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The effect of dabigatran and rivaroxaban on thrombin-and FXa-induced platelet aggregation

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INTRODUCTION-AIM

Thrombin and FXa are the major serine proteases of the coagulation cascade, which also activate various cell types through protease-activated receptors (PARs)[1]. Dabigatran and rivaroxaban are direct oral anticoagulants (DOACs) that inhibit thrombin's and FXa's activity, respectively, and are used in everyday clinical practice[2]. The aim of the present study was to investigate the effect of dabigatran and rivaroxaban on thrombin- and FXa-induced platelet aggregation, respectively, *in vitro*.

MATERIALS AND METHODS

Whole blood from apparently healthy volunteers was collected and washed platelets were isolated and adjusted to 250,000 platelets/μl. Platelets were activated with various concentrations of thrombin or FXa to establish the concentration exhibiting the maximum effect. In subsequent experiments, washed platelets were incubated with various concentrations of dabigatran (1-10 nM) and rivaroxaban (0.5-20 nM) for 1 min at 37^{o}C before activation with thrombin (0.1 U/mL) or FXa (0.025 nM), respectively. Platelet aggregation was monitored using light transmittance aggregometry, until the stabilization of the aggregation curve.

RESULTS

Thrombin induced platelet aggregation, which reached a maximum of 80-90% at 4 min, at a dose of 0.1 U/mL. FXa induced platelet aggregation, which reached a maximum of 80-90% at 20 min, at a dose of 0.025 nM (Figure 1). Dabigatran and rivaroxaban inhibited platelet aggregation induced by 0.1 U/mL thrombin and 0.025 nM FXa, respectively, in a dose-dependent manner, exhibiting IC_{50} values of 4.1 nM and 3.5 nM, respectively (Figures 2 and 3).

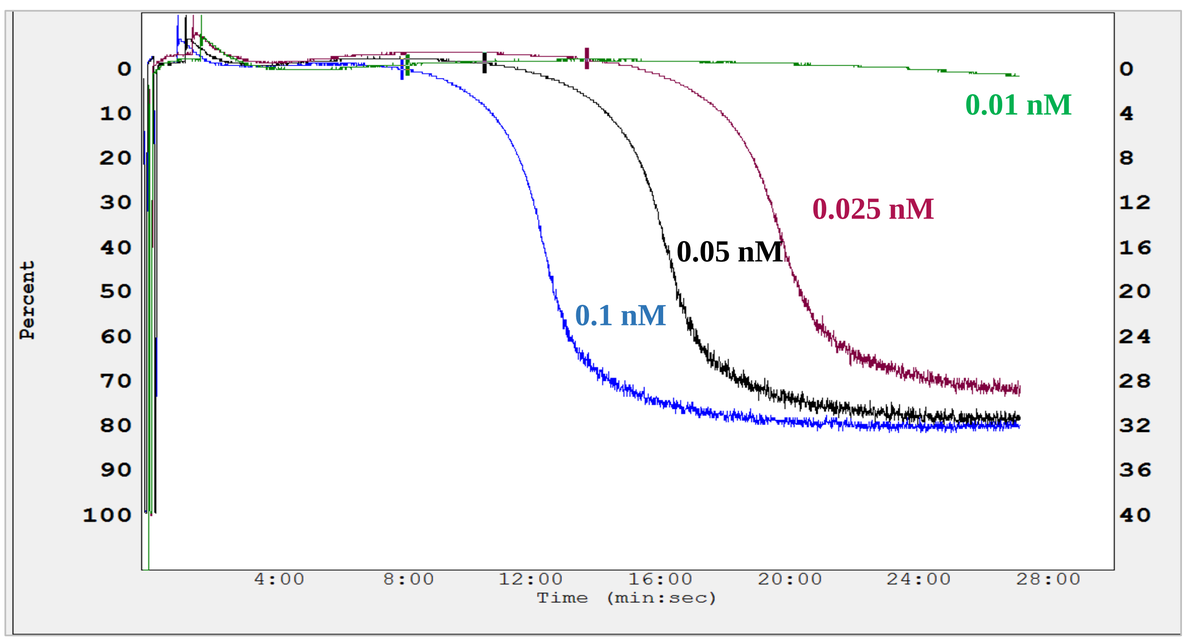

Figure 1. *Representative aggregation curves of the concentration-dependent effect of FXa on platelet aggregation.*

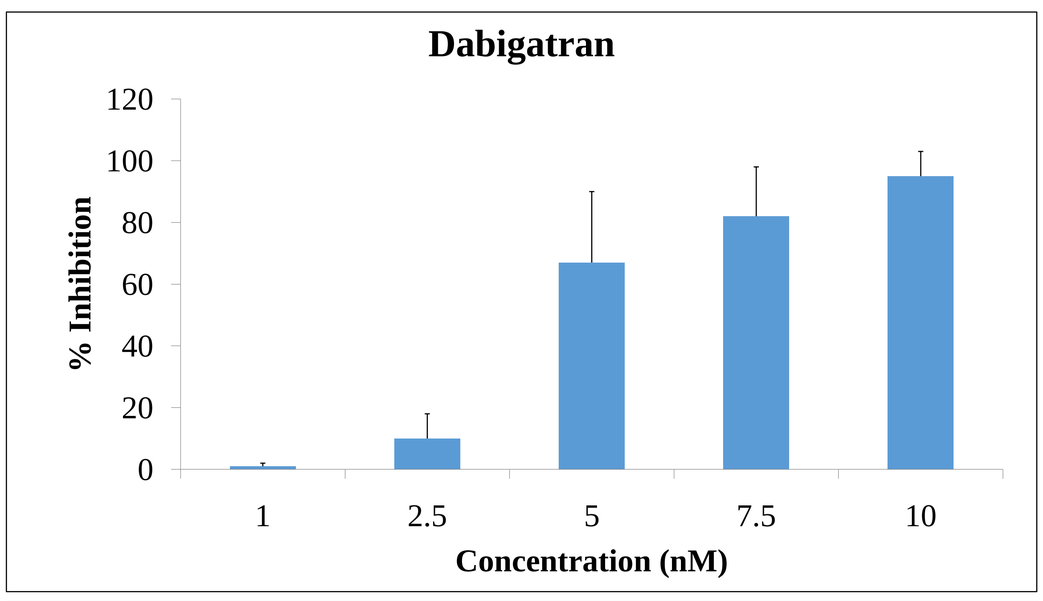

Figure 2. *The inhibitory effect of dabigatran on thrombin-induced platelet aggregation.* Values are expressed as mean±SD from at least three different platelet preparations.

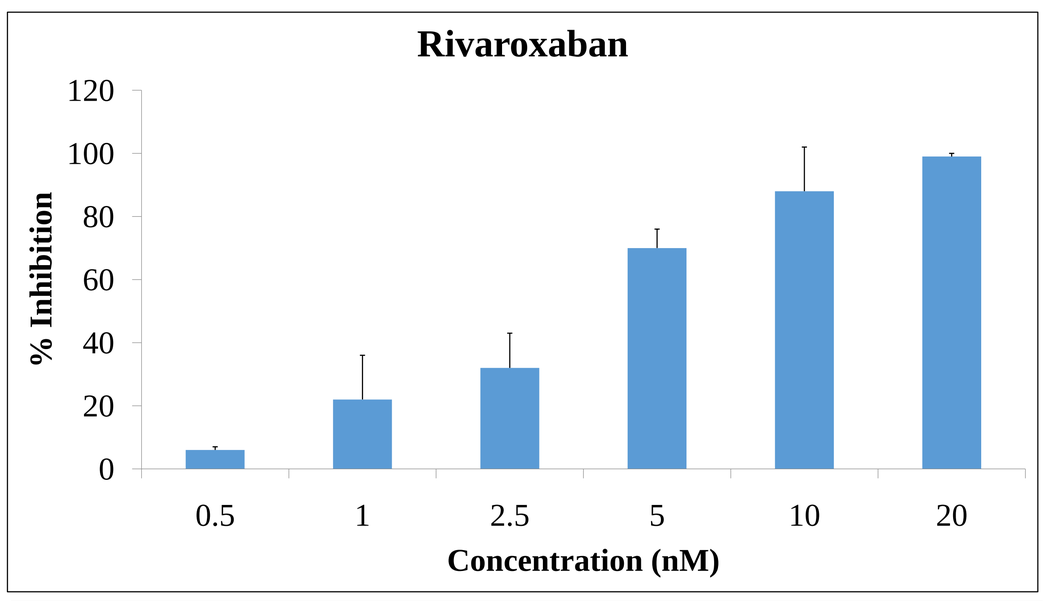

Figure 3. *The inhibitory effect of rivaroxaban on FXa-induced platelet aggregation.* Values are expressed as mean±SD from at least three different platelet preparations.

CONCLUSIONS

The present study showed that dabigatran and rivaroxaban strongly inhibit thrombin- and FXa-induced platelet aggregation, respectively. The above results suggest that through inhibition of platelet activation, these DOACs may prevent atherothrombotic events, in which platelets play a prominent role, in addition to their beneficial antithrombotic effects in venous thromboembolism.

REFERENCES

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2. N. van Es et al. Direct oral anticoagulants compareed with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood* 2014;**124**:1968-1975.

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