

**DU CEC 2025**

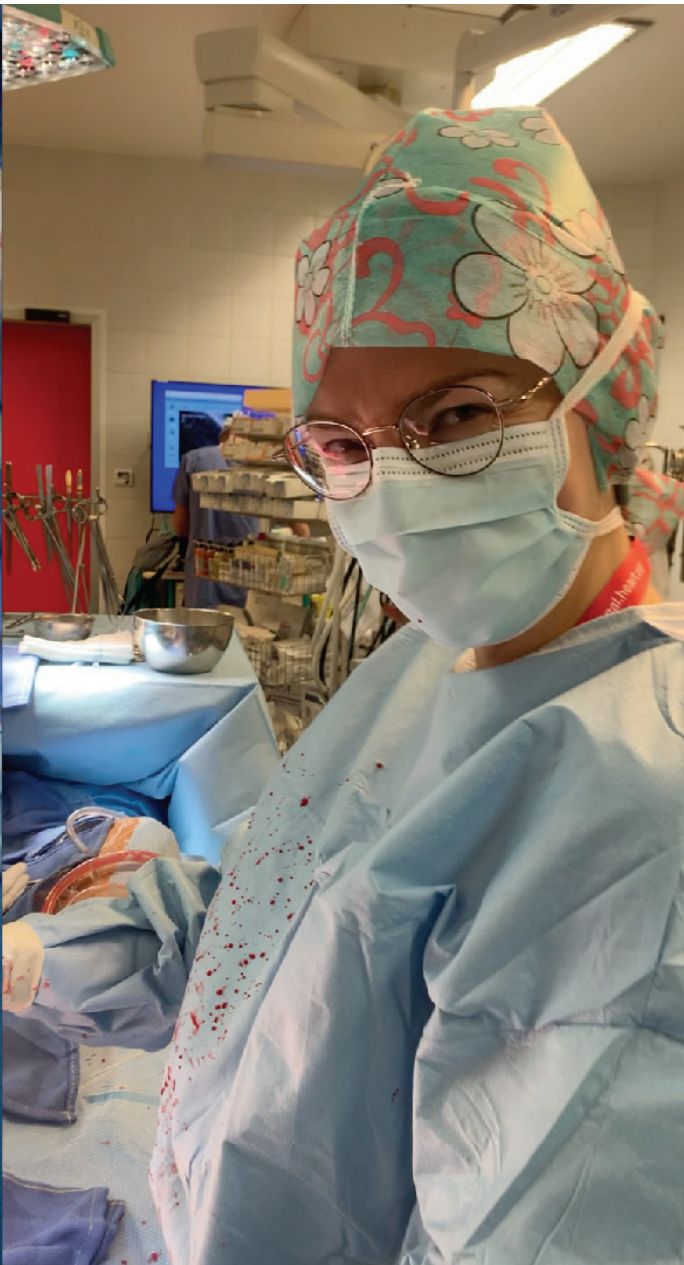
**PHYSIOPATHOLOGIE DE L'HÉMOSTASE EN CEC**

**Alexandre Mansour**

Anesthésie-Réanimation CTCV - CHU Rennes

[alexandre.mansour@chu-rennes.fr](mailto:alexandre.mansour@chu-rennes.fr)





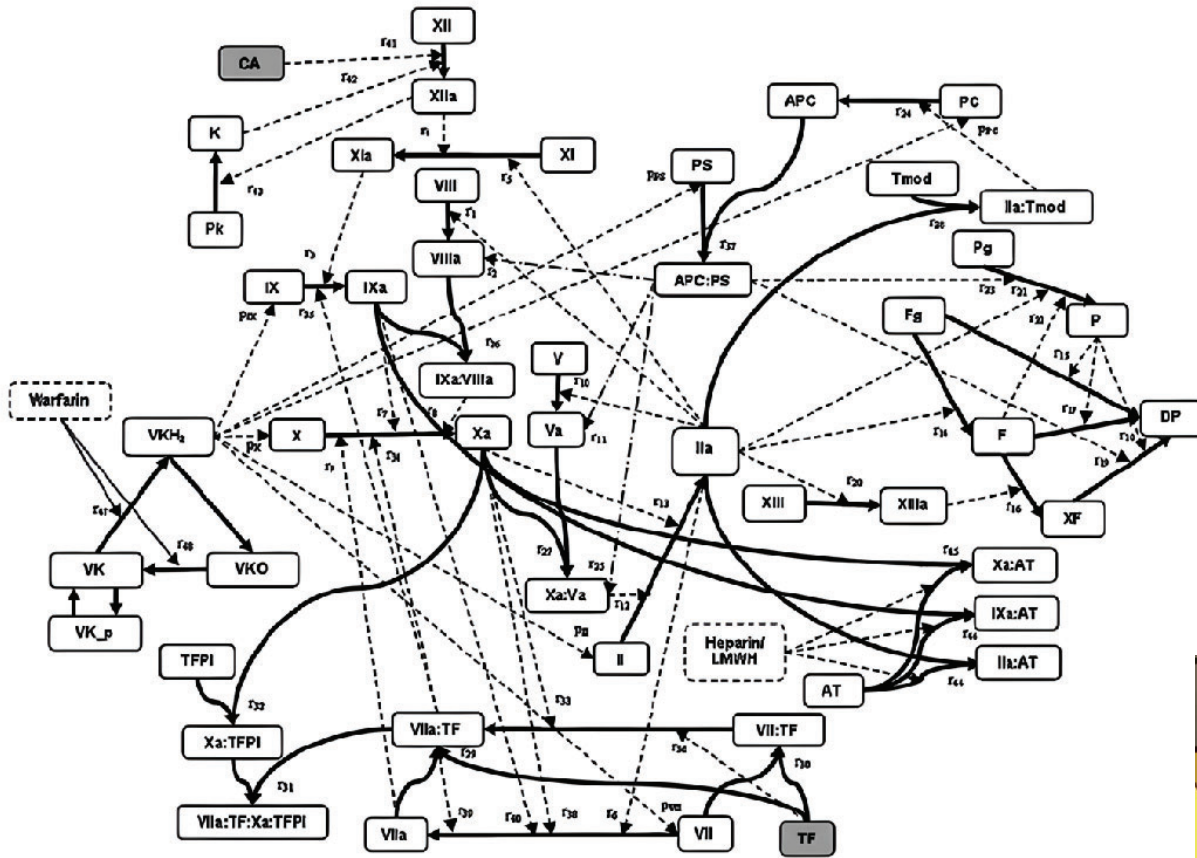
Bloc et Réa Cardiothoracique

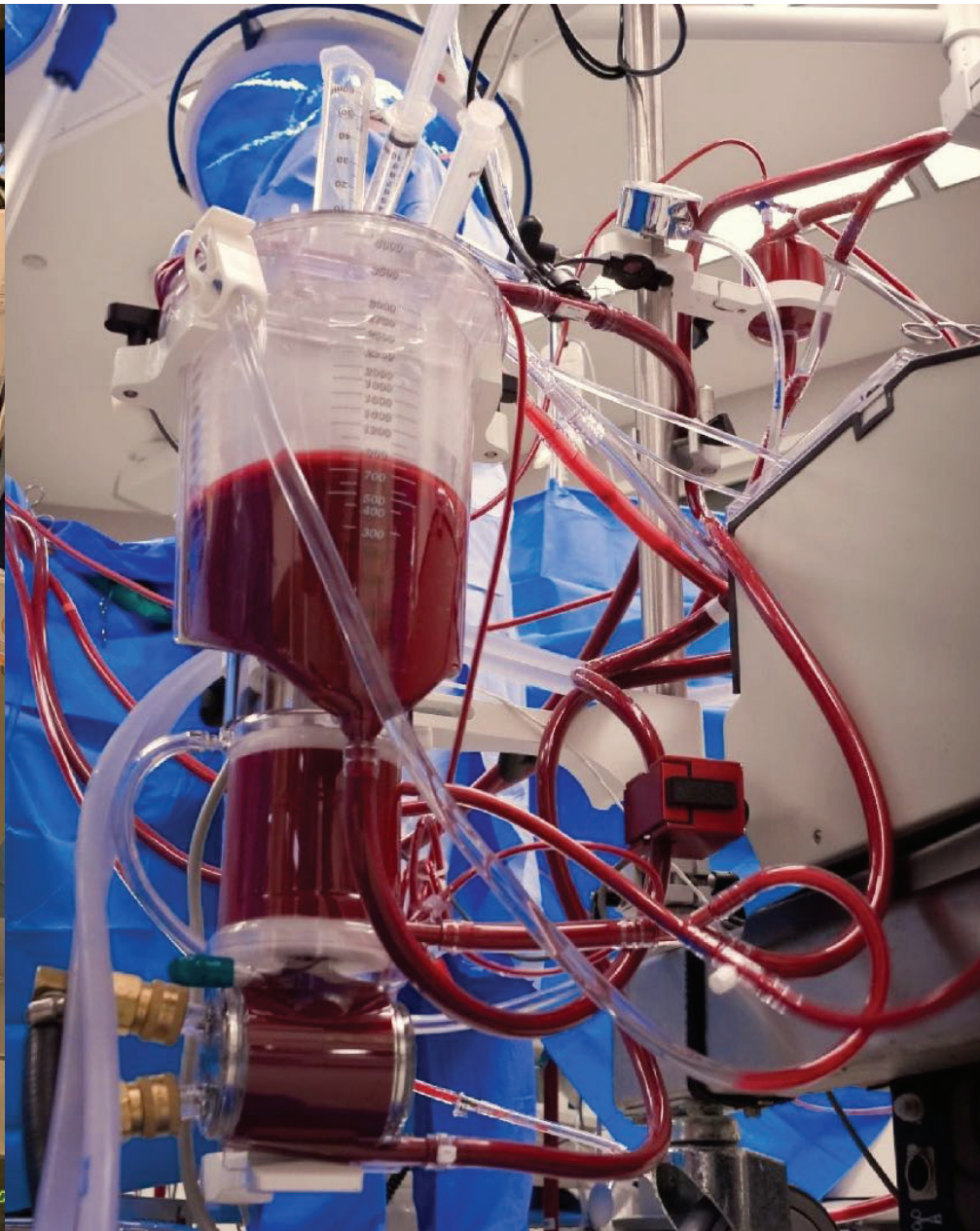
Réa CTCV 17 lits

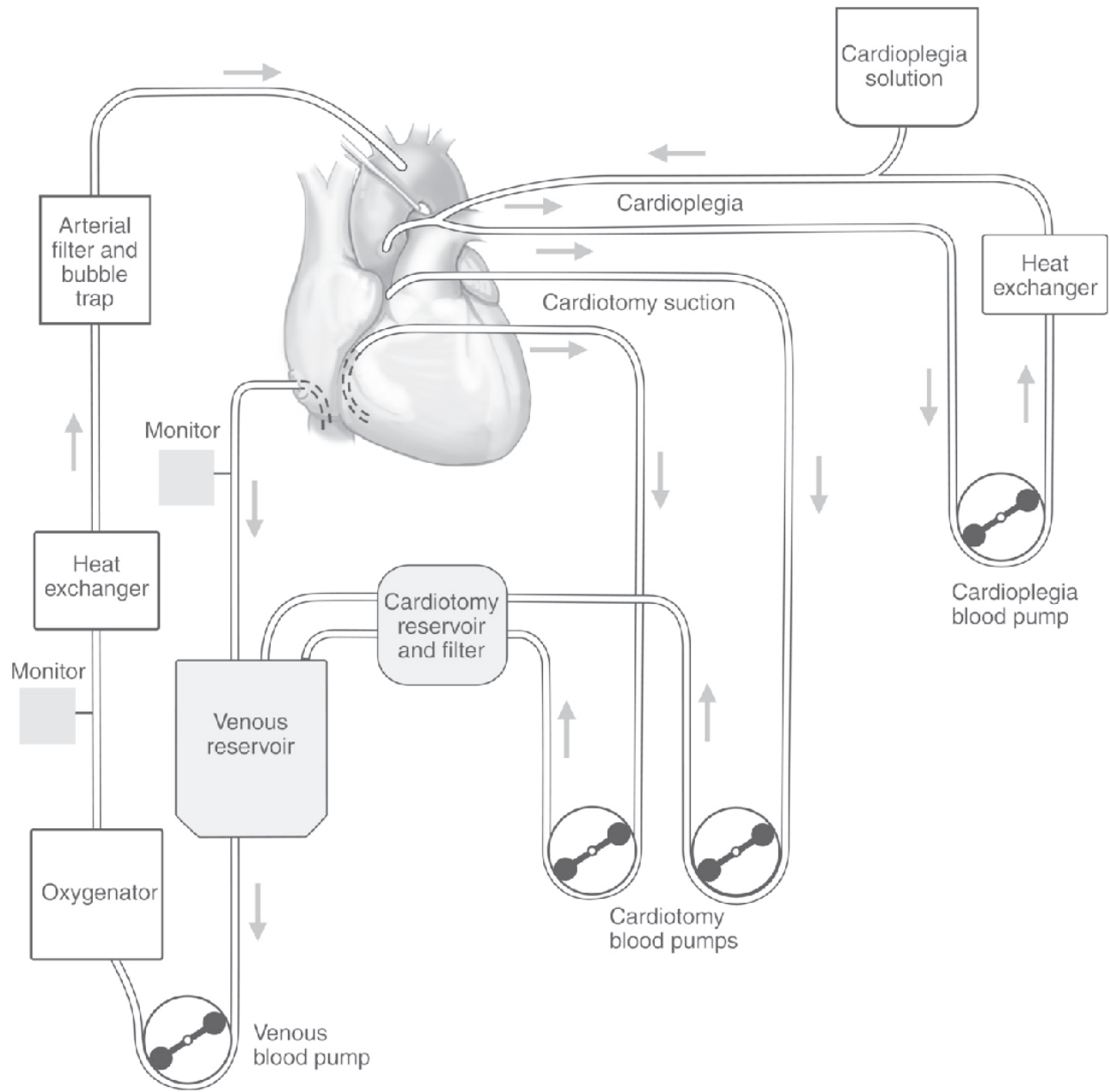
1200 CEC/an

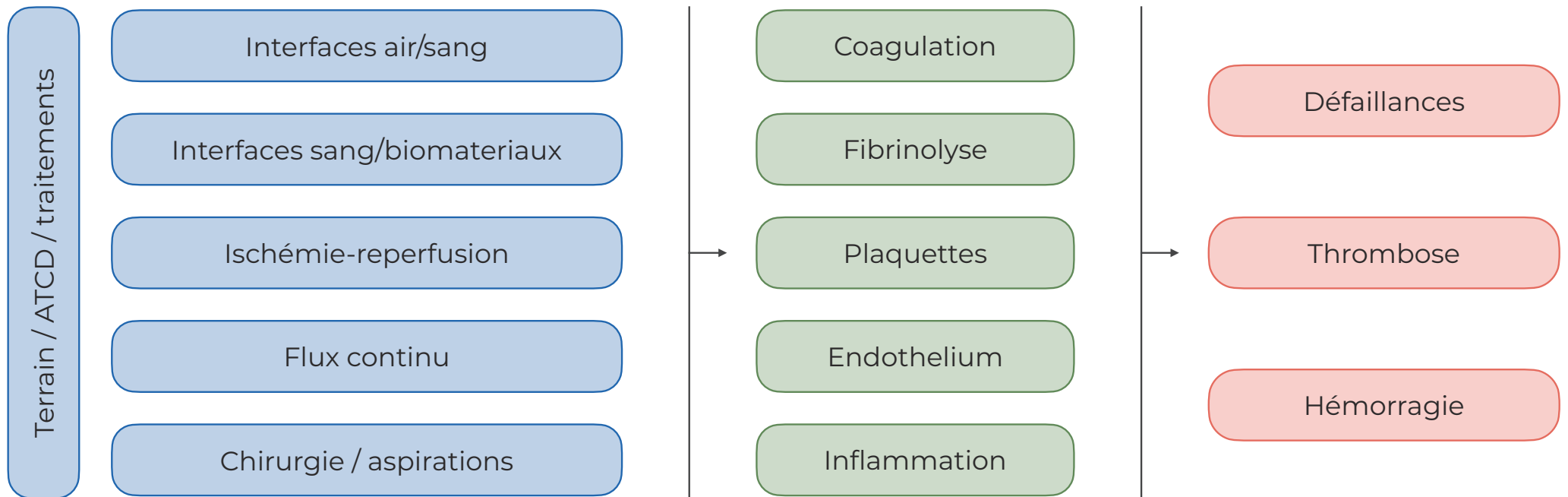
ECMO - Assistance - Greffe

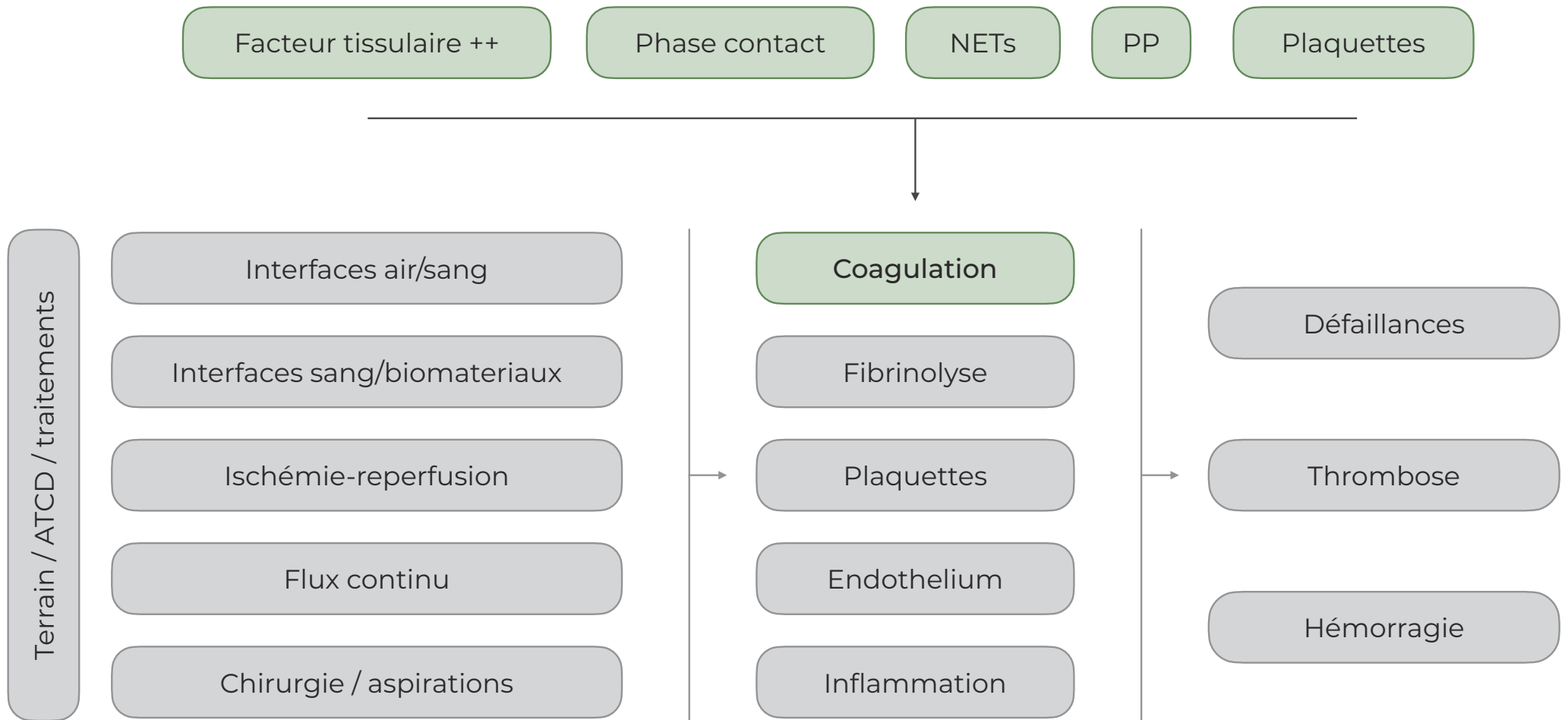
# Particularités de la chirurgie cardiaque





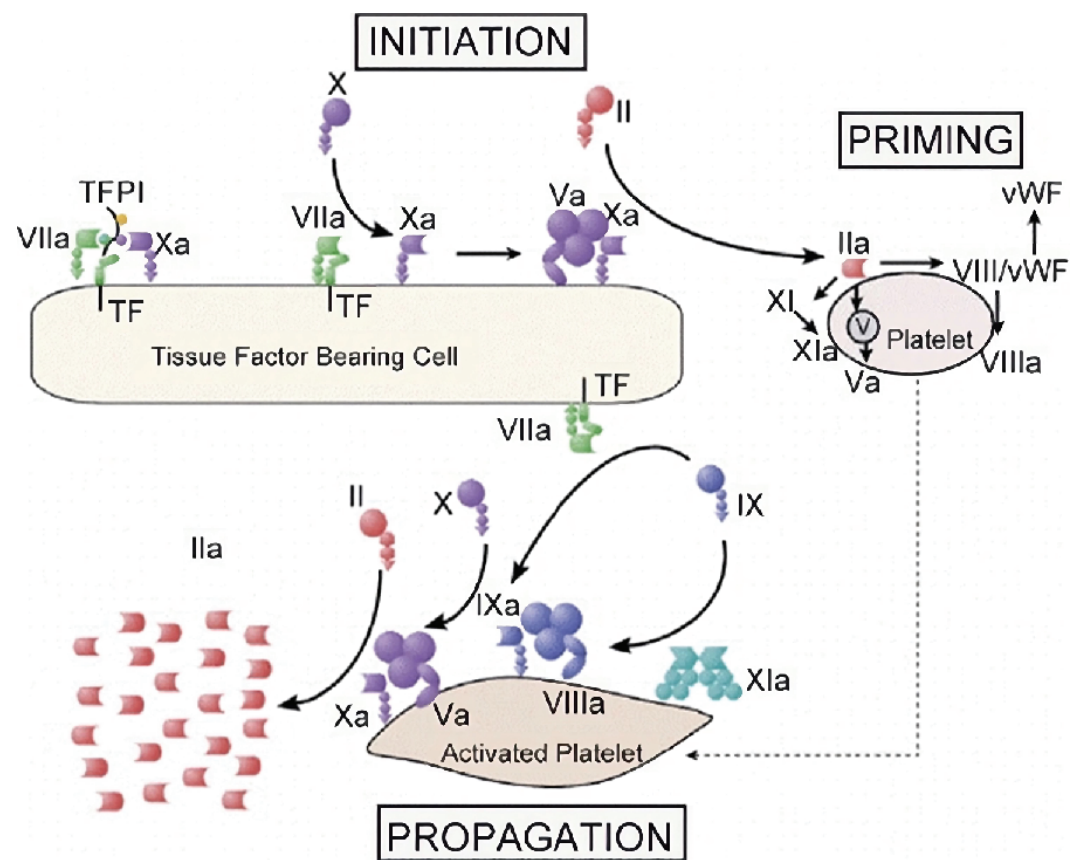
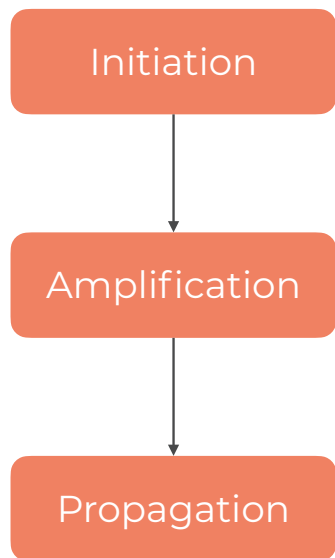


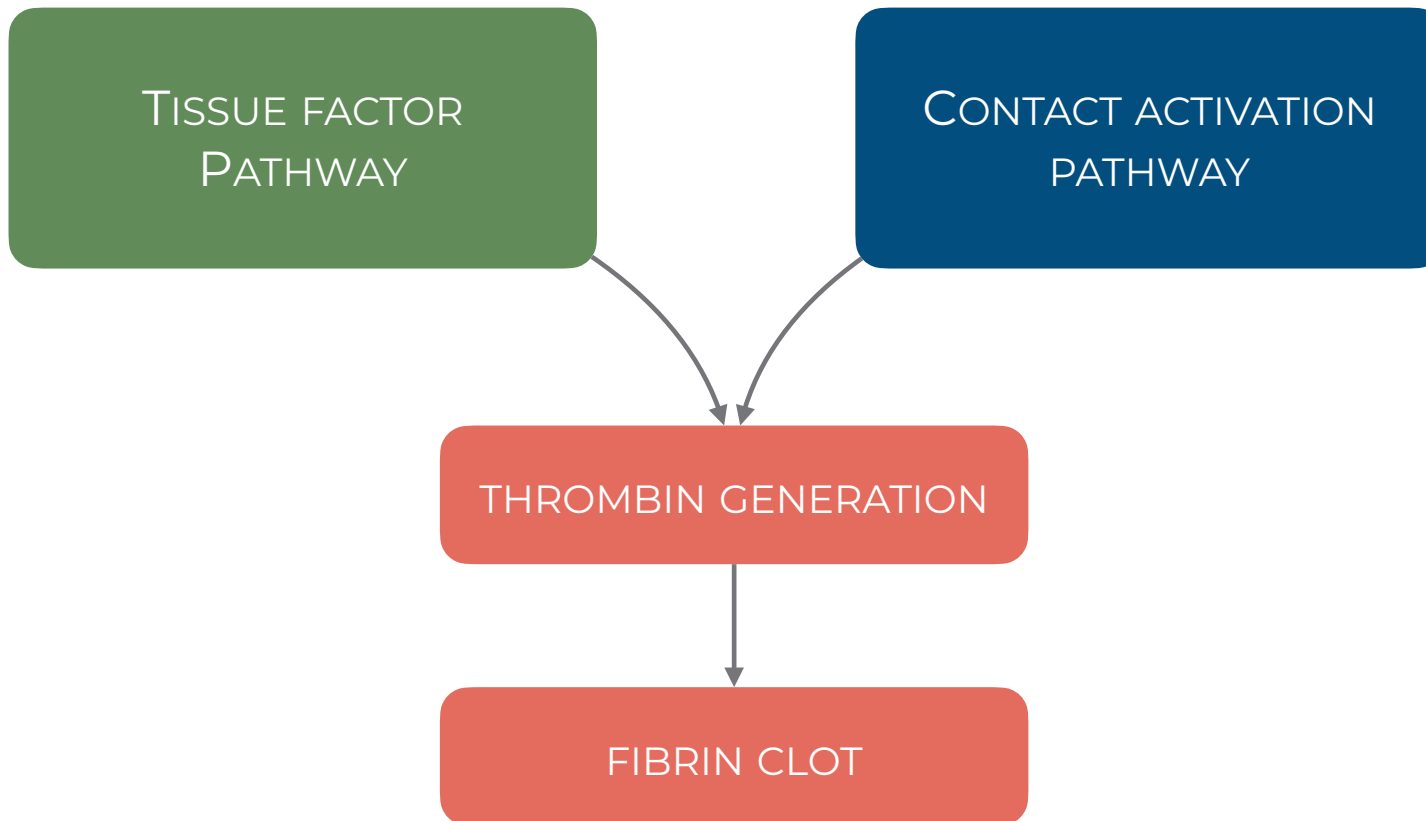




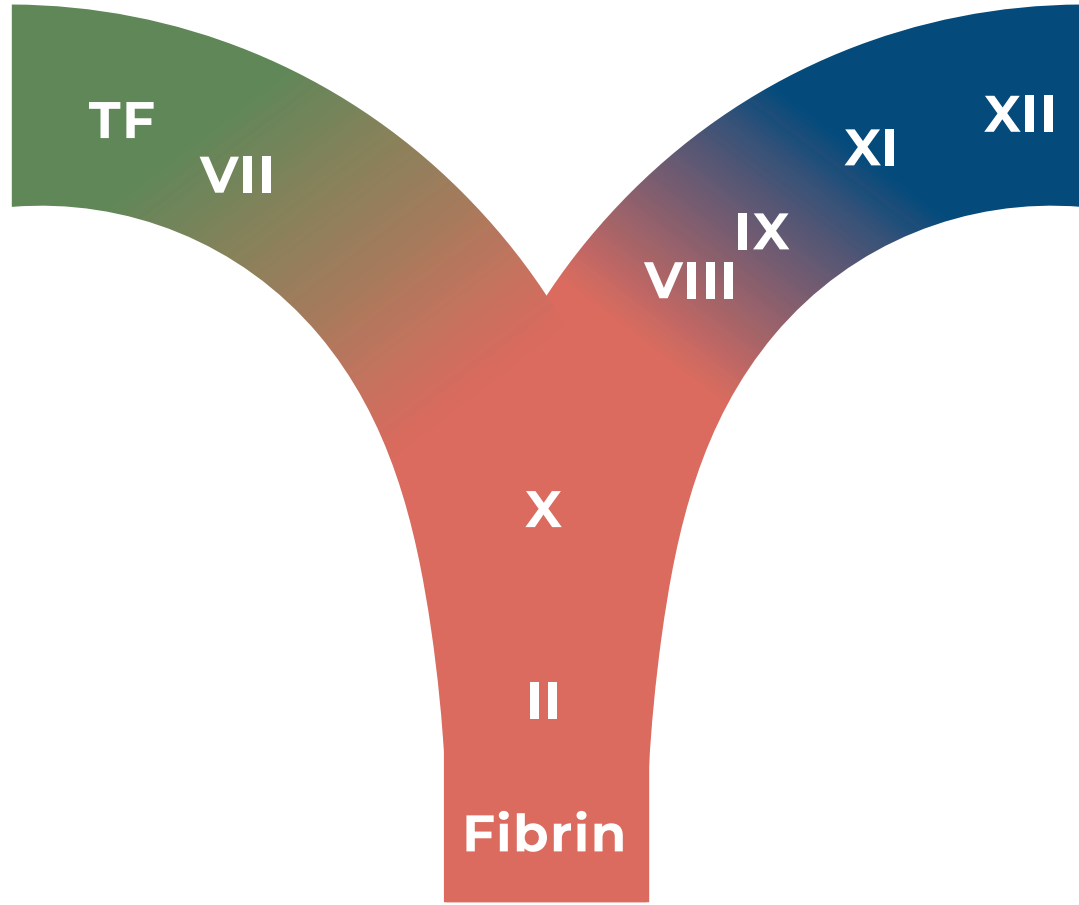
# A Cell-based Model of Hemostasis

Maureane Hoffman, Dougald M. Monroe III



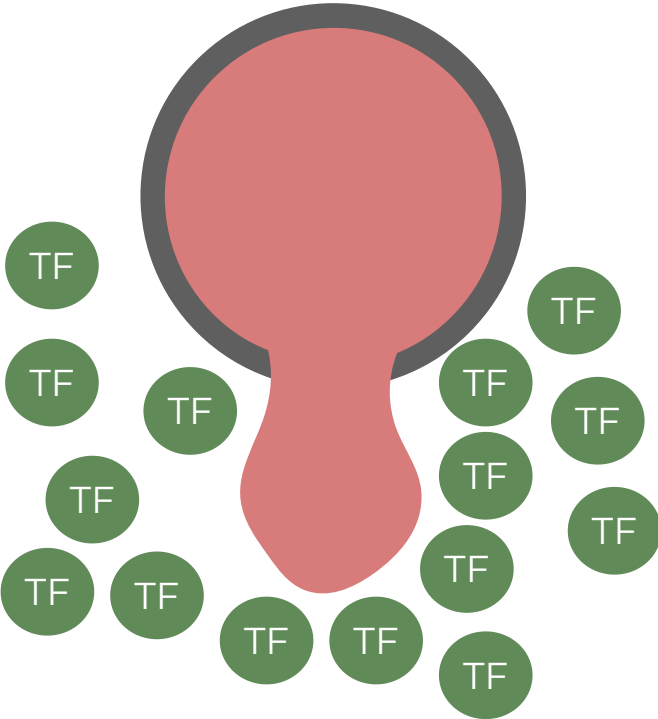


TISSUE FACTOR  
PATHWAY



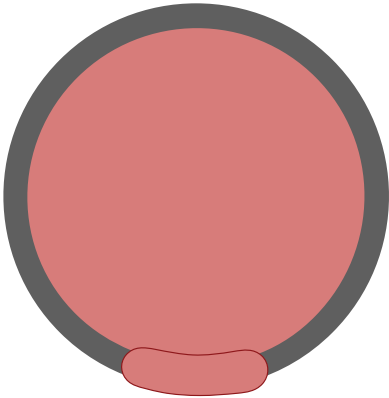
CONTACT ACTIVATION  
PATHWAY

# HEMOSTASIS

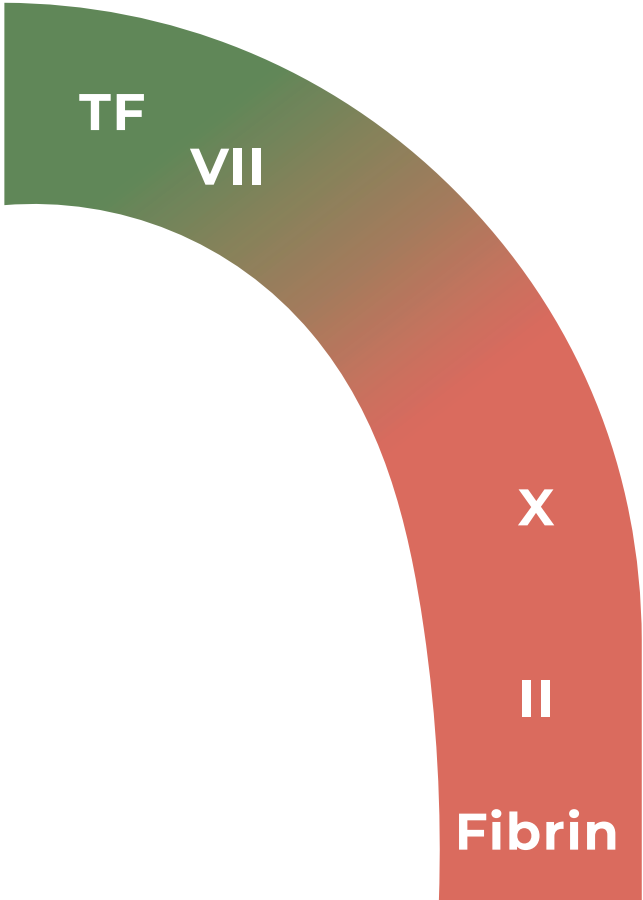


Vascular breach

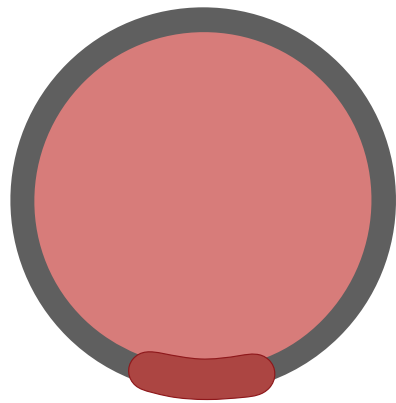
# HEMOSTASIS



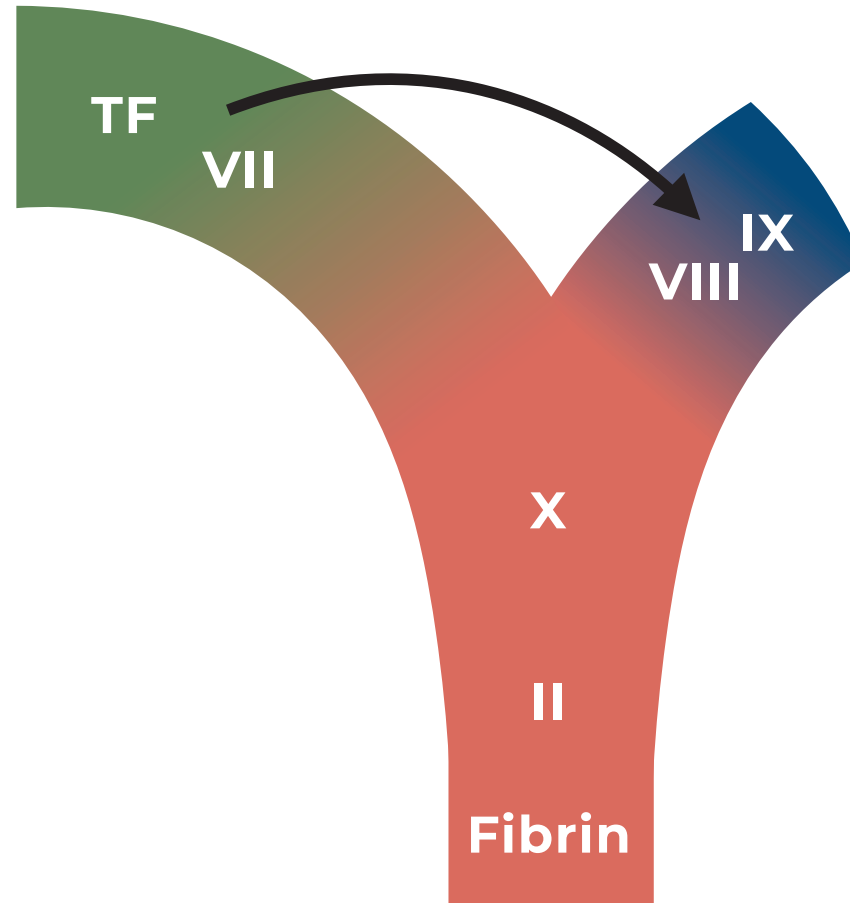
Unstable clot



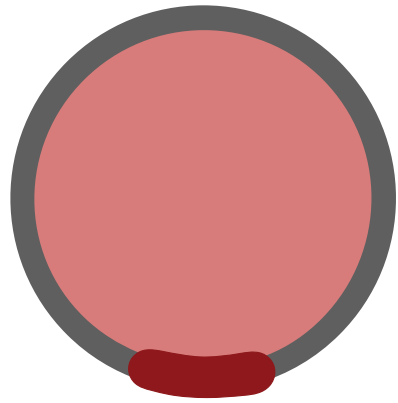
# HEMOSTASIS



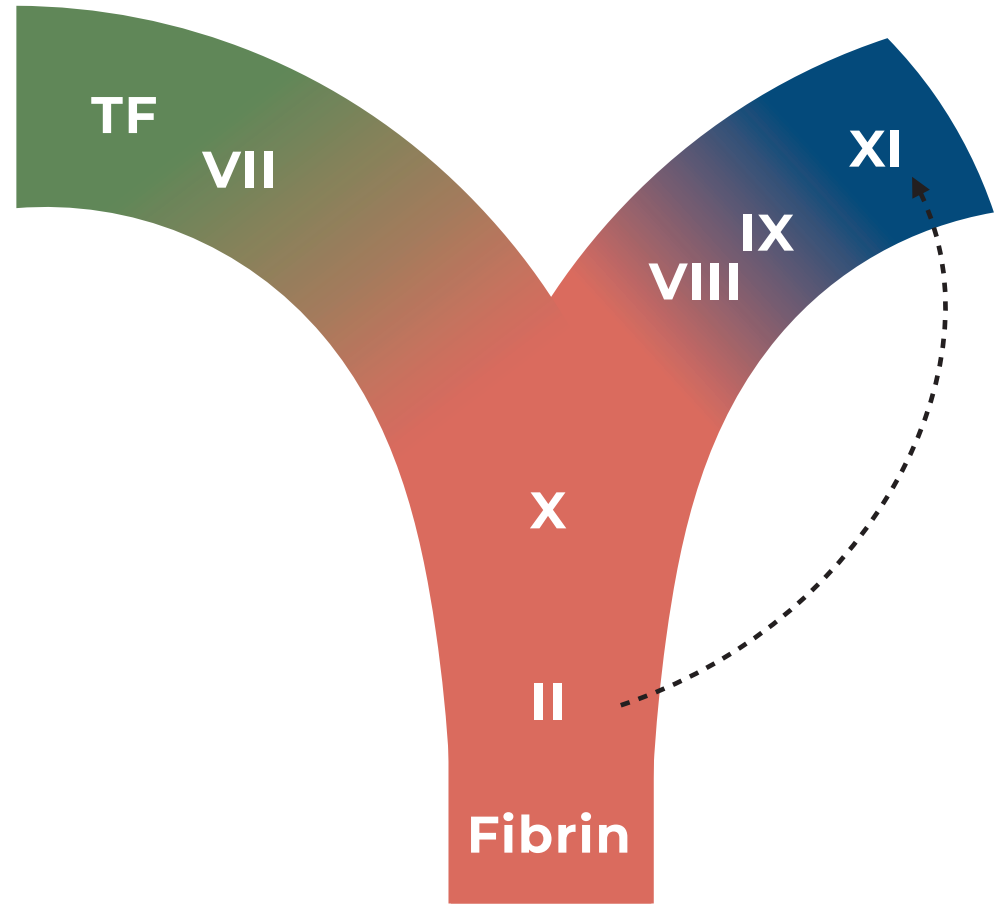
Stable clot



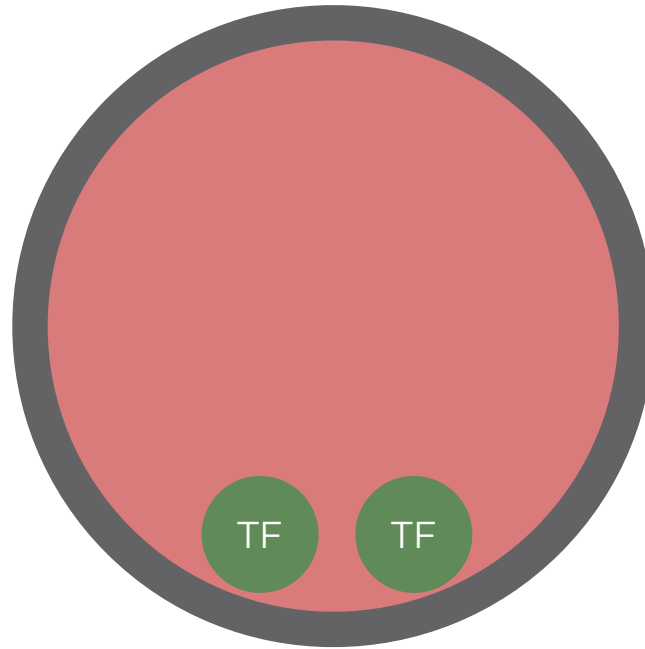
# HEMOSTASIS



Consolidated clot

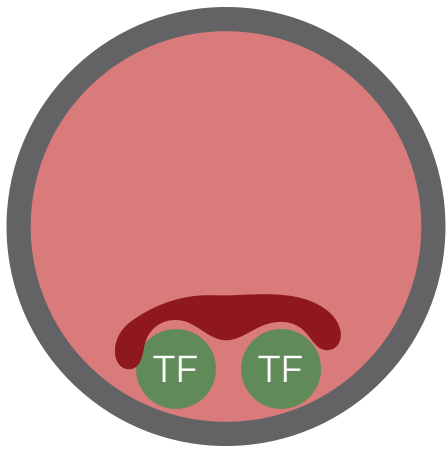


# THROMBOSIS (A/V)

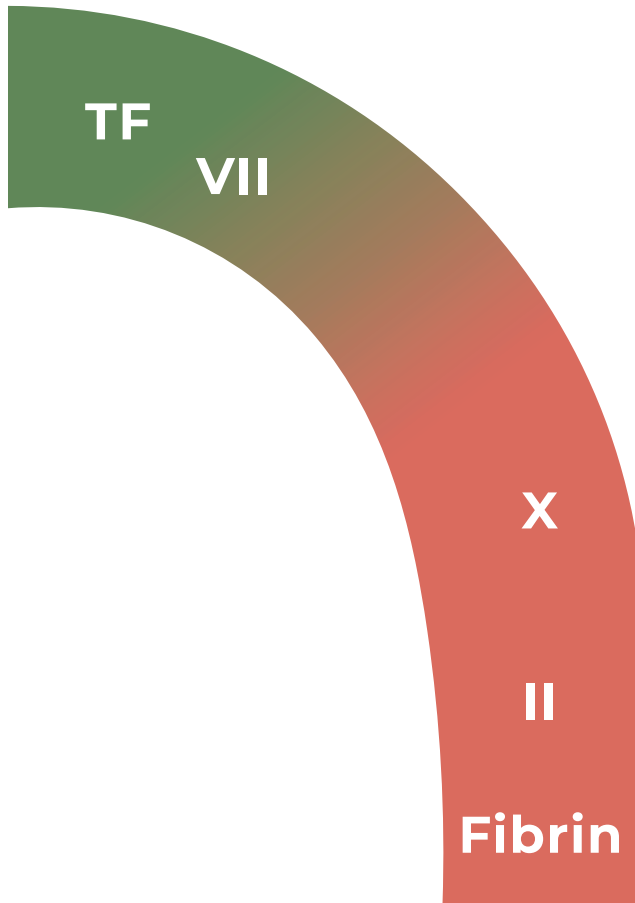


TF initiates thrombosis

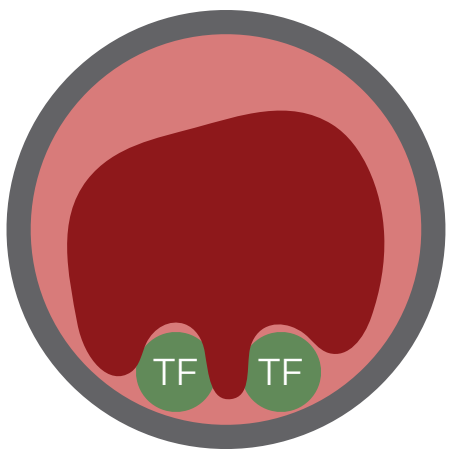
# THROMBOSIS (A/V)



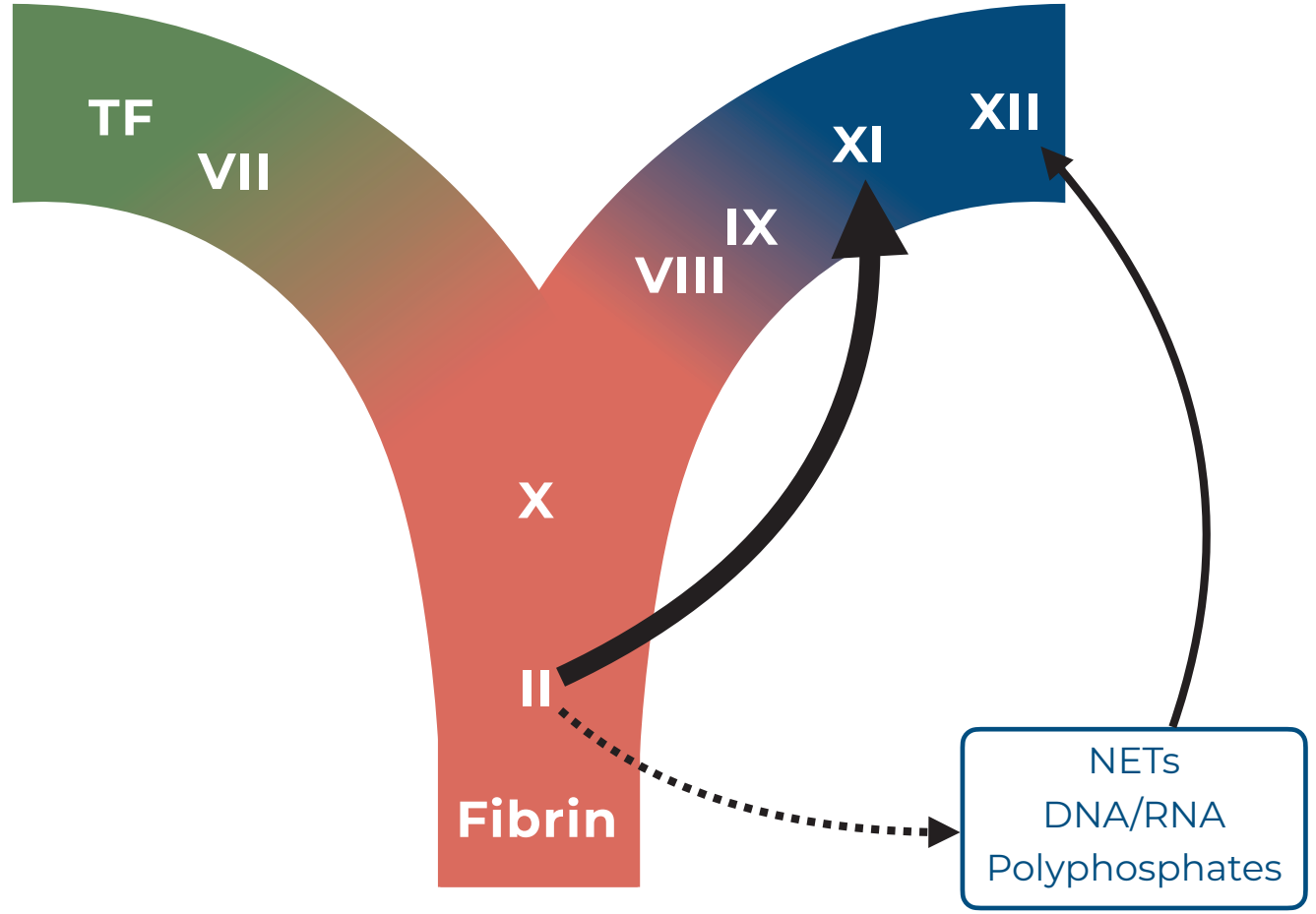
TF initiates thrombosis



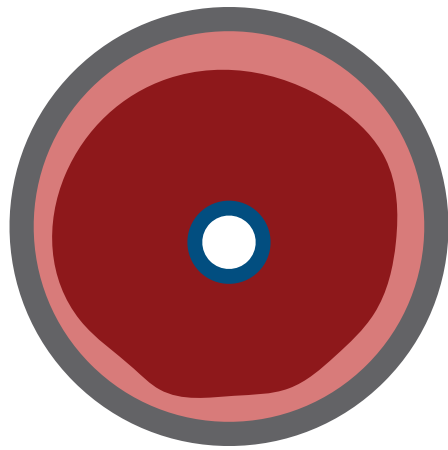
# THROMBOSIS (A/V)



Thrombus growth

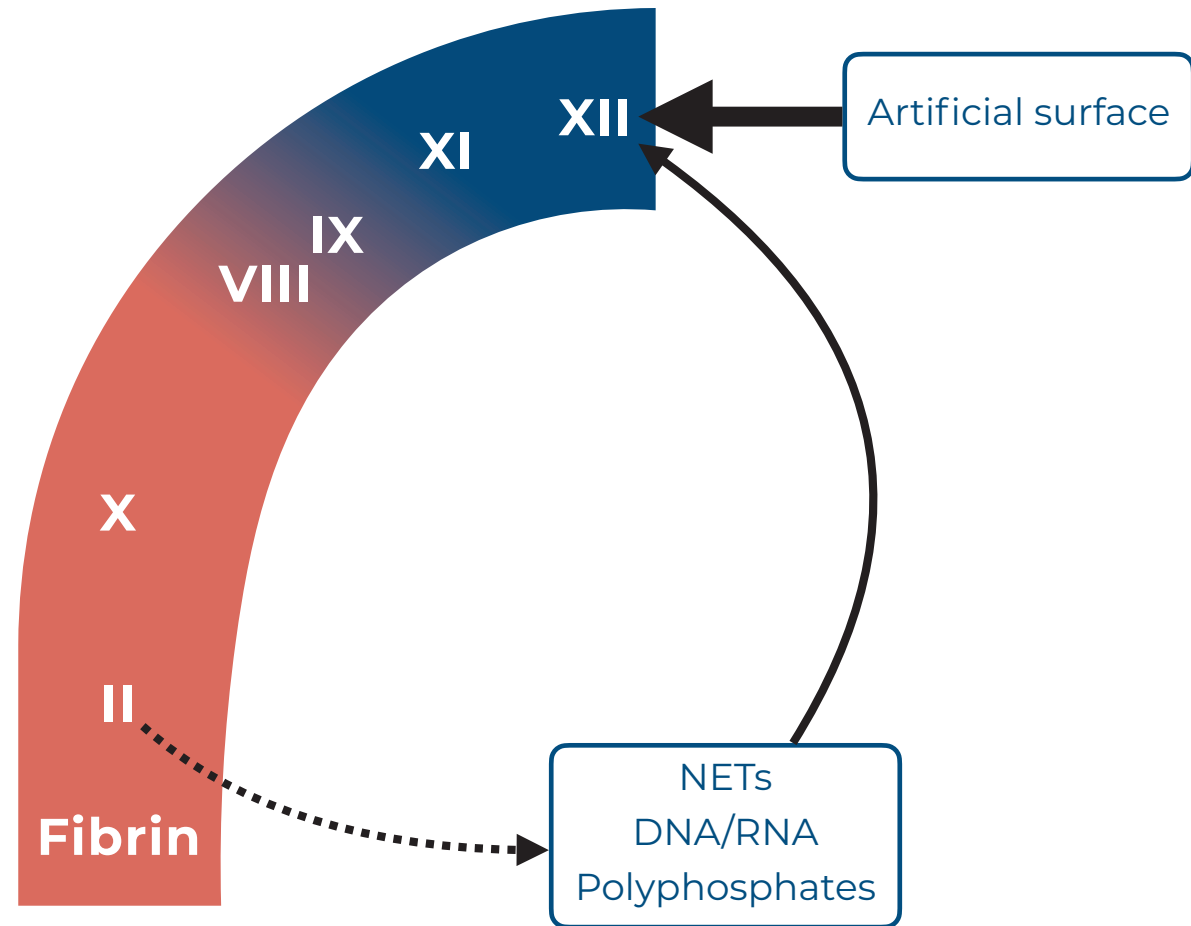


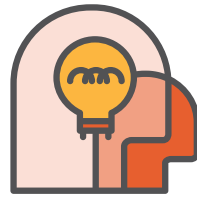
# Artificial surface-associated thrombosis



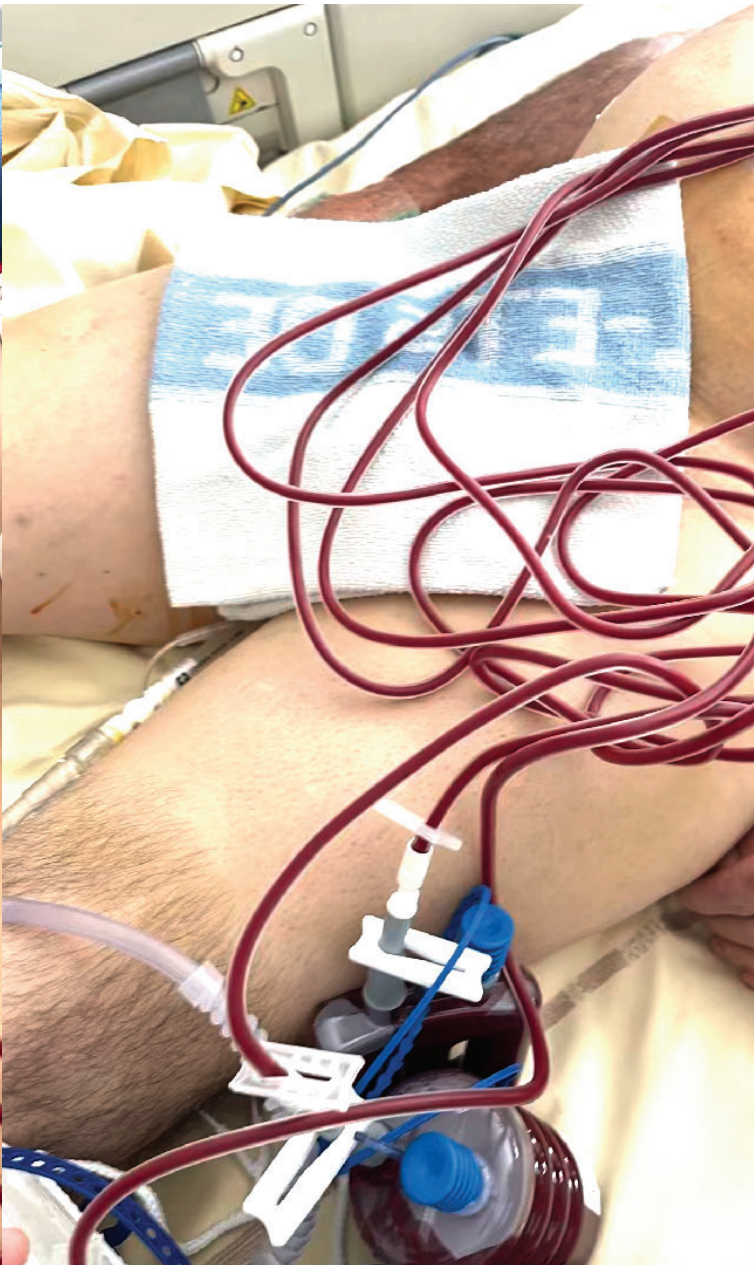
## Artificial surfaces

ECMO, CBP  
VAD  
A/V lines  
RRT





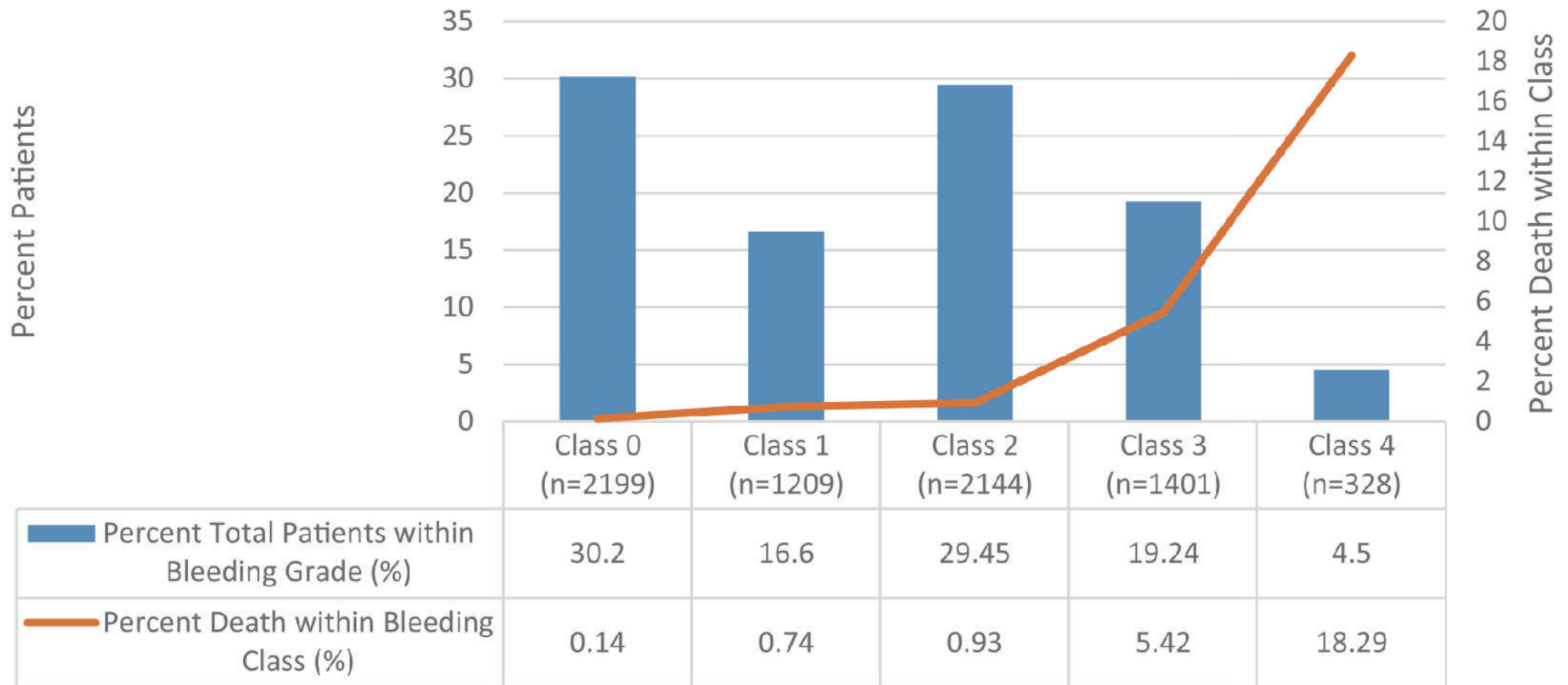
Quelles conséquences ?

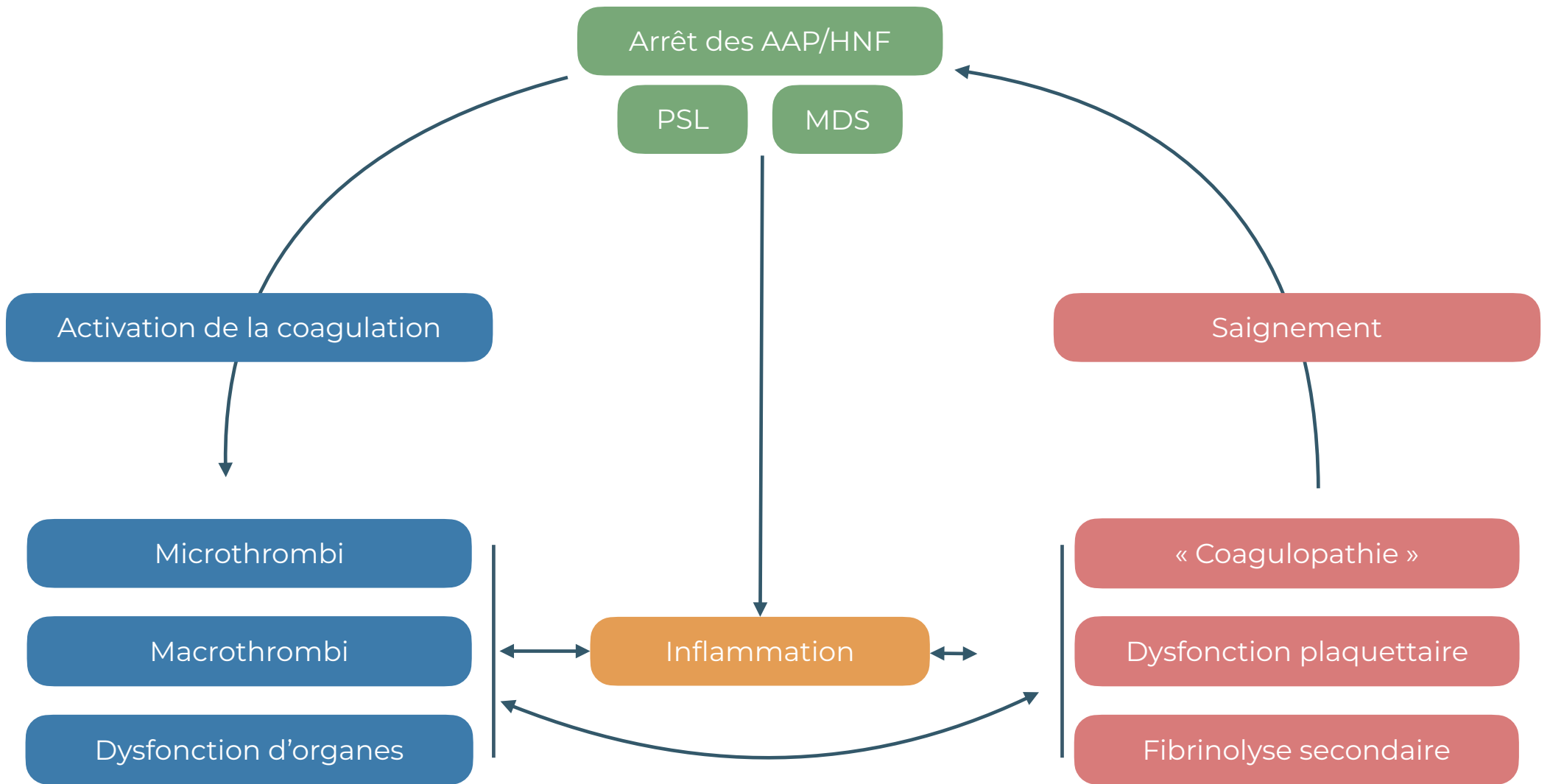


## Universal Definition of Perioperative Bleeding - UDPB

Bleeding definition	Sternal closure delayed	Postoperative chest tube blood loss within 12 hours (mL)	PRBC (units) <sup>a</sup>	FFP (units)	PLT	Cryoprecipitate	PCCs	rFVIIa	Reexploration/tamponade
Class 0	No	<600	0	0	No	No	No	No	No
Class 1	No	601-800	1	0	No	No	No	No	No
Class 2	No	801-1000	2-4	2-4	Yes	Yes	Yes	No	No
Class 3	Yes	1001-2000	5-10	5-10	N/A	N/A	N/A	No	Yes
Class 4	N/A	>2000	>10	>10	N/A	N/A	N/A	Yes	N/A

## Saignement en chirurgie cardiaque





Arrêt des AAP/HNF

PSL

MDS

Activation de la coagulation

Saignement

Microthrombi

Macrothrombi

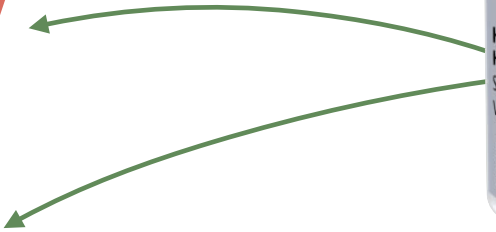
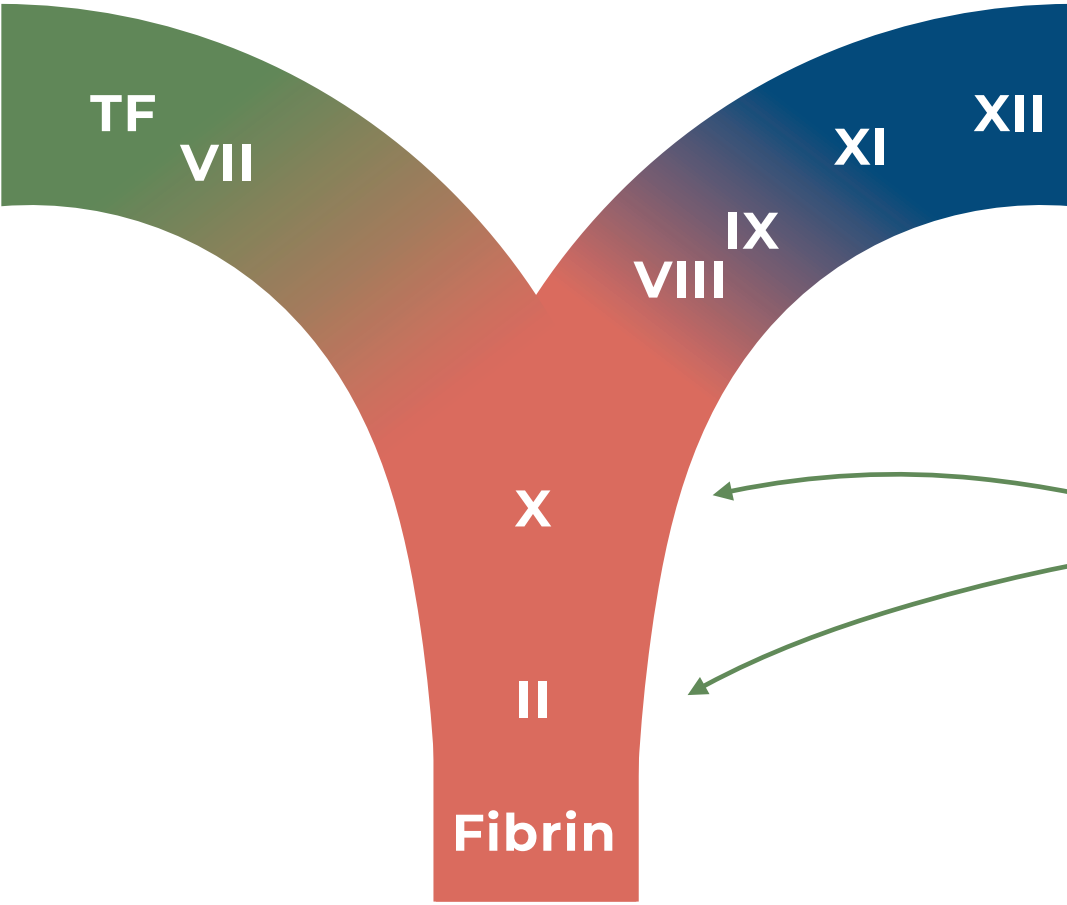
Dysfonction d'organes

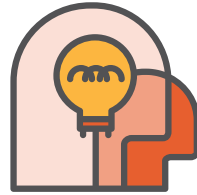
Inflammation

« Coagulopathie »

Dysfonction plaquettaire

Fibrinolyse secondaire





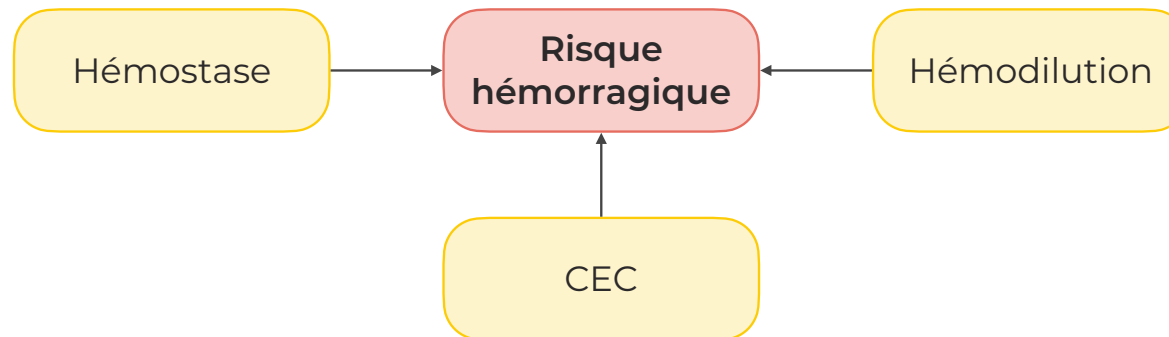
Deux objectifs majeurs en CEC

Minimiser le risque hémorragique

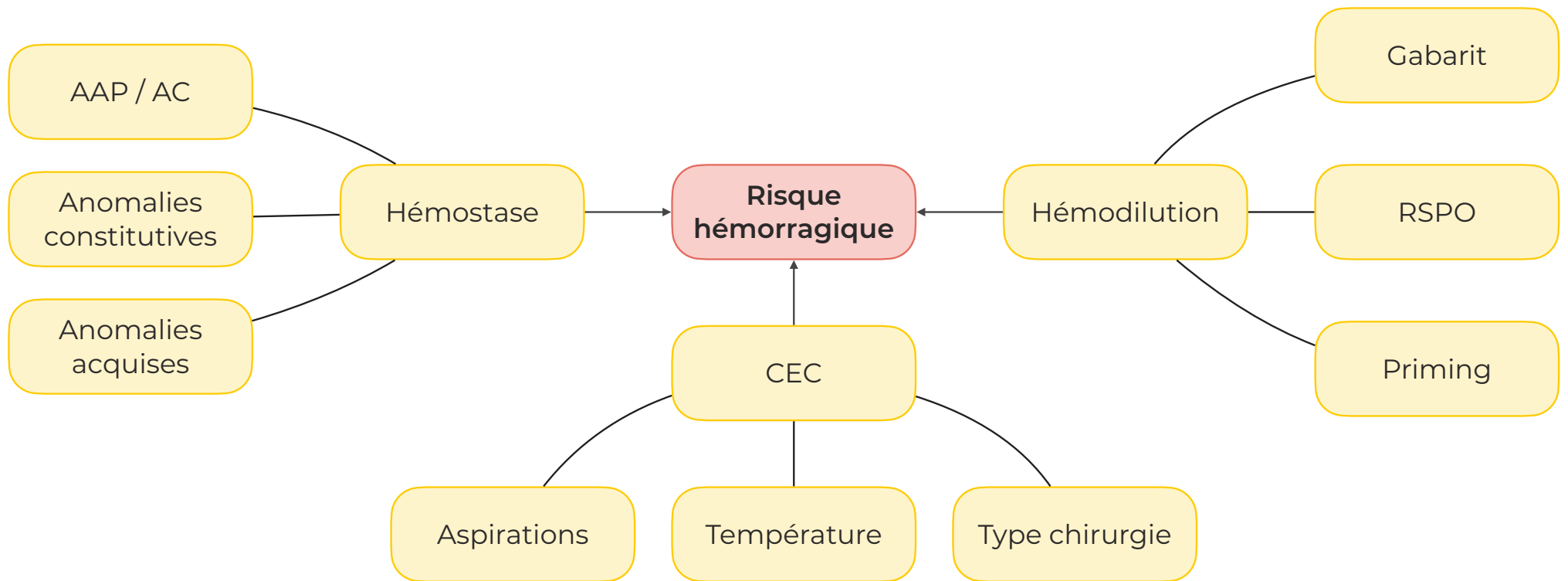
Optimiser la gestion de l'HNF

# Gestion pré-opératoire de l'hémostase

Comment évaluer le risque hémorragique en préopératoire ?

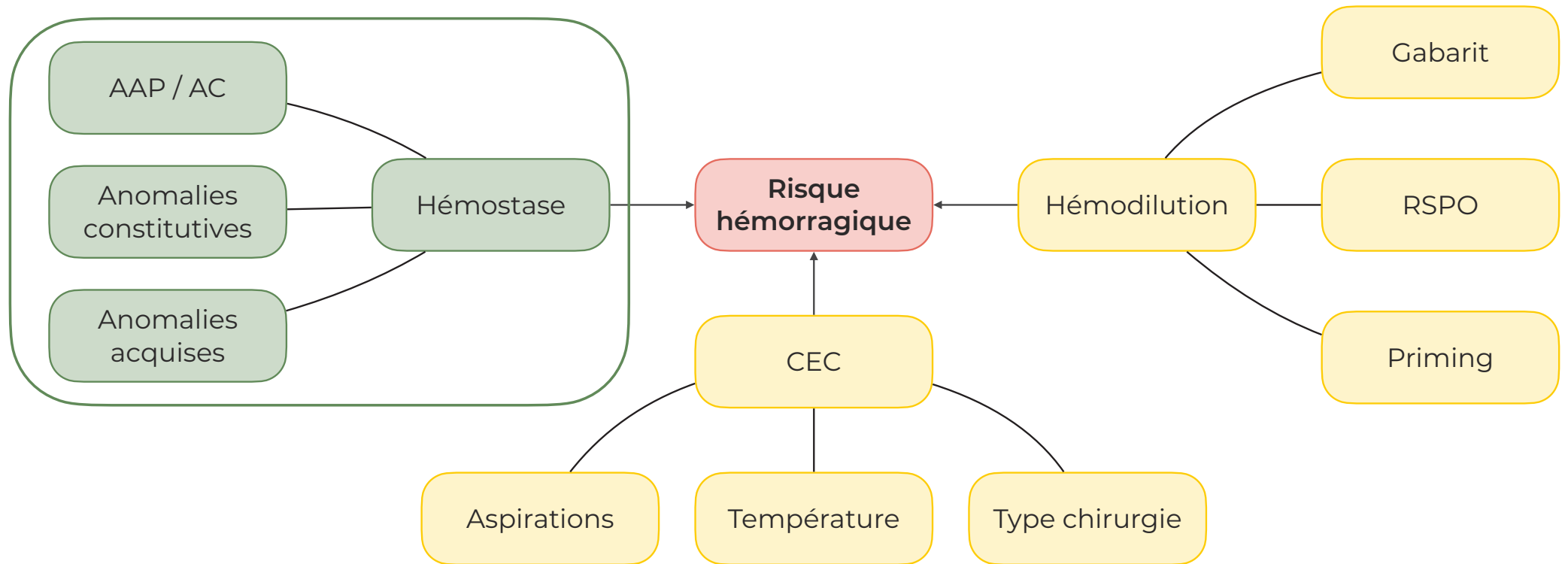


# Comment évaluer le risque hémorragique en préopératoire ?



# Comment évaluer le risque hémorragique en préopératoire ?

Consultation +++



Risk factor	Value = 0	Value = 1
Surgery priority	Elective	Urgent or emergency
Surgery type	CABG or single valve	All other surgery types
Aortic valve disease	None	Stenosis, regurgitation, both
BMI	BMI greater/equal to 25	BMI less than 25
Age	Younger than 75	75 years or older

**Table 1: Details of existing transfusion scoring systems**

Trust score	Score	Track score	Score
Hb <13.5 g/dl	1	Age >67 years	6
Weight <77 kg	1	Weight <60	2
Female sex	1	kg (female) or	
Age >65 years	1	<85 kg (male)	
Nonelective surgery	1	Gender-female	4
Creatinine >1.36 mg/dl	1	Complex surgery	7
Previous cardiac surgery	1	Hematocrit (continuous)	1 point per each value (%) below 40%
Nonisolated operation	1		

Hb: Hemoglobin

Score de risque hémorragique  
> intérêt limité +++

# Bilan d'hémostase préopératoire ?

Etude observationnelle  
Chirurgie cardiaque complexe  
N=101

**Table 3. Coagulation-Related Variables in Relation to Post-CPB Blood Loss**

Variables (normal range)	Pre-CPB value <sup>a</sup>	$\rho^b$	P	Post-CPB value <sup>a</sup>	$\rho^b$	P	$\Delta$ (%) <sup>c</sup>	$\rho^b$	P
Hemoglobin (140–180 g/L male; 120–160 g/L female)	137 ± 16	0.02	0.8	91 ± 13	-0.13	0.2	-33 ± 8	0.22	0.03
Platelet count (150–400 × 10 <sup>9</sup> /L)	240 ± 65	-0.18	0.06	122 ± 51	-0.38	0.0001	-49 ± 15	0.3	0.003
INR (0.8–1.2)	1.1 ± 0.1	0.08	0.4	1.8 ± 0.5	0.27	0.006	65 ± 41	-0.26	0.008
PTT (26–38 s)	31 ± 3	0.13	0.2	36 ± 12	0.17	0.1	17 ± 36	-0.06	0.5
Fibrinogen (2–4 g/L)	3.4 ± 0.7	0.00	0.9	2.1 ± 0.6	-0.26	0.008	-38 ± 11	0.37	0.0002
Factor II (0.7–1.4 U/mL)	0.9 ± 0.2	-0.09	0.3	0.5 ± 0.1	-0.29	0.003	-41 ± 11	0.3	0.003
Factor V (0.7–1.3 U/mL)	0.9 ± 0.2	0.05	0.6	0.5 ± 0.1	-0.13	0.2	-45 ± 13	0.18	0.07
Factor VIII (0.5–1.6 U/mL)	1.2 ± 0.4	-0.17	0.1	1.0 ± 0.4	-0.1	0.3	-17 ± 39	0.02	0.9
Factor X (0.7–1.3 U/mL)	0.9 ± 0.2	-0.02	0.8	0.5 ± 0.2	-0.17	0.09	-43 ± 16	0.16	0.1
Factor XIII (0.8–1.6 U/mL)	1.1 ± 0.3	-0.07	0.5	0.7 ± 0.2	-0.18	0.07	-35 ± 12	0.16	0.1
Antithrombin (0.9–1.2 U/mL)	0.9 ± 0.1	0.09	0.4	0.6 ± 0.1	-0.21	0.03	-38 ± 11	0.31	0.002
Prothrombin fragment F1 + 2 (69–229 $\mu$ mol/L)	203 ± 101	-0.18	0.07	735 ± 412	0.03	0.8	319 ± 275	-0.19	0.05
Thrombin-antithrombin complex (<400 $\mu$ g/mL)	5.3 ± 4.6	-0.12	0.2	95 ± 55	0.24	0.01	2397 ± 1891	-0.29	0.003
Fibrin monomer complex (<6.0 $\mu$ g/mL)	5.1 ± 4.3	0.05	0.6	27 ± 34	0.23	0.02	562 ± 837	-0.19	0.05
Plasmin-alpha-2-antiplasmin complex (74–134 $\eta$ g/mL)	135 ± 84	0.1	0.3	1746 ± 1306	0.11	0.3	1418 ± 1382	-0.07	0.5

## Bilan d'hémostase préopératoire ?

**Table 4. Regression Analysis of Post-CPB Blood Loss (Log Transformation)**

Variable	Coefficient ( <i>b</i> )	SE	Bootstrap coefficient median (95% CI)	<i>t</i>	Squared partial correlation	<i>P</i>	Tolerance
Constant	6.99	0.38					
Previous Sternotomies	0.64	0.25	0.64 (0.24–1.01)	2.6	0.07	0.01	0.9
Pre-CPB F1.2 level	−0.0022	0.0007	−0.0021 (−0.0035 to −0.0008)	3.3	0.1	0.001	0.9
Post-CPB platelet count	−0.0038	0.0015	−0.0037 (−0.007 to −0.0007)	2.6	0.07	0.01	0.8
Post-CPB FM level	0.013	0.003	0.012 (0.006 to 0.019)	4.3	0.17	<0.0001	0.8
δ Fibrinogen level	0.013	0.006	0.013 (−0.0005 to 0.028)	2.0	0.04	0.05	0.8
<b>Source of variation</b>	<b>Degrees of freedom</b>		<b>Sum of squares</b>	<b>Mean squares</b>		<b><i>F</i></b>	<b><i>P</i></b>
Regression	5		29.2	5.8		13.8	<0.0001
Residual	93		39.4	0.4			



## Bilan d'hémostase préopératoire ?

TP / TCA ne prédisent pas le risque hémorragique

Fibrinogène mieux corrélé mais pas de seuil de sécurité

Tests viscoélastométriques et tests fonctionnels plaquettaires peu prédictifs et non validés dans cette indication



## 2024 EACTS/EACTAIC Guidelines on patient blood management in adult cardiac surgery in collaboration with EBCP

Recommendations	Class	Level
Preoperative bleeding history, review of medications, and physical examination are recommended to identify patients at increased risk of bleeding.	I	C
Risk scores may be considered for initial screening to identify patients at increased risk of bleeding complications.	IIb	B
Preoperative fibrinogen levels may be considered to stratify the risk of bleeding.	IIb	B
Platelet function testing may be considered to guide the decision on the timing of cardiac surgery in patients who have recently received P2Y12 inhibitors.	IIb	B
Routine use of viscoelastic testing or platelet function testing is not recommended to predict bleeding.	III	C



# Gestion des anticoagulants en chirurgie programmée

Antithrombotique	Demi-vie	Pharmacologie	Dernière prise	Dosage préopératoire
Apixaban	12 h	Inhibition du facteur Xa Élimination rénale (≈ 30 %) et hépatique	J-3*	Non
Rivaroxaban	5-13 h	Inhibition du facteur Xa Élimination rénale (≈ 30 %) et hépatique	DFG ≥ 30 mL/min : J-3** DFG < 30 mL/min : J-5	Non
Dabigatran	12-14 h	Inhibition du facteur IIa Élimination rénale (≈ 80 %) et hépatique	DFG ≥ 50 mL/min : J-4 DFG < 50 mL/min : J-5	Non
AVK	30-45 h	Inhibition de la synthèse de la vitamine K Métabolisme hépatique Élimination sous forme inactive	J-5	INR < 1,5

\* sous réserve qu'une réduction posologique soit appliquée conformément au résumé des caractéristiques du produit si DFG < 30 mL/min ou si deux facteurs parmi : âge ≥ 80 ans, poids ≤ 60 kg, créatinémie ≥ 133 µmol/L.

\*\* Réduction posologique indiquée si DFG < 50 mL/min.

Antithrombotique parentéral	Demi-vie	Délai d'interruption préopératoire	Indication à un dosage préopératoire
HNF IVSE dose thérapeutique	60-120 min	6 h	Non
HNF SC dose préventive	4 h	4 h	Non
HBPM dose thérapeutique	5-7 h	24 h	Non
HBPM dose préventive	5-7 h	12 h	Non
Fondaparinux :			
• dose préventive	17-21 h	36 h	Oui si DFG < 50 mL/min Anti-Xa fondaparinux < 0,2 µg/mL
• dose thérapeutique	17-21 h	96 h	Oui Anti-Xa fondaparinux < 0,2 µg/mL
Danaparoïde sodique :			
• dose préventive	Anti-Xa : 25 h Anti-IIa : 7 h	36 h	Avis spécialisé hémostase Anti-Xa < 0,2 UI/mL
• dose curative	Anti-Xa : 25 h Anti-IIa : 7 h	96 h	Avis spécialisé hémostase Anti-Xa < 0,2 UI/mL
Argatroban IVSE	50-60 min	4 h	Non (sauf insuffisance hépatique)
Bivalirudine IVSE	25-60 min selon DFG	2 h	Non (sauf insuffisance rénale sévère)

# Gestion des AAP en chirurgie programmée

Antithrombotique	Demi-vie	Pharmacologie	Dernière prise	Dosage préopératoire
Clopidogrel	6 h	Inhibition irréversible du récepteur P2Y12	J-5	Non
Ticagrelor	6-9 h	Inhibition réversible du récepteur P2Y12	J-5***	Non***
Prasugrel	3-7 h	Inhibition réversible du récepteur P2Y12	J-7	Non

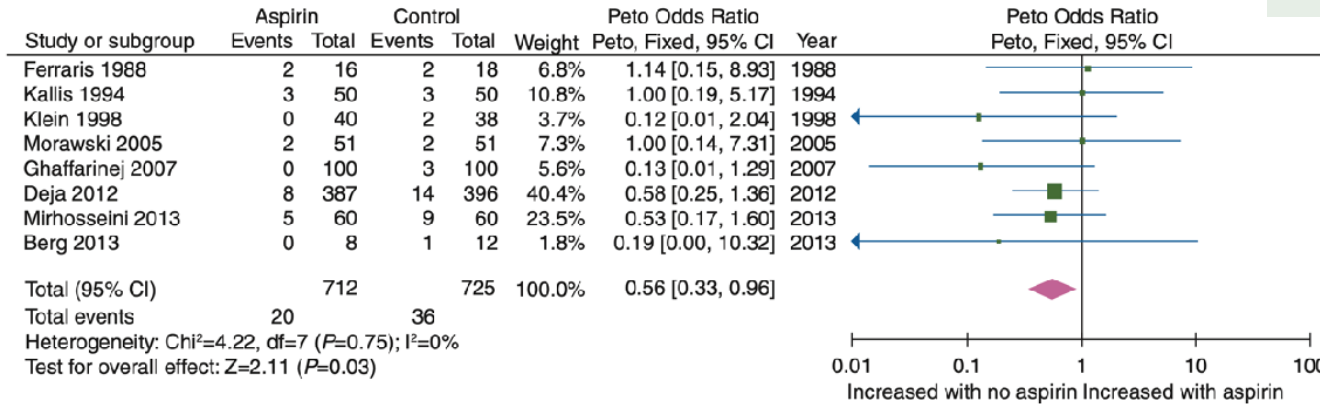
\*\*\* Une dernière prise à J-3 est possible, avec une vérification de la correction de l'inhibition plaquettaire par un test fonctionnel plaquettaire au sein d'une équipe experte. Près de 20 % des patients n'ont cependant pas récupéré des fonctions plaquettaires normales.

Antithrombotique parentéral	Demi-vie	Délai d'interruption préopératoire	Indication à un dosage préopératoire
Cangrelor	3-6 min	60 min	Non
Eptifibatide	2,5 h	4 à 8 h (> 12 h si insuffisance rénale)	Non
Tirofiban	1,5 h	4 à 8 h (> 12 h si insuffisance rénale)	Non

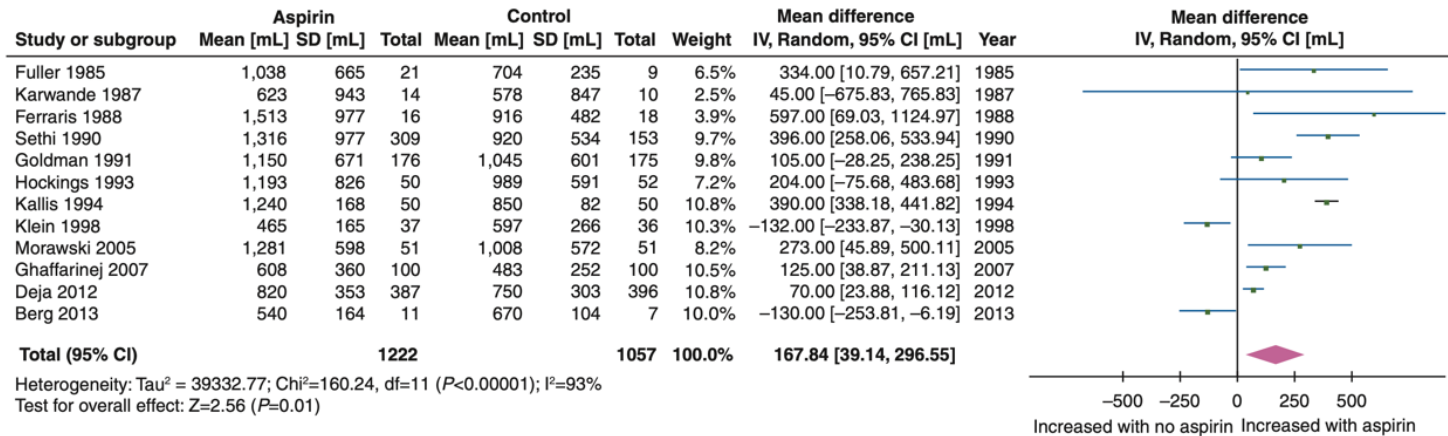
# Aspirine

Pontage uniquement  
13 RCT // N = 2399  
Études anciennes, pré-PBM  
Posologies variables

IDM post-op



Saignement





# Aspirine

## ATACAS

RCT 2x2 (aspirin et TXA)  
Pas d'aspirine préop ou  
STOP >4j

**Dose unique  
préopératoire**

Measure	Aspirin (n=1046)	Placebo (n=1052)	ARR % (95% CI)	P- Value
Death, Myocardial Infarction, Stroke, Renal Failure, PE, Bowel Infarction	202 (19.3%)	215 (20.4%)	1.13% (-2.29% - 4.54%)	0.55

Measure	Aspirin	Placebo	ARR % (95% CI)	P-Value
Death	14 (1.3%)	9 (0.9%)	-0.48 (-0.41 - 1.37)	0.30
Myocardial Infarction (MI)	144 (13.8%)	166 (15.2%)	2.01 (-1.02 - 5.05)	0.20
Stroke	14 (1.3%)	12 (1.1%)	-0.20 (-0.75 - 1.14)	0.70
Renal Failure	49 (4.7%)	41 (3.9%)	-0.79 (-0.95 - 2.52)	0.39
Pulmonary Embolism (PE)	8 (0.8%)	10 (1.0%)	0.19 (-0.60 - 0.97)	0.81
Bowel Infarction	0 (0.0%)	2 (0.2%)	0.19 (-0.07 - 0.45)	0.50
Reoperation for Hemorrhage	19 (1.8%)	22 (2.1%)	0.27 (-0.91 - 1.46)	0.75
Cardiac Tamponade	11 (1.1%)	4 (0.4%)	0.67 (-0.05 - 1.39)	0.08

## Bi-AAP et chirurgie cardiaque

Variable	Overall (n=2275)	ASA (n=1164)	DAPT (n=1111)	p-value
E-CABG score $\geq 2$ , n (%)	94 (4.11)	34 (2.92)	59 (5.31)	0.0065
UDPB score $\geq 3$ , n (%)	61 (2.68)	21 (1.8)	40 (3.57)	0.0162
BARC 4, n (%)	96 (4.2)	40 (3.44)	57 (5.09)	0.0626
Reoperation for bleeding, n (%)	75 (3.33)	29 (2.49)	46 (4.18)	0.03
Pleural effusion, n (%)	84 (3.70)	32 (2.75)	51 (4.62)	0.033
Units of RBC transfused, mean (SD)	0.402 (1.3)	0.248 (1.1)	0.56 (1.5)	<0.0001
Units of FFP transfused, mean (SD)	0.071 (0.5)	0.045 (0.5)	0.098 (0.5)	0.021
Units of PLT transfused, mean (SD)	0.016 (0.18)	0.009 (0.18)	0.023 (0.17)	0.08
Overall transfusion, n (%)	349 (15.3)	109 (9.5)	239 (21.5)	<0.0001
Chest tube blood loss at 12H (mL), mean (SD)	224 (161.9)	192 (136.4)	258 (178.8)	<0.0001
Chest tube blood loss at 24H (mL), mean (SD)	322 (211.3)	284 (187.8)	361 (226.9)	<0.0001
Overall chest tube blood loss (mL), mean (SD)	386 (296)	338 (274.8)	435 (309)	<0.0001

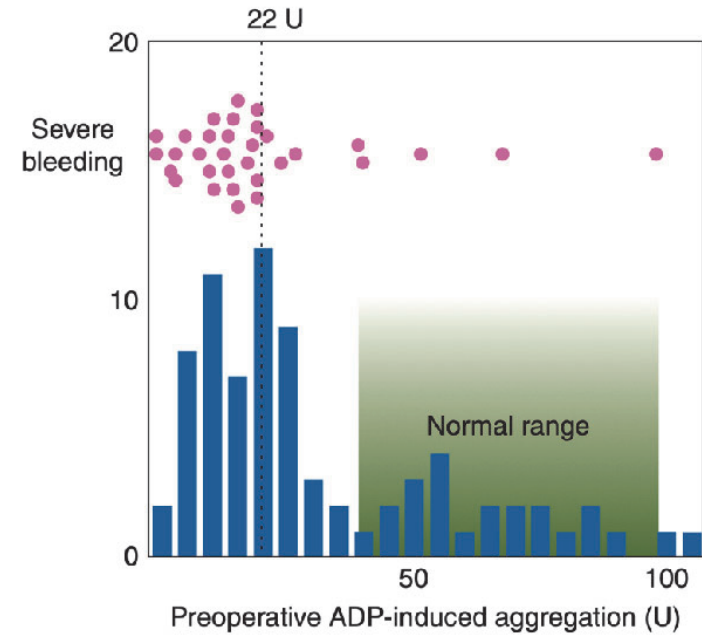
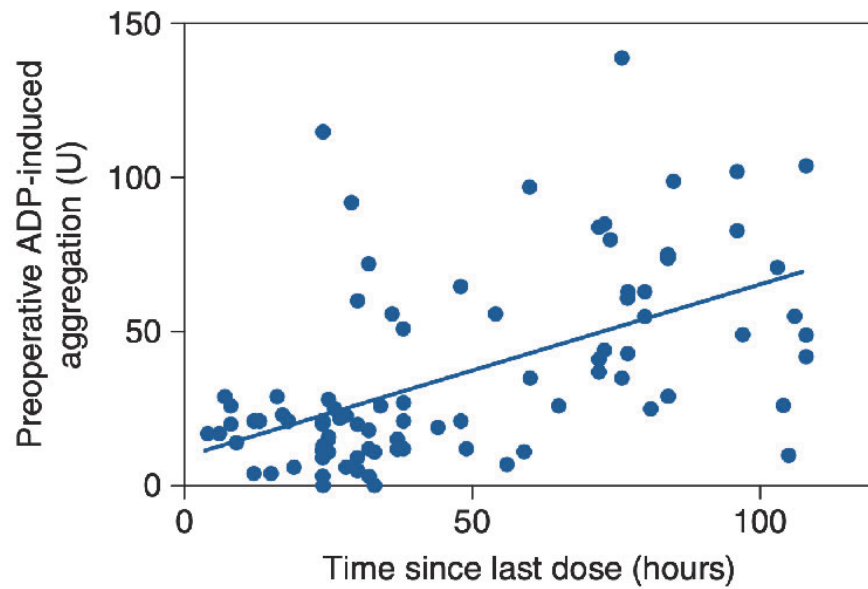
Observationnelle (Angers)  
Ajustement par PSM  
Gestion optimale de la CEC  
Aspirine vs biAAP

## Bi-AAP et chirurgie cardiaque

Variable	Overall (n=2275)	ASA (n=1164)	DAPT (n=1111)	p-value
30-days mortality, n (%)	25 (1.09)	11 (0.94)	14 (1.24)	0.497
Death of cardiac cause, n (%)	10 (0.44)	3 (0.26)	7 (0.64)	0.278
Postoperative myocardial infarction, n (%)	6 (0.26)	2 (0.17)	4 (0.34)	0.415
Stroke, n (%)	15 (0.67)	5 (0.43)	10 (0.91)	0.217
TIA, n (%)	9 (0.38)	2 (0.17)	7 (0.6)	0.185
AKI, n (%)	189 (8.3)	75 (6.44)	113 (10.17)	0.0025
Wound infection, n (%)	44 (1.94)	13 (1.11)	31 (2.8)	0.010
Ventilation time >24H, n (%)	71 (3.12)	24 (2.06)	47 (4.2)	0.0061
ICU time (hours), mean (SD)	88.8 (101.1)	86.4 (90.3)	91.3 (111.4)	0.301
Total hospitalization time (days), mean (SD)	10.3 (6.6)	9.8 (5.1)	10.8 (7.8)	0.0069

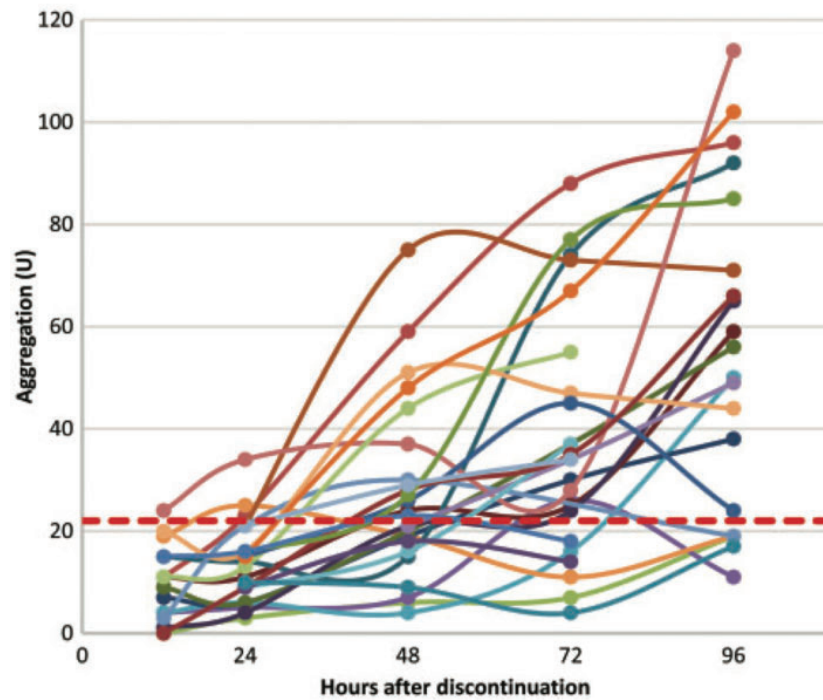
Observationnelle (Angers)  
Ajustement par PSM  
Gestion optimale de la CEC  
Aspirine vs biAAP

# Ticagrelor: arrêt J-3 ou J-5 ?



CABG // N=90  
Multiplate  
UDPB Score

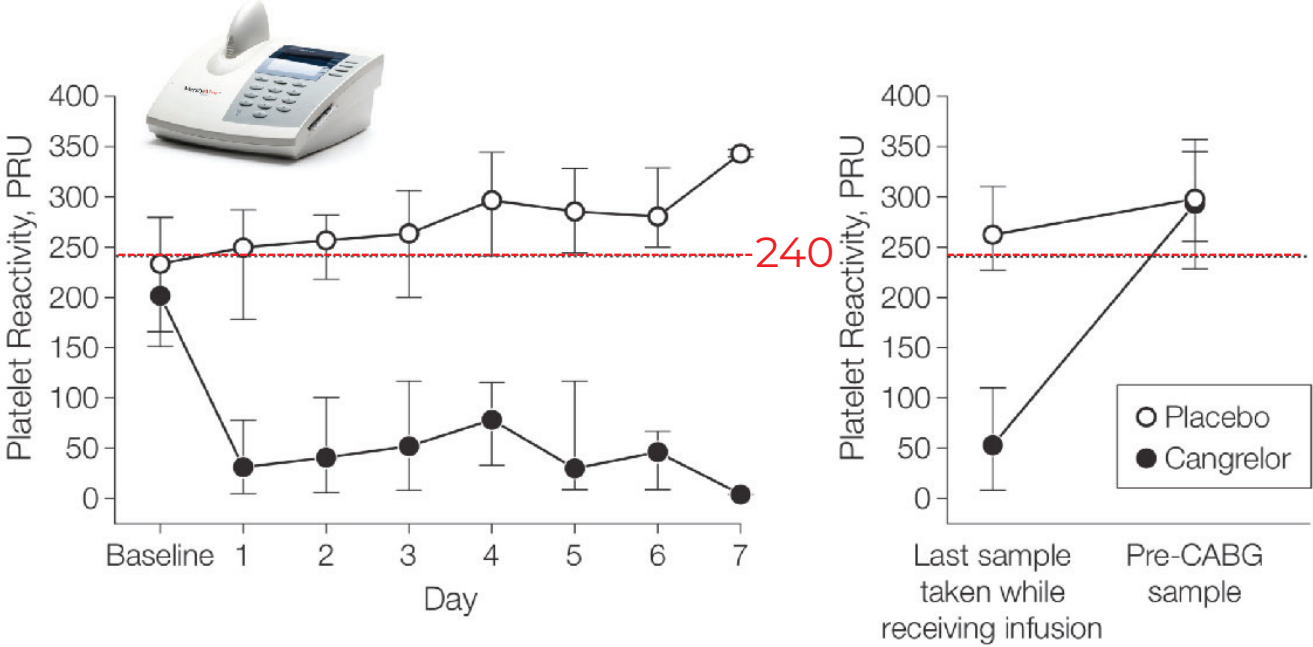
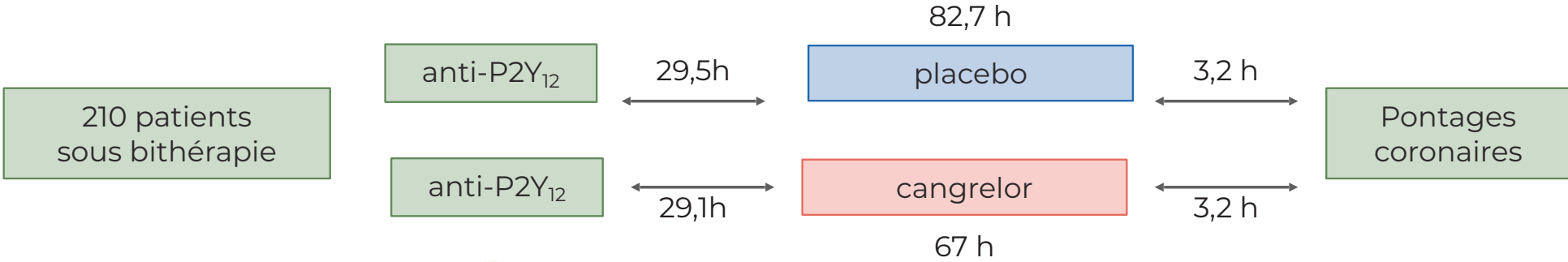
## Ticagrelor: arrêt J-3 ou J-5 ?



CABG // N=25  
Multiplate  
À 72H : 25% < 22U

# Bridging Antiplatelet Therapy With Cangrelor in Patients Undergoing Cardiac Surgery

A Randomized Controlled Trial



Angiolillo et al. JAMA. 2012 January 18; 307(3): 265-274

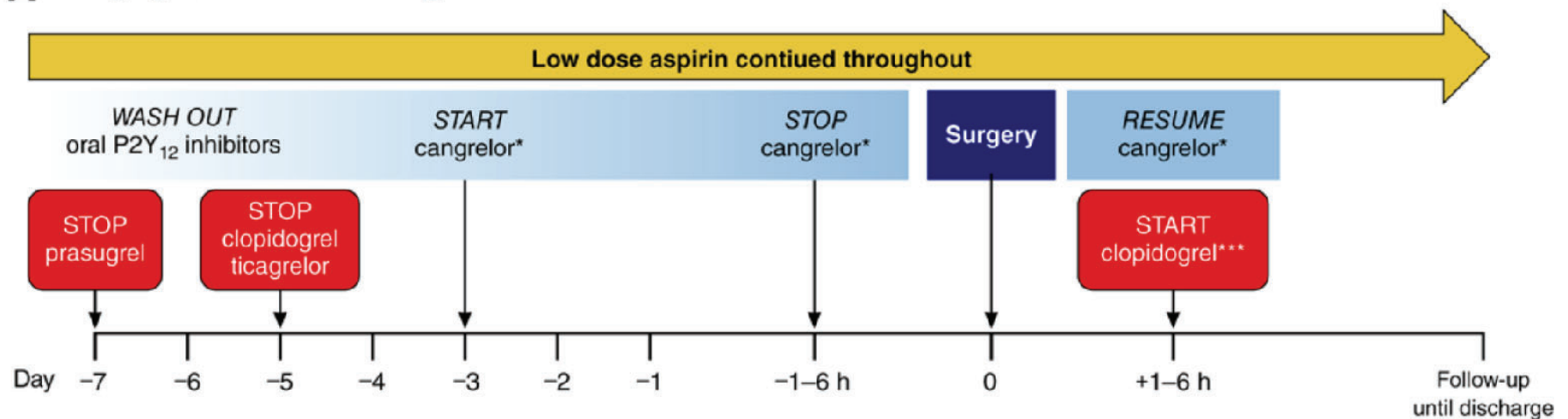
# Relais péri-opératoire par AAP IV

## Circulation

### International Expert Consensus on Switching Platelet P2Y<sub>12</sub> Receptor-Inhibiting Therapies

Dominick J. Angiolillo , Fabiana Rollini, Robert F. Storey, Deepak L. Bhatt, Stefan James, David J. Schneider, Dirk Sibbing, Derek Y.F. So, Dietmar Trenk, Dimitrios Alexopoulos, Paul A. Gurbel, Willibald Hochholzer, Leonardo De Luca, Laurent Bonello, Daniel Aradi, Thomas Cuisset, Udaya S. Tantry, Tracy Y. Wang, Marco Valgimigli, Ron Waksman, Roxana Mehran, Gilles Montalescot, Francesco Franchi and Matthew J. Price

#### A Bridging from oral to IV P2Y<sub>12</sub> inhibitors



\*Initiate within 72 hours from P2Y<sub>12</sub> inhibitor discontinuation at a dose of 0.75 µg/kg/min (no bolus) for a minimum of 48 hours and a maximum of 7 days.

\*\*If oral administration not possible

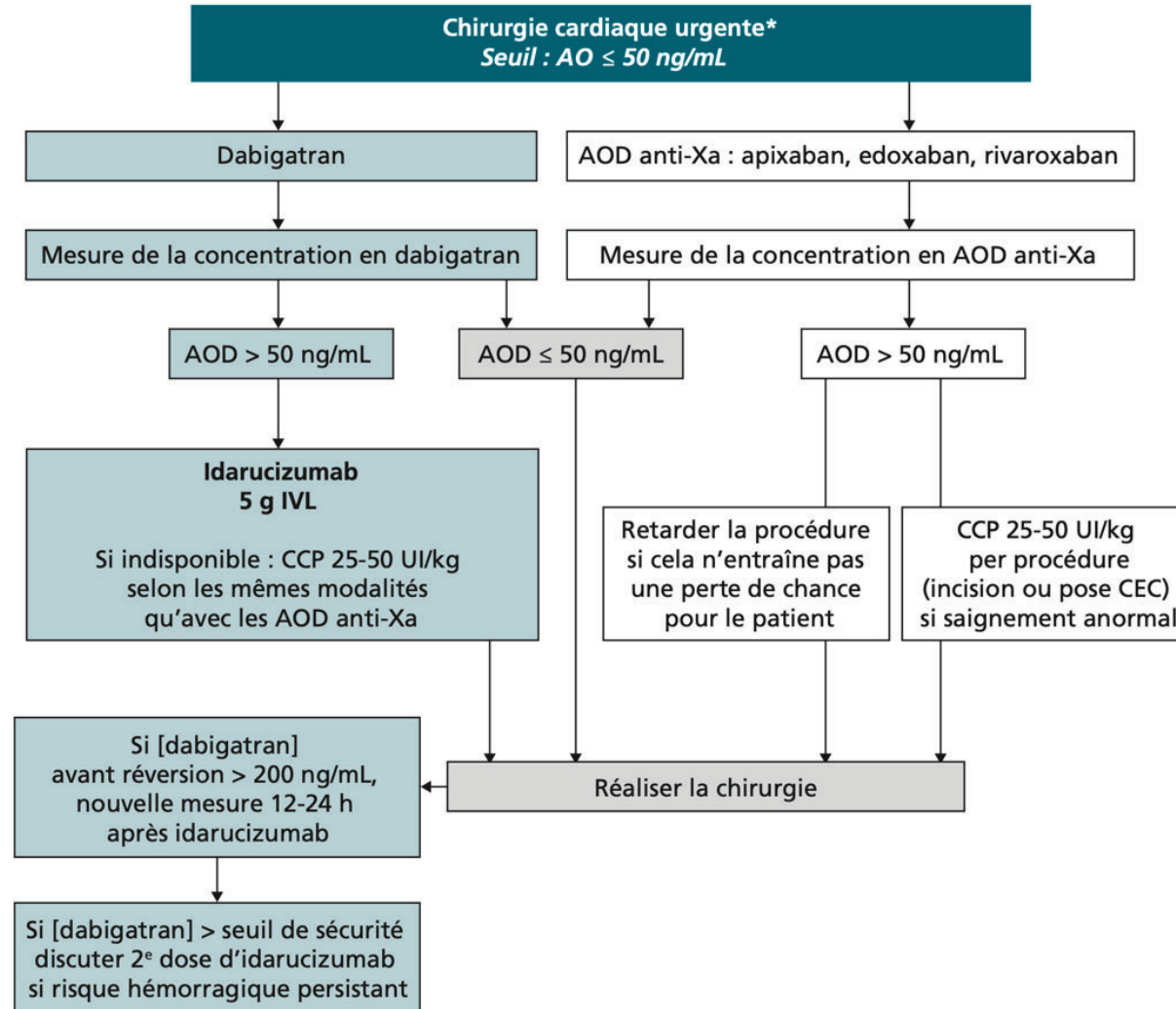
\*\*\*With 300–600 mg loading dose, as soon as oral administration possible. Prasugrel or ticagrelor discouraged



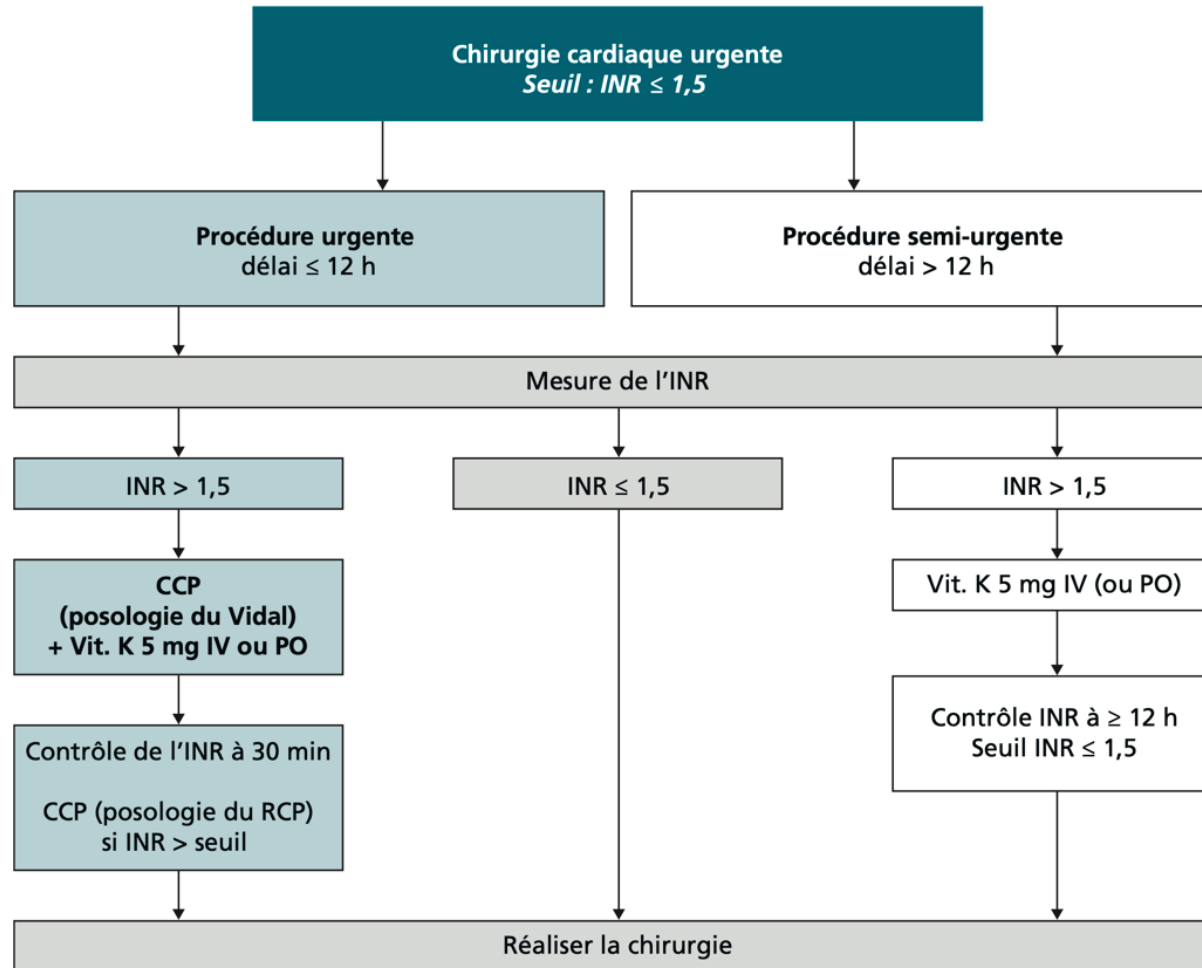
Recommendations	Class	Level
In patients undergoing CABG who are taking ASA preoperatively, continuing ASA throughout the perioperative period is recommended to reduce myocardial ischemic events.	I	B
In patients at high risk of bleeding and transfusion or refusing blood transfusions, stopping ASA should be considered at least 4 days preoperatively.	IIa	C
In patients undergoing CABG, (re)starting ASA within 24 hours postoperatively to reduce myocardial ischemic events is recommended.	I	B
In elective cardiac surgery patients taking DAPT, discontinuation of ticagrelor for at least 3 days, clopidogrel for at least 5 days, and prasugrel for at least 7 days is recommended prior to surgery to reduce bleeding complications.	I	B
Testing residual platelet function may be considered in patients who have received P2Y12 inhibitors <7 days for guidance on the timing of cardiac surgery to reduce bleeding complications.	IIb	B
Bridging P2Y12 inhibitors with low-dose cangrelor until surgery may be considered in patients with high myocardial ischemic risk to reduce thrombotic complications.	IIb	C



# Gestion préopératoire des AOD en chirurgie cardiaque urgente



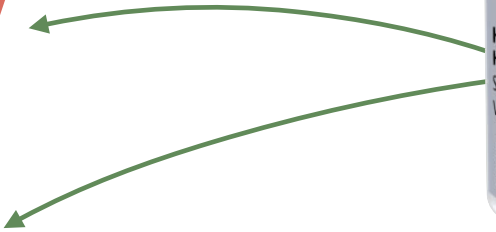
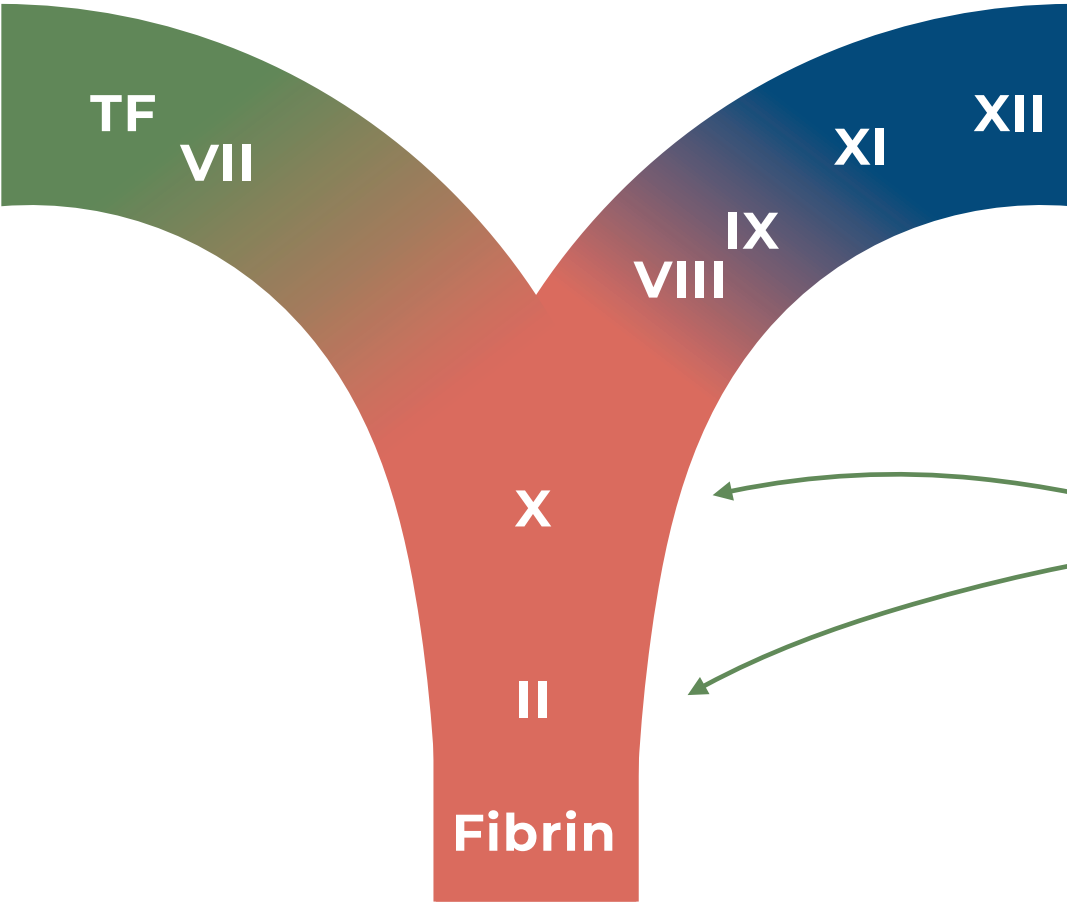
# Gestion préopératoire des AVK en chirurgie cardiaque urgente



## Gestion préopératoire des AAP en chirurgie cardiaque urgente

- Tests fonctionnels plaquettaires : identifier la présence d'un AAP P2Y12 // équipe entraînée
- Report si possible
- Sinon débiter l'intervention // neutralisation si saignement anormal
- Neutralisation des AAP P2Y12 : double dose standard de plaquettes (soit  $2 \times 0,5$  à  $0,7 \times 10^{11}$  par 10 kg de poids corporel)
- Clopidogrel / prasugrel : efficacité limitée si dernière prise <6h
- Ticagrelor: transfusion inefficace si dernière prise <24h

## Gestion per-opératoire de l'hémostase



# Adequate Anticoagulation During Cardiopulmonary Bypass Determined by Activated Clotting Time and the Appearance of Fibrin Monomer

John A. Young, M.D., C. Thomas Kisker, M.D., and Donald B. Doty, M.D.

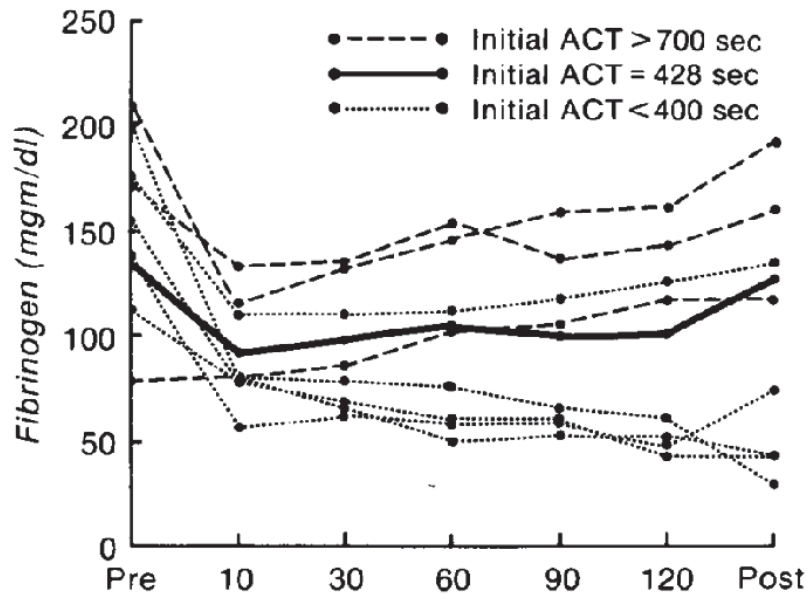


Table 3. Coagulation Measurements in 5 Pediatric Patients<sup>a</sup>

Clotting Factors	Before CPB	After CPB
Fibrinogen (mg/100 ml)	223 ± 39	152 ± 29
Antithrombin-III (%)	75 ± 10	49 ± 11
Platelet count (×10 <sup>3</sup> /mm <sup>3</sup> )	379 ± 179	148 ± 58

<sup>a</sup>Whole-blood activated clotting time was 450 to more than 600 seconds after 40 to 73 minutes of CPB.

HNF per-CEC depuis 50 ans



HNF per-CEC depuis 50 ans



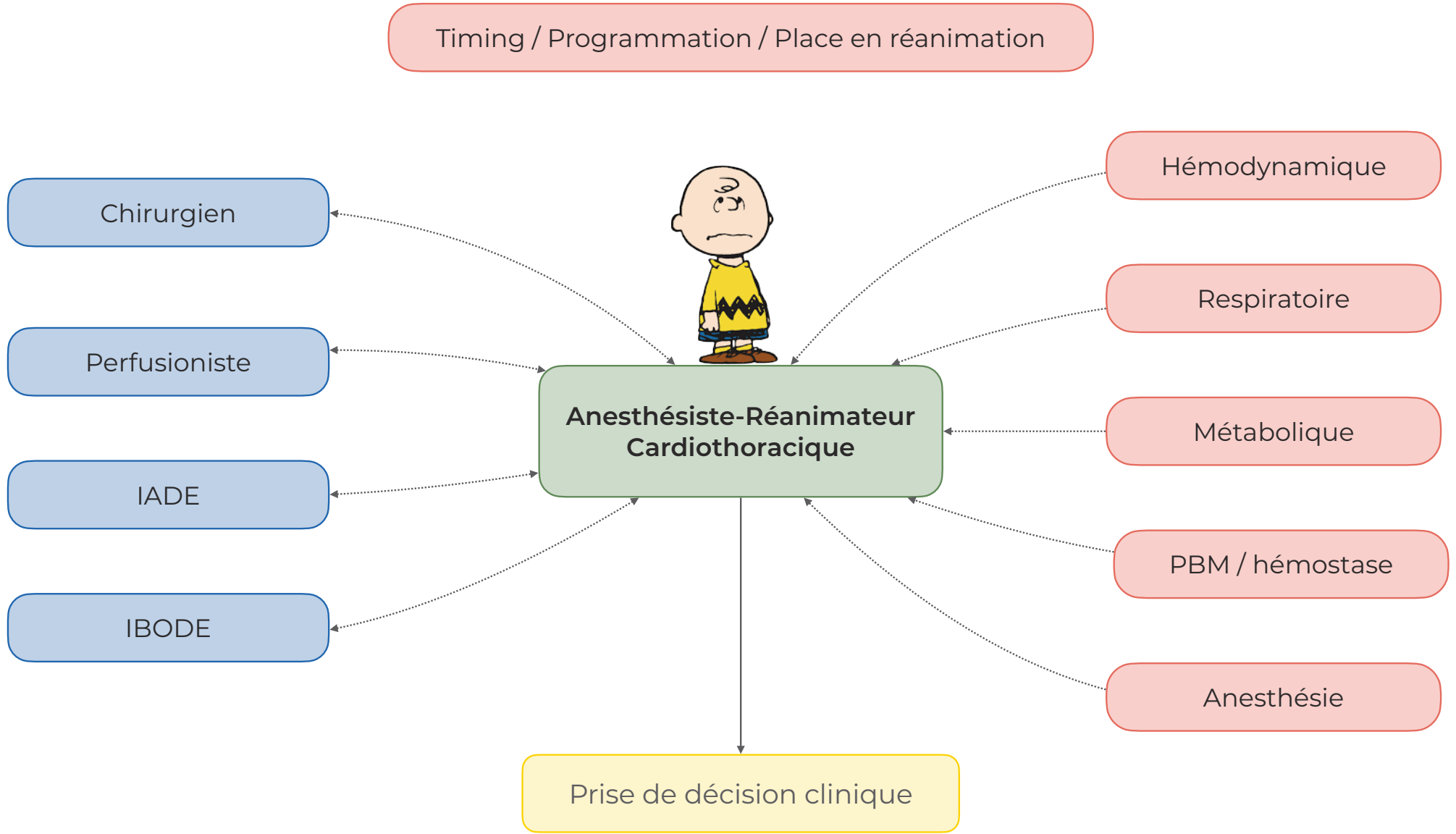
**MAIS...**

Niveau de preuve très faible

Pas de validation sur des critères robustes

Stratégies modernes CEC // Anesthésie-Réa // PBM

Variabilité importante entre les dispositifs de mesure ACT



## ACT pour la surveillance de l'HNF

Conditions pré-analytiques négligées

CV parfois élevés

Mauvaise sensibilité pour des héparinémies HNF  $< 0,5$  UI/mL

Variabilité inter-dispositifs majeure (parfois  $> 20\%$  !)

Effet variable des AC oraux : AVK/dabigatran vs AOD antiXa

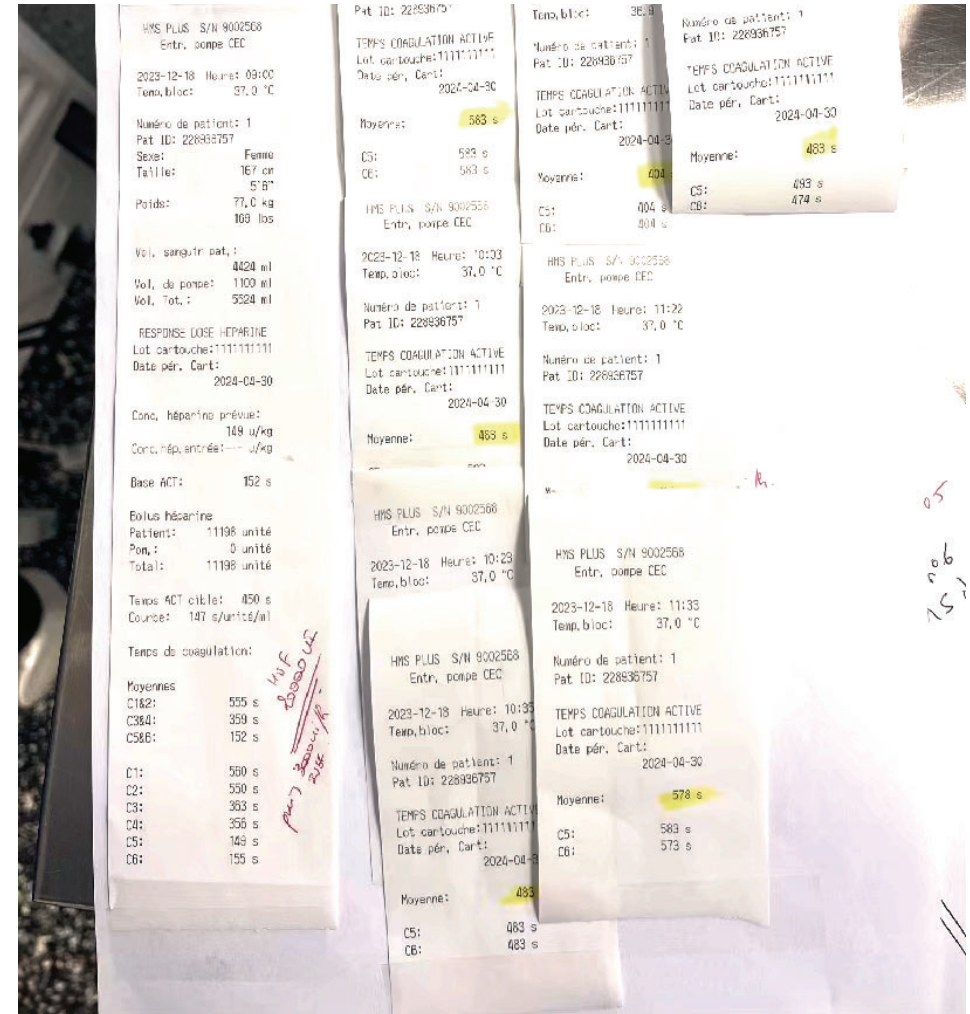
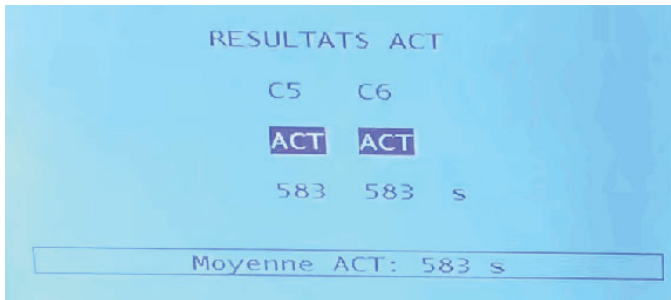
Formation // CQ // regimentation EBMD

Niveau preuve (très) limité pour justifier les cibles adoptées

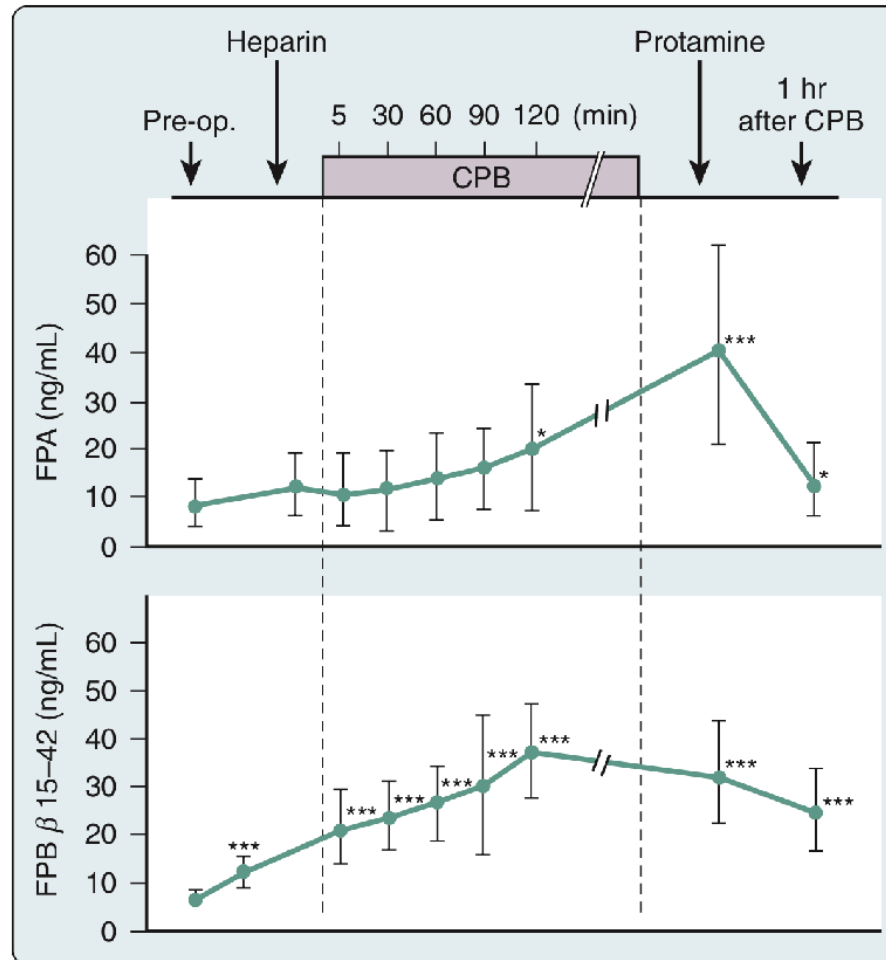
# **Recommandations pour l'accréditation de l'*Activated clotting time* (ACT) pour la surveillance de l'anticoagulation par l'héparine non fractionnée selon la norme EN ISO 22870**

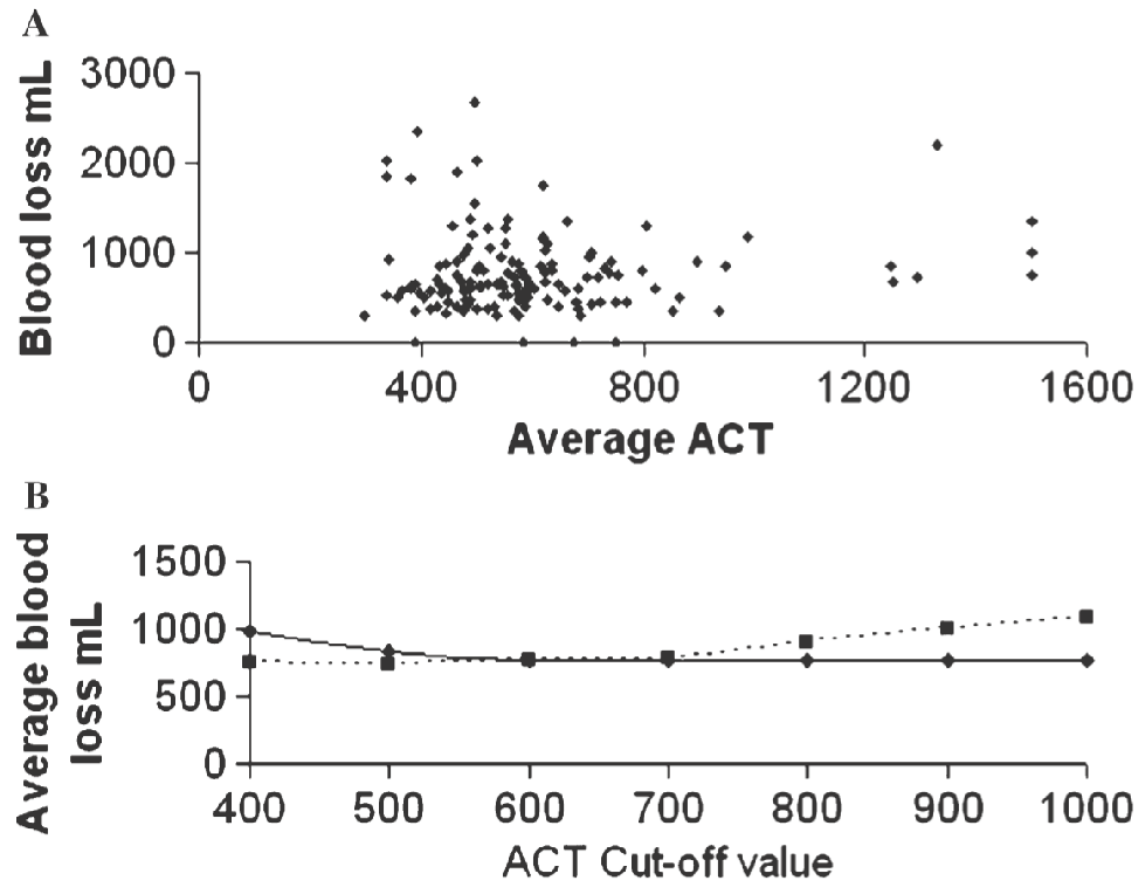
*Guidelines for certification of Activated clotting time (ACT)  
according to the EN ISO 22870 standards*

Dominique Lasne<sup>1</sup>  
Anne Bauters<sup>2</sup>  
Agnès Le Querrec<sup>3</sup>  
Carole Bourdin<sup>1</sup>  
Sophie Voisin<sup>4</sup>



# Une stratégie toujours non optimale





Palmer K, Ridgway T, Al-Rawi O, Poullis M. Heparin therapy during extracorporeal circulation: deriving an optimal activated clotting time during cardiopulmonary bypass for isolated coronary artery bypass grafting. *J Extra Corpor Technol.* 2012;44(3):145-150.



## 2024 EACTS/EACTAIC Guidelines on patient blood management in adult cardiac surgery in collaboration with EBCP

Plus de recommandation sur la cible d'ACT

« The efficacy of heparin anticoagulation is assessed using the ACT test, with target values between 300 and 600 s. These values vary depending on the measurement method and the heparin dosing strategy. »



“Finding a common definition of heparin resistance in adult cardiac surgery: Communication from the ISTH SSC Subcommittee on Perioperative and Critical Care Thrombosis and Hemostasis”

Comment

Alexandre Mansour, François Mullier, Thomas Lecompte  
Emmanuel de Maistre, Isabelle Guoin-Thibault, Michael Hardy

Response

« They do not suggest any reasonable alternative. This highlights a common theme: **while everyone laments the existence of the ACT**, there has yet to be any widespread adoption of any other test.

**Every major society** involved with the care of cardiac surgical patients **has incorporated the ACT** along **with suggested targets**, into guideline documents »

# Prescription de l'HNF en per-CEC

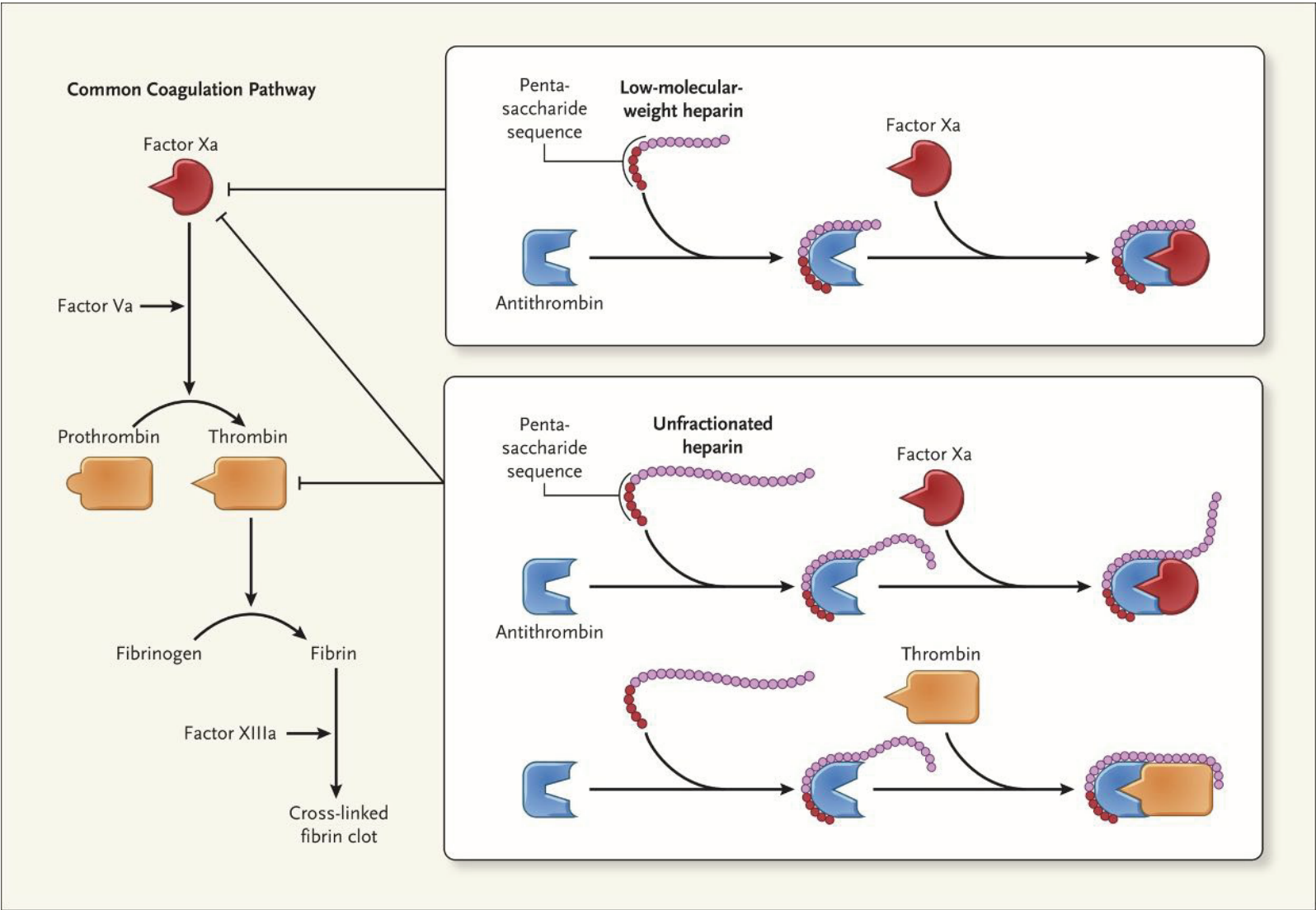
## En pratique

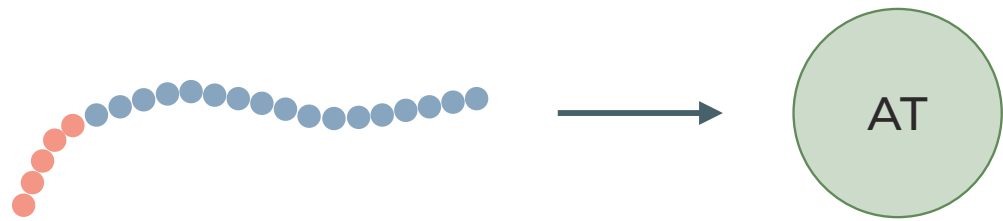
- Protocole défini dans chaque centre // cible variable
  - 300-400UI/kg puis bolus et/ou IVSE
  - Titration / courbe de réponse Hepcon HMS Plus
  - Modèles PK
- Examen de biologie médicale délocalisée : maintenance, validation,...
- Monitoring basé sur anti-Xa : faisable, 3-4 UI/mL mais non validé...

Réponse altérée à l'héparine ?

## Réponse altérée à l'héparine ?

- « Résistance à l'héparine » >>> Réponse altérée à l'héparine
- **ISTH** SSC 2024 : ACT <480s malgré >500UI/kg HNF
  - Définition non validée
  - Variabilité HNF // ACT // conduite CEC



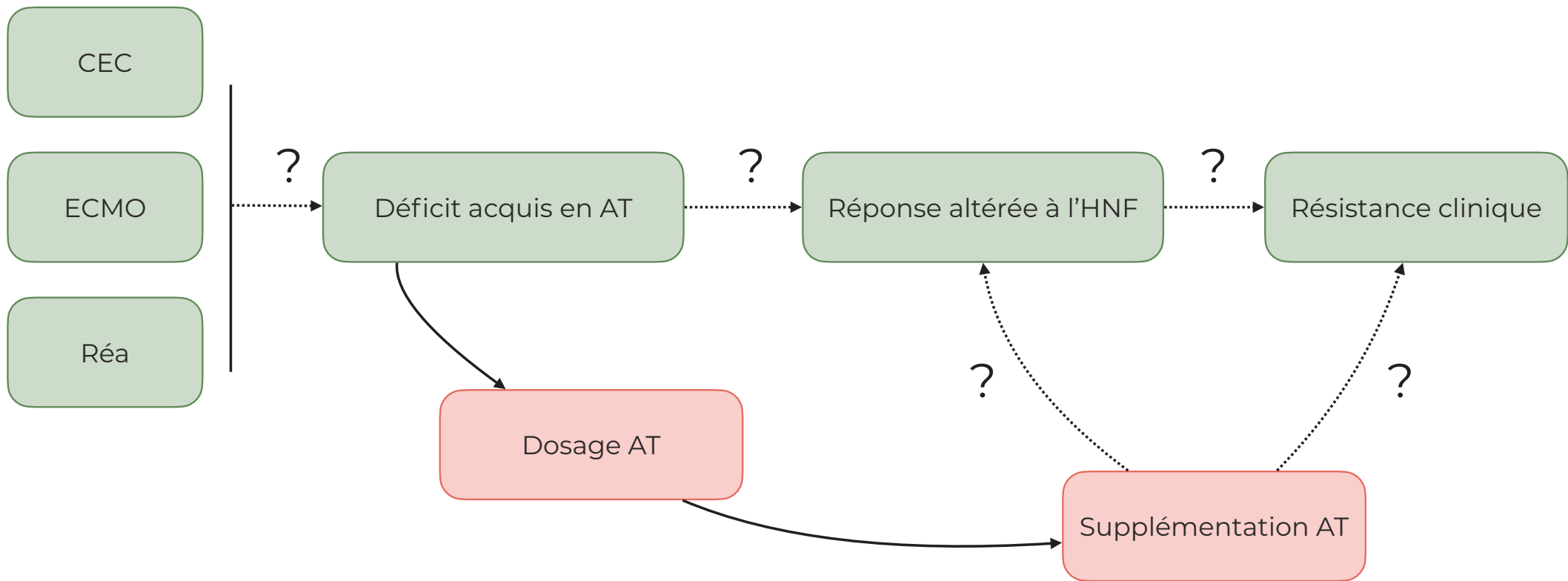


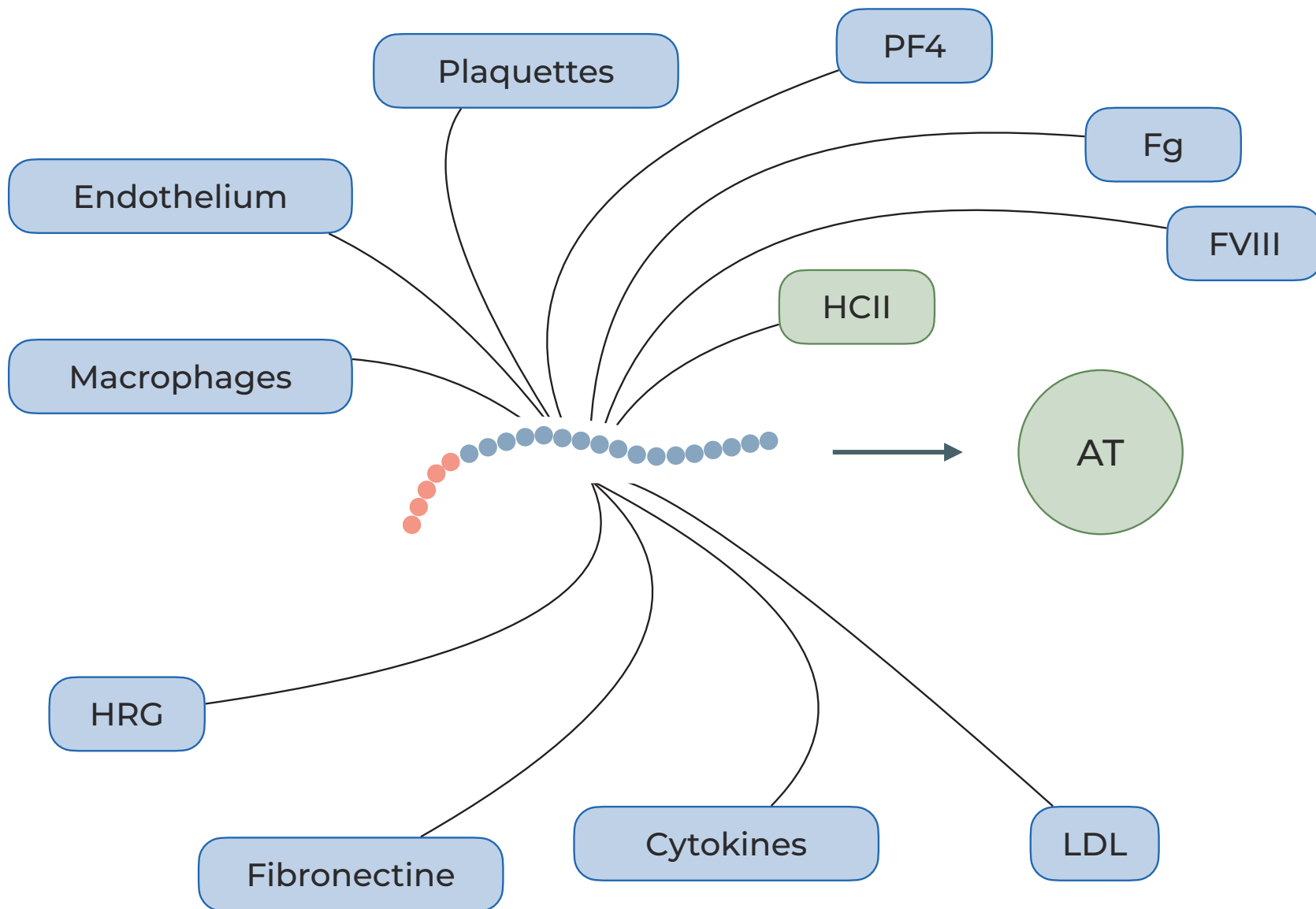
Déficit **Héréditaire** en AT

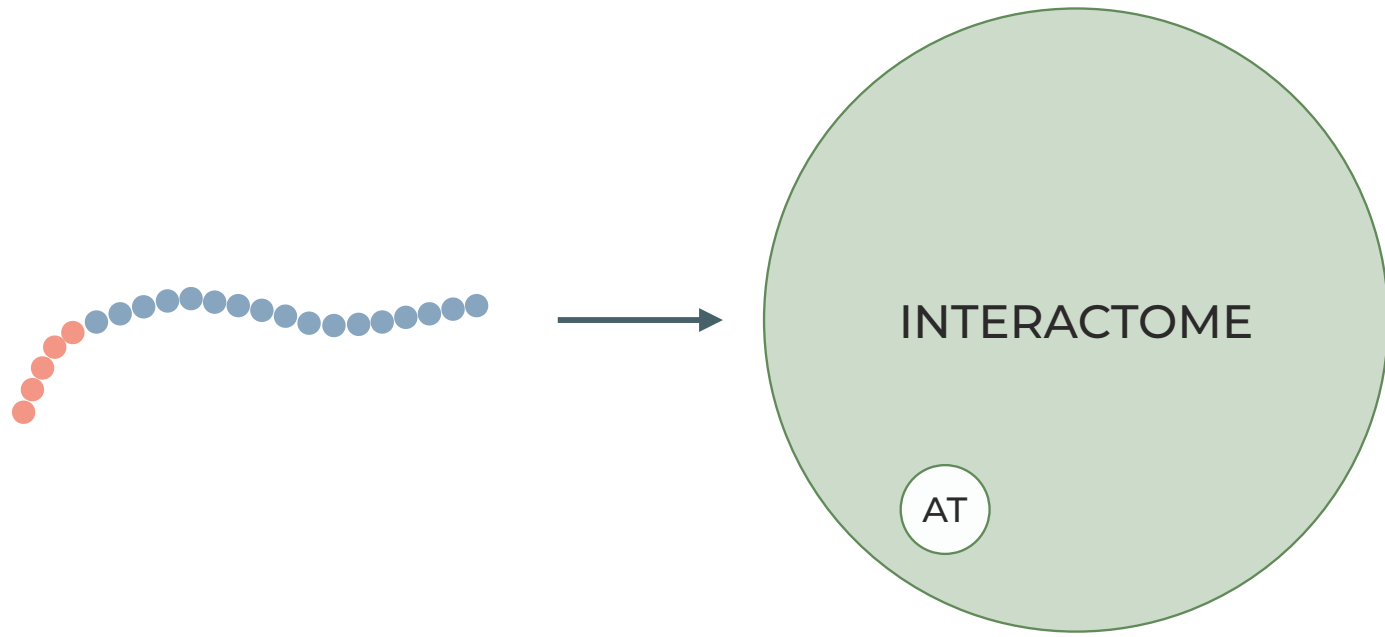
Réponse altérée à l'HNF

Supplémentation









# Déficit acquis en antithrombine

**Consommation**  
**Diminution  $\frac{1}{2}$  vie**  
**Dilution**

CIVD  
Thrombose extensive, SAPL  
CEC, ECMO

**Défaut de synthèse**

Ins. Hépatocellulaire

**Excès d'élimination**

Syndrome néphrotique

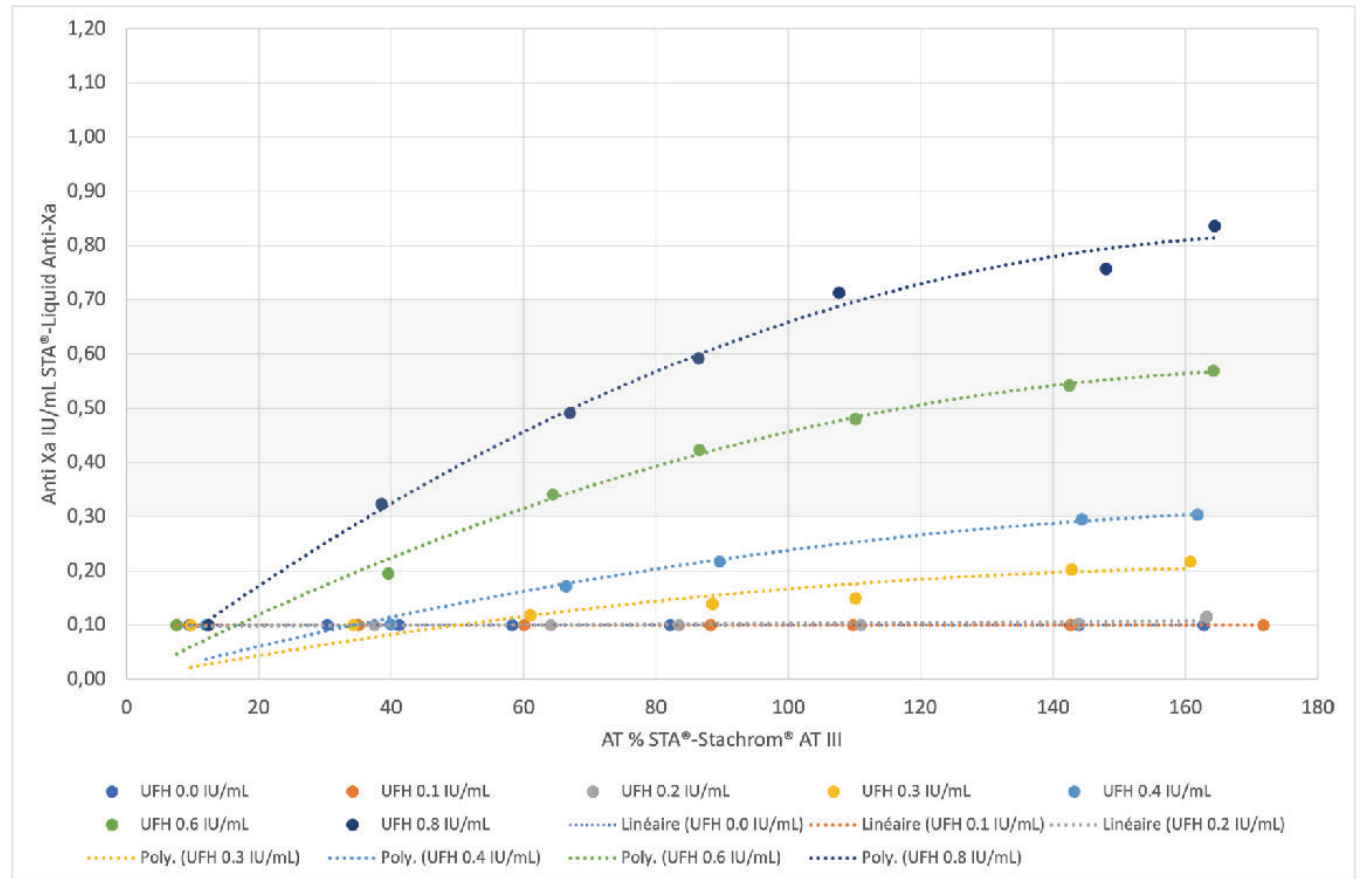
Déficit combiné acquis  $\neq$  isolé constitutionnel (< 80%)

Retentissement du déficit en AT sur la réponse à l'HNF : dépend des tests, de la cause

Balance hémostatique très différente // variabilité ++ de présentation

# Antithrombin level and UFH anticoagulant activity

- In vitro study
- AT deficient plasma spiked with increased concentrations:
  - AT
  - UFH
- Anti-Xa (STA-liquid anti-Xa®)



**Relationship between entre AT and anti-Xa levels, without AT threshold**

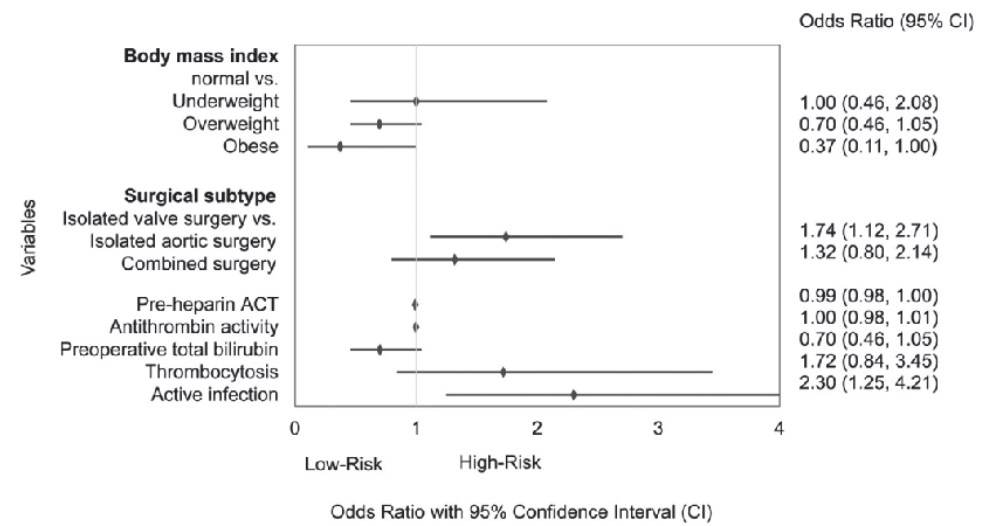
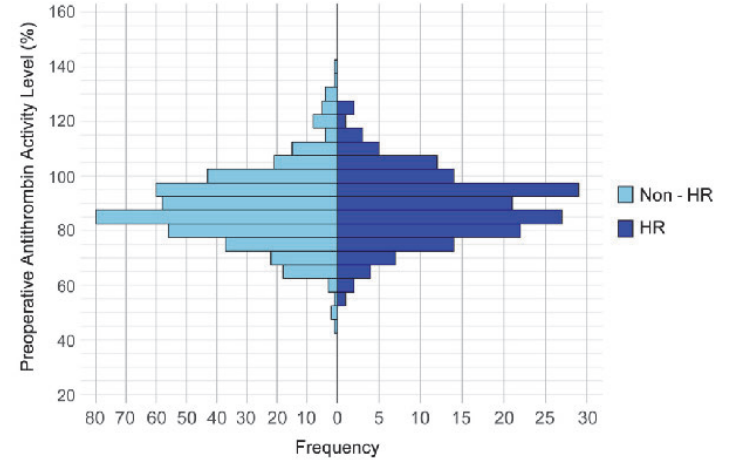
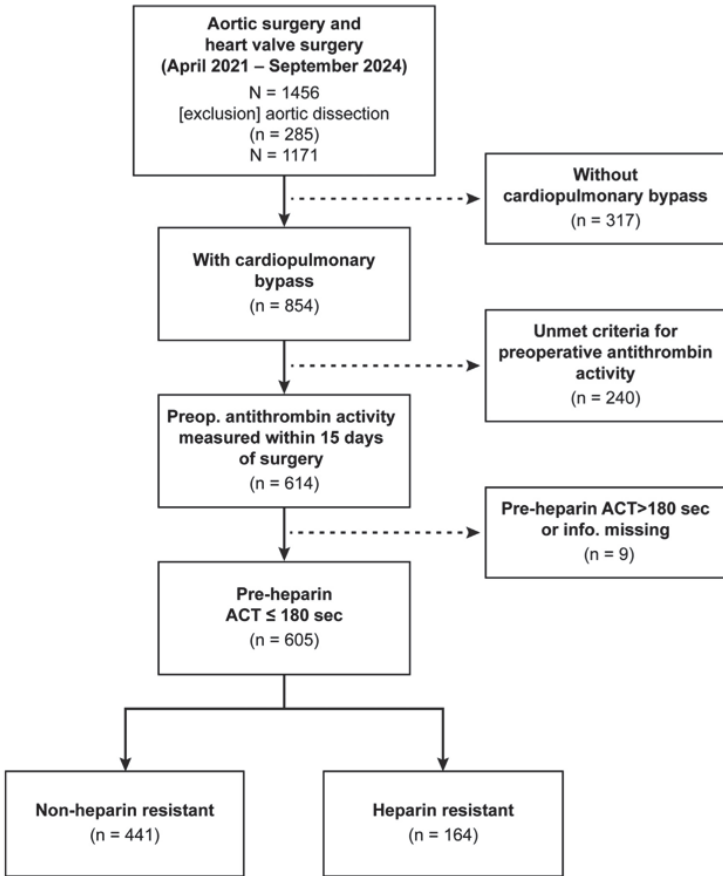
**Detectable UFH activity and anti-Xa within the therapeutic range at low AT concentration**

Gueret P  
Gouin-Thibault I  
Lecomte T

## Réponse altérée à l'héparine ?

- « Résistance à l'héparine » >>> Réponse altérée à l'héparine
- **ISTH** SSC 2024 : ACT <480s malgré >500UI/kg HNF
  - Définition non validée
  - Variabilité HNF // ACT // conduite CEC
- Que faire en pratique : majorer HNF ? mesurer // supplémenter AT ?

# Association réponse altérée - déficit AT ?



***A Phase III, Double-blind, Placebo-controlled, Multicenter Study on the Efficacy of Recombinant Human Antitbrombin in Heparin-resistant Patients Scheduled to Undergo Cardiac Surgery Necessitating Cardiopulmonary Bypass***

Michael S. Avidan, M.B.Ch.,\* Jerrold H. Levy, M.D.,† Jens Scholz, M.D.,‡ Elise Delphin, M.D.,§ Peter M. J. Rosseel, M.D.,|| Michael B. Howie, M.D.,# Irwin Gratz, D.O.,\*\* Charles R. Bush, M.D.,†† Nikolaos Skubas, M.D.,‡‡ Gabriel S. Aldea, M.D.,§§ Michael Licina, M.D.,||| Laura J. Bonfiglio, B.S.N., C.R.N.A.,## Daniel K. Kajdasz, Ph.D.,\*\*\* Elizabeth Ott, M.D.,††† George J. Despotis, M.D.†††

- Etude multicentrique (US et UE)
- 54 patients « résistants » (sur 296 inclus)
- Résistance : ACT < 480 sec après 400 U/kg d'HNF (dose initiale)
- Critère de jugement : proportion de patients nécessitant l'administration de 2 PFC per-CEC
- Randomisation :
  - Bolus de 75 U/kg AT (n=27)
  - Bolus de sérum physiologique (n=27)

**Résultats**

Aministration PFC : plus élevée placebo / AT  
Dose d'héparine : plus élevée placebo / AT  
6890 U/h (placebo) vs 3884 u/h (AT)  
Clinique : pas de différence

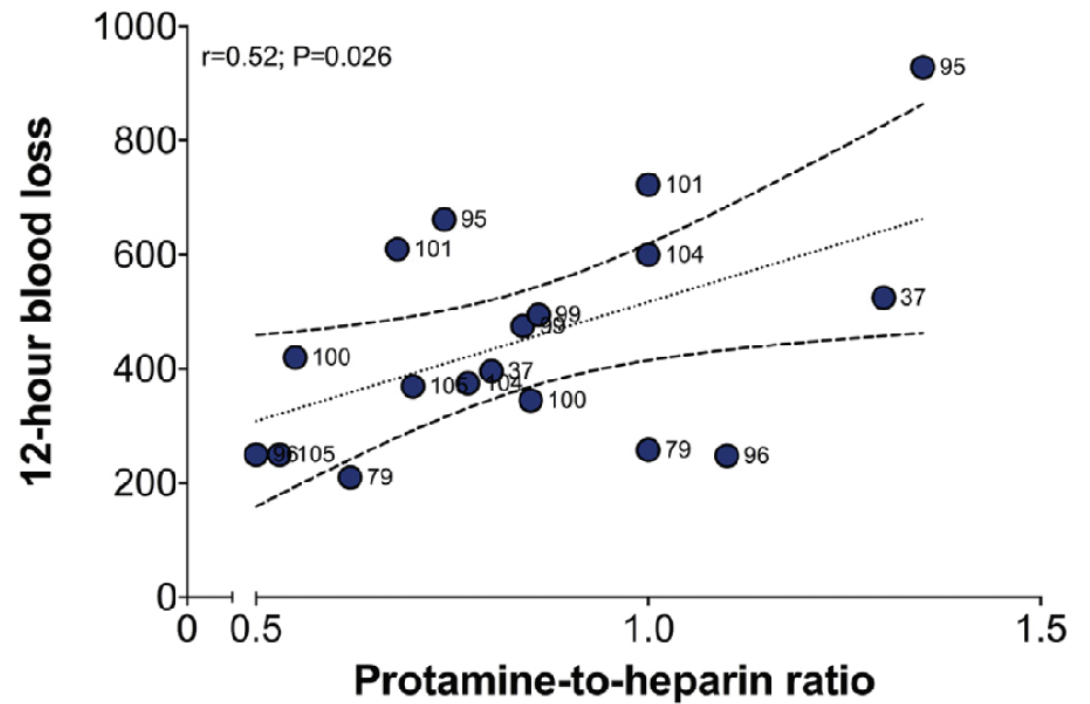
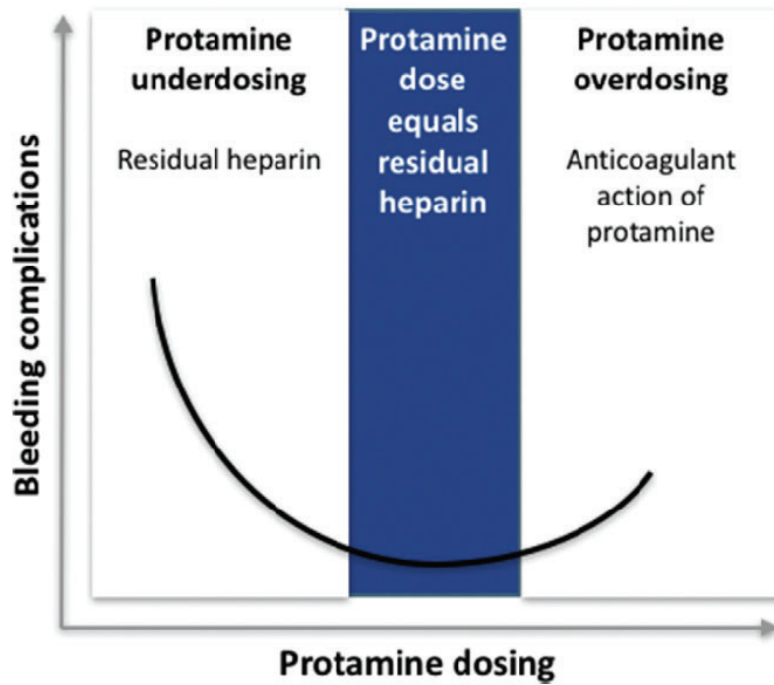
RCT AT (+20%) vs placebo  
N=425

Parameter	AT (n=198)	Placebo (n=194)
<b>ACT ≥480 sec after one heparin dose (400 IU/kg)</b>		
Yes	178 (89.9%)	152 (78.4%)
No	20 (10.1%)	42 (21.6%)
<b>ACT ≥480 sec after a maximum of three heparin doses</b>		
Yes	14 (7.1%)	25 (12.9%)
No	6 (3%)	17 (8.8%)
<b>Additional measures performed</b>		
Yes	3 (1.5%)	12 (6.2%)
No	3 (1.5%)	5 (2.6%)
<b>Lowest ACT during surgery, sec</b>		
Mean (SD)	548.1 (158.3)	480.9 (112.7)
Median (min, max)	492.5 (136, 1005)	462.0 (93, 1000)
<b>Protamine (15 mg/h during the first 5 h post-operation)</b>		
Yes	178 (89.9%)	173 (89.2%)

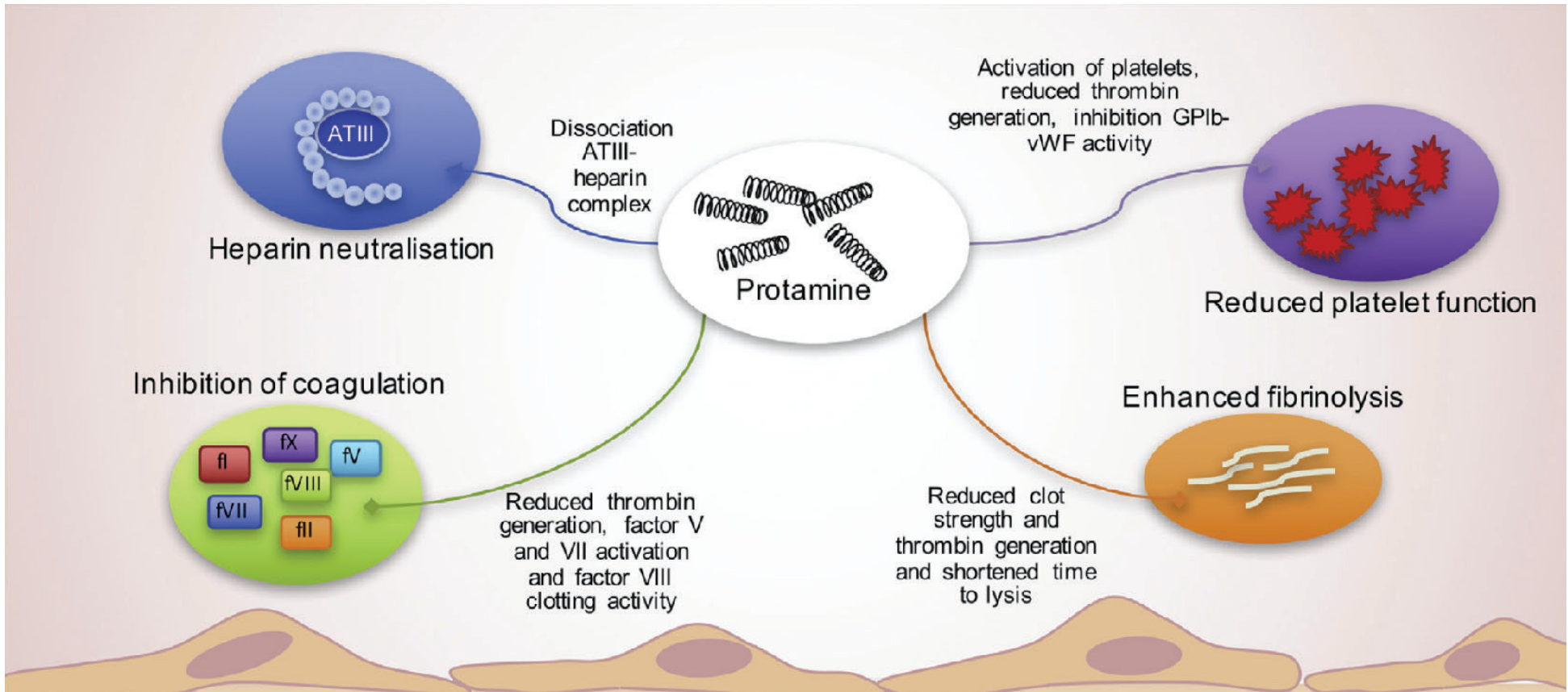
RCT AT (+20%) vs placebo  
N=425

Parameter	AT (n=198)	Placebo (n=194)	P-Value
<b>Component of the major morbidity composite, n (%)</b>			
Postoperative mortality	7 (3.5)	3 (1.5)	.338
Stroke	5 (2.5)	8 (4.1)	.372
AKI	23 (11.6)	5 (2.6)	<.001
Surgical reexploration	7 (3.5)	12 (6.2)	.217
Arterial or venous thromboembolic events	10 (5.1)	4 (2.1)	.172
Prolonged mechanical ventilation	45 (22.7)	43 (22.2)	.894
Infection	8 (4)	6 (3.1)	.620
<b>Postoperative chest tube output, mL, mean (SD)</b>			
12 h	548.2 (360.1)	586.8 (503.2)	.383
24 h	847.5 (506.7)	850.7 (605.9)	.955
<b>Transfusion requirements, n (%)</b>			
Apheresis platelets	61 (30.8)	55 (28.4)	.310
Cell saver	164 (82.8)	164 (84.5)	.447
Cryoprecipitate	22 (11.1)	21 (10.8)	.989
Fresh frozen plasma	35 (17.7)	33 (17.0)	.856
Red blood cells	90 (45.5)	81 (41.8)	.585
<b>Hospitalization, days, mean (SD)</b>			
Duration of ICU stay	5.0 (3.7)	5.1 (4.98)	.424
Duration of hospital stay	10.1 (6.41)	10.2 (6.07)	.747

# Antagonisation de l'HNF par la protamine



# Protamine



## Anticoagulation non-héparinique

- Situation rare // séries de cas
- TIH, allergie héparine ou protamine, ACC
- Bivalirudine ou argatroban
- Pas de reversion // risque hémorragique ++ // surveillance ?

Agent	Pump prime (mg)	Bolus (mg kg <sup>-1</sup> )	Infusion	Clearance	Adjustments
Bivalirudin	50	1	2.5 mg kg <sup>-1</sup> h <sup>-1</sup>	Proteolysis (80%); renal (20%)	(i) Reduced infusion with renal dysfunction (ii) Further bolus 0.1–0.2 mg kg <sup>-1</sup> to achieve an ACT >300
Argatroban	4	0.1–0.3	5–25 mcg kg <sup>-1</sup> min <sup>-1</sup>	Hepatobiliary	(i) Consider 0.1 mg kg <sup>-1</sup> bolus titration to effect (ii) Reduce infusion with liver disease (iii) Can increase infusion to 40 mcg kg <sup>-1</sup> min <sup>-1</sup>



## Anticoagulation per-CEC

Héparine non fractionnée // surveillance ACT

Niveau preuve faible // cibles non validées // limites des test

Réponse altérée à l'héparine : définition ? majorer HNF ? AT ?

Peut-on prévenir le saignement post-CEC ?





## Traitement antifibrinolytique - TXA

Chirurgie cardiaque // CEC  
 Activation fibrinolyse ++  
 Secrétion tPA par endothelium  
 Activation phase contact

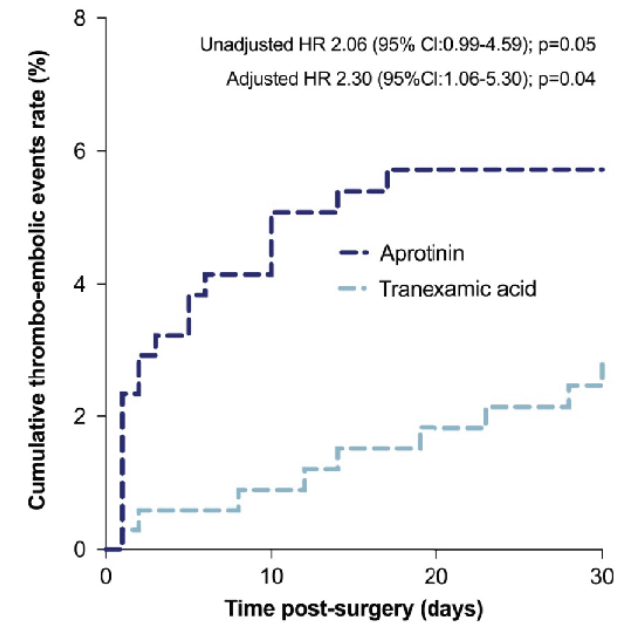
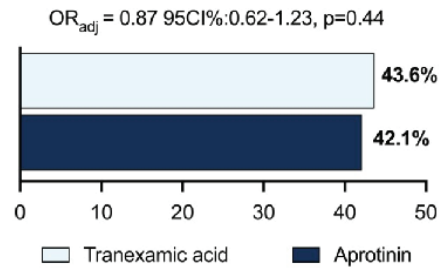
ATACAS  
 Plan factoriel 2x2 (aspirine et TXA)  
 TXA : 100 puis 50mg/kg

Outcome or Event	Tranexamic Acid Group (N=2311)	Placebo Group (N=2320)	Risk Ratio (95% CI)	P Value
<b>Primary outcome: death, myocardial infarction, stroke, renal failure, pulmonary embolism, or bowel infarction</b>	386/2310 (16.7%)	420/2320 (18.1%)	0.92 (0.81–1.05)	0.22
Myocardial infarction	269/2310 (11.6%)	300/2320 (12.9%)	0.90 (0.77–1.05)	0.19
Stroke	32/2309 (1.4%)	35/2320 (1.5%)	0.92 (0.57–1.48)	0.81
Renal failure	98/2309 (4.2%)	96/2320 (4.1%)	1.03 (0.78–1.35)	0.88
Pulmonary embolism	15/2309 (0.6%)	15/2320 (0.6%)	1.00 (0.49–2.05)	>0.99
Bowel infarction	8/2309 (0.3%)	3/2320 (0.1%)	2.68 (0.71–10.09)	0.15
<b>Reoperation</b>				
Due to any cause	32/2310 (1.4%)	65/2320 (2.8%)	0.49 (0.32–0.75)	0.001
Due to major hemorrhage	18/2310 (0.8%)	50/2320 (2.2%)	0.36 (0.21–0.62)	<0.001
Due to cardiac tamponade	14/2310 (0.6%)	23/2320 (1.0%)	0.61 (0.32–1.19)	0.19
<b>Transfusion of red cells during hospitalization</b>	759/2311 (32.8%)	1086/2320 (46.8%)		<0.001

# Aprotinine ?

Etude Observationnelle  
N= 693  
Chirurgie cardiaque à haut risque  
Aprotinine vs Ac Tranexamique  
UDPB score

Patients with severe or massive perioperative bleeding (UDPB class 3-4)



Number at risk	0	10	20	30
Aprotinine	347	302	289	284
Tranexamic acid	346	317	307	299



## Conduite de la CEC et prévention de l'hémodilution

Recommendations	Class	Level
Implementation of multiple institutional measures to reduce hemodilution during CPB is recommended to reduce anemia, transfusion, and postoperative bleeding.	I	B
Combining the priming volume with colloids to reduce transfusions is not recommended.	III	A
Optimizing CPB systems using coated and reduced surface areas and avoiding direct blood reinfusion are recommended to increase hemocompatibility and reduce bleeding complications.	I	B
MiECC should be considered over conventional CPB systems to reduce the risk of transfusions and bleeding.	Ila	B
The use of cell salvage should be considered in order to prevent transfusions.	Ila	B
Modified ultrafiltration should be considered as part of a blood conservation strategy.	Ila	A
Autologous priming, either retrograde or antegrade, is recommended as part of a blood conservation strategy.	I	A
Maintenance of normothermia during the entire surgical process should be considered to reduce coagulopathy and blood loss.	Ila	B
Maintenance of normal pH during the entire surgical process should be considered to reduce coagulopathy and blood loss.	Ila	B
In cases requiring hypothermia, mild hypothermia (above 28°C) is recommended over lower targeted temperatures to minimize postoperative blood loss.	I	B



# Conduite de la CEC et prévention de l'hémodilution

Observationnelle (Angers)

Gestion optimale de la CEC  
 Pas d'aspiration  
 Circuit clos hépariné  
 ACT 250s

Variable	Overall (n=2275)	ASA (n=1164)	DAPT (n=1111)	p-value
E-CABG score $\geq 2$ , n (%)	94 (4.11)	34 (2.92)	59 (5.31)	0.0065
UDPB score $\geq 3$ , n (%)	61 (2.68)	21 (1.8)	40 (3.57)	0.0162
BARC 4, n (%)	96 (4.2)	40 (3.44)	57 (5.09)	0.0626
Reoperation for bleeding, n (%)	75 (3.33)	29 (2.49)	46 (4.18)	0.03
Pleural effusion, n (%)	84 (3.70)	32 (2.75)	51 (4.62)	0.033
Units of RBC transfused, mean (SD)	0.402 (1.3)	0.248 (1.1)	0.56 (1.5)	<0.0001
Units of FFP transfused, mean (SD)	0.071 (0.5)	0.045 (0.5)	0.098 (0.5)	0.021
Units of PLT transfused, mean (SD)	0.016 (0.18)	0.009 (0.18)	0.023 (0.17)	0.08
Overall transfusion, n (%)	349 (15.3)	109 (9.5)	239 (21.5)	<0.0001
Chest tube blood loss at 12H (mL), mean (SD)	224 (161.9)	192 (136.4)	258 (178.8)	<0.0001
Chest tube blood loss at 24H (mL), mean (SD)	322 (211.3)	284 (187.8)	361 (226.9)	<0.0001
Overall chest tube blood loss (mL), mean (SD)	386 (296)	338 (274.8)	435 (309)	<0.0001



## Pas de place pour PSL/MDS/pro-hémostatiques en prophylaxie du saignement

Recommendations	Class	Level
Antifibrinolytic therapy is recommended to reduce bleeding and transfusions of blood products and reoperations for bleeding.	I	A
The prophylactic use of FFP to reduce bleeding is not recommended.	III	B
Prophylactic fibrinogen administration is not recommended.	III	A
The prophylactic use of DDAVP is not recommended to reduce bleeding complications.	III	A
The prophylactic use of rFVIIa is not recommended to prevent bleeding complications.	III	B



# Gestion post-opératoire de l'hémostase

## Prévention de la MVTE postopératoire

- Risque de MVTE élevé > thromboprophylaxie
- Contentions élastiques graduées non recommandées
- Compressions pneumatiques intermittentes si risque élevé et CI anticoagulation
  
- Anticoagulation à dose préventive H+12 à H+24
  - Enoxaparine : 4 000 UI/j SC (2 000 UI/j si DFG 15 à 30 mL/min)
  - Tinzaparine : 4 500 UI/j SC, si DFG > 20 mL/min
  - Si DFG < 15 mL/min : HNF IVSE à dose préventive

# Anticoagulation après chirurgie valvulaire mécanique

- Risque thrombotique élevé > anticoagulation curative précoce et continue
- AOD contre-indiqués
- HBPM préférées aux HNF : simplicité // moindre variabilité // efficacité // moins de TIH
- A titre indicatif:
  - HBPM dose préventive H+12 heures
  - pas d'AAP, sauf PAC associées, stent coronaire < 6 mois, SCA < 12 mois, stent vasculaire périphérique < 1 mois ou procédure neuro-interventionnelle < 3 mois
  - HBPM à dose thérapeutique au 2e jour postopératoire : enoxaparine 100 UI/kg SC, deux fois par jour si DFG  $\geq$  30 mL/min

# Gestion des AAP en postopératoire

- Aspirine faible dose (75-100 mg/j) <48h post-PAC : réduction morbidité CV
- Par extension indiquée en chirurgie non-coronarienne si pas d'anticoagulation curative
- Bithérapie antiplaquettaire (ticagrelor)
  - Diminue le risque de thrombose de pontage à 1 an
  - Augmente le risque hémorragique

TIH ?

# Diagnostic et prise en charge d'une thrombopénie induite par l'héparine

## 2019

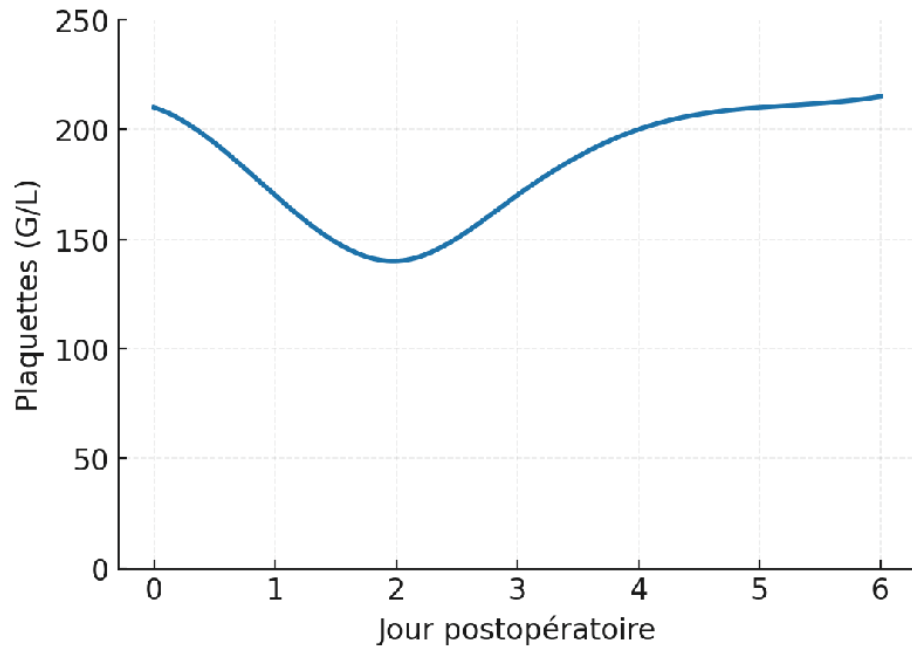
Propositions du Groupe d'Intérêt en Hémostase Périoopératoire (GIHP) et du Groupe  
Français d'études sur l'Hémostase et la Thrombose (GFHT)



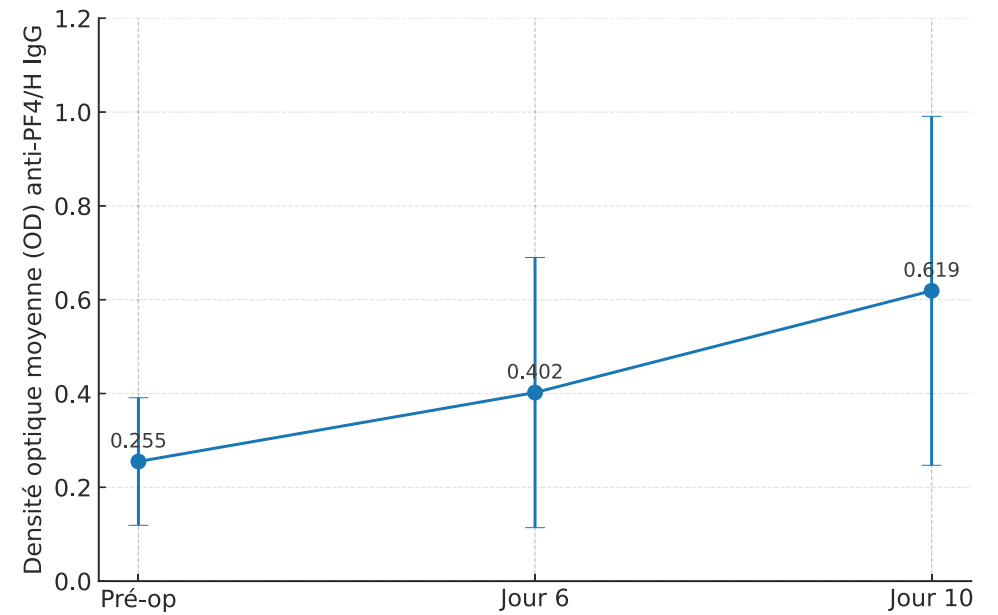
[www.gihp.org](http://www.gihp.org)

# En chirurgie cardiaque ?

Plaquettes : évolution normale

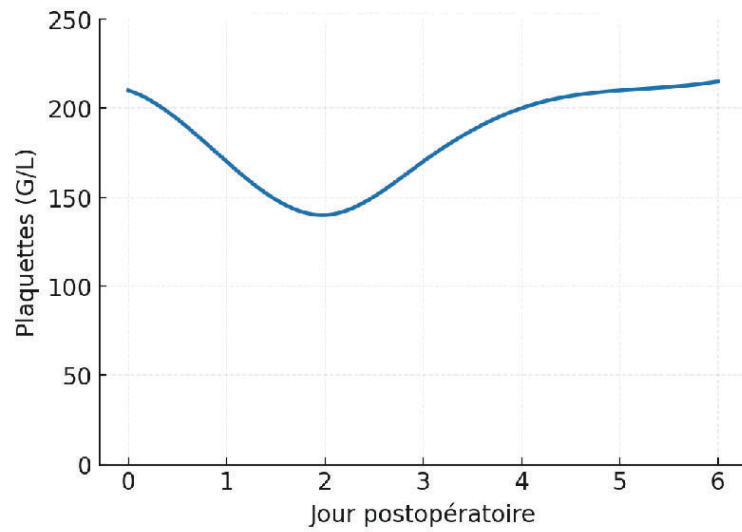


Ac anti-PF4/HNF : évolution normale

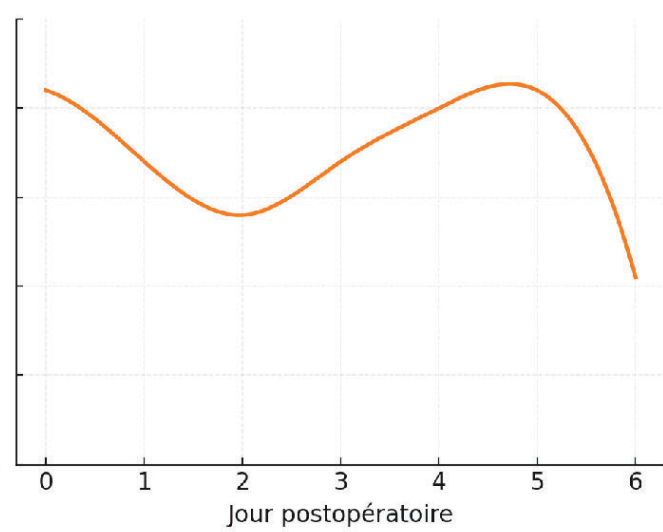


# En chirurgie cardiaque: profils de TIH

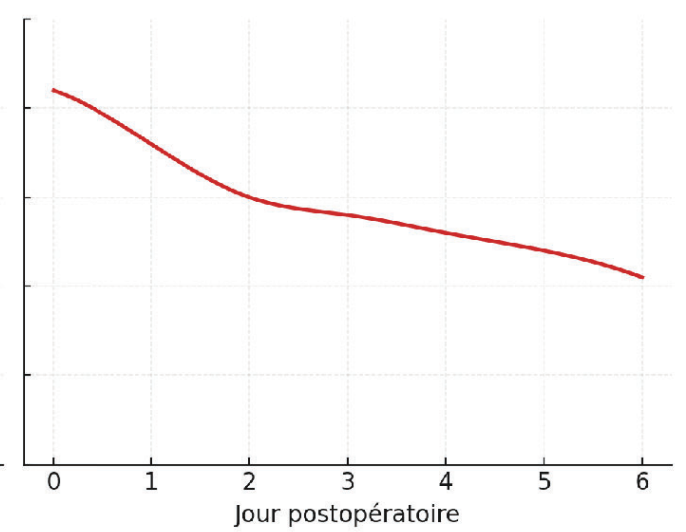
## Evolution normale



## Profil A



## Profil B



## En chirurgie cardiaque: pas de score 4T

Items		Points
Numération plaquettaire	Profil A	2
	Profil B	1
Délai entre la CEC et la date index	≥5 jours	2
	<5 jours	0
Durée de la CEC	≤118 min	1
	>118 min	0

Score total :

≥2 points = forte probabilité de TIH

<2 points = faible probabilité de TIH

Avant toute chirurgie cardiaque chez un patient ayant un antécédent documenté de TIH, il est proposé de rechercher systématiquement en ELISA des anticorps anti-FP4. (Accord fort)

Avant toute chirurgie cardiaque avec CEC chez un patient ayant une TIH aiguë ou subaiguë (<3 mois), il est proposé de définir le protocole d'anticoagulation péri- opératoire dans le cadre d'une concertation pluridisciplinaire. (Accord fort)

Chez un patient ayant une TIH aiguë ou subaiguë avec un titre significatif d'anticorps anti-FP4 (ELISA avec DO>1) et nécessitant une chirurgie cardiaque avec CEC, les stratégies possibles pour l'anticoagulation per-opératoire sont d'associer un agent antiplaquettaire IV (tirofiban ou cangrelor) et l'HNF, ou d'administrer une antithrombine directe IV (bivalirudine ou argatroban) avec une surveillance biologique étroite.

En urgence, Il est proposé de privilégier l'association d'un antiplaquettaire IV et d'héparine non fractionnée (Accord fort)

## Gestion du saignement post-CEC



# DIU FRANCOPHONE HÉMOSTASE ET THROMBOSE



[www.gihp.org](http://www.gihp.org)