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SFTH SOCIÉTÉ FRANÇAISE DE THROMBOSE ET D'HÉMOSTASE

Mesure de l'activité anti-Xa : quand, comment, pourquoi?

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TITANs : Thrombose, antIcoagulanTs et ANtiplaquettaires

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COI

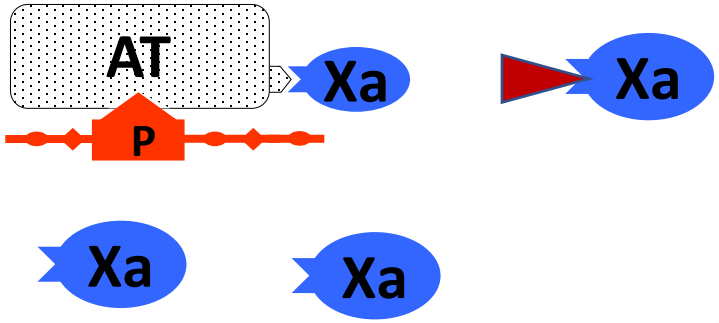
Aucun conflit d'intérêt en relation avec la présentation

Activité anti-Xa

Plasma contenant anti-Xa (HNF, HBPM, fondaparinux, danaparoïde, rivaroxaban, apixaban)

+ réactif contenant du facteur Xa
substrat chromogénique

Inhibition du facteur Xa



Coloration inversement proportionnelle à la quantité d'anti-Xa

Xa non inhibé : hydrolyse du substrat

Spécifique d'une activité anti-Xa

Même principe de mesure pour tous les anti-Xa

Méthodologie, expression différente

HNF / HBPM / danaparoïde : UI/mL
Fondaparinux : µg/mL
Apixaban ou rivaroxaban : ng/mL

Anti-Xa : différences entre les réactifs

- **Un ou deux temps**, tampons, facteurs de dilution, concentrations de Xa et type de substrat chromogénique
- HNF/HBPM : calibration hybride ou non, mode de calcul
- Addition ou non d'**antithrombine**
- Présence ou non **de sulfate de dextran**

	Calibrator LMWH and UFH	Dextran sulphate	Xa	Antithrombin
Chromogenix/IL Coamatic Heparin	Mixed	Present	Bovine origin	Absent
Hyphen Biomed Biophen	Single	Present	Bovine origin	Absent
IL HemosIL Liquid heparin	Mixed	Present	Bovine origin	Absent
Siemens Berichrom Heparin	Single	Present	Human origin	Present
Siemens Innovance Heparin	Mixed	Present	Bovine origin	Absent
Stago Liquid anti-Xa	Mixed	Absent	Bovine origin	Absent

The grey-coloured cells are the methods used for measuring all anti-FXa inhibitors. The other methods are used for measuring LMWH only.

Hollestelle M. Clin Chem Lab Med 2020

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Héparine Non Fractionnée (HNF)

Première utilisation : 1937

Murray DWG. **Heparin and the thrombosis of veins following injury**. *Surgery 1937*

Crafoord C. **Preliminary report on post-operative treatment with heparin as a preventive of thrombosis**. *Acta Chir Scand 1937*

2024

HNF : demi-vie courte, rapidement réversible

Réanimation

Chirurgie cardiaque (CEC)

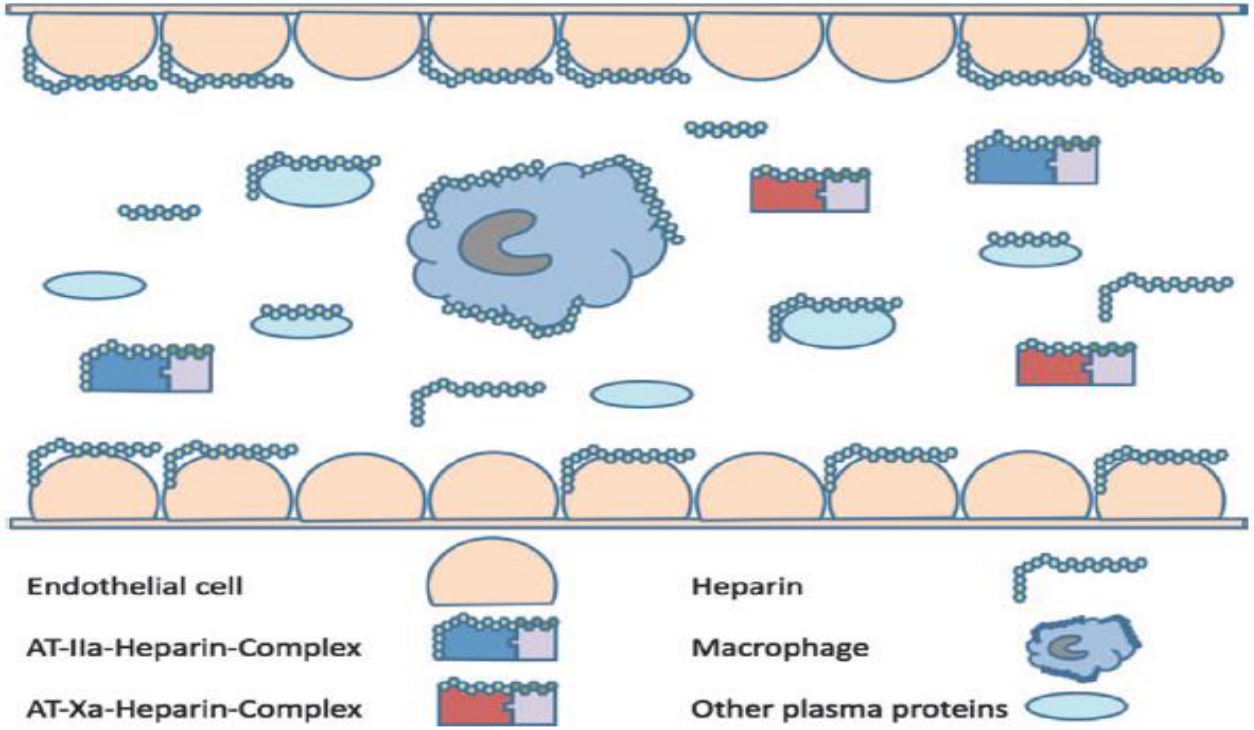
Extracorporeal membrane oxygenation (ECMO)

Thromboses artérielles

Insuffisance rénale sévère….

→ **Patients critiques, inflammatoires, risque thrombotique et hémorragique accru**

HNF : liaison non-antithrombine dépendante



Finley A. Anest Analg 2013

- Fixation aux cellules endothéliales, protéines plasmatiques (PF4, HRGP…), inflammation+++

Neutralisation de l'HNF

Importante variabilité inter- et intra- individuelle en réponse à l'HNF

HNF : problématiques

Tests (Anti-Xa, TCA….)

Cibles thérapeutiques

Relation niveau d'AT et activité anticoagulante de l'HNF

Réponse altérée à l'HNF

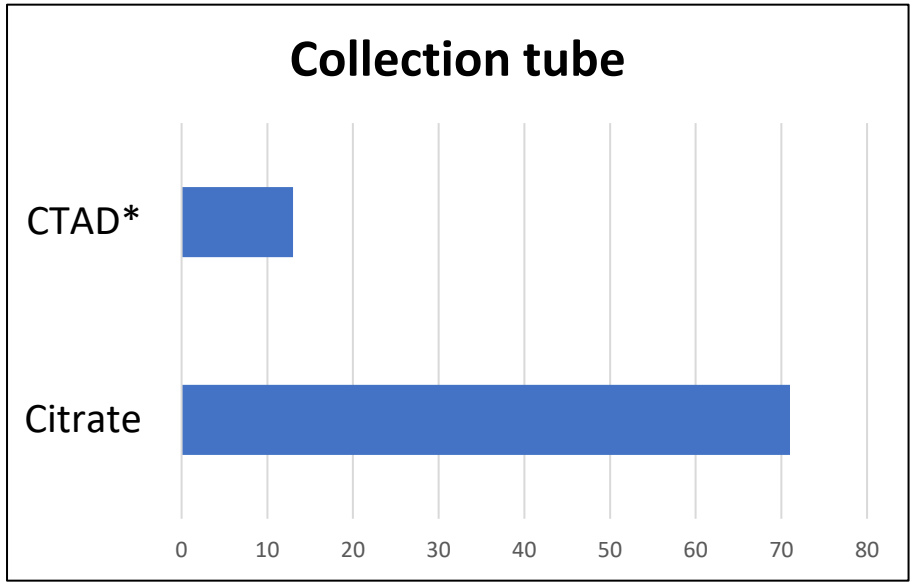
Gouin-Thibault I et al, JTH, 2023
Gouin-Thibault I et al, TH Open, 2024

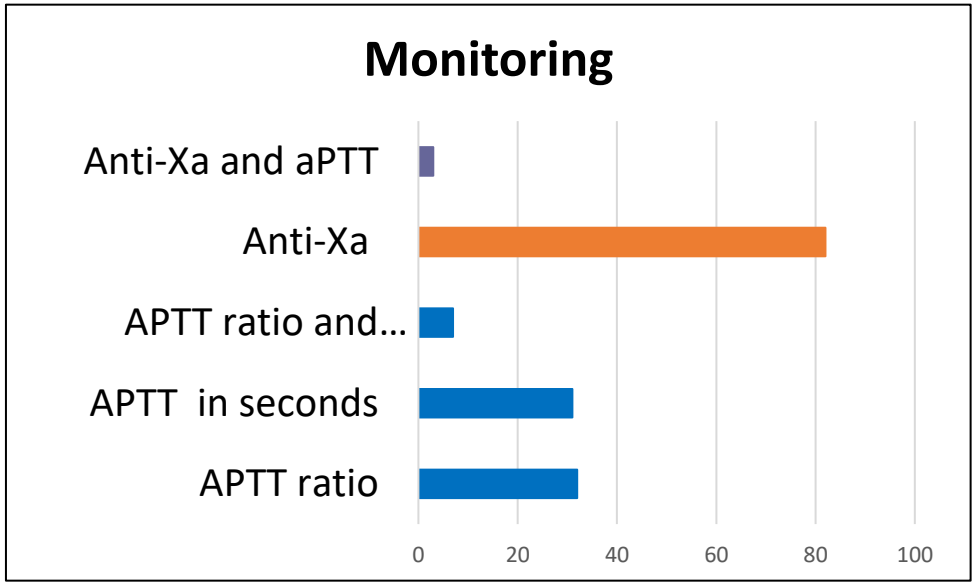
Enquête ISTH

- SSC "Control of anticoagulation" (Lana Castellucci, Adam Cuker, François Mullier)
- SSC "Perioperative and Critical Care" (Jean Connors, Jerrold Levy, Corinne Frère)
- Thomas Lecompte, Alexandre Mansour, Michael Hardy, Virginie Siguret

→ 142 réponses

Tubes de prélèvement, tests





**CTAD*
Citrate-theophylline-adenosine-dipyridamole: to avoid in vitro platelet activation

Anti-Xa : intérêt du CTAD?

- Stabilité anti-Xa : n=33, conservation en sang total ou plasma, **jusqu'à 6h après prélèvement en citrate ou CTAD**

Gremillet M, Thromb J 2023

- Anti-Xa **T4h / T1h**, **citrate**, conservation en sang total :

  n= 123, 0,35 IU/mL(range: 0,11–0,97) vs. 0,40 IU/mL (range: 0,10–0,99)

  Biais moyen : –0.05 IU/mL (95%CI=−0,13+0,03) → non cliniquement pertinent

Toulon P, Thromb Res 2020

- **Délai moyen** entre prélèvement et analyse , **119 ± 44 min :**
  - Anti-Xa : 0,18 ± 0,16 UI/ mL (**citrate**) and 0,21 ± 0,16 UI/mL (**CTAD**), (n= 93)
- **Citrate**, conservation sang total :
  - anti-Xa (n=30) : 0,37 ± 0,21 UI/mL (**1h**) ; 0,37 ± 0,20 UI/mL (**4h**) ; 0,35 ± 0,22 IU/ mL (**6 h**)

Billoir P, JTT 2019

Etude DEXHEP - Anti-Xa - différents réactifs/automates
Citrate versus CTAD

		HemosIL liquid anti-Xa® (Werfen)	Biophen heparin LRT® (Hyphen Biomed)	Biophen heparin LRT® (Hyphen Biomed)	Innovance heparin® (Siemens)	Berichrom heparin® (Siemens)	Berichrom heparin® (Siemens)	STA-Liquid anti-Xa® (Stago)
Dextran		Presence					Absence	
Analyzer		Werfen – ACL®		Stago-STAR®	Sysmex-CS®		Sysmex-CS®	Stago-STAR®
Citrate	n	162	164	162	164	164	164	165
	Median (IU/mL)	**0.32**	**0.30**	**0.28**	**0.23**	**0.25**	**0.15**	**0.05**
	min-max	0.05-1.76	0.05-2.60	0.05-1.89	0.05-1.50	0.05-2.16	0.05-1.84	0.05-1.75
CTAD	n	159	163	160	161	161	161	163
	Median (IU/mL)	**0.36**	**0.35**	**0.34**	**0.29**	**0.27**	**0.20**	**0.13**
	min-max	0.05-1.71	0.05-2.68	0.05-1.81	0.05-1.45	0.05-2.02	0.05-1.80	0.05-1.84

CTAD / Citrate

+15,1%, IC: [6,3; 24,7]

Lasne D, Thromb Haemost 2023

Test : anti-Xa, TCA?

	TCA	Anti-Xa
Disponibilité	Tous les laboratoires	Limitée
Coût	B16, 4€ (France)-B250, 1,95€ (Belgique)	B30, 7,5€ (France)-B1000, 7,81€ (Belgique)
Principe	Test de coagulation après activation de la phase contact Surface phospholipidique artificielle	Test spécifique de l'anti-Xa Système artificiel
Interprétation	**Prolongation** : - déficit en facteurs (phase contact) - Inflammation : anticoagulant lupique / interference avec la CRP	Interférence avec les antithrombotiques anti-Xa
	Raccourcissement : - Inflammation : FVIII élevé → *Très sensible à des conditions sans relation avec l'effet anticoagulant* → *Difficile à interpréter chez les patients inflammatoires*	
Sensibilité à l'HNF	**Très variable**, dépend des réactifs : → *"Therapeutic range should be adapted to each reagent/coagulometer combination (ACCP, 2012)"*	**Sensible** **Manque de standardisation** des differents réactifs

Anti-Xa chromogéniques : manque de standardisation

Concordance (k coefficient) entre les différents réactifs/analysers

Discordances des valeurs d'anti-Xa, dans / en dehors de la zone thérapeutique (0,3-0,7 IU/mL), 104 patients

	Biophen Heparin LRT (Hyphen)/ CS-5100 analyzer	HemosIL Liquid Anti-Xa (IL)	Innovance Heparin (Siemens)	STA-Liquid Anti-Xa 8 (Stago)
Biophen Heparin LRT (Hyphen) /ACL TOP 700 analyzer	0.898 (95% CI, 0.825-0.971) n = 7 (6.7%)	0.738 (95% CI, 0.626-0.849) n = 18 (17.3%)	0.714 (95% CI, 0.601-0.828) n = 20 (19.2%)	0.484 (95% CI, 0.363-0.604) n = 41 (39.4%)
Biophen Heparin LRT (Hyphen)/ CS-5100 analyzer	-	0.640 (95% CI, 0.516-0.763) n = 25 (24.0%)	0.619 (95% CI, 0.496-0.742) n = 27 (26.0%)	0.411 (95% CI, 0.293-0.528) n = 48 (46.2%)
HemosIL Liquid Anti-Xa (IL)	-	-	0.939 (95% CI, 0.880-0.998) n = 4 (3.8%)	0.652 (95% CI, 0.532-0.773) n = 24 (23.1%)
Innovance Heparin (Siemens)	-	-	-	0.710 (95% CI, 0.597-0.823) n = 21 (20.2%)

Discordances entre les valeurs d'anti-Xa mesurées avec les 4 réactifs
→ impact significatif sur la prise en charge des patients

Smahi M. JTH 2020

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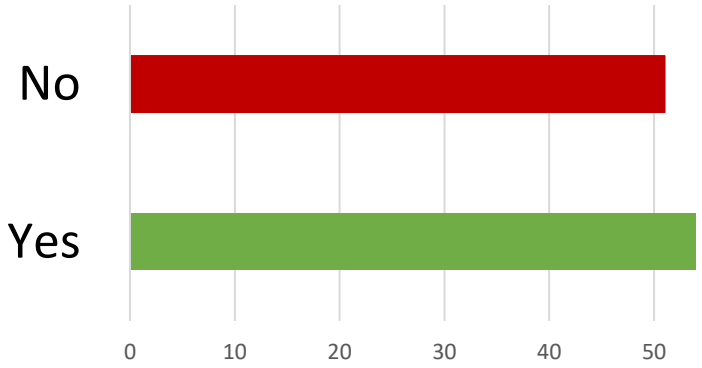
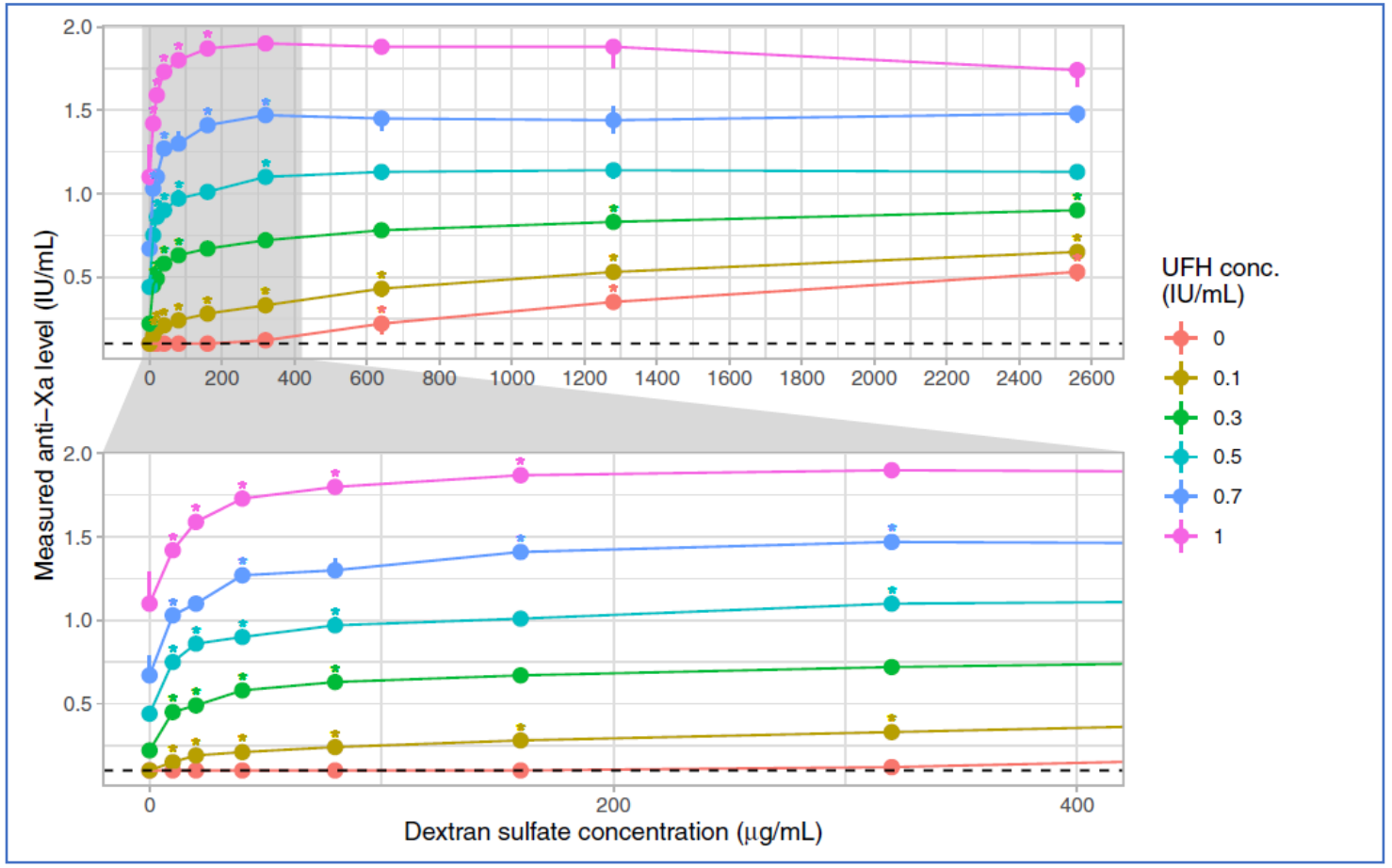
Présence de sulfate de dextran dans les réactifs

Etes-vous au courant des differences systématiques entre les tests anti-Xa contenant ou non du dextran (valeurs plus élevées en cas de présence de dextran) ?



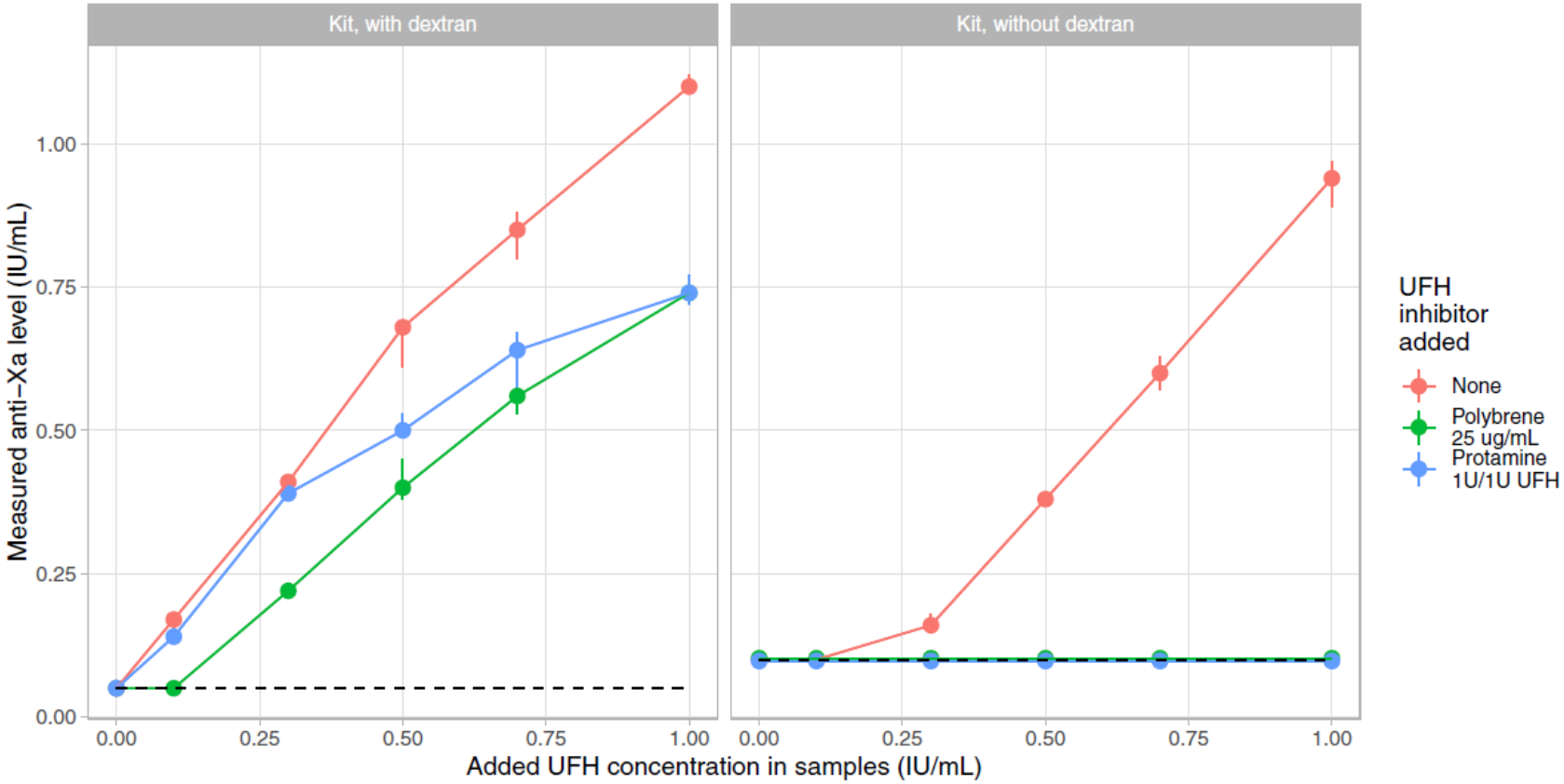
Présence de sulfate de dextran dans les réactifs anti-Xa



Sulfate de dextran : activité anti-Xa à forte concentration
Augmentation de l'effet anti-Xa de l'HNF en présence de dextran

Hardy M, RPTH 2023

Présence de sulfate de dextran dans les réactifs



Plasma surchargés en HNF ± polybrène ou protamine :
Anti-Xa mesurées variables en fonction du réactif
Polybrène ou protamine : pas d'effet inhibiteur sur l'anti-Xa l'HNF, avec réactif contenant du sulfate de dextran

Hardy M, RPTH 2023

Etude DEXHEP - Anti-Xa - différentes situations cliniques
Présence ou non de sulfate de dextran

N=160 patients/4 situations cliniques, CTAD et citrate, 7 réactifs/automates (5 avec dextran, 2 sans dextran)

Reagents		Post-CPB 5-10 min after protamine neutralization	Cardiothoracic ICU 1-5 days post-CPB	Medical ICU	Other medical patients
Reagents with dextran (n=5)	n	195	175	256	190
	Median (IU/mL)	**0.32**	**0.05**	**0.31**	**0.55**
	Min-max	0.05-1.60	0.05-0.71	0.05-2.60	0.05-2.16
	Values < LLOQ: n, (%)	**12 (6%)**	**88 (50%)**	**19 (7%)**	**27 (14%)**
Reagents without dextran (n=2)	n	78	70	105	76
	Median (IU/mL)	**0.05**	**0.05**	**0.22**	**0.47**
	Min-max	0.05-1.62	0.05-0.35	0.05-1.84	0.05-1.75
	Values < LLOQ: n, (%)	**60 (77%)**	**45 (64%)**	**29 (28%)**	**20 (26%)**
Dextran versus no dextran		**+296.0 %** CI: [257.7; 338.4]	**+37.8 %** CI: [23.7; 53.5]	**+53.5 %** CI: [40.3; 67.6]	**+30.9 %** CI: [17.4; 44.5]

Lasne D, Thromb Haemost 2023

Sulfate de dextran dans les réactifs anti-Xa

Dissociation des complexes HNF / PF4 formés *in-vitro* après prélèvement

Probable mobilisation de l'HNF des complexes HNF/protéines formés *in vivo* (HNF inactive)

En cas de neutralisation de l'HNF par la protamine, dissociation des complexes HNF / protamine

↓

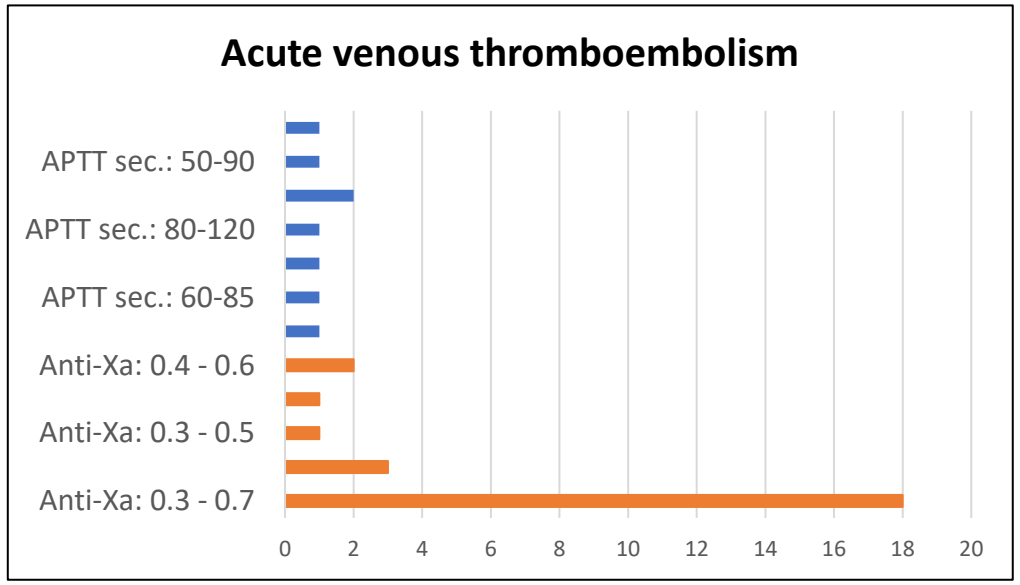
Niveaux d'anti-Xa plus élevés→ "Surestimation" de l'HNF active *in-vivo*?

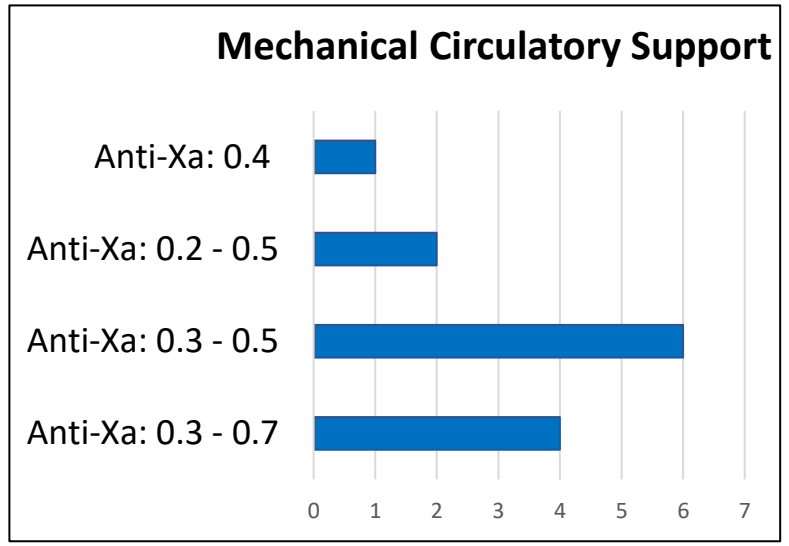
↓

Conséquences sur la prise en charge des patients?

Lyon S Thromb Hemost 1987 ; Mouton C. Thromb Res 2003 ; Lasne D, Thromb Hemost 2023 ; Hardy M, RPTH 2023

Zones thérapeutiques





Indications	Ranges
Stroke, n=1	Anti-Xa: 0.3-0.6
Acute limb ischemia, n=1	Anti-Xa: 0.3 - 0.7
Severe renal insufficiency, n=1	Anti-Xa: 0.3-0.6
Atrial fibrillation, n=2	Anti-Xa: 0.2-0.5; 0.3-0.7
All indications, n=1	Anti-Xa: 0.3-0.7
Mechanical heart valves, n=1	APTT ratio: 2-3
During PCI, n=2	APTT ratio: 2-3
ICU post cardiac surgery, n=1	APTT, sec: 60-100
Atrial fibrillation ablation, perprocedure, n=1	APTT, sec: 250-300

HNF : zones thérapeutiques

1970
MTEV / SCA (n=234)
TCA ratio : 1,5-2,5 (60-100 sec)
Basu D, NEJM

↓

Modèle lapin thrombose veineuse
Protamine titration
Chiu HM, Blood 1977

↓

1993
MTEV
Protamine titration: 0,2-0,4U/mL
Brill-Edwards P, Ann Intern Med 1993

↓

1994
MTEV (n=131)
Anti-Xa : 0,35 – 0,67 UI/mL / TCA (60-85 sec)
Levine MN, Arch Intern Med 1994

2024

- **Pas de validation prospective** des cibles thérapeutiques
- Réactifs, TCA et anti-Xa reagents, 1970-1990

(*Stachrom heparin®, two-stage, AT*) : **plus utilisés**

- **Réactifs actuels :** large variabilité

→ Cibles adoptées malgré un faible niveau de preuves et une pertinence clinique non démontrée

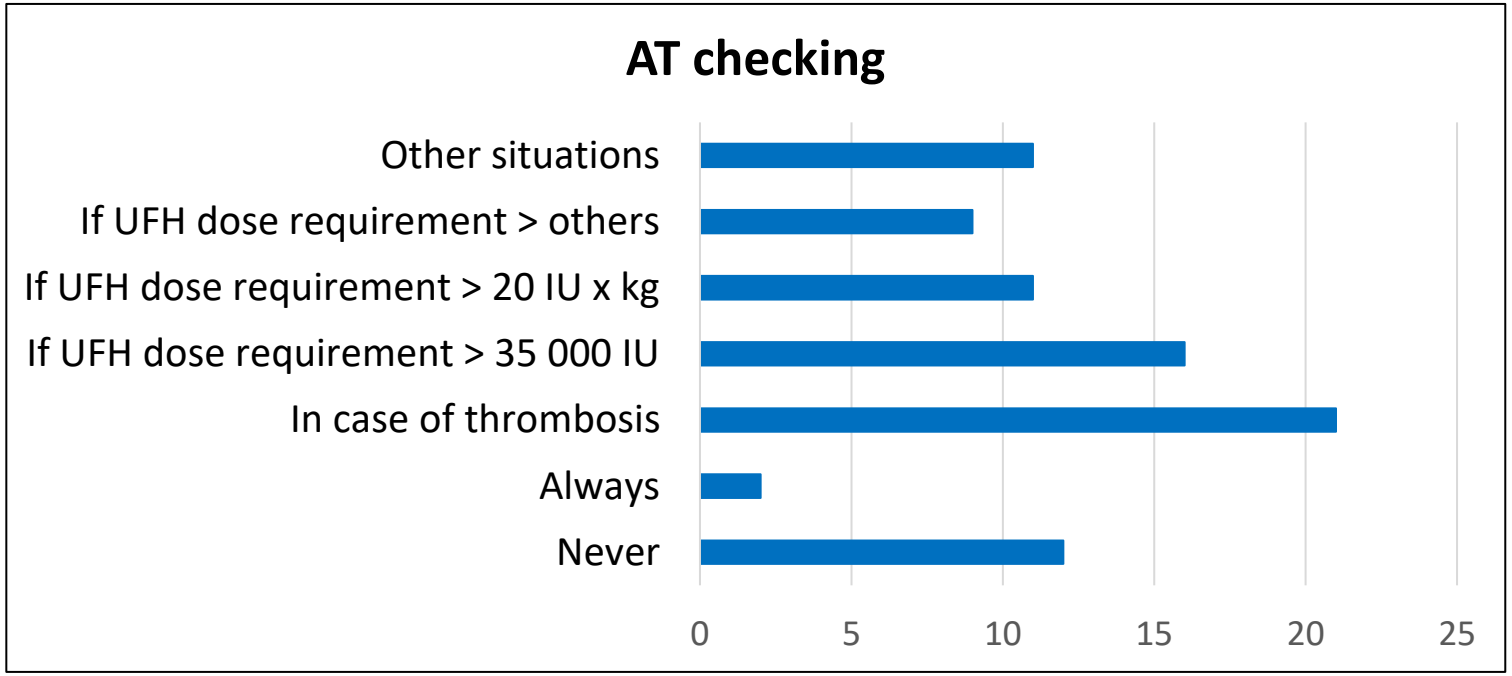
Garcia DA, ACCP, Chest 2012; Cuker A. Sem Thromb Hemost 2012; Baluwala I, Exp Rev Hematol 2017; Gouin-Thibault, TH Open 2024

Antithrombine et réponse à l'HNF

- **Mesure de l'AT en cas de réponse altérée à l'HNF ?**

- **Administration d'AT, en cas de réponse altérée à l'HNF ?**

Antithrombine et réponse à l'HNF



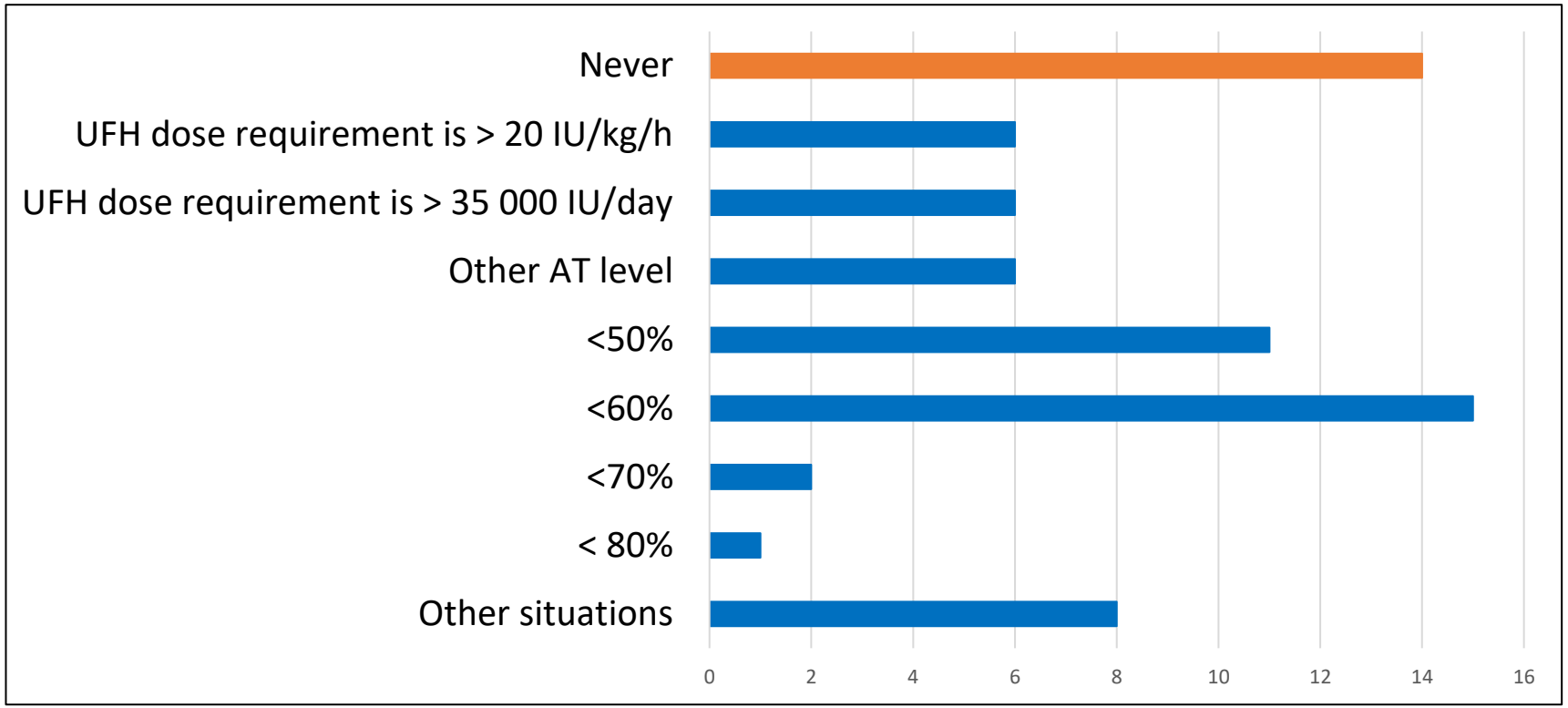
If dose requirement (others):

- 700 IU x kg -1 x d-1
- >800 IU/kg/24h
- if target APTTratio and/or antiXa is not achieved
- >600 IU x kg-1
- 25 IU/Kg/24h
- Too much, as defined by the clinician
- > 40000 IU/24h
- >35 IU kg-1 h-1

AT checking, other situations:

- in case of asparaginase treatment; in case of AT supplementation (in patients with AT hereditary deficiency)
- If anti-Xa still< 0.1 IU/mL despite UFH dose increase
- If anti-Xa level is below 0.3 IU/ml despite increasing dosage
- heparin resistance
- specific conditions: DIC, ECMO
- antiXa lower than expected
- If patient is subtherapeutic after 3 dose escalations

Administration d'antithrombine



Other situations

- Other dose requirement
- Depend on patient and situation
- Prefer switching to DTI

Antithrombine et réponse à l'HNF

Déficit acquis en antithrombine

Thrombose extensive, SAPL, CIVD, CEC, ECMO, insuffisance hépato-cellulaire, syndrome néphrotique….

→ Retentissement sur la réponse à l'HNF?

Déficit acquis en antithrombine et réponse à l'héparine

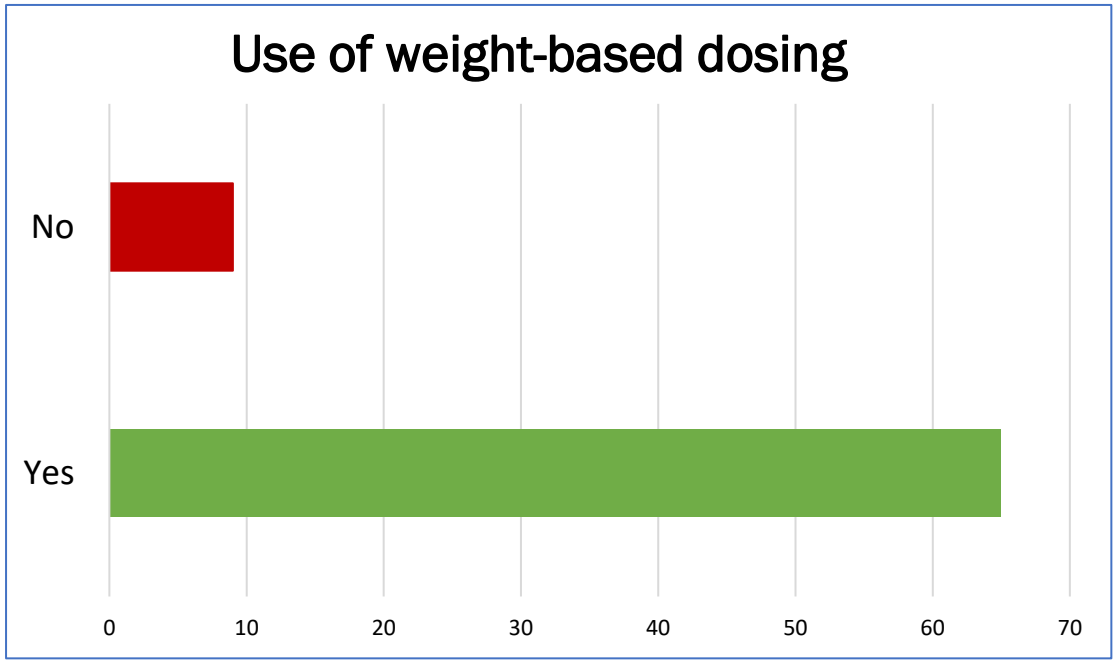
- **Pas de seuil d'AT**
- **Variable en fonction des patients, situations, tests….**
- **Administration d'AT : absence de bénéfice clinique démontré**

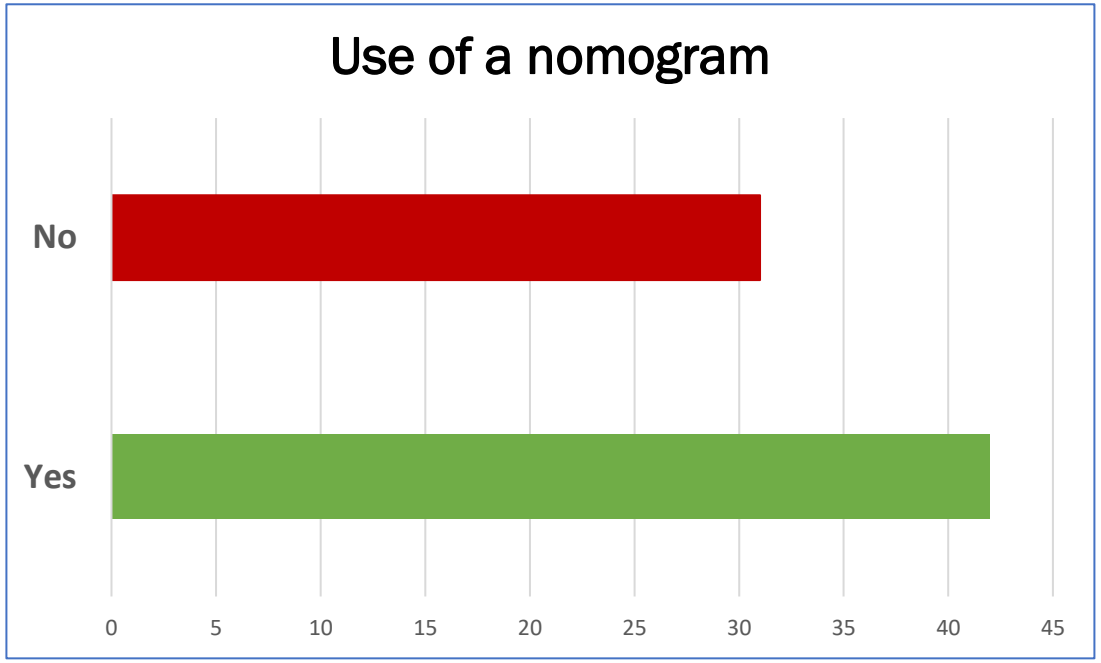
→ Pas d'administration systématique d'AT en cas de réponse altérée

→ Augmentation des doses d'HNF

Finley A, Anest Analg 2013 ; Levy J, NEJM 2021 ; Ranucci M, Anest Analg 2023 ; Helms J, JTH 2023 ; Levy J, JTH 2023 ; Gouin-Thibault, JTH 2023 ; Levy J, JTH 2024 ; Mansour A, Anesthesiology 2024 ; Mansour A. JTH 2024 ; Gouin-Thibault I, TH Open 2024

Ajustement des doses : utilisation d'un nomogramme





Nomogram based on
- APTT, n=6
- Anti-Xa, n=36

Ajustement des doses : utilisation de nomogramme

- **115 patients traités IV, HNF pour thrombose veineuse ou artérielle**
- **Etude randomisée :** nomogamme basé sur poids ou standard care
- **TCA :** Dade Actin thromboplastin

Initial dose	80 units/kg bolus, then 18 units/kg/h
aPTT, < 35 s	80 units/kg bolus, then increase 4 units/kg/h
aPTT, 35-45 s	40 units/kg bolus, then increase 2 units/kg/h
aPTT, 46-70 s[a]	No change
aPTT, 71-90 s	Decrease infusion rate by 2 units/kg/h
aPTT, > 90 s	Hold infusion 1 h, then decrease infusion rate by 3 units/kg/h

- **Patients au-dessus du seuil thérapeutique dans les 24h :**

97% (nomogam) vs 77% (standard care group) (p<0.002)

- **Récidives thromboemboliques :**

Plus fréquentes dans le groupe standard care (RR : 5 (95%CI : 1,1 to 21,9)

Raschke Ann Intern Med. 1993

Nomogramme anti-Xa

Zone thérapeutique : 0,30 to 0,70 UI/mL
Posologie initiale : 80 UI/kg bolus, puis 18 UI/kg/h
Activité **anti-Xa HNF : 6 h** après l'initiation de la perfusion et 6 h après tout changement de dose

Activité anti-Xa HNF (UI/mL)	Bolus IVD	Ajustement de la dose
Anti Xa < 0,20	Bolus 80 UI/kg	puis augmenter de 4 UI/kg/h
0,20-0,29	Bolus 40 UI/kg	puis augmenter de 2 UI/kg/h
0,30-0,70	Pas de changement	
0,71-0,80	Non	Diminuer d'une 1 UI/kg/h
0,81-0,99	Non	Diminuer de 2 UI/kg/h
Anti Xa > 1,00	Stopper la perfusion 1h et reprendre en baissant de 3 UI/kg/h	

Adapté de Raschke Ann Intern Med. 1993

Nomogramme anti-Xa : ECMO

Zone thérapeutique, anti-Xa 0,3 à 0,5 UI/mL
Ajustements posologiques (4h après chaque modification)

Activité anti-Xa HNF (UI/mL)	Bolus IVD	Ajustement de la dose
<0,10	80 UI/kg	+ 4 UI/kg/h
0,10 – 0,19	40 UI/kg	+ 3 UI/kg/h
0,20 – 0,29	20 UI/kg	+ 2 UI/kg/h
0,30 – 0,49	-	-
0,5 – 0,59	-	- 1 UI/kg/h
0,6 – 0,69	-	- 2 UI/kg/h
>0,7	Stop 1h	- 3 UI/kg/h

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Nomogramme anti-Xa

Zone thérapeutiques : **0,30 à 0,70** UI/mL
26 units/kg bolus, puis 15 units/kg/h
Anti-Xa toutes les 6h, puis toutes les 24h

Table 1.
Protocol for Adjusting Heparin Dosage

Antifactor Xa Concentration (units/mL)	Repeat Heparin Bolus Dose	Infusion Adjustment
<0.20	26 units/kg	Increase by 4 units/kg/hr
0.20–0.29	None	Increase by 2 units/kg/hr
0.30–0.70	None	No change
0.71–0.80	None	Decrease by 1 unit/kg/hr
0.81–0.99	None	Decrease by 2 units/kg/hr
≥1.00	None	Interrupt for 1 hr, then decrease by 3 units/kg/hr

Smith ML, Am J Health Syst Pharma 2010

Nomogram	Initial Bolus Dose (Maximum)	Initial Infusion Dose (Maximum)	Goal aPTT (Seconds)	Goal Anti-Xa Concentration (U/mL)
DVT/PE	80 U/kg (10 000 U)	18 U/kg/h (1600 U/h)	68-106	0.3-0.7
UA/NSTEMI	60 U/kg (4000 U)	12 U/kg/h (1000 U/h)	68-96	0.3-0.6
Afib/Post-Op	60 U/kg (10 000 U)	10 U/kg/h (1600 U/h)	68-82	0.3-0.45
Stroke/EP/VAD/high-risk bleed	NA	8 U/kg/h (1600 U/h)	59-72	0.25-0.35

Whitman-Purves E, Clin App Thromb Hemost 2018

Non validés. Utilisation anti-Xa :
améliore le temps pour atteindre une anticoagulation efficace, moins d'ajustements de doses

HBPM-fondaparinux
Principales caractéristiques pharmacologiques

	Tinzaparine	Daltéparine	Nadroparine	Enoxaparine	Fondaparinux
MM (Da) moy	6500	5600	4500	4200	1728
Rapport anti-Xa / anti-IIa	2	2,5	3,2	3,6	infini
Pic d'activité (h)	4 - 6	4 - 6	3 - 4	3 - 4	3
½ vie élimination (h)	3 - 4	3 - 4	3 - 4	5 - 7	17
Elimination	En partie rénale →				Exclusivement rénale

RCP HBPM

HBPM : anti-Xa

- **But** : **dépister une accumulation**

- **Indications** : complications hémorragiques
  insuffisants rénaux (sévères) / sujets âgés > 75 ans
  poids extrêmes….

Les HBPM ne nécessitent pas de surveillance biologique systématique de l'activité anti-facteur Xa (Grade B). Cette surveillance est suggérée en cas de situation à risque d'accumulation et/ou de risque hémorragique (insuffisant rénal modéré, âge élevé, petit poids corporel) 3 ou 4 heure après l'initiation afin de vérifier que les activités anti-facteur Xa obtenues sont de l'ordre de celles attendues dans la population générale (Accord professionnel).

ANSM 2009

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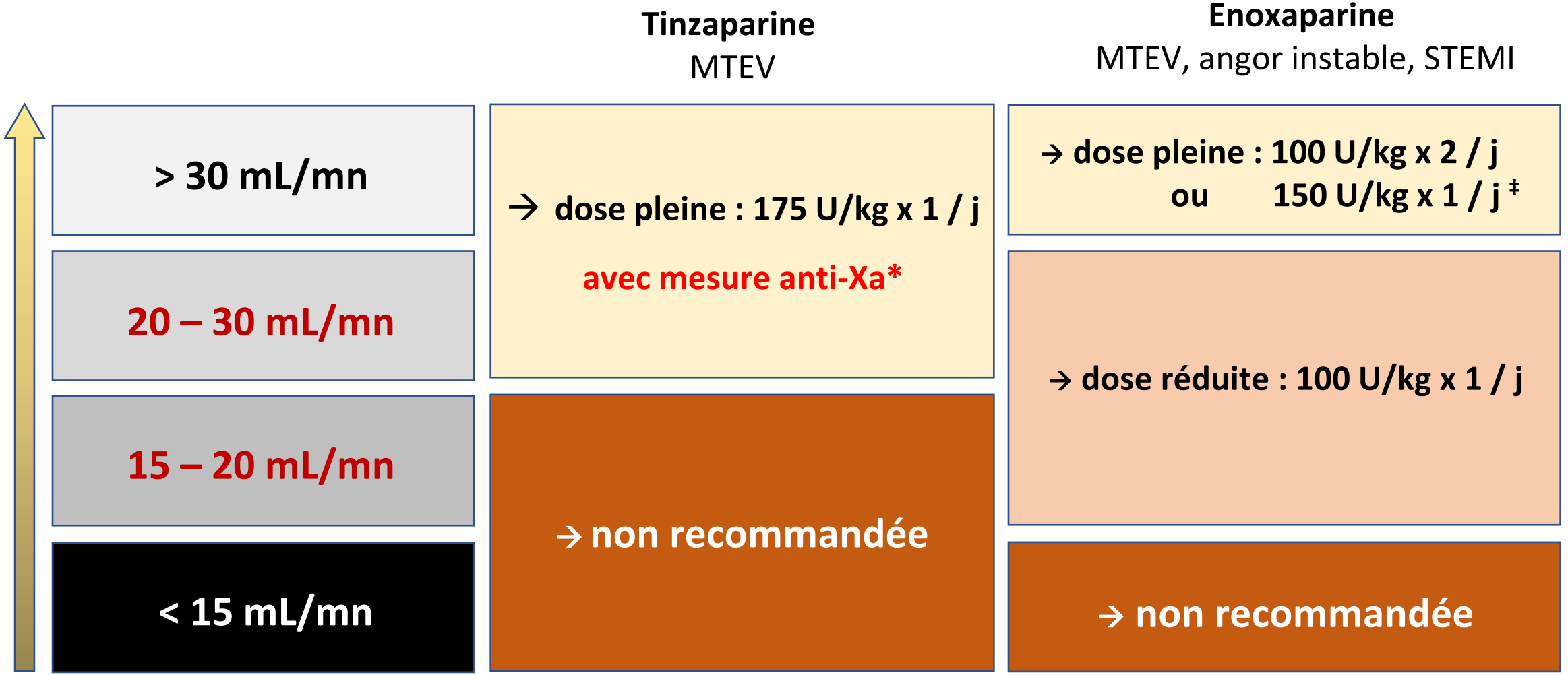
HBPM dose curative et insuffisance rénale



‡ en l'absence d'obésité ou de cancer ou de MTEV non ambulatoire (EP ou TVP iliocave)

***Mesure de l'activité anti-Xa au pic (5 à 6h après injection), après 3 à 4 injections : < 1,5 UI/mL**

Activité anti-Xa au pic : valeur moyennes

Deux injections par jour *(environ 4 heures après inj.)*	Injection unique par jour *(environ 4 heures après inj.)*
Nadroparine 1,0 ± 0,2	Nadroparine 1,34 ± 0,15
Enoxaparine 1,2 ± 0,14	Enoxaparine ND
Daltéparine 0,6 ± 0,25	Tinzaparine 0,87 ± 0,15

Boneu et al. STV 2003 https://doi.org/10.1007/s00277-003-0815
Gouin-Thibault et al, Encycl Med Chir, AKOS, 2013, doi : 10.1016/S1634-6939(13)59295-7 sous l'égide du GFHT

Activité anti-Xa au pic : seuil d'accumulation

Deux injections par jour *(environ 4 heures après inj.)*		Injection unique par jour *(environ 4 heures après inj.)*	
Nadroparine	ND	Nadroparine	1,8
Enoxaparine	~ 1,5	Enoxaparine	ND
Daltéparine	1,0	Tinzaparine	1,5

Boneu et al. STV 2003 https://doi.org/10.1007/s00277-003-0815
Gouin-Thibault et al, Encycl Med Chir, AKOS, 2013, doi : 10.1016/S1634-6939(13)59295-7 sous l'égide du GFHT

Interférence des AOD avec mesure de l'anti-Xa HNF : neutralisation in vitro des AOD / mesure anti-IIa / TCA

	Avantages	Inconvénients
Systèmes d'élimination *in vitro* des AOD	• Facilité d'utilisation • Disponible • Élimination suffisante des AOD dans la majorité des échantillons • Permet la surveillance par mesure de l'activité anti-Xa	• Validation locale préalable • Surcoût et temps technique • Risque d'élimination insuffisante
Activité anti-IIa	• Disponible • Pas d'interférence des AOD anti-Xa	• Mise en place nécessaire • Surcoût • Apport exogène d'antithrombine • Non validée pour cette indication
TCA	• Sensible à l'héparine • Test usuel d'hémostase disponible dans tous les laboratoires • Interférence moindre des AOD anti-Xa	• Manque de spécificité • Variabilité de la sensibilité à l'héparine selon le réactif

Mesure de la concentration d'AOD avant la mise sous HNF
Nécessité pour le biologiste d'avoir connaissance des traitements en cours et des jours précédents
→ Interaction clinico-biologique

Melicine S, RFHT 2023

Interférence des héparines avec la mesure des AOD : neutralisation *in vitro* de l'héparine / réactif non sensible à HNF

Neutralisation HNF

Protamine
Heparinase
Polybrène

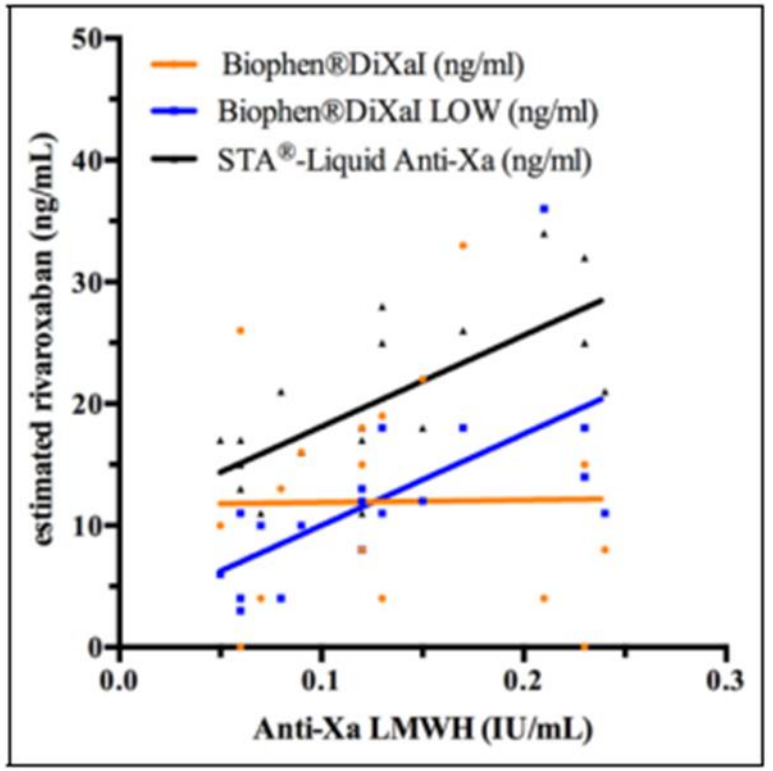
Božič-Mijovski Thromb Res. 2015
Hardy M Int J Lab Hematol 2022

Neutralisation HBPM

Heparinase
Polybrène

Hardy M Int J Lab Hematol 2022

Réactif mesure AOD non sensible à l'HNF



Biophen® DiXaI (Hyphen BioMed)

Lessire S et al, Clin.Applied Thromb.Haemost. 2018
Samama MM et al, Thromb.Haemost. 2010

Danaparoide

Characteristic	Argatroban	Danaparoid	Bivalirudin	Fondaparinux
Target	Thrombin	Factor Xa (predominantly)	Thrombin	Factor Xa
Half-life	40-50 min	24 h	25 min	17-20 h
Elimination	Hepatobiliary	Renal	Enzymatic (80%) Renal (20%)	Renal
Approved for patients with HIT[a]	Treatment/PCI	Treatment	PCI/cardiac surgery	No
Method of administration	IV	IV, SC	IV	SC
Monitoring	aPTT ACT	Anti-Xa level	aPTT ACT or ECT (high doses)	Anti-Xa level
Effect on INR	+++	0	++	0
Immunologic features	None	5% cross-reactivity with HIT Ab[c]	Potentially cross-reactive with anti-lepirudin Ab	May cause HIT[d]
Antidote available	No	No	No	No
Crosses placenta	Unclear[e]	No[e]	Unclear[e]	Yes[e]
Dialyzable	20%	Yes	25%	20%

Adapted from Linkins et al, Chest 141(2):e495S–e530S

Danaparoide

- BCSH: Monitoring the anticoagulant effect of danaparoid using an anti-Xa assay with specific danaparoid calibrators should be considered in patients >90 kg and in patients with renal impairment (glomerular filtration rate <30 ml/min) (2C).
- Target range: 0,5-0,8 anti Xa units/ml (higher in autoimmune HIT: 0,6-1,2 antiXa units/ml)

Watson H et al. Br J Haematol 2012 Dec;159(5):528-40.

Greinacher A et al. J Thromb Haemost. 2017 Aug 28. doi: 10.1111/jth.13813. [Epub ahead of print]

DOAC measurement

Emergency situations	Other situations
■ Bleeding	• Older patients
■ Reversal	• Renal insufficiency
■ Stroke	• Drug-drug interactions
■ Surgery	• Extreme body weight
	• Thrombosis on DOAC

Management guidelines

Interpretation ?

DOAC measurement:
Interpretation of coagulation assays in DOAC-treated patients

Table 4
Interpretation of coagulation assays in DOAC-treated patients. Below on-therapy, on-therapy, and above on-therapy ranges are listed in Table 1 and relate specifically to the doses shown in Table 1.

Test	Dabigatran		Xa Inhibitors	
	Normal	Abnormal/prolonged*	Normal	Abnormal/prolonged*
APTT	Does not exclude on-therapy levels	On-therapy or above on-therapy levels likely present	Does not exclude on-therapy levels	On-therapy or above on-therapy levels likely present
PT	Does not exclude on-therapy levels	On-therapy or above on-therapy levels likely present	Does not exclude on-therapy levels	On-therapy or above on-therapy levels likely present
TT	Excludes clinically significant levels	Below on-therapy, on-therapy, or above on-therapy levels likely present	Not useful	Not useful
dTT	Likely excludes clinically significant levels	May be used to quantify drug levels	Not useful	Not useful
Ecarin-based assay	Likely excludes clinically significant levels	May be used to quantify drug levels	Not useful	Not useful

Test	Dabigatran		Xa Inhibitors	
	<Lower limit of quantification	Analytical measurement range	<Lower limit of quantification	Analytical measurement range
Anti-Xa assay (UFH/LMWH calibrated)	Not useful	Not useful	Likely excludes clinically significant levels	May be used to estimate drug levels
Anti-Xa assay (DOAC calibrated)	Not useful	Not useful	Likely excludes clinically significant levels	May be used to quantify drug levels

DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; UFH, unfractionated heparin.
* Alternative etiologies for coagulopathy should also be considered (e.g. disseminated intravascular coagulation, liver injury, etc.)

Samuelson BT, Cuker A. Blood Rev 2016

DOAC measurement:
Interpretation of coagulation assays in DOAC-treated patients

- Limitation of APTT-PT in DOAC-treated patients
  - Variable sensitivity of reagents
  - Lack of sensitivity of low DOAC concentrations

- Normal PT, APTT, TT + anti-Xa < 0,10 IU/mL
  - exclusion clinically significant levels
  - Only true for some reagents!

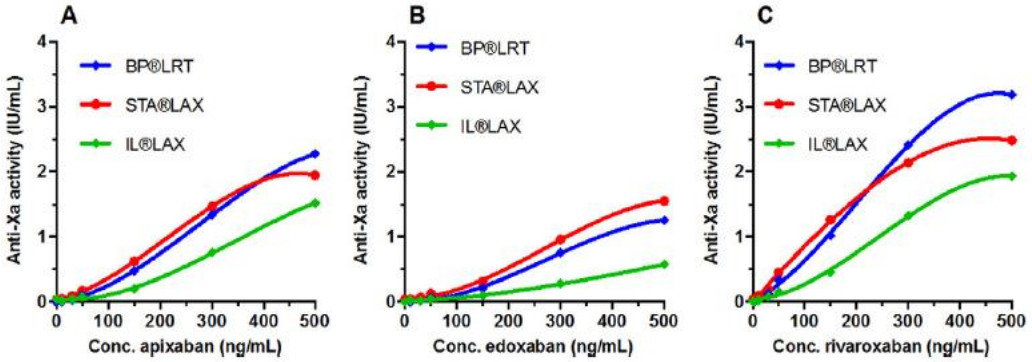


Fig. 1. Direct FXa inhibitors response to heparin-calibrated chromogenic assays. All heparin-calibrated chromogenic anti-Xa assays demonstrate a different anti-Xa response depending on the drug.

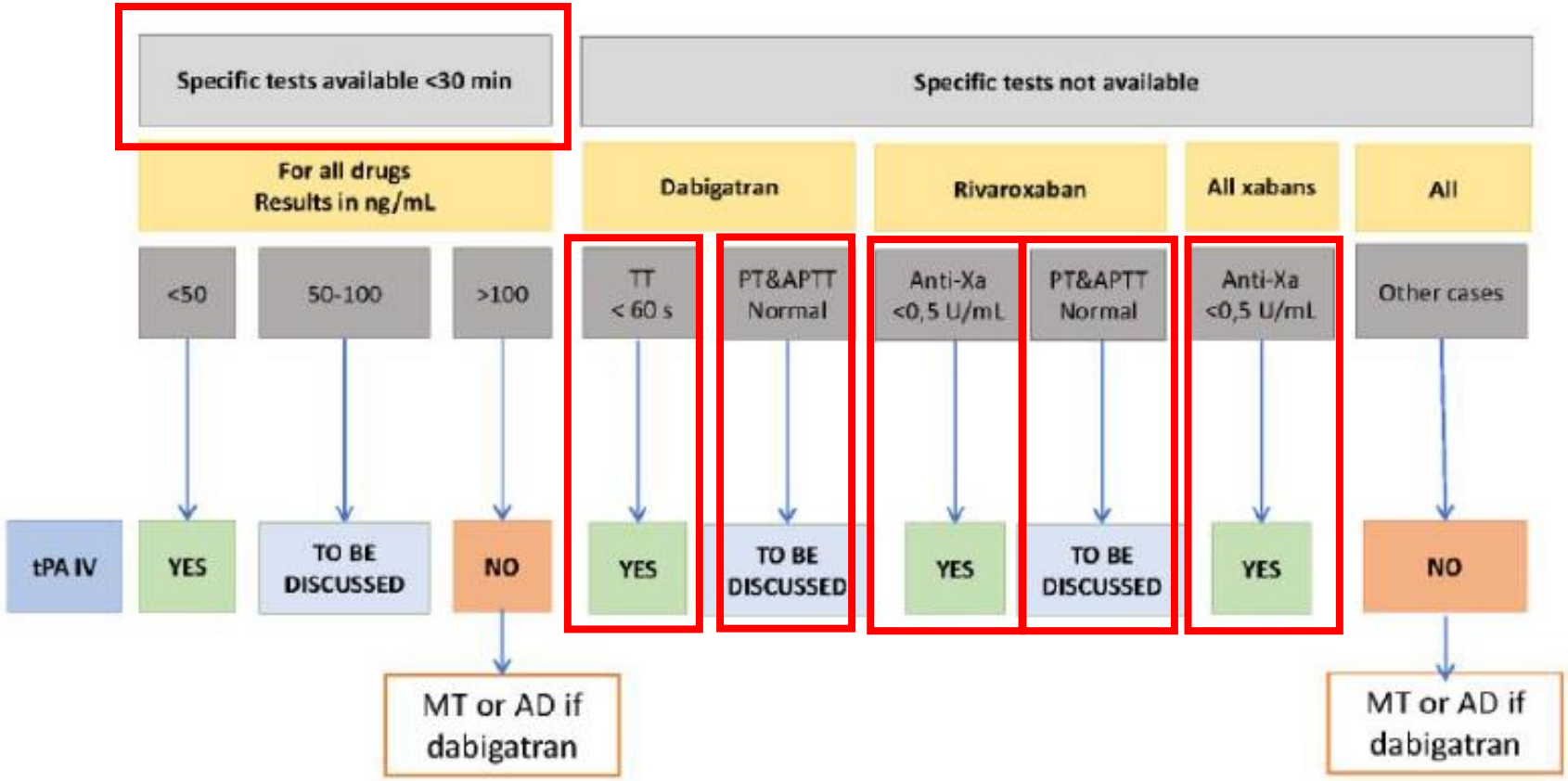
Table 1
Raw data of anti-Xa activities at 30 and 50 ng/mL. Differences between kits are statistically significant for rivaroxaban at 30 ng/mL while all kits showed differences at 50 ng/mL. At similar concentrations, all molecules demonstrate different anti-Xa activities, except with the BP®LRT at 30 ng/mL. However, the *p*-value is borderline significant ($p = 0.06$; Friedman *p*-value).

Concentration (ng/ml)	Anticoagulant	Anti-Xa activity (UI anti-Xa/mL ± SD)			*P-value*‡
		STA®LAX ($n = 3$)	BP®LRT ($n = 3$)	IL®LAX ($n = 3$)	
30	Rivaroxaban	0.19 (±0.02)	0.12 (±0.01)	0.08 (±0.02)	*<0.05*
	Apixaban	0.09 (±0.01)	0.03 (±0.01)	0.04 (±0.01)	*=0.06*
	Edoxaban	0.07 (±0.01)	0.02 (±0.01)	0.02 (±0.01)	*=0.11*
	P-value†	*<0.05*	*=0.06*	*<0.05*	
50	Rivaroxaban	0.45 (±0.01)	0.34 (0.02)	0.16 (±0.02)	*<0.05*
	Apixaban	0.17 (±0.02)	0.10 (±0.02)	0.07 (±0.01)	*<0.05*
	Edoxaban	0.13 (±0.01)	0.06 (±0.01)	0.04 (±0.01)	*<0.05*
	P-value†	<0.05	<0.05	<0.05	

† *P*-value is given for difference between drugs for a same heparin calibrated chromogenic anti-Xa assay (Friedman *p*-value).
‡ *P*-value is given for difference between assays for a given direct FXa inhibitor (Friedman *p*-value).

Sabor L. Thromb Res 2016

Specific tests with short turn around time (TAT) are required in urgent situations (stroke)



Touzé E and coll. Eur J Neurol. 2018

TAT! :

-<30min: not so easy: (Seiffge DJ, Journal of thrombosis and thrombolysis 2017; 43(1): 112-6) (Dincq et al. Int J Lab Hematol. 2018 Dec;40(6):e105-e108.)

-How to improve? (short centrifugation, reagents/controls preparation, dedicated procedure: call to the laboratory from the ambulance)

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Heparin-calibrated chromogenic anti-Xa assay for the detection of threshold-levels of DOACs?

- Data are available
  - Brakta et al.2022:
    - Prospective study : apixaban (n=325) , rivaroxaban (n=276)
    - STAR-Liquid-Anti-Xa (Stago) with specific DOAC- or LMWH-calibrators (Multi-HEP [Stago])
    - Derivation cohort and validation cohort (50/50)

Table 1. Nomogram converting LMWH anti-Xa activity (STA®-Liquid-Anti-Xa, Stago) into apixaban or rivaroxaban concentrations

LMWH anti-Xa activity (IU/mL)	Concentration (ng/mL) [95% CI]	
	Apixaban	Rivaroxaban
≤0.10	≤23 [18, 30]	≤20 [13, 31]
0.15	24 [19, 31]	21 [14, 32]
0.20	26 [20, 33]	22 [14, 33]
0.25	27 [21, 34]	23 [15, 35]
0.30	28 [22, 36]	24 [15, 36]
0.35	30 [23, 38]	25 [16, 37]
0.40	31 [24, 40]	26 [17, 39]
0.45	32 [25, 42]	27 [18, 41]
0.50*	34 [27, 44]*	28 [18, 42]*
0.55	36 [28, 46]	29 [19, 44]
0.60	37 [29, 48]	30 [20, 46]
0.65	39 [31, 50]	31 [21, 48]
0.70	41 [32, 53]	33 [22, 50]
0.75	43 [34, 55]	34 [23, 52]
0.80	45 [35, 58]	36 [24, 54]
0.85	48 [37, 61]	37 [25, 56]
0.90	50 [39, 64]	39 [26, 58]
0.95	52 [41, 67]	40 [27, 61]
1.00	55 [43, 70]	42 [28, 63]
1.05	58 [45, 74]	44 [29, 66]
1.10	60 [47, 77]	46 [30, 69]
1.15	63 [50, 81]	48 [32, 72]
1.20	66 [52, 85]	50 [33, 75]
1.25	70 [54, 89]	52 [34, 78]
1.30	73 [57, 93]	54 [36, 81]
1.35†	77 [60, 98]†	56 [37, 85]
1.40	80 [63, 103]	59 [39, 88]
1.45	84 [66, 108]	61 [41, 92]
1.50	88 [69, 113]	64 [42, 96]
1.55†	93 [73, 118]	66 [44, 100]†
1.60	97 [76, 124]	69 [46, 104]
1.65	102 [80, 130]	72 [48, 108]
1.70	107 [84, 137]	75 [50, 113]
1.75	112 [88, 144]	78 [52, 118]
1.80	118 [92, 151]	82 [54, 123]
1.85	123 [96, 158]	85 [56, 128]
1.90	129 [101, 166]	89 [59, 134]
1.95	136 [106, 174]	92 [61, 140]
≥2.00	≥142 [111, 182]	≥96 [64, 146]

LMWH, low-molecular-weight heparin; DOAC, direct oral factor-Xa anti-coagulant; CI, confidence interval.
*The recommended 0.5 IU/mL limit[2] corresponding DOAC concentrations;
†Anti-Xa value corresponding to apixaban concentration <100 ng/mL;
†Anti-Xa value corresponding to rivaroxaban concentration <100 ng/mL

Adapted from Brakta Journal of Stroke 2023

Heparin-calibrated chromogenic anti-Xa assay for the detection of threshold-levels of DOACs?

- Data are available
  - Brakta et al.2022:

Table 2. Model performances in the validation cohort

DOAC threshold (ng/mL)	LMWH anti-Xa (IU/mL)	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]	True positive rate* (%) [95% CI]
Apixaban				
<30	<0.10	25 [3.2, 65.1]	100 [97.6, 100]	100 [15.8, 100]
<50	<0.64	66.7 [48.1, 73.4]	99.3 [95.9, 100]	94.7 [74.0, 99.9]
<75	<1.07	61.3 [46.0, 83.5]	100 [96.3, 100]	100 [90.8, 100]
<100	<1.37	63.6 [53.4, 73.1]	100 [94.1, 100]	100 [94.3, 100]
Rivaroxaban				
<30	<0.10	6.1 [0.7, 20.2]	100 [96.6, 100]	100 [15.8, 100]
<50	<0.71	58.9 [45.0, 71.9]	100 [95.6, 100]	100 [89.4, 100]
<75	<1.21	68.1 [56.0, 78.6]	100 [94.6, 100]	100 [92.8, 100]
<100	<1.55	75.9 [65.5, 84.4]	100 [93.0, 100]	100 [94.6, 100]

DOAC, direct oral factor-Xa anticoagulant; LMWH, low-molecular-weight heparin; CI: confidence interval.
*Percentage of values correctly predicted.

Brakta Journal of Stroke 2023

Heparin-calibrated chromogenic anti-Xa assay for the detection of threshold-levels of DOACs?

- Data are available
- BUT:
  - Interreagent variability : STAR-Liquid-Anti-Xa (Stago)
  - InterDOAC variability: only validated for rivaroxaban and apixaban
  - Limitations:
    - Unknown impact of measurement uncertainty (large CI!)
    - Practical difficulties for clinicians (different cut-off for each (some of the) DOAC, change with each batch, ...)
    - A result of > 0.1, 0.6, 1.4 IU/mL did not always correspond with a concentration of DOAC >30,50,100 ng/mL. This could falsely lead to exclusion of the patient from thrombolysis treatment (cfr sensitivity previous slide)

Beyer J, et al. Clin Appl Thromb Hemost 2016
Maier CL, et al. Am J Hematol 2019
Boissier E et al.Anesth Analg 2021, Willekens G, et alBr J Haematol 2021
Meihandoest T, et al. Front Cardiovasc Med 2022, Mithoowani S et al. Thromb Res 2022, von Horn H, Int J Lab Hematol 2022
Delassasseigne ABC 2023, Brakta Journal of Stroke 2023
Amundsen RPTH 2024, De Smet IJLH 2024

Heparin-calibrated chromogenic anti-Xa assay for the detection of threshold-levels of DOACs?

- Data are available
  - De Smet et al.2024:
    - In vitro study (spiking) and retrospective study : apixaban (n=25) , rivaroxaban (n=28) , edoxaban (n=24)
    - STAR-Liquid-Anti-Xa (Stago) with specific DOAC- or LMWH-calibrators (Multi-HEP [Stago])= Brakta
    - <0.3 IU/mL obtained with the STA-Liquid heparin-calibrated anti-Xa assay rules out significant (>30 ng/mL) levels of apixaban, rivaroxaban and edoxaban → vs Brakta 0.1IU/ml
    - Agreement between spiked and patient samples was best for edoxaban, followed by rivaroxaban and apixaban.

De Smet IJLH 2024

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Heparin-calibrated chromogenic anti-Xa assay for the detection of threshold-levels of DOACs?

Received: 15 May 2024 | Revised: 4 July 2024 | Accepted: 8 July 2024
https://doi.org/10.1016/j.jtha.2024.07.009

jth

ISTH SSC COMMUNICATIONS

Reversal of direct oral anticoagulants: guidance from the SSC of the ISTH

Jerrold H. Levy[1] | Joseph R. Shaw[2] | Lana A. Castellucci[3] | Jean M. Connors[4] | James Douketis[5] | Edelgard Lindhoff-Last[6] | Bianca Rocca[7,8] | Charles Marc Samama[9] | Deborah Siegal[3] | Jeffrey I. Weitz[10]

For FXaI, the drug levels of apixaban, rivaroxaban, or edoxaban are best quantified using calibrated chromogenic anti-FXa assays. Heparin-calibrated anti-FXa assays show an approximately linear relationship for FXaI levels of 30 to 100 ng/mL with acceptable sensitivity and specificity, but the relationship is nonlinear with concentrations <30 ng/mL or >150 ng/mL [49,50]. Heparin-calibrated anti-FXa assays are therefore not recommended to exclude concentration thresholds of 30 to 50 ng/mL without a rigorous and well-defined in-house laboratory validation process [6].

Levy J et al. JTH 2024

Cut-off of 30-50 ng/ml?

- DOAC concentrations of 30 ng/mL and 50 mg/mL are considered clinically relevant thresholds (Levy et al JTH 2024, Shaw JR et al 2023, Douketis JD et al. JAMA Intern Med 2019, Douketis JD Thromb Res 2016):
  - Douketis JD, JAMA Intern Med. 2019;179:1469–78:
    - Preoperative DOAC treatment levels were measured for 2541 patients (84.5%)
    - The proportion of patients with a level less than 50 ng/mL was 90.5% in the apixaban cohort, 95.1% in the dabigatran cohort, and 96.8% in the rivaroxaban cohort.
    - Among 1007 patients who had a high–bleeding-risk procedure, 832 (82.6%) had anticoagulant measurements, of whom the proportion with a residual anticoagulant level less than 50 ng/mL was 98.8%.
    - The proportion of patients with a residual anticoagulant level of 30 to 49.9 ng/mL in the high–bleeding-risk procedure group was 4.8% in the apixaban cohort, 0.55% in the dabigatran cohort, and 14.0% in the rivaroxaban cohort

- 30ng/ml is not equivalent for all DOACs (Evrard J et al. Int J Lab Hematol 2021)

- Measurement uncertainty (IQC +EQC) : eg: Liquid antiXa on STAR MAX 2
  - For 50ng/mL the result is comprised between 40 and 60ng/mL /ml
  - For 30 ng/ml, the result is comprised between 20 and 40ng/mL (LOQ!)

DOAC measurement in non urgent situations

Non-vitamin-K oral anticoagulants and laboratory testing: now and in the future

Views from a workshop at the European Medicines Agency (EMA)

- **No therapeutic range**
- "**On-therapy range**" for each molecule and indication
- **No dose adjustment on plasma concentration:** adjustment on age, renal function, drugs, bleeding risk
- **DOAC** concentration: one factor in determining bleeding risk

Salmonson T, Eur Heart J 2017

DOAC measurement in non urgent situations

- The Kidoac study

Essentials

- It is not well known whether direct oral anticoagulant (DOAC) concentrations are stable over time within and between patients.
- DOAC peak and trough concentrations were determined for 152 patients at three different time points.
- Inter-individual variability was substantial and higher than intra-individual variability.
- These findings support further study into an optimal target range for DOACs.

Toorop MMA et al. J Thromb Haemost.2022

DOAC measurement in non urgent situations

- The MAS study
  - Observational, prospective, multicenter Measure and See (MAS) study
  - Blood was collected 15 to 30 days after starting DOAC treatment in patients with AF who were followed-up for 1 year (thrombosis, major and clinically relevant non-major bleeding)
  - Trough and peak DOAC levels were assessed in 1657[957 (57.7%) and 700 treated with standard and low-dose, respectively] and 1303 patients, respectively.
  - In total, 21 thrombotic complications were recorded during 1606 years of follow-up (incidence of 1.31% of patients per year).
  - Of 21 thrombotic events, 17 occurred in patients whose standardized activity levels were below the mean of each DOAC (0); the incidence was the highest (4.82% of patients per year) in patients whose standardized values were in the lowest class (-1.00 or less).

Palareti G et al. Blood Adv June 6
Testa S. et al. Blood Adv. 2024 Apr 23;8(8):1846-1856.

DOAC measurement in non urgent situations

- The MAS study
  - Fifty bleeding events were recorded during 1606 years of follow-up (3.11% pt/yrs).
  - Fifteen bleeding events (4.97% pt/yrs) occurred in patients with C-trough standardized values in the highest activity class (> 0.50); whereas 35 events (2.69% pt/yrs) occurred in those with values in the two lower classes (<= 0.50, p= 0.0401).
  - Increasing DOAC levels and low-dose DOAC use were associated with increased bleeding risk in the first three months of treatment.
  - 19% of patients receiving low doses had standardized activity values in the highest class.
  - More bleeding occurred in patients treated with low (4.3% pt/yrs) than standard (2.2% pt/yrs; p= 0.0160) dose DOAC.

Palareti G et al. Blood Adv June 6
Testa S. et al. Blood Adv. 2024 Apr 23;8(8):1846-1856.

DOAC measurement in non urgent situations

- The MAS study
  - Early measurement of DOAC levels in patients with AF allowed us to identify most of the patients who, having low baseline DOAC levels, subsequently developed thrombotic complications.
  - Further studies are warranted to assess whether thrombotic complications may be reduced by measuring baseline DOAC levels and modifying treatment when indicated.
  - Early measurement of DOAC levels in AF patients identified many subjects with high activity levels despite the low doses use and had more bleeding risk during the first 3 months of treatment.

Palareti G et al. Blood Adv June 6
Testa S. et al. Blood Adv. 2024 Apr 23;8(8):1846-1856.

DOAC measurement in non urgent situations: Reduced DOAC doses

- Substudy of the MAS study
  - Seven hundred AF patients (42% of the total 1657) received a reduced dose (considered inappropriate in 140 [20%]).
  - They were older, more frequently women, with lower body mass index (BMI), hemoglobin levels, and creatinine clearance.
  - They more often had cerebral or cardiovascular diseases, were taking more medications, with higher scores for thrombotic or bleeding risk.
  - Despite the use of low doses, 133 (19.0%) patients had high standardized C-trough DOAC levels and experienced a high proportion of bleeding events (8.3% per year).
  - Conversely, some patients (4.7%) had very low levels, resulting in a high incidence of thrombotic events (6.7% per year). No difference was detected if the reduced dose was appropriate or not.
  - *Conclusion*: The unpredictable, highly variable inter-individual anticoagulant effect of DOACs may lead to either too low or too high anticoagulant levels, increasing the risk of thrombotic or bleeding events. This is particularly relevant for patients with high-risk conditions, such as those chosen for reduced-dose treatment.
  - Further studies are needed to investigate this important clinical issue.

Palareti G et al. Int J Cardiol. 2024 Aug 24:132484.

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DOAC measurement in non urgent situations

Table 2 Examples of Clinical Management

No	DOAC	DOAC Plasma Level	Action	Details
1	Apixaban 2.5 mg BID	Trough: 36 ng/mL Range: 34-162 ng/mL	DOAC dose increase	Carbamazepine 200 mg BID had been started for >1 month, for epilepsy. Given a CHA_2DS_2-VASc score of 7, apixaban dose regimen was increased to 5 mg BID. A new specific assay was performed after 3 days of intake, with an apixaban trough level of 139 ng/mL.
8	Apixaban 5 mg BID	Trough: 25 ng/mL Range: 41-230 ng/mL	Switch to LMWH	Rifampicin 450 mg BID had been started for 8 days, for prosthetic material infection. The patient was switched to enoxaparin 80 mg BID, until 2 weeks after rifampicin discontinuation.
5	Apixaban 5 mg BID	Trough: 19 ng/mL Range: 41-230 ng/mL Peak: 66 ng/mL Range: 91-321 ng/mL	Switch to VKA	Carbamazepine 400 mg BID had been started for >1 month, for migraine. Apixaban treatment started 3 days prior to measurement, in a context of postoperative atrial fibrillation. The patient was switched to acenocoumarol (no history of labile INR).
17	Rivaroxaban 20 mg OD	Trough: 20 ng/mL Range: 12-137 ng/mL Peak: 112 ng/mL Range: 184-343 ng/mL	Switch to another DOAC	Rifampicin 300 mg OD had been started for >1 month, for mycobacteriosis. Given eating disorders limiting rivaroxaban absorption, the patient was switched to edoxaban 60 mg OD. A new specific assay was performed after 3 days of intake, with an edoxaban trough level of 18 ng/mL and peak level of 218 ng/mL. The patient was also switched from azithromycin to clarithromycin (for a more potent inhibitory effect).

BID = twice daily; CHA2DS2-VASC = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category; DOAC = direct oral anticoagulant; INR = international normalized ratio; LMWH = low-molecular-weight heparin; OD = once daily; VKA = vitamin K antagonist.

BRIEF OBSERVATION

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The Impact of Strong Inducers on Direct Oral Anticoagulant Levels

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Monitoring of heparins and measurement of DOACs: Conclusions

- Heparins:
  - Anti-Xa > TCA
  - Anti-Xa: variability (<APTT) between reagents but is not a global assay
  - Anti-Xa: Dextran (UFH>LMWH, appropriate?), AT or not
  - UFH
    - "Heparin resistance"
    - Need for additional clinical data and guidance on the management including nomogram, therapeutic range and tests
  - LMWH
    - To detect an accumulation
    - At peak activity (4-6h post administration)
    - Interpretation according to the drug

Monitoring of heparins and measurement of DOACs: Conclusions

- DOACs:
  - PT-APTT: interreagent variability, low sensitivity, should not be used
  - Specific assays: Interlaboratory variability between reagents ~ INR
  - Specific assays: Be careful in the low range
  - Specific assays: Short TAT (<30min) is possible
  - Specific assays: Interference of heparins (some assays)
  - heparin-calibrated DOAC measurement: caution
  - Management according to the guidelines (urgent situations) or to the On-therapy range (non-urgent situations)

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