Effects of Direct Oral Anticoagulants

on Hemostasis testing

About this guide

The ISTH SCC[1] and British Committee for Standards in Haematology[2] recommend that laboratories understand the effects of direct oral anticoagulants (DOACs) on Hemostasis assays. This guide provides detailed reference data to illustrate the impact of DOACs on HemosIL® assays.

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What has changed in anticoagulant therapy?

Hemostasis testing is critical in the overall clinical assessment of patients requiring anticoagulant therapy. Warfarin has been the gold standard in oral anticoagulant therapy for many years. DOACs, such as dabigatran, rivaroxaban, apixaban, edoxaban and betrixaban,* have been approved for clinical use in many countries and do not require routine monitoring. Therefore, understanding the characteristics of DOACs and differentiating their effects on routine Hemostasis tests is essential.

DOACs vs. Warfarin[3,8]

		Dosing	Time to Peak Anticoagulation	Half-life	Antidote	Renal Excretion (%)	Drug Interaction Potential
	Warfarin	Once Daily	3–5 Days	20-60 Hours	Vitamin K	0	Multiple, Especially CP2C9 Inhibitors
DOAC	Dabigatran Etexilate	Twice Daily	~2 Hours	12-17 Hours	Idarucizumab	~80	P-Glycoprotein Inhibitors and Inducers
DOAC	Rivaroxaban	Once Daily	2–4 Hours	5-9 Hours	Andexanet alfa	~36	CYP3A4 and P-Glycoprotein, Inhibitors and Inducers
DOAC	Apixaban	Twice Daily	3-4 Hours	12 Hours	Andexanet alfa	~25	CYP3A4 and P-Glycoprotein, Inhibitors and Inducers
DOAC	Edoxaban	Once Daily	1-2 Hours	10-14 Hours	In Development	~50	CYP3A4 and P-Glycoprotein, Inhibitors and Inducers
DOAC	Betrixaban	Once Daily	3-4 Hours	19-27 Hours	In Development	~11	P-Glycoprotein Inhibitors

* Betrixaban was recently FDA 510(k)-cleared and is not be available in all territories. There is currently limited data available on the effect of betrixaban on Hemostasis assays.

How do DOACs affect Routine Hemostasis tests?

PT, APTT, Fibrinogen and Thrombin Time (TT) results can be affected by DOACs. Potential effects are described below.

Effects of DOACs on PT, APTT, Fibrinogen, TT and D-Dimer Results

	PT	APTT	Fibrinogen Activity	TT	D-Dimer
Dabigatran Etexilate	Prolonged +[3,†]	Prolonged ++[3,†]	No Effect or Falsely Low[6,#]	Prolonged +++[3]	No Effect[4]
Rivaroxaban	No Effect or Prolonged ++[**,3,†]	No Effect or Prolonged +[**,3,†]	No Effect[3]	No Effect[3]	No Effect[4]
Apixaban	No Effect or Prolonged ++[**,3,†]	No Effect or Prolonged +[**,3,†]	No Effect[3]	No Effect[3]	No Effect[4]
Edoxaban	No Effect or Prolonged ++[**,11,†]	No Effect or Prolonged +[11,†]	No Effect[11]	No Effect[11]	No Effect[11]

\+ slight increase ++ moderate increase +++ marked increase

** Data on file, IL.
† Direct IIa/Xa inhibitors may show variable effects, depending on the drug and drug concentration. In addition, different reagents may have different sensitivities.
# Effect is assay-method-and drug-dependent. Most fibrinogen assays will show no effect with dabigatran.

References

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How do DOACs affect HemosIL PT and APTT assays?

Effect of DOACs on HemosIL PT Results

Drug Concentration (ng/mL)	Dabigatran			Rivaroxaban			Apixaban			Edoxaban		
	RdPTn*	RPT 2G	PT HS Plus	RdPTn*	RPT 2G	PT HS Plus	RdPTn*	RPT 2G	PT HS Plus	RdPTn*	RPT 2G	PT HS Plus
0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
50	1.04	1.02	1.05	1.16	1.13	1.19	1.07	1.06	1.07	1.04	1.04	1.14
100	1.05	1.02	1.08	1.30	1.28	1.33	1.15	1.13	1.12	1.10	1.10	1.34
200	1.08	1.02	1.13	1.62	1.58	1.70	1.28	1.27	1.23	1.28	1.27	1.64
300	1.11	1.04	1.18	1.94	1.89	1.98	1.45	1.40	1.32	1.43	1.41	1.97
400	1.26	1.18	1.34	2.24	2.18	2.31	1.61	1.56	1.44	1.62	1.59	2.24
500	1.63	1.60	1.68	2.59	2.50	2.56	1.78	1.71	1.54	1.76	1.73	2.50

* Currently available on ACL TOP® Family and ACL TOP Family 50 Series Hemostasis Testing Systems.
RdPTn = ReadiPlasTin®; RPT 2G = RecombiPlasTin 2G®
PT ratios (drug concentration vs. no drug) measure the effect of the DOACs at increasing concentrations. 1.00 = no effect. Normal range PT ratio < 1.25.

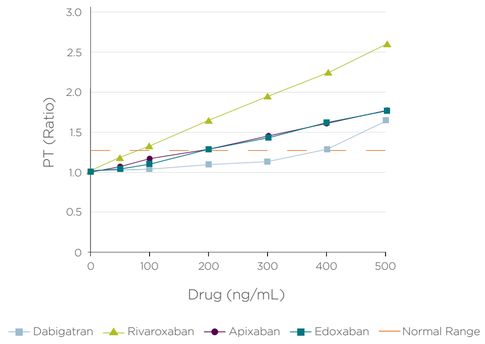
Effect of DOACs on HemosIL APTT Results

Drug Concentration (ng/mL)	Dabigatran			Rivaroxaban			Apixaban			Edoxaban		
	SynthASil®	APTT-SP	SynthAFax®	SynthASil	APTT-SP	SynthAFax	SynthASil	APTT-SP	SynthAFax	SynthASil	APTT-SP	SynthAFax
0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
50	1.41	1.47	1.39	1.18	1.14	1.17	1.09	1.09	1.08	1.17	1.07	1.13
100	1.64	1.66	1.70	1.26	1.22	1.29	1.14	1.14	1.13	1.22	1.15	1.23
200	2.09	2.01	2.14	1.39	1.34	1.45	1.21	1.20	1.20	1.32	1.27	1.40
300	2.42	2.23	2.52	1.52	1.51	1.60	1.25	1.23	1.25	1.41	1.39	1.54
400	2.65	2.46	2.80	1.63	1.59	1.76	1.29	1.28	1.29	1.49	1.50	1.70
500	2.93	2.66	3.07	1.72	1.71	1.89	1.32	1.31	1.34	1.56	1.59	1.83

APTT ratios (drug concentration vs. no drug) measure the effect of the DOACs at increasing concentrations. 1.00 = no effect. Normal range APTT ratio < 1.25.

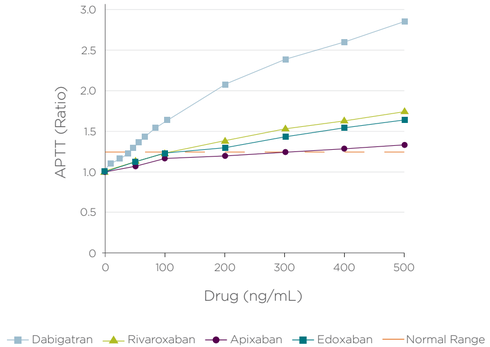
Highlighted areas show ratios above the normal range.

DOAC Effects on HemosIL ReadiPlasTin*



*Available on ACL TOP Family and ACL TOP Family 50 Series Hemostasis Testing Systems.

DOAC Effects on HemosIL SynthASil



DOACs target Factor IIa and Factor Xa, key proteins in the coagulation cascade that can interfere with Hemostasis specialty tests.

Effects of DOACs on Specialty Tests

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Protein S (Antigen)	No Effect[3]	No Effect[3]	No Effect[3]	No Effect[11]
Protein S (Clotting)	Falsely Increased[3]	Falsely Increased[3]	Falsely Increased[3]	Falsely Increased[11]
Protein C (Chromogenic)	No Effect[3]	No Effect[3]	No Effect[3]	No Effect[11]
Protein C (Clotting)	Falsely Increased[3]	Falsely Increased[3]	Falsely Increased[3]	Falsely Increased[11]
Antithrombin (Xa)	No Effect[3]	Falsely Increased[3]	Falsely Increased[3]	Falsely Increased[11]
Antithrombin (IIa)	Falsely Increased[3]	No Effect[3]	No Effect[3]	No Effect[11]
Liquid Anti-Xa	No Effect[4]	Increased[4]	Increased[4]	Increased[11]
dRVVT Screen & Confirm	Likely to Misclassify as LA[8,†]	Possible to Misclassify as LA[7,†]	Possible to Misclassify as LA[7,†]	Possible to Misclassify as LA[11,†]
PT-Based Factor Assays (FII, FV, FVII, FX)	Falsely Low[3,**]	Falsely Low[3,**]	Falsely Low[3,**]	Falsely Low[11,**]
APTT-Based Factor Assays (FVIII, FIX, FXI, FXII)	Falsely Low[3,4,**]	Falsely Low[3,4,**]	Falsely Low[3,4,**]	Falsely Low[11,**]
APC Resistance	Falsely Elevated Ratio[3]	Mild False Elevations in Ratio, but Assay Remains Accurate[9]	Mild False Elevations in Ratio, but Assay Remains Accurate[3]	Mild False Elevations in Ratio, but Assay Remains Accurate[11]
Factor VIII (Chromogenic)	No Effect[3]	Falsely Low[3]	Falsely Low[3]	Falsely Low[3]
Factor XIII (Immunologic)	No Effect[5]	No Effect[5]	No Effect[10]	No Effect[10]

† Data on file, IL.
** Falsely low, may yield false impression of an inhibitor.
LA = Lupus anticoagulant