

## LONGITUDINAL THROMBIN GENERATION PROFILING IN A PATIENT WITH SEVERE HEMOPHILIA A DURING ANTITHROMBIN-LOWERING THERAPY, CANCER, AND MAJOR SURGERY

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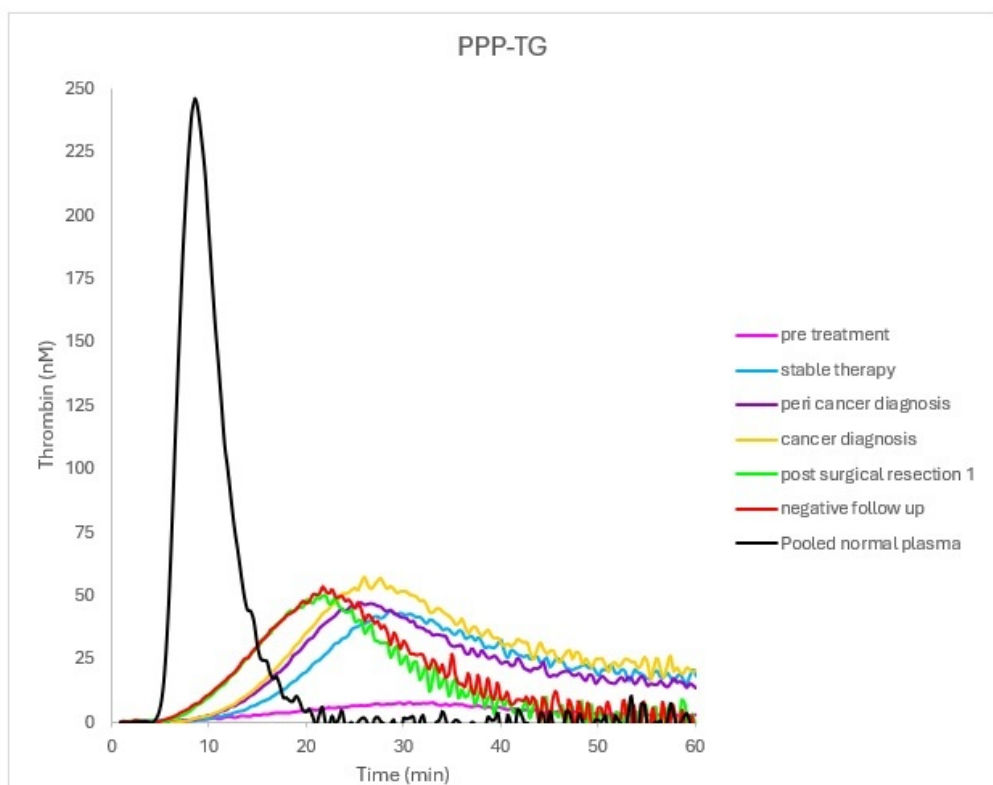
**Background and Aims.** Thrombin generation (TG) is one of the few functional assays available to assess global hemostatic balance in patients with hemophilia receiving non-replacement therapies. However, longitudinal TG data over extended periods and during major biological stressors, such as cancer and surgery, remain limited. We aimed to describe five-year longitudinal changes in plasma TG in a patient with severe hemophilia A receiving the antithrombin-lowering siRNA therapy fitusiran, including the impact of cancer diagnosis and major surgery.

**Materials and Methods.** Serial TG measurements were performed in platelet-poor plasma from 2020 to 2025 using the calibrated automated thrombogram (CAT). TG was assessed at low (1 pM) and intermediate (5 pM) tissue factor (TF) concentrations at predefined clinical timepoints: pre-treatment, stable therapy, peri-cancer diagnosis, and post-surgical resection. Lag time, endogenous thrombin potential (ETP), peak thrombin, velocity index, and tail formation were analyzed. Antithrombin levels were measured in parallel. Pooled normal plasma was included as a reference. Written informed consent was obtained according to local ethical standards.

**Results.** At 1 pM TF, a trend toward shorter lag time and higher peak thrombin was observed during the pre-tumor

phase compared with stable therapy, while ETP remained non-measurable due to persistent thrombin activity. No relevant changes were observed around colorectal cancer diagnosis. Following colorectal cancer resection in March 2024, thrombin generation at 1 pM TF became fully measurable at the first post-surgical assessment, with ETP increasing from unmeasurable to 895 nM·min and late-phase tail formation (StartTail 55 min), despite only moderate peak thrombin (45 nM) (Figure 1). Antithrombin levels ranged between approximately 15-30% during stable follow-up before surgery and decreased to about 10-26% after surgery. At 5 pM TF, TG remained consistently high throughout the entire observation period, confirming preserved thrombin-generating capacity.

**Conclusions.** In this long-term longitudinal case, colorectal cancer diagnosis was not associated with major changes in low-trigger TG, consistent with a localized disease stage. In contrast, surgical resection induced a distinct qualitative shift in TG dynamics, with the emergence of sustained thrombin activity despite moderate peak values. These findings suggest that, in pharmacologically rebalanced hemophilia, major biological stressors may primarily affect thrombin persistence rather than overall thrombin generation.



**Figure 1.** Platelet-poor plasma thrombin generation (PPP-TG) assessed at low tissue factor concentration (1 pM TF) at different longitudinal time points in a patient with severe hemophilia A under antithrombin-lowering non-replacement therapy. Curves represent pre-treatment, stable antithrombin-lowering therapy, peri-cancer diagnosis, cancer diagnosis, post-surgical resection, and negative follow-up phases. Pooled normal plasma is shown for reference. Low-TF conditions allow visualization of qualitative differences in thrombin generation dynamics, particularly in the decay phase and curve closure over time.