Pivotal study on hemostats & their mechanism of action in controlling massive bleeding

PNAS RESEARCH ARTICLE | ENGINEERING MEDICAL SCIENCES

An architecturally rational hemostat for rapid stopping of massive bleeding on anticoagulation therapy

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Hemostatic devices are critical for managing emergent severe bleeding. With the increased use of anticoagulant therapy, there is a need for next-generation hemostats. We rationalized that a hemostat with an architecture designed to increase contact with blood, and engineered from a material that activates a distinct and undrugged coagulation pathway can address the emerging need. Inspired by lung alveolar architecture, here, we describe the engineering of a next-generation single-phase chitosan hemostat with a tortuous spherical microporous design that enables rapid blood absorption and concentrated platelets and fibrin microthrombi in localized regions, a phenomenon less observed with other classical hemostats without structural optimization. The interaction between blood components and the porous hemostat was further amplified based on the charged surface of chitosan. Contrary to the dogma that chitosan does not directly affect physiological clotting mechanism, the hemostat induced coagulation via a direct activation of platelet Toll-like receptor 2. Our engineered porous hemostat effectively stopped the bleeding from murine liver wounds, swine liver and carotid artery injuries, and the human radial artery puncture site within a few minutes with significantly reduced blood loss, even under the anticoagulant treatment. The integration of engineering design principles with an understanding of the molecular mechanisms can lead to hemostats with improved functions to address emerging medical needs.

clotting | hemostasis | trauma | biomaterial | hemostat

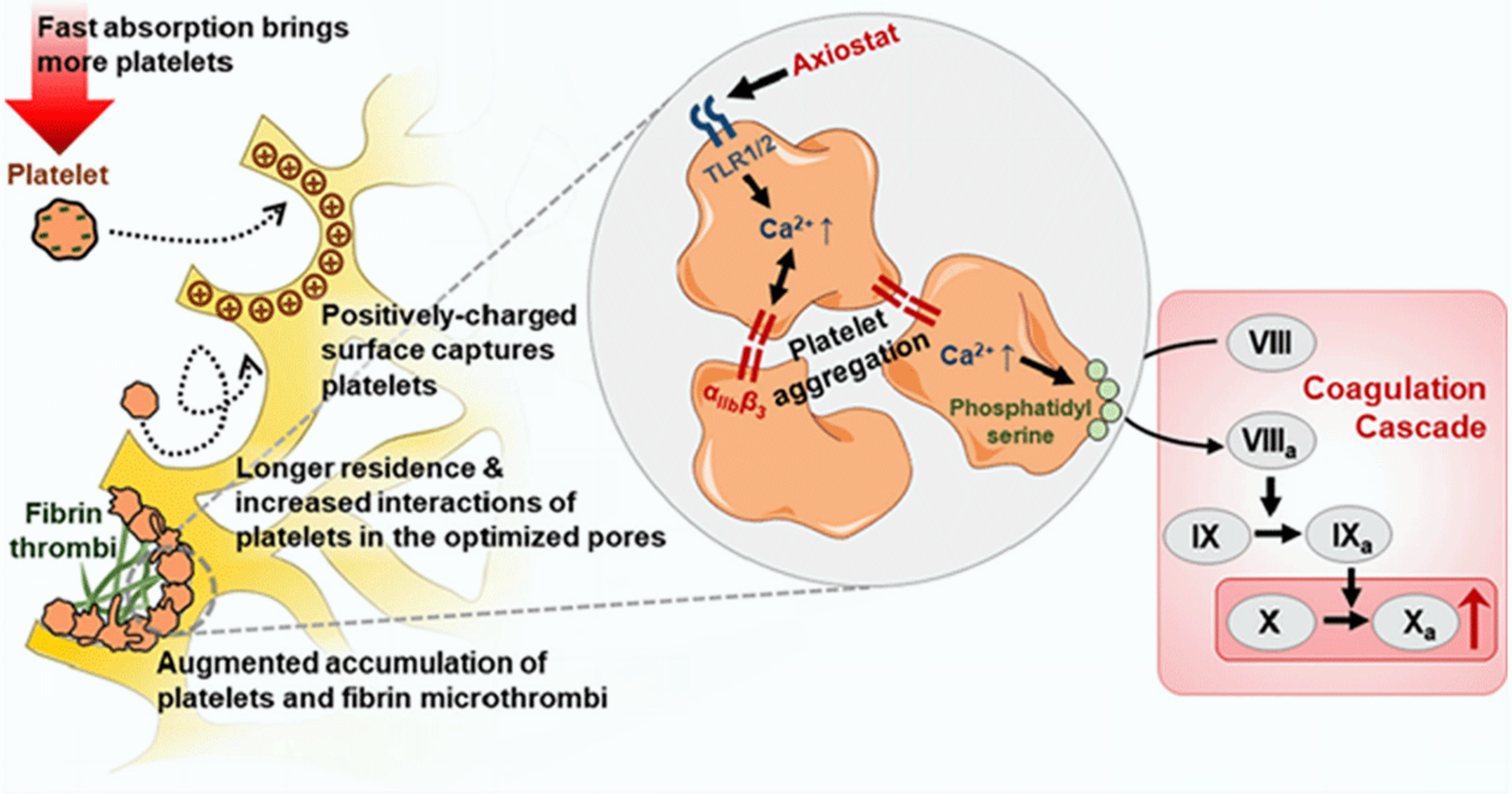
Significance

Approximately 35% of hemorrhagic deaths occur before hospital arrival, with the risk amplified by anticoagulant therapies. To address this, our research introduces a next-generation chitosan hemostat, rationally designed with optimized pore size and connectivity. This design allows the hemostat to quickly absorb blood and concentrate clotting components, effectively counteracting anticoagulant effects. Contrary to previous beliefs that chitosan does not participate in the physiological

Major Findings

Axiostat Chitosan hemostasis mechanism involves 4 major steps

1. Charged–based adhesion between blood components and Axiostat
2. Platelet Activation via Toll-like receptors **(TLR)**
3. Clotting cascade activation
4. Fibrin Microthrombi (Plug) Formation at the bleeding site



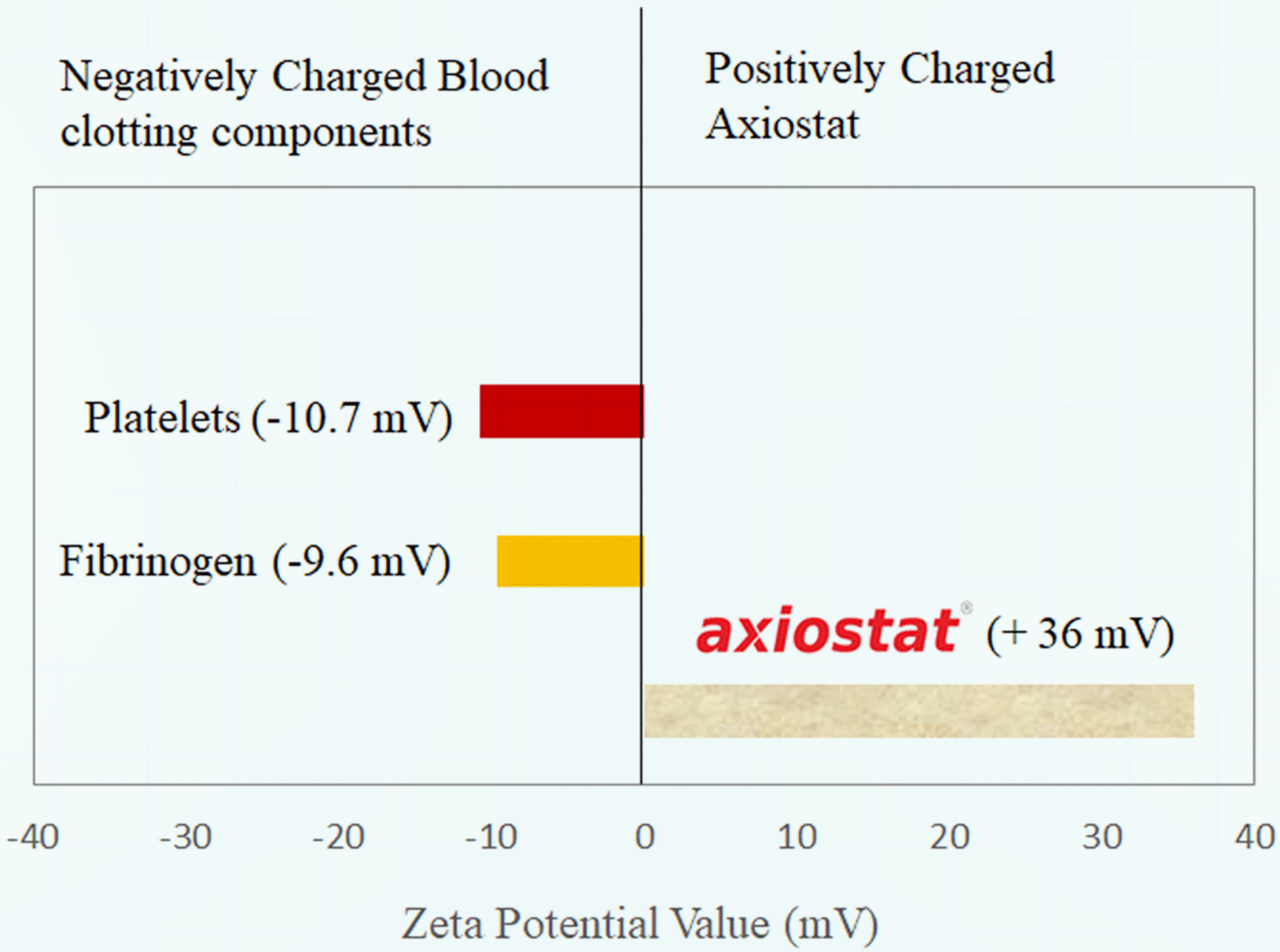
(Mechanism of Action of Axiostat Hemostats in Controlling Massive Bleeding)

1.

Charge based interaction

- Differences in the positive and negative charge result into a strong electrostatic interaction which helps in the capturing of major blood clotting components such as platelets, RBCs, and fibrinogen within the Axiostat

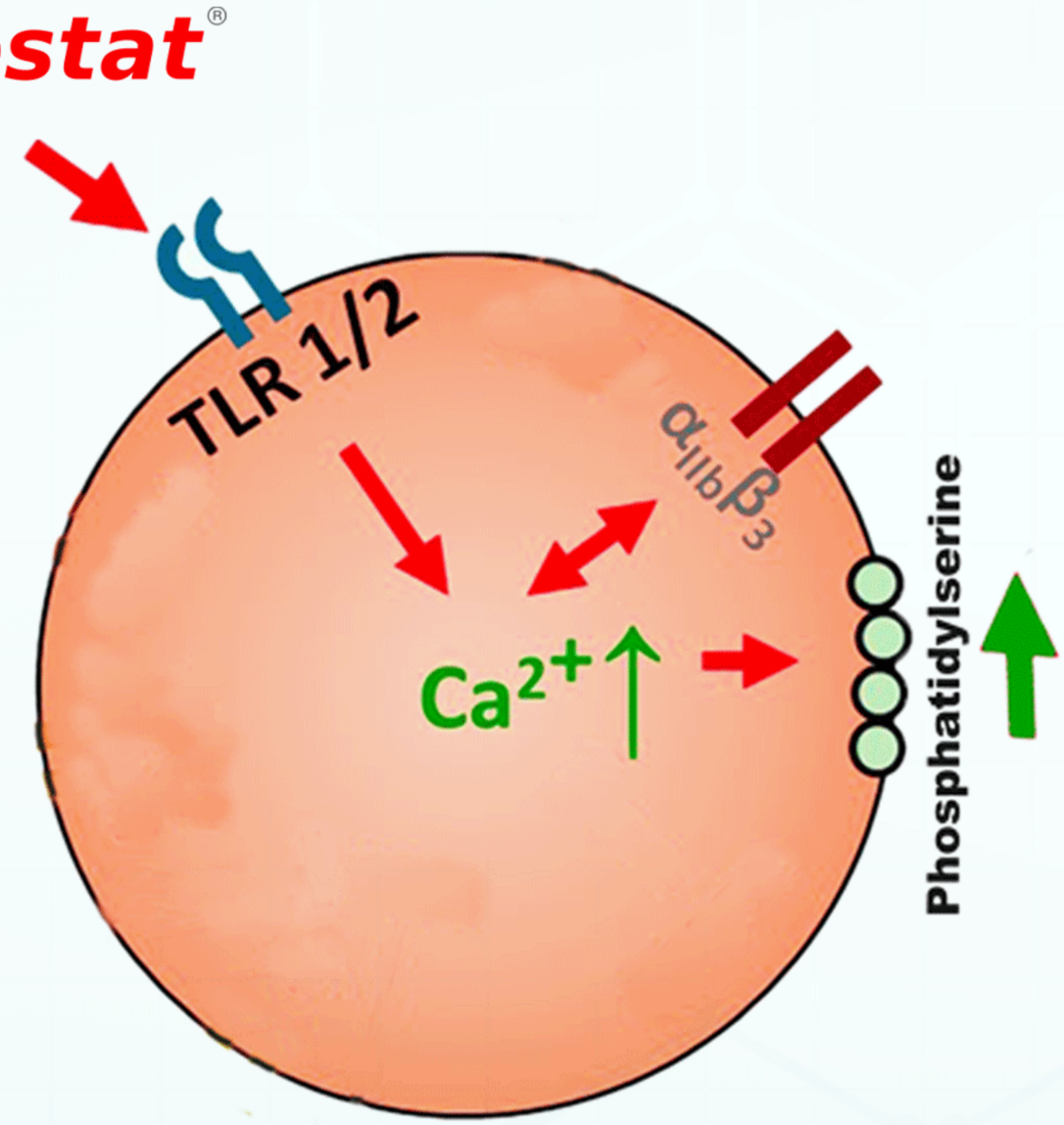
- Research through light on difference in charge densities



2.

Platelet Activation via Toll-like receptors (TLR)

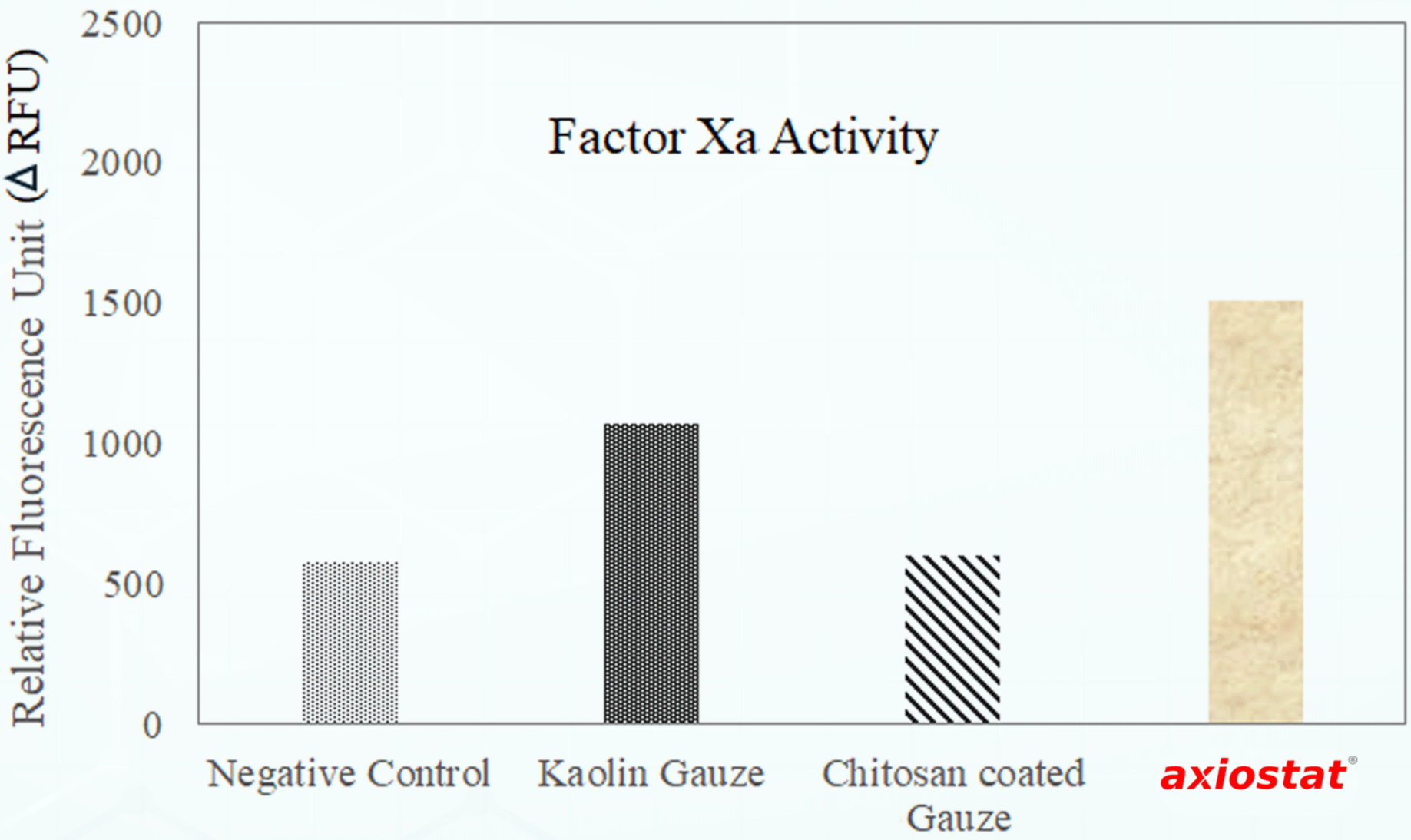
- Research discover Toll-like receptor (TLR) is one of the key receptors via which platelet gets activated.
- Anticoagulation therapy does not interfere the stimulation of TLR receptors in the presence of axiostat.
- Axiostat stimulates the TLR receptor, which activates the platelet activation pathway.



3.

Clotting cascade activation

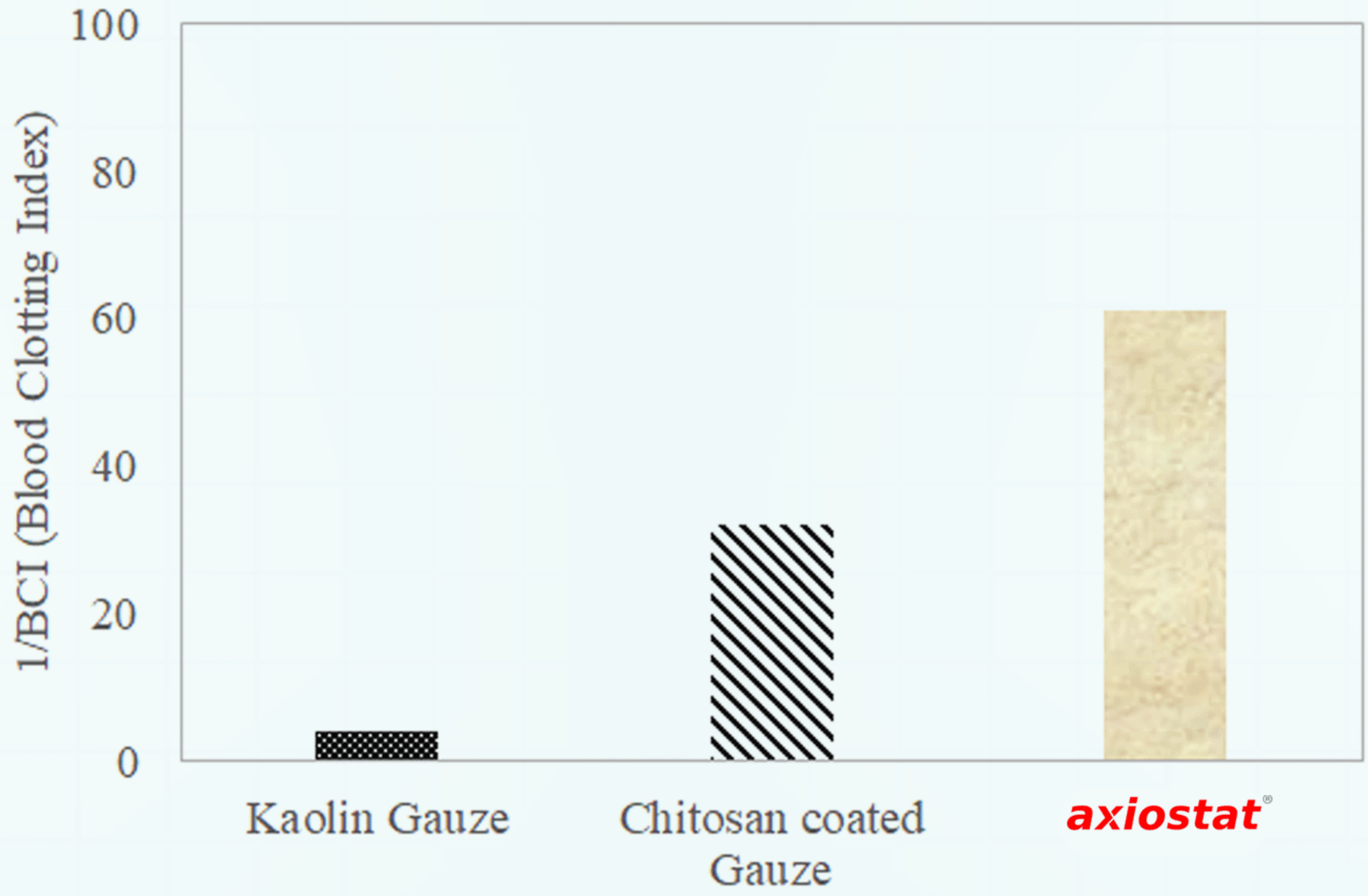
- Factor Xa (FXa) is the key factor in the blood clotting cascade where the intrinsic and extrinsic pathways join together and generate the thrombin formation
- Axiostat exhibited significantly higher FXa activity and thrombin generation compared to the other control groups.



4.

Fibrin Microthrombi (Plug) Formation

- A higher value of (1/BCI) indicates more faster hemostasis process
- Axiostat showed a significantly higher (1/BCI) value compared to the other groups indicating rapid plug formation and controlling massive bleeding



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