Impact of FXIa inhibitors on coagulation testing

asundexian and milvexian

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Conflicts of interest

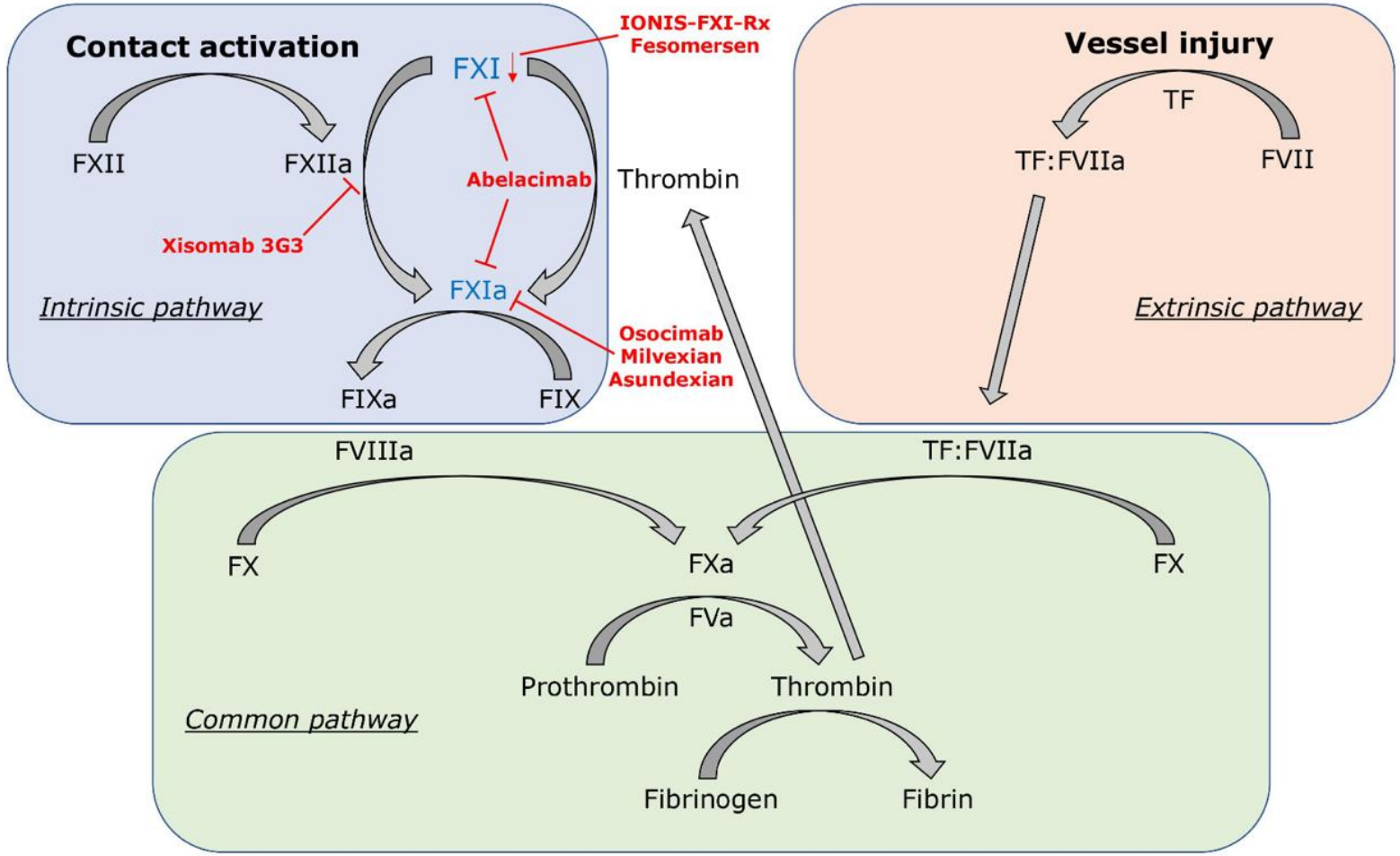
None

Introduction – Molecules

- asundexian
- milvexian
- …

- Abelacimab
- Osocimab
- Xisomab 3G3
- …

- Fesomersen
- IONIS-FXI$_{Rx}$
- …



Nopp S, Kraemmer D, Ay C. Factor XI Inhibitors for Prevention and Treatment of Venous Thromboembolism: A Review on the Rationale and Update on Current Evidence. Front Cardiovasc Med. 2022;9:903029.

Introduction – Indications

Post-TKR VTE prophylaxis	Abelacimab (ANT-005 TKA) Osocimab (FOXTROT) Milvexian (AXIOMATIC-TKR) IONIS-FXI-RX/ISIS 416858 (FXI-ASO TKA)
Cancer-associated VTE treatment/prophylaxis	Abelacimab (**ASTER + MAGNOLIA**) Xisomab 3G3/gruticibart (NCT04465760)
Atrial fibrillation	Asundexian (PACIFIC-AF + ***OCEANIC-AF***) Abelacimab (*AZALEA-TIMI 71* + **LILAC-TIMI 76**) Milvexian (**LIBREXIA-AF**)
After myocardial infarction	Asundexian (PACIFIC-AMI)
After acute coronary syndrome	Milvexian (**LIBREXIA-ACS**)
After ischemic stroke and transient ischemic attack	Asundexian (PACIFIC-STROKE + **OCEANIC-STROKE**) Milvexian (AXIOMATIC-SSP **+ LIBREXIA-STROKE**)
Chronic hemodialysis (ESRD)	Osocimab (CONVERT) Xisomab 3G3 (NCT03612856) IONIS-FXI-RX (EMERALD), fesomersen (RE-THINc ESRD)

Material and methods – Samples

- Normal pooled plasma (NPP)
- **asundexian: 0 – 2000 ng/mL**
  - 50 mg OD (8 days) → C_{max}= 963 ng/mL[1]
  - OCEANIC AF (NCT05643573): 50 mg OD

[1] Kubitza D, Heckmann M, Distler J, Koechel A, Schwers S, Kanefendt F. Pharmacokinetics, pharmacodynamics and safety of BAY 2433334, a novel activated factor XI inhibitor, in healthy volunteers: A randomized phase 1 multiple-dose study. *Br J Clin Pharmacol*. 2022; 88(7): 3447-3462. doi:10.1111/bcp.15230

- **milvexian: 0 – 5000 ng/mL**
  - 200 mg fasted BID (14 days) → C_{max}= 3579 ng/mL[2]
  - AXIOMATIC-TKR (NCT03891524): 200 mg BID

[2] V. Perera, Z. Wang, J. Luettgen, D. Li, M. Desouza, M. Cerra, D. Seiffert, First-in-human study of milvexian, an oral, direct, small molecule factor XIa inhibitor, Clin. Transl. Sci. 15 (2) (2022) 330–342.

Material and methods – Assays

Thrombin Generation Assay (CAT)

- TF 1 – 5 – 20 pM + 4 µM PLs
- Ellagic acid 0.42 µM + PLs

aPTT (4 reagents)

PT (2 reagents)

Fibrinogen

- PT-derived
- Clauss method

One-stage aPTT-based clotting factors assays

FVIII, FIX, FXI and FXII

One-stage PT-based clotting factors assays

FII, FV, FVII and FX

Protein C

aPTT-based assay - Protac®

Free Protein S

Latex particle-based agglutination assay

Ecarin chromogenic assay

Reptilase time

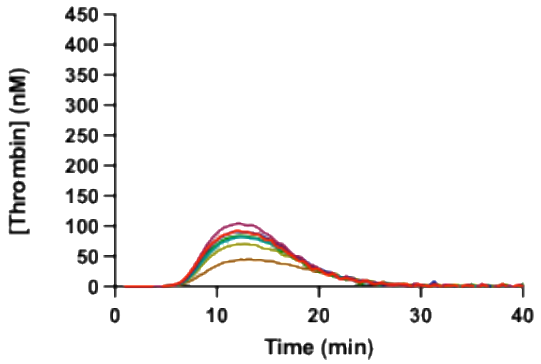
Lupus Anticoagulant (LA) testing

dRVVT

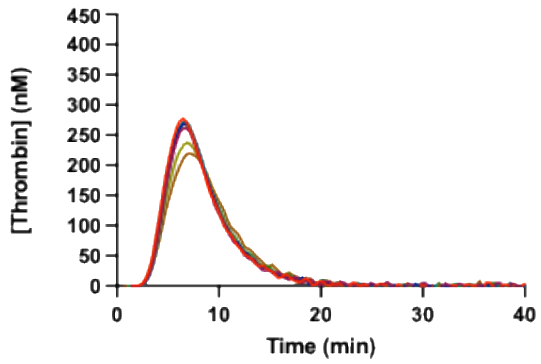
Results – TGA

asundexian

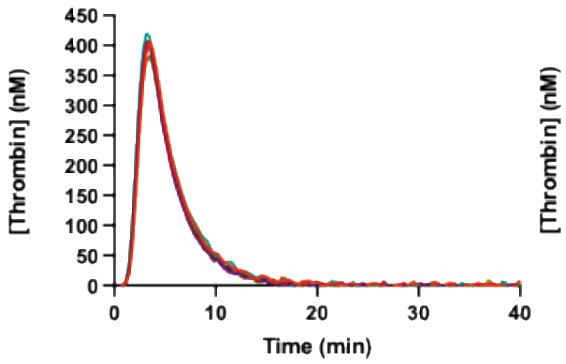
PPP Reagent Low



PPP Reagent



PPP Reagent High



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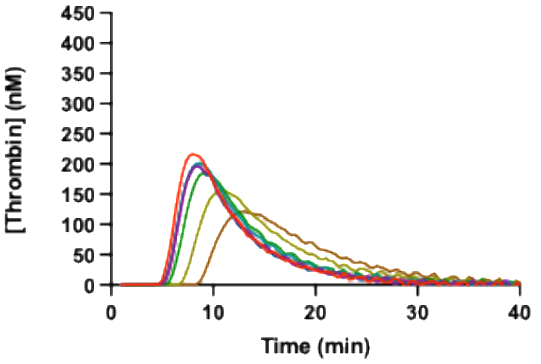
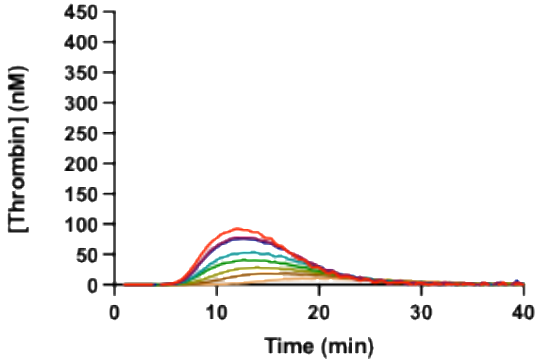
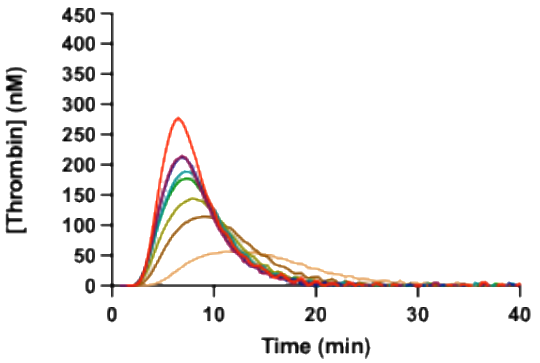
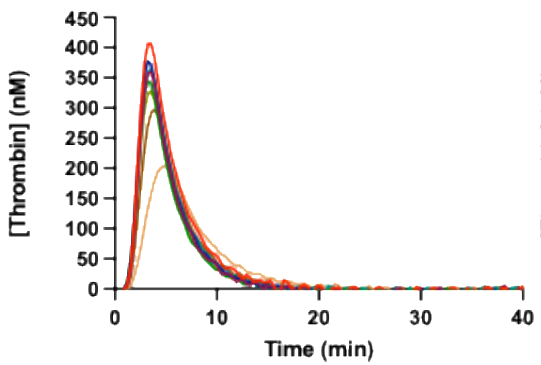
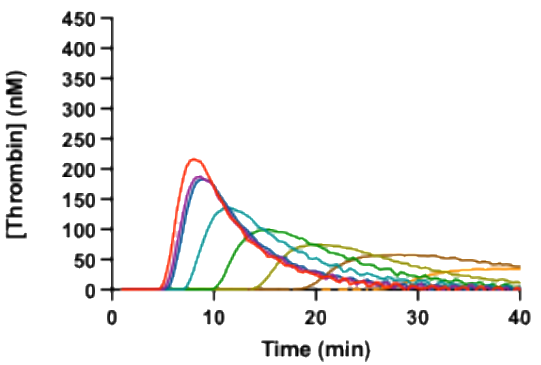


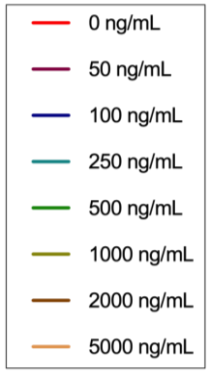
milvexian





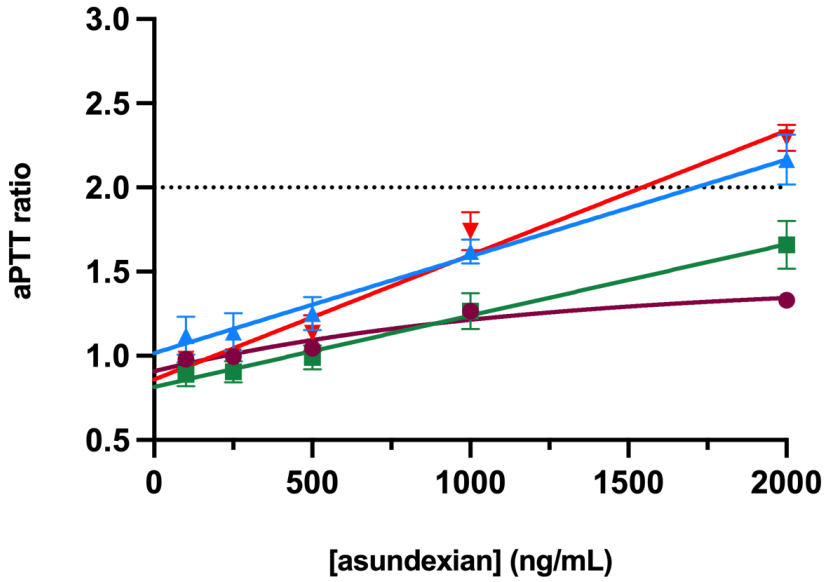




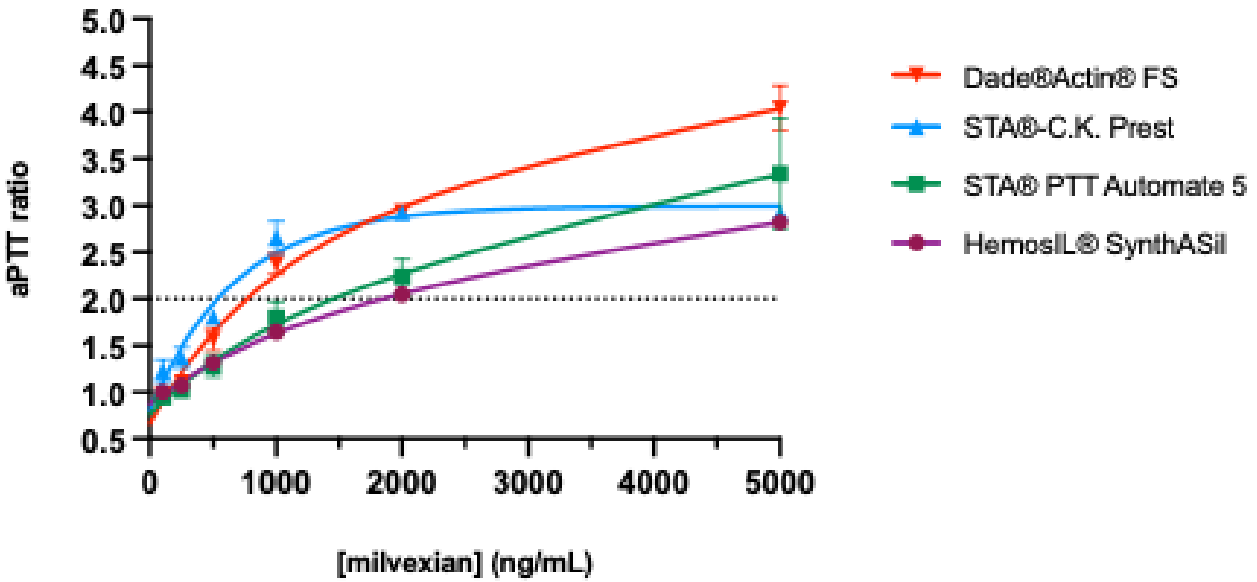


Results – aPTT

asundexian

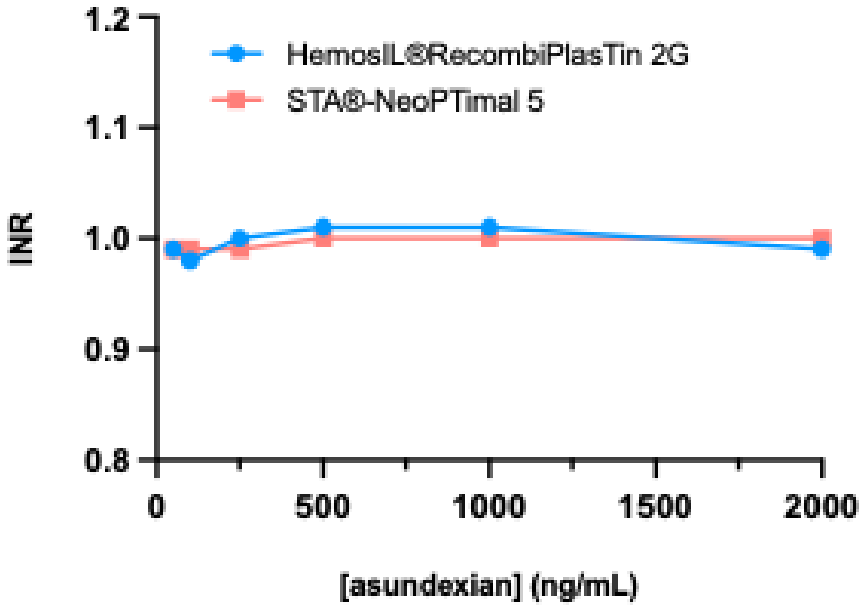


milvexian

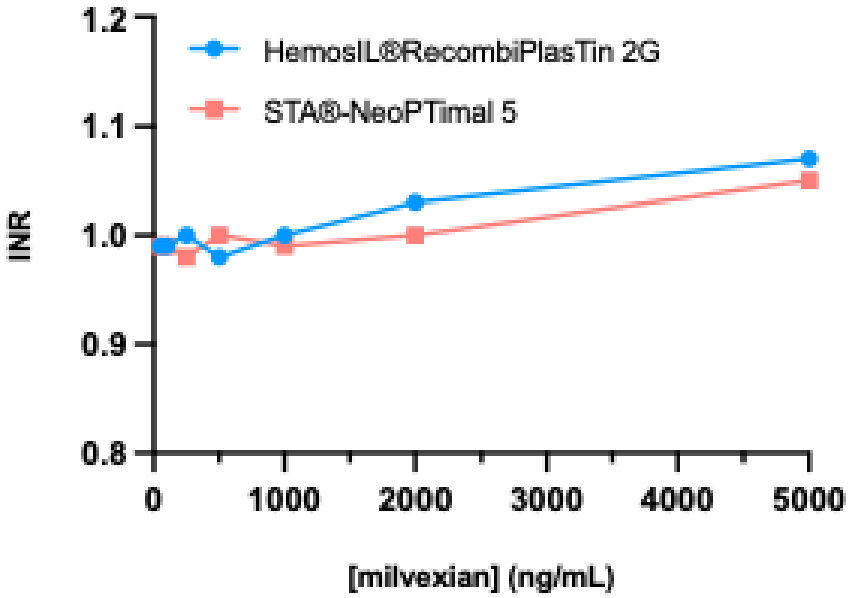


Results – PT

asundexian

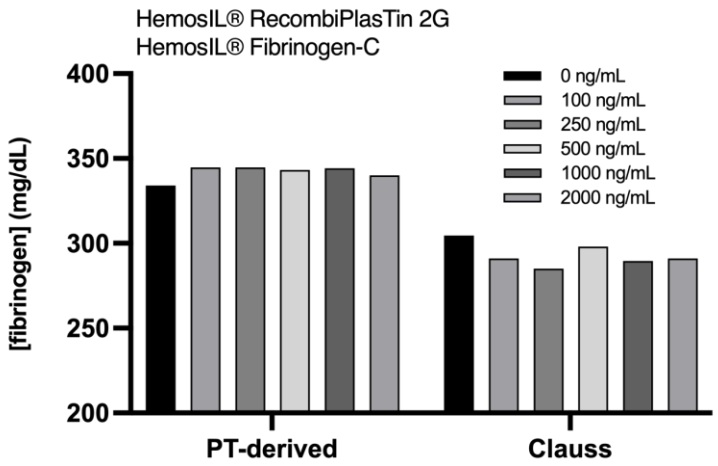


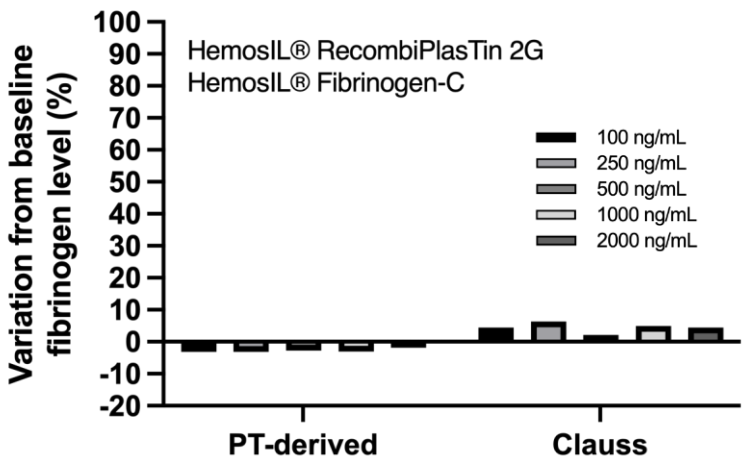
milvexian



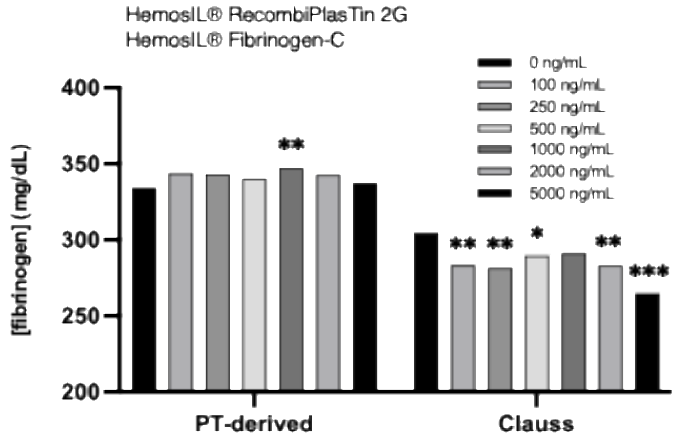
Results – Fibrinogen

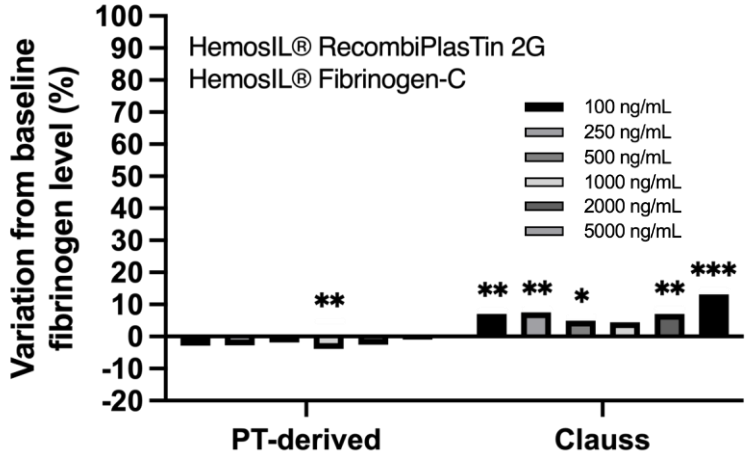
asundexian





milvexian





*P< 0.05
**P <0.01
***P <0.001
****P<0.0001

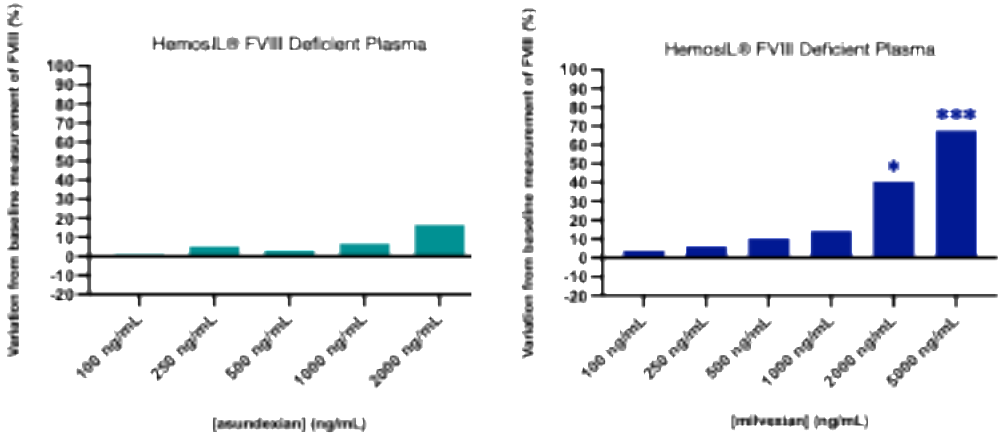
CV: 10.2 [9.3 – 11.9][1]

[1] Intraindividual biological variation as median CV(%) estimates [95%CI] from the EFLM Biological Variation Database

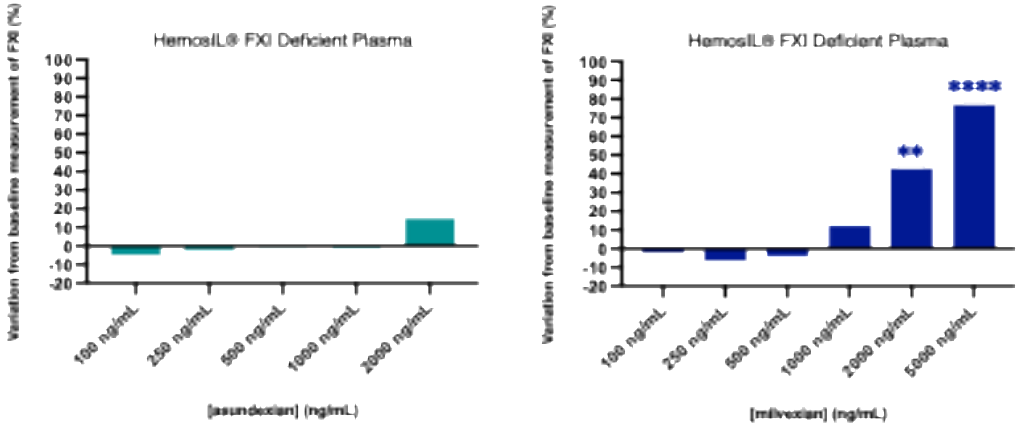
Results – aPTT-based factors assays

*P< 0.05
**P <0.01
***P <0.001
****P<0.0001

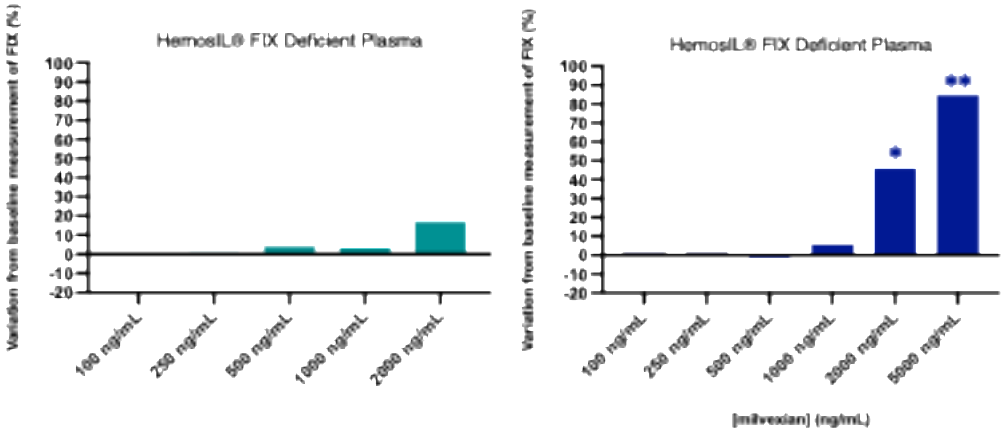
FVIII CV: 8.7 [4.9 – 16.0] [1]



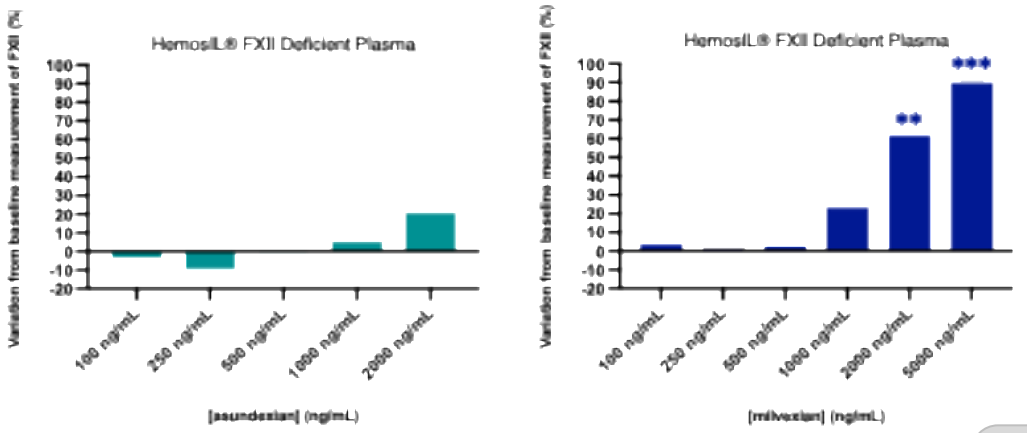
FXI CV: 5.1 [4.1 – 6.3] [1]



FIX CV: 6.9 [5.8 – 9.1] [1]



FXII CV: 4.0 [3.0 – 5.1] [1]

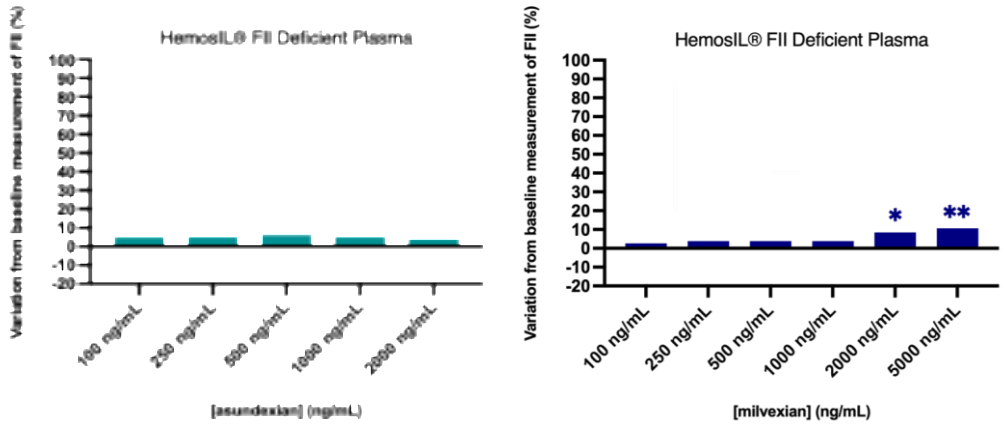


[1] Intraindividual biological variation as median CV(%) estimates [95%CI] from the **EFLM** Biological Variation Database

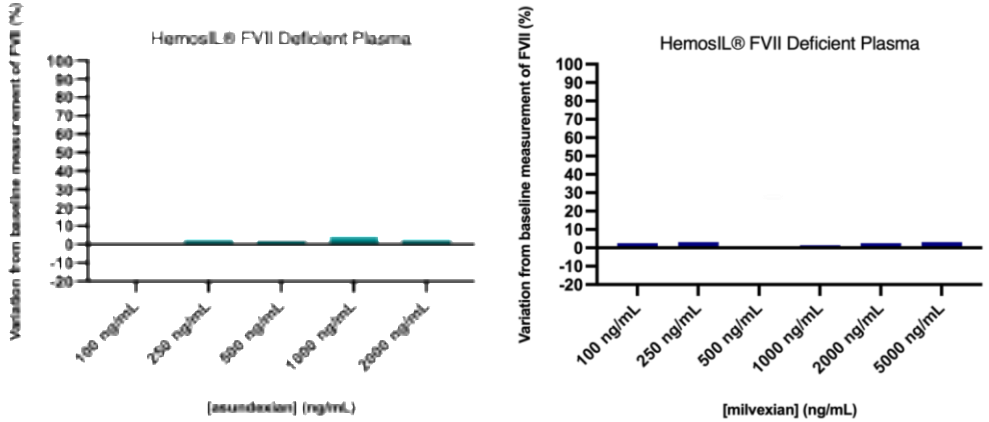
Results – PT-based factors assays

*P< 0.05
**P <0.01
***P <0.001
****P<0.0001

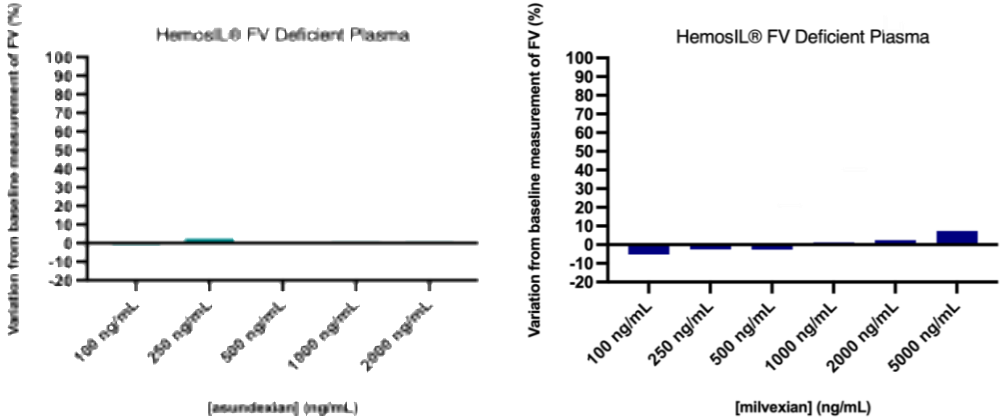
FII CV: 5.8 [5.7 – 5.9] [1]



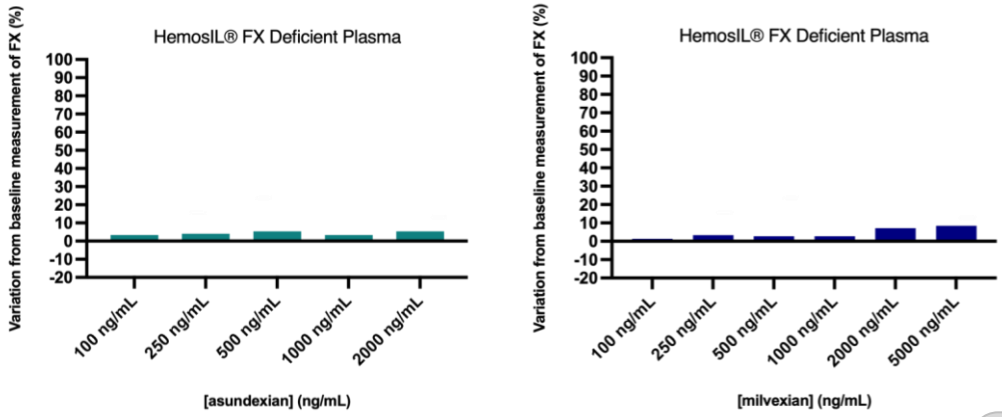
FVII CV: 8.2 [6.9 – 14.2] [1]



FV CV: 5.3 [3.6 – 6.6] [1]



FX CV: 5.9 [4.5 – 8.5] [1]

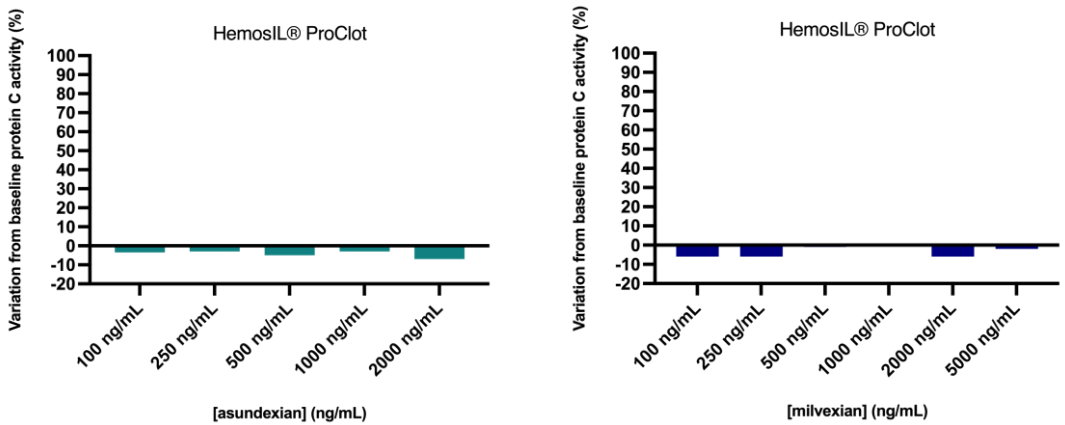


[1] Intraindividual biological variation as median CV(%) estimates [95%CI] from the **EFLM** Biological Variation Database

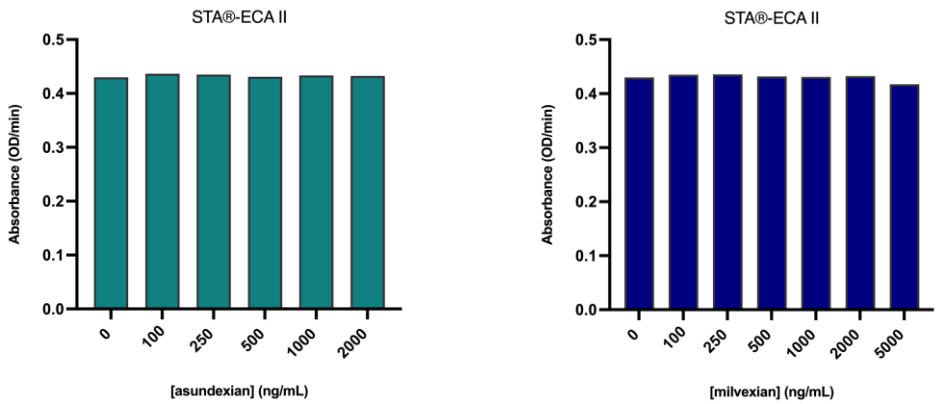
Results – proteins C-S, ECA, reptilase time

*P< 0.05
**P <0.01
***P <0.001
****P<0.0001

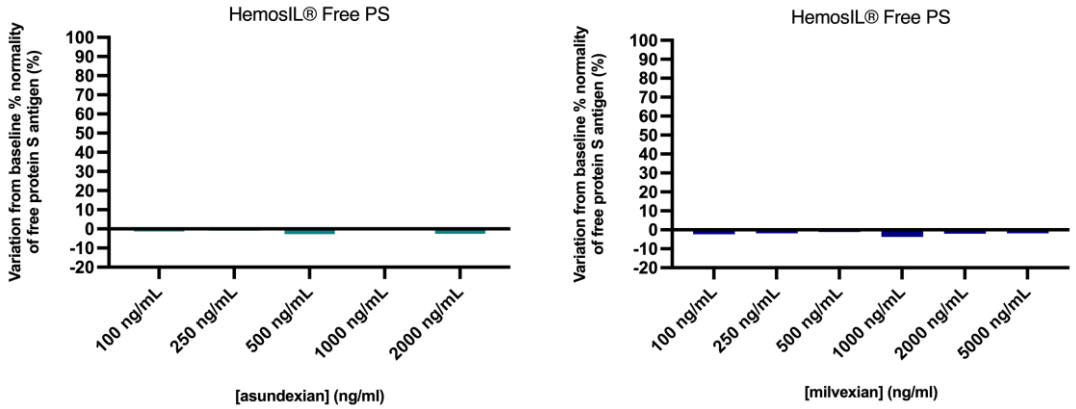
Protein C CV: 5.5 [5.3 – 7.9] [1]



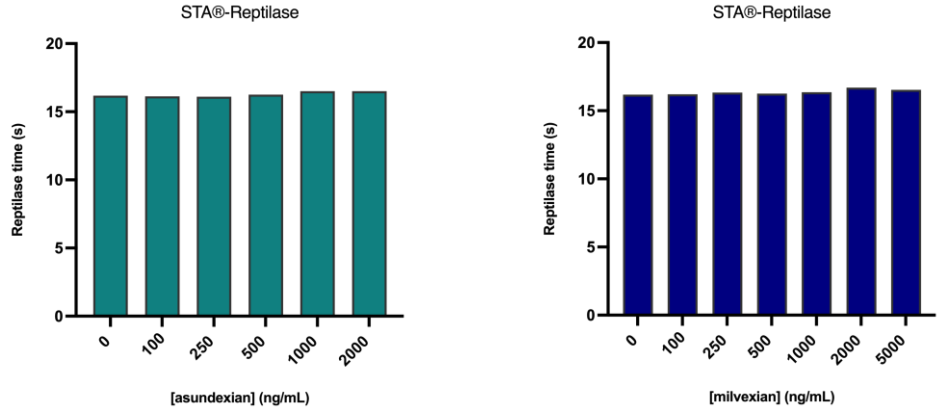
Ecarin chromogenic assay [dabigatran] = 15 ng/mL (LOD)



Free protein S CV: 4.2 [4.0 – 8.7] [1]



Reptilase time

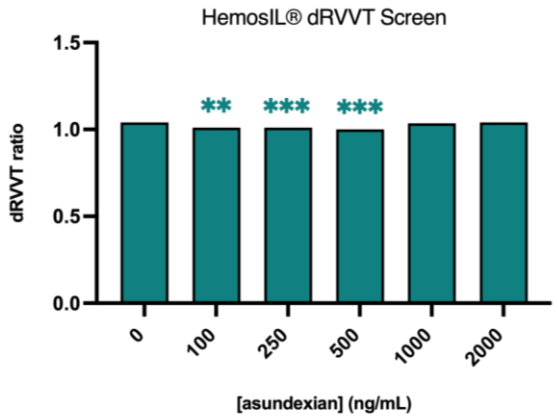


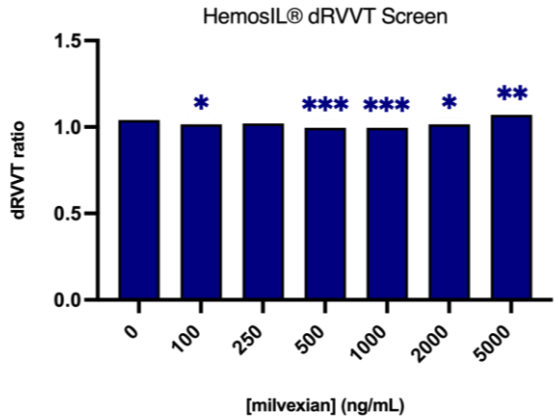
[1] Intraindividual biological variation as median CV(%) estimates [95%CI] from the **EFLM** Biological Variation Database

Results – dRVVT

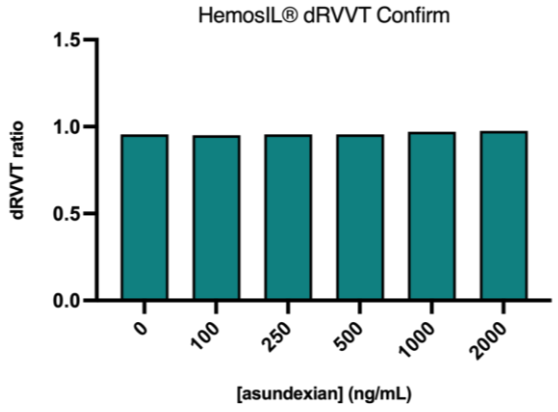
*P< 0.05
**P <0.01
***P <0.001
****P<0.0001

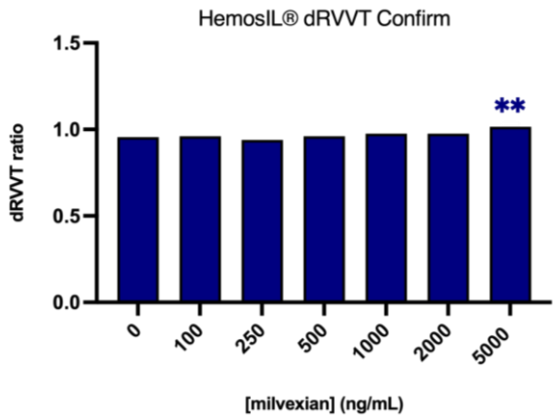
dRVVT Screen

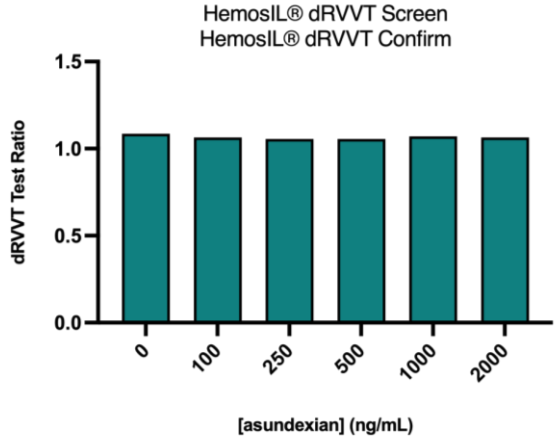


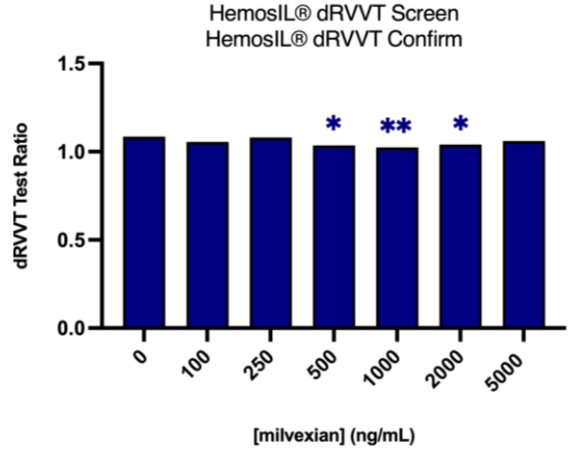


dRVVT Confirm









Conclusion and perspectives

- Impact of asundexian and milvexian on:
  - TGA (TF 1 >>5 >>> 20 pM, ellagic acid 0.42 µM)
  - aPTT (+++ variability)
  - One-stage aPTT/PT-based clotting factors assays

- Data from clinical trials
  - Limited
  - Not (very) detailed
  - → still needed ! (drug metabolization, ...)

Thank you for your attention

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Material and methods – Assays (1)

aPTT

- Micronized silica + synthetic PLs → HemosIL® SynthASil
- Ellagic acid + soy PLs → Dade®Actin®FS
- Kaolin + rabbit brain PLs → STA®-C.K. Prest
- Silica + rabbit brain PLs → STA®PTT Automate 5

→ **One-stage aPTT-based clotting factors assays FVIII, FIX, FXI and FXII**

- HemosIL®Factor Deficient Plasmas

PT

- Human recombinant tissue factor + synthetic PLs → HemosIL®RecombiPlasTin 2G
- Rabbit brain thromboplastin → STA®-NeoPTimal 5

→ **One-stage PT-based clotting factors assays FII, FV, FVII and FX**

- HemosIL®Factor Deficient Plasmas

Fibrinogen

- PT-derived: HemosIL® RecombiPlasTin 2G
- Clauss method: HemosIL® Fibrinogen-C

Material and methods – Assays (2)

Protein C

- aPTT-based assay
- Protac® → HemosIL® ProClot
- Colloidal silica + synthetic PLs → HemosIL® APTT-SP

Free Protein S

- Latex particle-based agglutination assay
- HemosIL® Free Protein S

Ecarin chromogenic assay

- STA®-ECA II

Reptilase time

- STA®-Reptilase

Lupus Anticoagulant (LA) testing

- dRVVT
- HemosIL® dRVVT Screen + Confirm

TGA Results – Parameters (1)

	Reagent	asundexian	milvexian	apixaban
2x Lag time (ng/mL) [95% CI]	PPP Low	n.c. (>2000)	n.c. (>5000)	304.2 [250.2 – 358.5]
	PPP	n.c. (>2000)	n.c. (>5000)	209.4 [194.4 – 225.1]
	PPP High	n.c. (>2000)	n.c. (>5000)	279.6 [228.9 – 372.3]
	ACTIN FS/40	n.c. (>2000)	501.3 [482.3 – 521.3]	n.c. (>500)
IC_{50} ETP (ng/mL) [95% CI]	PPP Low	n.c. (>2000)	643.8 [558.2 – 742.4]	100.3 [80.6 – 124.4]
	PPP	n.c. (>2000)	n.c. (>5000)	151.1 [130.7 -174.0]
	PPP High	n.c. (>2000)	n.c. (>5000)	345.0 [325.5 – 365.9]
	ACTIN FS/40	n.c. (>2000)	n.c. (>5000)	n.c. (>500)

J. Vassart, M. Didembourg, L. Morimont, C. Brisbois, L. Jamart, A. Lebreton, F. Mullier, N. Donis, J. Favresse, J.-M. Dogné, J. Douxfils, Asundexian in atrial fibrillation: Can pharmacodynamic data explain the failure?, Thrombosis Research 236 (2024) 236-239.

TGA Results – Parameters (2)

	Reagent	asundexian	milvexian	apixaban
IC_{50} Peak (ng/mL) [95% CI]	PPP Low	1876.0 [1598.1 – >2000]	419.4 [360.4 – 489.9]	51.5 [42.7 – 61.9]
	PPP	n.c. (>2000)	1893.8 [1633.4 – 2188.7]	40.5 [37.5 – 43.7]
	PPP High	n.c. (>2000)	n.c. (>5000)	80.5 [69.3 – 93.5]
	ACTIN FS/40	n.c. (>2000)	486.0 [435.1 – 542.8]	80.5 [72.6 – 89.2]
2x Time to peak (ng/mL) [95% CI]	PPP Low	n.c. (>2000)	n.c. (>5000)	n.c. (>500)
	PPP	n.c. (>2000)	n.c. (>5000)	164.4 [121.8 – 222.1]
	PPP High	n.c. (>2000)	n.c. (>5000)	408.2 [262.7 – >500.0]
	ACTIN FS/40	n.c. (>2000)	599.8 [580.3 – 620.2]	n.c. (>500)

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TGA Results – Parameters (3)

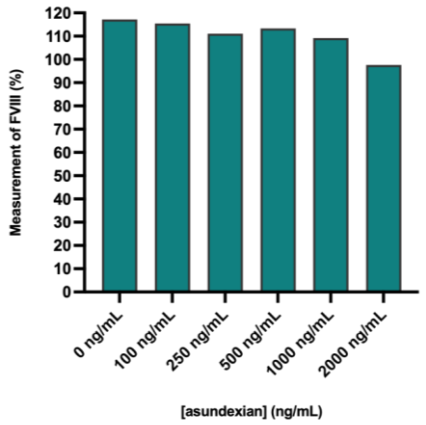
	Reagent	asundexian	milvexian	apixaban
IC_{50} mVRI (ng/mL) [95% CI]	PPP Low	1428.4 [1053.6 – 1855.3]	342.0 [287.3 – 409.8]	88.1 [70.3 – 110.7]
	PPP	n.c. (>2000)	1008.6 [833.6 – 1225.5]	34.6 [29.4 – 40.6]
	PPP High	n.c. (>2000)	3791.9 [3558.8 – 4227.5]	58.8 [50.9 – 67.9]
	ACTIN FS/40	1435.3 [1214.9 – 1743.4]	262,8 [228.9 – 303.3]	70.5 [60.3 – 82.2]

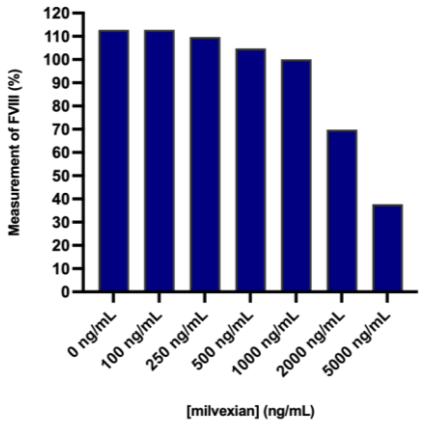
J. Vassart, M. Didembourg, L. Morimont, C. Brisbois, L. Jamart, A. Lebreton, F. Mullier, N. Donis, J. Favresse, J.-M. Dogné, J. Douxfils, Asundexian in atrial fibrillation: Can pharmacodynamic data explain the failure?, Thrombosis Research 236 (2024) 236-239.

Results – aPTT-based factors assays

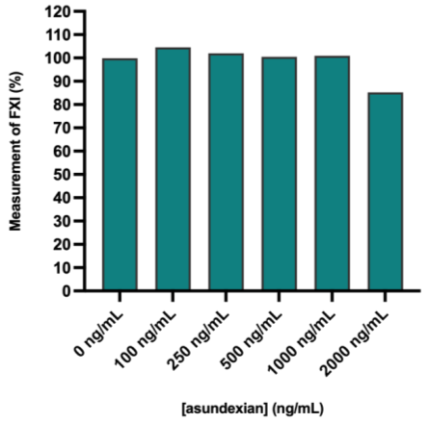
*P< 0.05
**P <0.01
***P <0.001
****P<0.0001

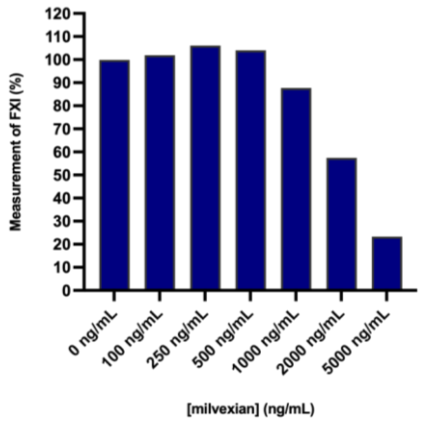
FVIII





FXI





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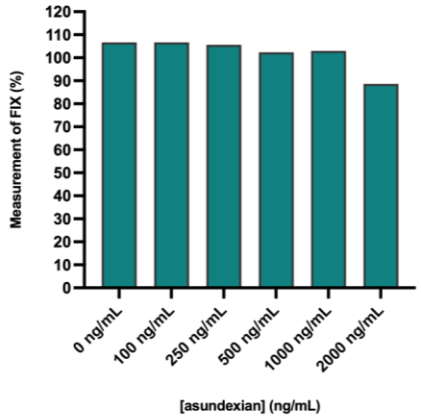

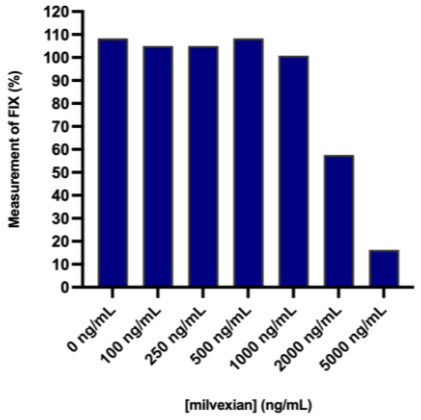

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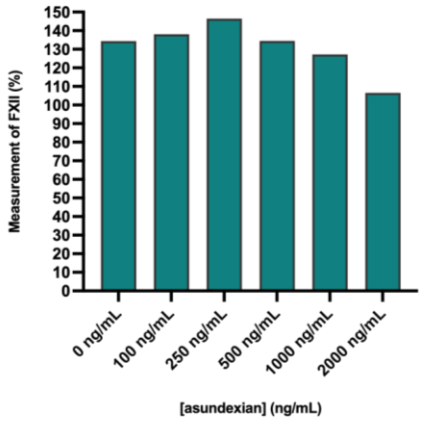
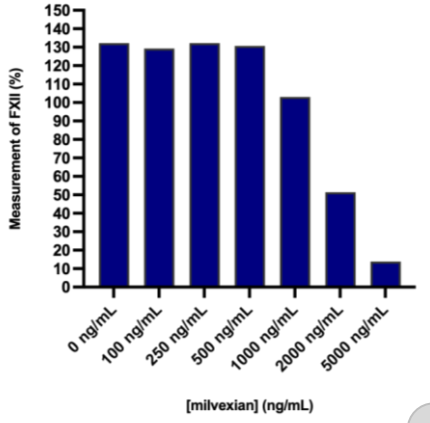
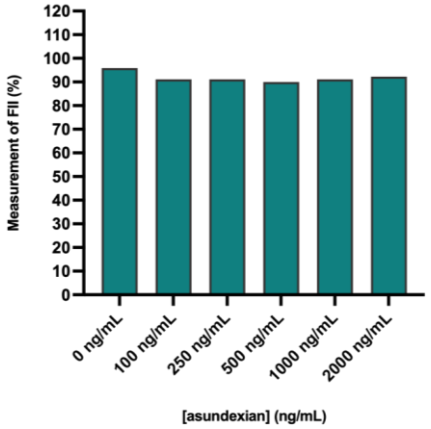


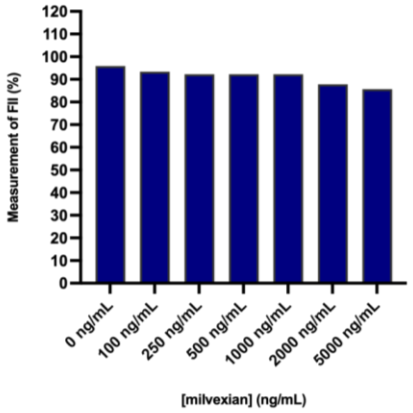


Results – PT-based factors assays

*P< 0.05
**P <0.01
***P <0.001
****P<0.0001

FII





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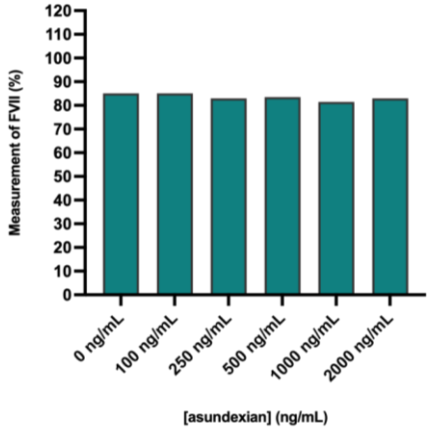

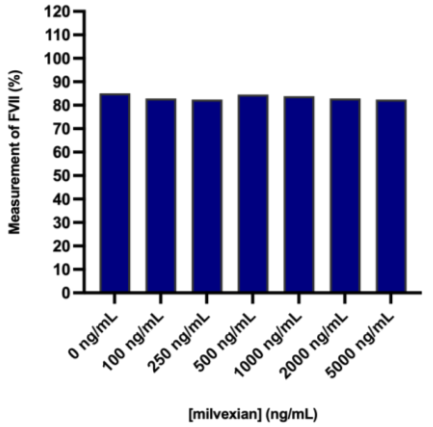

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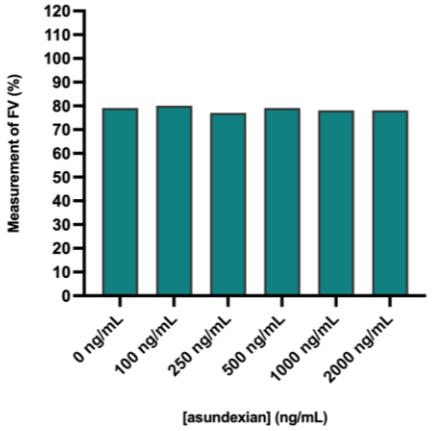
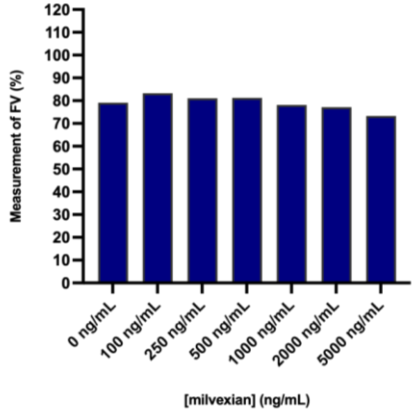
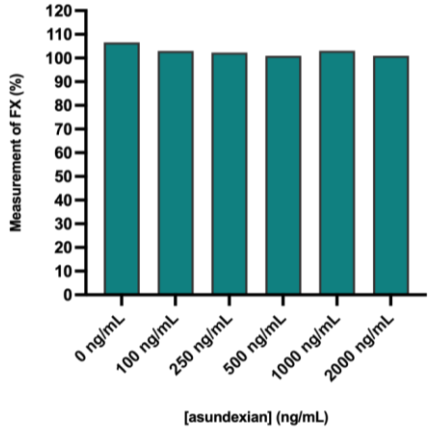
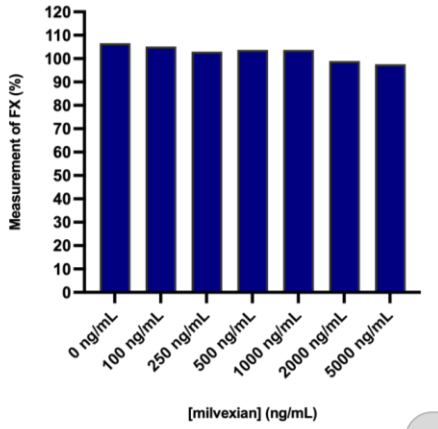




FX

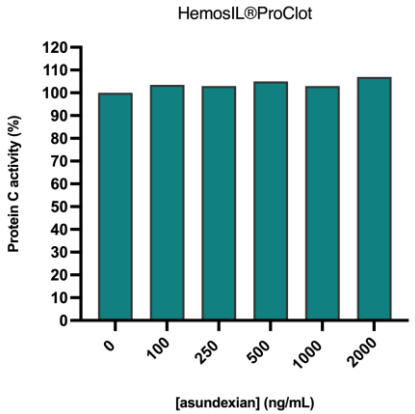


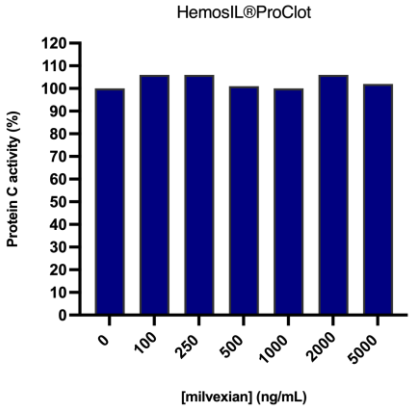


Results – proteins C-S, ECA, reptilase time

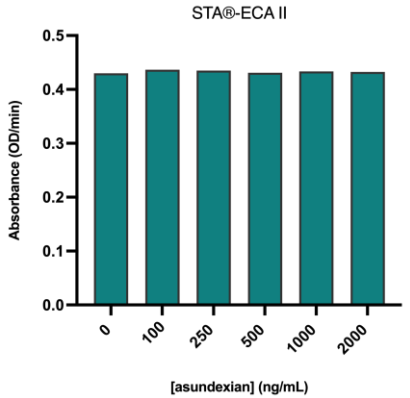
*P< 0.05
**P <0.01
***P <0.001
****P<0.0001

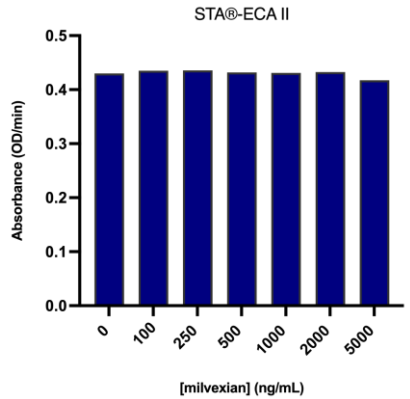
Protein C CV: 5.5 [5.3 – 7.9] [1]



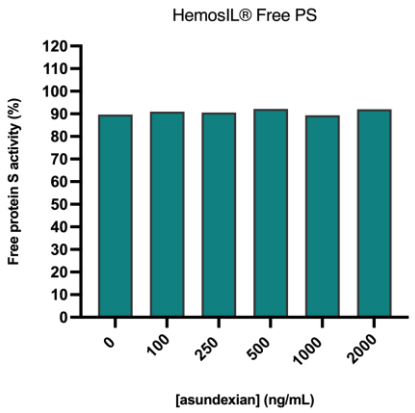


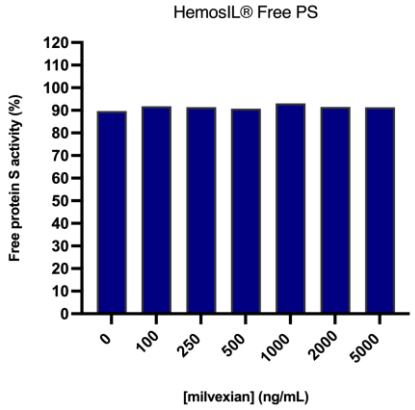
Ecarin chromogenic assay



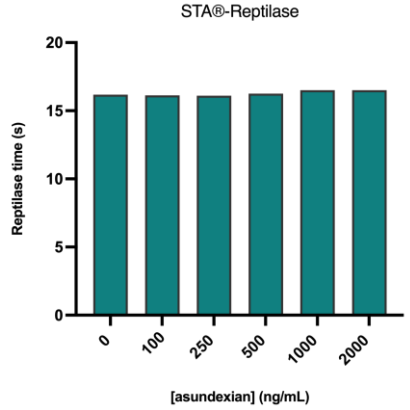


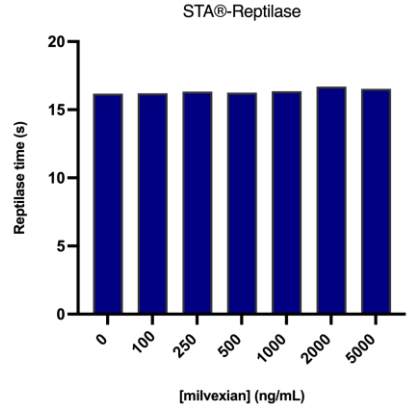
Free protein S CV: 4.2 [4.0 – 8.7] [1]





Reptilase time





[1] Intraindividual biological variation as median CV(%) estimates [95%CI] from the EFLM Biological Variation Database

Clinical trials in AF patients

Accronym	Study ID	Phase	FXI inhibitor	Dose regimen	Comparator	Status
PACIFIC-AF	NCT04218266	2	asundexian	20 – 50 mg qd	apixaban 5 or 2.5 mg bid	Completed
OCEANIC-AF	NCT05643573	3	asundexian	50 mg qd	apixaban 5 or 2.5 mg bid	Terminated (lack of efficacy)
LIBREXIA-AF	NCT05757869	3	milvexian	100 mg bid	apixaban 5 mg or 2.5 bid	Recruiting
AZALEA-TIMI 71	NCT04755283	2	abelacimab	90 – 150 mg s.c. monthly	rivaroxaban 20 mg or 15 mg od	Terminated (overwhelming reduction in bleeding)
LILAC-TIMI 76	NCT05712200	3	abelacimab	150 mg s.c. monthly	Placebo	Recruiting

PACIFIC-AF

12 weeks

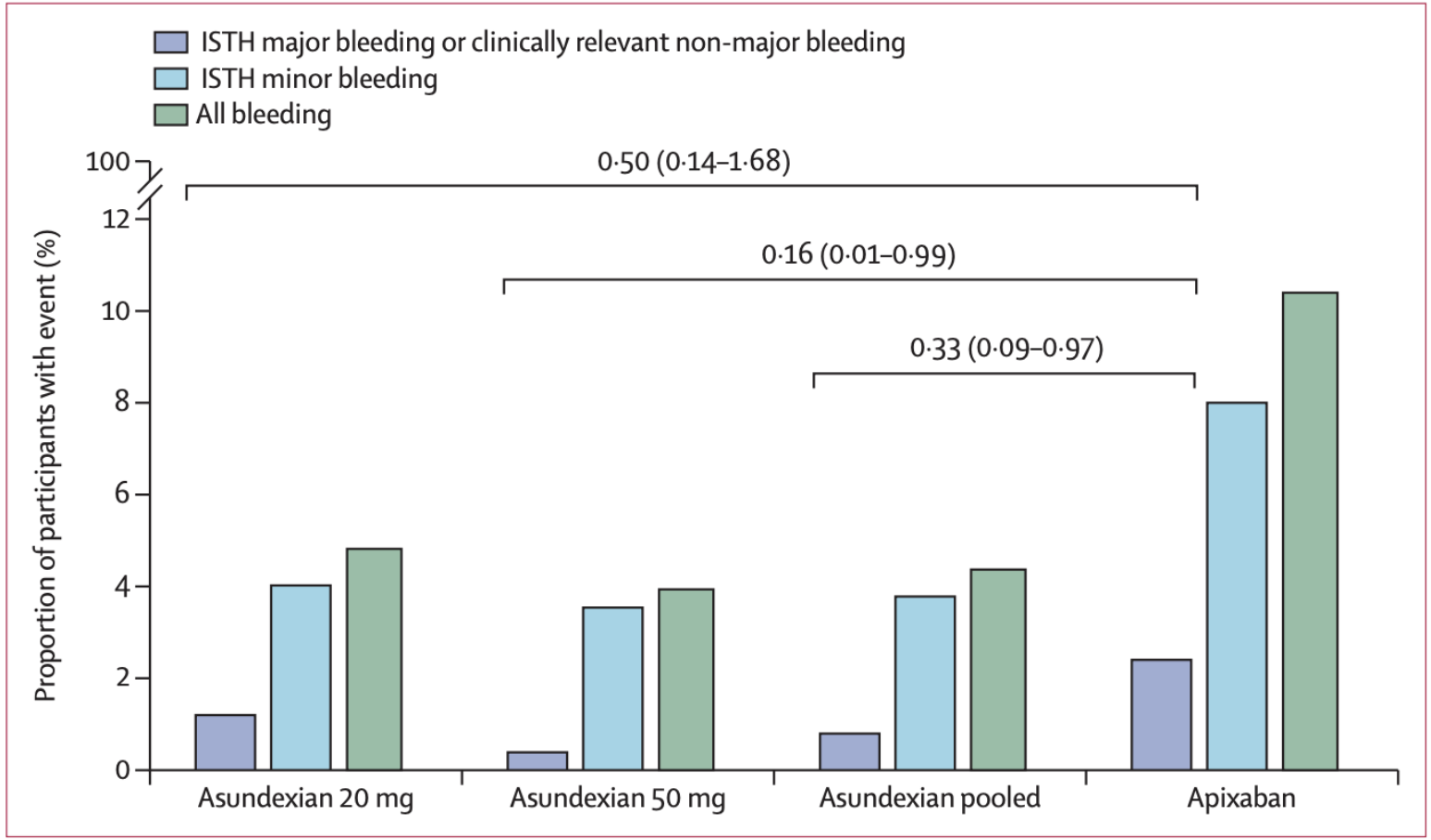


Figure 2: **Safety endpoints according to treatment assignment**
Horizontal bars show the ratio of incidence proportions (90% CIs) between asundexian and apixaban for the primary endpoint, ISTH major bleeding or clinically relevant non-major bleeding. No ISTH major bleeding events occurred in any treatment group. ISTH=International Society on Thrombosis and Haemostasis.

Piccini JP, Caso V, Connolly SJ, Fox KAA, Oldgren J, Jones WS, Gorog DA, Durdil V, Viethen T, Neumann C, Mundl H, Patel MR; PACIFIC-AF Investigators. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet. 2022 Apr 9;399(10333):1383-1390. doi: 10.1016/S0140-6736(22)00456-1. Epub 2022 Apr 3.

PACIFIC-AF

12 weeks

	Asundexian 20 mg (n=251)	Asundexian 50 mg (n=254)	Apixaban (n=250)	Total (n=755)
Cardiovascular death, myocardial infarction, ischaemic stroke, or systemic embolism	2	4	3	9
Cardiovascular death	1	3	3	7
Myocardial infarction	0	1	0	1
Ischaemic stroke	2	1	0	3
Systemic embolism	0	0	0	0
All-cause mortality	2	4	4	10

Data are numbers of participants.

Table 2: **Exploratory thrombotic endpoints**

Piccini JP, Caso V, Connolly SJ, Fox KAA, Oldgren J, Jones WS, Gorog DA, Durdil V, Viethen T, Neumann C, Mundl H, Patel MR; PACIFIC-AF Investigators. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet. 2022 Apr 9;399(10333):1383-1390. doi: 10.1016/S0140-6736(22)00456-1. Epub 2022 Apr 3.

PACIFIC-AF

Piccini JP, Caso V, Connolly SJ, Fox KAA, Oldgren J, Jones WS, Gorog DA, Durdil V, Viethen T, Neumann C, Mundl H, Patel MR; PACIFIC-AF Investigators. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet. 2022 Apr 9;399(10333):1383-1390. doi: 10.1016/S0140-6736(22)00456-1. Epub 2022 Apr 3.

12 weeks

	Asundexian 20 mg (n=249)*	Asundexian 50 mg (n=254)	Apixaban (n=250)	Asundexian total (n=503)	Total (n=753)
Any AE	118 (47%)	120 (47%)	122 (49%)	238 (47%)	360 (48%)
Any study drug-related AE	29 (12%)	26 (10%)	37 (15%)	55 (11%)	92 (12%)
Any AE leading to discontinuation of study drug	15 (6%)	16 (6%)	13 (5%)	31 (6%)	44 (6%)
AE of special interest	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Any SAE	22 (9%)	20 (8%)	20 (8%)	42 (8%)	62 (8%)
Any study drug-related SAE	4 (2%)	0	0	4 (1%)	4 (1%)
Any SAE leading to discontinuation of study drug	4 (2%)	4 (2%)	4 (2%)	8 (2%)	12 (2%)
AE with outcome of death	1 (<1%)	3 (1%)	2 (1%)	4 (1%)	6 (1%)
Deaths	1 (<1%)	3 (1%)	2 (1%)	4 (1%)	6 (1%)
Heart failure	0	0	1 (<1%)	0	1 (<1%)
Coronary artery disease	0	1 (<1%)	0	1 (<1%)	1 (<1%)
Sudden cardiac death	0	0	1 (<1%)	0	1 (<1%)
Cerebrovascular accident	1 (<1%)	1 (<1%)	0	2 (<1%)	2 (<1%)
Completed suicide	0	1 (<1%)	0	1 (<1%)	1 (<1%)

Data are presented as n (%), unless otherwise indicated. AE=adverse event. SAE=serious adverse event. *Table includes only patients who took at least one dose of study drug (two patients did not take study drug).

Table 3: **AEs according to treatment assignment**

OCEANIC-AF

Piccini JP, Patel MR, Steffel J, Ferdinand K, Van Gelder IC, Russo AM, Ma CS, Goodman SG, Oldgren J, Hammett C, Lopes RD, Akao M, De Caterina R, Kirchhof P, Gorog DA, Hemels M, Rienstra M, Jones WS, Harrington J, Lip GYH, Ellis SJ, Rockhold FW, Neumann C, Alexander JH, Viethen T, Hung J, Coppolecchia R, Mundl H, Caso V; OCEANIC-AF Steering Committee and Investigators. Asundexian versus Apixaban in Patients with Atrial Fibrillation. N Engl J Med. 2025 Jan 2;392(1):23-32. doi: 10.1056/NEJMoa2407105. Epub 2024 Sep 1. PMID: 39225267.

December 2022 → November 2023

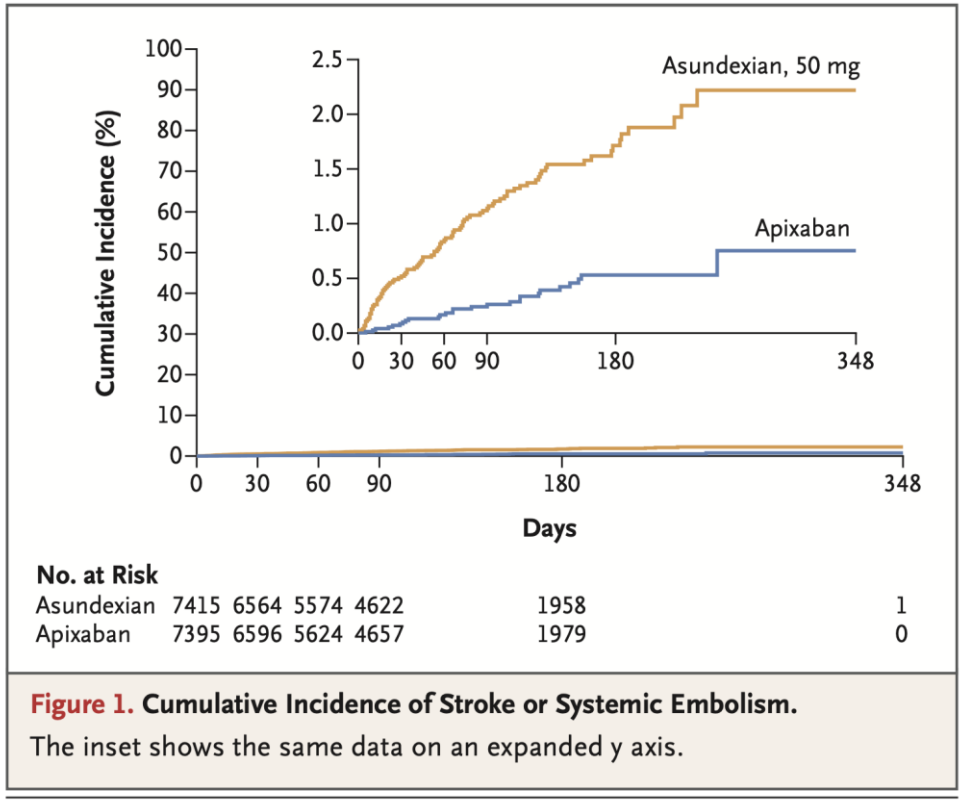


Figure 1. Cumulative Incidence of Stroke or Systemic Embolism.
The inset shows the same data on an expanded y axis.

Hazard ratio, 3.79; 95% CI, 2.46 to 5.83

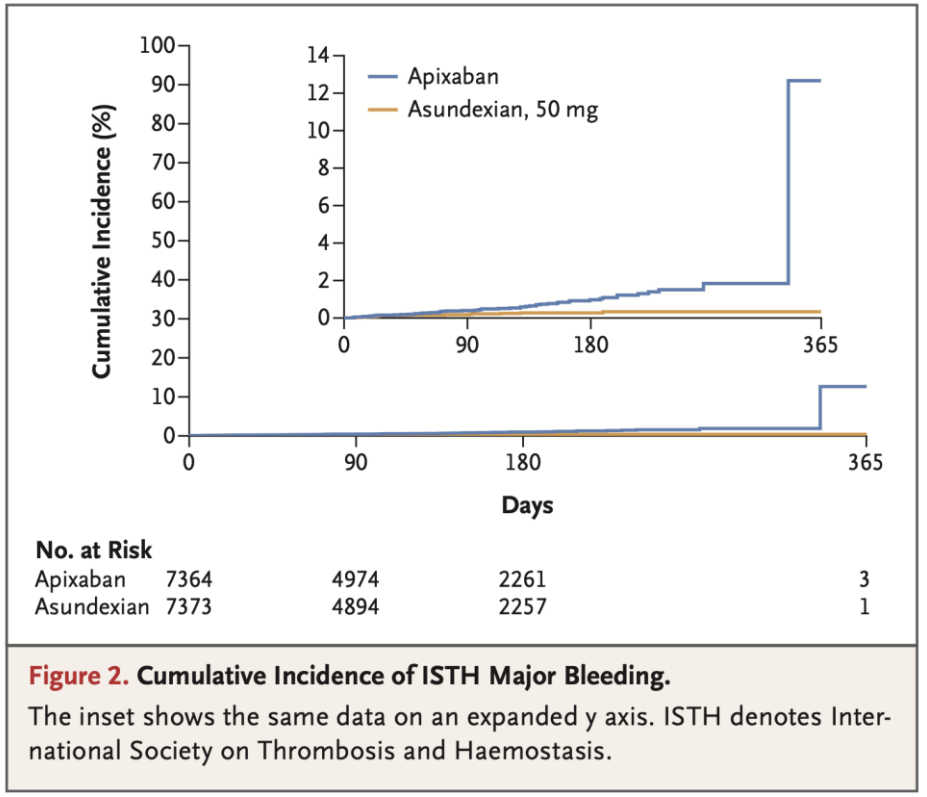
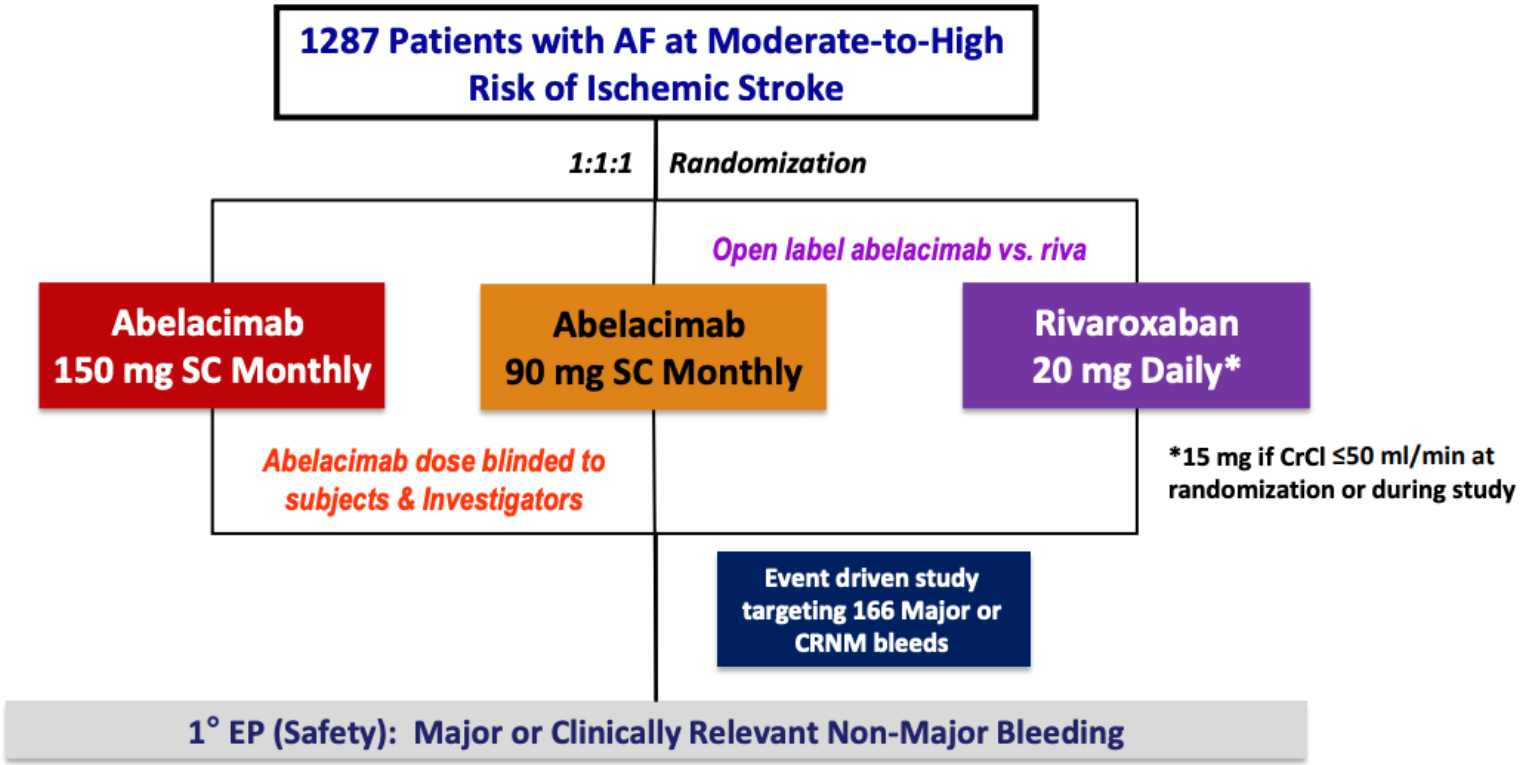


Figure 2. Cumulative Incidence of ISTH Major Bleeding.
The inset shows the same data on an expanded y axis. ISTH denotes International Society on Thrombosis and Haemostasis.

Hazard ratio, 0.32; 95% CI, 0.18 to 0.55

AZALEA-TIMI 71

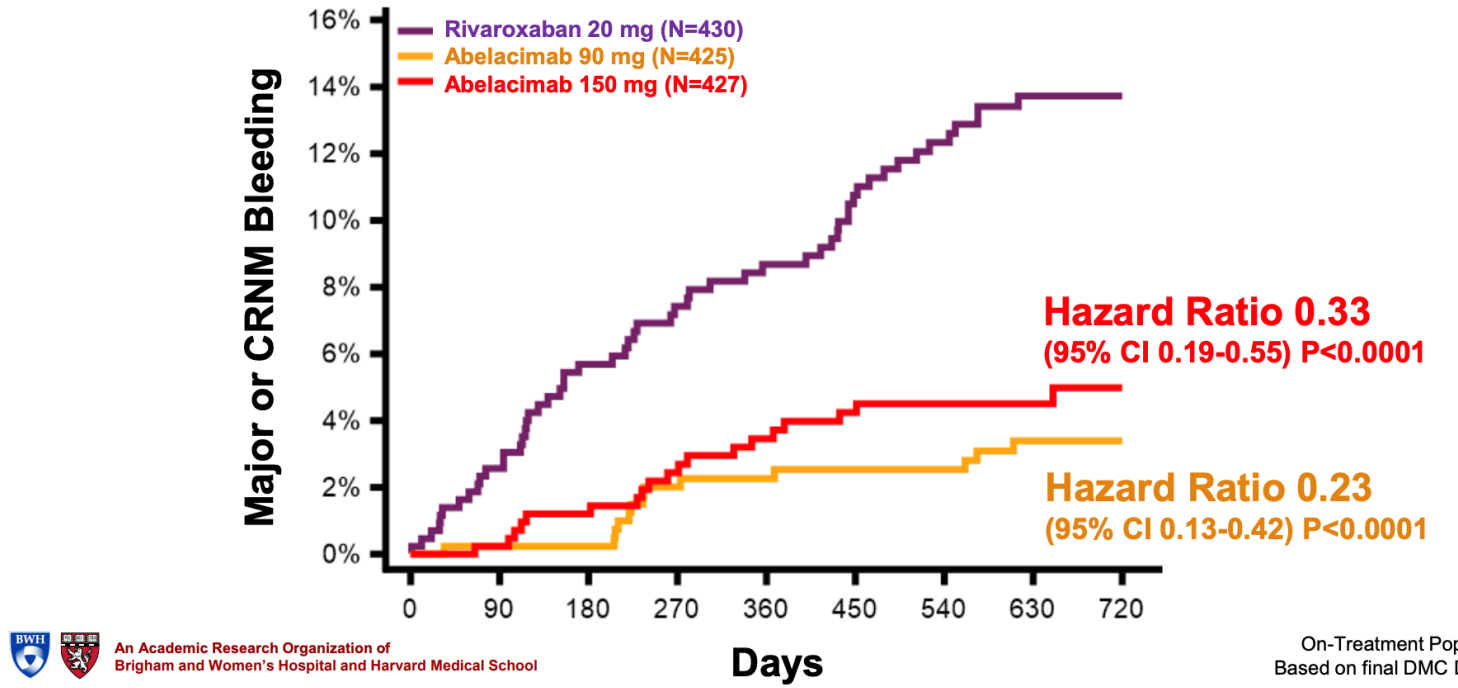


https://timi.org/wp-content/uploads/2023/11/Christian-Ruff-AZALEA-TIMI-71-A-Multicenter-RandomiZed-Active-ControLled-Study-to-Evaluate-the-Safety-and-Tolerability-of-Two-Blinded-Doses-of-Abelacimab-Compared-with-Open-Labe.pdf

AZALEA-TIMI 71

Stoped early (September 2023): « overwhelming reduction in bleeding »

Results presented in November 2023 at the American Heart Association (AHA) meeting



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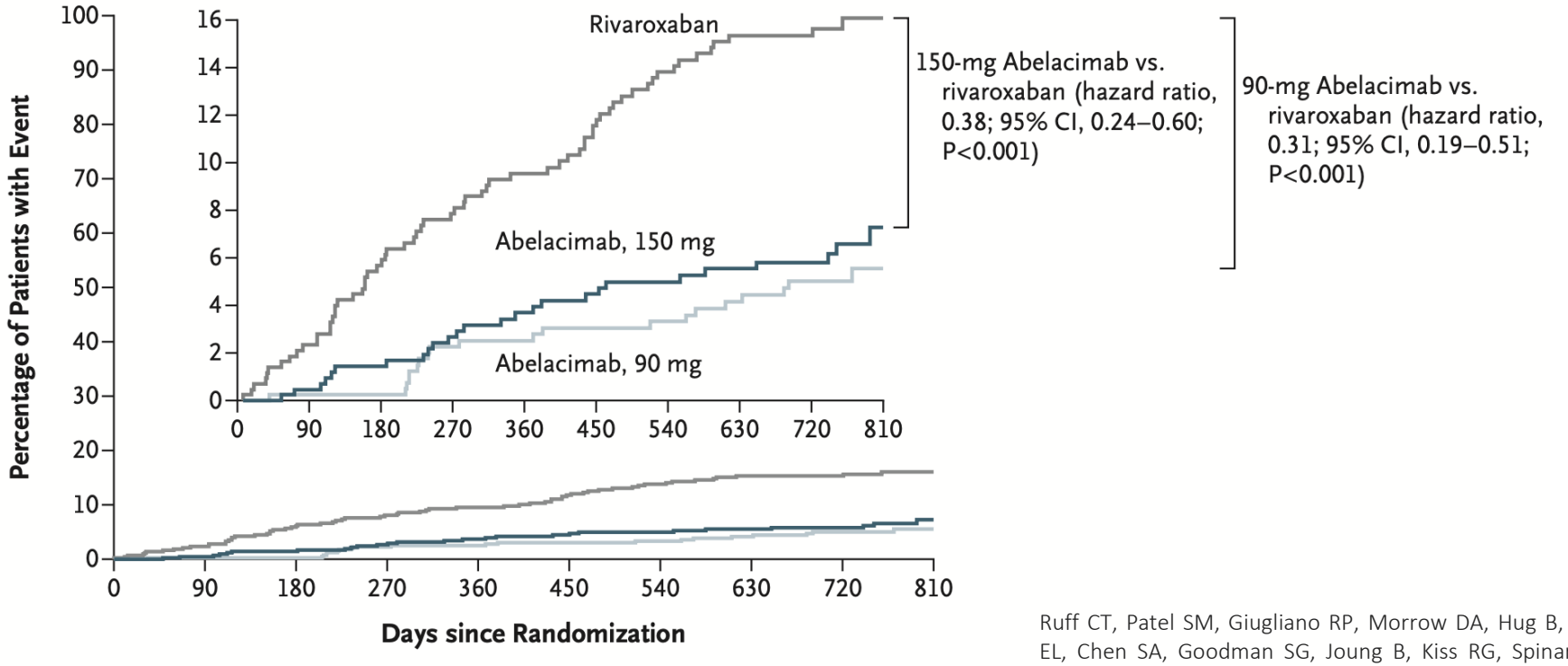
AZALEA-TIMI 71

Major or Clinically Relevant Nonmajor Bleeding



No. at Risk										
Rivaroxaban	428	415	392	375	365	352	339	328	310	121
Abelacimab, 150 mg	427	419	404	386	375	363	353	343	324	117
Abelacimab, 90 mg	425	413	398	378	372	357	349	338	308	117

Ruff CT, Patel SM, Giugliano RP, Morrow DA, Hug B, Kuder JF, Goodrich EL, Chen SA, Goodman SG, Joung B, Kiss RG, Spinar J, Wojakowski W, Weitz JI, Murphy SA, Wiviott SD, Parkar S, Bloomfield D, Sabatine MS; AZALEA–TIMI 71 Investigators. Abelacimab versus Rivaroxaban in Patients with Atrial Fibrillation. N Engl J Med. 2025 Jan 23;392(4):361-371. doi: 10.1056/NEJMoa2406674. PMID: 39842011.

AZALEA-TIMI 71

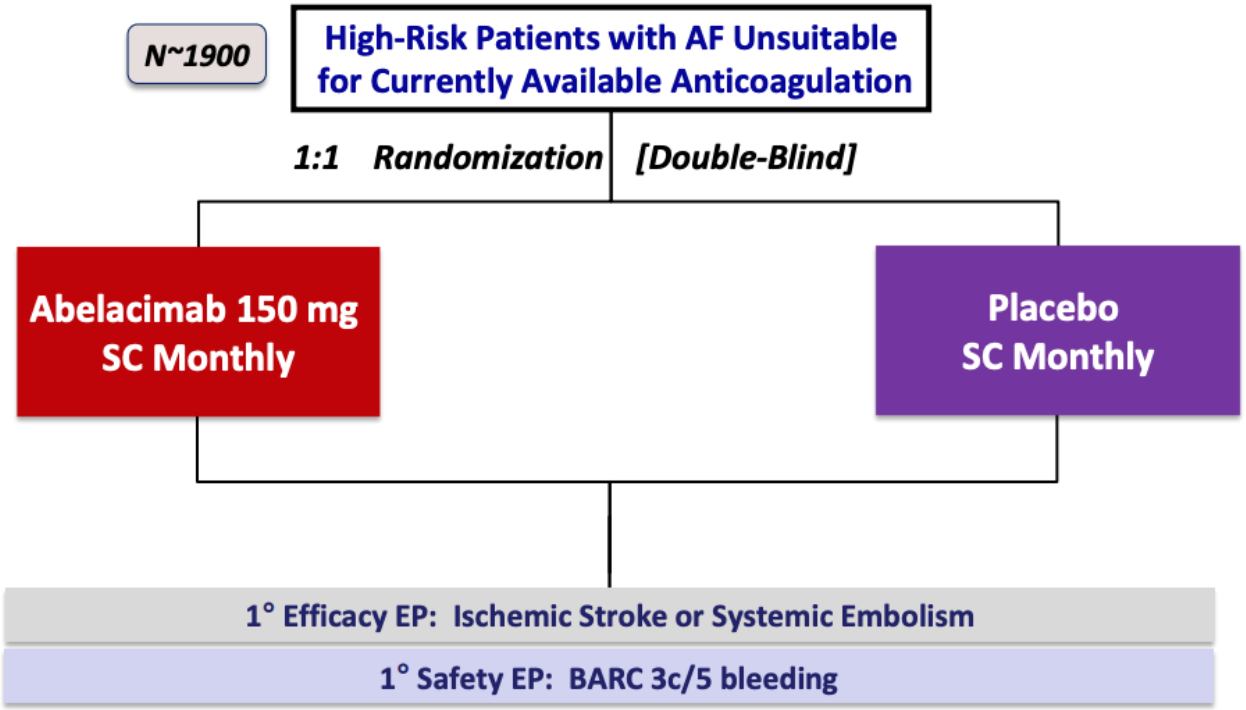
Table 2. End Points.*

End Point	Rivaroxaban (N=428)		Abelacimab, 150 mg (N=427)			Abelacimab, 90 mg (N=425)		
	Patients with Event	Incidence Rate	Patients with Event	Incidence Rate	Hazard Ratio vs. Rivaroxaban (95% CI)	Patients with Event	Incidence Rate	Hazard Ratio vs. Rivaroxaban (95% CI)
	no. (%)	*events/100 person-yr*	*no. (%)*	*events/100 person-yr*		*no. (%)*	*events/100 person-yr*	
Primary end point: major or clinically relevant nonmajor bleeding	66 (15.4)	8.38	26 (6.1)	3.22	0.38 (0.24–0.60)†	21 (4.9)	2.64	0.31 (0.19–0.51)†
Secondary end points								
Major bleeding	31 (7.2)	3.73	10 (2.3)	1.22	0.33 (0.16–0.66)	8 (1.9)	0.99	0.26 (0.12–0.57)
Gastrointestinal bleeding	18 (4.2)	2.14	2 (0.5)	0.24	0.11 (0.03–0.48)	2 (0.5)	0.25	0.11 (0.03–0.49)
Intracranial hemorrhage	4 (0.9)	0.47	2 (0.5)	0.24	0.51 (0.09–2.78)	4 (0.9)	0.49	1.05 (0.26–4.19)
Other major bleeding	9 (2.1)	1.06	6 (1.4)	0.73	0.68 (0.24–1.91)	2 (0.5)	0.25	0.23 (0.05–1.06)
Major, clinically relevant nonmajor, or minor bleeding	112 (26.2)	15.30	78 (18.3)	10.43	0.68 (0.51–0.91)	53 (12.5)	7.04	0.46 (0.33–0.64)
Exploratory end points								
Stroke or systemic embolism	7 (1.6)	0.83	10 (2.3)	1.21	1.47 (0.56–3.85)	11 (2.6)	1.36	1.65 (0.64–4.25)
Ischemic stroke	5 (1.2)	0.59	10 (2.3)	1.21	2.06 (0.70–6.02)	10 (2.4)	1.24	2.10 (0.72–6.14)
Hemorrhagic stroke	2 (0.5)	0.23	0	0	0	1 (0.2)	0.12	0.52 (0.05–5.72)
Systemic embolism	0	0	1 (0.2)	0.12	NA	0	0	NA
Death from any cause	30 (7.0)	3.52	22 (5.2)	2.65	0.77 (0.44–1.34)	26 (6.1)	3.20	0.93 (0.55–1.58)
Net clinical outcome‡	92 (21.5)	11.75	52 (12.2)	6.45	0.55 (0.39–0.77)	54 (12.7)	6.82	0.58 (0.41–0.81)
Death or any stroke	36 (8.4)	4.25	31 (7.3)	3.75	0.90 (0.56–1.46)	36 (8.5)	4.45	1.07 (0.67–1.70)

* The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. NA denotes not applicable.
† P<0.001.
‡ Net clinical outcome is a composite of ischemic stroke, systemic embolism, major or clinically relevant nonmajor bleeding, or death from any cause.

Ruff CT, Patel SM, Giugliano RP, Morrow DA, Hug B, Kuder JF, Goodrich EL, Chen SA, Goodman SG, Joung B, Kiss RG, Spinar J, Wojakowski W, Weitz JI, Murphy SA, Wiviott SD, Parkar S, Bloomfield D, Sabatine MS; AZALEA–TIMI 71 Investigators. Abelacimab versus Rivaroxaban in Patients with Atrial Fibrillation. N Engl J Med. 2025 Jan 23;392(4):361-371. doi: 10.1056/NEJMoa2406674. PMID: 39842011.

LILAC-TIMI 76



- 65-74 years + CHA2DS2VASc ≥ 5
- ≥75 ans + CHA2DS2VASc ≥ 4

- At least one of the following criteria:
  - Severe renal insufficiency
  - Daily use of antiplatelet therapy
  - History of bleeding from a critical area
  - NSAIDs
  - Frailty
  - Multiple falls

https://timi.org/wp-content/uploads/2023/11/Christian-Ruff-AZALEA-TIMI-71-A-Multicenter-RandomiZed-Active-ControLled-Study-to-Evaluate-the-Safety-and-Tolerability-of-Two-Blinded-Doses-of-Abelacimab-Compared-with-Open-Labe.pdf

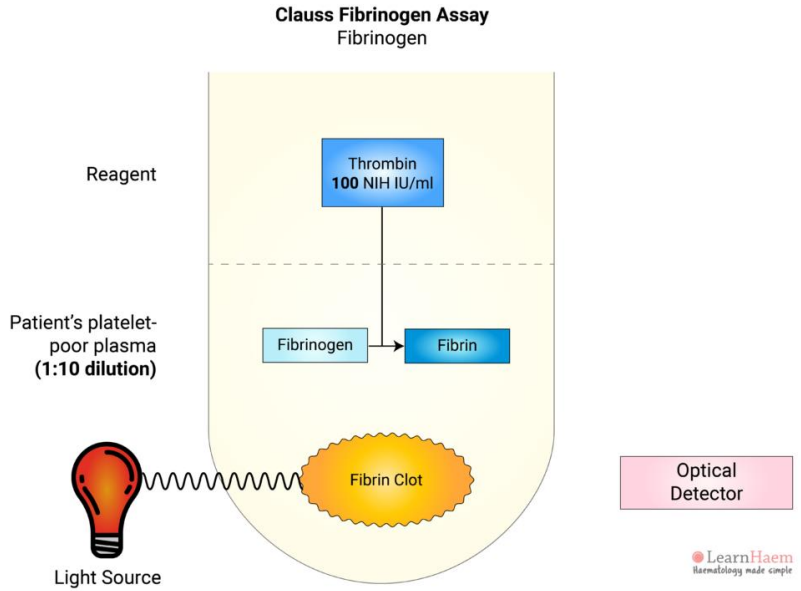
Clauss fibrinogen assay

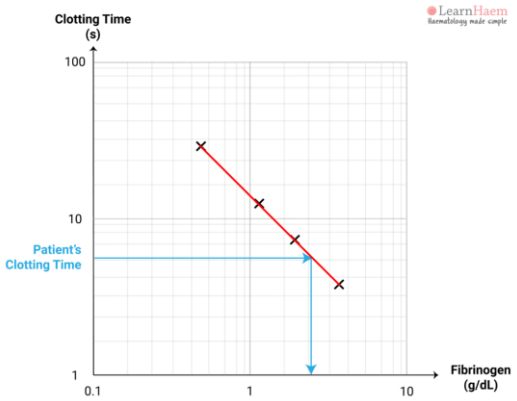
1. Reference (normal) plasma

- Serial dilutions
- + excess of thrombin (100 IU/mL)
- Time for fibrin clot formation
- Calibration curve (Log-Log)

2. Patient plasma

- + excess of thrombin (100 IU/m)
- Time for fibrin clot formation





Illustrations retrieved from:
https://www.learnhaem.com/courses/coag/lessons/coagulation-tests/topic/clauss-fibrinogen-assay/

One-stage CT-based clotting factors assays (1)

1. Reference (normal) plasma

- Serial dilutions
- + equal volume of factor-deficient plasma
- aPTT/PT

2. Patient plasma

- Serial dilutions
- + equal volume of factor-deficient plasma
- aPTT/PT

3. Log-Lin modelization

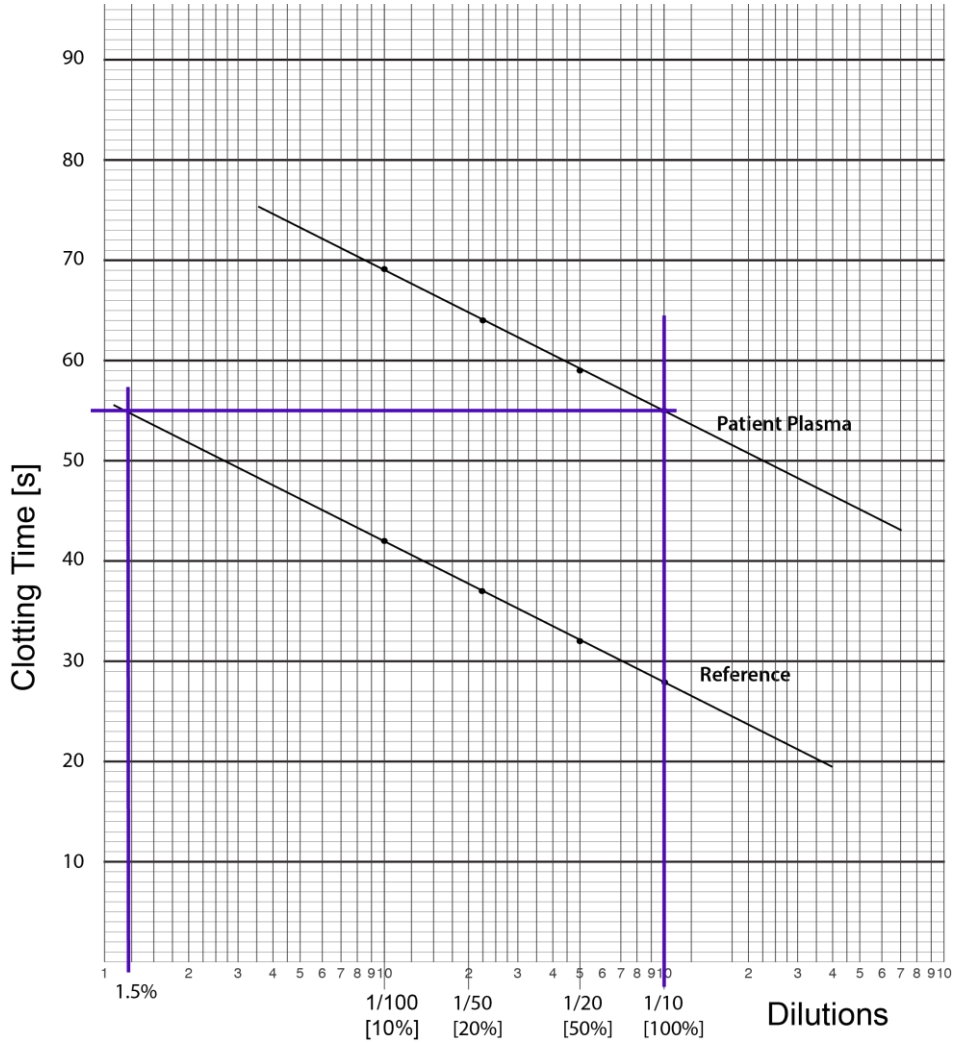


Illustration retrieved from: https://practical-haemostasis.com/Factor%20Assays/1_stage_aptt_factor_assay.html

aPTT-based protein C assay

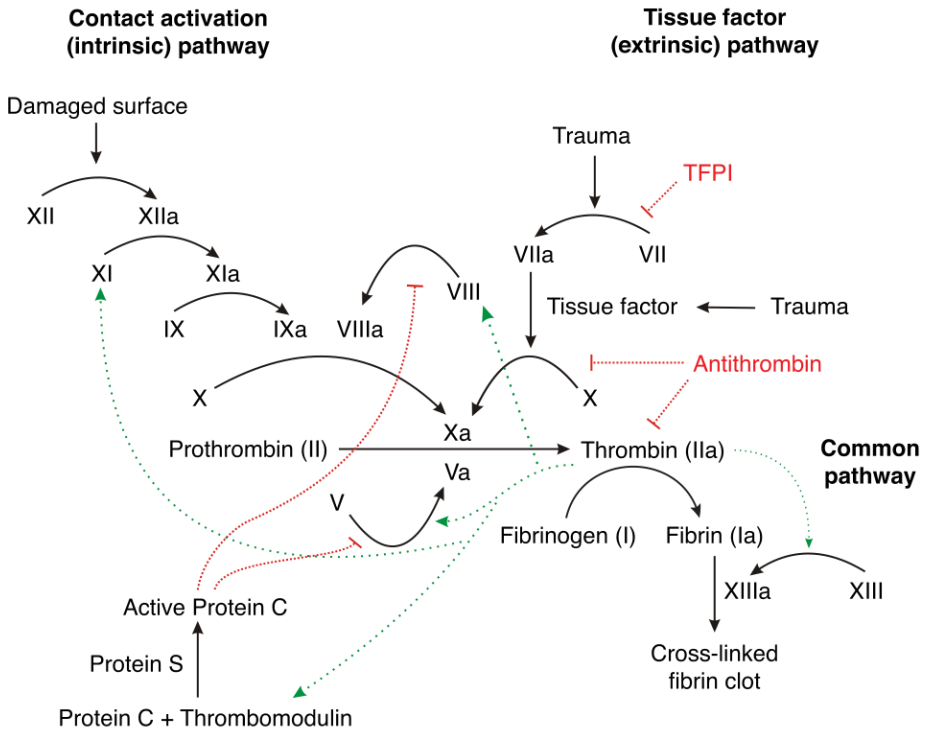


Illustration retrieved from: https://epomedicine.com/medical-students/protein-c-and-s-pathway-mnemonic/

- Plasma sample
- + synthetic phospholipids + contact activator (colloidal silica dispersion) = HemosIL®APTT-SP
- + protein C activator (Protac®)
- Incubation
- + Calcium chloride
- Recording of clotting time (aPTT)

Agkistrodon contortrix

Illustration retrieved from: http://www.herpnet.net/Iowa-Herpetology/reptiles/snakes/copperhead-agkistrodon-contortrix/

Latex particle-based agglutination protein S assay

Protein S

- ~60% bound to C4b-binding protein (C4bBP)
- Active form = free protein S

Assay

- Plasma sample + C4bBP-coated latex particles
- Incubation

-> Adsorption of free PS on C4bBP-coated latex particles

- + Anti-PS Mab Latex particles
- Agglutination
- ↑ Turbidity (405 nm)

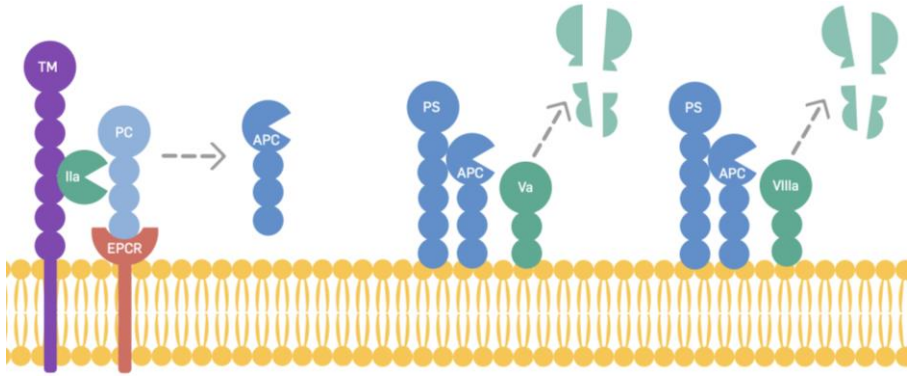


Illustration retrieved from:
https://www.nordicbiomarker.com/products/free-protein-s/

Ecarin chromogenic assay (ECA)

Plasma sample

- + human prothrombin
- + chromogenic substrate
- + ecarin
- Absorbance (405 nm)

Echis carinatus

Illustration retrieved from: https://www.inaturalist.org/taxa/31084-Echis-carinatus-carinatus

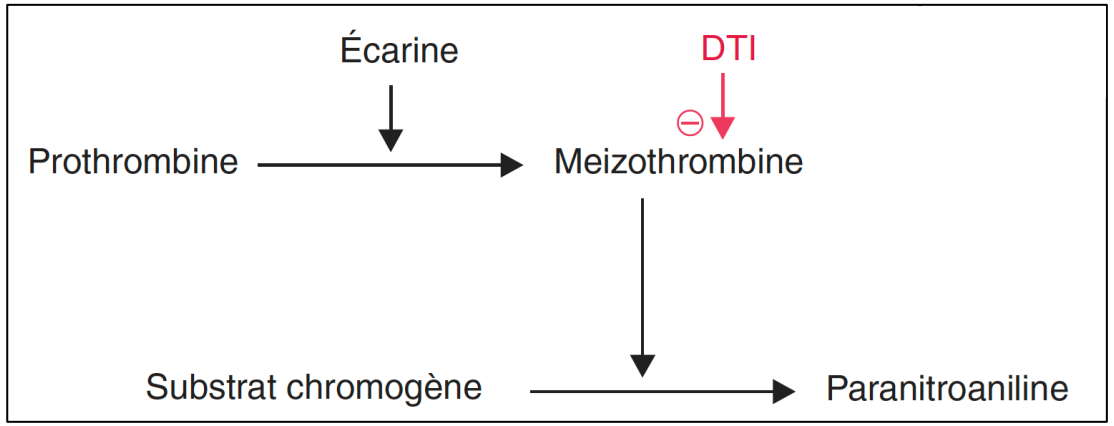


Illustration retrieved from the insert sheet of the STA®ECA II reagent kit (Diagnostica Stago)

Reptilase time

Plasma sample

- + Batroxobin (« thrombin like » toxin from *Bothrops atrox*)
- Clotting time

Bothrops atrox

Illustration retrieved from: https://www.inaturalist.org/taxa/49001-Bothrops-atrox

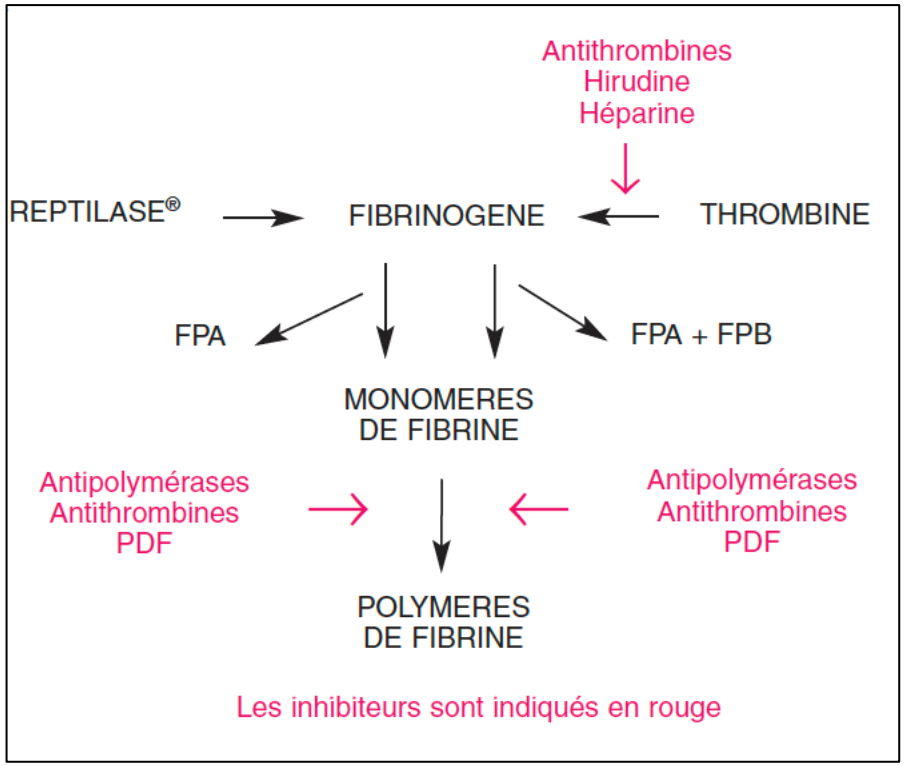


Illustration retrieved from the insert sheet of the STA®Reptilase II reagent kit (Diagnostica Stago)

Dilute Russel's viper venom time (dRVVT)

Plasma sample

- + phospholipids
- + diluted Russel's viper venom (FX activator)
- + calcium chloride
- Recording of clotting time

$$dRVVT\ Screen\ Ratio = \frac{Patient\ dRVVT\ Screen\ (s)}{Mean\ of\ dRVVT\ Screen\ normal\ range}$$

$$dRVVT\ Confirm\ Ratio = \frac{Patient\ dRVVT\ Confirm\ (s)}{Mean\ of\ dRVVT\ Confirm\ normal\ range}$$

$$dRVVT\ Test\ Ratio = \frac{dRVVT\ Screen\ Ratio}{dRVVT\ Confirm\ Ratio}$$

Daboia russelii

Illustration retrieved from: https://www.srilankansafari.com/reptiles_russellsviper.php

Bleeding classification – ISTH

Major:

- **fatal** bleeding,
- and/or symptomatic bleeding **in a critical area or organ**, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome,
- and/or bleeding causing a fall in **hemoglobin levels** of 1.24 mmol/L (20 g/L or greater) or more, or leading to a **transfusion** of 2 units or more of whole blood or red cells.

Minor: all reported bleedings not classified as major.

Clinically Relevant Non-Major Bleeding:

- Not a major bleeding
- at least one of the following criteria
  - requiring **medical intervention** by a healthcare professional.
  - leading to **hospitalization** or **increased level of care**.
  - prompting a **face to face** (i.e. not just a telephone or electronic communication) **evaluation**.

Wells GA, Elliott J, Kelly S, et al. Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention: Clinical and Economic Impact of Standard Versus Extended Duration [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019 Mar. (CADTH Optimal Use Report, No. 9.2b.) Appendix 10, Bleeding Classification System Definitions.