

## **Effects of rivaroxaban on thrombin generation is modified by a P2Y<sub>12</sub> receptor blocker**

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**Purpose** Rivaroxaban, a highly selective, potent, reversible, oral, direct FXa inhibitor, concentration-dependently inhibits FXa activity and thrombin generation (TG). It is in phase III trials for secondary prevention of acute coronary syndrome in patients on acetylsalicylic acid (ASA) and/or a thienopyridine. The aim of this study was to evaluate the effects on TG of rivaroxaban with and without a P2Y<sub>12</sub> receptor blocker. TG is a dynamic measurement of thrombin activity, which is a sensitive coagulation marker and may be affected by antiplatelet drugs.

**Methods** TG was triggered with 0.5 pM tissue factor in human platelet-rich plasma (PRP) from 11 healthy volunteers and measured using the calibrated automated thrombogram method (Thrombinoscope®). PRP was spiked with rivaroxaban (15, 30, 60 ng/ml), ticagrelor (100, 300, 1000 ng/ml), their combination, 100 µg/ml ASA and appropriate controls. Ticagrelor was used as it does not need the metabolic activation of thienopyridines.

**Results** Rivaroxaban concentration-dependently inhibited peak TG ( $C_{max}$ ), prolonged lag time and time to peak thrombin formation ( $t_{max}$ ) (Table). ASA had no influence on any parameters. Ticagrelor had no effect on lag time, but slightly and consistently increased  $t_{max}$  at 300 and 1000 ng/ml;  $C_{max}$  was slightly inhibited at 1000 ng/ml. Rivaroxaban (30, 60 ng/ml) and ticagrelor (1000, 300 ng/ml) combined prolonged lag time and further prolonged  $t_{max}$ . Ticagrelor 100 ng/ml alone or in combination did not affect TG.

**Conclusion** The effects of rivaroxaban on TG are slightly but consistently increased by P2Y<sub>12</sub> receptor blockers, most obviously on the prolongation of  $t_{max}$  due to decreased velocity of TG. This might be explained by delayed platelet activation in the presence of a P2Y<sub>12</sub> receptor antagonist.

Ticagrelor	Thrombin generation	Rivaroxaban (ng/ml)			
		0	15	30	60
<b>0 (ng/ml)</b>	C <sub>max</sub> (%)	–	19±8	33±7	50±7
	lag time (x-fold)	–	1.5±0.1	1.8±0.1	2.2±0.3
	t <sub>max</sub> (x-fold)	–	1.5±0.2	1.7±0.2	1.9±0.1
<b>1000 (ng/ml)</b>	C <sub>max</sub> (%)	16±12	33±10	48±11	62±10
	lag time (x-fold)	1.0±0.1	1.6±0.2	1.9±0.2	2.2±0.3
	t <sub>max</sub> (x-fold)	1.2±0.1	1.7±0.2	2.0±0.2	2.3±0.3
<b>300 (ng/ml)</b>	C <sub>max</sub> (%)	5±13	26±13	39±10	57±12
	lag time (x-fold)	1.1±0.1	1.6±0.1	1.9±0.2	2.2±0.3
	t <sub>max</sub> (x-fold)	1.2±0.1	1.6±0.2	1.8±0.2	2.1±0.2

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