROXI-VTE studies mark a significant step towards precision anticoagulation. They not only validate the potential of FXI as a highly effective antithrombotic target but also, through the comparison of mechanism-specific drugs, deepen our understanding of the differing dominant pathways in thrombus formation across various clinical scenarios. In the future, we may ultimately achieve the ultimate goal of maximizing antithrombotic efficacy while minimizing bleeding risk, based on FXI inhibitors.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.