I Reunión de Expertos en Generación de Trombina

19 y 26 Noviembre 2020

Innovation

Automated System

Complete Solution

Standardisation

Potencial uso del DrugScreen

PROYECTO GENERACIÓN DE TROMBINA

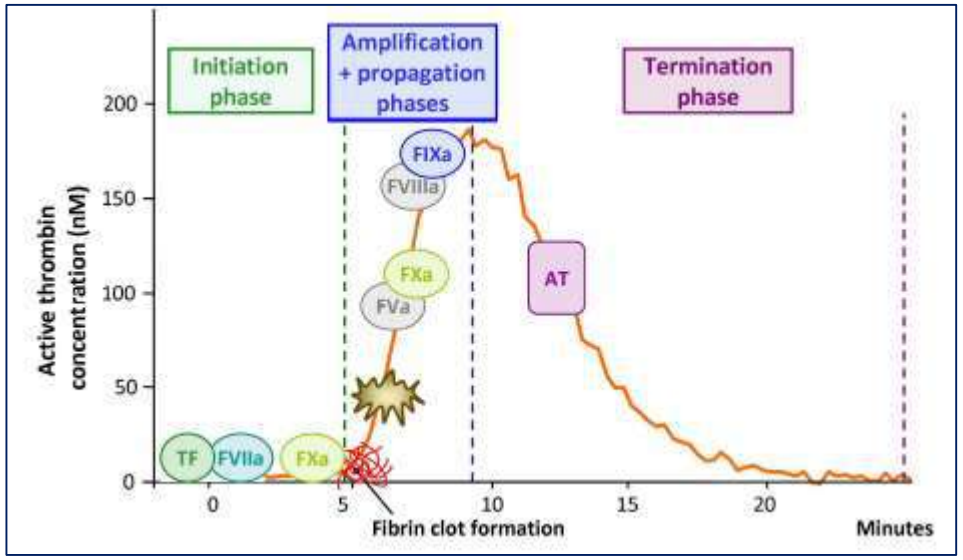
Stago

Table 1 – Potential clinical applications of the thrombin generation test.

Author	Main objectives of the study
Kessels et al.,[26] Arachchillage et al.[27] and Zabczyk et al.[28]	To monitor treatment with oral anticoagulants and antiplatelet drugs.
Al Dieri et al.[29]	To assess bleeding risk in patients with von Willebrand disease.
Simioni et al.,[30] Castoldi et al.,[31] Alhenc-Gelas et al.[32] and Castoldi at al.[33]	To evaluate hypercoagulable states in patients with the prothrombin G20210A mutation, factor V Leiden, and antithrombin or protein S deficiency.
Tripodi et al.[34] and Hron et al.[35]	To use the thrombin generation test to predict the recurrence of venous thromboembolism.
Lewis et al.[36] and Matsumoto et al.[37]	To estimate bleeding risk in patients with hemophilia using factor VIII or factor VIIa.
van Hylckama et al.[38]	To assess risk of deep venous thrombosis.
Brummel-Ziedins et al.[39]	To discriminate between acute and stable coronary artery disease.
Segers et al.[40]	To use the thrombin generation test to identify novel genetic risk factors for venous thromboembolism.
Carcaillon et al.[41]	To correlate thrombin generation with coronary heart disease and acute ischemic stroke in the elderly.
Tchaikovski et al.[42]	To investigate changes and determinants of thrombin generation and activated protein C resistance in the first 16 weeks of gestation in women with a history of preeclampsia.
Bosch et al.[43]	To evaluate patients undergoing cardiac surgery.
Orsi et al.[44]	To evaluate possible pathophysiological mechanisms that may contribute to the bleeding tendency observed in patients with dengue fever.
Kamphuisen et al.[45]	To evaluate cardiovascular risk in patients with hemophilia.
Gould et al.[46]	To assess procoagulant potential of intact neutrophil extracellular traps released from activated neutrophils.
Picoli-Quaino et al.[47]	To investigate hypercoagulability during the very early phases of the host response to an infection over the clinical course of sepsis and septic shock.
Loeffen et al.[48]	To evaluate the hypercoagulable profile of patients with stent thrombosis.
Zia et al.[49] and Glintborg et al.[50]	To evaluate hypercoagulability in women using oral contraceptives.
Dargaud et al.[51]	To identify an autosomal dominant bleeding disorder in a family, caused by a thrombomodulin mutation.
Barco et al.[52] and Honickel et al.[53]	To evaluate the effect of prothrombin complex concentrate in reversing the anticoagulant effect of rivaroxaban and dabigatran.

Figueiredo Duarte RC et al. Braz J Hematol Hemother 2017;39: 259-265

Desarrollo de **nuevos tests capaces de dar información sobre la respuesta individualizada al tratamiento** no solo de medir niveles plasmáticos (variación interindividual de proteínas plasmáticas, contribución de antiagregantes plaquetarios…)



Contexto de terapia anticoagulante

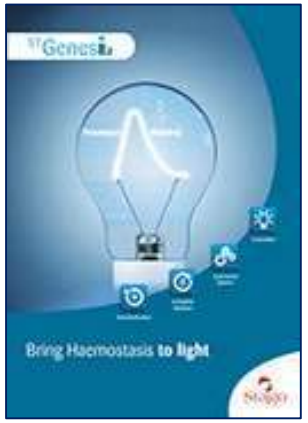
Estudiar el efecto individual de los tratamientos anticoagulantes

Evaluar la variabilidad intraindividual

¿Decisión sobre diferentes fármacos?

¿Decisión sobre la dosis?

Se pasa de un concepto de concentración a medir funcionalmente la actividad anticoagulante de estos fármacos



STG-ThromboScreen: Thrombin generation assessment in patients who are likely to suffer from thrombophilia.
STG-BleedScreen: Thrombin generation assessment in patients with bleeding risk, such as haemophiliacs.
STG-DrugScreen: Assessment of the effect of anticoagulants on treated patients, which could be useful for people at risk of drug accumulation (impaired renal function, people over 75, etc.).

ST Genesia

Página web Stago

TGT- Estandarización

- **Muchos factores influyen el TGT**
  - El plasma del paciente (the inner-filter effect)
  - Variables preanalíticas
    - Tubo, aguja/palomilla, muestras frescas/congeladas
  - Reactivos
    - PPP-Reagent Low (1 pM TF + 4 µM PL)
    - PPP-Reagent High (20 pM TF + 4 µM PL)
    - PPP-Reagent (5 pM TF + 4 µM PL)
    - MP-Reagent (4 µM PL)
    - PRP Reagent (1 pM TF)
    - Reactivos”caseros”
  - Lote
  - Método usado (distinto según fabricante)

STG® - DrugScreen

Quantitative determination of thrombin generation using a fluorogenic method - high concentration of tissue factor

- Kit Containing:
  - 3 x 1-ml Vials of Reagent 1 (STG® - DrugScreen)
  - 3 x 1-ml Vials of Reagent 2 (STG® - RefPlasma DS)
  - 3 x 1-ml Vials of Reagent 3 (STG® - QualiTest Low DS)
  - 3 x 1-ml Vials of Reagent 4 (STG® - QualiTest Norm DS)

Reactivo 1: Trigger. FT y fosfolípidos a concentraciones elevadas
Reactivo 2: Plasma referencia normal.
Reactivo 3: Plasma control hipocoagulable
Reactivo 4: Plasma control normal

Intra-assay reproducibility (n = 21):

	Sample 1			Sample 2		
	Mean	SD	CV (%)	Mean	SD	CV (%)
Lag Time (min)	1.04	0.03	2.66	1.30	0.04	2.93
Lag Time (ratio)	0.91	0.03	3.67	1.14	0.05	4.40
Peak Height (nM)	453.13	14.61	3.22	198.01	6.11	3.09
Peak Height (%)	97.06	3.37	3.47	42.41	1.41	3.31
ETP (nM.min)	1366.57	69.04	5.05	487.59	15.43	3.16
ETP (%)	84.15	4.96	5.90	30.03	1.37	4.55

Inter-assay reproducibility (n = 10):

	Sample 1			Sample 2		
	Mean	SD	CV (%)	Mean	SD	CV (%)
Lag Time (min)	1.03	0.05	4.54	1.28	0.05	3.51
Lag Time (ratio)	0.90	0.04	3.99	1.11	0.04	3.66
Peak Height (nM)	464.07	12.52	2.70	203.16	10.82	5.32
Peak Height (%)	100.33	3.35	3.34	43.9	2.13	4.85
ETP (nM.min)	1385.5	50.04	3.61	503.97	17.21	3.41
ETP (%)	83.89	4.57	5.45	30.49	1.16	3.79

ORIGINAL ARTICLE

jth

Assessment of the analytical performances and sample stability on ST Genesia system using the STG-DrugScreen application

Jonathan Douxfils[1,2] | Laure Morimont[1] | Céline Bouvy[2] | Marie de Saint-Hubert[3] | Bérangère Devalet[4] | Célia Devroye[5] | Anne-Sophie Dincq[6] | Jean-Michel Dogné[1] | Maïté Guldenpfennig[5] | Justine Baudar[5] | Anne-Sophie Larock[7] | Sarah Lessire[6] | François Mullier[5]

Essentials

- Thrombin generation testing is widely used to provide information on the coagulation phenotype of patients.
- Some limitations have been highlighted such as the lack of established standardization.
- This is the first study reporting precision results of the ST Genesia.
- Normal range of the STG-DrugScreen application has been assessed in healthy subjects.
- The ST Genesia may facilitate the implementation of thrombin generation in the routine laboratory.

TABLE 4 Normal range definition of the STG-DrugScreen application on the ST Genesia system using plasma sample from 42 healthy individuals

Healthy (n = 42)	Lag time absolute	Peak height absolute	Time-to-peak absolute	ETP absolute	Lag time normalized (ratio)	Peak height normalized	Time-to-peak normalized (ratio)	ETP normalized
Mean	0.93 min	456.20 nmol/L	2.03 min	1418 nmol/L	1.16	97%	0.98	83%
SD	0.09 min	56.35 nmol/L	0.16 min	270 nmol/L	0.10	12%	0.08	15%
CV (%)	9.8	12.4	7.9	19.1	9.6	12.1	7.9	18
Minimum	0.73 min	355.90 nmol/L	1.80 min	1027 nmol/L	0.81	75%	0.87	56%
Maximum	1.22 min	571.40 nmol/L	2.69 min	1993 nmol/L	1.33	120%	1.29	118%
10%	0.82 min	380.20 nmol/L	1.87 min	1122 nmol/L	0.90	81%	0.90	68%
90%	1.00 min	538.90 nmol/L	2.17 min	1851 nmol/L	1.11	115%	1.29	109%

Rango normal percentil 10º-90º

J Thromb Haemost 2018; 40: e11-e14

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J Thromb Haemost 2018; 40: e11-e14

- STG-DrugScreen para ST-Genesia simplifica y estandariza TG en anticoagulados
- CV parámetros TG 5-10%
- Congelación no tiene impacto sobre parámetros generación trombina
    - Estabilidad máxima 11 meses -70ºC para ACOD
    - Estabilidad máxima 6 meses -70ºC para HBPM
- Plasma referencia comercial específico y resultados normalizados reducen variabilidad entre lotes

Valores normalidad- DrugScreen/ ST Genesia

Parámetro TG	Valor*
Lag time (LT)	1.50 (1.19-2.06) min
Time to peak (TTP)	2.79 (2.24-3.56) min
Thrombin peak (TP)	448 (323-674) mmol/L
Endogenous thrombin potential (ETP)	1803 (1129-3211) mmol/L
Velocity index (VI)	517 (268-769) mmol/min

* Media (2.5º-97.5º percentil)
N=42

Pfrepper C et al. Res Pract Thromb Haemost 2020;23: 619-627

How the Direct Oral Anticoagulant Apixaban Affects Thrombin Generation Parameters

Armando Tripodi [a,b,*], Lidia Padovan [a,b], Veena Chantarangkul [a,b], Erica Scalambrino [a,b], Sophie Testa [c], Flora Peyvandi [a,b,d]

Test Plasma	Lag-Time (min)		ETP (nM•Min)		Peak (nM)		Velocity Index	
	No TM	TM	No TM	TM	No TM	TM	No TM	TM
0 ng/mL	4,7 (0.21)	7.1 (0.52)	1,935 (20.2)	938 (78.2)	307 (5.1)	190 (14.3)	108 (7.1)	81 (6.2)
10	5.4 (0.28	9.8 (0.58)	1,813 (42.6)	848 (67.3)	287 (3.6)	188 (14.7)	100 (2.9)	87 (12.6)
20	6.3 (0.29)	12.1 (1.07)	1,780 (75.3)	756 (50.5)	272 (8.0)	177 (13.0)	95 (7.3)	80 (13.1)
50	8.0 (0.49)	15.6 (1.41)	1,685 (27.3)	591 (96.6)	237 (18.7)	150 (26.6)	88 (7.8)	82 (17.1)
100	10.1 (0.64)	19.2 (1.21)	1,564 (45.5)	385 (24.2)	180 (9.2)	93 (4.9)	75 (5.4)	48 (5.0)
200	11.9 (0.47)	25.9 (1.52)	1,394 (43.0)	255 (28.6)	129 (7.7)	58 (7.7)	56 (3.4)	28 (4.7)
500	15.6 (0.95)	36.8 (7.89)	954 (11.56)	85 (23.9)	78 (1.3)	9 (5.7)	35 (1.6)	3 (2.05)
1,000	21. 1 (1.63)	ND	708 (66.9)	ND	52 (6.5)	ND	22 (4.8)	ND

Parameter	Without TM	With TM
Lag-time	2.53	3.65
ETP	0.72	0.27
Peak thrombin	0.42	0.31
Velocity Index	0.52	0.35

a 200 ng/mL

20 voluntarios sanos
CAT

Thromb Res 2015; 135: 1188-1190

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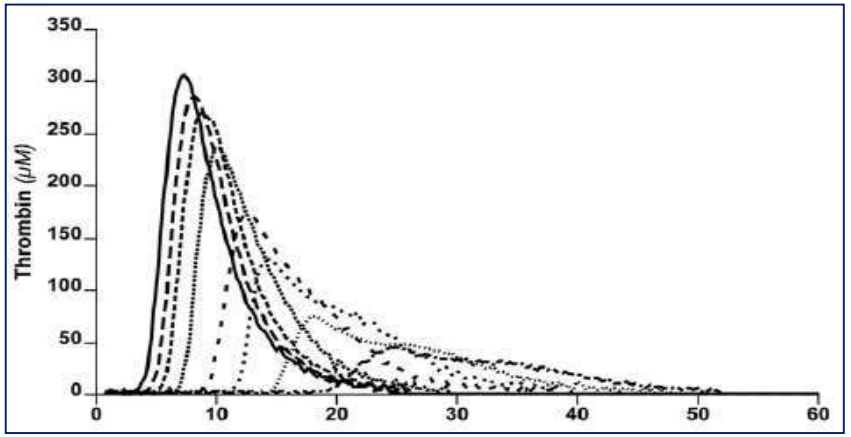
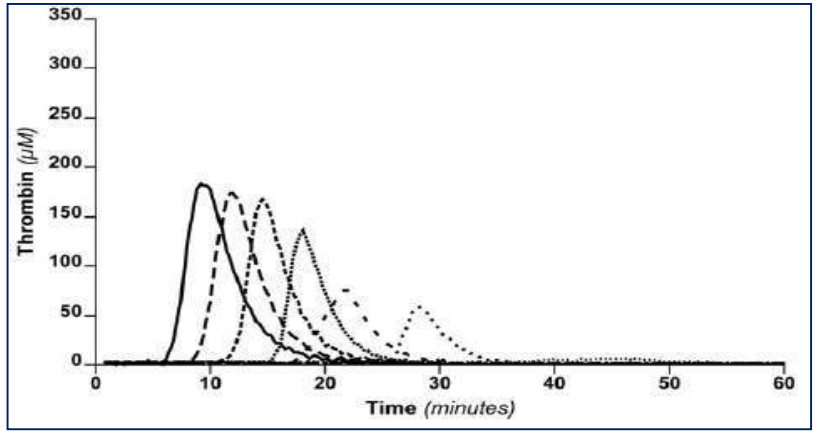
- **Lag-time mucho más sensible que TP/TTPA ¿?**
- **Reducción ETP 30% ≈ seguridad/eficacia ¿?**
- **Reducción pico ≈58%/velocity index ≈48%**
- **Resultados más afectados en presencia de TM**
- **ETP/peak (ratio con TM/sin TM) ↑ Hiper ↓ Hipo-coagulabilidad+++???**



Sin TM



Con TM

20 voluntarios sanos CAT

Thromb Res 2015; 135: 1188-1190

TG- Apixabán *vs* rivaroxabán

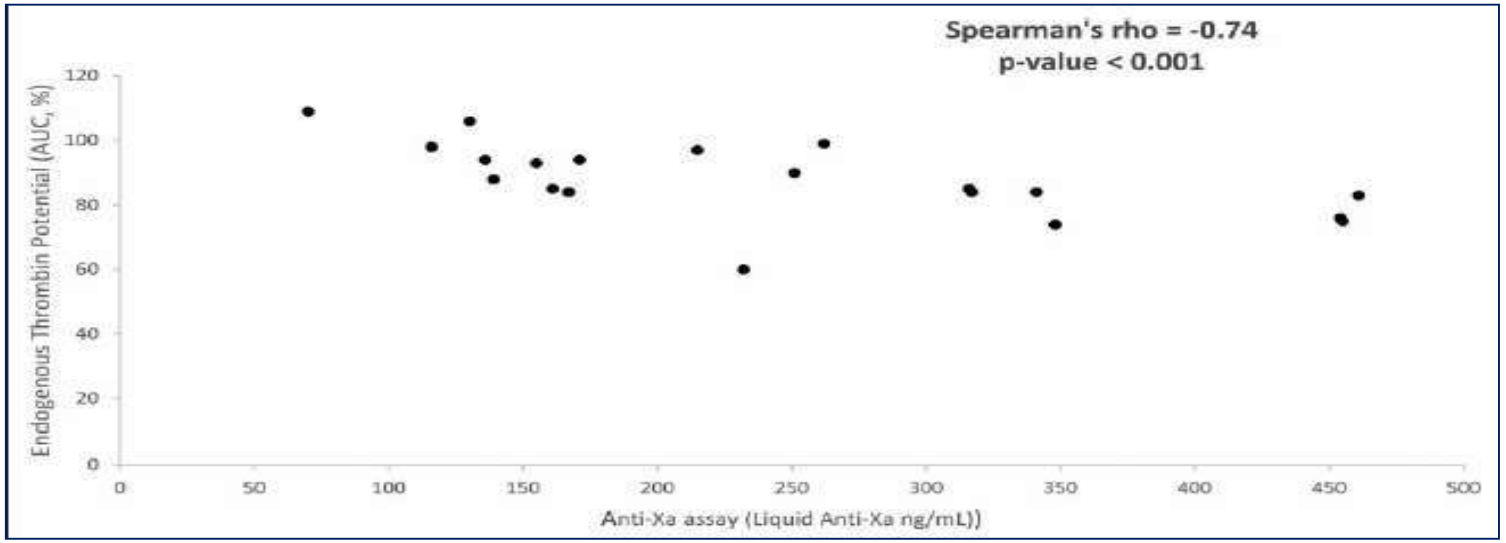
	Group A	Group B	Control	*P* Value (A vs B; A vs Co; B vs Co)
Coagulation parameters				
INR	1.58 (0.60); 1.39 (1.15-1.83)	1.26 (0.29); 1.14 (1.08-1.34)	0.99 (0.08); 0.99 (0.92-1.04)	.036; <.001; <.001
aPTT, seconds	45.4 (15.3); 42.6 (38.9-48.4)	31.8 (3.3); 31.5 (29.6-34.0)	30.5 (3.7); 29.2 (28.0-31.9)	<.001; <.001; .070
Fibrinogen, mg/dL	372.4 (71.4); 369.0 (326.0-407.0)	446.8 (114.6); 429.5 (358.4-514.2)	290.2 (94.5); 262.0 (213.0-343.0)	.036; .003; <.001
D-dimers, ng/mL	615.6 (787.0); 296.5 (199.5-754.0)	1128.3 (2880.2); 447.0 (329.0-779.4)	317.6 (173.0); 274.5 (170.0-368.5)	.256; .255; .007
ROTEM (NATEM)				
CT, seconds	916 (414); 767 (676-1074)	750 (150); 763 (660-841)	499 (116); 491 (412-584)	.245; <.001; <.001
CFT, seconds	310 (265); 188 (151-379)	232 (128); 205 (157-296)	133 (31); 125 (113-163)	.695; .001; .002
α, °	50.5 (17.1); 56.0 (39.0-62.0)	54.5 (12.0); 55.0 (47.0-60.0)	64.5 (5.0); 65.5 (59.5-68.0)	.787; .001; .003
MCF, mm	59.9 (6.2); 59.0 (56.0-64.0)	60.2 (7.6); 60.0 (56.0-64.5)	58.8 (4.0); 58.0 (56.0-61.0)	.839; .524;.401
Li60, %	95.4 (3.5); 95.5 (92.5-98.5)	94.6 (3.3); 94.5 (92.0-96.0)	95.4 (2.8); 95.5 (94.0-97.0)	.499; .957; .347
Endogenous thrombin potential				
Lag time, seconds	48.2 (16.2); 47.5 (35.7-56.2)	39.7 (7.6); 39.1 (34.4-42.7)	30.1 (5.0); 29.3 (27.0-31.7)	.079; <.001; <.001
Tmax, seconds	109.3 (47.1); 109.1 (70.6-124.2)	89.7 (24.5); 89.6 (66.2-107.2)	83.6 (16.6); 80.3 (70.2-90.3)	.204; .079; .543
Cmax, %/min	70.2 (18.8); 71.4 (58.7-84.2)	86.1 (12.3); 86.5 (75.5-91)	113.4 (13.2); 111.2 (105.5-119.0)	.009; <.001; <.001
AUC, %	71.4 (18.7); 75.0 (60.5-85.5)	87.9 (11.6); 86.5 (83.5-95.5)	101.5 (13.0); 97.5 (92.5-112.5)	.003; <.001; .003
Plasma drug concentrations				
Anti-Xa assays, ng/mL	217.0 (152.8); 200.0 (85.0-345.0)	244.9 (120.6); 223.5 (147.0-329.0)	–	.387

Rivaroxaban (n=20)* ↓↓

Apixaban (n=20)* ↓

*pacientes con ACxFA
CAT

Kyriakou E et al. Clin Appl Thromb Haemost 2018; 24: 1945-2015



No relación concentración - ETP

Rivaroxaban

Endogenous thrombin potential			
Lag time, seconds	+0.60	.005	Statistically significant, moderate positive correlation
Tmax, seconds	+0.40	.081	No correlation
Cmax, seconds	−0.74	<.001	Statistically significant, strong inverse correlation
AUC, %	−0.74	<.001	Statistically significant, strong inverse correlation

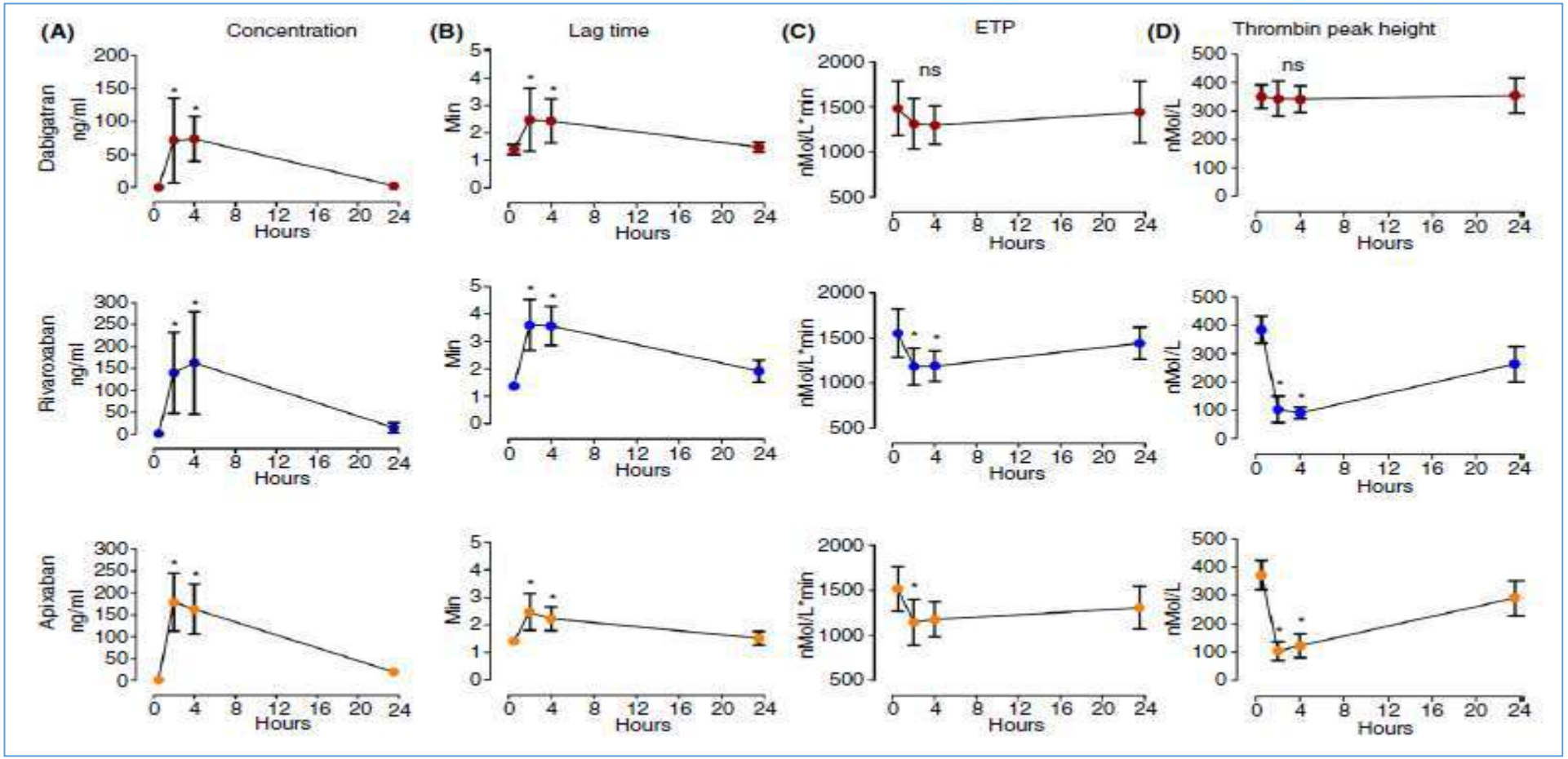
Apixaban

Relación inversa concentración – ETP/Pico/lag time

Kyriakou E et al. Clin Appl Thromb Haemost 2018; 24: 1945-2015

- **Mayor potencia anticoagulante rivaroxaban que apixaban**
- **Apixaban reduce ETP frente a controles sanos pero menos que rivaroxaban**
- **Relación dosis-dependiente apixabán- ETP**
- **Posible relación mejor perfil beneficio-riesgo apixabán**
- **¿Posible valor en valorar actividad anticoagulante apixabán?**
- **“Rangos terapéuticos”**
- **¿Comparación actividad anticoagulante ≠ACODs en vida real?**

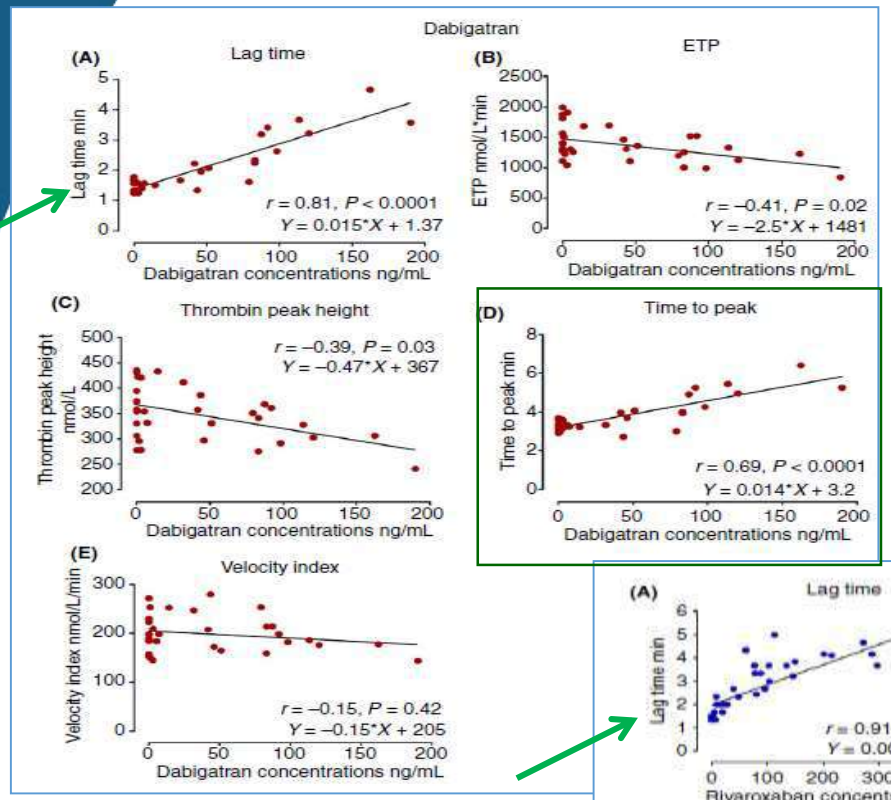
Kyriakou E et al. Clin Appl Thromb Haemost 2018; 24: 1945-2015

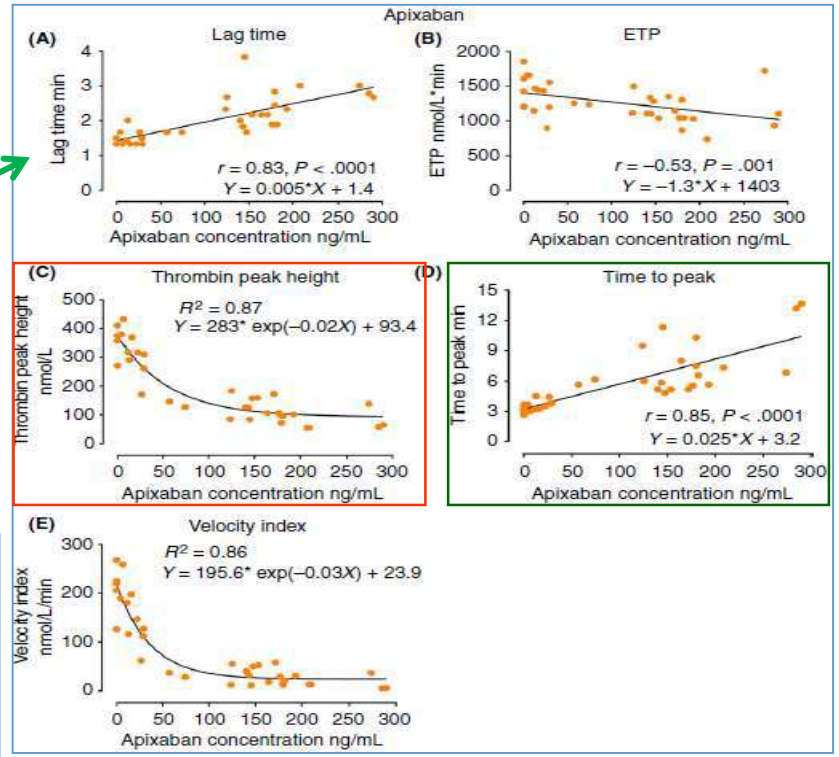


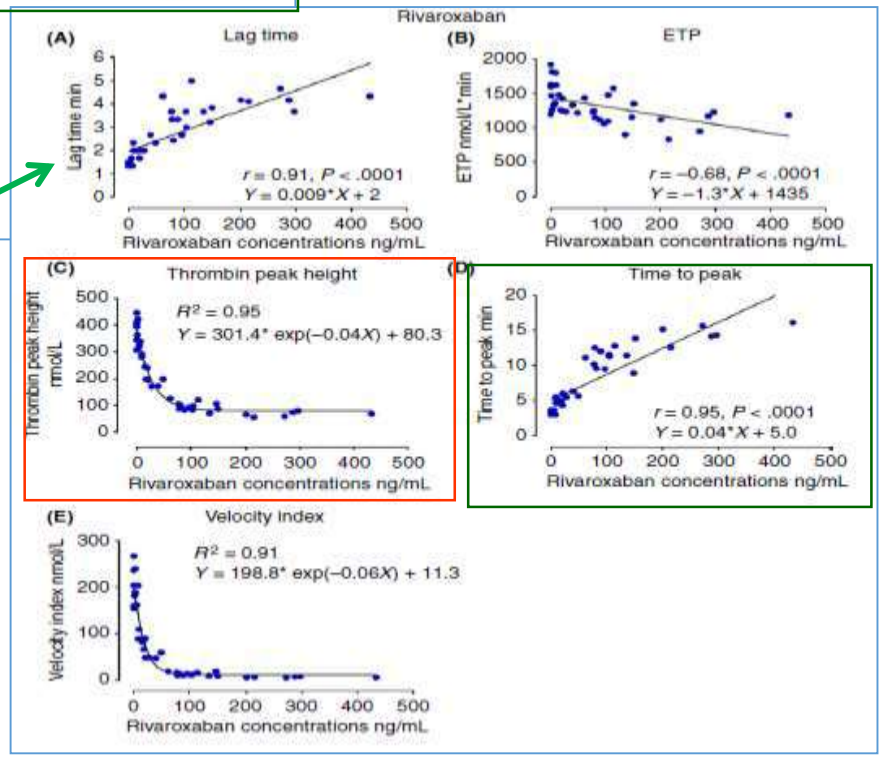
Lag time- Correlación con concentraciones Riv/Apix/Dabi
ETP- Relacion moderada con concentraciones Riv/Apix. No dabi
Pico. No relacion concentración Dabi. Fuerte relacion Riv/Apix

Voluntarios sanos
CAT

Artang R et al. Res Pract Thromb Haemost 2017; 1:194-201







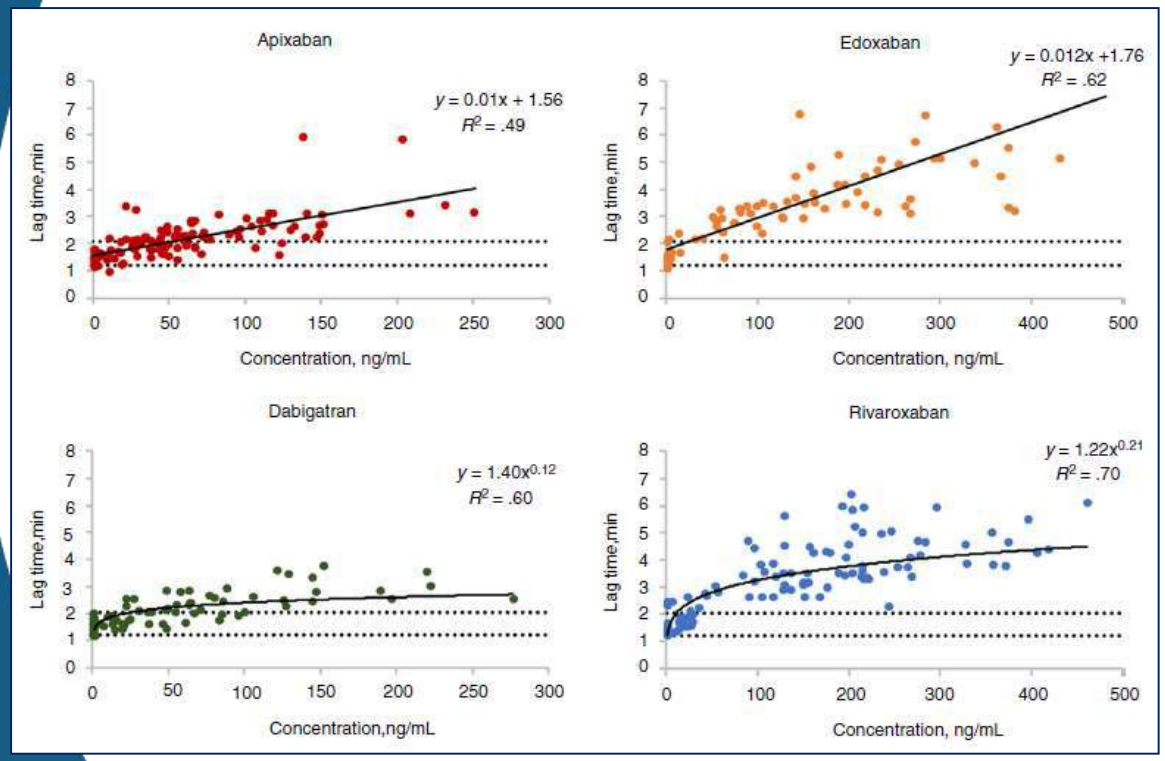
- **Lag time** único parámetro sensible a Riv/Apix/Dabi
- ETP no correlación concentración
- **Pico** mayor correlación para Riv/Apix*
- **TTP** correlación similar para Riv/Apix/Dabi
- **VI** ≈ pico

*≤100 ng/ml Riv-≤150 ng/mL Apix

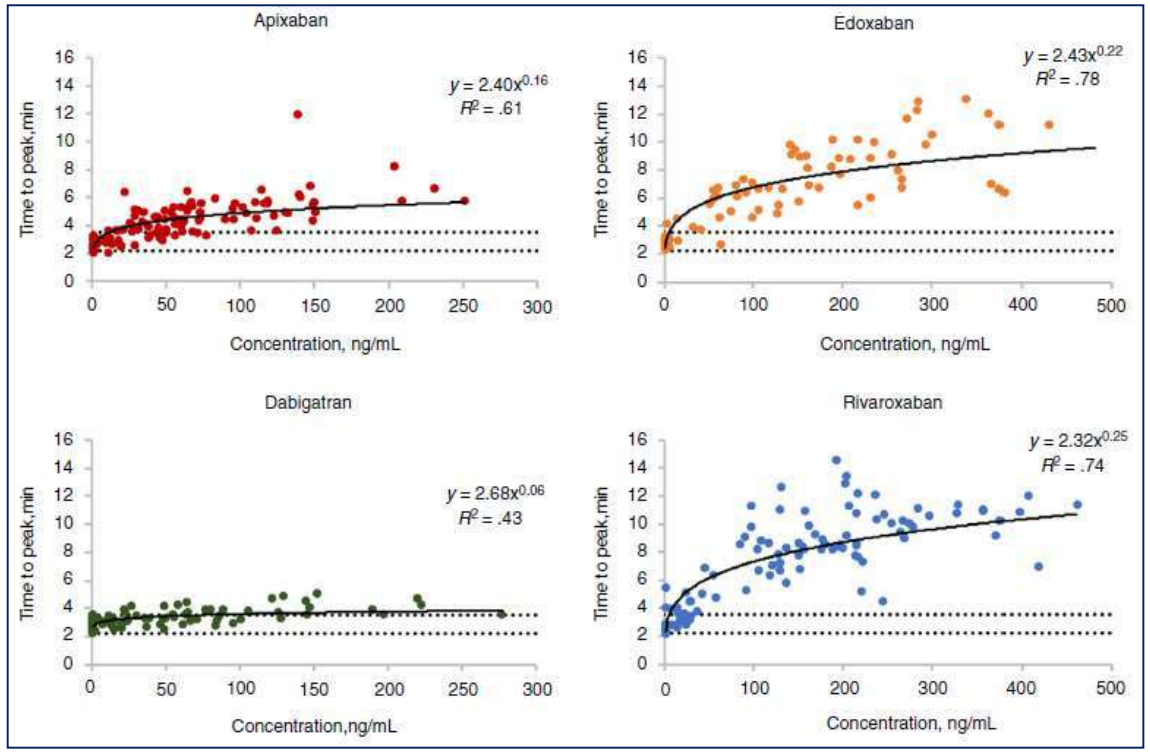
Artang R et al. Res Pract Thromb Haemost 2017; 1.194-201

Voluntarios sanos CAT

Direct oral anticoagulant plasma levels and thrombin generation on ST Genesia system



Lag time

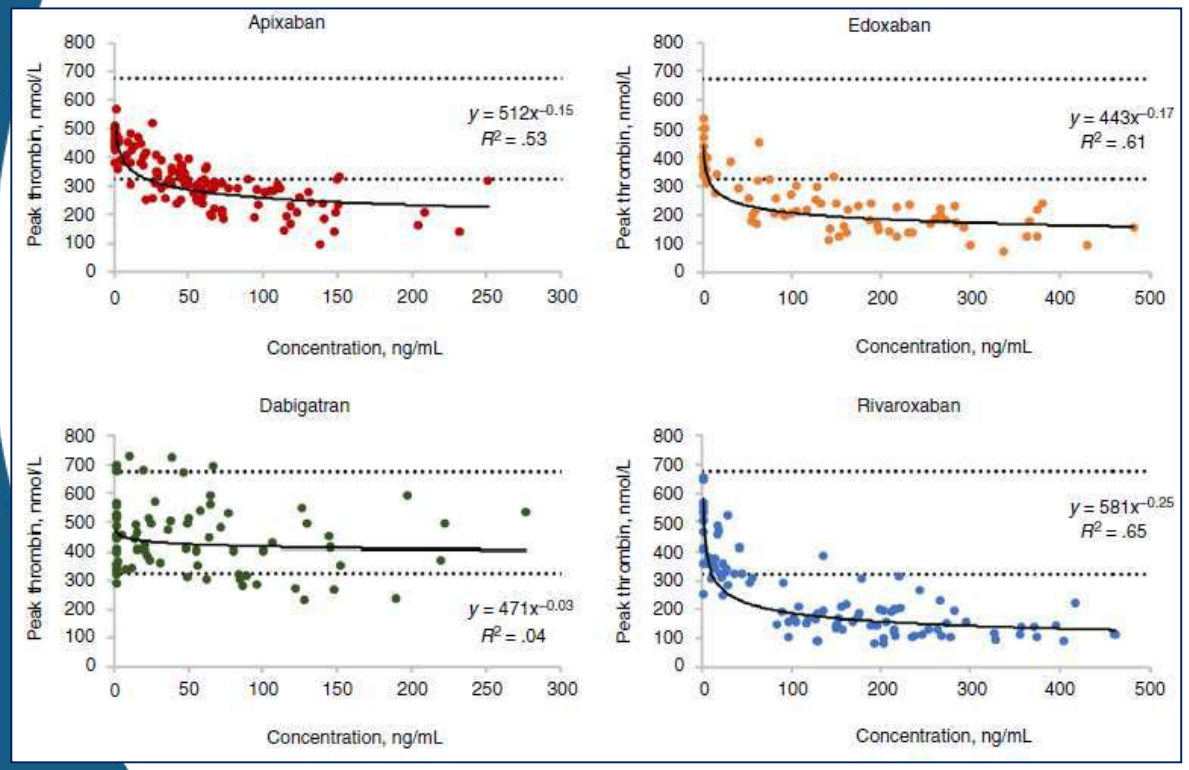


Time to peak

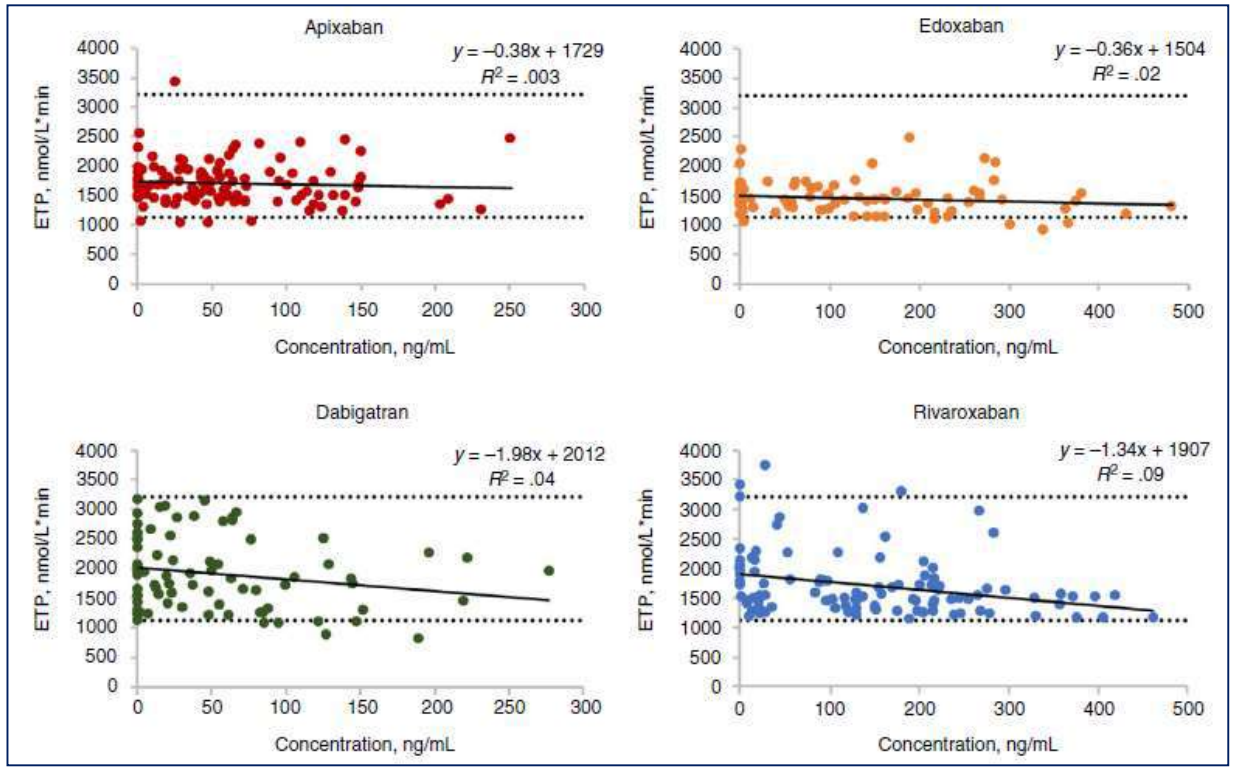
80 pacientes. 320 muestras

Pfrepper C et al. Res Pract Thromb Haemost 2020;4: 619-627

Direct oral anticoagulant plasma levels and thrombin generation on ST Genesia system



Pico



ETP

Pfrepper C et al. Res Pract Thromb Haemost 2020;4: 619-627

Sensibilidad/especificidad parámetros TG para predecir niveles <30 ng/mL

		Sensitivity		PPV		Specificity		NPV	
Assay	DOAC	n	%	n	%	n	%	n	%
Lag time	Apixaban	36/43	83.7	36/60	60.0	53/77	68.8	53/60	88.3
	Dabigatran	36/39	92.3	36/46	78.3	30/40	75.0	30/33	90.9
	Edoxaban	19/21	90.5	19/20	95.0	57/58	98.3	57/59	96.6
	Rivaroxaban	24/29	82.8	24/24	100	73/73	100	73/78	93.6
TTP	Apixaban	32/43	74.4	32/43	74.4	66/77	85.7	66/77	85.7
	Dabigatran	35/39	89.7	35/55	63.6	20/40	50.0	20/24	83.3
	Edoxaban	19/21	90.5	19/20	95.0	57/58	98.3	57/59	96.6
	Rivaroxaban	19/29	65.5	19/19	100	73/73	100	73/83	88.0
Peak	Apixaban	39/43	90.7	39/58	67.2	58/77	75.3	58/62	93.5
	Dabigatran	38/39	97.4	38/67	56.7	11/40	27.5	11/12	91.7
	Edoxaban	19/21	90.5	19/23	82.6	54/58	93.1	54/56	96.4
	Rivaroxaban	24/29	82.8	24/28	85.7	69/73	94.5	69/74	93.2
Velocity index	Apixaban	37/43	86.0	37/49	75.5	65/77	84.4	65/71	91.5
	Dabigatran	38/39	97.4	38/78	48.7	0/40	0	0/1	0
	Edoxaban	19/21	90.5	19/21	90.5	55/58	96.6	55/58	96.6
	Rivaroxaban	20/29	69.0	20/20	100	73/73	100	73/83	89.0

Direct oral anticoagulant plasma levels and thrombin generation on ST Genesia system

Pfrepper C et al. Res Pract Thromb Haemost 2020;4: 619-627

Inhibition of thrombin generation 12 hours after intake of direct oral anticoagulants

- **Prolongación LT/TTP/descenso en pico trombina >rivaroxabán/edoxabán que apixabán (No ETP)**
- **Recuperación LT/pico trombina a nivel basal no fue completa a las 12 h de la toma pero mayor para apixabán que rivaroxabán/edoxabán**
- **Dabigatrán- aumento LT/TTP. ≈ Pico/ETP. No recuperación**

N=80
ST Genesia

Metze M et al. Res Pract Thromb Haemost 2020;4: 610-618

Inhibition of thrombin generation 12 hours after intake of direct oral anticoagulants

- **TG significativamente reducida (excepto ETP) a 12 h de toma todos ACOD frente a basal y controles sanos = efecto antitrombótico mantenido aun a concentraciones bajas (<50 ng/mL)**
- **Deben estandarizarse las condiciones (factor tisular) para predecir mejor riesgo trombótico y hemorrágico**
- **Encontrar rangos referencia para parámetros TG en pacientes que toman ACOD para apoyar la toma de decisiones clínicas**

N=80
ST Genesia

Metze M et al. Res Pract Thromb Haemost 2020;; 4: 610-618

	Lag time, min	Thrombin peak, nmol/L	Time to peak, min	Velocity index, nmol/L/min	ETP, nmol/L*min	Plasma level, ng/mL
Apixaban						
t_{0h}	1.5 (1.4-1.5)	459 (421-480)	2.7 (2.6-3.0)	538 (460-612)	1656 (1601-1893)	42 ± 13
t_{12h}	2.0 (1.9-2.3)	348 (306-372)	3.9 (3.6-4.5)	235 (196-303)	1659 (1474-1802)	
t_{12h}/t_{0h}	137%[a]	76%[a]	146%[a]	44%[a]	100%[b]	
Edoxaban						
t_{0h}	1.5 (1.4-1.6)	393 (346-441)	2.8 (2.5-3.1)	403 (344-607)	1458 (1344-1681)	83 ± 49
t_{12h}	3.0 (2.4-3.4)	247 (207-298)	6.1 (4.8-6.7)	109 (68-162)	1451 (1341-1670)	
t_{12h}/t_{0h}	200%[a]	63%[a]	214%[a]	27%[a]	99%[b]	
Rivaroxaban						
t_{0h}	1.5 (1.4-1.9)	356 (308-476)	2.9 (2.8-3.6)	300 (248-507)	1529 (1388-1901)	118 ± 48
t_{12h}	3.3 (2.8-3.5)	169 (155-223)	8.1 (6.6-8.4)	52 (45-93)	1547 (1433-1755)	
t_{12h}/t_{0h}	219%[a]	47%[a]	278%[a]	17%[a]	101%[b]	
Dabigatran						
t_{0h}	1.5 (1.2-1.7)	451 (357-521)	2.8 (2.4-3.0)	510 (451-668)	1921 (1399-2394)	35 ± 26
t_{12h}	2.0 (1.6-2.3)	444 (358-527)	3.3 (2.7-3.6)	515 (412-616)	1772 (1368-2561)	
t_{12h}/t_{0h}	133%[a]	98%[b]	119%[a]	101%[b]	92%[b]	
Healthy control group						
All donors	1.4 (1.3-1.5)	429 (402-465)	2.7 (2.6-2.9)	463 (371-529)	1648 (1482-1855)	
Men	1.4 (1.3-1.5)	422 (399-461)	2.8 (2.6-3.0)	454 (349-495)	1664 (1465-1848)	
Women	1.4 (1.3-1.5)	440 (412-474)	2.6 (2.5-2.9)	529 (439-569)	1611 (1482-1813)	

Metze M et al. Res Pract Thromb Haemost 2020;4: 610-618

Inhibition of thrombin generation 12 hours after intake of direct oral anticoagulants

Parámetros TG frente a donantes sanos a las 12 h toma

	Anti-Xa	Dabigatrán
Lag time	↓↓	↓↓
Pico trombina	↓↓	≈
ETP	≈	≈

Pico trombina reducido ≈30% a niveles edoxabán <50 ng/mL

Metze M et al. Res Pract Thromb Haemost 2020; 4: 610-618

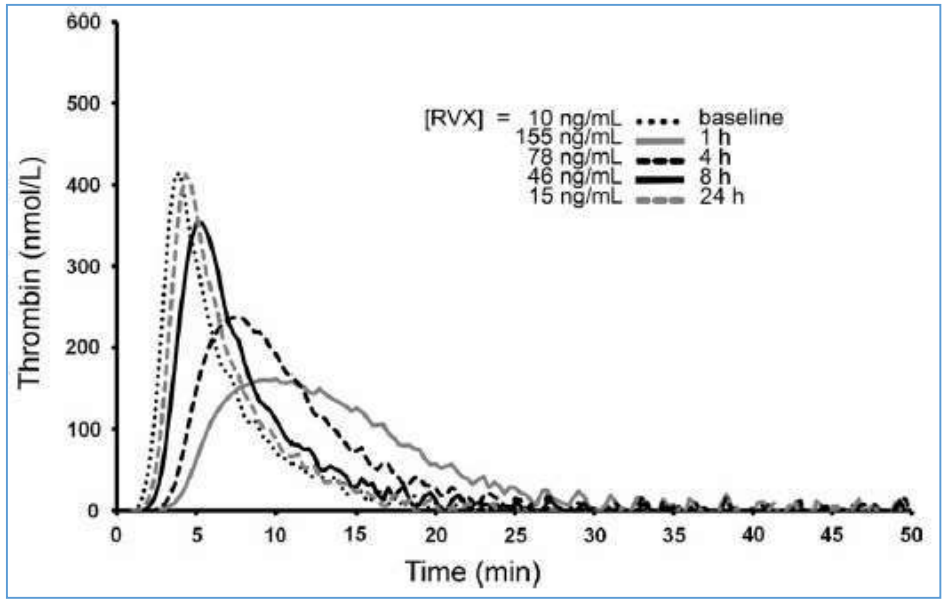
LETTER TO THE EDITOR

WILEY ISLH International Journal of Laboratory Hematology

Effect of Rivaroxaban on thrombin generation in vivo. A study in obese patients

- 12 pacientes. IMC ≥35 kg/m^2. 1 día antes cirugía bariátrica. **CAT**.
- No efecto dosis-dependiente ETP
- Resto parámetros buena correlación *ex vivo* aun a concentraciones bajas de rivaroxabán (30-15 ng/mL)

- Concentraciones **>80 ng/mL inhiben** la TG de modo eficiente
- Concentraciones **<50 ng/mL no** consiguen dicha inhibición
- **VI>40% Pico>60% no efecto anticoagulante in vivo**



¿El TGT serviría para valorar la utilidad de ACODs en pacientes obesos?

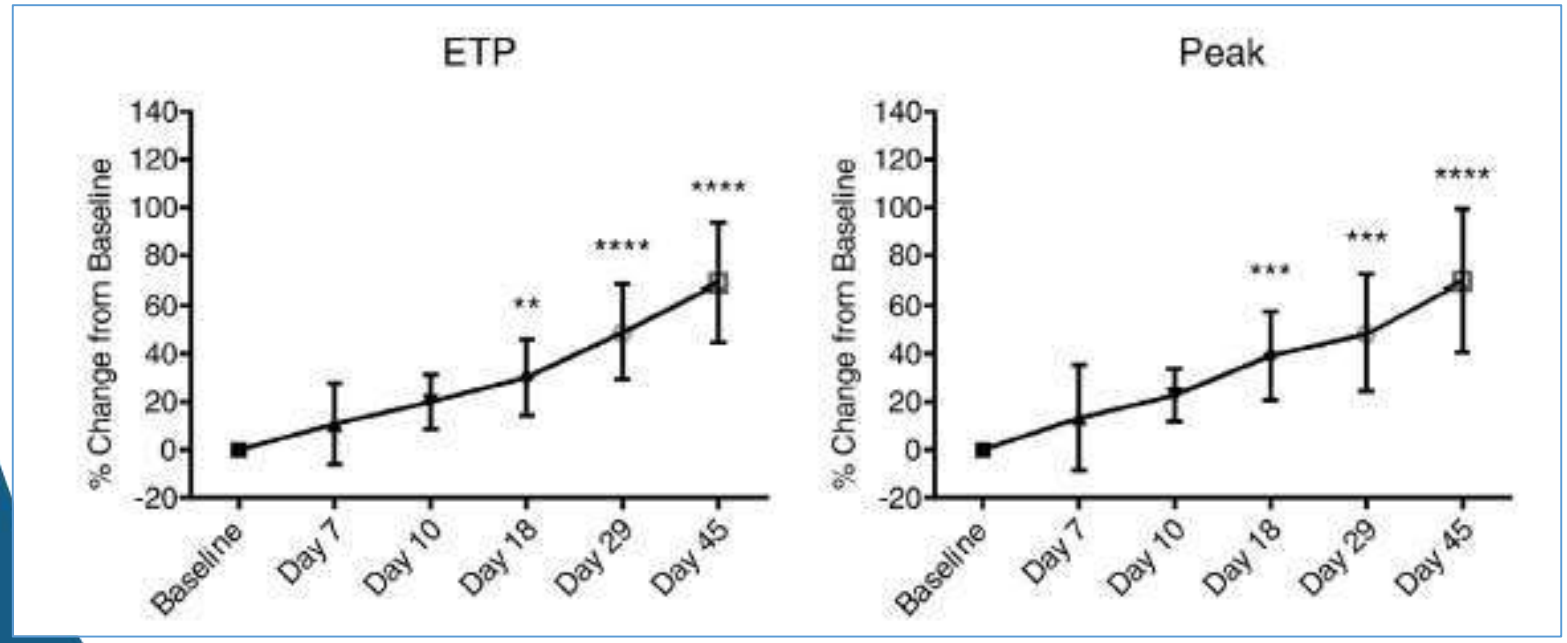
Bertaggia-Calderara D et al. Int J Lab Haematol 2018; 40: e11-e14

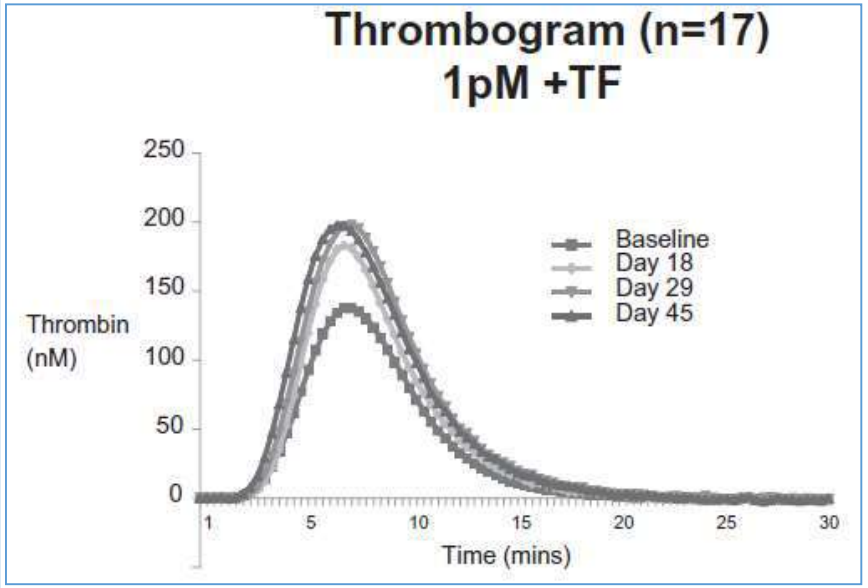
LA GENERACIÓN DE TROMBINA Y EL EMBARAZO

Thromb Res. 2017 Sep;157:49-54. doi: 10.1016/j.thromres.2017.06.027. Epub 2017 Jun 29.

Normal pregnancy is associated with an increase in thrombin generation from the very early stages of the first trimester.

Bagot CN[1], Leishman E[2], Onyiaodike CC[3], Jordan F[3], Freeman DJ[3].





La TG aumenta 5ª semana de embarazo

Mujeres con alto riesgo de trombosis gestacional se deben de tratar profilácticamente cuanto antes

LA GENERACIÓN DE TROMBINA Y EL EMBARAZO

BMC Pregnancy Childbirth. 2014 Nov 19;14:384. doi: 10.1186/s12884-014-0384-0.

Changes in thrombin generation and D-dimer concentrations in women injecting enoxaparin during pregnancy and the puerperium.

Patel JP[1,2], Patel RK[3], Roberts LN[4], Marsh MS[5], Green B[6], Davies JG[7], Arya R[8].

con enoxaparina

(N=83)
dosis profiláctica

(N=19)
dosis terapéutica

durante el embarazo

≥8 semanas
(para determinar la TG basal)

TG parameter	1st trimester	2nd trimester	3rd trimester	Within 1 week of delivery	≥8 weeks pp
	N = 58; n = 44	*N = 117; n = 94*	*N = 132; n = 108*	*N = 93; n = 93*	*N = 98; n = 98*
Lag time (min)	4.27 (3.81)	3.53 (1.26)	3.88 (2.46)	3.14 (1.32)	3.13 (1.34)
ETP (nmol/Lmin)	1391 (795)	1757 (706)	1692 (631)	1857 (633)	1293 (409)
Peak height (nmol/L)	208 (141)	277 (136)	262 (116)	356 (127)	261 (80)
Time to Peak (min)	8.09 (5.18)	7.05 (3.27)	7.36 (3.91)	5.57 (2.83)	5.68 (1.58)

N=119
CAT

Stago

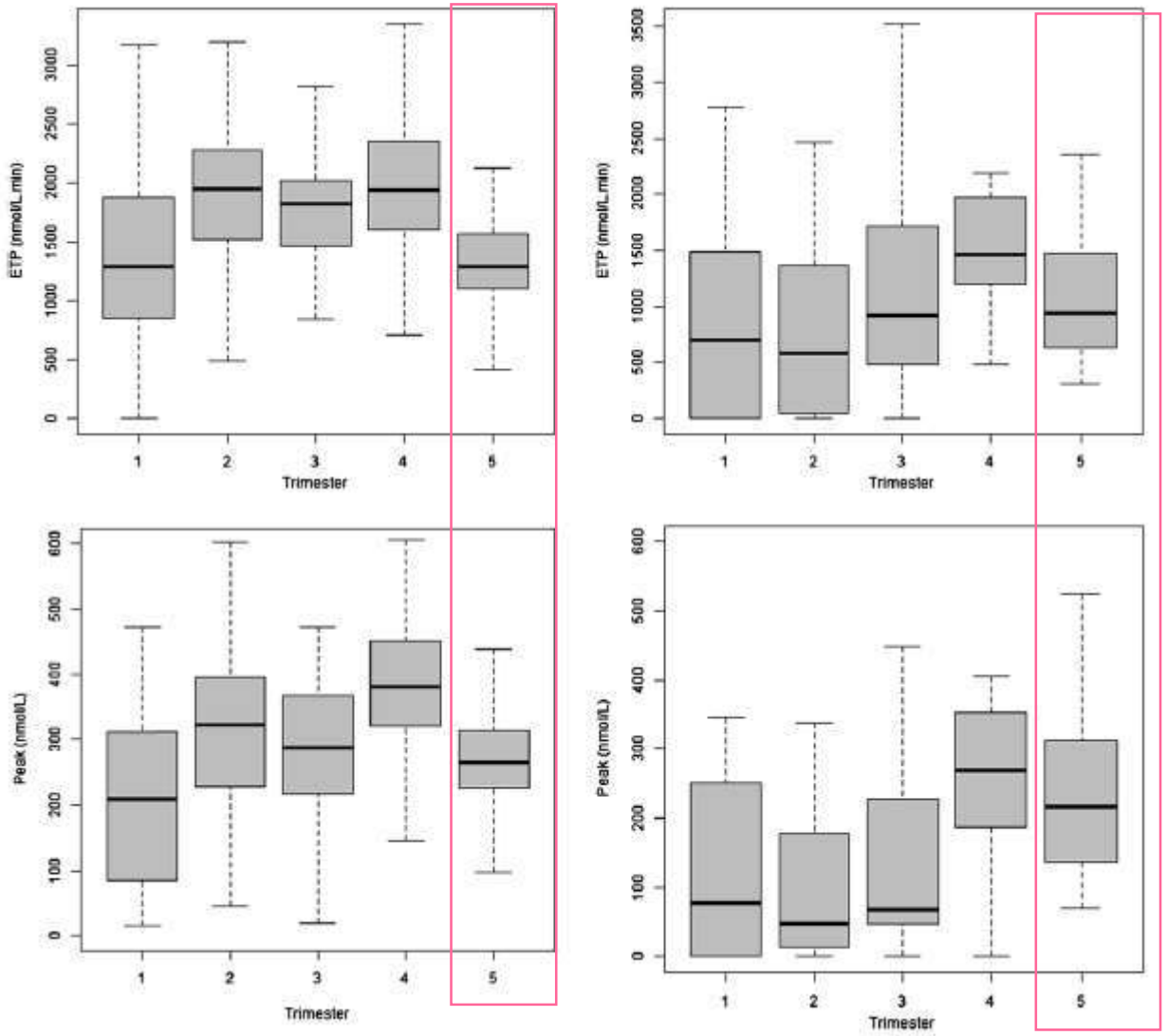
La heparina a dosis terapéuticas disminuye más la TG que a dosis profiláctica

Anti-Xa <0.2 UI/mL- TGT≈
Anti-Xa >0.4 UI/mL- ETP ↓↓

Gerotziafas GT et al. J Thromb Haemost 2007: 5: 955-962

¿El test de generación de trombina serviría para ajustar las dosis de heparina?

Enoxaparina profilaxis | **Enoxaparina terapéutica**



>8 semanas post-parto | >8 semanas post-parto

LA GENERACIÓN DE TROMBINA Y EL EMBARAZO

Thrombin generation and low-molecular-weight heparin prophylaxis in pregnant women with thrombophilia

Anna Selmeczi[1]; Rachel E. J. Roach[2]; Csaba Móré[3]; Zoltán Batta[4]; Jolán Hársfalvi[4]; Johanna G. van der Bom[2]; Zoltán Boda[1]; Zsolt Oláh[1]

[1]Center of Thrombosis and Haemostasis, Institute of Internal Medicine, University of Debrecen, Debrecen, Hungary; [2]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands; [3]Department of Obstetrics and Gynecology, University of Debrecen, Debrecen, Hungary; [4]Clinical Research Center, University of Debrecen, Debrecen, Hungary

8 mujeres embarazadas con trombofilia severa

47 mujeres embarazadas con trombofilia moderada

15 mujeres embarazadas sin trombofilia

TG sin enoxaparina

TG con enoxaparina * después de la administración de heparina (efecto pico)

*100 UI/kg/día

Table 2: Thrombin generation over the course of pregnancy. Levels denoted as median (interquartile range), PT denotes peak thrombin, ETP denotes endogenous thrombin potential. Data were missing for some participants of some subgroups. *These measurements represent the lowest and the highest values in this group as measurements were only available for three women.

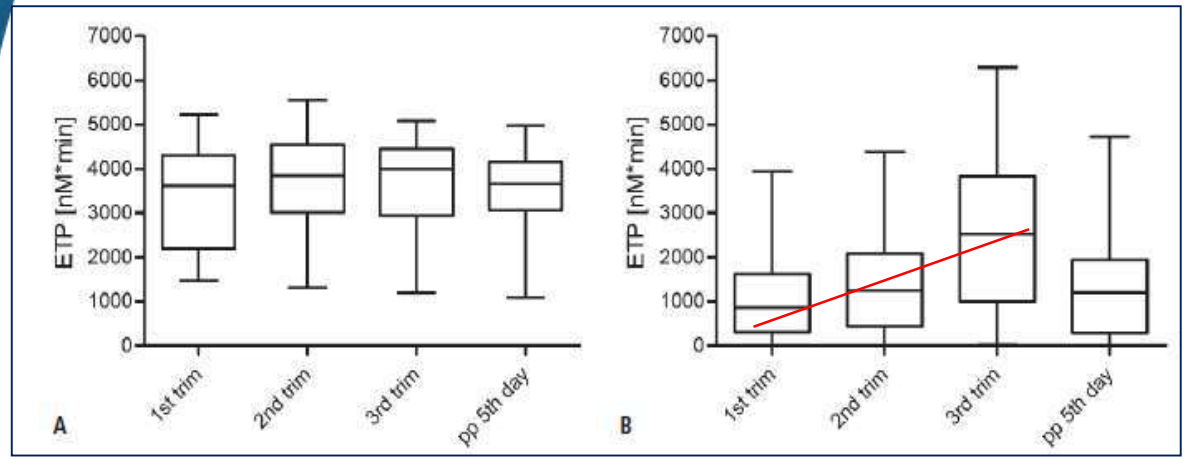
		1st trimester		2nd trimester		3rd trimester		postpartum 5th day		postpartum 8th week	
Peak thrombin (nM)											
No Thrombophilia	n = 15	211	(164–330)	265	(140–377)	233	(208–330)	234	(205–288)	145	(122–256)
Mild Thrombophilia	n = 47	208	(147–278)	243	(152–297)	259	(193–338)	278	(161–302)	140	(101–199)
Severe Thrombophilia	n = 8	278	(201–324)	326	(265–431)	301	(149–380)	319	(250–471)	290	(256–437)*
ETP (nM*min)											
No Thrombophilia	n = 15	3207	(2712–3828)	3832	(2820–4470)	3441	(2408–4537)	3108	(2776–3727)	2664	(2194–3123)
Mild Thrombophilia	n = 47	3266	(2025–4066)	3499	(2768–4478)	4011	(3518–4456)	3666	(2971–4089)	2664	(1787–3471)
Severe Thrombophilia	n = 8	4408	(3855–4643)	4313	(3993–5287)	3980	(3355–4603)	4156	(3593–4883)	4715	(3471–5313)*

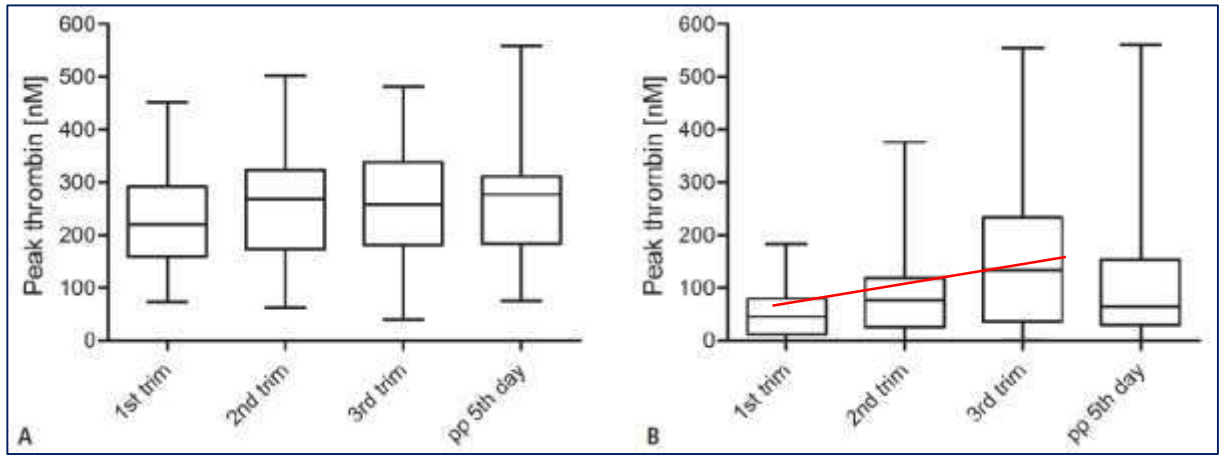
Stago

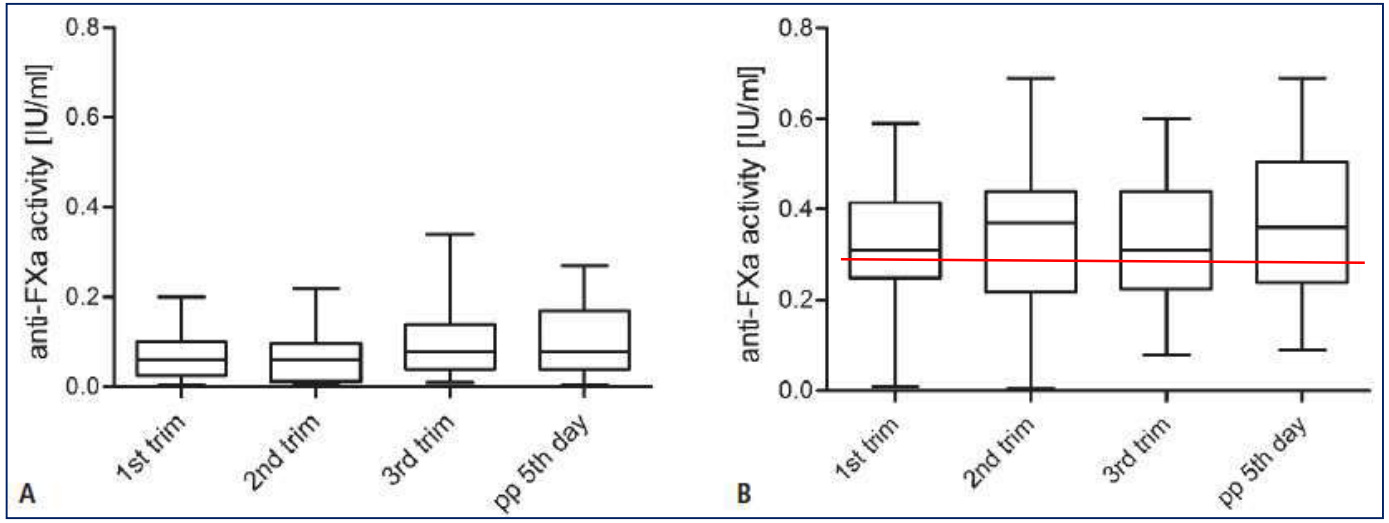
LA GENERACIÓN DE TROMBINA Y EL EMBARAZO

TG sin heparina (A)
antes administración heparina

TG con heparina (B): 4 h después de la administración de heparina (efecto pico)







Stago

LA GENERACIÓN DE TROMBINA Y EL EMBARAZO

Thrombin generation and low-molecular-weight heparin prophylaxis in pregnant women with thrombophilia

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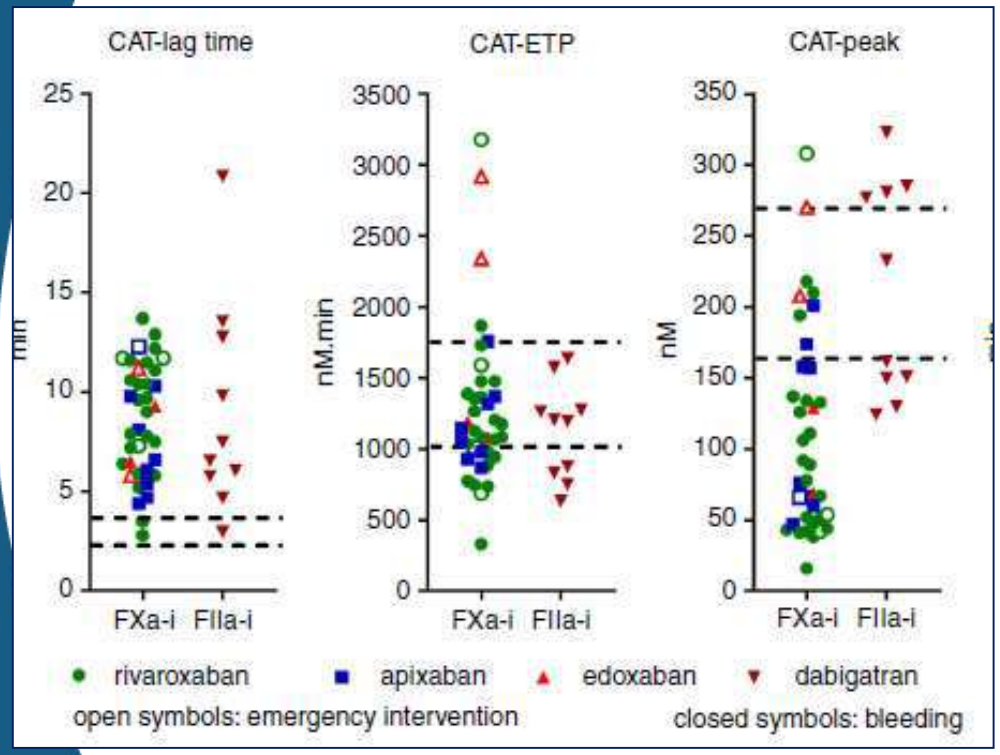
[1]Center of Thrombosis and Haemostasis, Institute of Internal Medicine, University of Debrecen, Debrecen, Hungary; [2]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands; [3]Department of Obstetrics and Gynecology, University of Debrecen, Debrecen, Hungary; [4]Clinical Research Center, University of Debrecen, Debrecen, Hungary

What does this paper add?

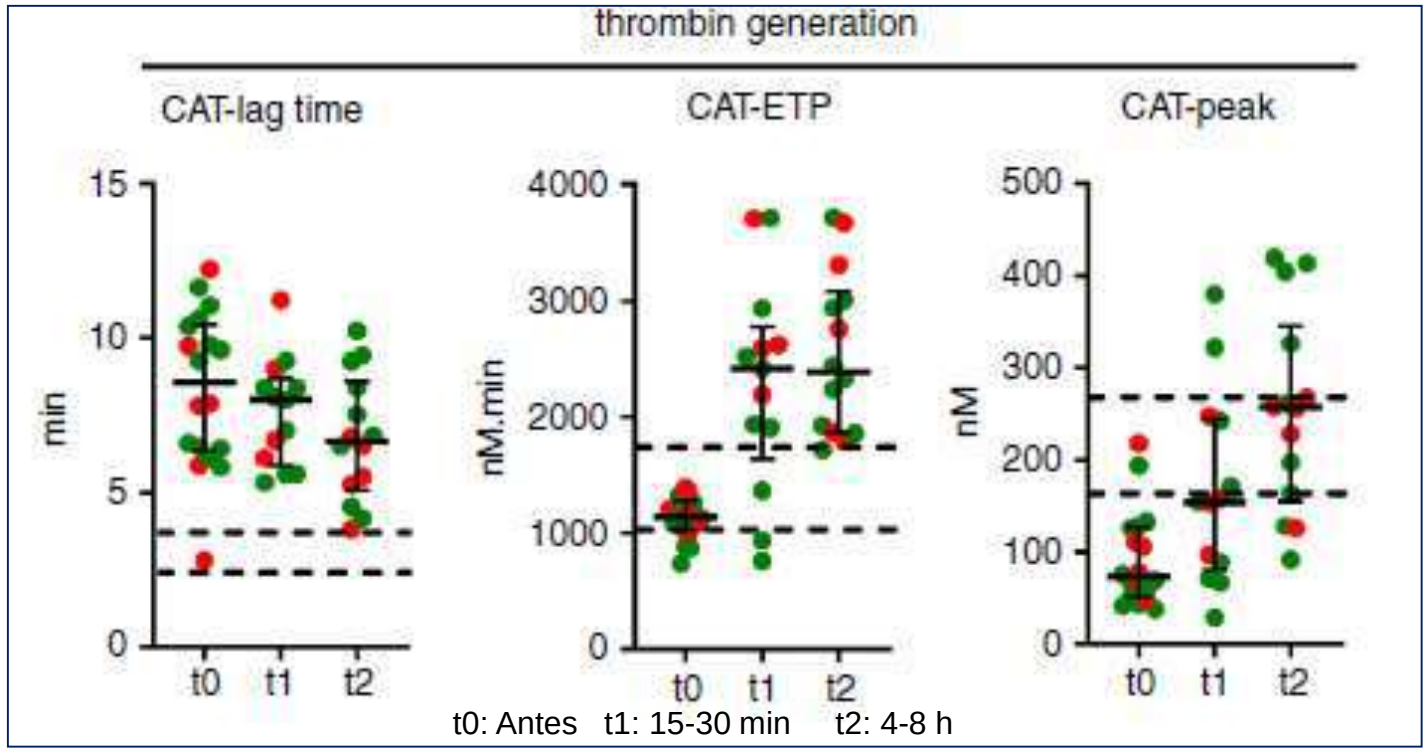
- Thrombin generation demonstrates the hypercoagulable state in thrombophilic pregnancies.
- Thrombin generation measurements revealed that the effect of LMWH prophylaxis progressively decreases with advancing stages of pregnancy.
- The same tendency was not detectable with anti-Factor-Xa activity.

¿El test de generación de trombina serviría para ajustar las dosis de heparina?

Emergencies on direct oral anticoagulants: Management, outcomes, and laboratory effects of prothrombin complex concentrate



TG en pacientes con urgencias relacionadas con ACOD *vs* voluntarios sanos



TG en pacientes anti-Xa y sangrado mayor neutralizados con CFCP

Thromboniscope (CAT)

Bavalia R et al. Res Pract Thromb Haemost 2020; 4:569-581