



Les subtilités de l'anticoagulation en hémodialyse

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CHU REIMS

Technologie des Dialyseurs

Cellophane
(1940)

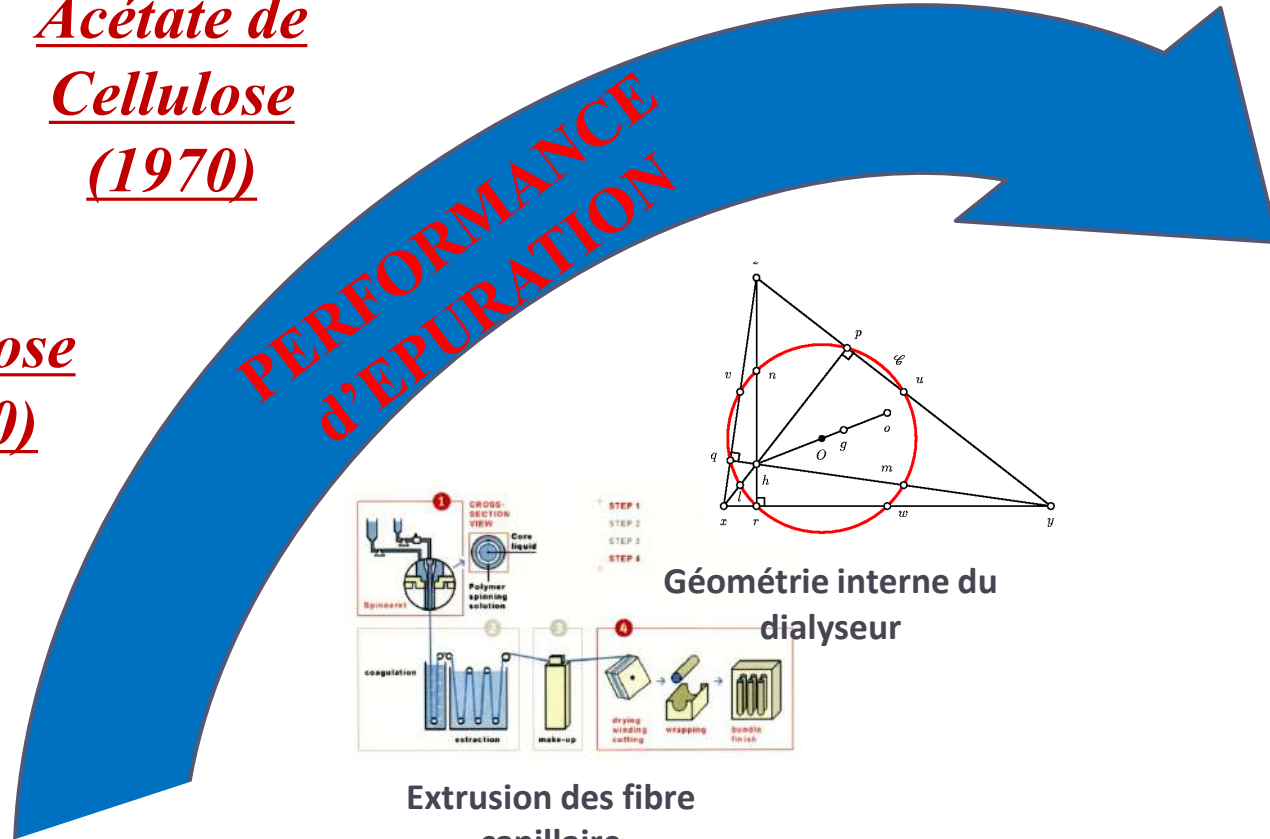


Cellulose
(1960)

Acétate de Cellulose
(1970)

Synthétique
(1980)

Synthétique HF
(2000)



- Membrane
- Agent stérilisant
- Dialysat

Inflammation Chronique

Intéraction Sang/Membrane

Activation du complément

-> Activation monocytes (IL-1, IL-6, TNF α)

Thrombose

- Agrégation plaquettaire
- Activation de la cascade de coagulation

BIO(IN)COMPATIBILITE
De la membrane

Urémie

(du patient)

Stress Oxydant

↑ Anémie

↑ Amylose β 2M

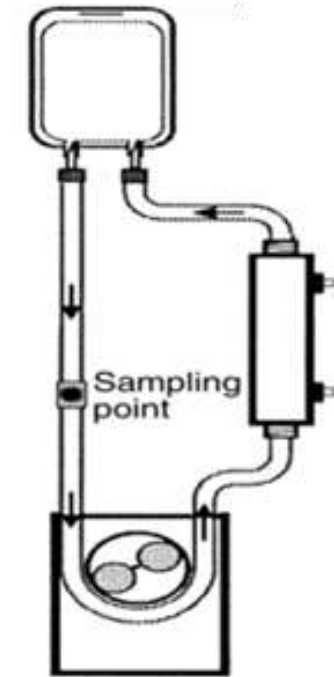
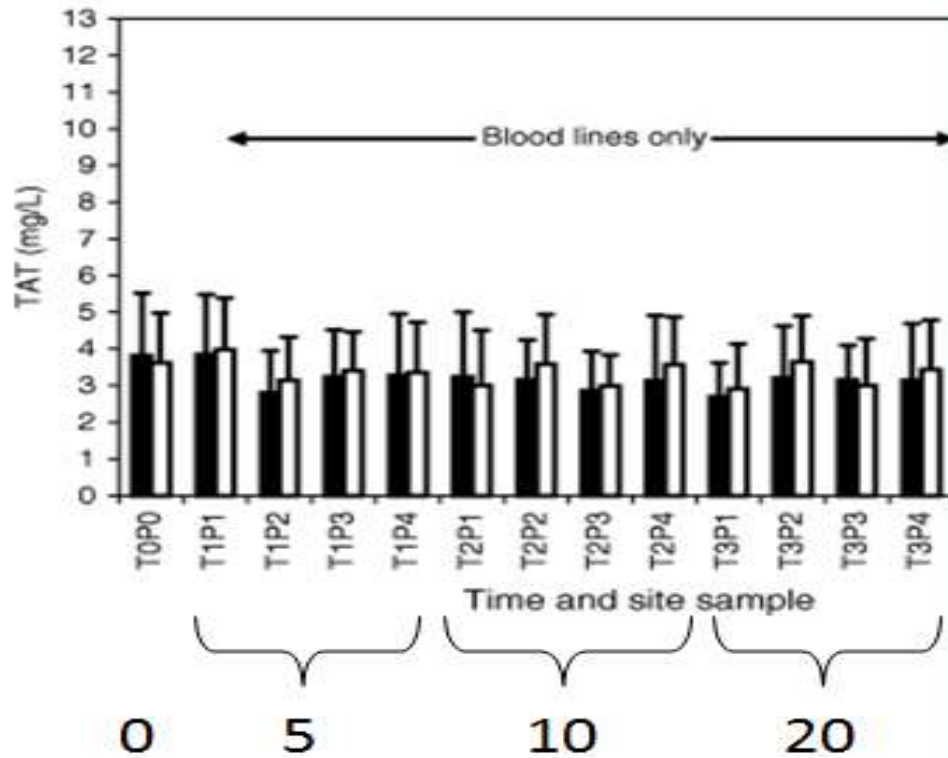
↑ Athérosclérose
accélérée

↑ Catabolisme
musculaire

Ce que l'on veut éviter...



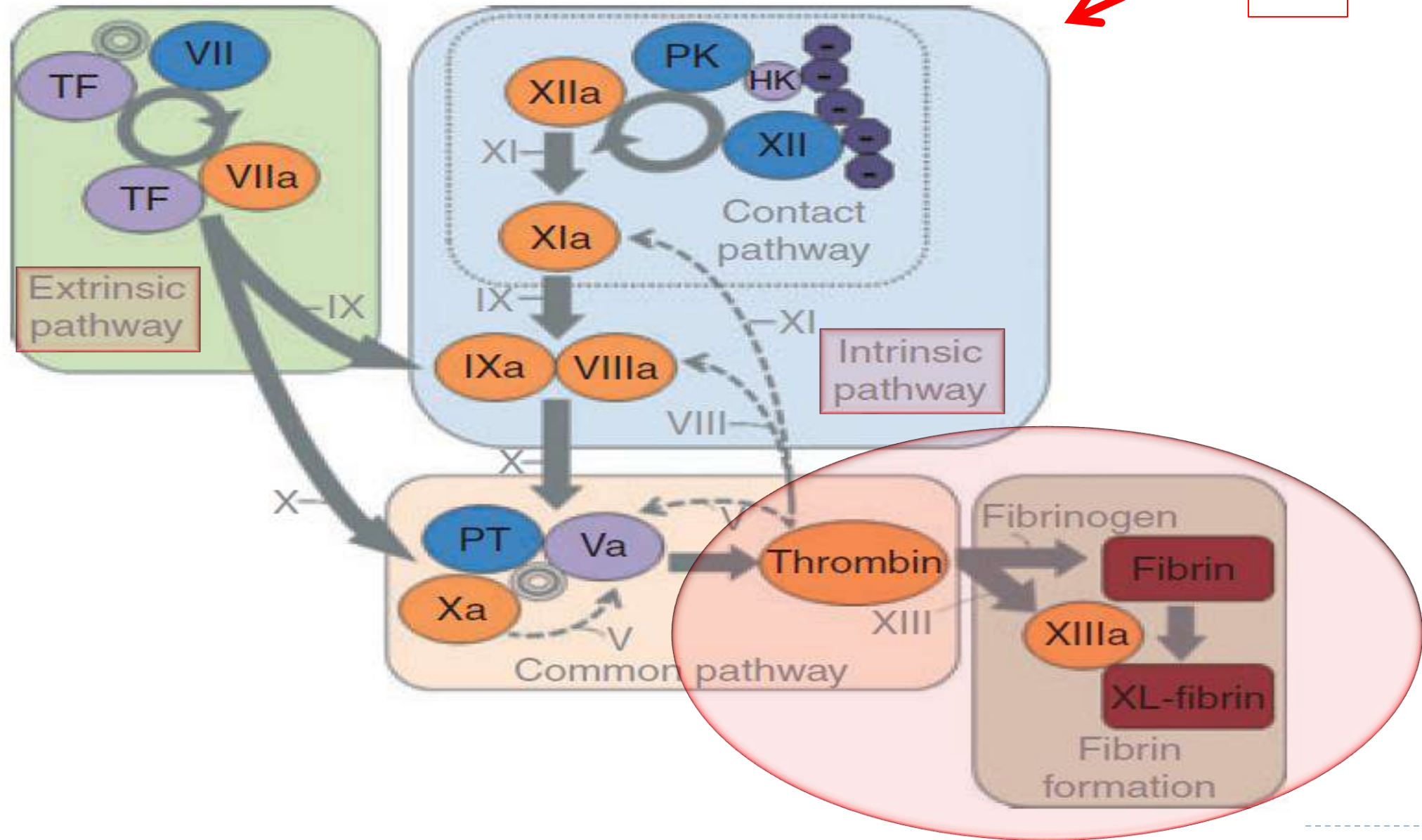
Circuit de dialyse : Ou cela coagule-t-il?



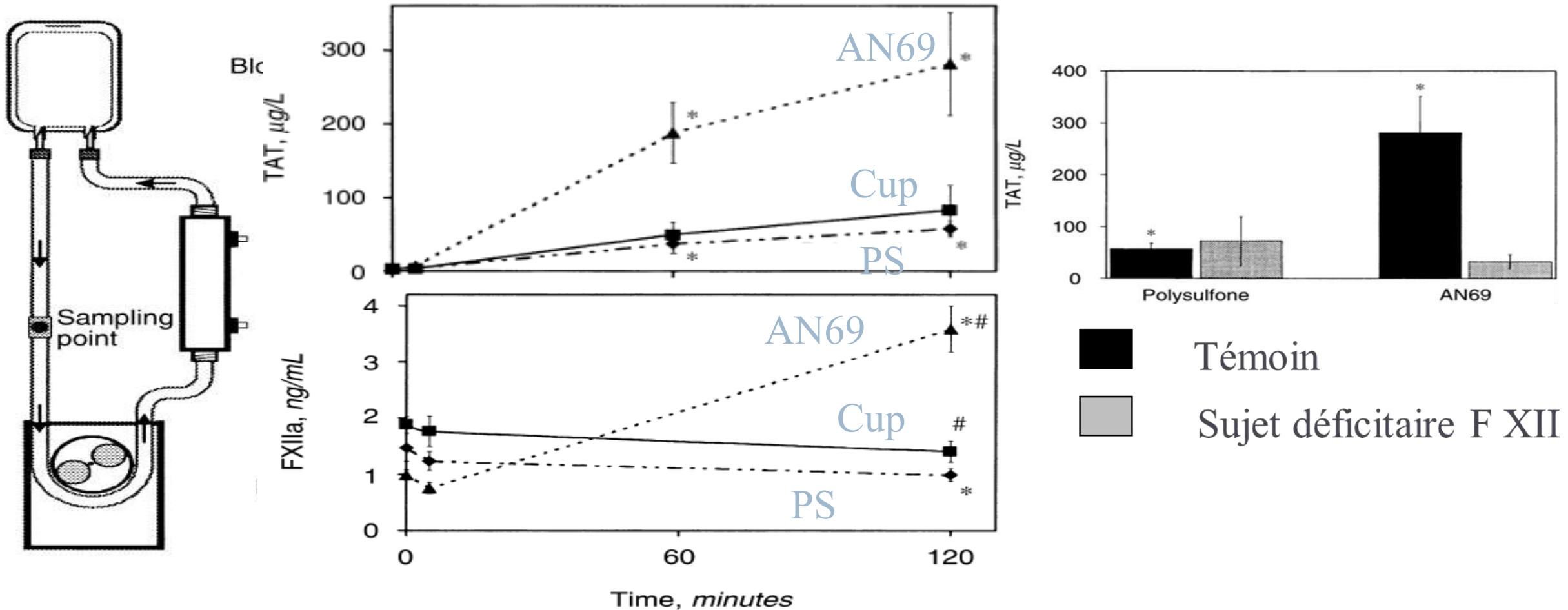
⇒ C'est la membrane qui, principalement, active la coagulation

2

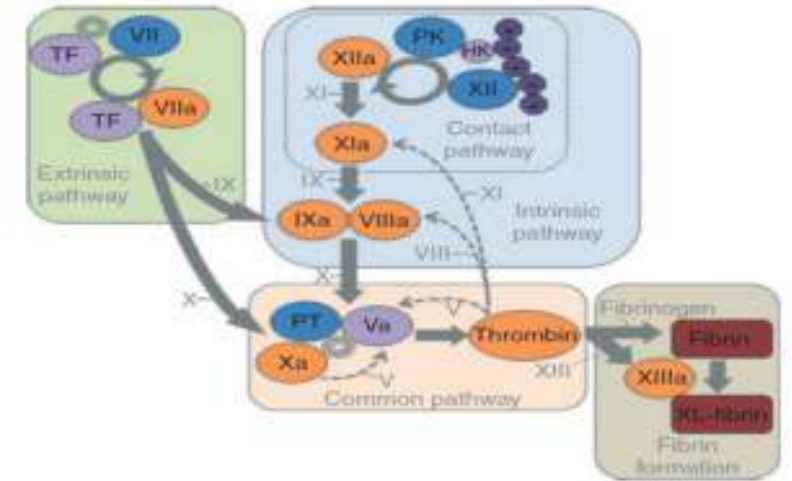
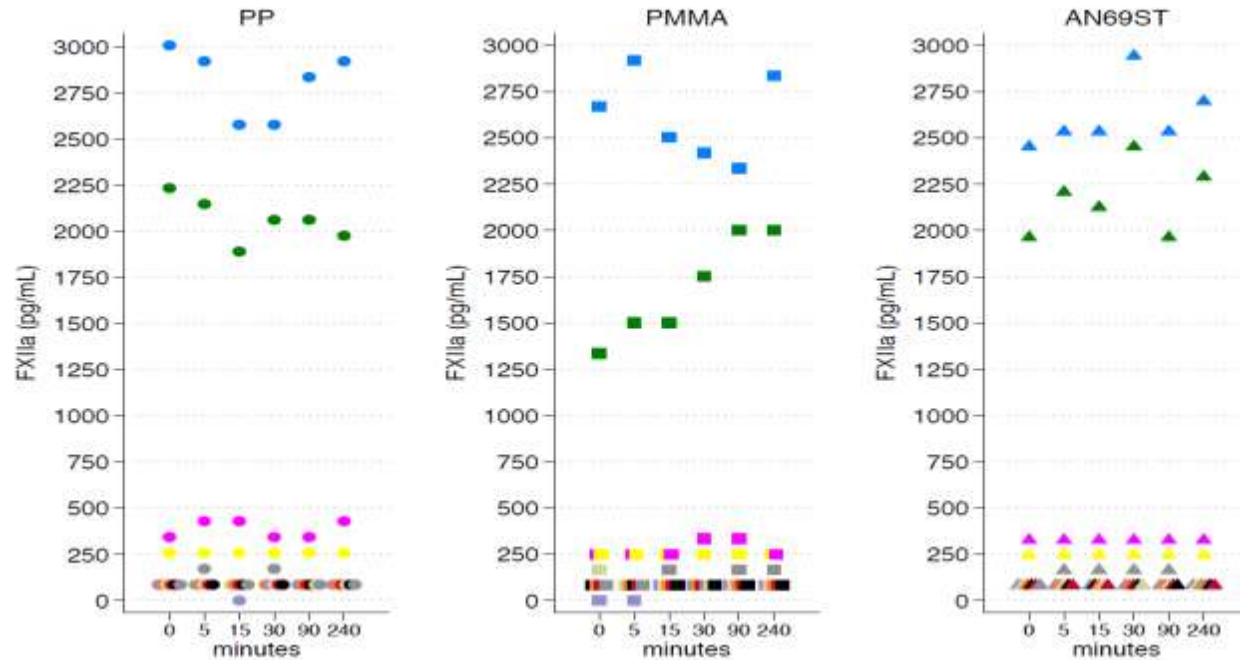
1



1- Voie Intrinsèque et Membrane



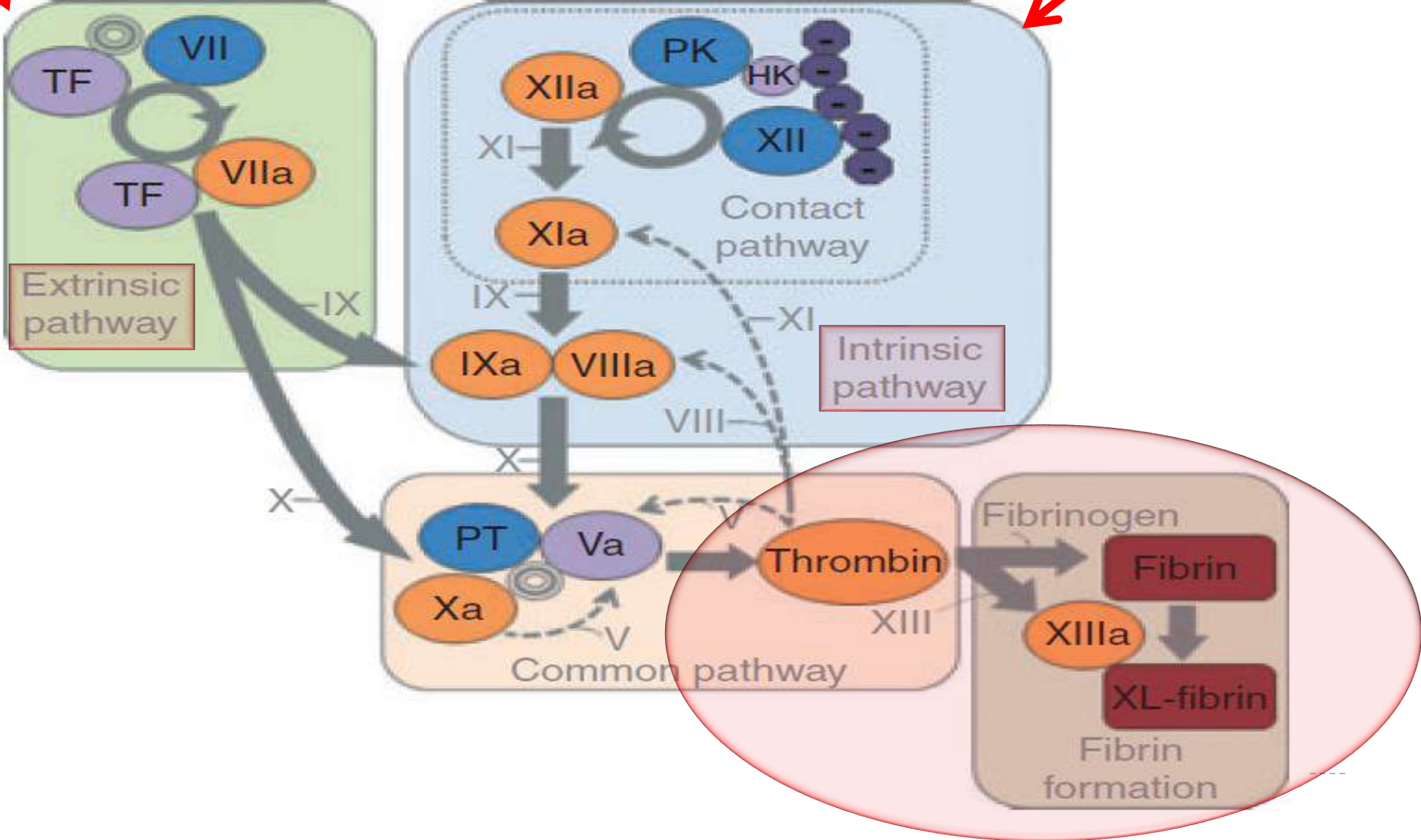
Cinétique Per Dialytique : F-XIIa



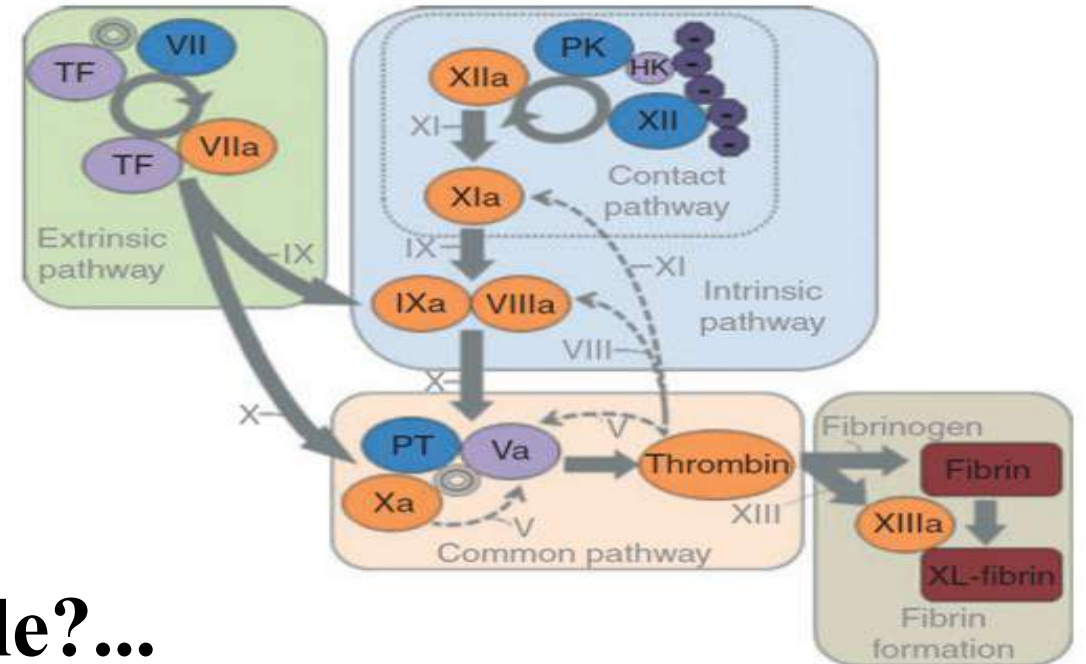
Coagulation marker	Dialyzer membrane	t0	t5	t15	t30	t90	t240
FXIIa (pg/ml)	PP	113 (82–335)	118 (90–415)	112 (62–422)	125 (82–303)	117 (87–307)	113 (89–448)
	PMMA	123 (84–231)	109 (81–268)	112 (87–290)	112 (91–308)	112 (71–343)	116 (82–289)
	AN69-ST	109 (68–303)	118 (96–328)	112 (87–347)	120 (92–318)	120 (95–345)	119 (88–356)

2

+/- Membrane

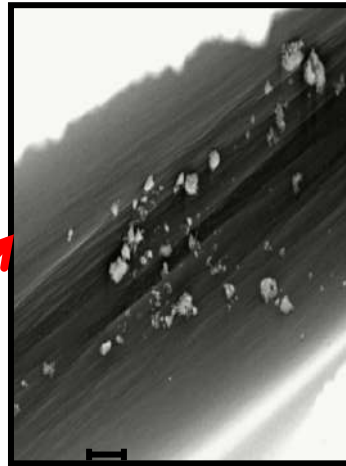


2- Facteur Tissulaire et Membrane

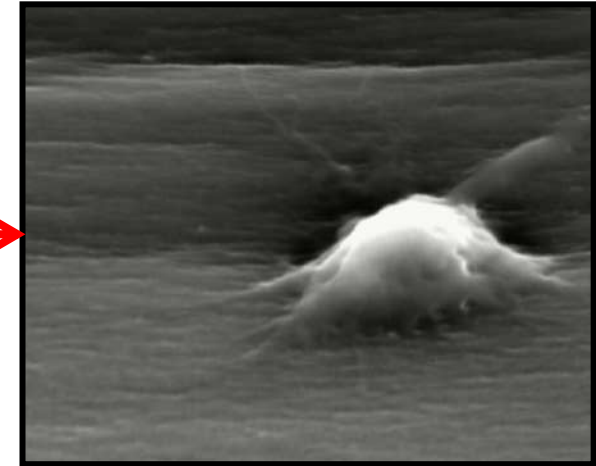


**Pourtant la membrane
n'est pas une cellule endothéliale?...**

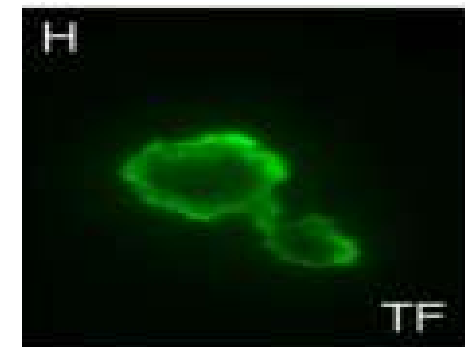
2- Facteur Tissulaire et Membrane



20 μm



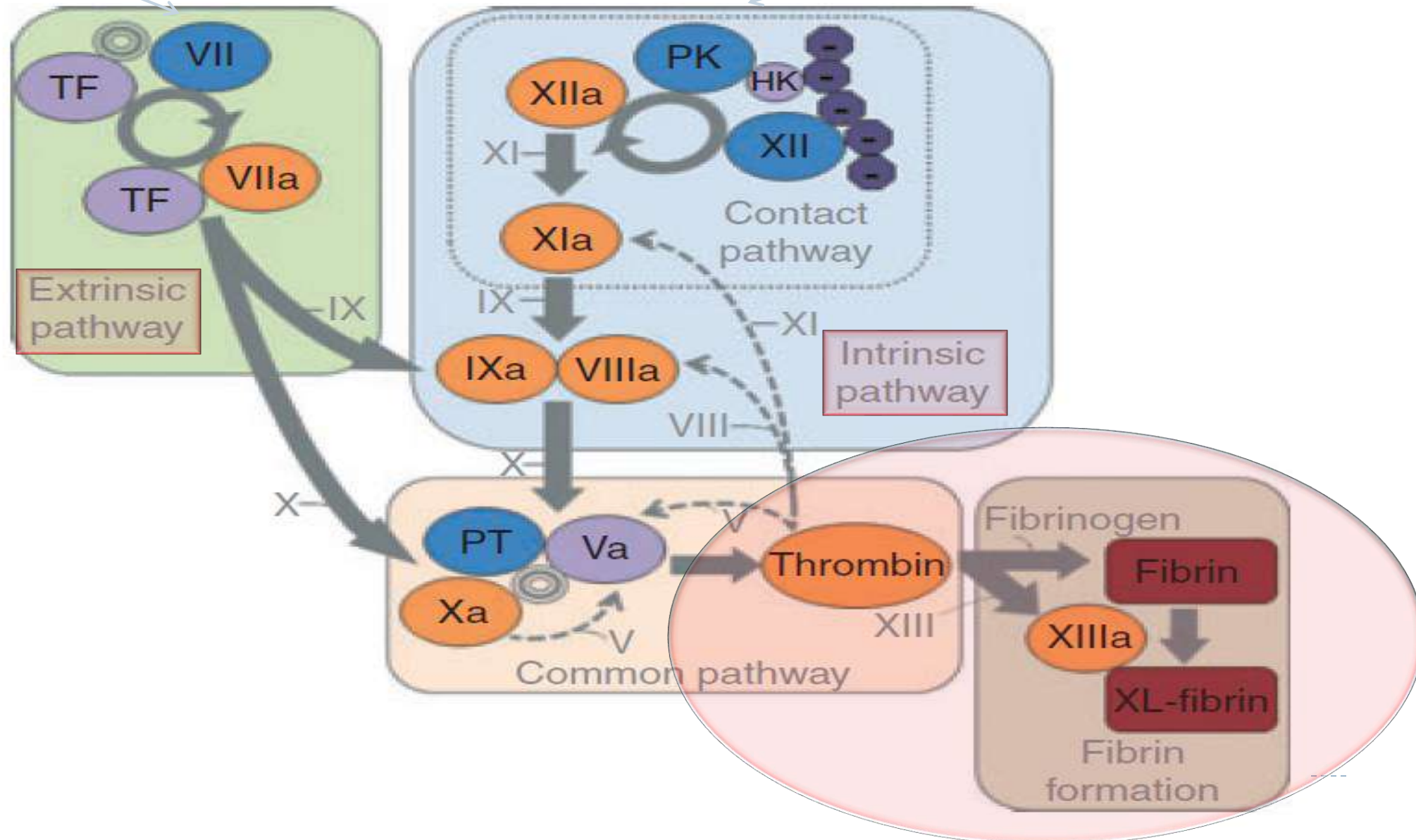
Cellules (PMNs,
monocytes, plaquettes)
et microparticules
adhérentes au dialyseur



*mAb anti-
TF*

Cellules (PMNs, monocytes, plaquettes)
et microparticules adhérentes au dialyseur

Membrane





Que faire?

Les (vieilles) recommandations

V.2 Prevention of clotting in the HD patient with normal bleeding risk

Guideline V.2.1

A. In patients without elevated bleeding risk low-dose unfractionated heparin or LMWH can be used to prevent clotting of the extracorporeal system during haemodialysis.

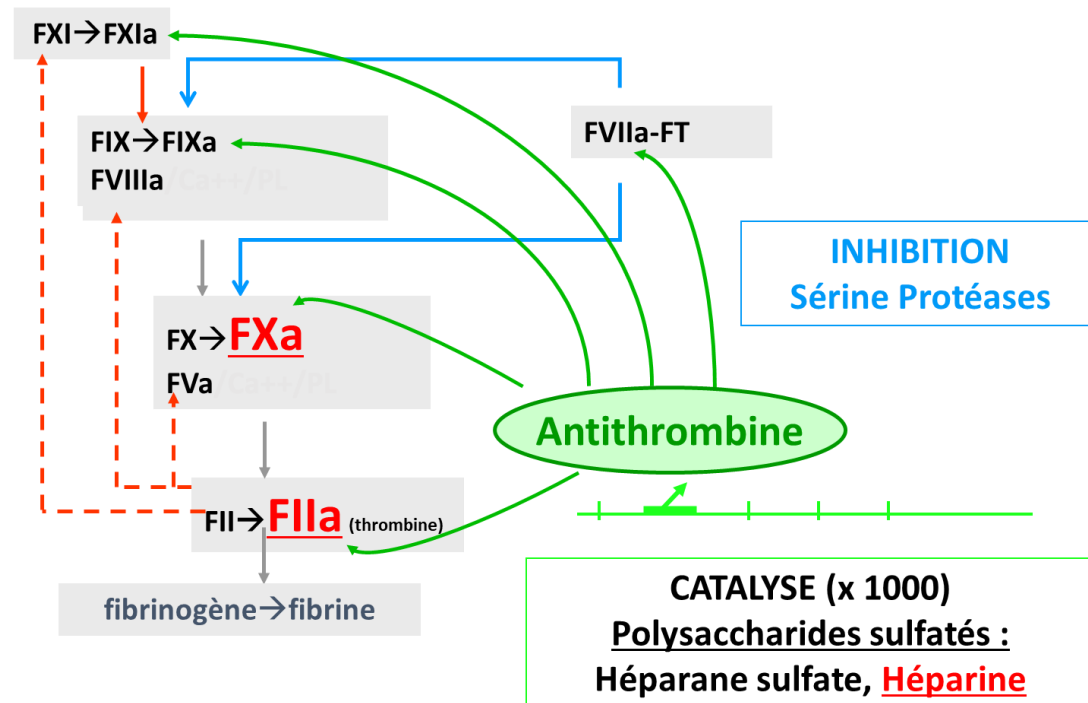
(Evidence level: A)

Guideline V.2.2

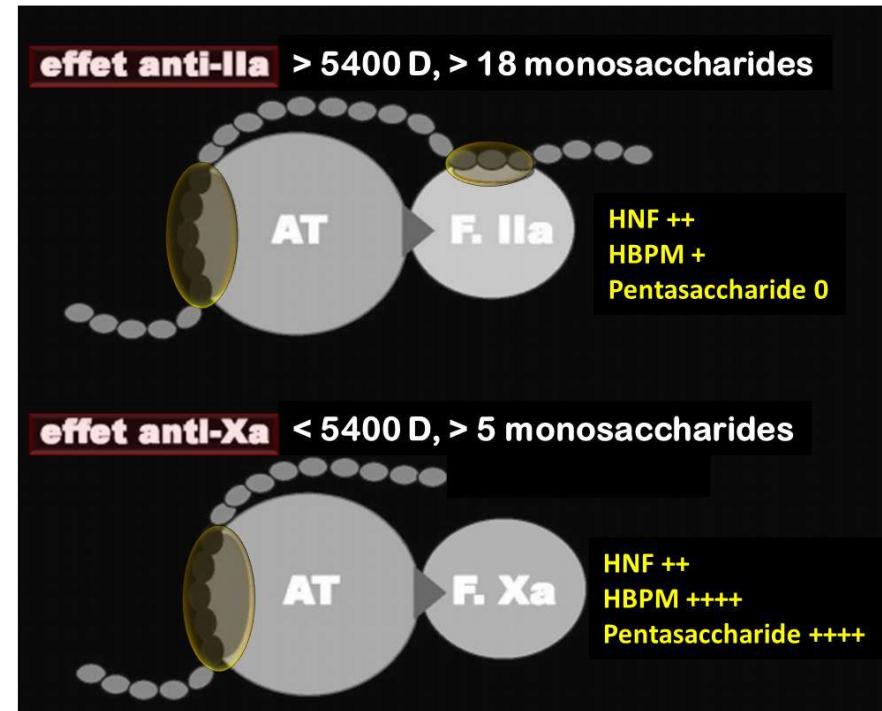
A. Because of proven safety (evidence level: A), equal efficacy (evidence level: A), and easy handling (evidence level: C) the use of LMWHs is to be preferred over unfractionated heparin. Other benefits of LMWH are an improved lipid profile (evidence level B), less hyperkalaemia (evidence level: B) and less blood loss
(Evidence level: C).

Les HEPARINES

La solution historique



Un « Mélange » de glycoaminoglycanes



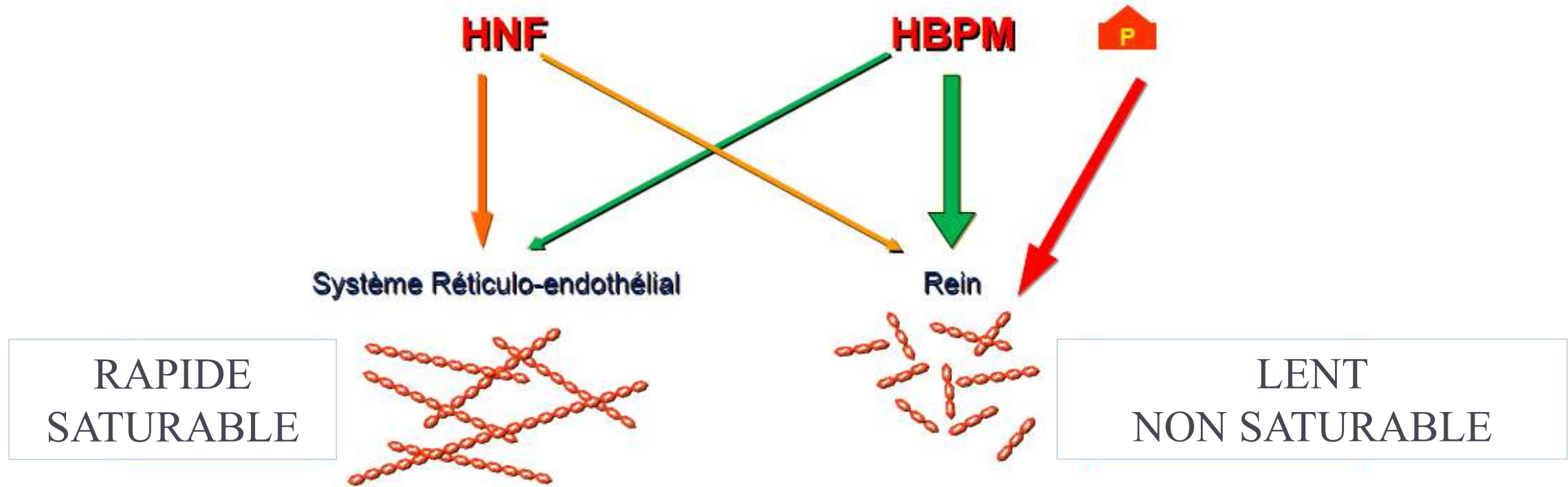
HNF

- 4 à 30 kD
- ≈ 45 monosaccharides
- TCA et héparinémie

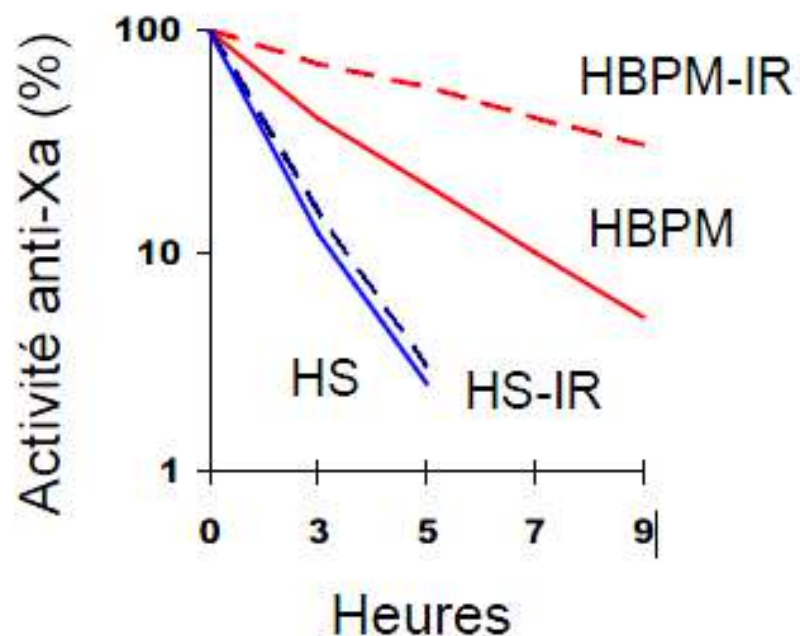
HBPM

- 2 à 9 kD
- ≈ 15 monosaccharides
- Anti Xa

Elimination des dérivés hépariniques



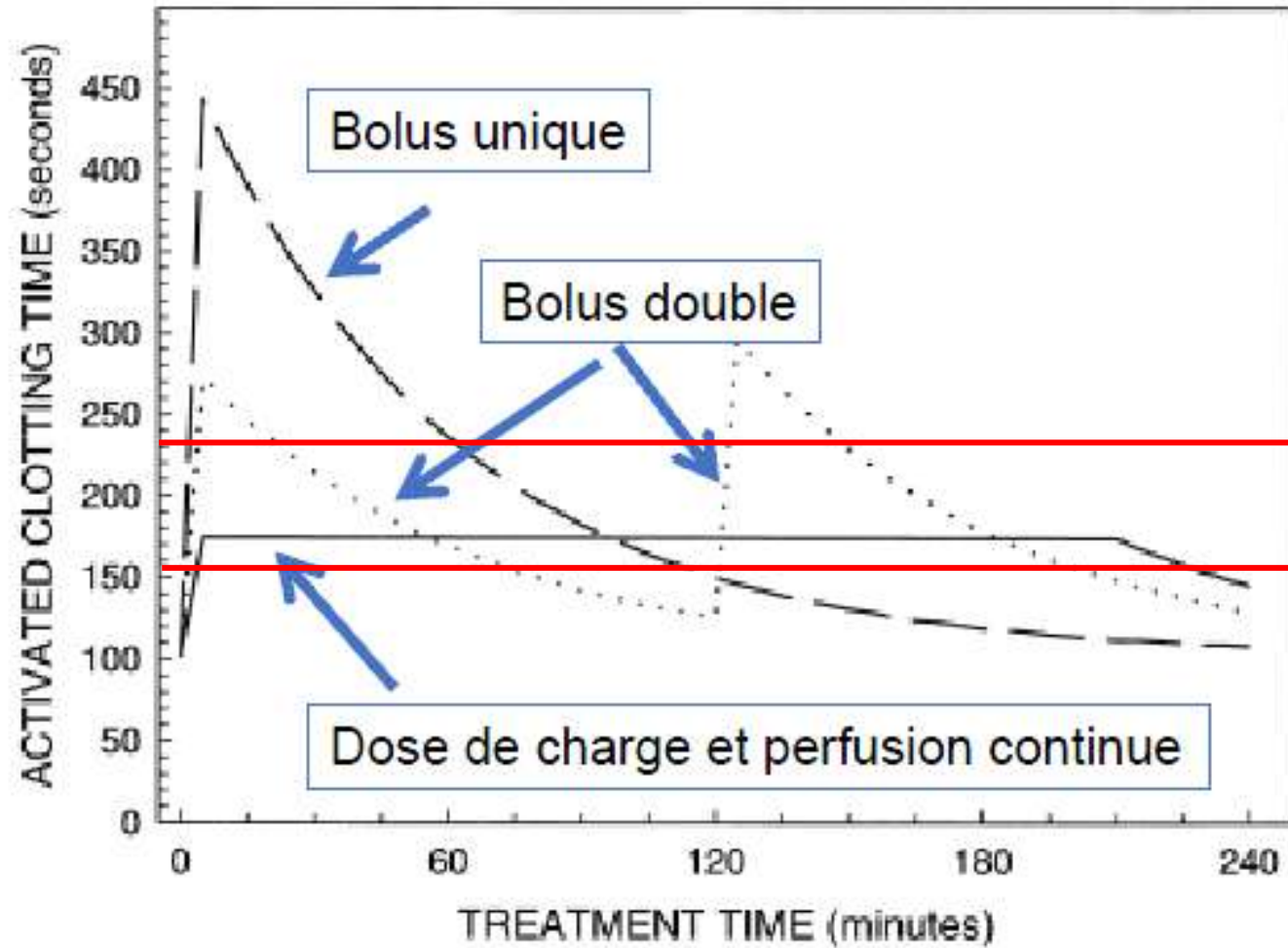
$\frac{1}{2}$ vie des Héparines en Hémodialyse



▶ HNF : $\frac{1}{2}$ vie non modifiée

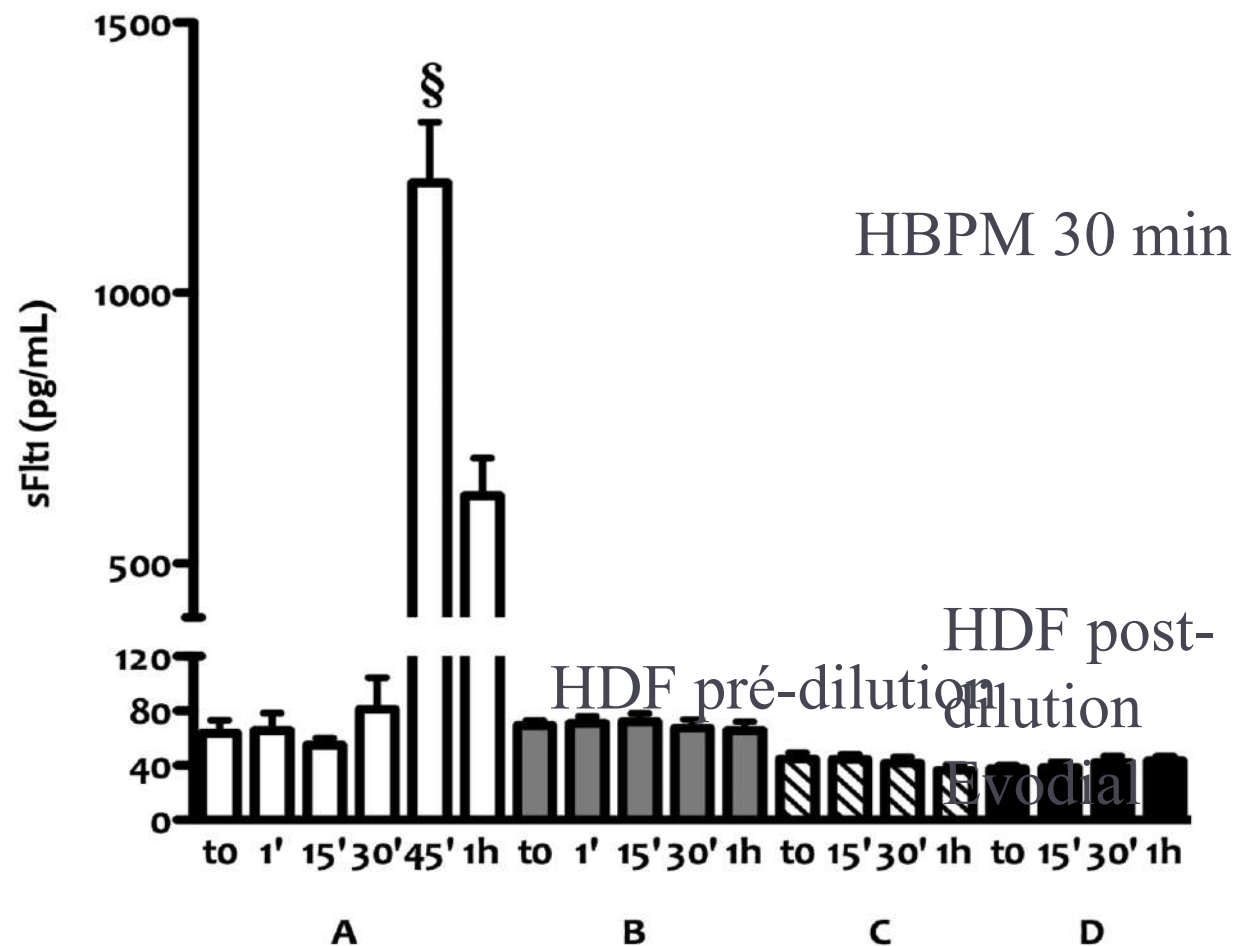
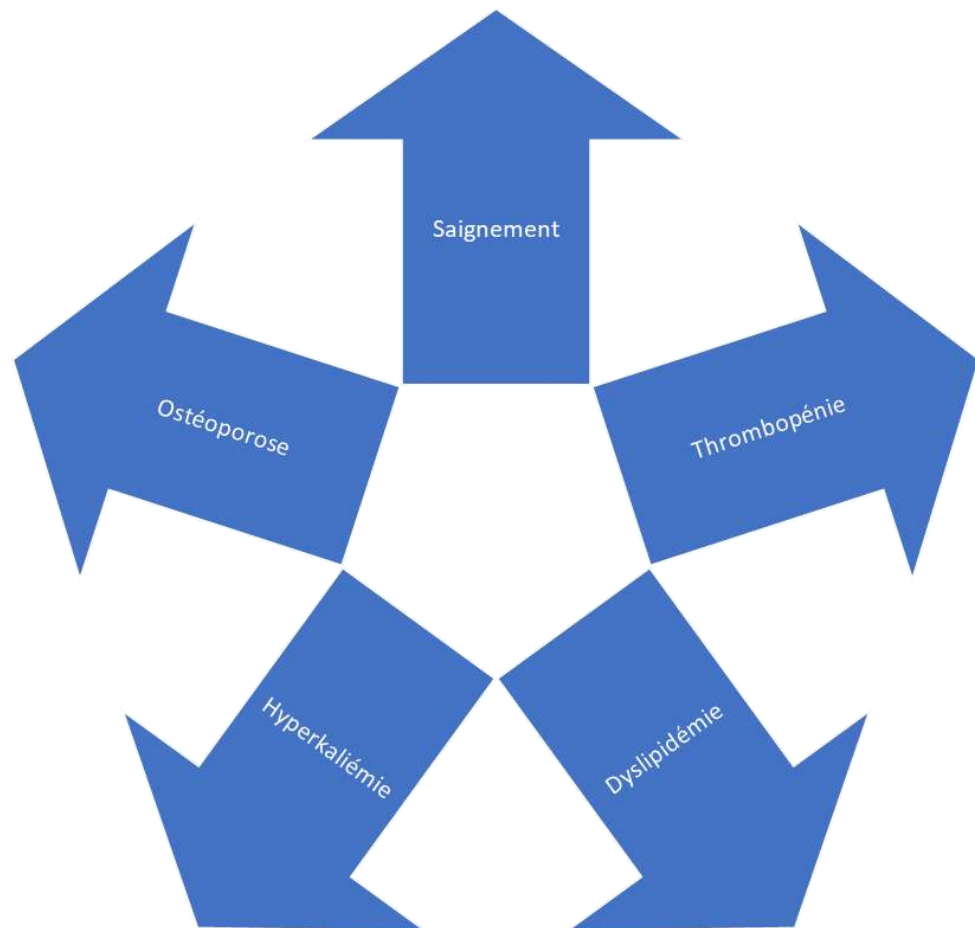
▶ HBPM : $\frac{1}{2}$ vie x 2

Bolus ou continue ?



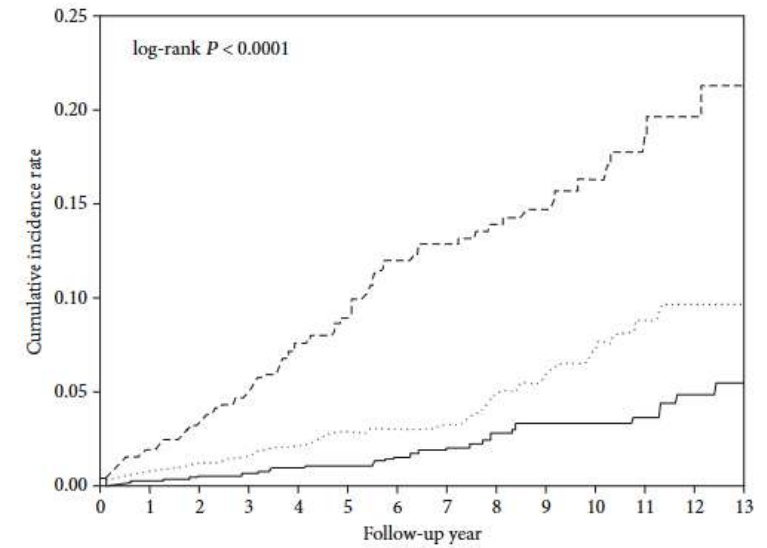
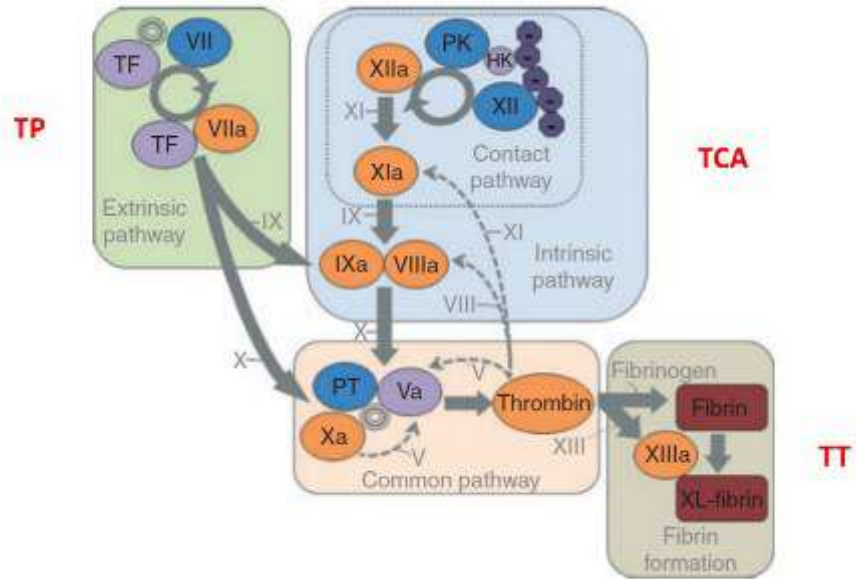
*Zone
Thérapeutique
0,3-0,7*

L'héparine à long terme...



Le problème

Un circuit qui coagule
Un patient qui saigne



Patients at risk

Control	1148	1133	1090	1051	985	898	799	699	575	478	366	275	171	4
Dialysis CKD	574	551	518	481	437	385	320	272	220	174	126	92	53	2
Dialysis-free CKD	1148	993	824	753	649	563	478	389	290	244	188	122	66	0

FIGURE 2: Cumulative incidence of lower gastrointestinal bleeding in dialysis CKD, dialysis-free CKD, and control groups.

Table III Thrombin Generation Time Parameter Estimates Following a Single-Dose of Enoxaparin 1 mg/kg

Parameter	Control (n = 8)	HD (n = 8)	PD (n = 8)	P Value
TGT _{baseline} , min	4.3 ± 0.8	4.3 ± 1.3	4.3 ± 1.7	NS
TGT _{max} , min	10.8 ± 1.8	13.0 ± 4.5	12.8 ± 2.9	.001 ^a
TGT AUEC ₀₋₁₂ , min/h	91.3 ± 14.3	115.8 ± 34.6	122.6 ± 28.3	.07
TGT _{12h} - TGT _{baseline} , min	0.8 ± 1.0	3.9 ± 1.3	3.9 ± 1.8	.002 ^a

Data presented as mean ± SD. TGT, thrombin generation time; HD, hemodialysis; PD, peritoneal dialysis; NS, not significantly different; TGT_{max}, maximal TGT effect; AUEC₀₋₁₂, area under the effect-time curve from 0 to 12 hours; TGT_{12h} - TGT_{baseline}, difference in TGT at 12 hours compared to the baseline TGT.

a. Both hemodialysis and peritoneal dialysis groups are significantly different from the control group.

Gestion du Risque hémorragique en Hémodialyse

▶ Quelle situation?

- ▶ Péri-Opératoire (Neurochirurgie, ...)
- ▶ **Saignement** actif ou dans les 7j (digestif, rétinien, ...)
- ▶ AVC récent (hémorragique ou non), Malformation vasculaire cérébrale
- ▶ **HTA non contrôlée**
- ▶ **AVK**, trouble de la coagulation...
- ▶ Cathéter épidural, PBR, ...

Kessler et al., Seminars in Dialysis, 2015 pp. 474–489

Shen JI et al., Nephrol Dial Transplant 2013; 28: 1589–1602.

EBPG, Nephrol Dial Transplant 2002; 17(suppl 7): 63–71.

Kidney International Supplements (2012) 2, 8–12 11

Gestion du Risque hémorragique

éviter une anticoagulation systémique pour éviter une thrombose « localisée »

▶ Quelles solutions?

▶ **Titrer à la baisse** => pratique hétérogène +++ et le risque persiste

▶ Héparine (art.)/Protamine (vei.)

▶ **Membranes**

Bioactives

Modification Physicochimique

▶ ~~Rincage~~ au NaCl 0,9% à intervalle régulier

▶ **HDF en mode Prédilution**

▶ **Anticoagulation au(x) citrate(s) avec ou sans calcium**

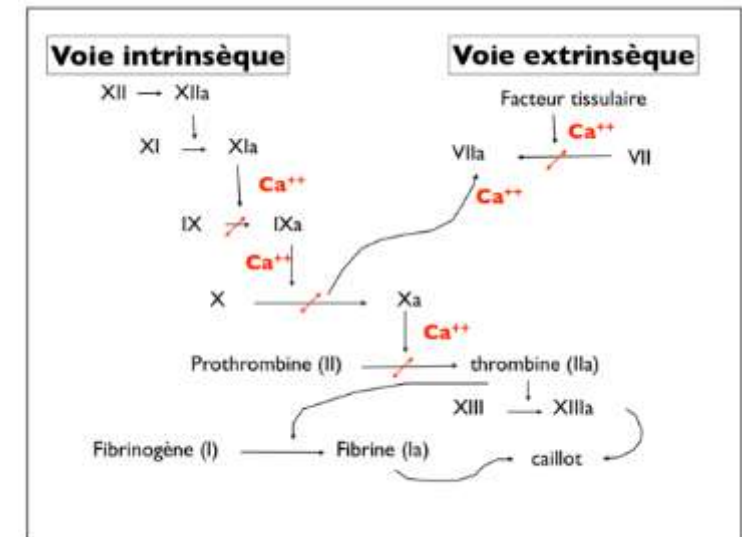
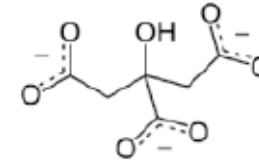
Kessler et al., Seminars in Dialysis, 2015 pp. 474–489

Shen JJ et al., Nephrol Dial Transplant 2013; 28: 1589–1602.

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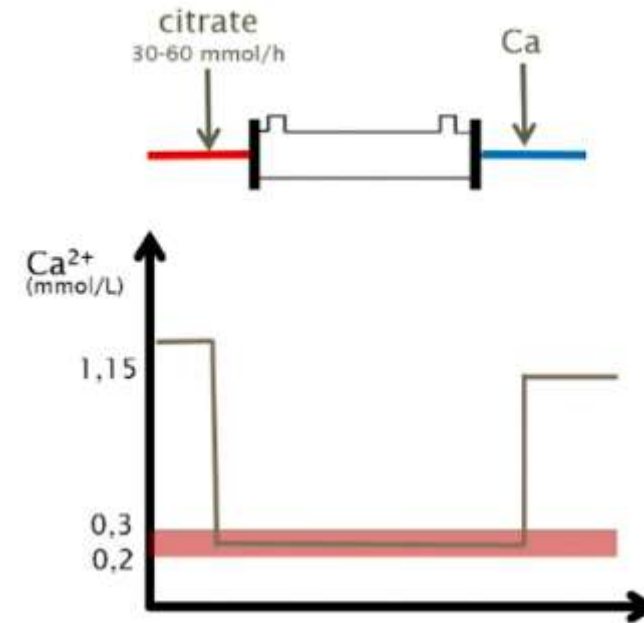
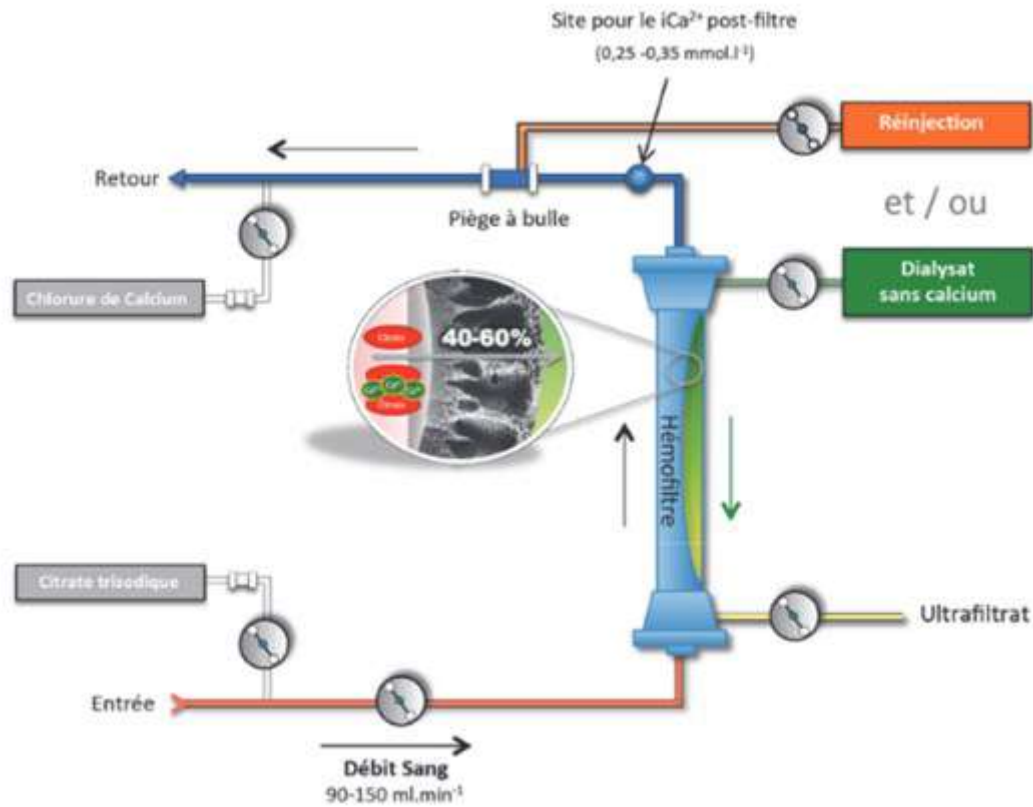
Pourquoi le citrate?

- ▶ Parce qu'il chélate le calcium ++
- ▶ Calcium co-facteur indispensable
 - ▶ Enzyme de la coagulation
 - ▶ Activation plaquettaire...



Anticoagulation Régionale au citrate

Citrate + dialysat sans calcium



Risque de l'utilisation du citrate

- ▶ **Hypernatrémie**

- ▶ Citrate trisodique

- ▶ **Alcalose**

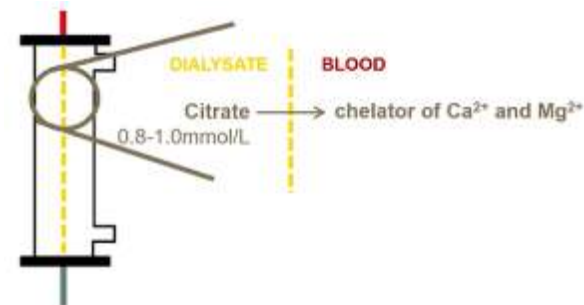
- ▶ Transformation en bicarbonate

- ▶ **Hypocalcémie et Hypomagnésémie**

- ▶ Si surdosé

- ▶ **Hypercalcémie**

- ▶ Si compensation mal ajustée



« Des » dialyses au citrate

Citrate + dialysat AVEC calcium

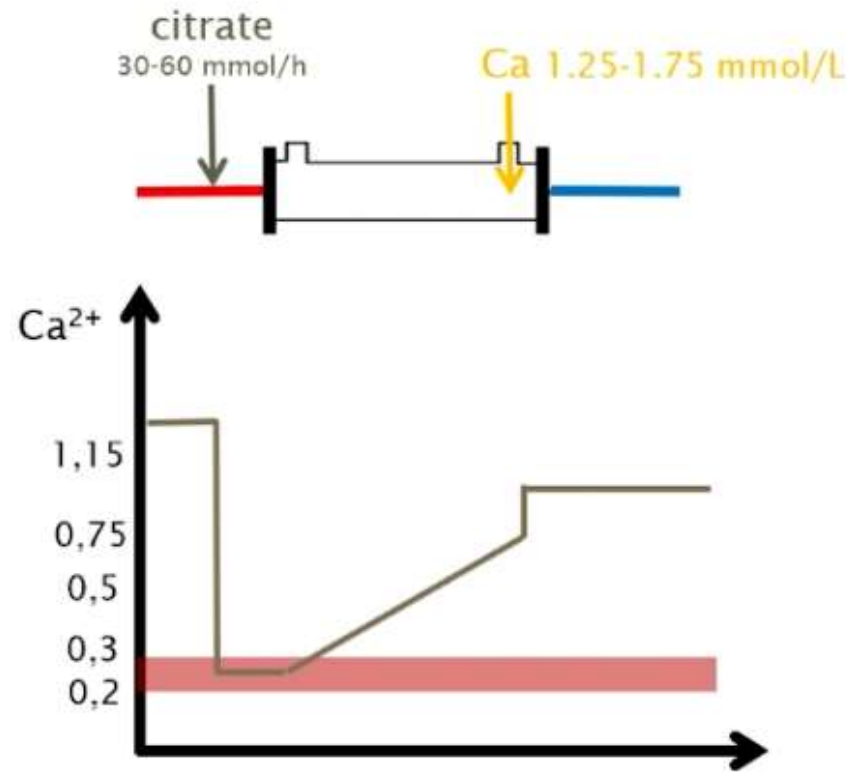


Table 3. Clotting and Thrombus Formation in Stable Chronic Hemodialysis Patients During Citrate and Heparin Anticoagulation

	Citrate Dialysis No. (%)	Heparin Dialysis No. (%)	<i>P</i> Value
Clotting phenomena	6 (32)	1 (5)	0.036
Thrombus formation			0.24
Clean	11 (58)	13 (68)	
Moderate blood clots	3 (16)	5 (26)	
Full of blood clots	5 (26)	1 (5)	
Early termination of dialysis session due to clotting or thrombus formation	2 (11)	0 (0)	0.15

75 mmol/h, n = 19, PS

« Des » dialyses au citrate

Citrate + dialysat AVEC calcium

Table 3. Clotting Phenomena

	AN69ST	RCA-Ca0	RCA-Ca3.0	P
No. of sessions	31	32	30	
Clotting events	14 (45) ^a	1 (3) ^a	5 (17)	<0.05
Clotting events necessitating early termination	12 (39) ^a	0 (0) ^a	4 (13)	<0.005
Time to clotting (min)	181 (135-235)	30	172 (18-223)	
Dialysis duration (min)	220 ± 32 ^a	240 ± 0 ^a	236 ± 12	<0.005
Clotting score dialyzer	2.7 ± 1.0 ^{a,b}	1.1 ± 1.0 ^a	1.5 ± 1.0 ^b	<0.0001
Clean, white (%)	0	6.5	10.7	<0.0001
White, limited fibrin deposits, head of dialyzer (%)	16.7	77.4	42.9	
White, mild fibrin deposits, head and along body dialyzer (%)	20.0	12.9	32.1	
Completely clotted, rinse back successful (%)	43.3	3.2	10.7	
Completely clotted, rinse back unsuccessful (%)	20.0	0.0	3.6	
Clotting arterial expansion chamber (%)	76.7 ^{a,b}	22.6 ^a	14.3 ^b	<0.0001
Clotting venous expansion chamber (%)	86.7 ^a	12.9 ^{a,b}	75.9 ^b	<0.0001

Note: Values expressed as number (percent), mean (range), or mean ± SD.

^{a,b}Parameters with same suffix differ significantly (analysis of variance).

Pourcentage de Réussite 61% 100% 87%

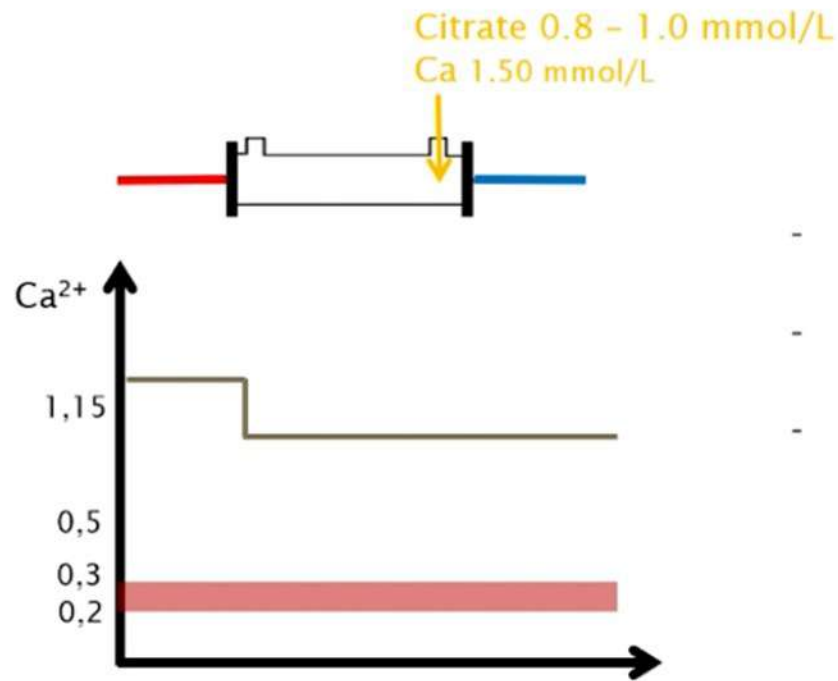
60 mmol/h, CaCl 10%, PS

AJKD, Vol 49, February 2007: p. 642

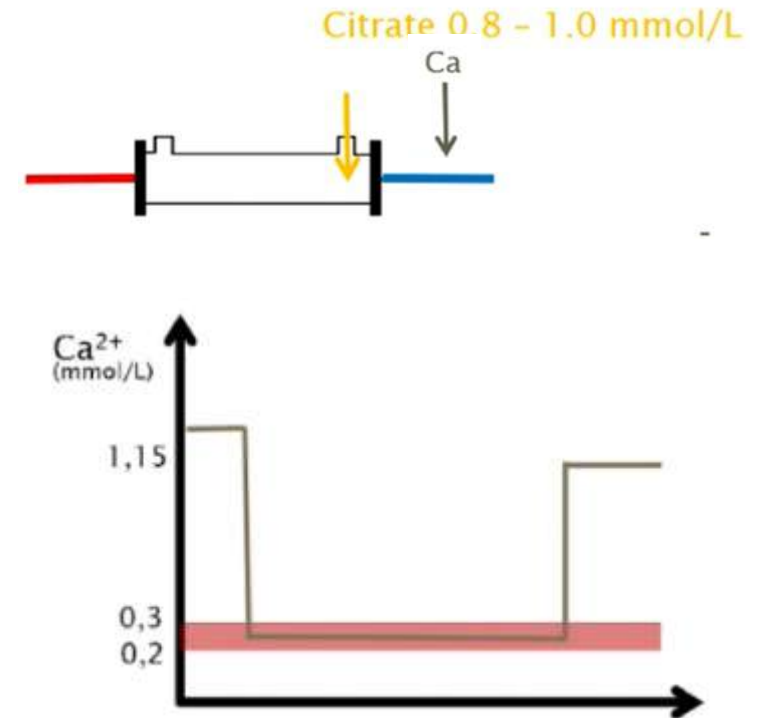
« Des » dialyses au citrate

DIALYSAT citraté

Avec Calcium



Sans Calcium



Membrane

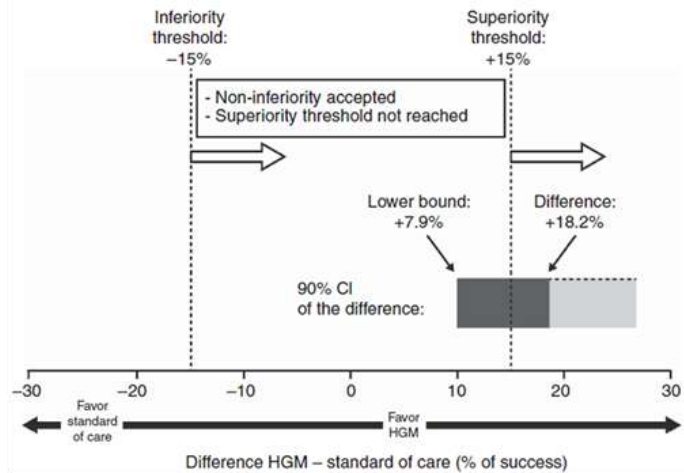
Approche

« Biopharmacologique »

Approche

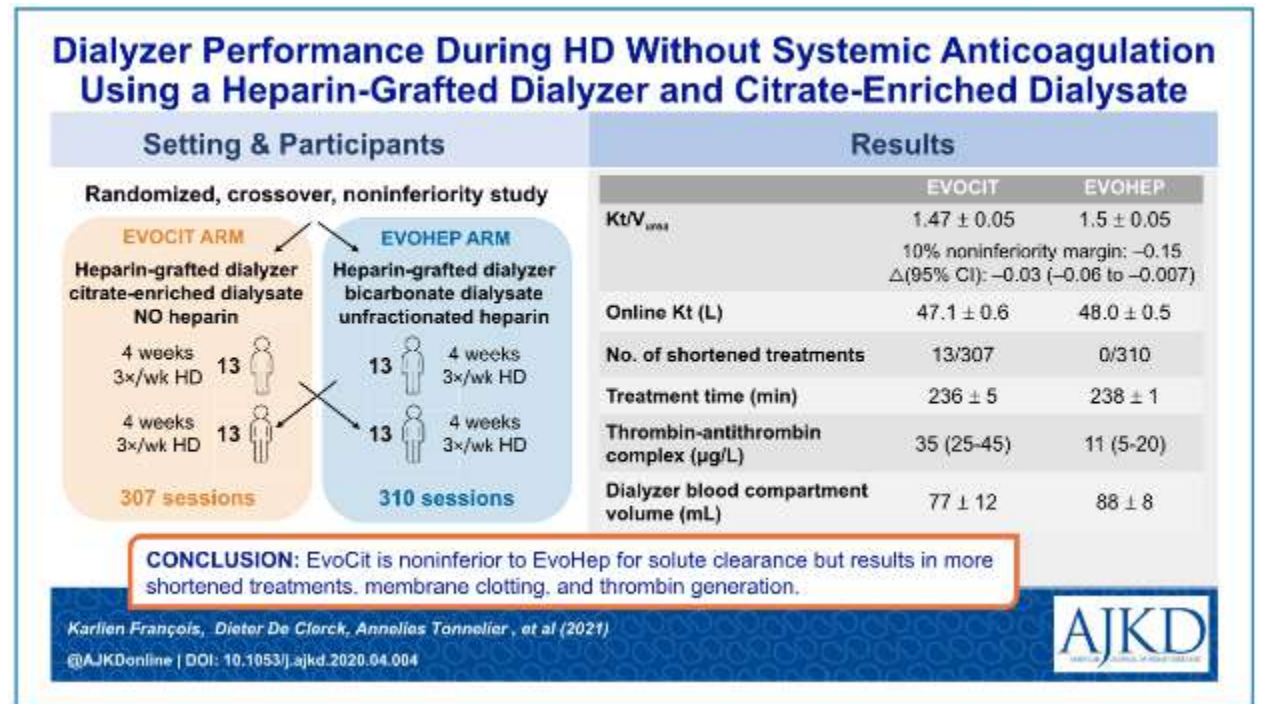
« Physico-chimique »

Hepran


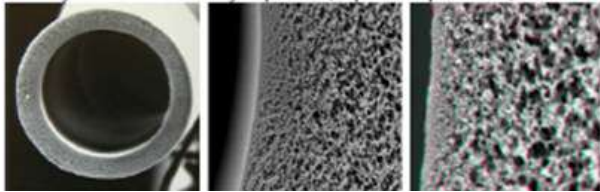


Echec sur la supériorité
Temps de séance > dans le Groupe Membrane greffée
 3,65h vs 3,45h, $p = 0,018$
Qualité de la séance équivalente (Kt/V)
 31,5% d'échec de séance

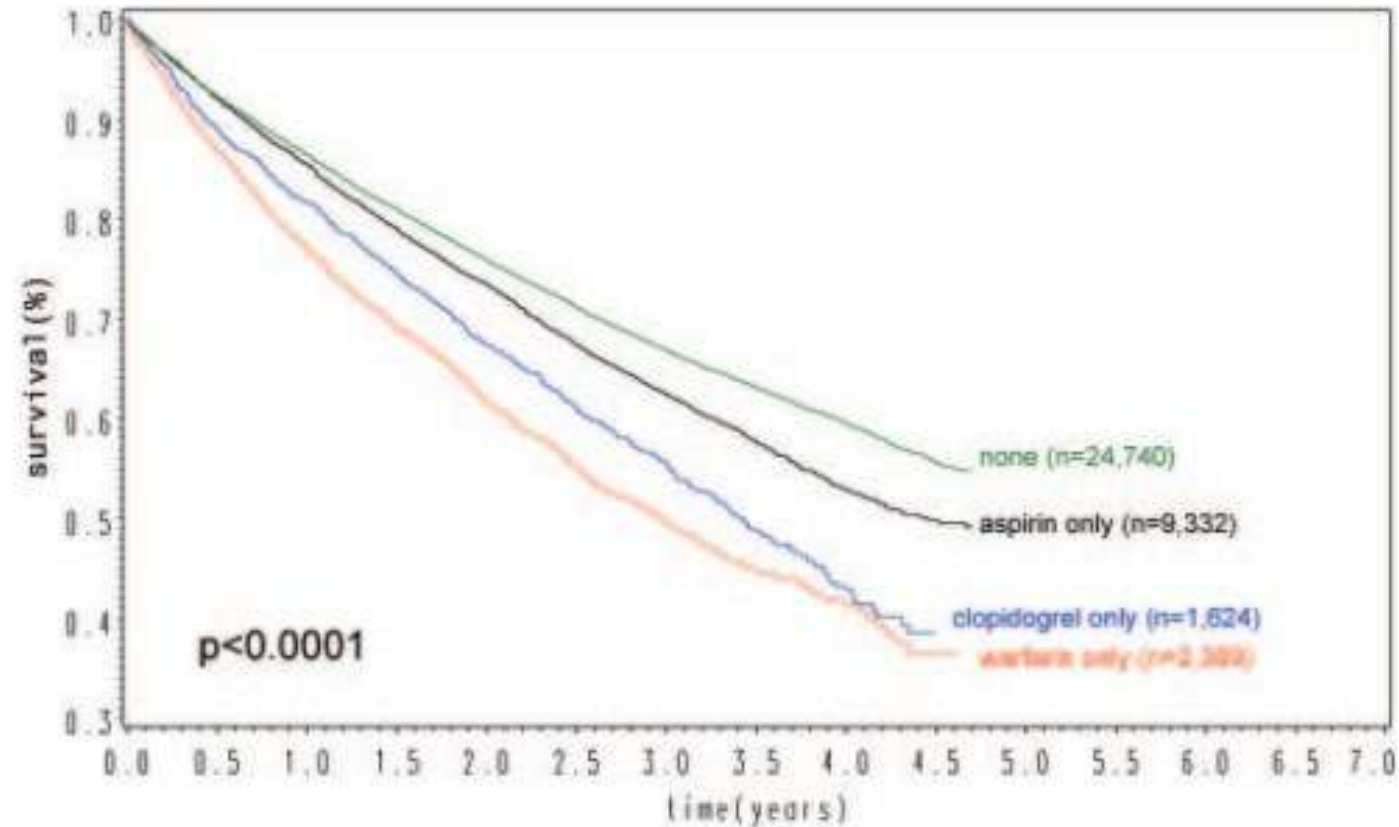
Kidney International (2014) 86, 1260–1267



Approche « Physicochimique »

Membrane		Modifications	Résultats clés
Asymmetric Triacetate		Pores asymétriques, surface lisse	↓ adsorption protéique, ↓ activation coagulation → HD possible avec demi-dose ou zéro héparine.
Hydrophilic PSF		Greffage polymère hydrophile interne	↓ activation plaquettaire/leucocytaire ↓ microparticules, ↓ IDH, possible amélioration de la résistance à l'ESA.

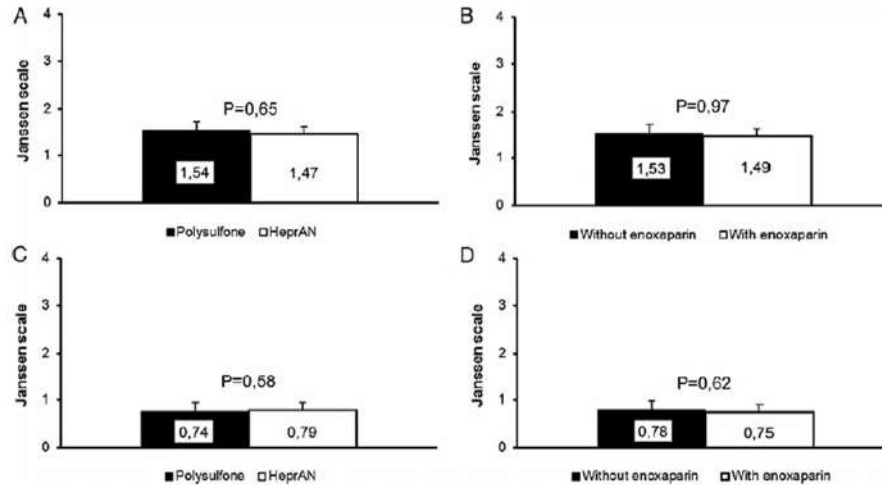
Utiliser la présence des AVK



AVK et HD :

CHAMO study

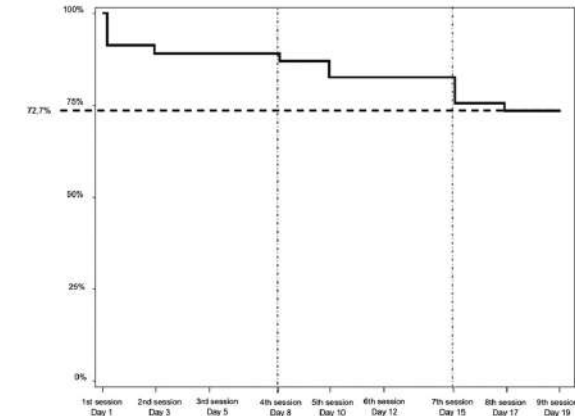
N = 10 sous AVK, 1 séance Ps vs Hepran
*40 séances : **Aucun évènement***



Nephrol Dial Transplant (2014) 29: 906–913

REMARK study

N = 46 sous AVK, sur 3 semaines
73% de réussite



Chaix et al., SFNDT 2022

Poids des AVK vs héparine durant la séance de dialyse

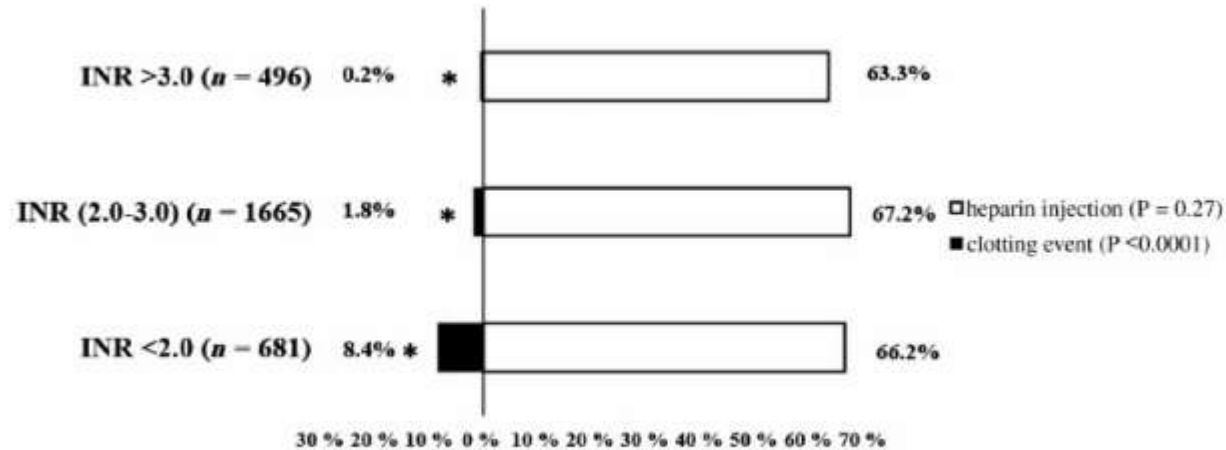
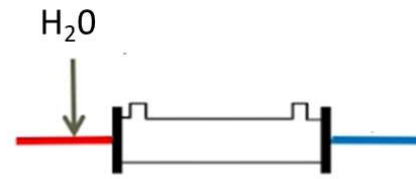


FIGURE 2: Frequencies of heparin injection and clotting events according to INR range. *P < 0.05 sessions with INR <2.0 versus INR 2.0–3.0 or INR >3.0, and sessions with INR 2.0–3.0 versus INR >3.0.

Conclusion. Our study established a predictive model of thrombosis risk of dialysis circuits in patients treated by VKA for a given heparin dose and a given INR. This model shows a marginal contribution of heparin to protect against the risk of thrombosis compared with VKA. Moreover, heparin would not appear to be necessary for patients with an INR >2.2.

Rincages et autres dilutions

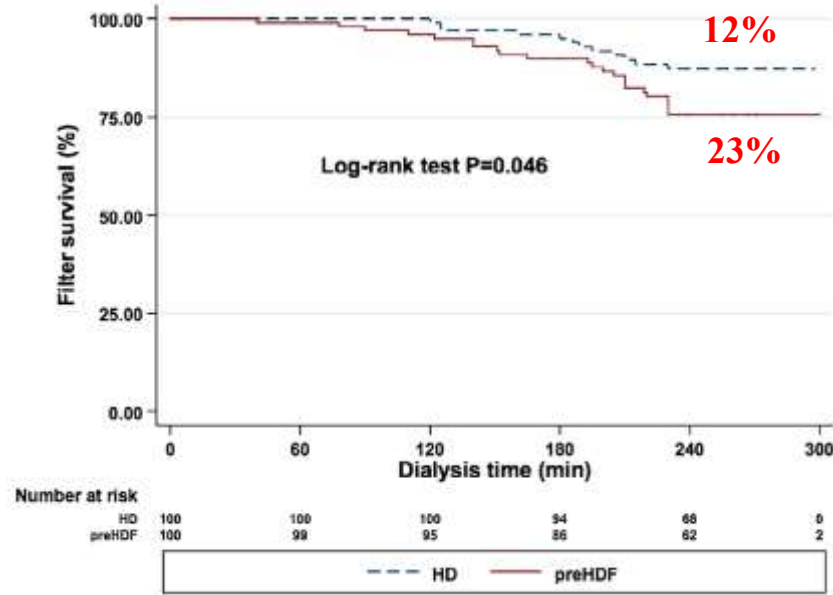
HDF Prédilution



HD (PS + Dialysat citrate 0,8mmol/L)

VS

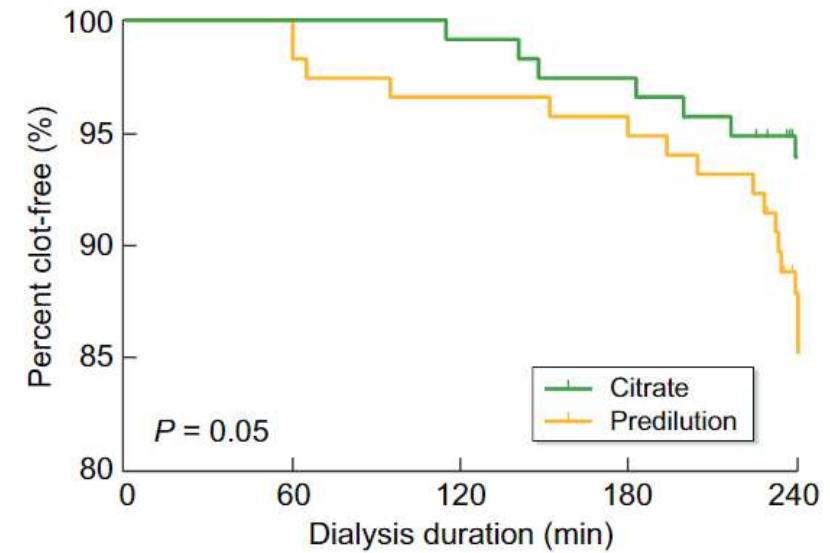
HDF prédilution (50ml/h)



HD (Triacetate Asym + Dialysat citrate 1 mmol/L)

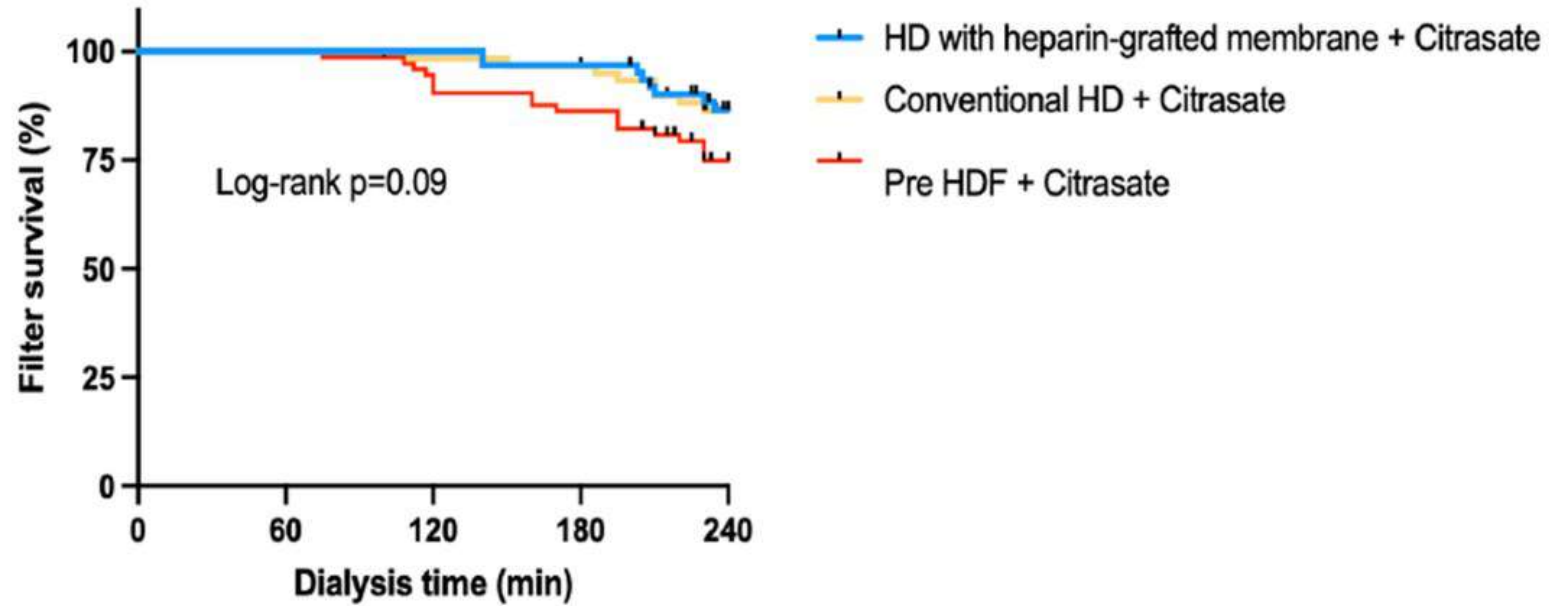
VS

HDF prédilution (60ml/h)



240 séances, 20 patients, cross over

HDF Pré-dilution

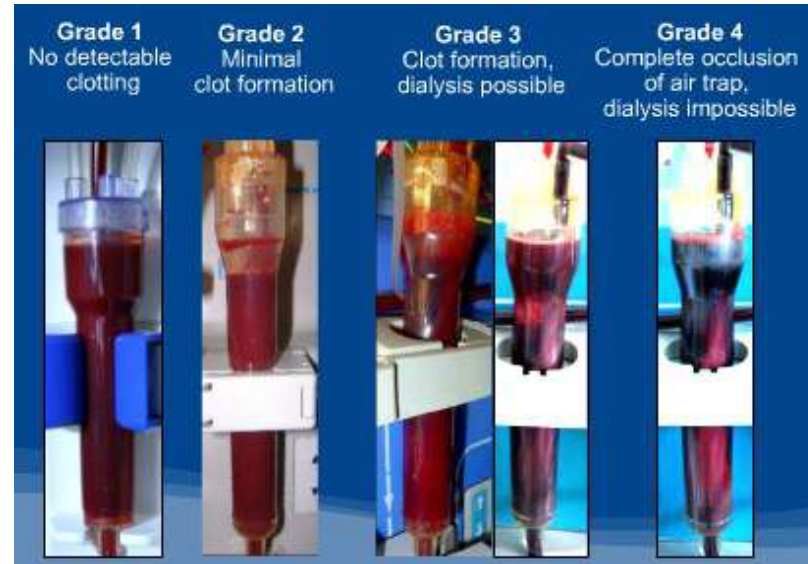


NUMBER AT RISK

Conventional HD	60	60	60	58	47
Pre HDF	74	74	69	64	48
HD with heparin-grafted membrane	62	62	62	62	47

Rinçage du circuit = NON!

Score /H



Mécanisme?

- Décolle les caillots
- Nécessité d'augmenté l'UF

Etude prospective:
↓ HBPM et rinçage
n= 8 avec PS

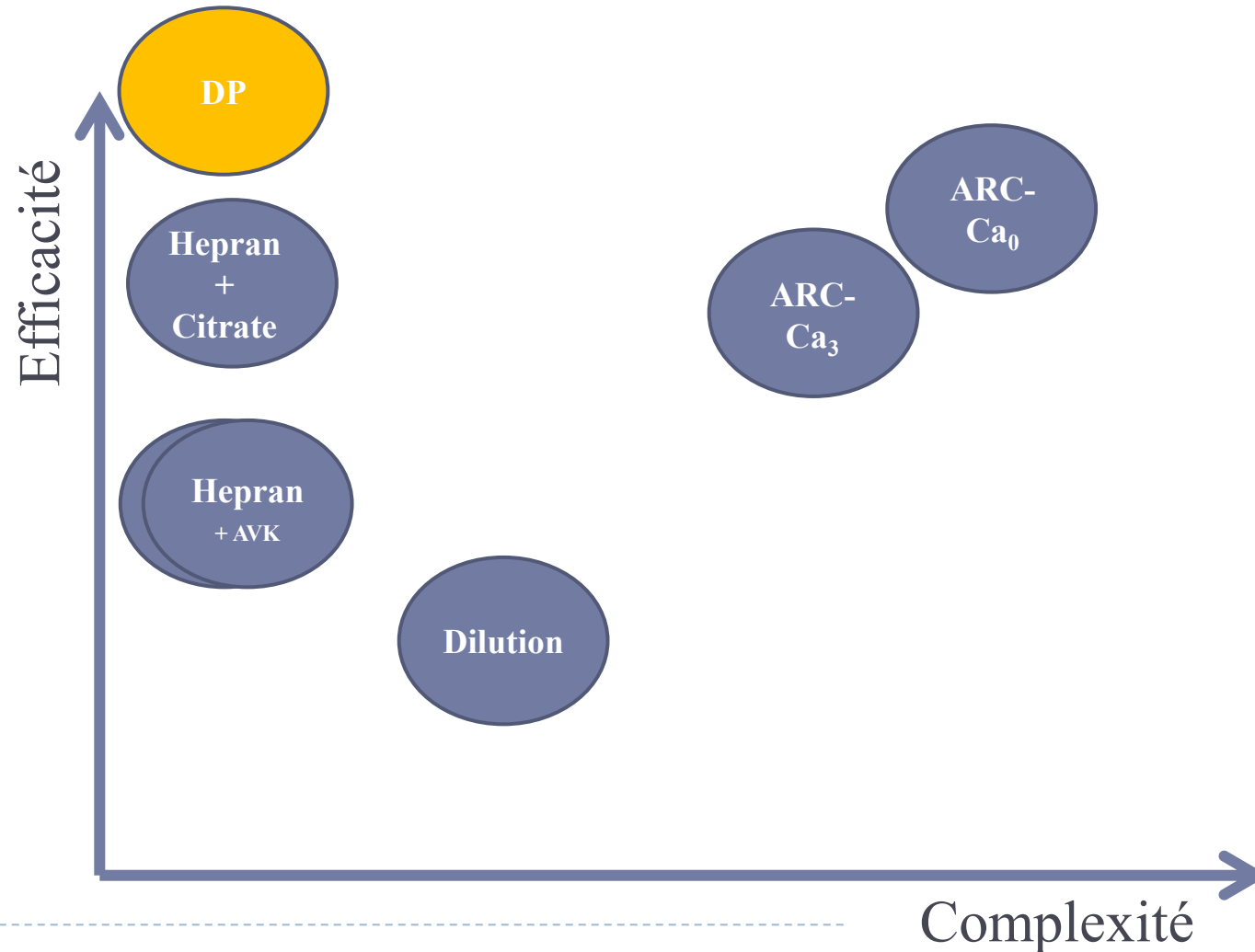
Score	Avec Rinçage	Sans Rinçage	
Grade 3	54	26	$p < 0,001$
Grade 4	4/24	0/24	



En conclusion

Chacun son protocole

Entre efficacité et sécurité, A vous de choisir votre protocole





Dans le futur

Inhibiteurs du Facteur XI : Le Futur ?

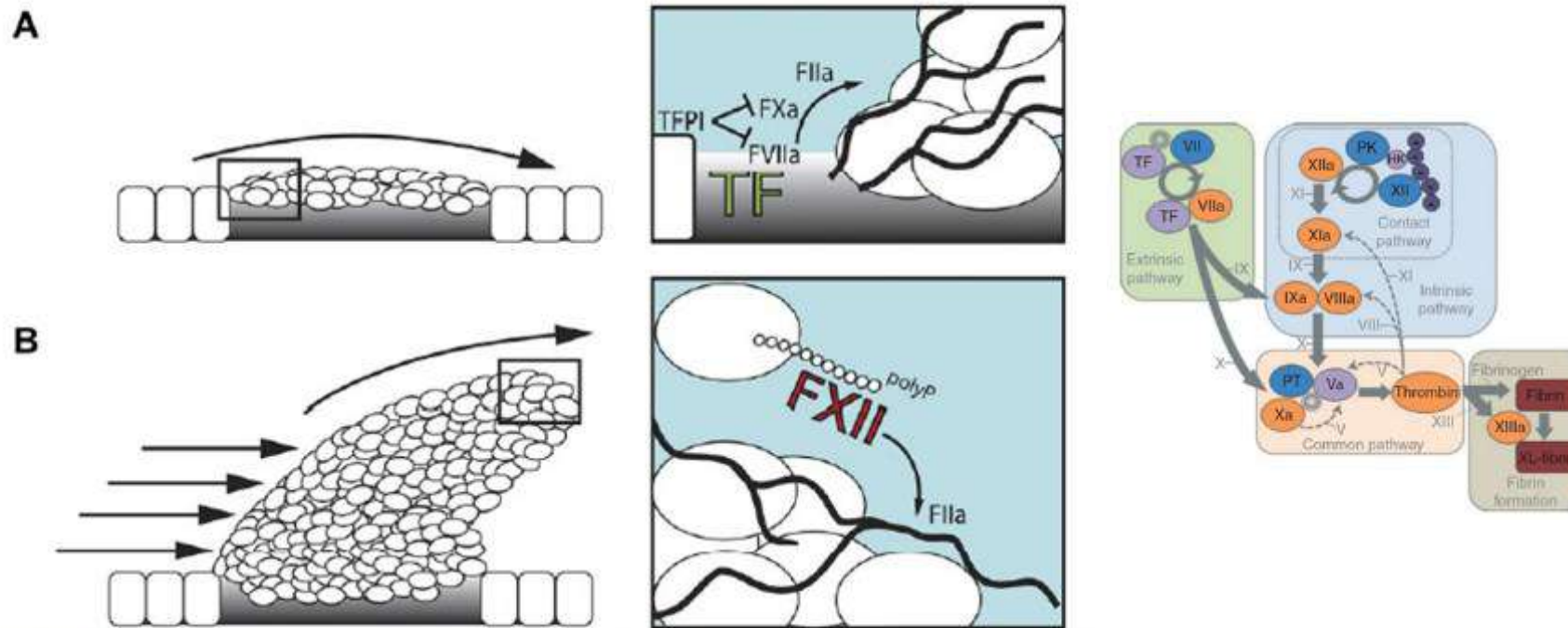
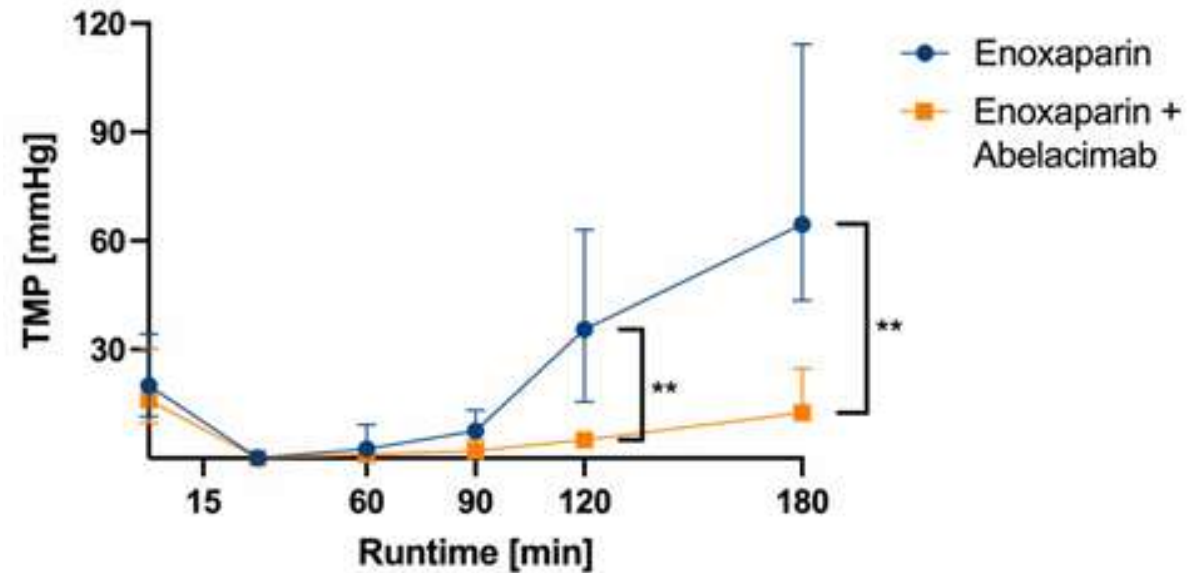
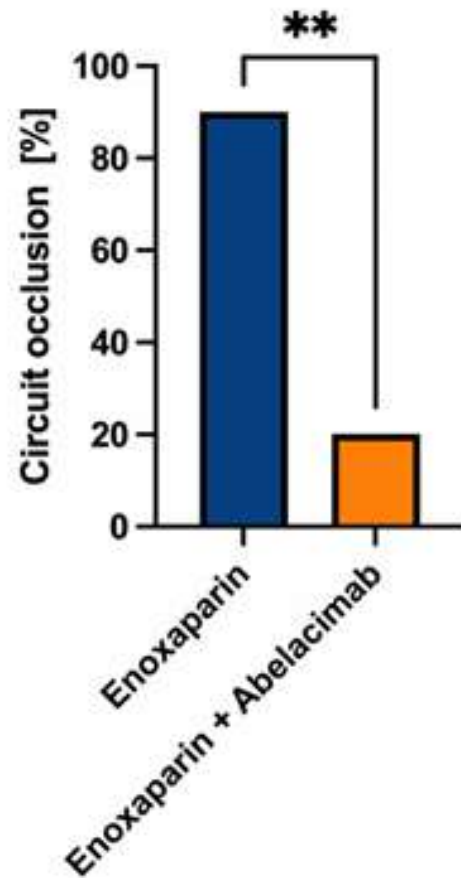


Figure 2. The role of polyP/FXII in thrombosis. (A) Initially, the TF/FVIIa-driven "extrinsic" coagulation pathway triggers fibrin formation at sites of injury. FXII has no function during this stage. Tissue factor pathway inhibitor (TFPI) is released from endothelial cells and adherent platelets and blocks TF activity. (B) In the developing thrombus, activated platelet-released polyP triggers fibrin production via activation of FXII that drives the "intrinsic" coagulation cascade. polyP/FXII-driven fibrin formation operates distant from the injured vessel wall and, hence, does not contribute to hemostasis.

Ex vivo, 10 volontaires « sains », 3h de « séances »



Inhibiteurs du Facteur XI : Le Futur ?

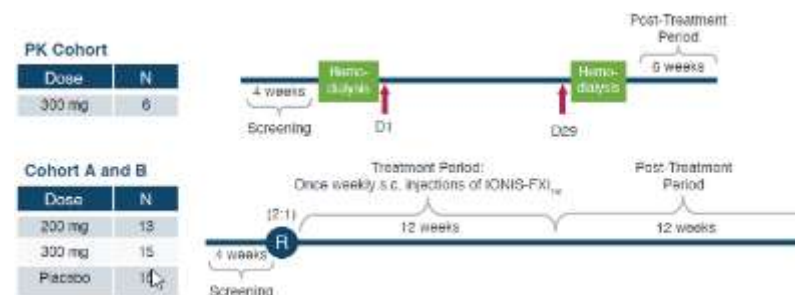
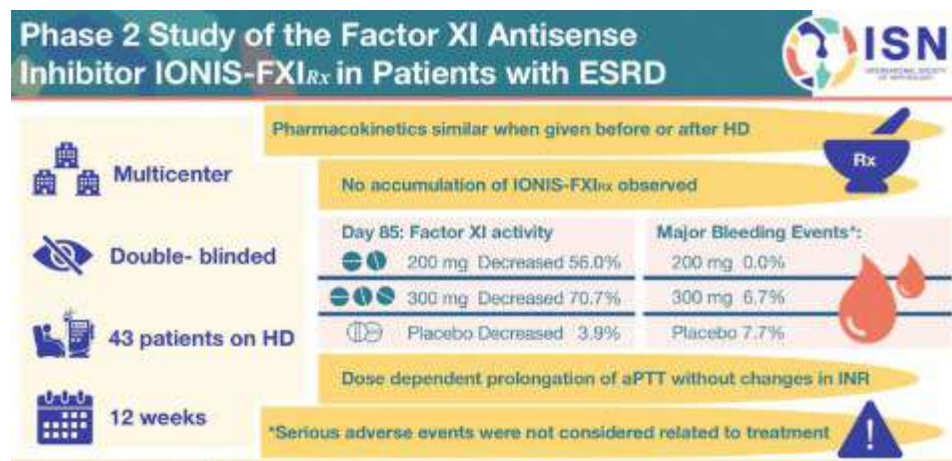
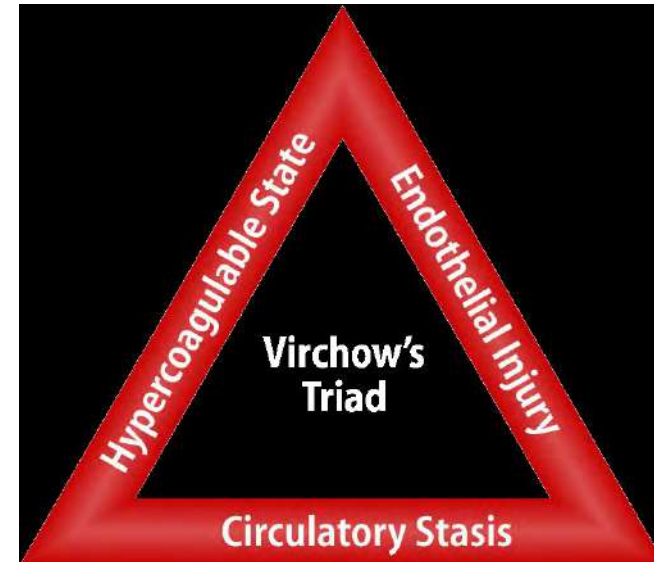


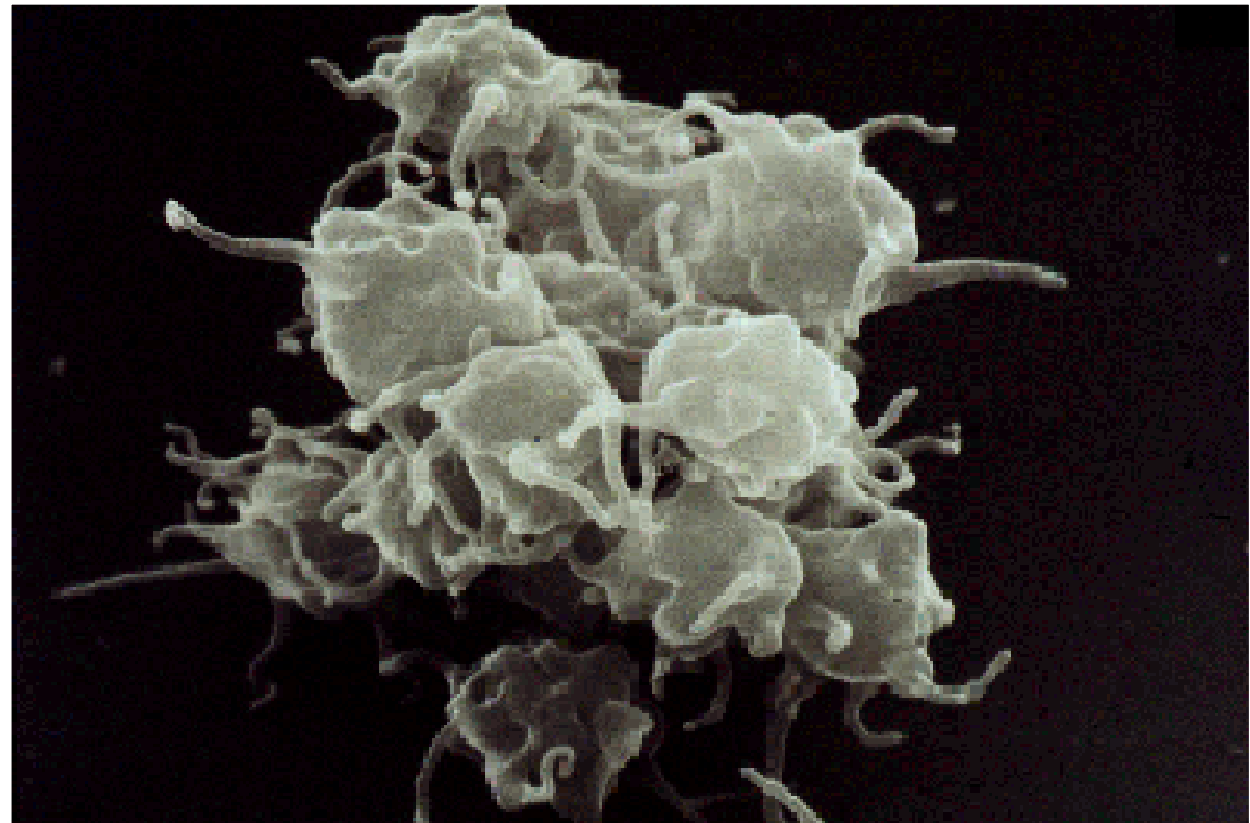
Table 3. HD circuit clotting results for patients included in the randomized IONIS-FXI_{RX} and placebo groups (per-protocol and ITT populations)

Overall air trap and dialyzer events with a clotting category ≥ 3				Pooled placebo ($n = 10$)	IONIS-FXI _{RX} 200 mg ($n = 12$)	IONIS-FXI _{RX} 300 mg ($n = 12$)
Number of category ≥ 3 events/total events, (%) ^a						
Before week 6 (baseline)						
Per-protocol population	Inspection site	Category 3	Category 4	43/70 (61.4%)	60/83 (72.3%)	38/85 (44.7%)
Intent-to-treat population	Air Trap	Clot formation on venous chamber	Coagulated system (treatment cannot continue without new setup)	47/91 (51.6%)	73/99 (73.7%)	41/103 (39.8%)
Between week 6 and week 13						
Per-protocol population				49/79 (62.0%)	38/95 (40.0%)	18/90 (20.0%)
Intent-to-treat population	Dialyzer	Blood stripes affecting 5% or more of the fibers seen at the surface of the dialyzer	Coagulated filter	52/102 (51.0%)	41/98 (41.8%)	19/101 (18.8%)

Ces petits « rien(s) » qui changent tout...

- ▶ Le Débit Sang (> 250mL/h?)
 - ▶ Qualité de la FAV
- ▶ La Membrane +++
 - ▶ Taille +, « débullage »
- ▶ L'Inflammation+++, le dialysat
- ▶ L'Hématocrite (Anémie, Transfusion, Recirculation)
- ▶ L'Ultrafiltration





Merci de votre attention
