Stago

Diagnostics is in our blood.

MAYO formación

Face to face: ¿Monitorización del tratamiento con emicizumab?

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18/11/2022

No conflictos intereses para realización esta presentación

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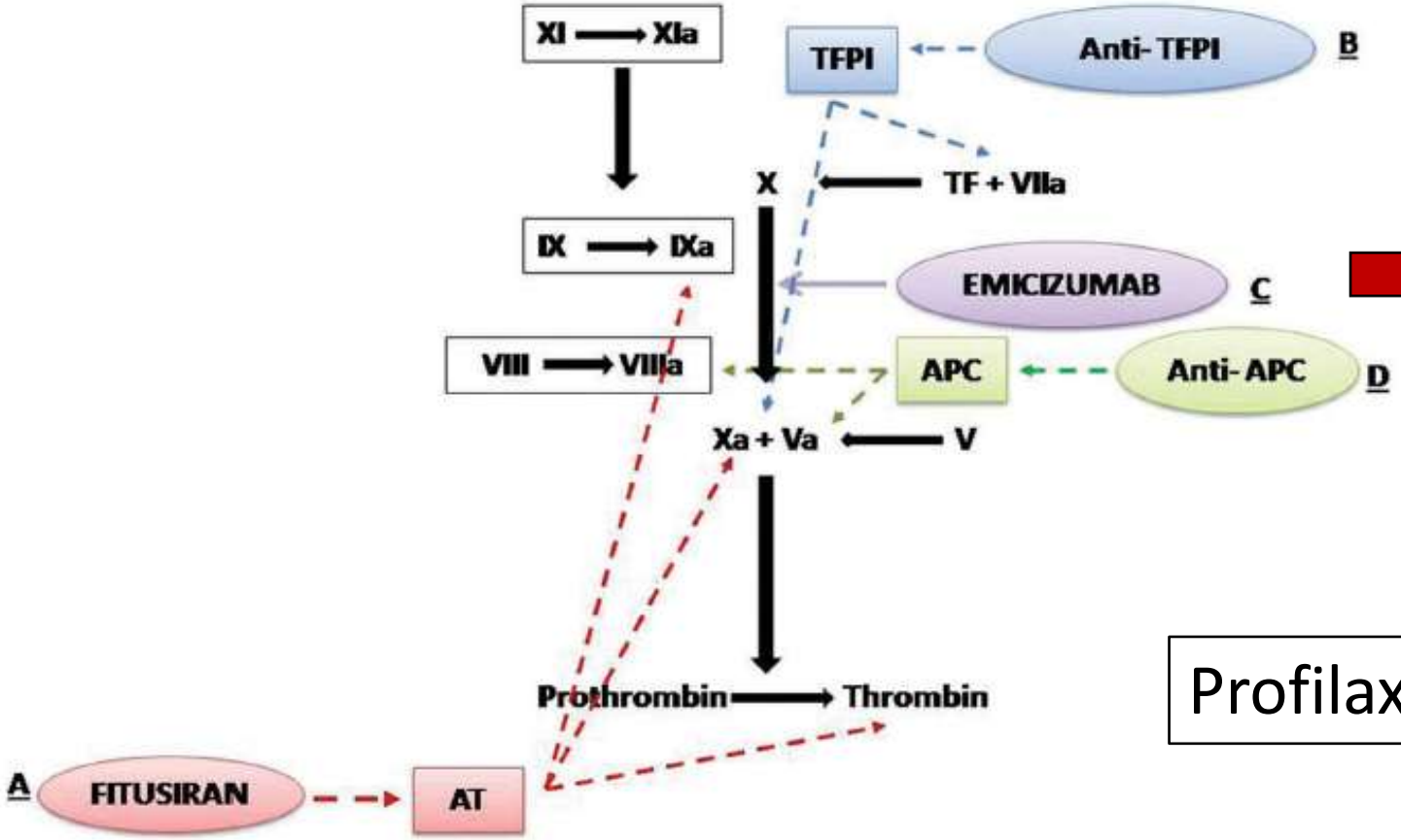
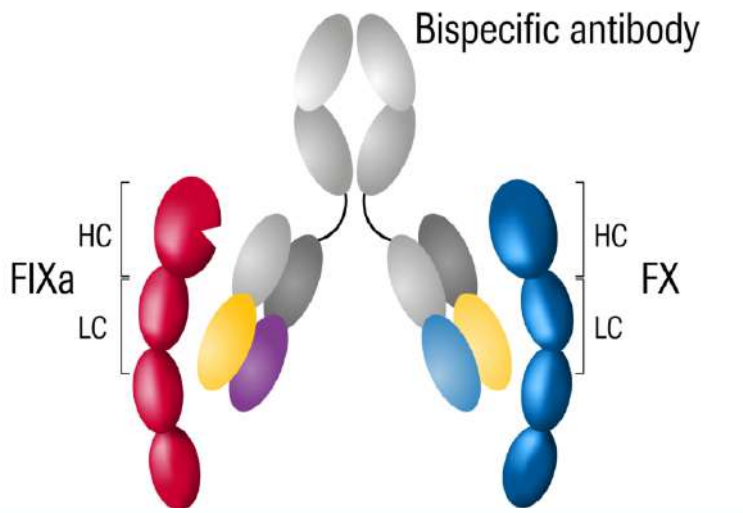
Emicizumab





Profilaxis en HAG con/sin inhibidores

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Emicizumab

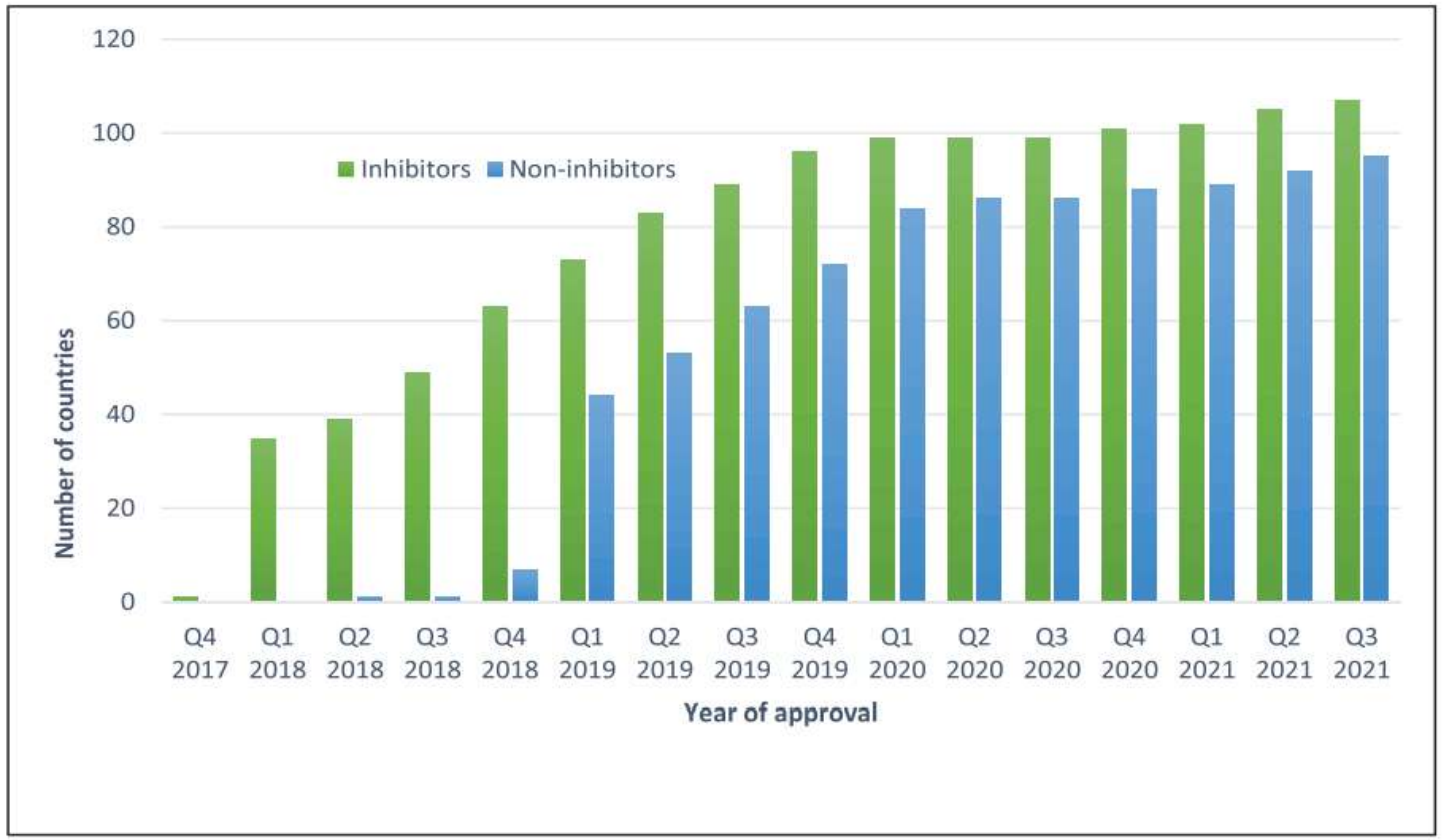
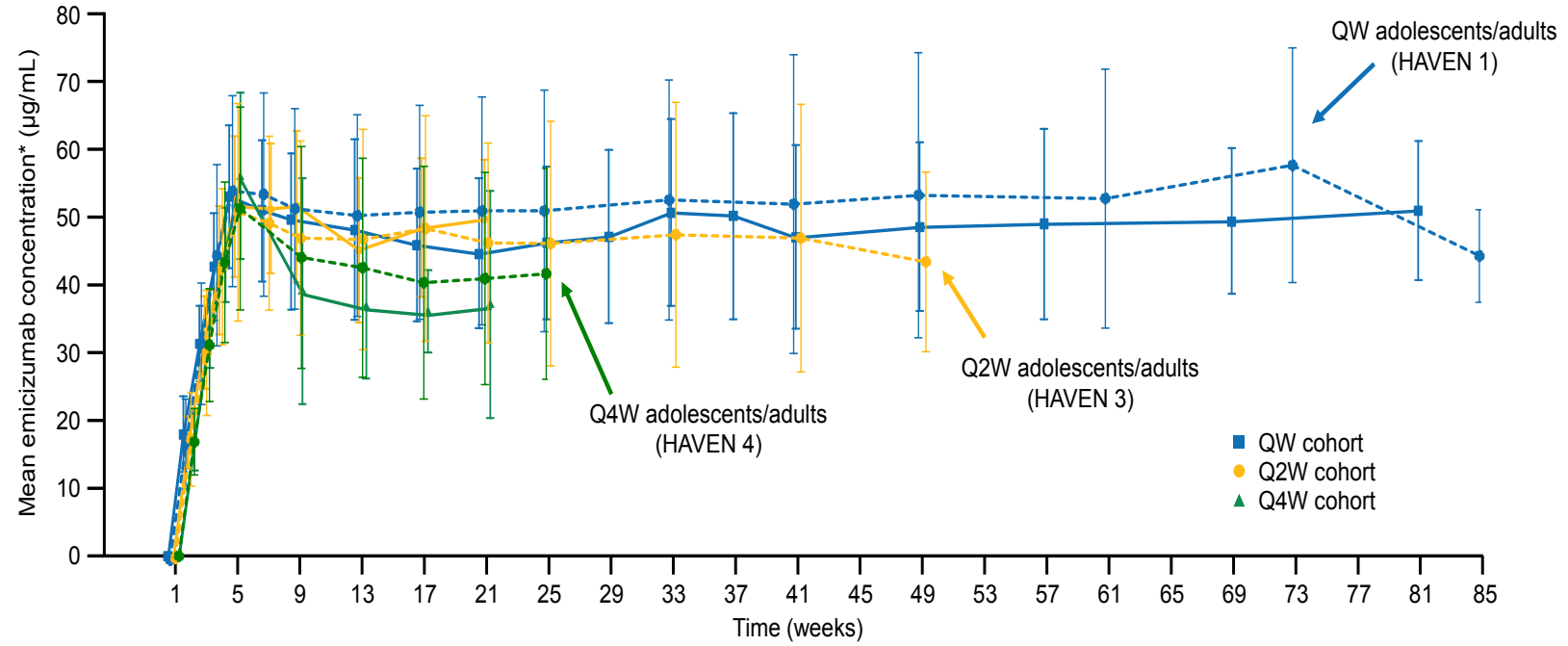


FIGURE 2 Regulatory approval of emicizumab for inhibitor and non-inhibitor indications by year of approval. Data supplied courtesy of Roche Global, Switzerland

Haemophilia. 2022 May;28 Suppl 4(Suppl 4):103-110.

Emicizumab

La farmacocinética se mantiene estable en todos los regímenes



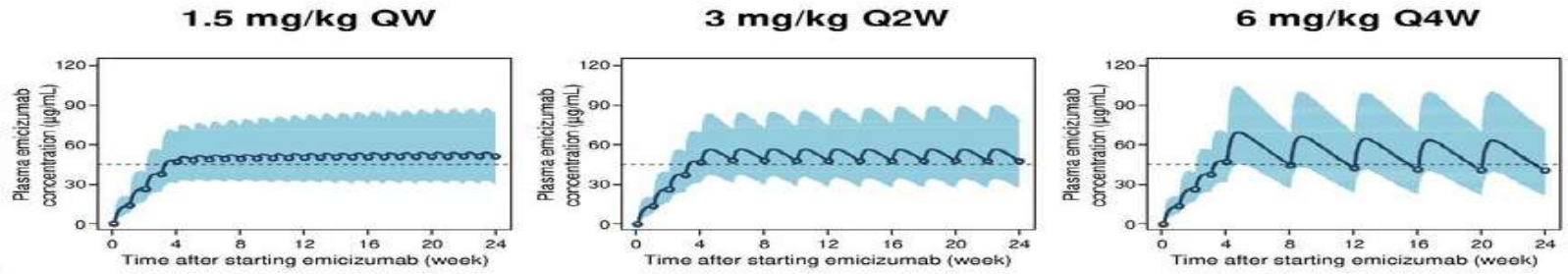


Table 1. Bleeding rates and proportion of patients with zero treated bleeds reported in clinical trials of emicizumab-kxwh.

	Emicizumab-kxwh dose 1.5 mg/kg QW		
	HAVEN 1* [16]	HAVEN 2 [17]	HAVEN 3 [18]
Population	≥12 YO	<12 YO (and 12–17 YO if under 40 kg)	≥12 YO
Inhibitor status	Inhibitor	Inhibitor	Non-inhibitor
N patients	35	65	36
Treated bleeds			
ABR, model based (95% CI)	2.9 (1.69, 5.02)	0.3 (0.17, 0.50)	1.5 (0.9, 2.5)
% reduction (RR)#, *P*-value	87% (0.13), $P < 0.0001$	–	96%
Median ABR, calculated (IQR)	0.0 (0.0–3.7)	0.0 (0.0–0.0)	0.0 (0.0–2.5)
Zero bleeds, % (95% CI)	–	76.9% (64.8, 86.5)	56% (38, 72)
All bleeds			
ABR, model based (95% CI)	5.5 (3.58, 8.60)	3.2 (1.94, 5.22)	2.5 (1.6, 3.9)
% reduction (RR)#, *P*-value	80% (0.20), $P < 0.0001$	–	95%
Median ABR, calculated (IQR)	2.0 (0.0–9.9)	0.6 (0.00, 2.92)	0.6 (0.0–3.9)
Zero bleeds, % (95% CI)	–	49.2% (36.6, 61.9)	50% (33, 67)

	Emicizumab-kxwh dose 3 mg/kg Q2W		
	HAVEN 2 [17]	HAVEN 3 [18]	HOHOEMI [19]
Population	<12 YO (and 12–17 YO if under 40 kg)	≥12 YO	<12 YO
Inhibitor status	Inhibitor	Non-inhibitor	Non-inhibitor
N patients	10	35	6
Treated bleeds			
ABR, model based (95% CI)	0.2 (0.03, 1.72)	1.3 (0.8, 2.3)	1.3 (0.59, 2.92)
% reduction (RR)#, *P*-value	–	97%	–
Median ABR, calculated (IQR)	0.0 (0.0–0.0)	0.0 (0.0–1.9)	1.4 (0.0–2.52)
Zero bleeds, % (95% CI)	90% (55.5, 99.7)	60% (42, 76)	33.3%
All bleeds			
ABR, model based (95% CI)	1.5 (0.62, 3.40)	2.6 (1.6, 4.3)	14.1 (7.63, 26.17)
% reduction (RR)#, *P*-value	–	94%	–
Median ABR, calculated (IQR)	0.0 (0.00, 2.81)	1.6 (0.0–4.0)	10.7 (5.51–20.37)
Zero bleeds, % (95% CI)	60% (26.2, 87.8)	40% (24, 58)	0

	Emicizumab-kxwh dose 6 mg/kg Q4W		
	HAVEN 2 [17]	HAVEN 4 [14]	HOHOEMI [19]
Population	<12 YO (and 12–17 YO if under 40 kg)	≥12 YO	<12 YO
Inhibitor status	Inhibitor	Inhibitor/Non-inhibitor	Non-inhibitor
N patients	10	41[$]	7
Treated bleeds			
ABR, model based (95% CI)	2.2 (0.69, 6.81)	2.4 (1.4, 4.3)	0.7 (0.18, 2.65)
Median ABR, calculated (IQR)	0.0 (0.0–3.26)	0.0 (0.0–2.1)	0.0 (0.0–1.73)
Zero bleeds, % (95% CI)	60% (26.2, 87.8)	56% (39.7, 71.5)	71.4%
All bleeds			
ABR, model based (95% CI)	3.8 (1.42, 10.11)	4.5 (3.1, 6.6)	21.8 (9.16, 51.80)
Median ABR, calculated (IQR)	1.6 (0.00, 4.84)	2.1 (0.0–5.9)	13.8 (4.58, 27.51)
Zero bleeds, % (95% CI)	50% (18.7, 81.3)	29% (16.1, 45.5)	14.3%

Mg, milligram; kg, kilogram; YO, year old; N, number; ABR, annualized bleeding rate; CI, confidence interval; RR, risk ratio; IQR, interquartile range.
* Bleeding rates of participants assigned to Group A (emicizumab-kxwh 1.5 mg/kg/wk) of HAVEN 1 who were receiving episodic treatment with BPAs prior to trial enrollment.
# Percent risk reduction in bleeding compared to no emicizumab-kxwh prophylaxis.
$ 5 patients with inhibitors present at study entry.

Cafuir L. Expert Rev Hematol. 2019 Jul;12(7):515-524.

Emicizumab → Monitorización

NO REQUIERE MONITORIZACIÓN

Emicizumab → Monitorización

- *Situaciones en las que sería deseable monitorizar*

- *Cómo deberíamos monitorizar*

Emicizumab *Situaciones especiales donde monitorizar*

Valorar eficacia emicizumab

- Comprobar adherencia al tratamiento
- Comprobar presencia de ADA con efecto neutralizante
- Efectuar tratamientos individualizados

Valorar la hemostasia global

- Tratamiento episodios hemorrágicos con agentes bypass (FVIII)
- Preoperatorio/cirugía en combinación con agentes bypass (FVIII)
- Junto al tratamiento de inmunotolerancia
- Nuevas indicaciones del producto

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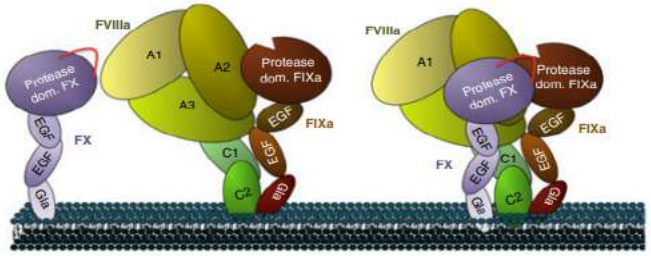
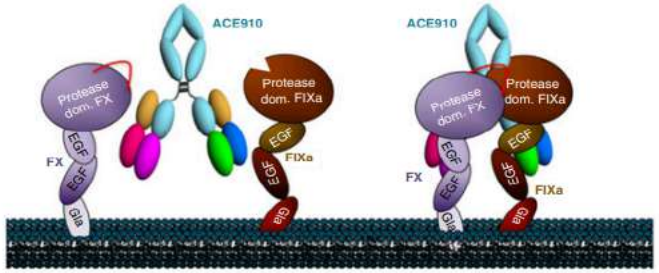
Emicizumab

Diferencias con el FVIII

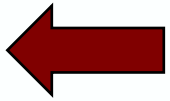
FVIIIa	ACE910/Emicizumab
	
Multiple sites of interaction	Single sites of interaction
High affinity for enzyme & substrate *(low to high nanomolar range)*	Low affinity for enzyme & substrate *(micromolar range)*
Specific for FIXa and FX *(no binding to FIX and FXa)*	No distinction between zymogen and enzyme *(FIX vs FIXa and FX vs FXa)*
Full cofactor activity - *promotes phospholipid binding* - *stabilizes FIXa active site* - *bridges FIXa to FX*	Partial cofactor activity - *bridges FIXa to FX*
Enzyme and substrate are in excess over cofactor	Antibody is in excess over enzyme and substrate
FVIIIa has on/off mechanism	Emicizumab has no on/off mechanism
High level of self-regulation	Low level of self-regulation

Lenting PJ. Blood. 2017 Dec 7;130(23):2463-2468.

Emicizumab

Efecto sobre los test de laboratorio

Test results affected by emicizumab	Test results unaffected by emicizumab
APTT reduced	
PT reduced [described as a clinically insignificant effect]	PT-based assays
APTT-based single factor assays (increased)	Thrombin time
APTT-based inhibitor screens (false negative)	Clauss fibrinogen
APTT-based factor inhibitor titres (false negative)	Immuno-based assays
Chromogenic FVIII assays using human-derived FIXa and FX (increased)	Chromogenic FVIII assays using bovine-derived FIXa and FX
Activated clotting time (ACT) (possibly reduced)	Chromogenic assays for coagulation factors or treatments other than FVIII.



Jenkins PV, Haemophilia. 2020 Jan;26(1):151-155

Emicizumab

Interacción emicizumab en los análisis utilizados en la monitorización

FVIII activity assays	FVIII OSA (aPTT-based)	FVIII: sensitive Emicizumab: oversensitive; normalizes at very low concentrations of emicizumab[16,36]	Cannot be used to measure emicizumab or FVIII activity
	Modified FVIII OSA calibrated against emicizumab	FVIII: slightly sensitive Emicizumab: sensitive[41,46]	May be used to measure emicizumab plasma levels
	FVIII CSA (bovine components: Siemens, etc.)	FVIII: sensitive Emicizumab: insensitive; emicizumab does not accelerate FXa formation by bovine FIXa[57]	Cannot be used to measure emicizumab activity. May be used to measure FVIII activity without interference from emicizumab in the sample
	FVIII CSA (human components: Hyphen BIOPHEN)	FVIII: sensitive Emicizumab: sensitive (within the dynamic range of the assay)[41]	Reported FVIII cannot be viewed as equivalent to FVIII activity measured in patients treated with FVIII. May only provide a relative indication of the procoagulant activity of emicizumab

Müller J. Thromb Haemost . *2019; 119 (9): 1384-1393.*

Emicizumab

Interacción emicizumab en los análisis utilizados en la monitorización

Inhibitor assays	Bethesda assays using FVIII OSA	FVIII: sensitive Emicizumab: false negative; as emicizumab is not deactivated by heat, it drives coagulation via human FIX and FX in human plasma, regardless of presence of inhibitors to FVIII[31]	Cannot be used to measure FVIII inhibitor titers in the presence of emicizumab
	CBA	FVIII: sensitive Emicizumab: insensitive; this assay uses a bovine protein-based chromogenic FVIII assay, which is not affected by emicizumab[42]	Can be used to measure FVIII inhibitor titers in the presence of emicizumab

Abbreviations: aPTT, activated partial thromboplastin time; CBA, chromogenic Bethesda Assay; CSA, chromogenic assay; F, coagulation factor; OSA, one-stage clotting assay.

Müller J. Thromb Haemost . *2019; 119 (9): 1384-1393.*

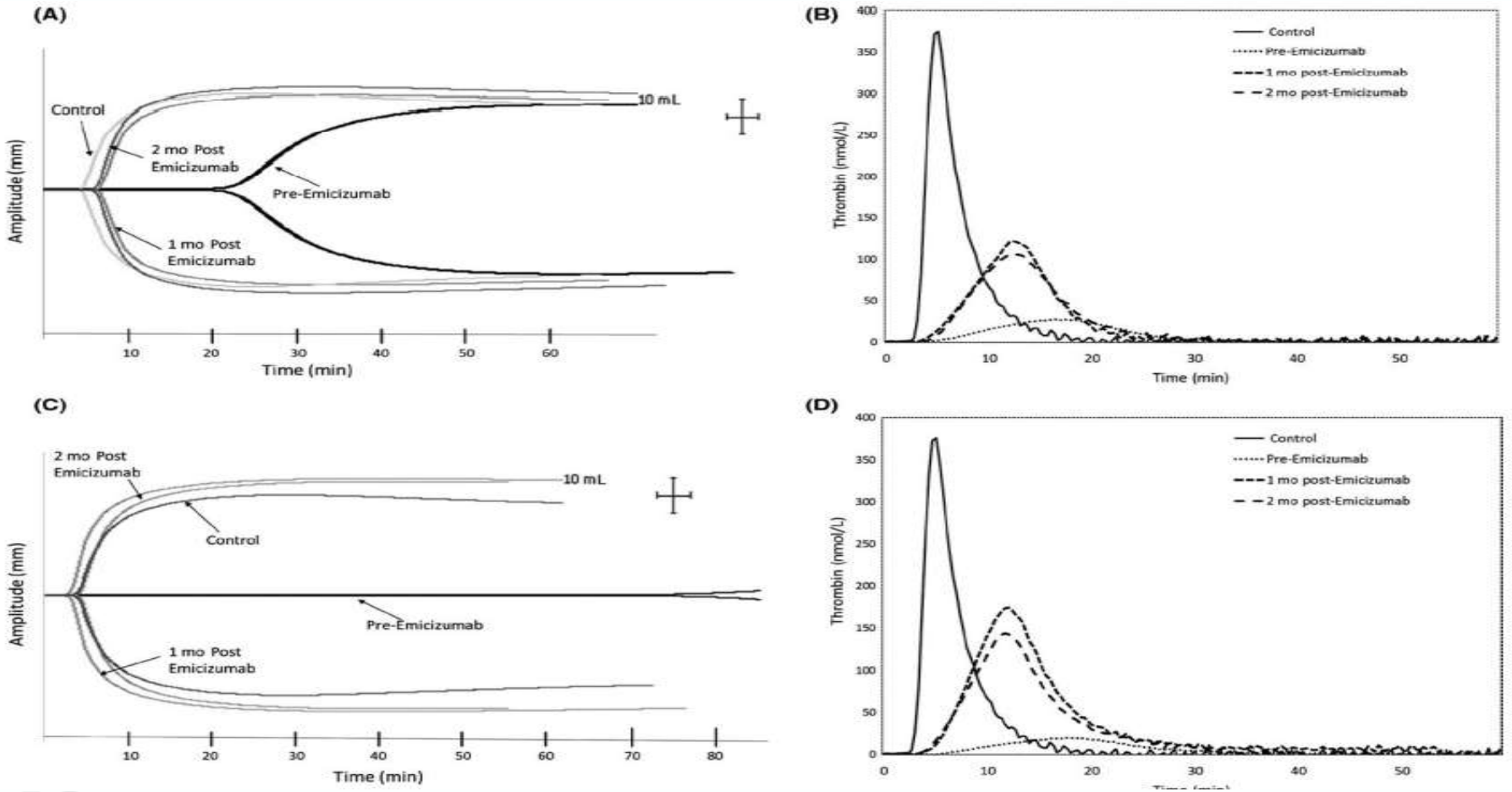
Emicizumab

Interacción emicizumab en los análisis utilizados en la monitorización

	Standard assay	Sensitivity to FVIII/emicizumab	Recommendations for use in the presence of emicizumab
Global coagulation assays	aPTT	FVIII: sensitive Emicizumab: oversensitive; normalizes at very low concentrations of emicizumab[39]	Cannot be used to measure the hemostatic potential of a patient
	ROTEM	FVIII: sensitive Emicizumab: sensitive; EXTEM has little-to-no response in the presence of emicizumab and INTEM shows marked response in the presence of emicizumab, but no dose-dependent effect, while NATEM shows a significant dose-dependent response to emicizumab[52]	May be used to measure global coagulation in the presence of emicizumab
	TGA	FVIII: sensitive Emicizumab: sensitive; shows a linear, dose-dependent increase in thrombin generation when triggered with FXIa[48]	May be used to measure global coagulation in the presence of emicizumab

Müller J. Thromb Haemost . *2019; 119 (9): 1384-1393.*

Emicizumab *Análisis globales de coagulación*



Brophy DF. Haemophilia. 2018 Sep;24(5):815-822.

Valores emicizumab	• *Screening* TTPA • Niveles de emicizumab • Test especiales para descartar ADA
Cuantificar FVIII/inhibidor	• Análisis FVIII cromogénico reactivos bovinos • Bethesda con reactivos bovinos
Efecto global en la coagulación	• Test viscoelásticos • Test generación de trombina

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Emicizumab: Experiencia propia

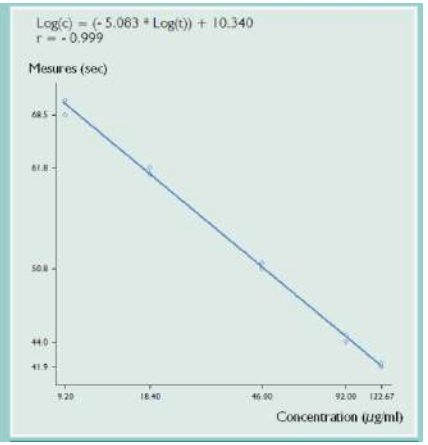
TTPA

Plasma deficiente de VIII **(<1%)**

Emicizumab **(calibrador)**

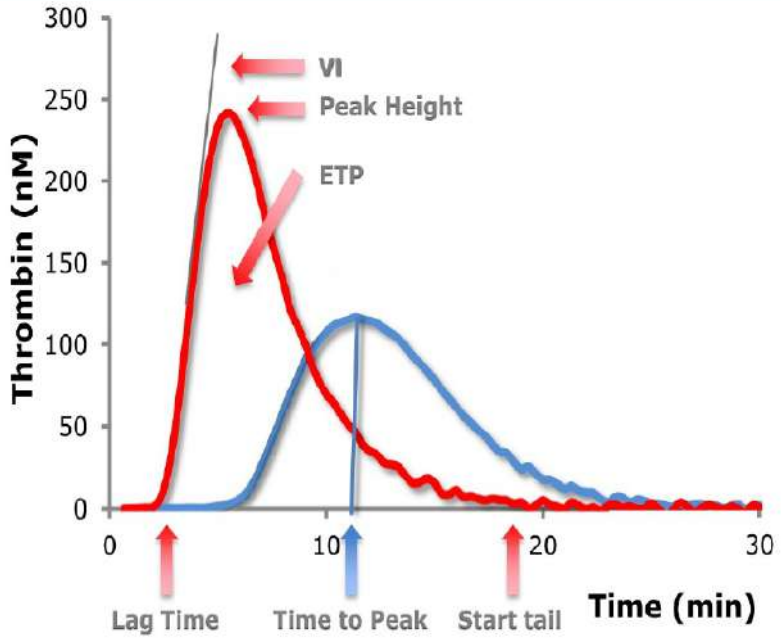
Controles de calidad

Points		
Etalons (µg/ml)	Mesures (sec)	Interpol. (µg/ml)
9.20	68.5	10.22
9.20	70.5	8.83
18.40	61.8	17.25
18.40	61.1	18.27
46.00	50.8	46.71
46.00	51.3	44.44
92.00	44.0	96.96
92.00	44.6	90.51
122.67	41.9	124.32
122.67	42.2	119.89



Tiempo de coagulación = **Concentración de emicizumab en plasma (µg/mL)**

Test generación trombina: Experiencia propia



N = 58 muestras

Estudio HAG con/sin inhibidor

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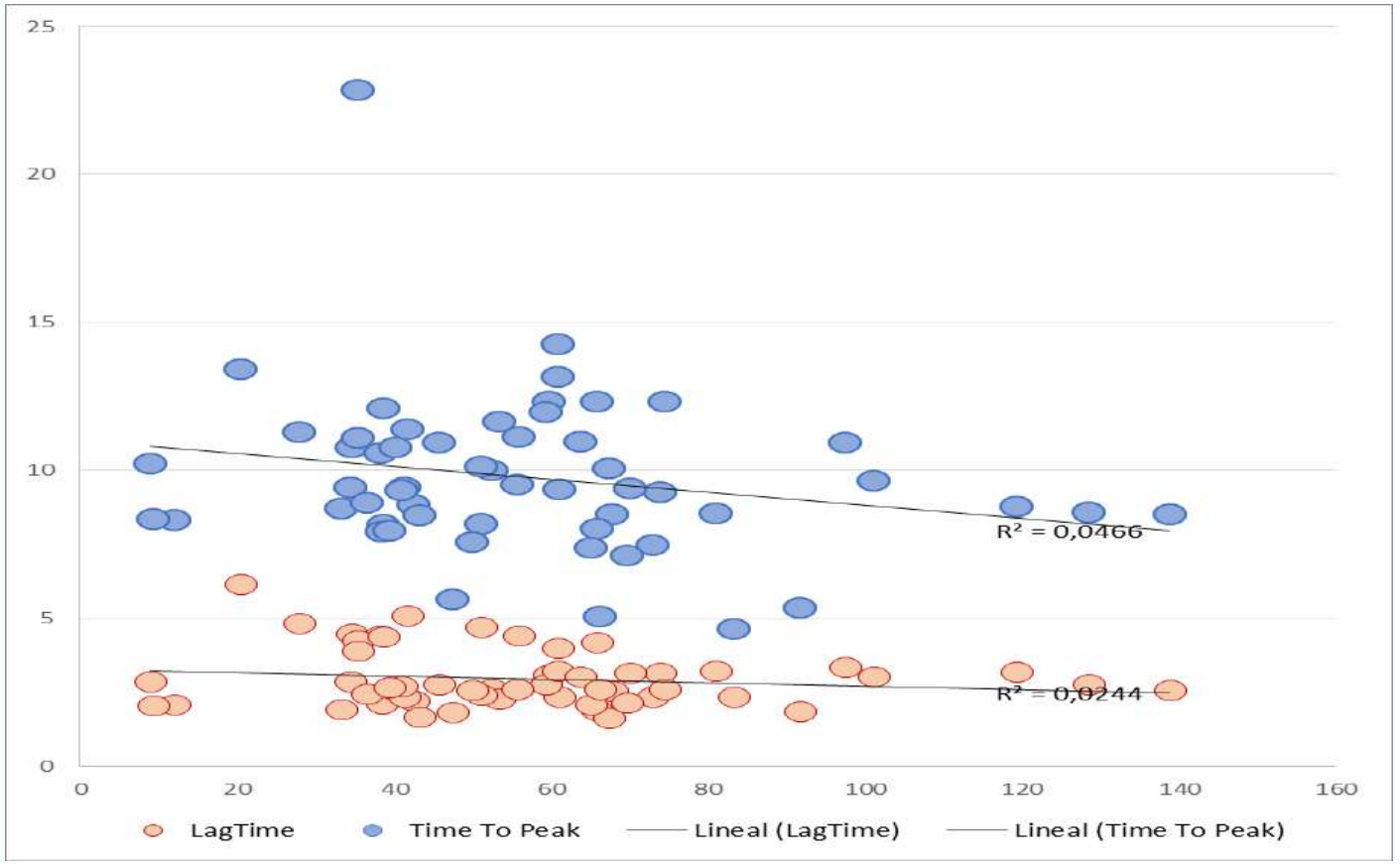
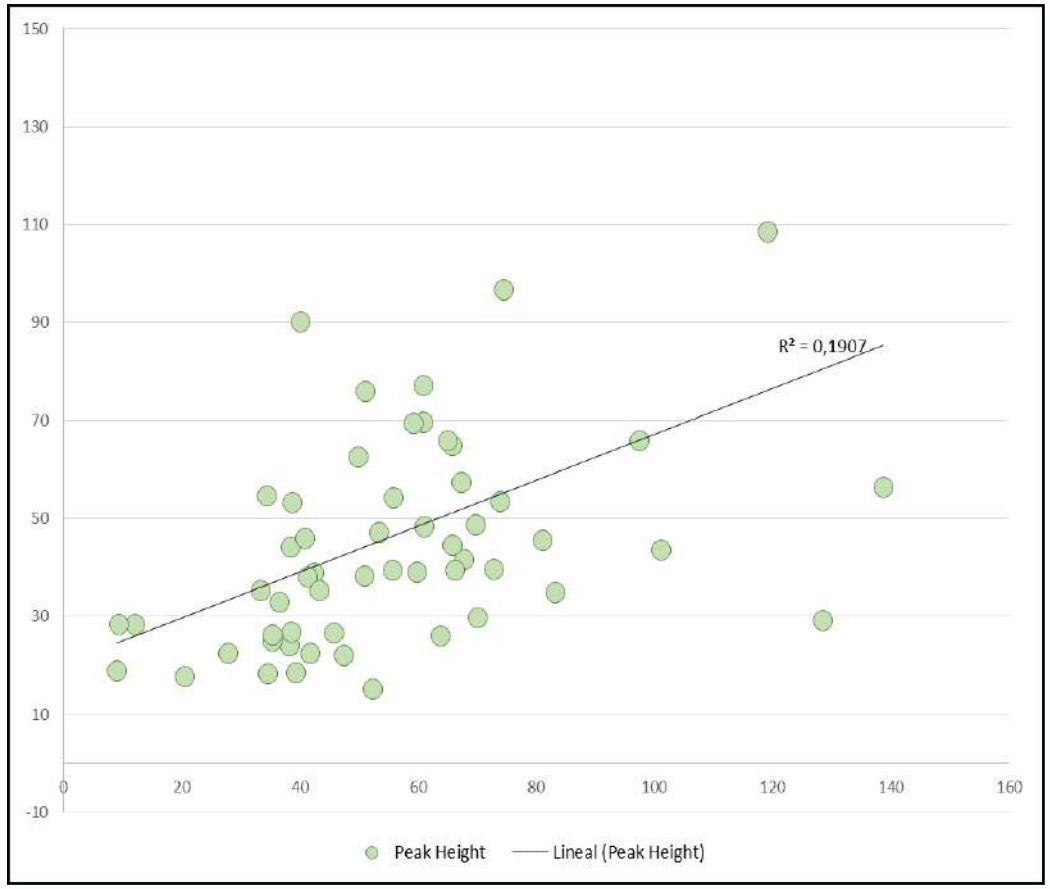
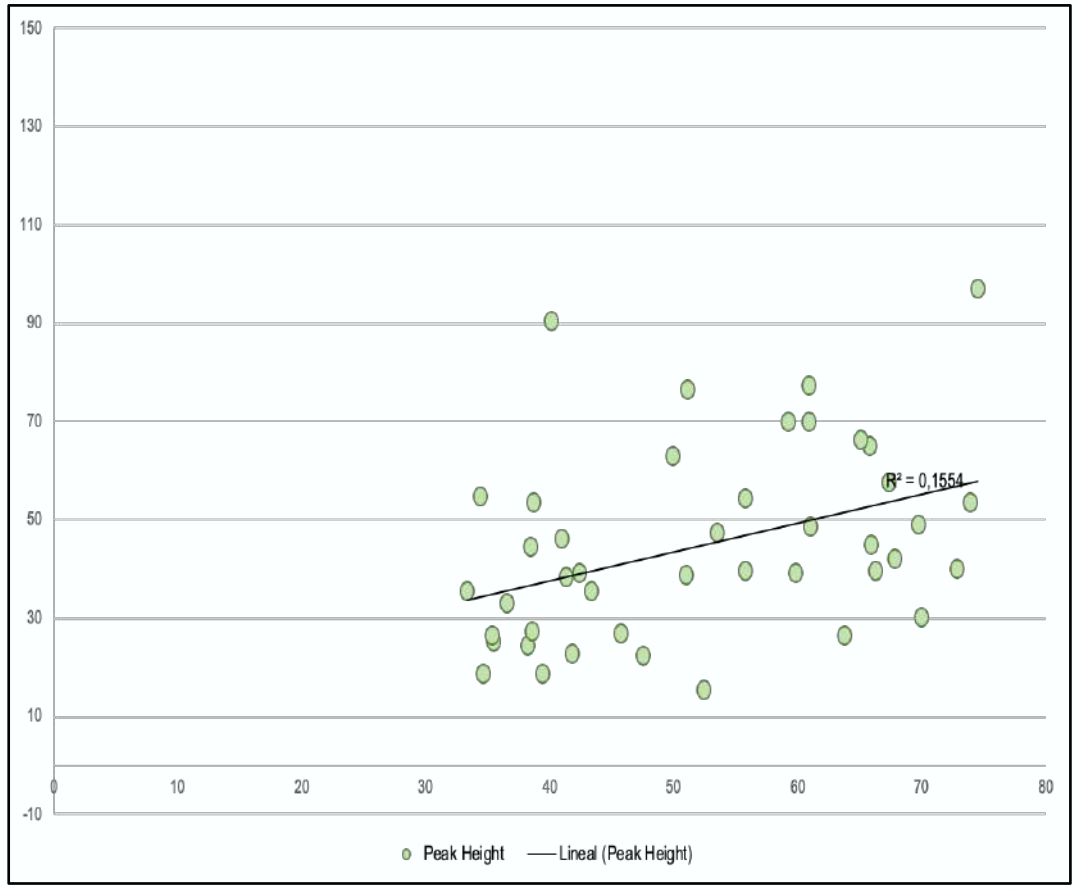
Niveles de emicizumab vs Lag Time y Time to Peak

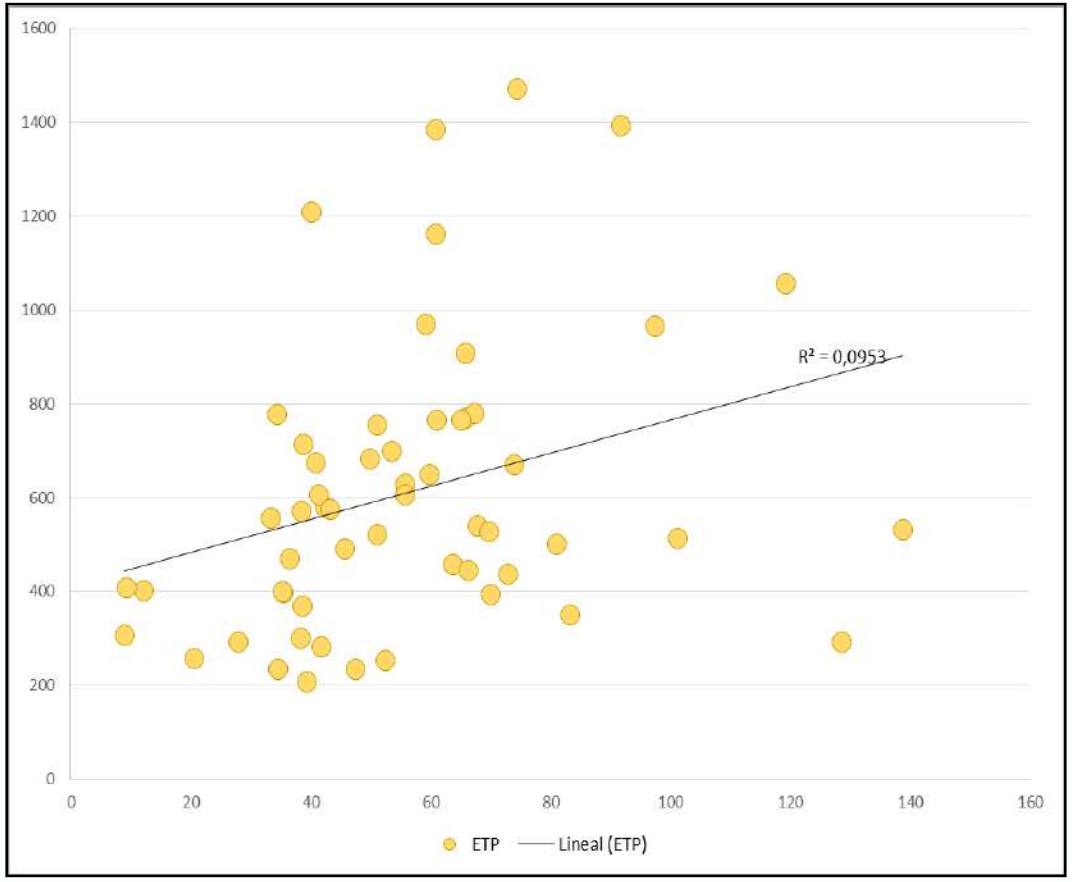


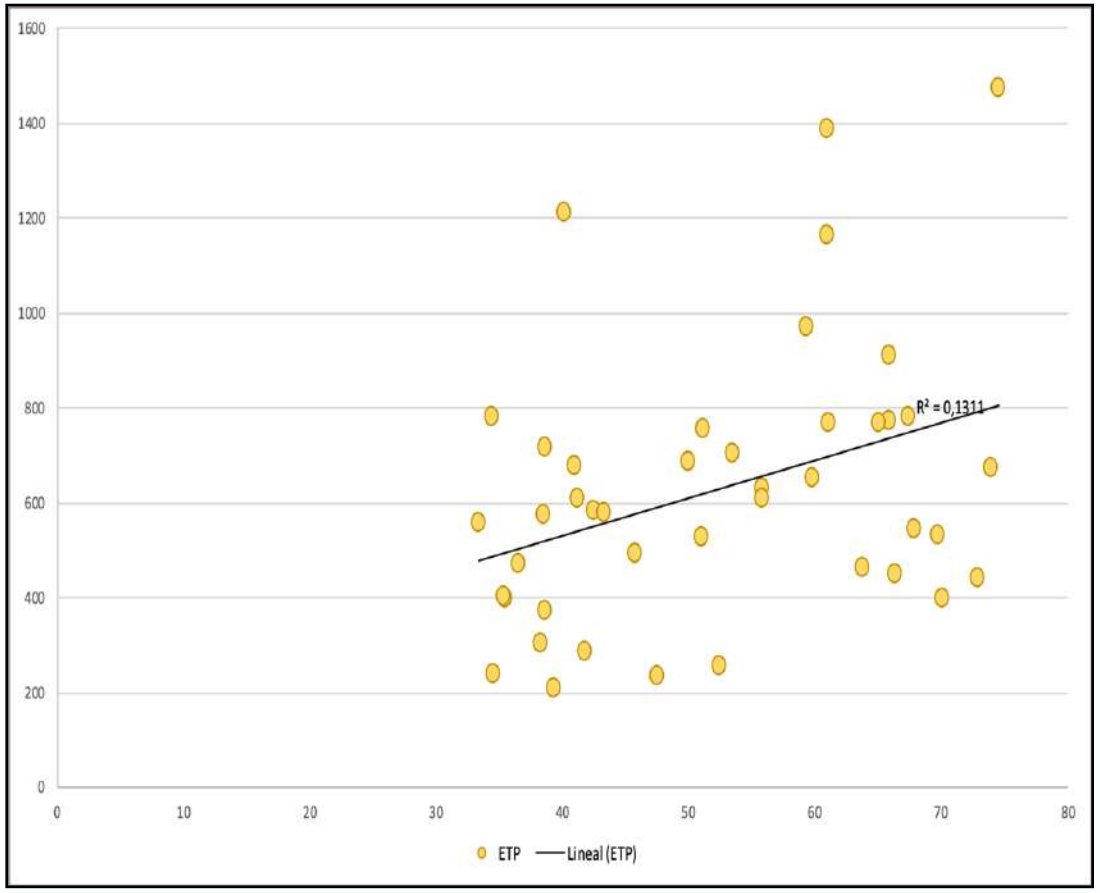
Niveles de emicizumab vs Pico TGT





Niveles de emicizumab vs ETP





Monitorización emicizumab: Conclusiones

- *En general, NO MONITORIZACIÓN en los pacientes con emicizumab*

- *MONITORIZACIÓN en situaciones especiales:*
  - **Laboratorios generales:** TTPA (precaución técnica!!!)
  - **Unidades tratamiento hemofilia:**
    - Cuantificación emicizumab
    - Valores de FVIII método cromogénico con reactivo bovino
    - Cuantificación inhibidor por método cromogénico con reactivo bovino
    - Generación trombina por método estandarizado
  - **Unidades especiales** para monitorización/estudios de investigación:
    - Test globales de coagulación con posibilidad variación condiciones ensayo

Thanks for your participation

MAYO formación

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Diagnostics is in our blood.