

FXIII and Post Partum Hemorrhage

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Potential COI for this presentation

- AxonLab
- CSL Behring
- NovoNordisk
- patent (ZLM): FXIII measurement by thrombelastography
- patent (ZLM): preoperative laboratory risk stratification for bleeding
- Siemens
- Werfen

Agenda

- what we know
- why F XIII ?
- the PPH1300 study – known results
- the PPH1300 study – new results
- whats next ?

Background 1: definition - magnitude of problem - incidence and severity

- Definition PPH (WHO): blood loss ≥ 500 ml within 24 hours postpartum
- responsible for up to 30% of maternal deaths worldwide *GBD 2015, Lancet 2016*
- equivalent to the deaths of 10 women every hour *Weeks A, BJOG 2015*
- US incidence of severe PPH has doubled in the decade before 2008, 26.6% increase in maternal mortality between 2000 and 2014 *Kramer M, AJOG, 2013*
- scottish data suggesting a rise in major obstetric hemorrhages (i.e. blood loss ≥ 2.5 l, ≥ 5 RBCs, treatment for coagulopathy) with an incidence rate of 4.7 per 1000 deliveries *MacDorman M, Obstet Gynecol, 2016*

Background 2: postpartum blood loss: underreported

	11.2%, 95% CI 10.2-12.2	11.0%, 95% CI 10.0-12.0	
	UPPBL ^a (n = 439)	PPH ^b (n = 430)	Control ^c (n = 3048)
Measured blood loss at bag removal (mL)	200 [110–350]	600 [500–800]	100 [50–200]
Peripartum change in Hb level (g/dL)	2.5 [2.2–3.0]	2.4 [1.5–3.3]	0.5 [0–1.1]
Prepartum Hb level (g/dL)	12.5 [11.8–13.3]	12.1 [11.3–12.8]	12.0 [11.3–12.7]
Postpartum day two Hb level (g/dL)	9.8 [9.1–10.7]	9.6 [8.7–10.6]	11.6 [10.7–12.4]
Postpartum Hb level $\leq$ 10g/dL, n(%)	248 (56.5)	250 (58.1)	300 (9.7)

Data are median [interquartile range (IQR)] or n(%) if specified

Σ n = 3917, vaginal delivery

^a: UPPBL defined by peripartum change in haemoglobin level $\geq$ 2 g/dL with no PPH diagnosed

^b: Defined by a measured blood loss $\geq$ 500 mL in the collector bag and/or any second line treatment for PPH

^c: neither PPH nor UPPBL

Giraud et al., PLOS one 2018

Background 3: therapeutic approach with TXA , rFVIIa

- TXA significantly reduces death, especially when given within 3 h of delivery
(1.2% vs. 1.7% (placebo), RR 0.69, 95% CI 0.52-0.91; p=0.008) *WT Coll., Lancet, 2017*
- highly cost effective (Nigeria, Pakistan) [and others] *Li, Lancet Glob Health 2018*
- can be given im. (active in ~ 10 min.) if no iv. line, oral route to slow *Shakur-Still, BJOG, 2023*
- prophylactic TXA ...feasible ...
... but not recommended *Binyamin, J Clin Med, 2023; Lee, BJOG, 2023; ...*
AWMF 015/063 08/2022, Kowalczyk, Curr Opin Obstet Gynecol, 2024 ...
- rFVIIa approved by EMA in "...severe PPH when uterotonics are insufficient to achieve haemostasis."
EMA/CHMP/2055442022
- AWMF guideline 015-063 08/2022: rFVIIa as a treatment option in refractory PPH
Schlembach, Geburtsh Frauenheilk, 2023

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PPH1300 – result 1: peripartal course (loss) of fibrinogen

Fibrinogen prepartum (< 36 h)			Fibrinogen post partum (24-48 h)	
4.5 [3.9-5.0]	no PPH		4.3 [3.8-4.9]	} Korte, ISTH 2023
4.3 [3.9-5.0]	non-severe	PPH	4.3 [3.8-4.9]	
4.5 [3.9-5.1]		severe PPH	3.8 [3.1-4.4]	

PPH1300 – result 1: peripartal course (loss) of fibrinogen

	Fibrinogen g/l at dx non-severe PPH	Fibrinogen g/l at dx severe PPH	Fibrinogen g/l post partum (24-48 h)	Reference
median [IQR]	3.8 [3.2-4,4]	2.1 [1.5-2.8]		Epstein, BJA, 2021
	4.4 [3.7-5.1]	3.3 [2.5-4.2]		Charbit, JTH, 2007
		3.8 [3.1-4.5]		Collins, BLOOD, 2012
mean $\pm$ SD		2.9 $\pm$ 0.6	4.0 $\pm$ 0.9	Collins, BJA, 2017
	4.2 $\pm$ 1.2	3.4 $\pm$ 0.9		Cortet, BJA, 2012
		4.5 $\pm$ 1.2		Wikkelso, BJA, 2015

Randomized, controlled intervention trials with fibrinogen were unsuccessful

- severe PPH (1459 ± 476 ml), preemptive fibrinogen 2g, pc db RCT
- PPH 1000 - 1500 ml, TEM-directed (Fibtem A5 ≤ 15 mm) infusion of fibrinogen, RCT
- PPH and 2nd uterotonic, fibrinogen 3g, pc db RCT

Wikkelsø, BJA, 2015

Collins, BJA, 2017

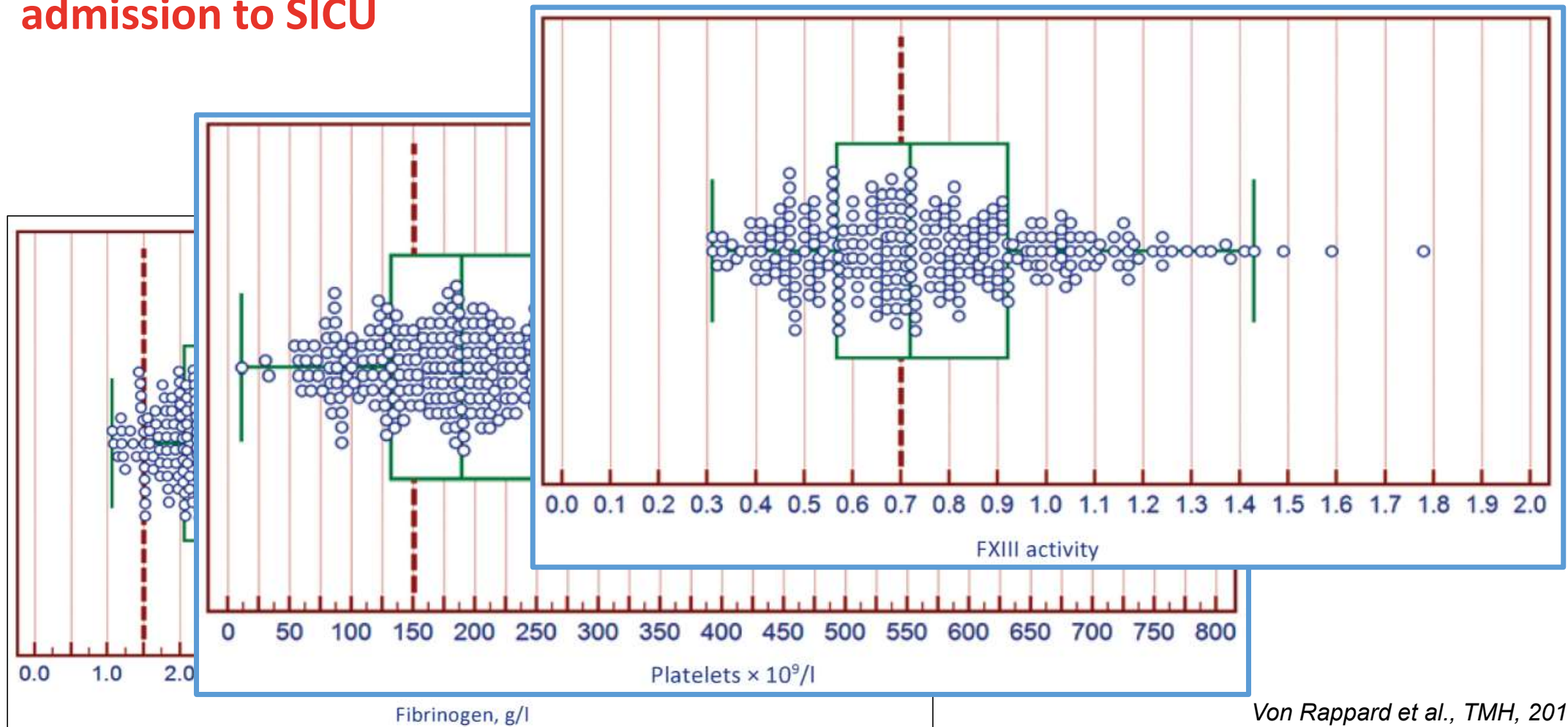
Ducloy, BJOG, 2021

Discussion: experiences from surgical studies; factors associated with clot firmness (ROTEM Extem) upon admission to SICU

Independent variables	r partial	p
Age	0.05233	0.4710
ASA class	0.02046	0.7782
Length of operation	-0.01710	0.8139
Fibrinogen	0.4011	<0.0001
Hemoglobin	-0.1192	0.0997
Colloids	-0.2285	0.0014
Cristalloids	0.05251	0.4695
pH	-0.005996	0.9342
Platelets	0.5321	<0.0001
Temperature (on admission to SICU)	0.02355	0.7458
FXIII	0.2986	<0.0001

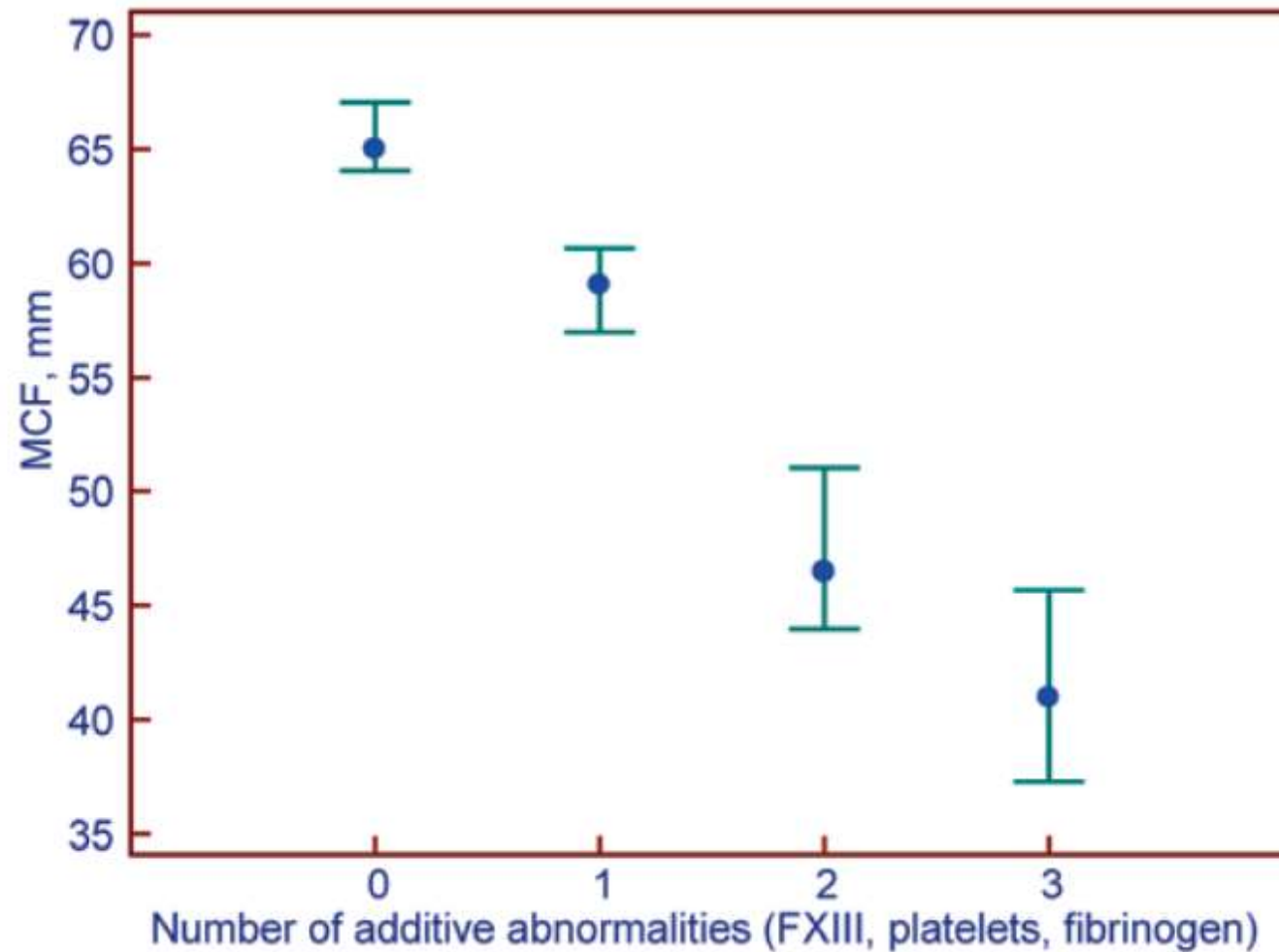
Von Rappard et al., TMH, 2017

Prevalence of deficiencies in factors relevant for clot firmness upon admission to SICU



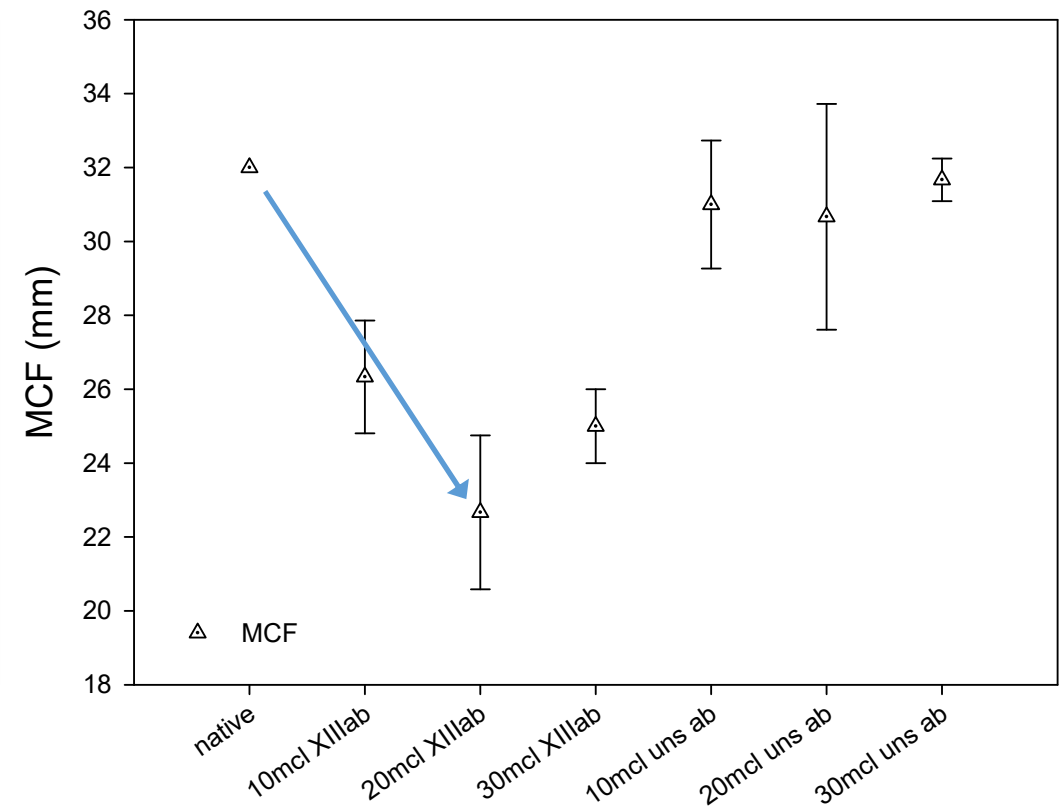
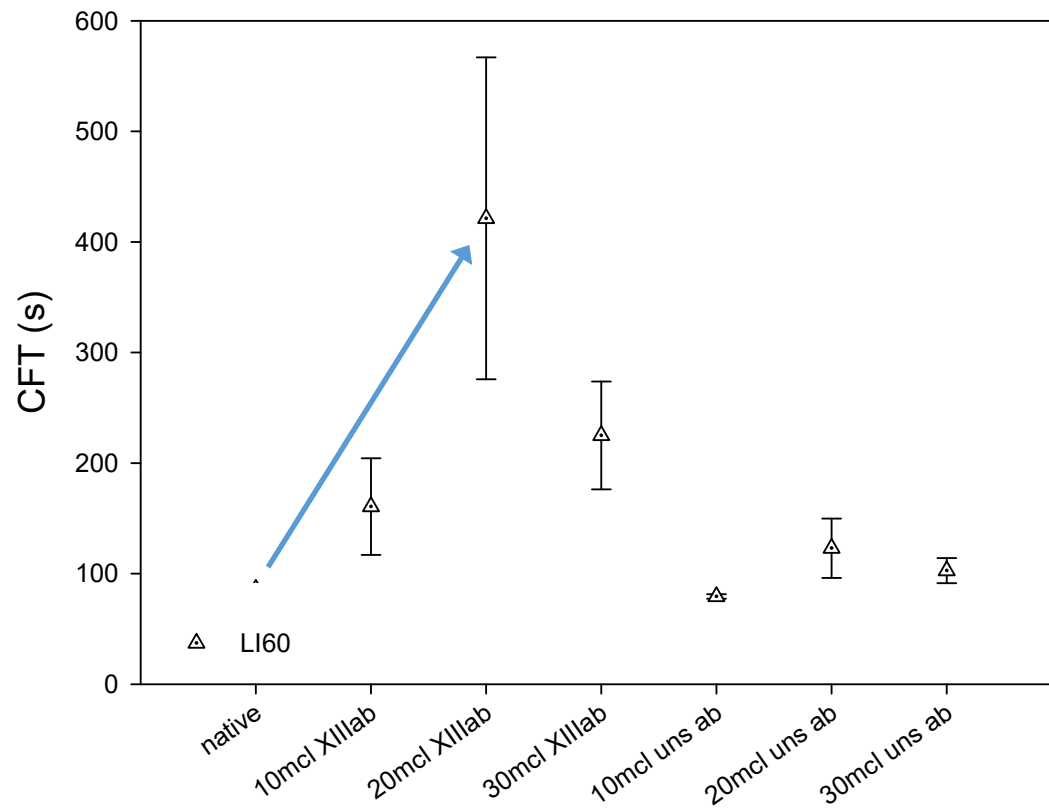
Von Rappard et al., TMH, 2017

Additive effect of deficiencies on clot firmness upon admission to SICU



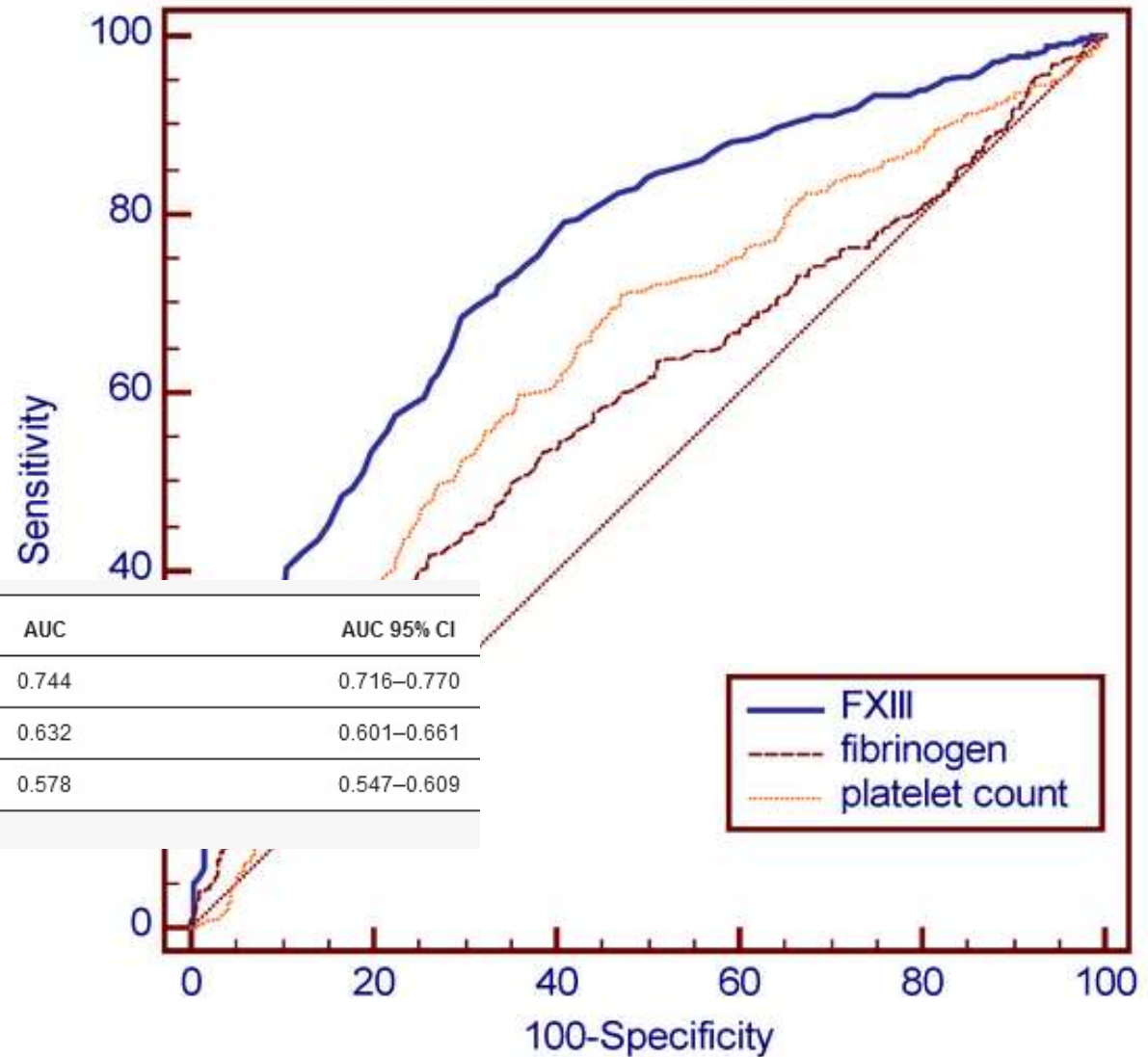
Von Rappard et al., TMH, 2017

Thrombelastographic results on F XIII blockade in whole blood



Jambor et al., Anesth Analg, 2009

ROC curve for RBC transfusions according to intra-operative, pretransfusional levels of fibrinogen, platelets and F XIII (n = 1023)



Listyo et al., J Clin Med, 2020

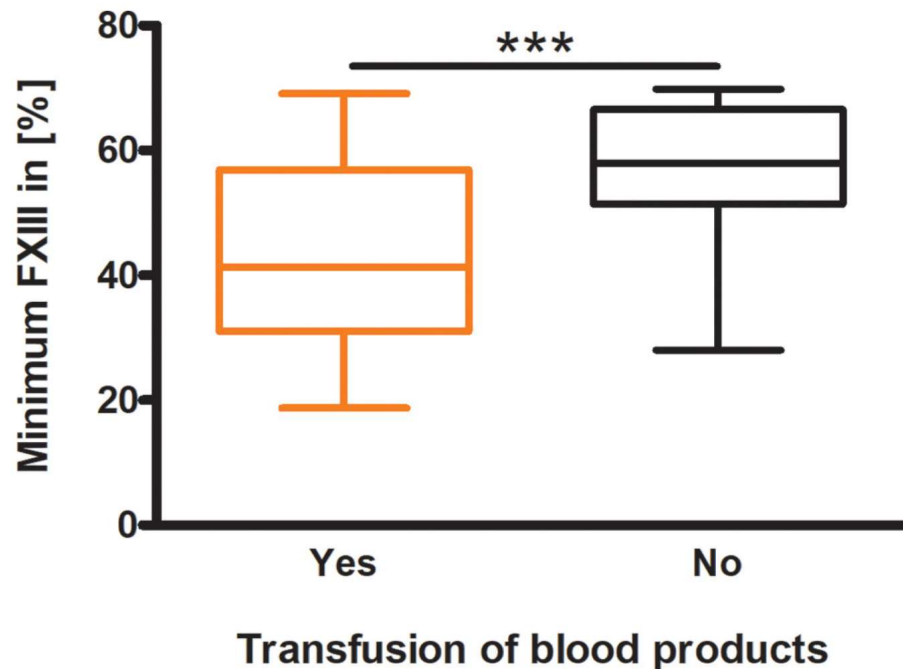
Acquired F XIII deficiency in the ICU

Mild Acquired Factor XIII Deficiency and Clinical Relevance at the ICU—A Retrospective Analysis

Clinical and Applied
Thrombosis/Hemostasis
Volume 27: 1-7
© The Author(s) 2021
DOI: 10.1177/10760296211024741
journals.sagepub.com/home/cat
SAGE

Conclusion

Taken together, these results indicate that a mild FXIII deficiency occurring at any point of ICU stay is also probably relevant for the total need of PRBC, independent of pro-coagulatory management, which did not differ between the groups. Based on the underlying data and the literature, it is important raising awareness of mild FXIII deficiency in the intensive care setting and we recommend providing routine measurements in patients at high risk of bleeding. At present, in alignment with the ESAIC guidelines, an early management with the substitution of FXIII at levels <50-60% could be suggested.^{32,40}



Schmitt et al., Clin Appl Thromb Hemost 2021

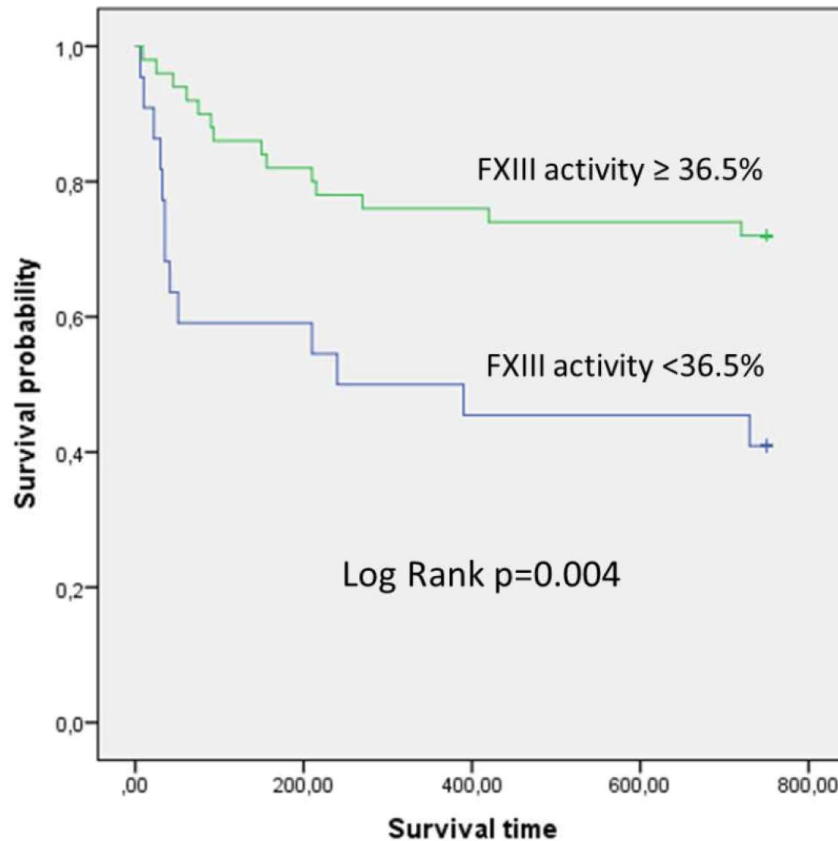
Acquired F XIII deficiency in the ICU

Hemorrhage continuous to be the leading

cause of death

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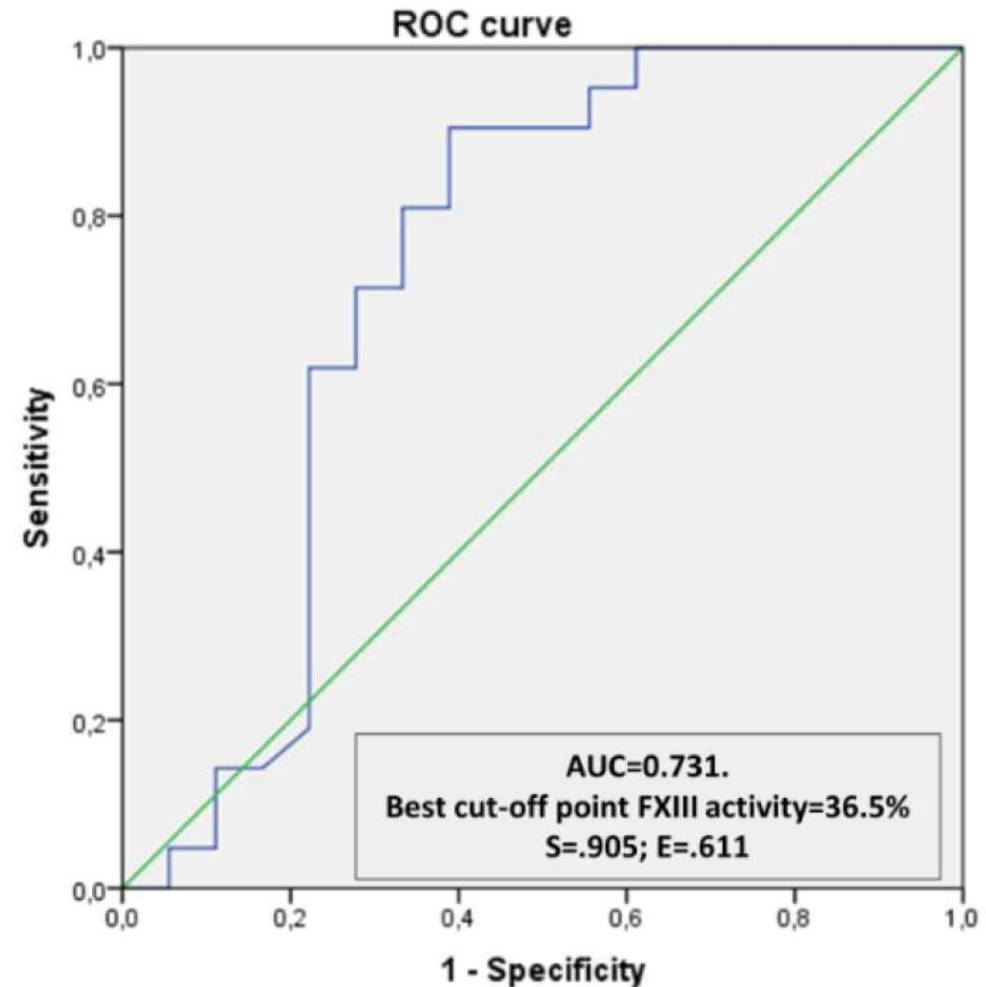
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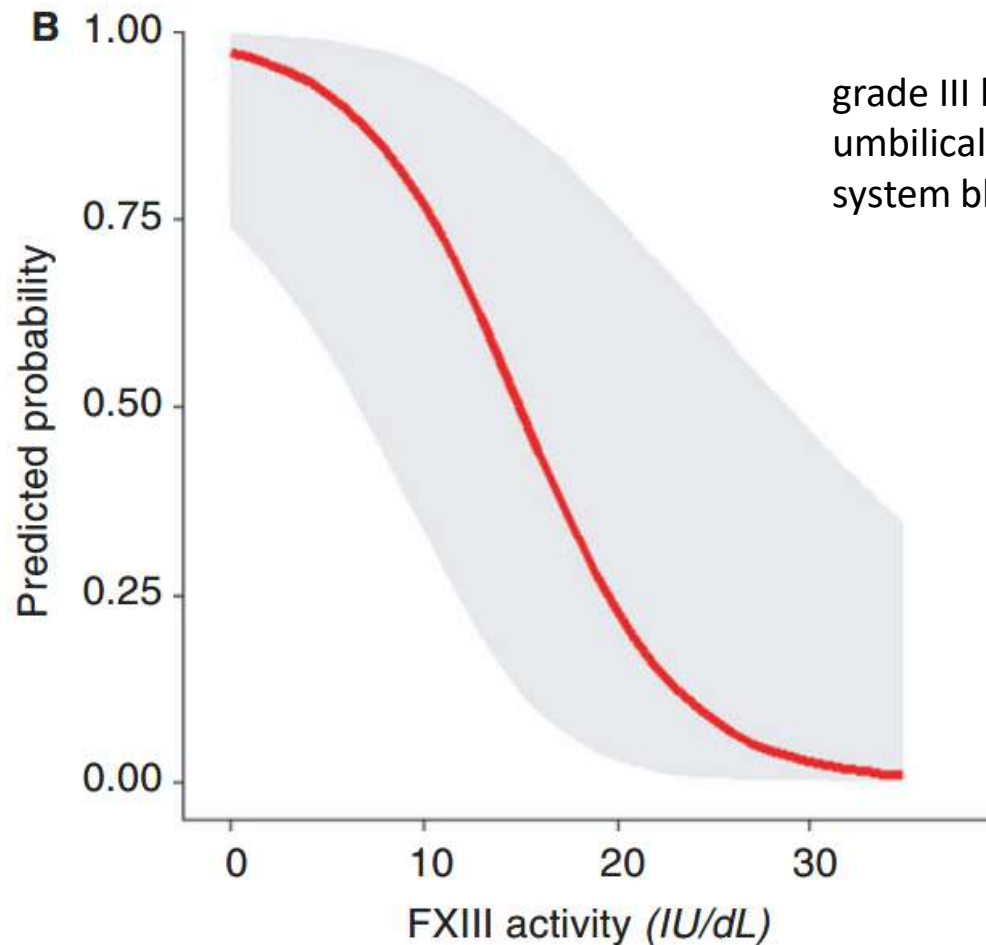
tted to
ary 2017

IS, ICU



Duque et al., *Thromb Haemost*, 2021

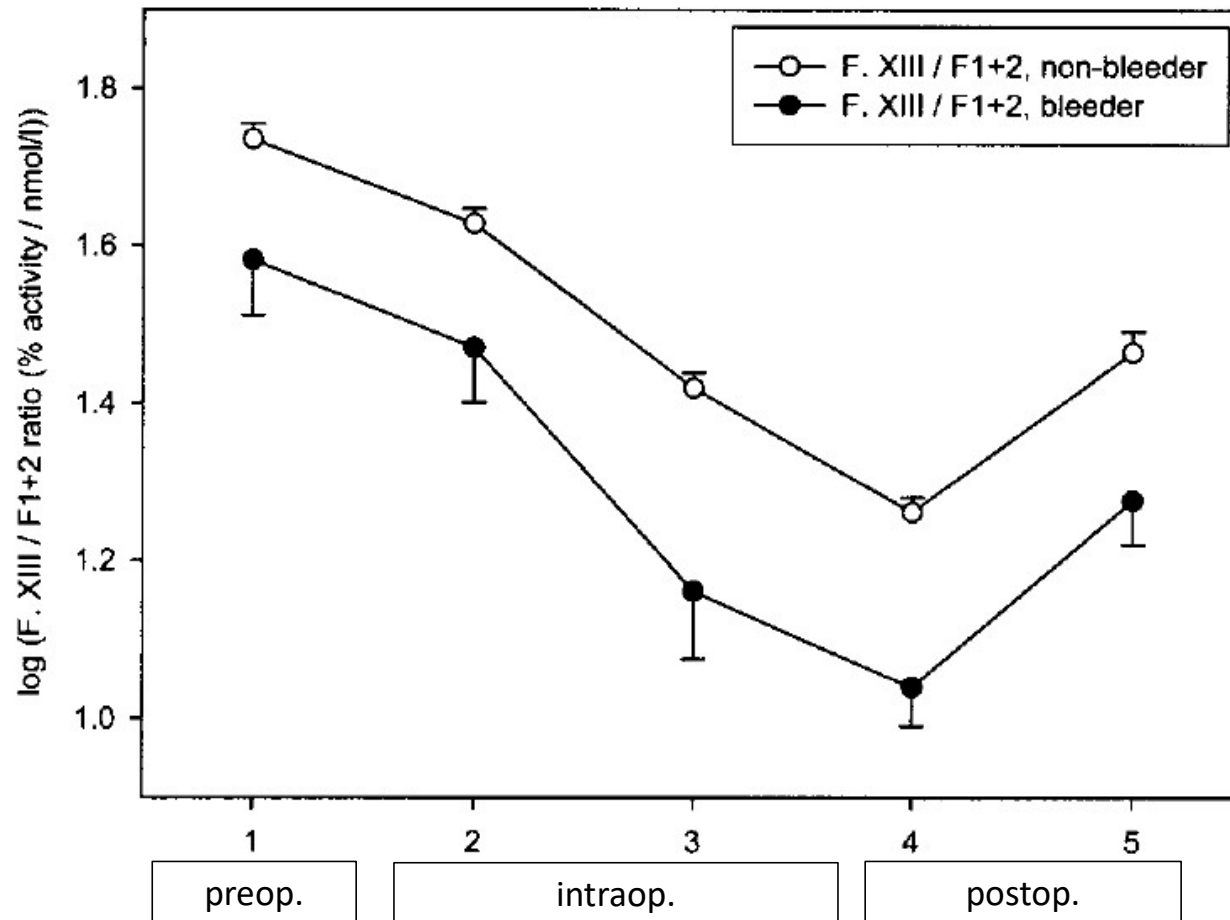
Predicted grade III bleeding in congenital F XIII deficiency



grade III bleeding (spontaneous major bleeding):
umbilical, gastrointestinal and central nervous
system bleeding, hemarthrosis and hematoma

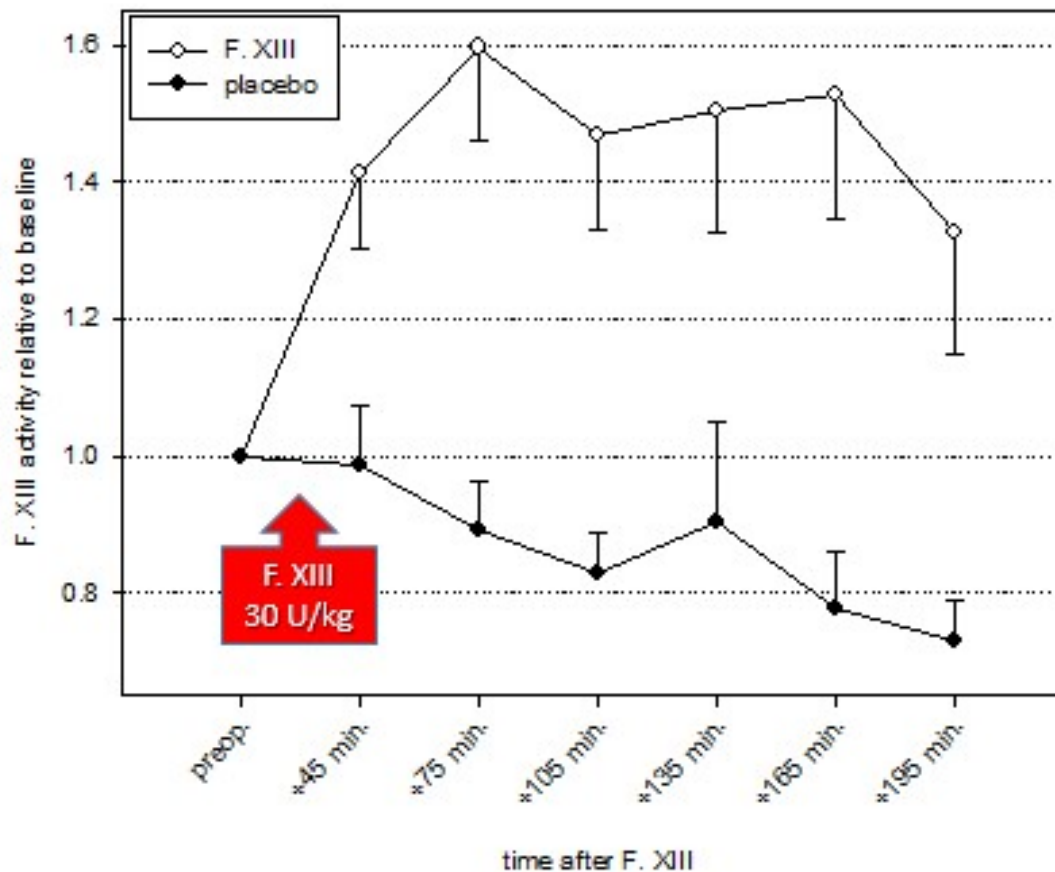
Menegatti et al., JTH 2005

F. XIII / F1+2 and bleeding in a prospective surgical cohort study



Wettstein, Korte et al., *Anesth Analg*, 2004

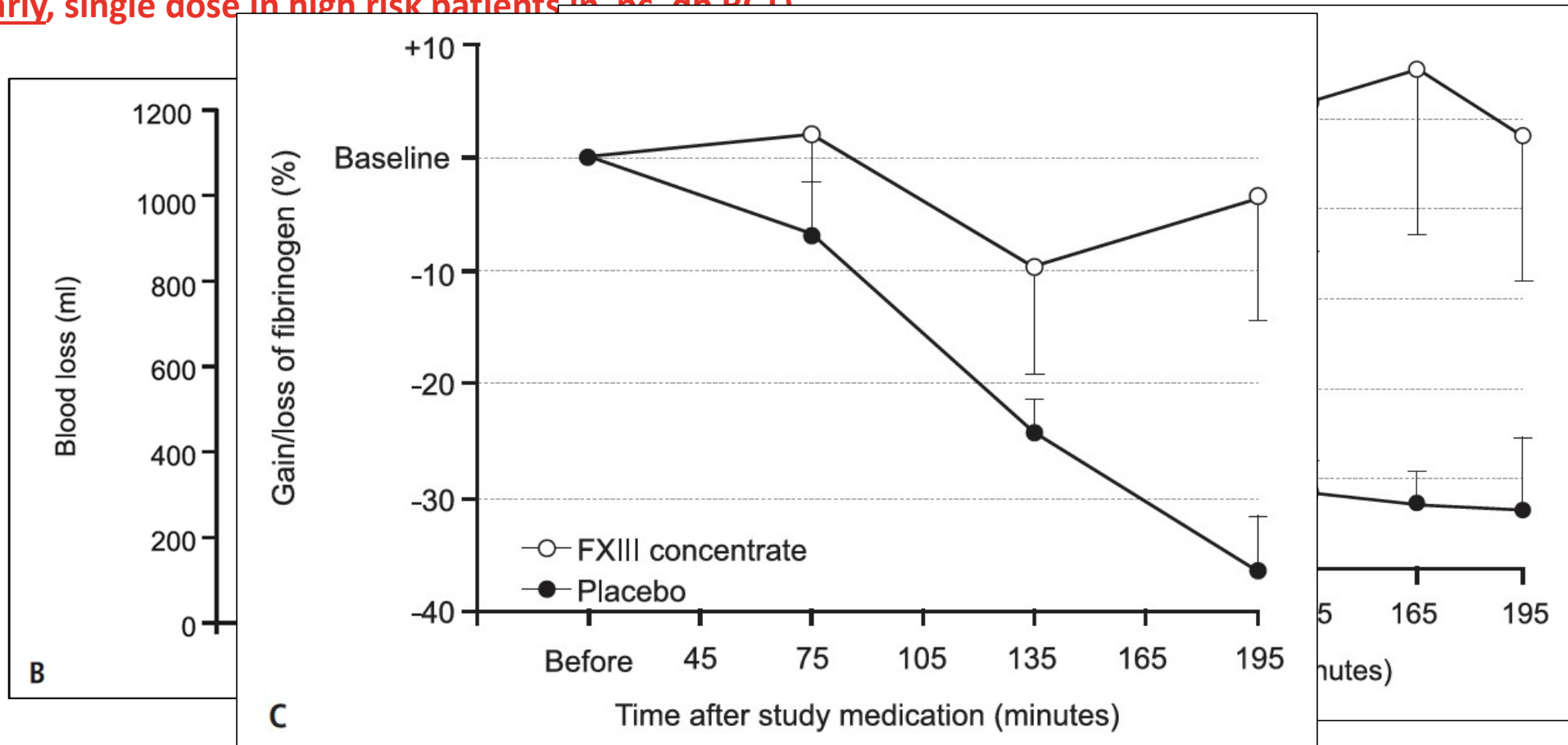
Discussion: experiences from surgical studies (early, single dose in high risk patients in pc, db RCT)



Acc. Korte et al., Anesthesiology, 2009

Discussion: experiences from surgical studies

(early, single dose in high risk patients in on- and off-PCT)



Dickneite et al., Thromb Haemost, 2015

Korte et al., Anesthesiology, 2009

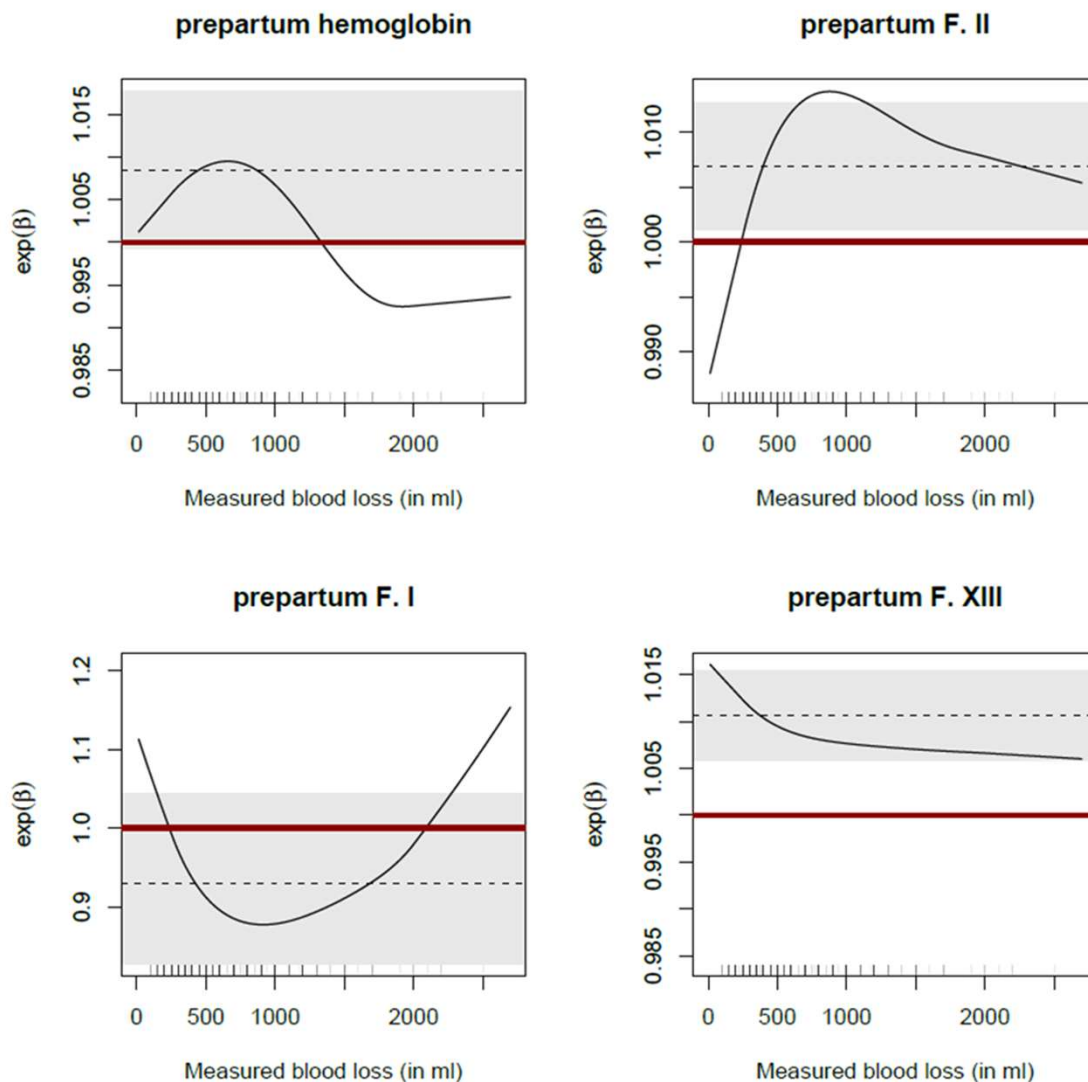
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The PPH1300 study

- prospective study of >1300 parturient women undergoing standardized and validated measurements of blood loss (MBL)
- PPH defined as MBL > 500 ml (WHO) within 24 hours of delivery, major (RCOG) / severe (WHO) PPH as MBL > 1000 ml
- determination of fibrinogen (FIB), factors II (F II) and XIII (F XIII), hemoglobin (HGB) and platelet count (PLT) within 36 hours before and after delivery, standard methods;
ratio post-/prepartum result
- results not known to caregivers, no bias in treatment

*Kahr et al., Arch Gynecol Obstet, 2018
Geneva: World Health Organization; 2012
Green-top guideline No. 52, BJOG, 2017
Haslinger, Korte et al., JTH, 2020
Brun et al., TMH, 2023*



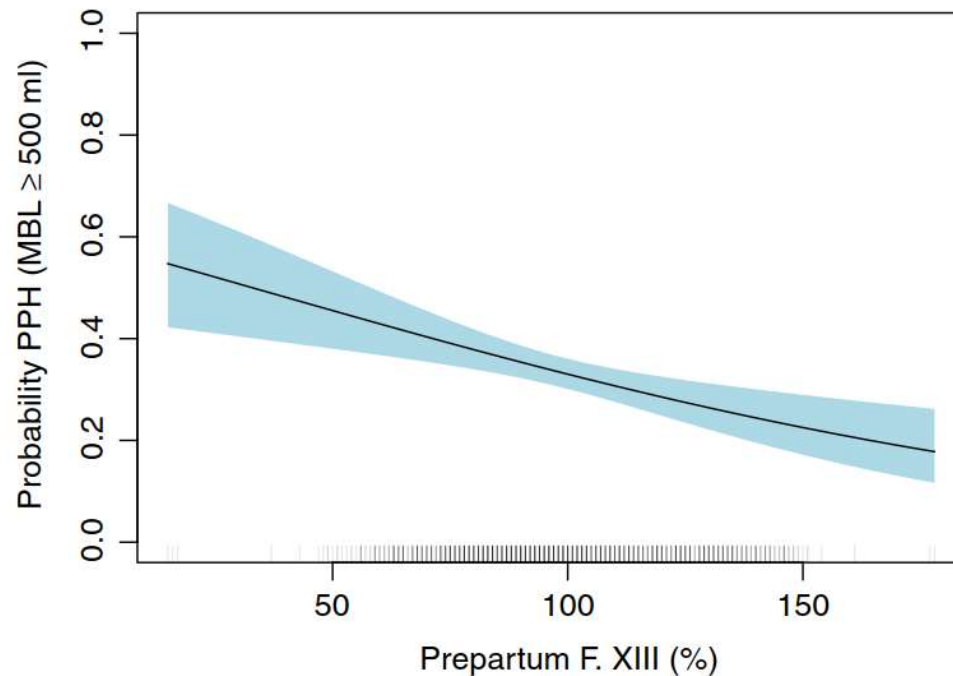
Prepartum F XIII and Postpartum Blood Loss – PPH1300 – result 2

- Odds Ratio to remain below a certain volume of postpartum blood loss (based on response-varying regression coefficients)
 - Dashed lines represent the response-constant regression coefficients from the continuous outcome logistic regression model.
 - Grey area: the corresponding confidence interval.
 - thick line: an absent effect (odds ratio 1.0).
 - The F. XIII odds ratio graph is the only one not to cross the thick line that represents an absent effect: **F. XIII is the only parameter evaluated with a statistically significant impact on blood loss for any blood volume measured.**

Haslinger, Korte et al., JTH, 2020

PPH1300 – result 3

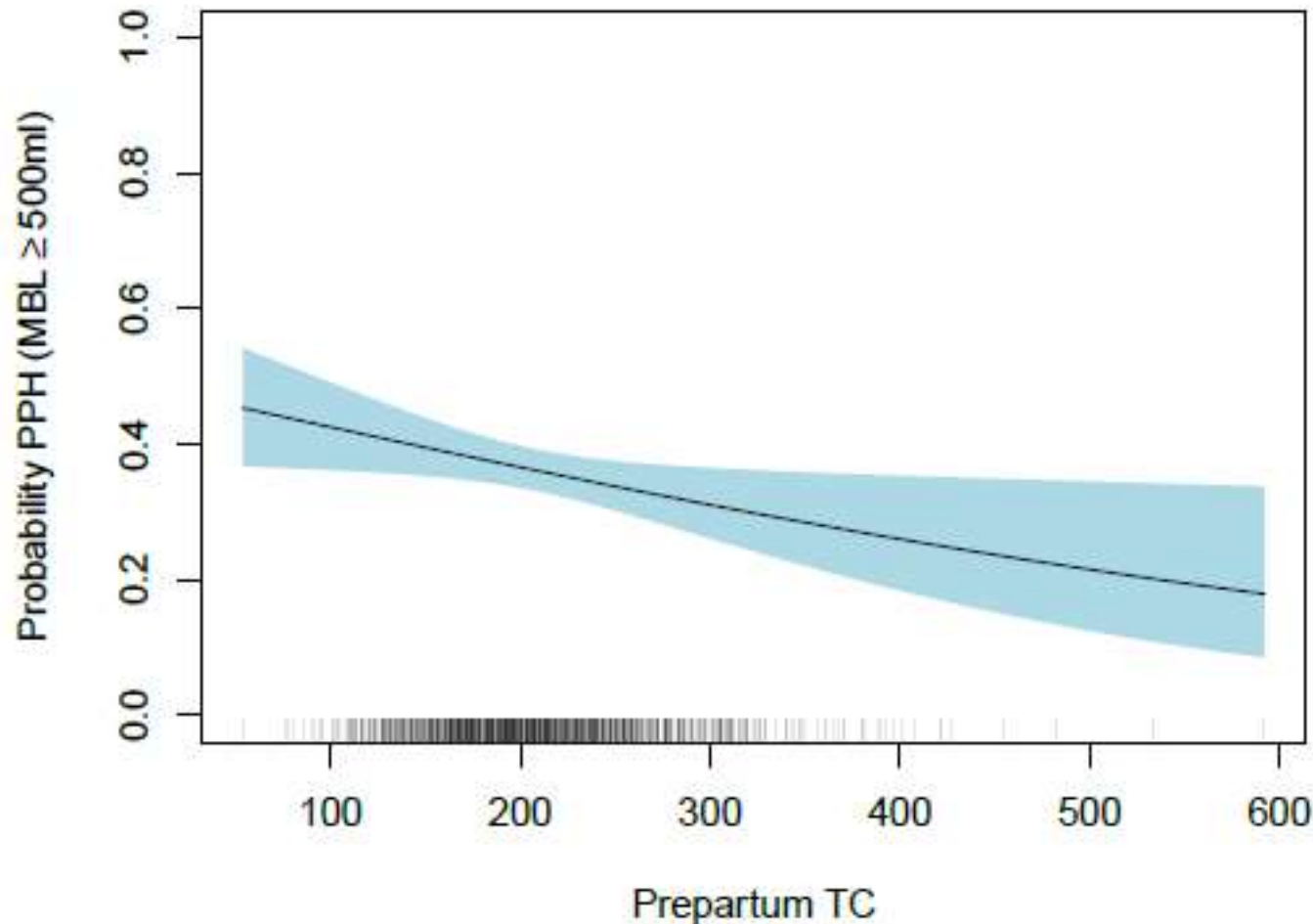
- **F XIII is the major prepartum** coagulation factor influencing postpartum blood loss (over fibrinogen, F II, platelets)



continuous effect of measured prepartum F XIII on the probability to sustain a PPH at prepartum hemoglobin 127 g/l, F II 128%, fibrinogen 4.5 g/l

Haslinger, Korte, et al., JTH, 2020

PPH1300 – result 4



the continuous effect of
measured prepartum platelet
count on the probability to
sustain a PPH at prepartum
hemoglobin 127 g/l,
F II activity 128%,
fibrinogen 4.5 g/l

Brun et al., TMH, 2023

Agenda

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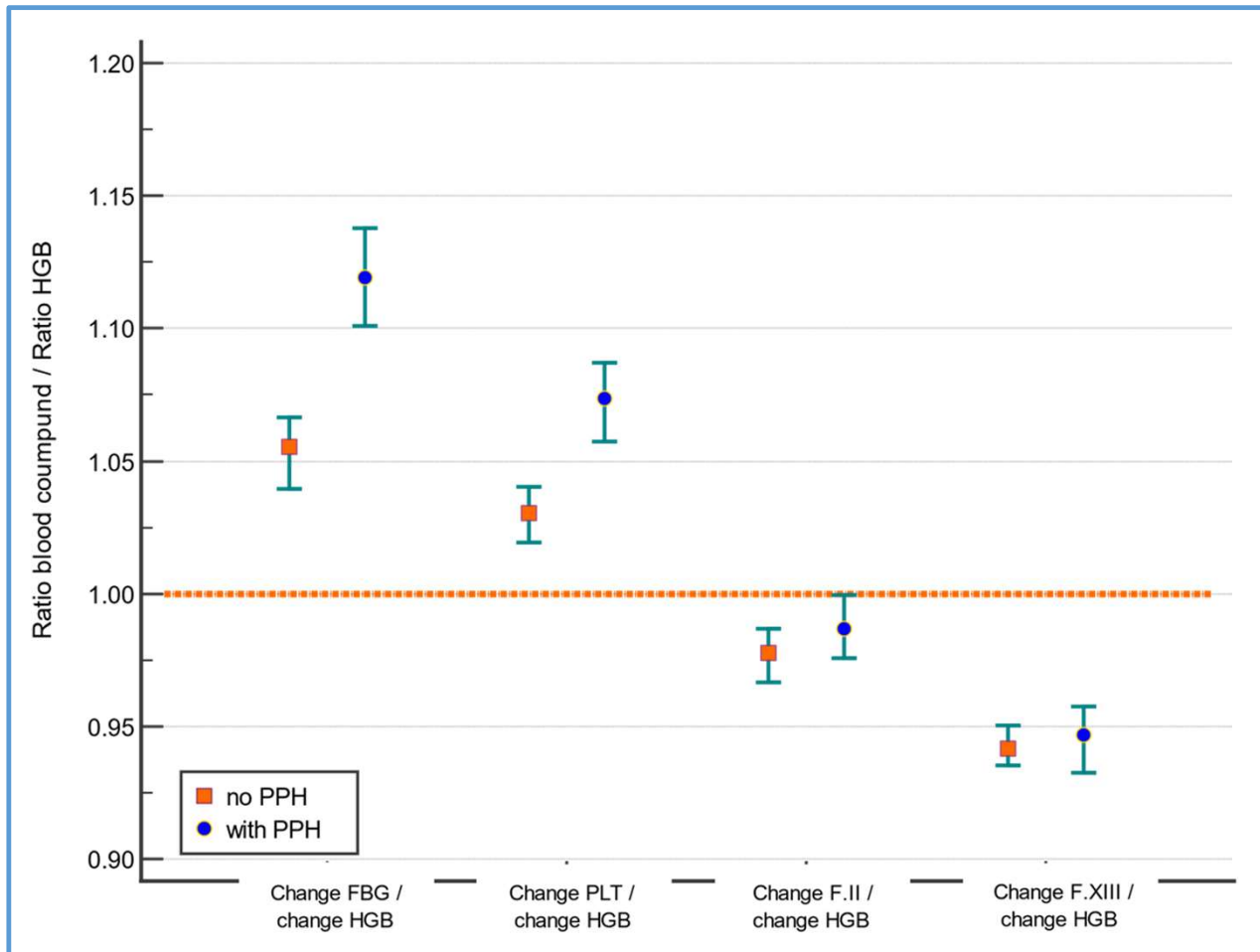
PPH1300 – result 5: peripartal course (loss) of coagulation factors and hemoglobin

	NO PPH (n=724)			PPH 500-1000 ml / 24h (n=489)			PPH > 1000 ml / 24 h (n=96)	
	median ratio (95% CI)	median loss		median ratio (95% CI)	median loss		median ratio (95% CI)	median loss
HGB	0.92 (0.91 – 0.92)	8%		0.86 (0.86 – 0.88)	14%		0.76 (0.72 – 0.79)	24%
FIB	0.98 (0.96 – 0.98)	2%		0.98 (0.96 – 1.00)	2%		0.88 (0.84 – 0.92)	12%
PLT	0.94 (0.93 – 0.95)	6%		0.91 (0.91 – 0.93)	9%		0.84 (0.79 – 0.87)	16%
F II	0.89 (0.88 – 0.90)	11%		0.86 (0.85 – 0.86)	14%		0.80 (0.77 – 0.81)	20%
F XIII	0.86 (0.85 – 0.87)	14%		0.80 (0.80 – 0.81)	20%		0.71 (0.68 – 0.75)	29%

changes always most extensive for F XIII (over F II, PLT and FIB) and highly statistically significant (between all components; Friedman test, Kruskal-Wallis test, all $p < 0.0001$)

Korte, Haslinger et al., ISTH 2023

PPH1300 – result 6: peripartal loss of coagulation factors vs loss of hemoglobin

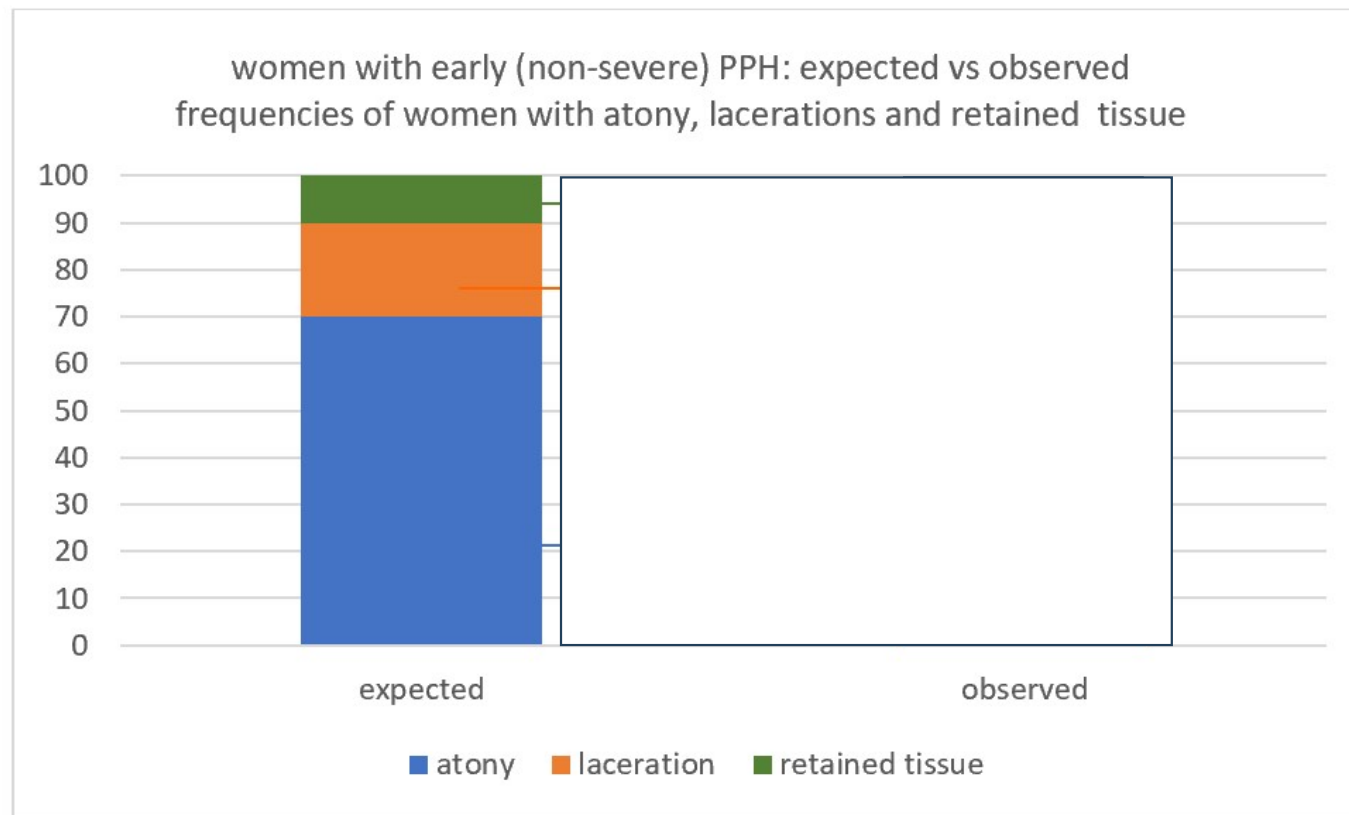


- **FBG and PLT** show a **decreased loss vs. hemoglobin**, indicating a **relative increase**
- (F II and) **F XIII** show an increased loss vs. hemoglobin, indicating a **relative decrease**
- repeated measures ANOVA, all $p < 0.0001$ between all components

Korte, Haslinger et al., ISTH 2023

PPH1300 – result 7: development of PPH in non-CS

etiologies of PPH according to the literature: uterine atony 70%, lacerations 20%, placental tissue 10%



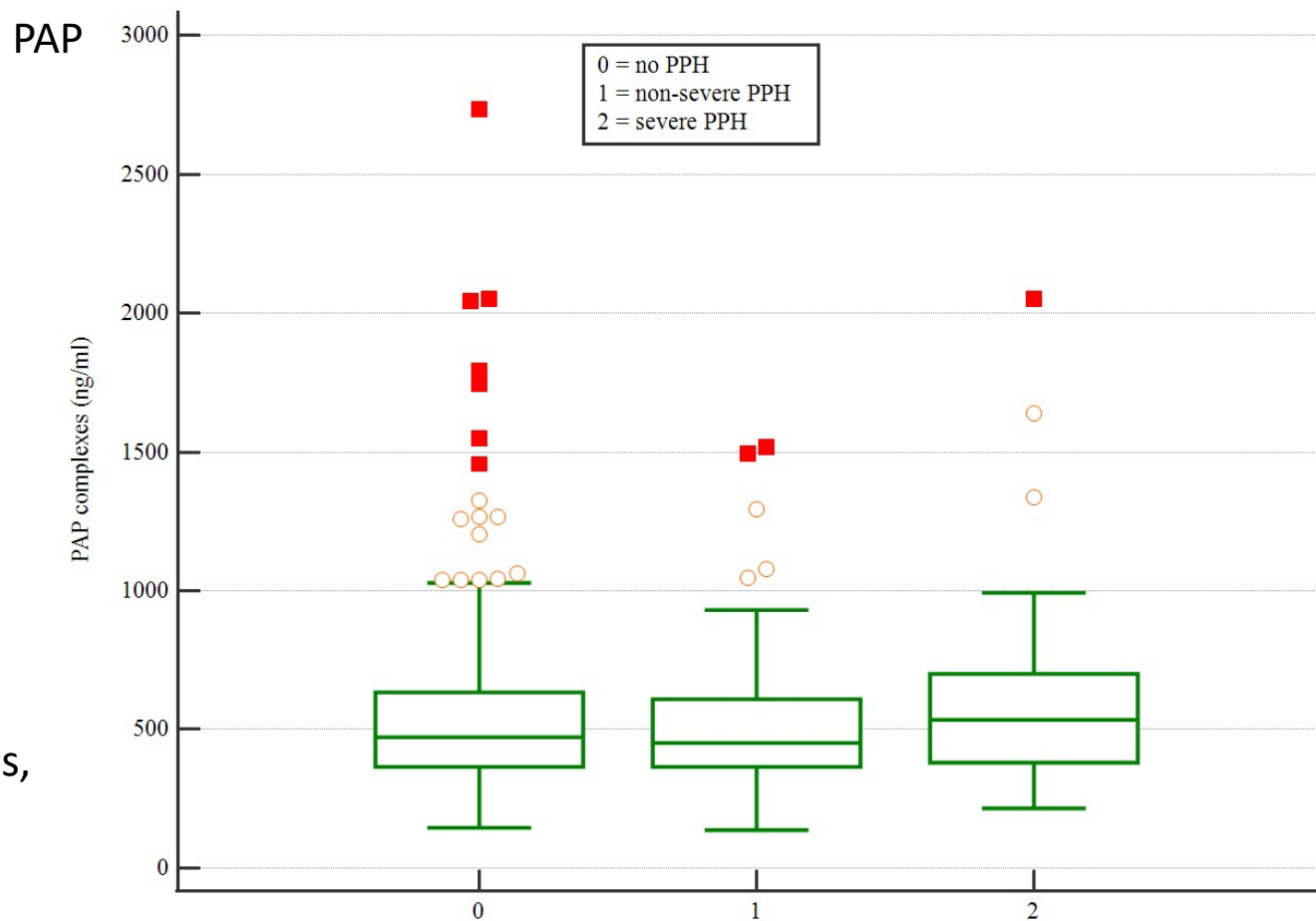
Korte, Haslinger et al., ASH 2024

Literature: development of PPH in non-CS

etiologies of PPH according to the literature: frequency of atony in PPH

First author	Year	Journal	Patient population / definition of PPH	Observed frequency of uterine atony
Glaze	2008	Obstet Gynecol	need for postpartum hysterectomy < 24 h	37%
Mouasa	2008	Acta Obstet Gynecol Scand	> 1000 ml blood loss or need for blood transfusion < 24 h	no response to 1st line therapy: 36%, +response to 1st line therapy: 52%
Bodelon	2009	Obstet Gynecol	need for hysterectomy < 30 days postpartum	29.2%
Guasch	2009	Rev Esp Anesthesiol Reanim	admission to IMC unit due to PPH (RBC transfusion rate 96.8%)	45.2%
Green	2016	BJOG	need for transfusion $\geq$ 8 U of RBC	40%
Hu	2017	Chin Med J	2011-2015: need for transfusion $\geq$ 5 U of RBC	50%
Widmer	2019	BJOG	> 1000 ml blood loss; need for 2 nd line therapy	31.5%
Greene	2021	Eur J Obstet Gynecol Reprod Biol	> 2500 ml blood loss or need for transfusion $\geq$ 5 U of RBC or need for treatment of coagulopathy	39.8%, as a single cause 20.7%

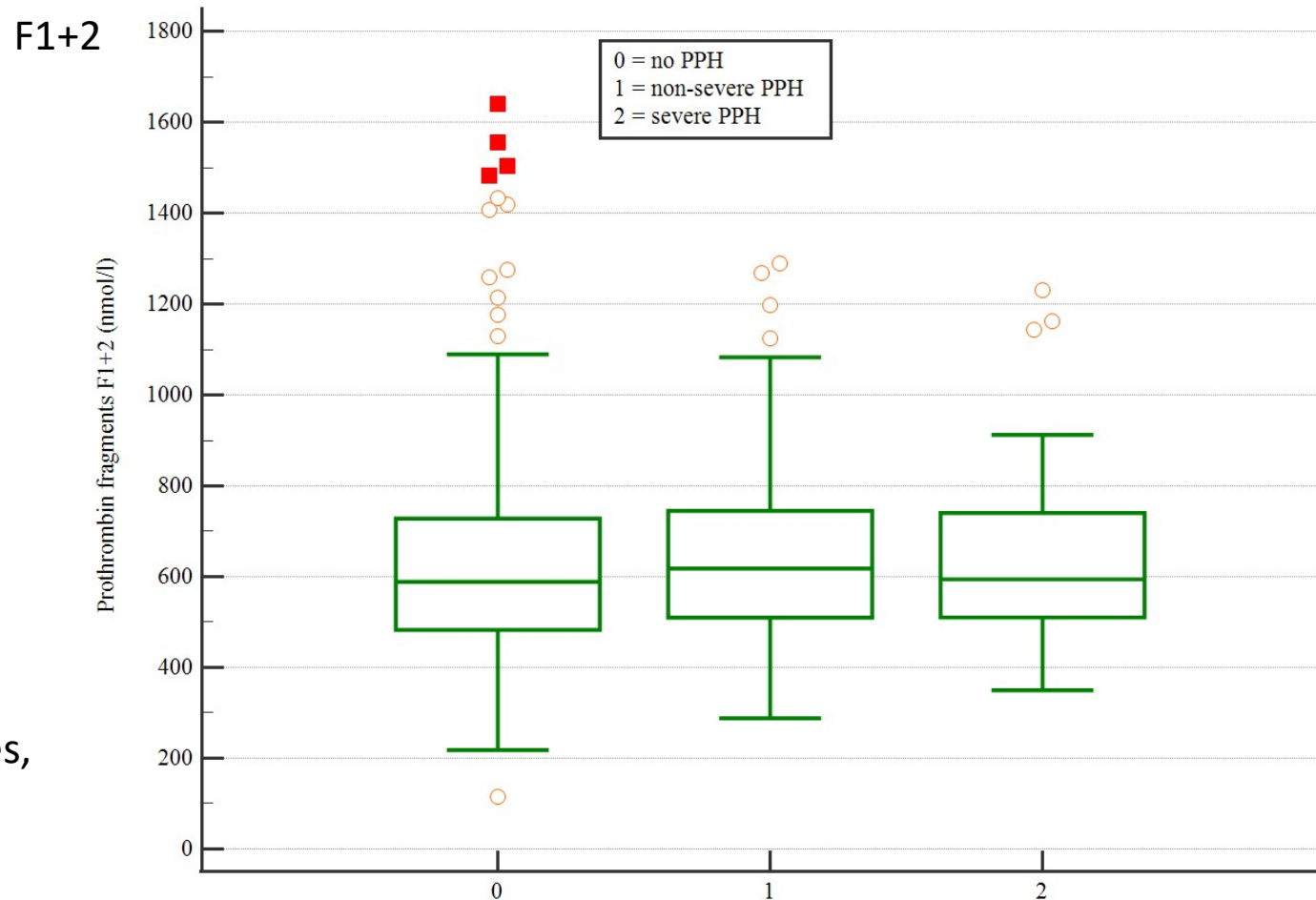
PPH1300 – result 8: prepartum PAP in no, non-severe and severe PPH



vaginal deliveries,
no significant
differences

Korte, Haslinger et al.,
GTH 2025

PPH1300 – result 9: prepartum F1+2 in no, non-severe and severe PPH



vaginal deliveries,
no significant
differences

Korte, Haslinger et al.,
GTH 2025

PPH1300 – result 10: pre- to postpartum course of coagulation parameters

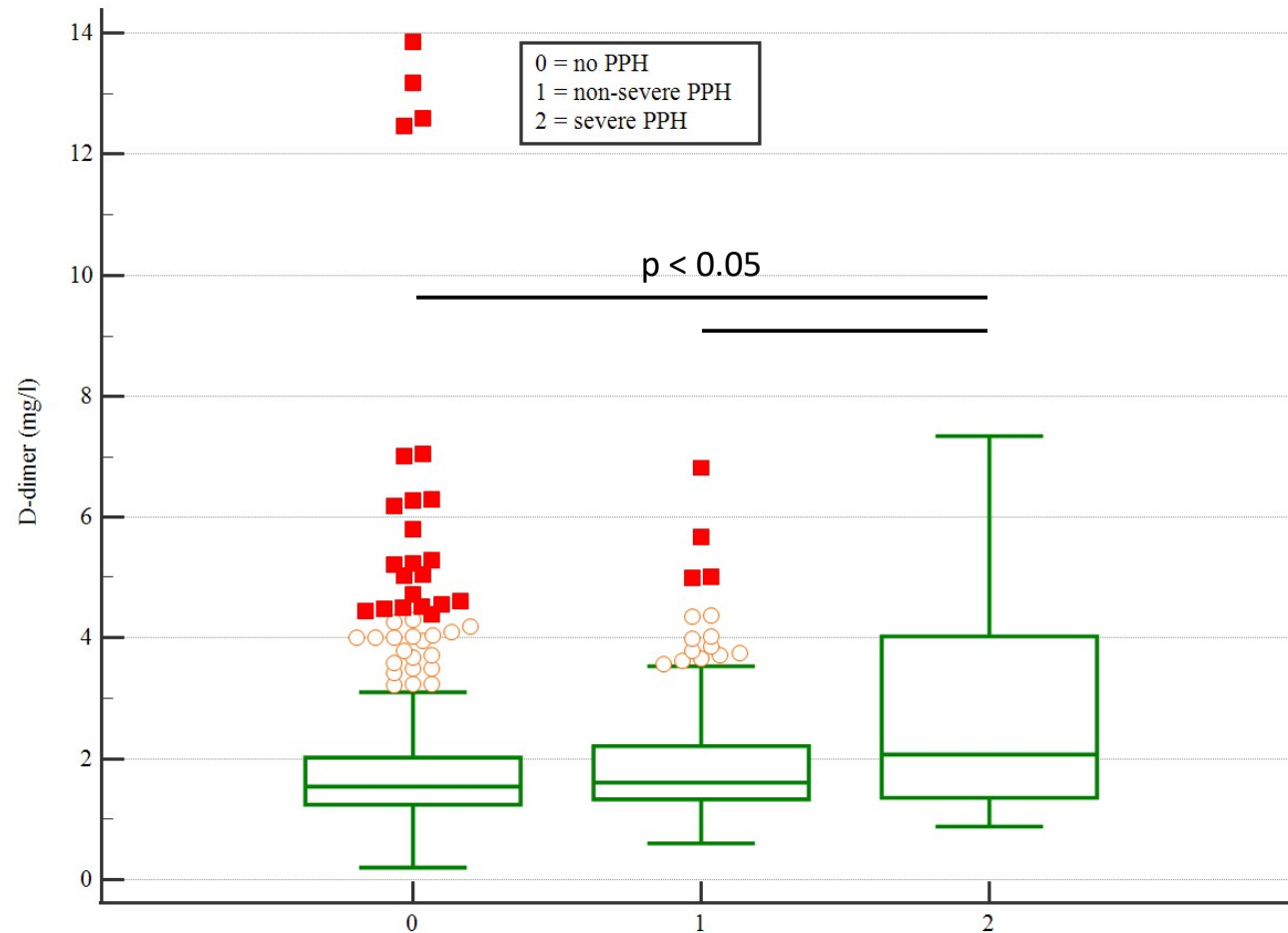
Results of coag studies in 10 different subsets evaluated

- grey rows: with PPH
- white rows: no PPH
- yellow: largest decrease of all coagulation components
- most pronounced decrease for FXIII in all subsets (10/10)
→ FXIII most sensitive to peripartum consumption/loss

	FIB ratio, % from prepartum	Plt. ratio, % from prepartum	F II ratio, % from prepartum	F XIII ratio, % from prepartum	p<0.05 for F XIII vs
No KEs, no PPH	0.95 - 5%	0.95 - 5%	0.92 - 8%	0.87 - 13%	Fib., Plt., F II
No KEs, PPH	0.92 - 8%	0.96 - 4%	0.89 - 11%	0.81 - 19%	Fib., Plt., F II
Atony, PPH	0.86 - 14%	0.94 - 6%	0.86 - 14%	0.76 - 24%	Fib., Plt.
Ret. Plac., no PPH	1.04 + 4%	0.95 - 5%	0.93 - 7%	0.92 - 8%	Fib.
Ret. Plac., PPH	0.84 - 16%	0.94 - 6%	0.84 - 16%	0.73 - 27%	Fib., Plt., F II
Lacerations, no PPH	0.88 - 12%	0.92 - 8%	0.87 - 13%	0.83 - 17%	Plt.
Lacerations, PPH	0.87 - 13%	0.97 - 3%	0.88 - 12%	0.80 - 20%	Fib., Plt., F II
> 1 KEs, PPH	0.80 - 20%	0.88 - 12%	0.76 - 24%	0.69 - 31%	Fib., Plt., F II
All, no PPH	0.95 - 5%	0.95 - 5%	0.91 - 9%	0.87 - 13%	Fib., Plt., F II
All, PPH	0.88 - 12%	0.95 - 5%	0.87 - 13%	0.79 - 21%	Fib., Plt., F II

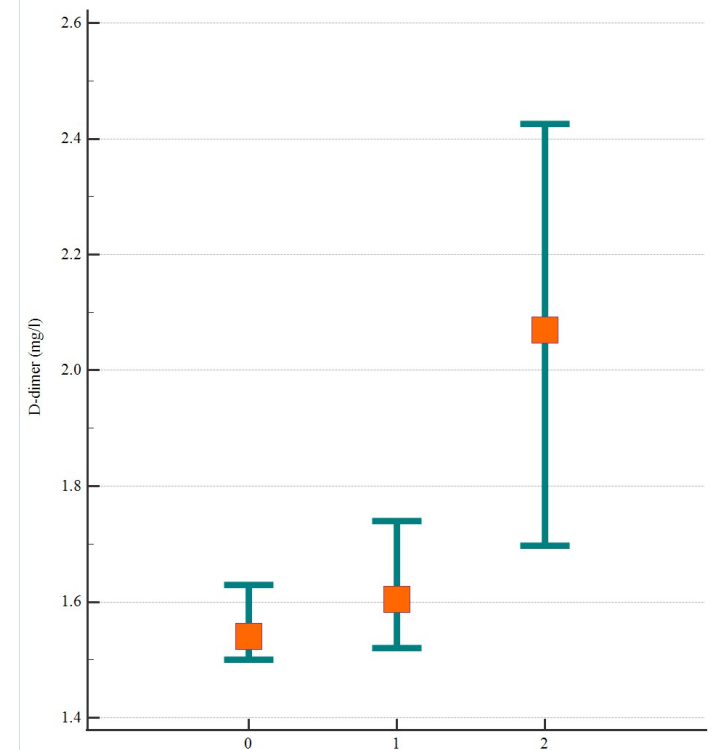
Korte et al., ASH, 2024

PPH1300 – result 11: prepartum D-dimer in no, non-severe and severe PPH



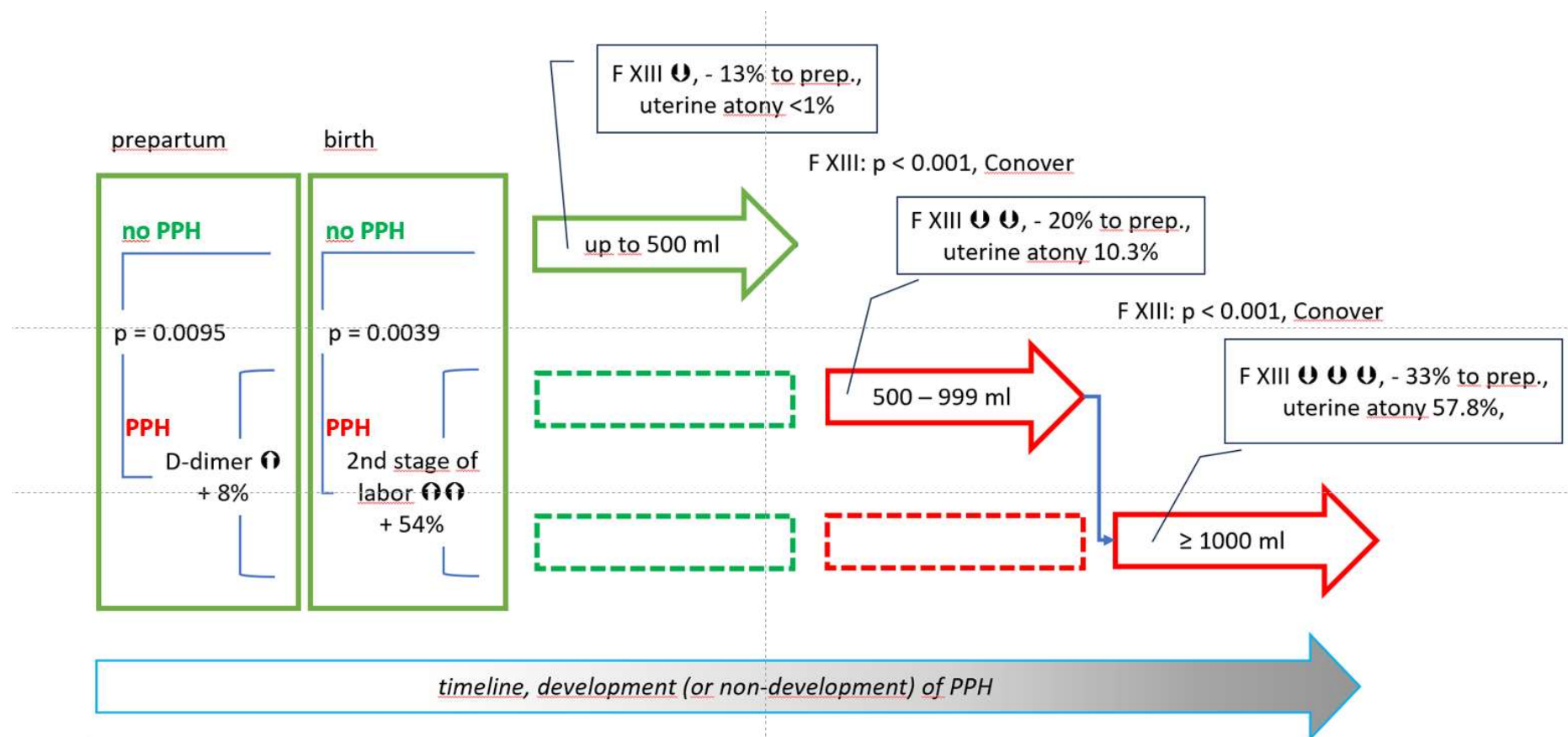
vaginal deliveries only

Kruskal-Wallis $p=0.002$



Korte, Haslinger et al., GTH 2025

The PPH1300 study – result 12: provisional new concept of a PPH genesis



Korte et al., ASH, 2024

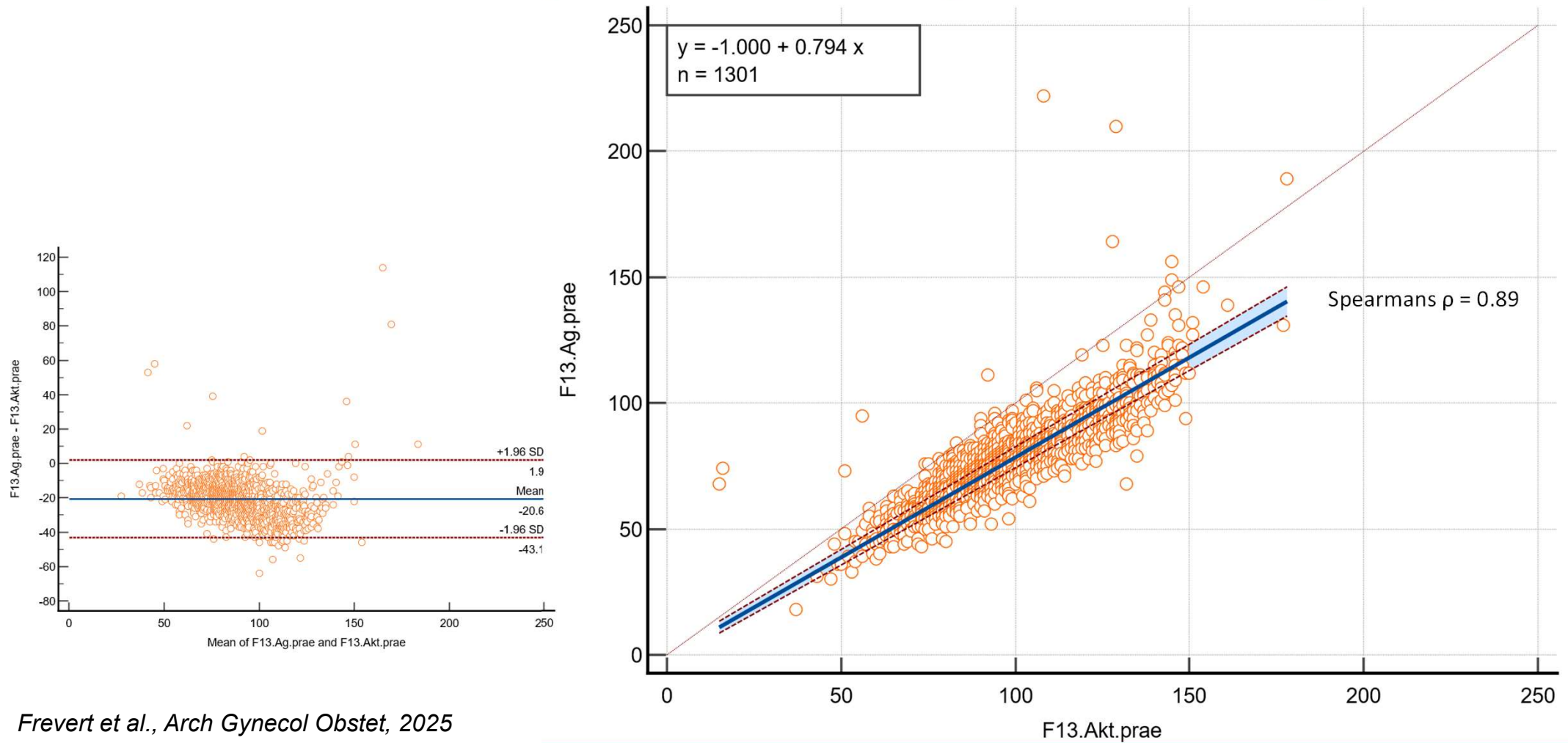
Conclusions

- **F XIII** is the coagulation factor **most susceptible to peripartum loss** and/or consumption (**>> F II > platelets > fibrinogen**) in patients **with or without PPH**
- **F XIII** has a **disproportional high tendency to peripartum loss** in relationship to the change in hemoglobin (loss and/or dilution)
- earlier modelling results suggest that increasing F XIII is able to reduce peripartum blood loss (and PPH accordingly), probably through more efficient clot formation
- → **F XIII is the prime candidate for (an) intervention (trial) in early haemostaseological therapy to improve outcome in women with PPH**

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PPH1300 – result 13: comparison of F XIII antigenetic and activity assay



Frevert et al., Arch Gynecol Obstet, 2025

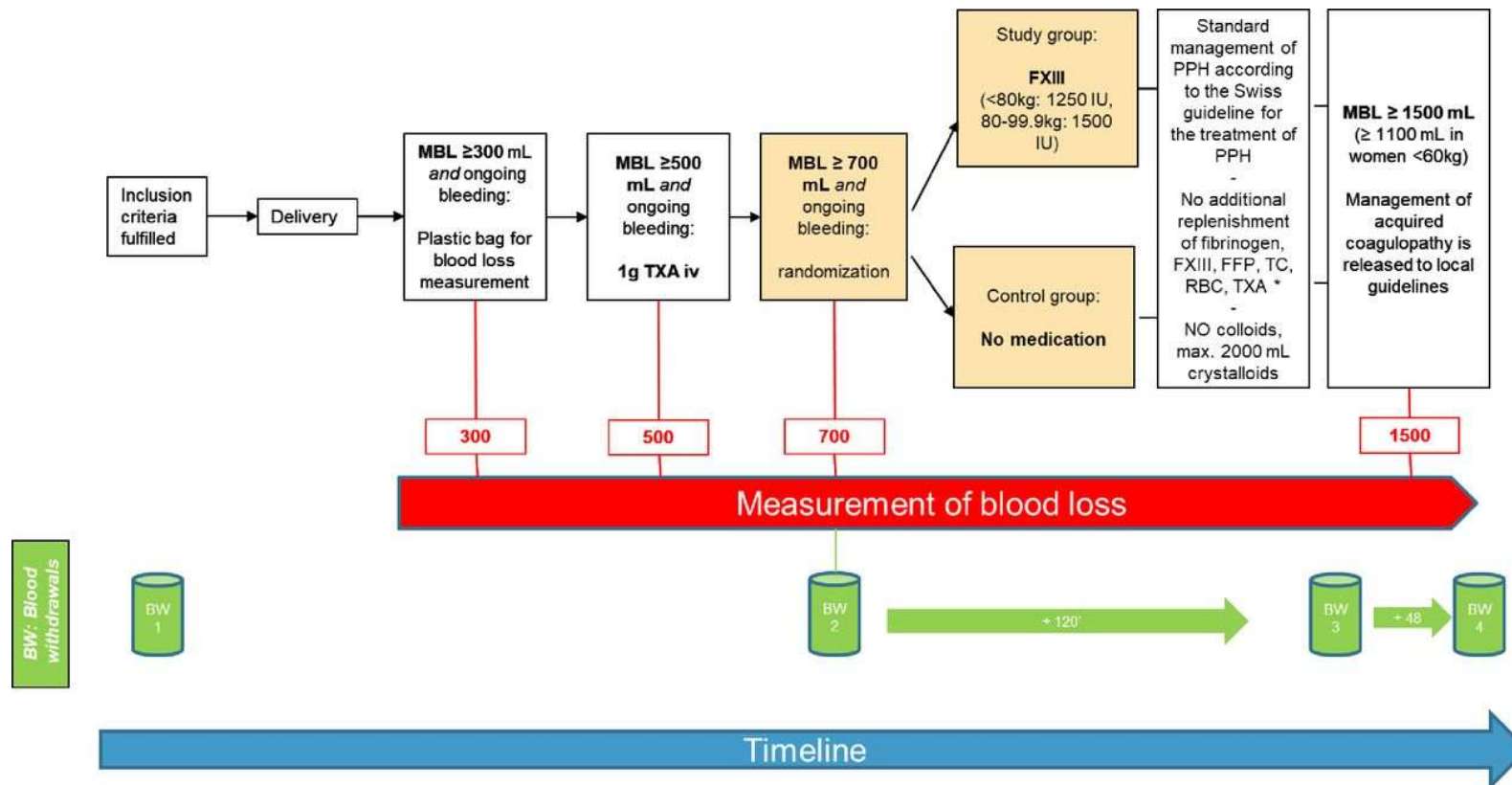
Randomized control trial: the SWiss Factor XIII Trial – SWIFT

BMJ Open Effects of early factor XIII replacement in postpartum haemorrhage: study protocol for a multicentre, open-label, randomised, controlled, investigator-initiated trial

Christian Haslinger ^{1,2} Torsten Hothorn ³ Verena Bossung,¹
Stylianos Kalimeris,¹ Elisabetta Ranieri,¹ Nicole Ochsenbein-Koelble,^{1,2}
Wolfgang Korte⁴

Haslinger et al., BMJ Open, 2025

Randomized control trial: the SWiss Factor XIII Trial – SWIFT



Haslinger et al., BMJ Open, 2025

Thank you!

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Justus Bürgi

Rita Bischof

Isabelle Kamm

***Zurich International
Symposium on Post Partum
Hemorrhage, www.usz.ch
October 24/25 2025***

***Haemostasis in Critical Care
www.hicc.ch, St. Gallen
April 24/25 2026***

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