

# *The Key Role of Thrombin in Hemophilia*

## **Background**

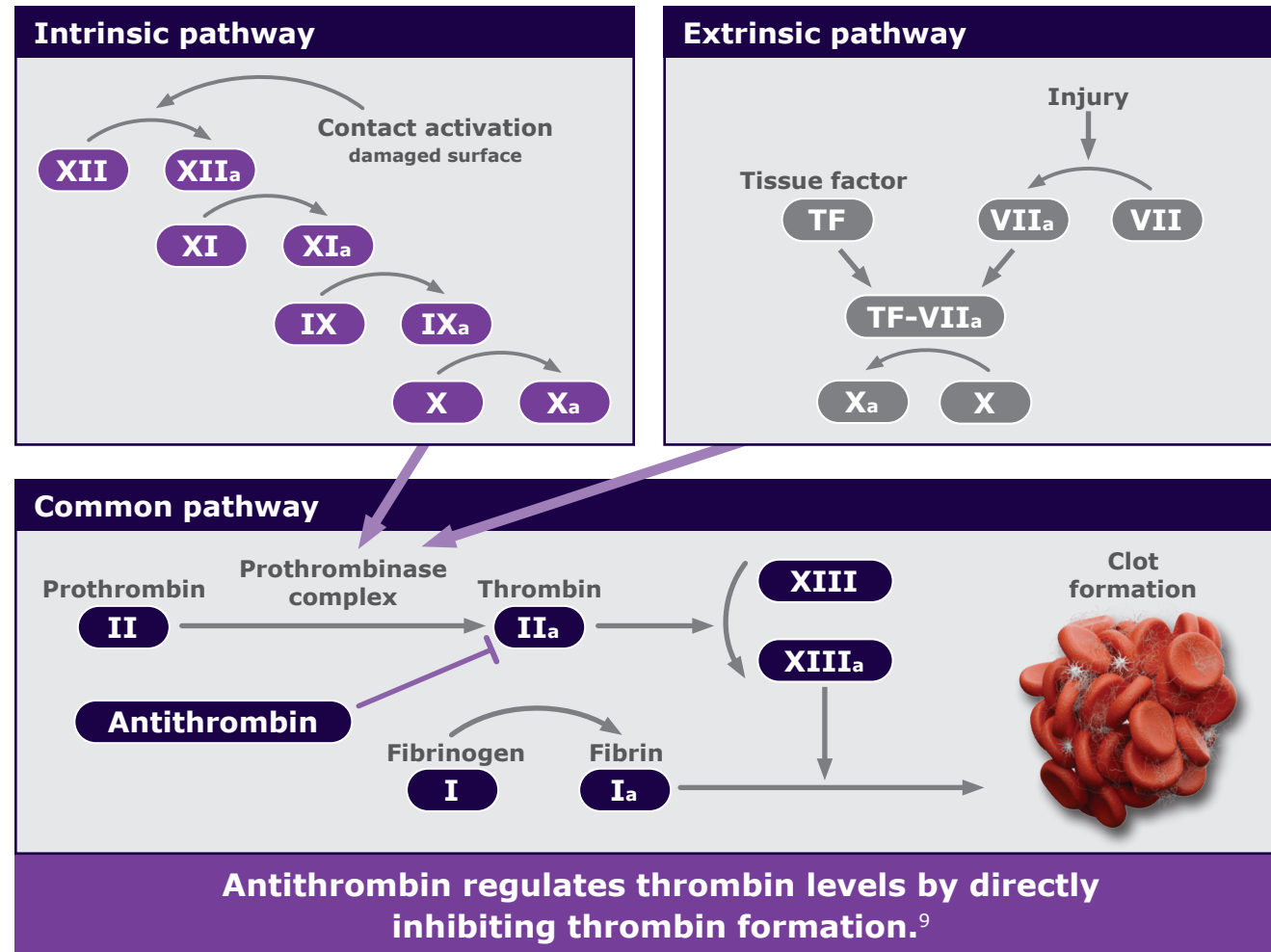
Hemophilia is an X-linked recessive hereditary bleeding disorder that primarily affects males.<sup>1,2</sup> There are an estimated 30,000 to 33,000 males in the United States living with hemophilia.<sup>1,3</sup> Approximately 40% of individuals with hemophilia have the severe form of the disorder, characterized by spontaneous or traumatic joint and muscle bleeds.<sup>3,4</sup> The most common forms of hemophilia are hemophilia A and B, which account for 12 cases and 3.7 cases per 100,000 US males, respectively.<sup>3</sup>

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males in the United States living with hemophilia.

Patients with hemophilia lack the ability to achieve hemostasis, a process known to stop bleeding at the site of injury, in which thrombin plays a crucial role.<sup>1,4</sup> Hemophilia is the result of a deficiency in procoagulants factor VIII (FVIII) or factor IX (FIX), leading to reduced thrombin generation, which causes diminished clot stability and consequently various bleeding manifestations.<sup>4</sup> The amount of thrombin generated is governed by a balance of procoagulant and anticoagulant proteins (eg, antithrombin).<sup>4</sup> In a healthy individual, upon vascular damage, hemostasis is achieved through the formation of a platelet plug that leads to a stable fibrin clot.<sup>5</sup> From the time of injury to clot formation, thrombin is the key driver in a sequence of steps that take place leading to clotting.<sup>5</sup> The process of hemostasis that begins immediately following injury is known as the coagulation cascade.<sup>6</sup>

## Coagulation cascade pathways

In the coagulation cascade, there are 2 different pathways involved that lead to clot formation and prevention of bleeds—the intrinsic and extrinsic pathways.<sup>6</sup> These pathways are the primary pathways that converge at factor X (FX) before entering the common pathway.<sup>6,7</sup> The common pathway where thrombin is a key player is necessary to lead to clot formation. Figure 1 shows how the coagulation process occurs in plasma-based in vitro coagulation.<sup>8</sup>



**Figure 1.** Once the intrinsic or extrinsic pathways are activated, it leads to various downstream processes that converge at the common pathway in which thrombin plays its major role in clot formation.<sup>6,7</sup>

### Intrinsic pathway

Upon internal damage to the vascular endothelium, the intrinsic pathway is initiated by exposure to endothelial collagen.<sup>7,10</sup> This pathway leads to the sequential activation of factor XII (FXII), factor XI (FXI), and FIX, leading to the formation of active FIX and FX.<sup>6,7,10</sup>

### Extrinsic pathway

Upon an external injury, the extrinsic pathway is initiated by exposure to subendothelial tissue factor (TF), which combines with activated factor VII (FVII) to generate activated FX.<sup>6,10</sup>

### Common pathway

In the common pathway, active FX joins active factor V (FV) to form a prothrombinase complex.<sup>6</sup> This complex converts prothrombin into thrombin.<sup>7</sup> Thrombin is responsible for cleaving fibrinogen into fibrin and activating factor XIII (FXIII).<sup>6</sup> Activated FXIII then converts the fibrin to a stabilized cross-linked fibrin clot.<sup>5</sup>

## Thrombin as a key player in the coagulation cascade

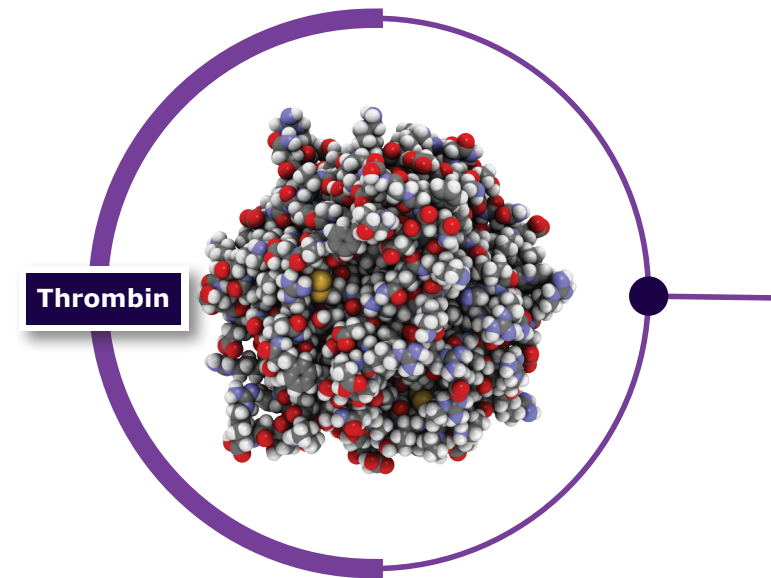
In the coagulation cascade, thrombin serves as a key player in achieving hemostasis.<sup>4</sup> Thrombin (Figure 2) sits at the hub of the coagulation process and has various roles, including full activation of platelet cells to promote platelet aggregation at the site of injury; activation of FV, FVIII, FXI, and FXIII proteins to further increase the production of thrombin and fibrin; and, most importantly, cleave fibrinogen into fibrin to form a stable clot.<sup>4,6</sup> Due to its essential role in the coagulation process, low concentrations of thrombin result in loosely woven fibrin strands that have low stability.<sup>4</sup> In addition, it has been found that in patients with a severe clinical bleeding phenotype, thrombin peak height and potential were decreased regardless of the FVIII and FIX activity level.<sup>2</sup> This suggests that effective hemostasis hinges on adequate thrombin generation regardless of FVIII or FIX activity. For this reason, patients with hemophilia A or B can still achieve hemostasis through sufficient thrombin generation.

### Determinants of thrombin generation

The overall goal of hemostasis is to generate sufficient thrombin to form a stable clot.<sup>4</sup> As discussed, the generation of thrombin is tightly managed by the balance between anticoagulants and procoagulants within the hemostatic system.<sup>4</sup> In patients with hemophilia, the deficiency in procoagulants FVIII or FIX results in ineffective thrombin generation, which results in reduced clot stability.<sup>4</sup> Anticoagulants such as TF pathway inhibitor (TFPI) and antithrombin can reduce the amount of thrombin generated.<sup>4</sup> Antithrombin inhibits thrombin generation in the plasma by directly inhibiting thrombin and inactivating any uncomplexed active FX.<sup>2</sup> TFPI regulates the production of active FX, which helps generate thrombin during the initiation phase of coagulation.<sup>5</sup>

### The association between thrombin generation and bleeding phenotype

There exists a correlation between thrombin generation and bleeding phenotype in which patients with lower levels of thrombin

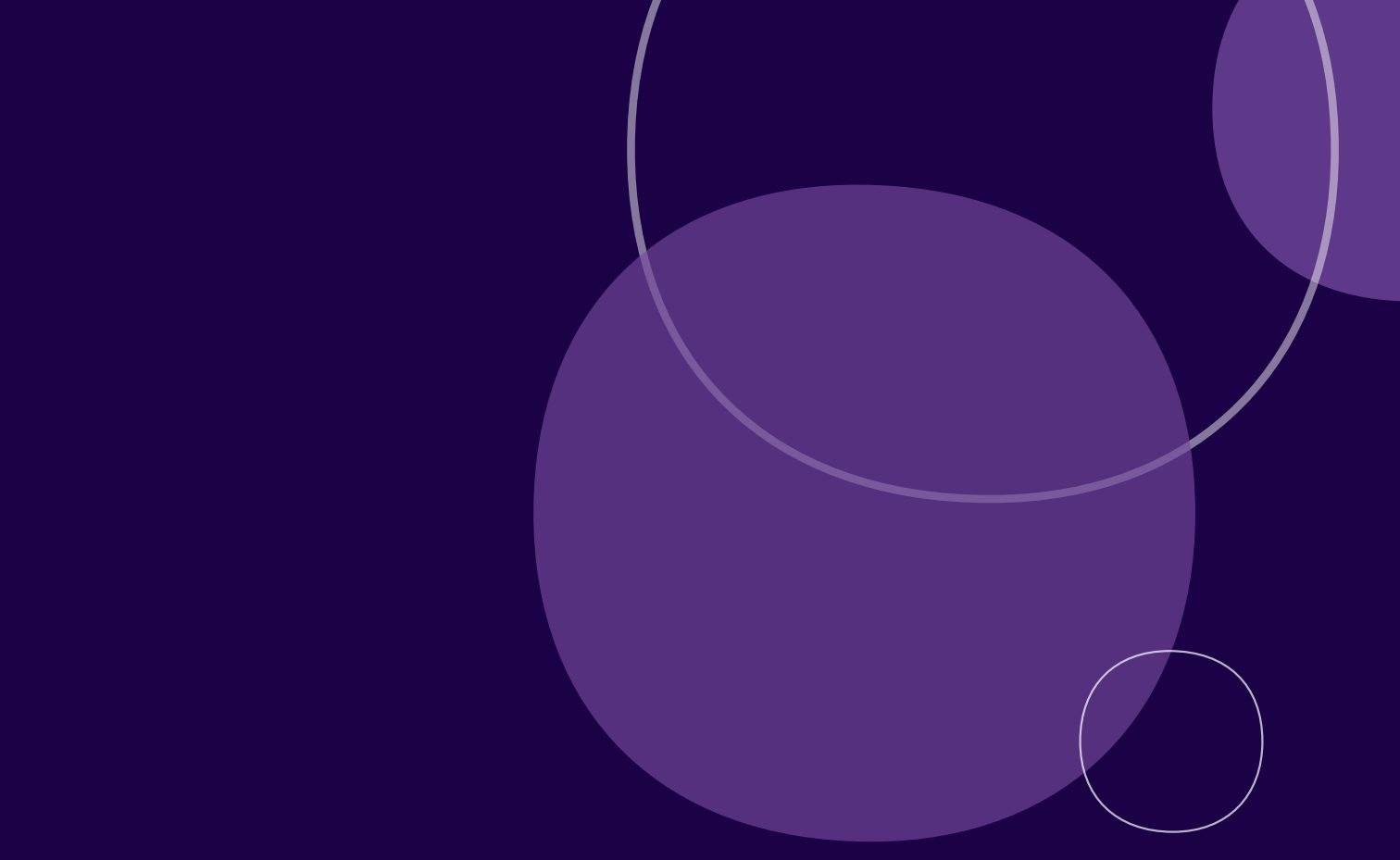


**Figure 2.** Thrombin is a multifunctional serine protease molecule generated in injured cells that plays a central role in achieving hemostasis.<sup>12</sup>

generation have a severe clinical bleeding phenotype.<sup>2</sup> Individuals with increased thrombin generation have been found to be protected from bleeding, whereas those with lower thrombin generation had an increase in bleeding complications.<sup>4</sup> Moreover, there is an inverse association between thrombin potential and both annualized bleeding rate (ABR) and annualized joint bleeding rate (AJBR) in which patients with higher thrombin generation have lower ABR and AJBR, and therefore better clinical outcomes.<sup>2</sup>

### Hemophilia therapies

Ultimately, all approved and investigational therapies for hemophilia enhance thrombin generation with the aim of restoring effective hemostasis.<sup>4</sup> Current hemophilia treatments such as factor replacement work to increase procoagulants (eg, FVIII and FIX) while nonfactor therapies aim to enhance procoagulants.<sup>4,11</sup> Due to the pivotal role of thrombin in the coagulation process and its association with bleeding phenotype, there may be a need for innovative rebalancing therapies that directly target anticoagulants to help achieve hemostasis.



**References:** **1.** Centers for Disease Control and Prevention. A new study of hemophilia occurrence finds many more cases in the United States. Accessed November 27, 2023. <https://www.cdc.gov/ncbddd/hemophilia/features/keyfinding-hemophilia-occurrence-US.html> **2.** Verhagen MJA, van Heerde WL, van der Bom JG, et al. In patients with hemophilia, a decreased thrombin generation profile is associated with a severe bleeding phenotype. *Res Pract Thromb Haemost.* 2023;7(2):100062. **3.** Soucie JM, Miller CH, Dupervil B, Le B, Buckner TW. Occurrence rates of haemophilia among males in the United States based on surveillance conducted in specialized haemophilia treatment centres. *Haemophilia.* 2020;26(3):487-493. **4.** Sidonio RF, Hoffman M, Kenet G, Dargaud Y. Thrombin generation and implications for hemophilia therapies: a narrative review. *Res Pract Thromb Haemost.* 2022;7(1):100018. **5.** Negrier C, Shima M, Hoffman M. The central role of thrombin in bleeding disorders. *Blood Rev.* 2019;38:100582. **6.** Grover SP, Mackman N. Intrinsic pathway of coagulation and thrombosis. *Arterioscler Thromb Vasc Biol.* 2019;39(3):331-338. **7.** Chaudhry R, Usama SM, Babiker HM. Physiology, coagulation pathways. In: *StatPearls.* StatPearls Publishing; 2022. **8.** Robertson S, Miller MR. Ambient air pollution and thrombosis. *Part Fibre Toxicol.* 2018;15(1):1. **9.** Bravo-Pérez C, Vicente V, Corral J. Management of antithrombin deficiency: an update for clinicians. *Expert Rev Hematol.* 2019;12(6):397-405. **10.** Barmore W, Bajwa T, Burns B. Biochemistry, clotting factors. In: *StatPearls.* StatPearls Publishing; 2023. **11.** Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia.* 2020;26(suppl 6):1-158. **12.** Al-Amer OM. The role of thrombin in haemostasis. *Blood Coagul Fibrinolysis.* 2022;33(3):145-148.

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