DU CEC 2025

PHYSIOPATHOLOGIE DE L'HÉMOSTASE SOUS ECMO

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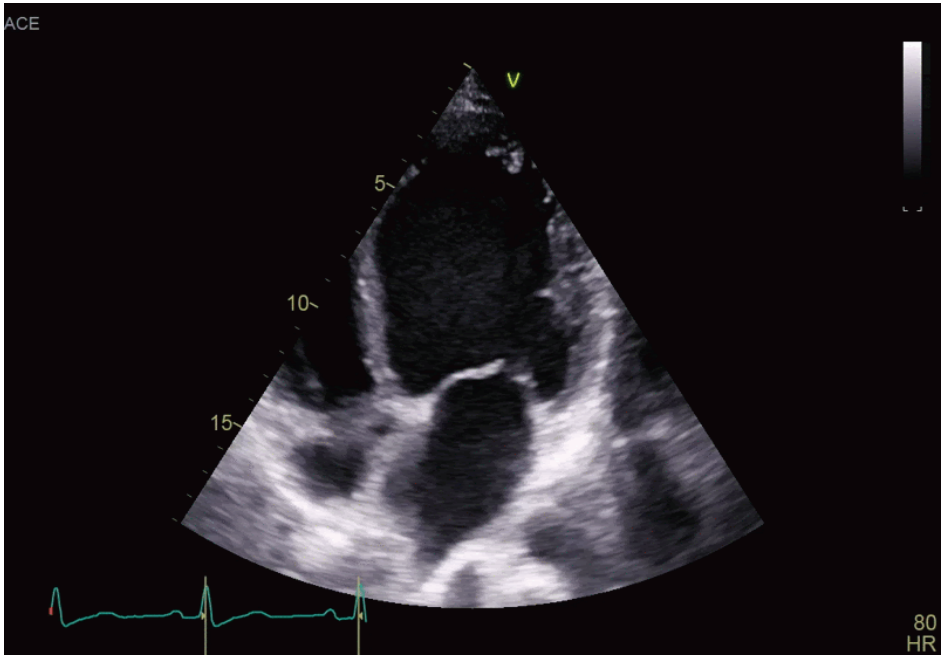
Mr L. 59 ans
Cardiopathie dilatée idiopathique
Admis en réanimation pour un état de choc cardiogénique
Dégradation sous traitement maximal - SCAI D

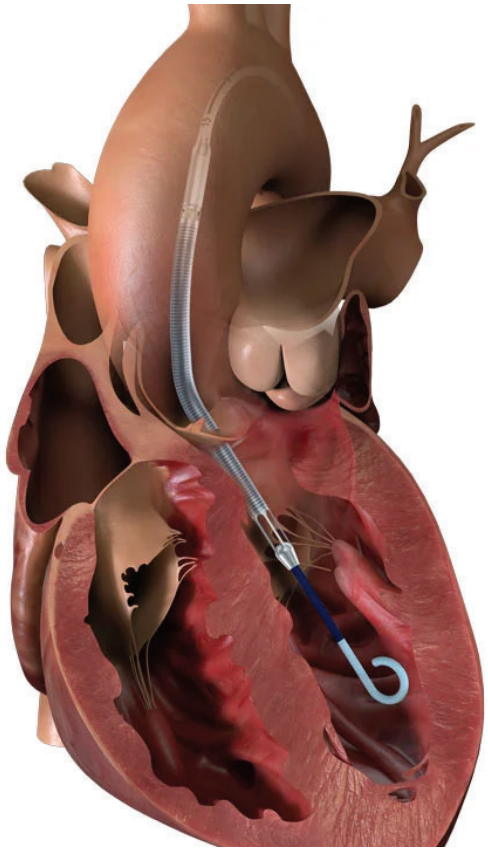
ASAT/ALAT 10N Lactatémie 6mM DFG 40
Hb 11.6g/dL Plaquettes 160G/L

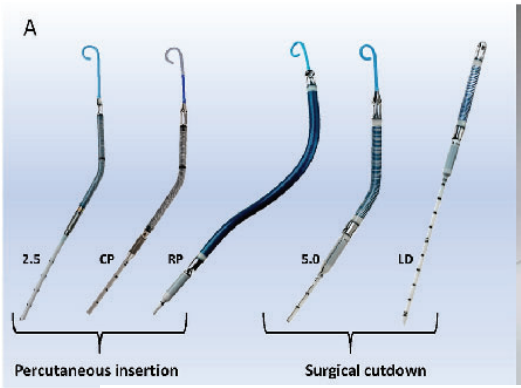
>>> décision d'implanter une ECMO-VA



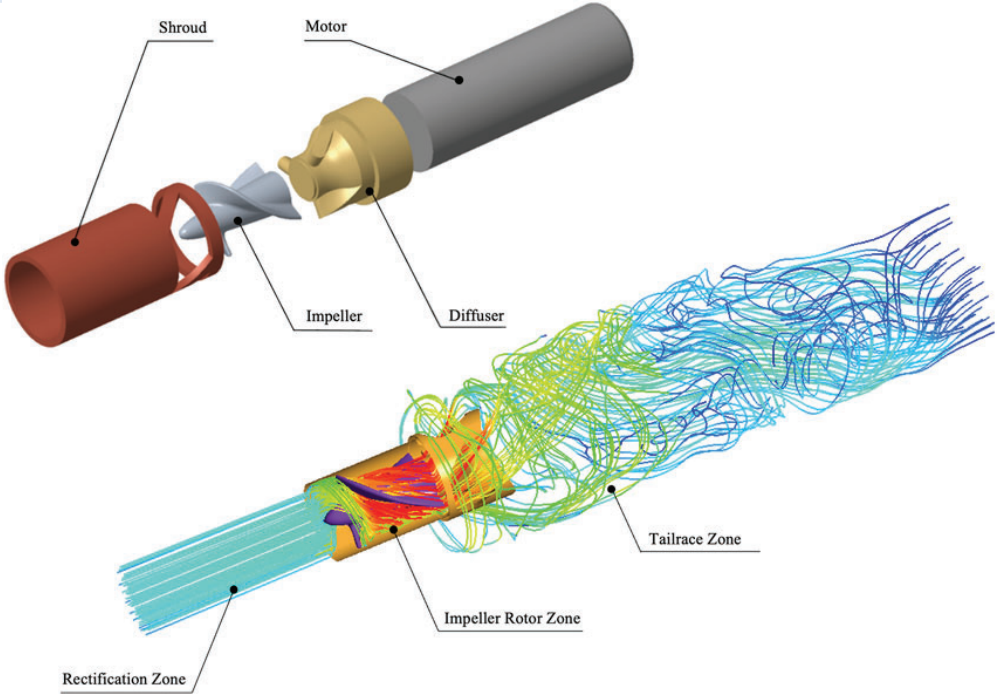
Assistance circulatoire de courte durée ?

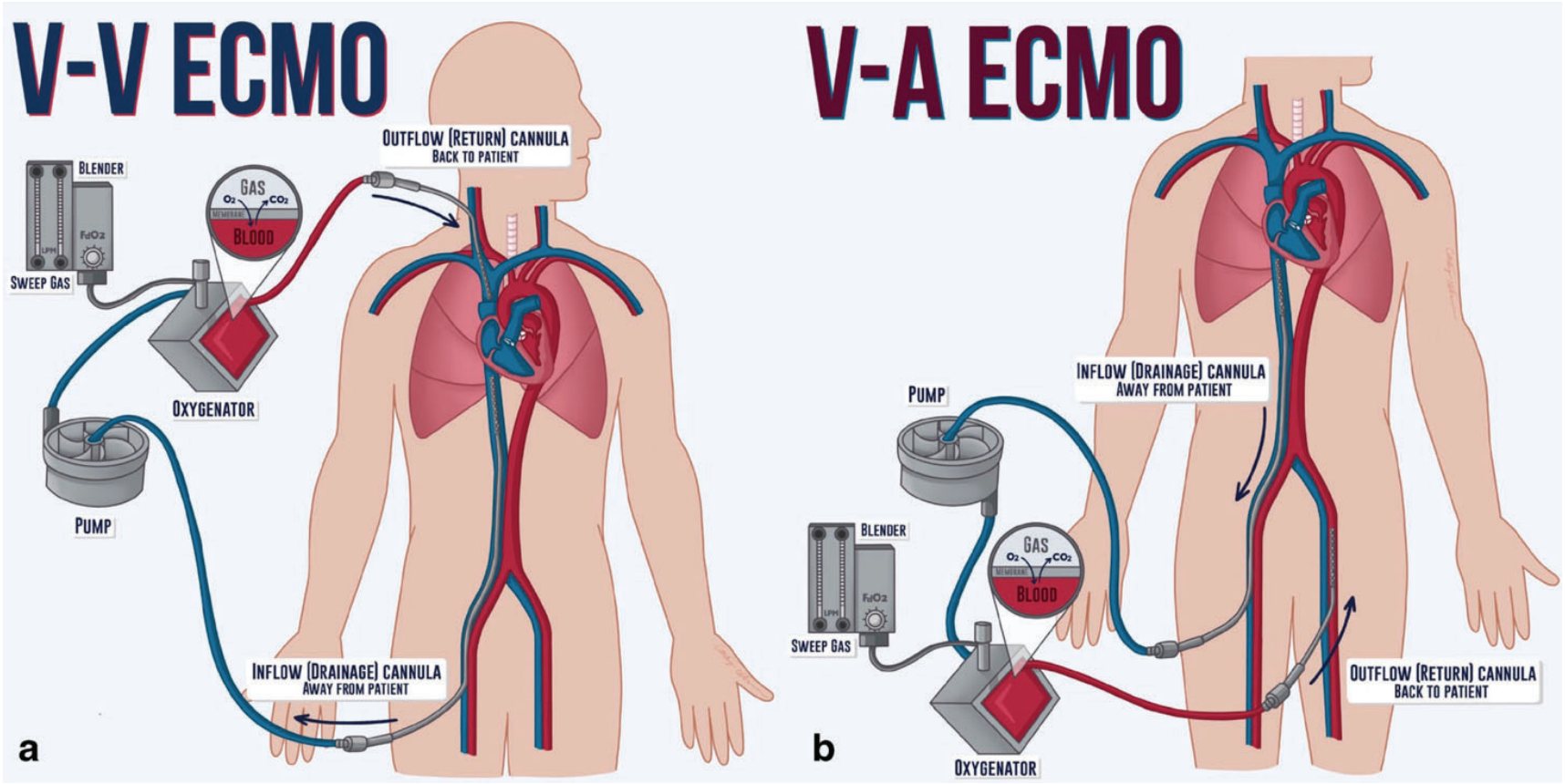
IMPELLA



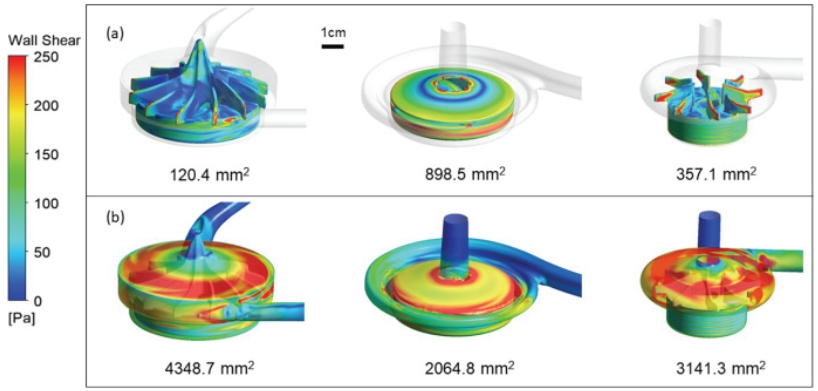

A
2.5
CP
RP
5.0
LD
Percutaneous insertion
Surgical cutdown

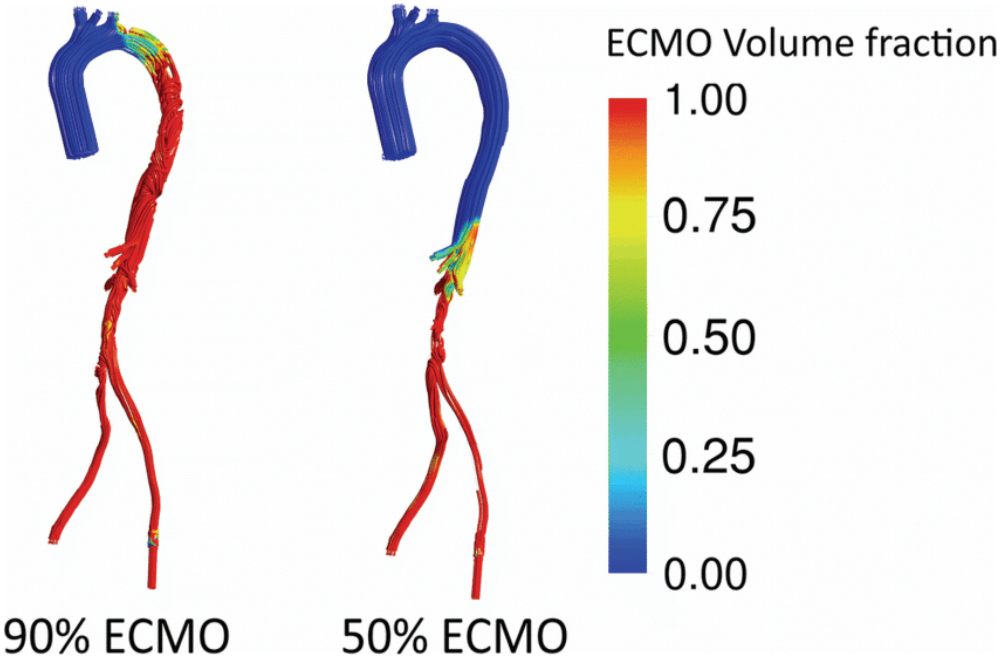

B

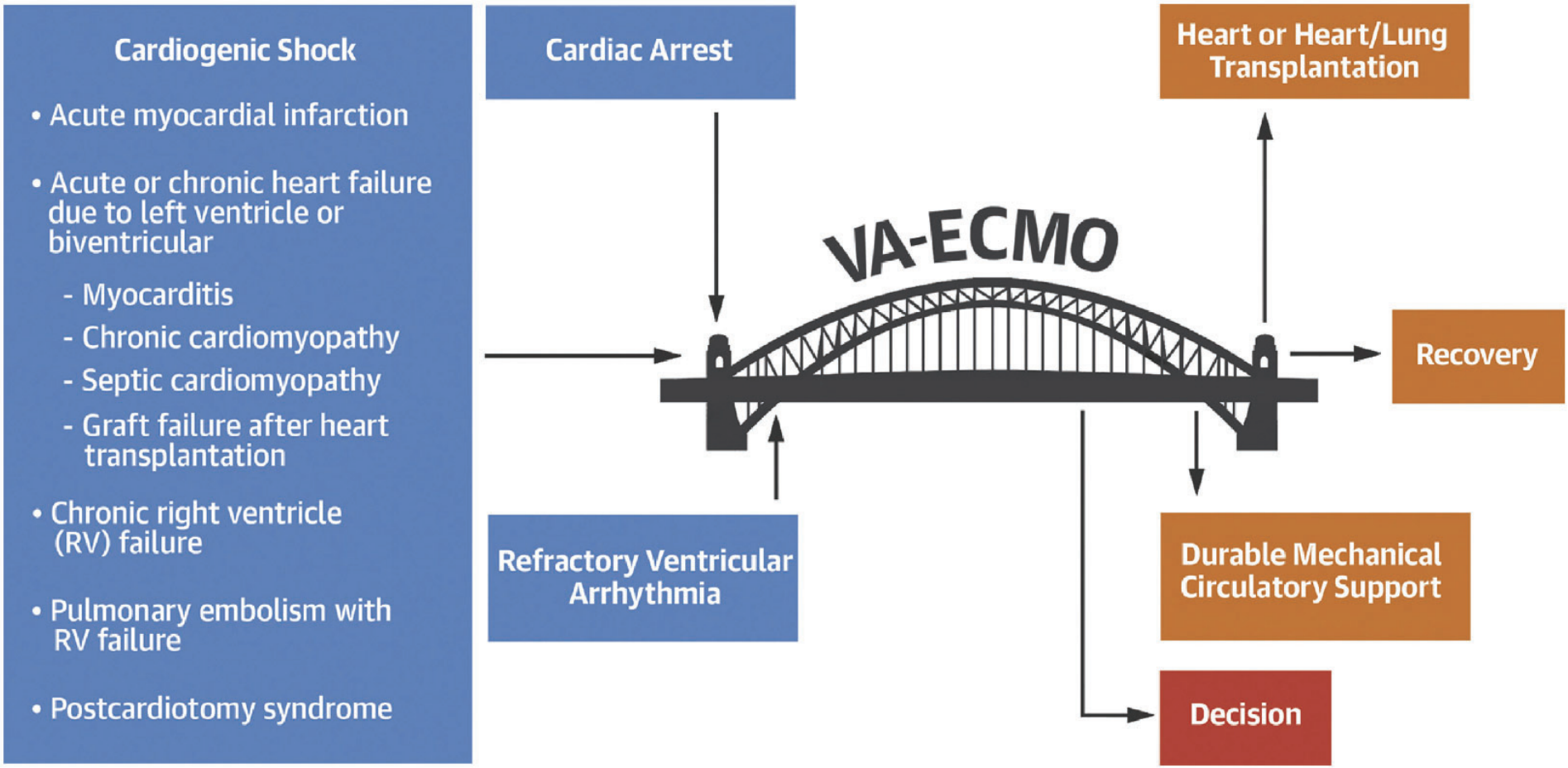

Shroud
Motor
Impeller
Diffuser
Tailrace Zone
Impeller Rotor Zone
Rectification Zone


V-V ECMO
OUTFLOW (RETURN) CANNULA
BACK TO PATIENT
BLENDER
GAS
O_2
CO_2
MEMBRANE
BLOOD
LPM
F_IO_2
SWEEP GAS
OXYGENATOR
PUMP
INFLOW (DRAINAGE) CANNULA
AWAY FROM PATIENT
a
V-A ECMO
INFLOW (DRAINAGE) CANNULA
AWAY FROM PATIENT
PUMP
BLENDER
GAS
O_2
CO_2
MEMBRANE
BLOOD
LPM
F_IO_2
SWEEP GAS
OUTFLOW (RETURN) CANNULA
BACK TO PATIENT
OXYGENATOR
b

ECMO


Wall Shear
250
200
150
100
50
0
[Pa]
(a)
1cm
120.4 mm²
898.5 mm²
357.1 mm²
(b)
4348.7 mm²
2064.8 mm²
3141.3 mm²

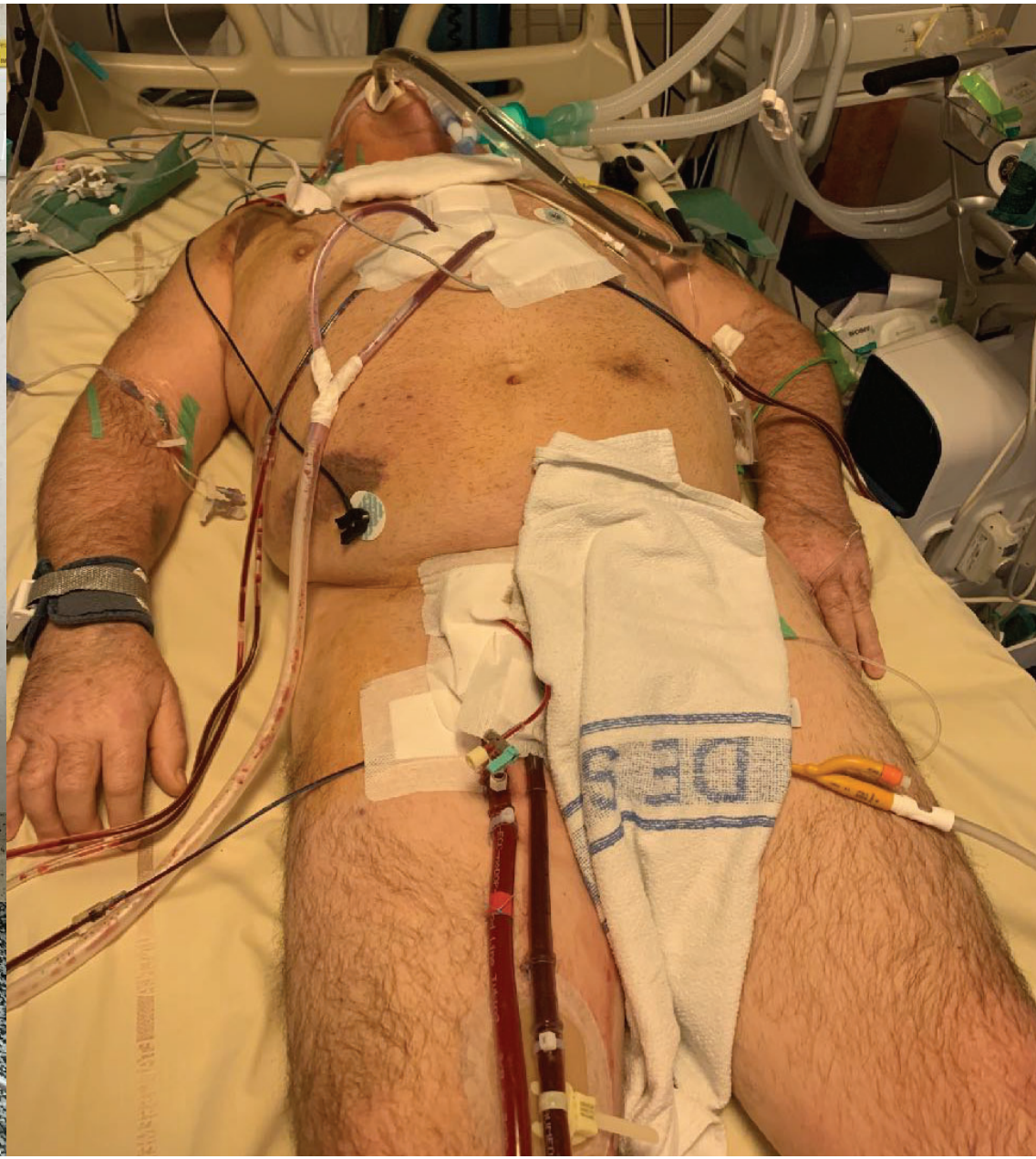

ECMO Volume fraction
1.00
0.75
0.50
0.25
0.00
90% ECMO
50% ECMO

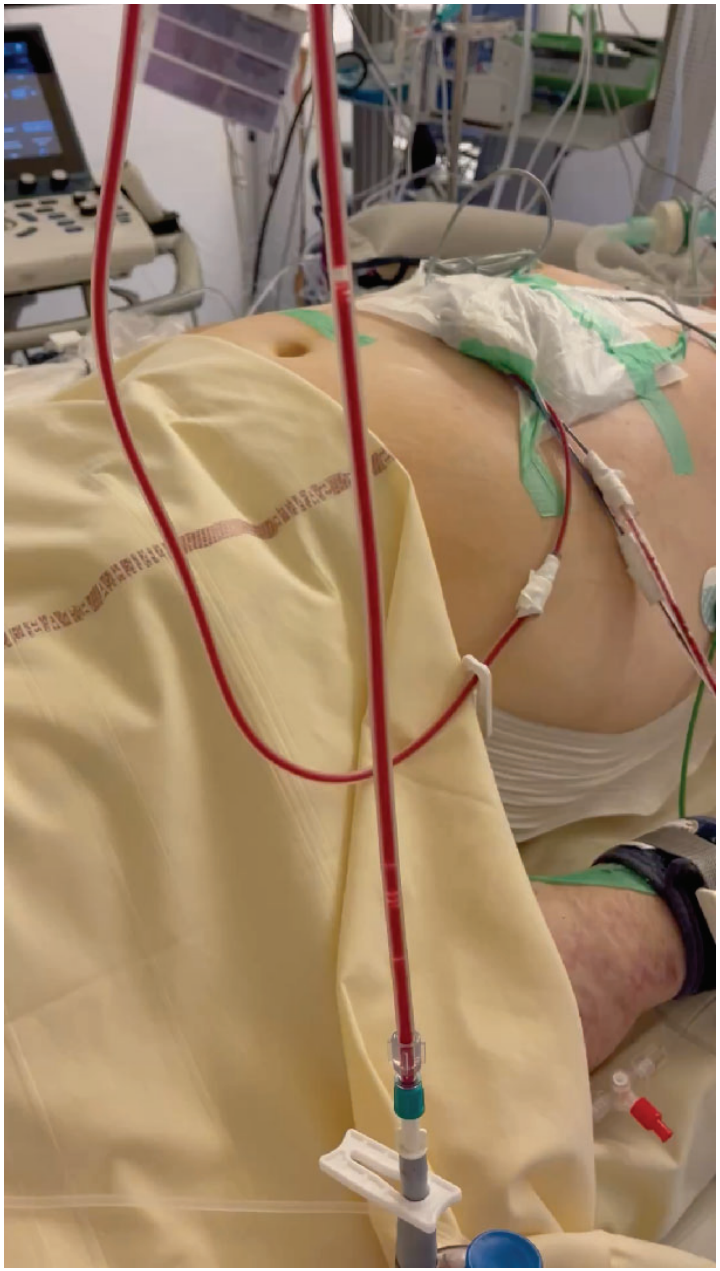


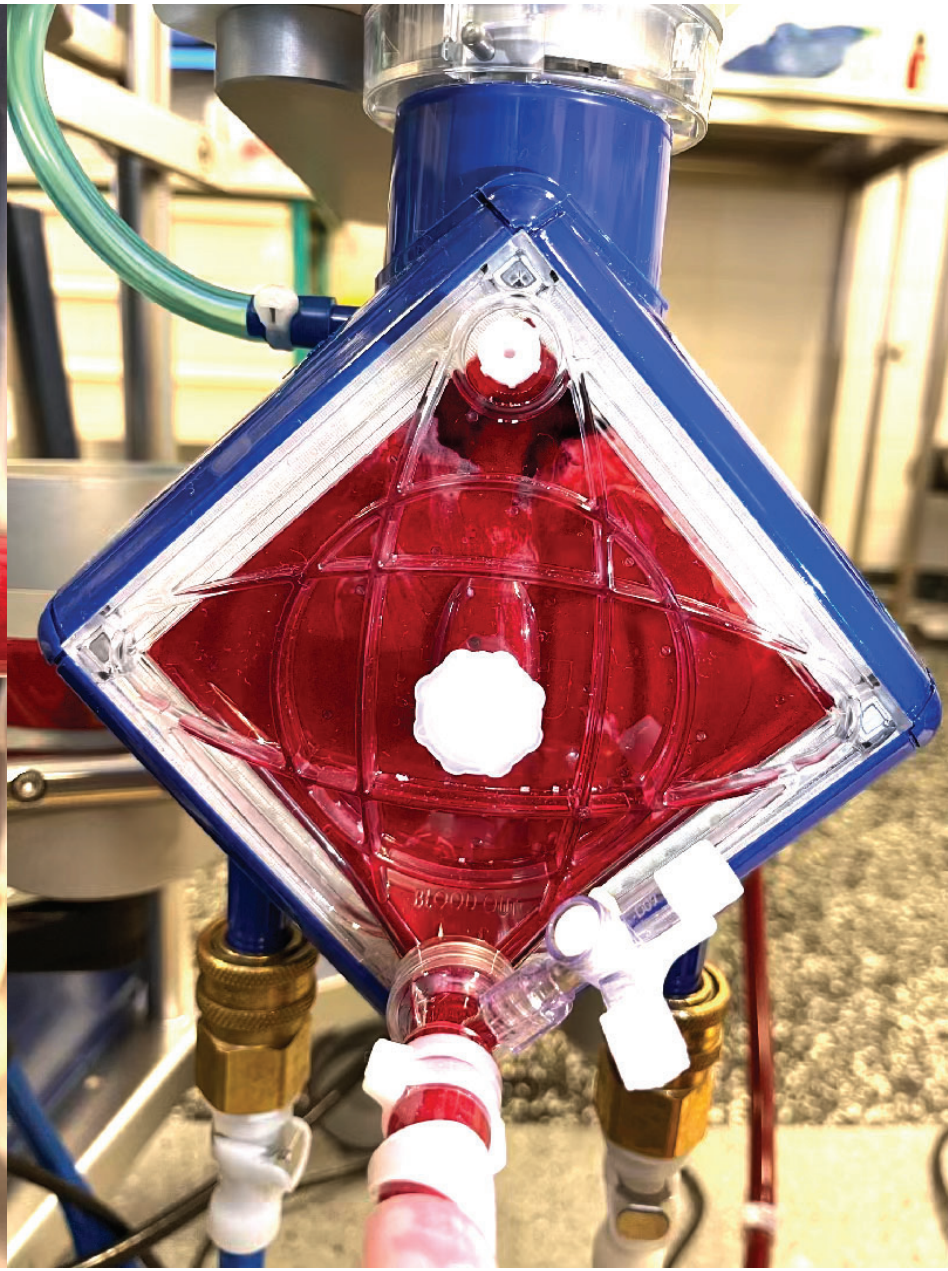
Guglin, M. et al. J Am Coll Cardiol. 2019;73(6):698-716.

ECMO-VA

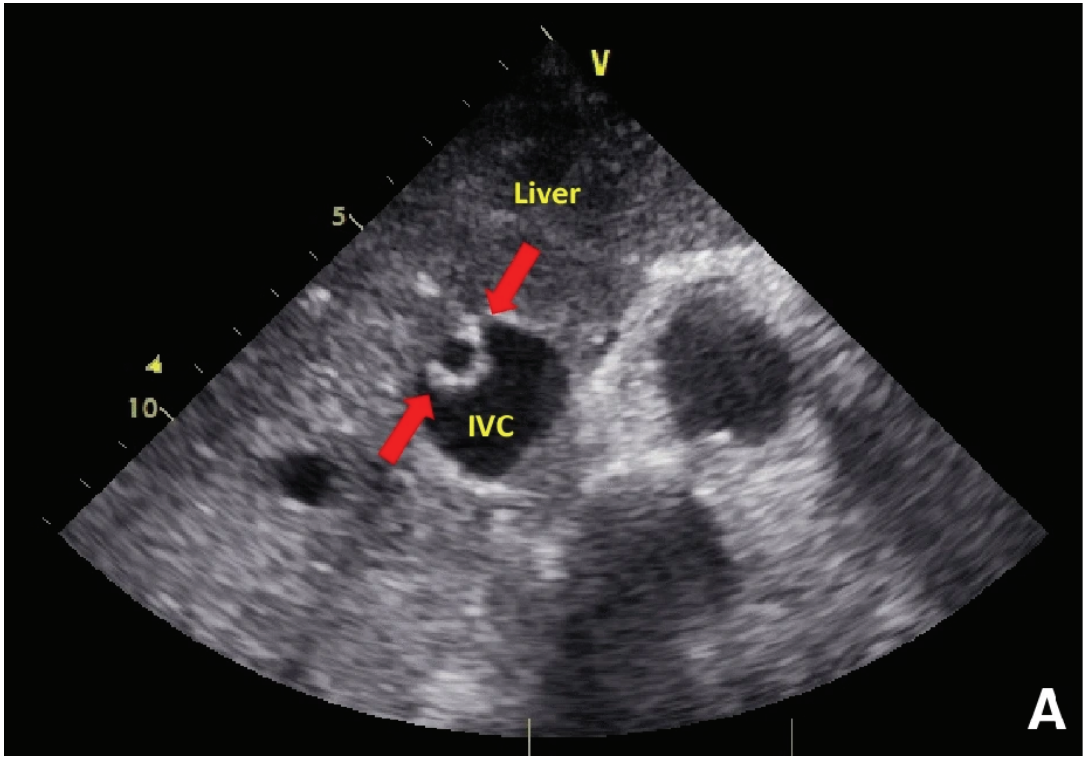

4.84
2420
968
970

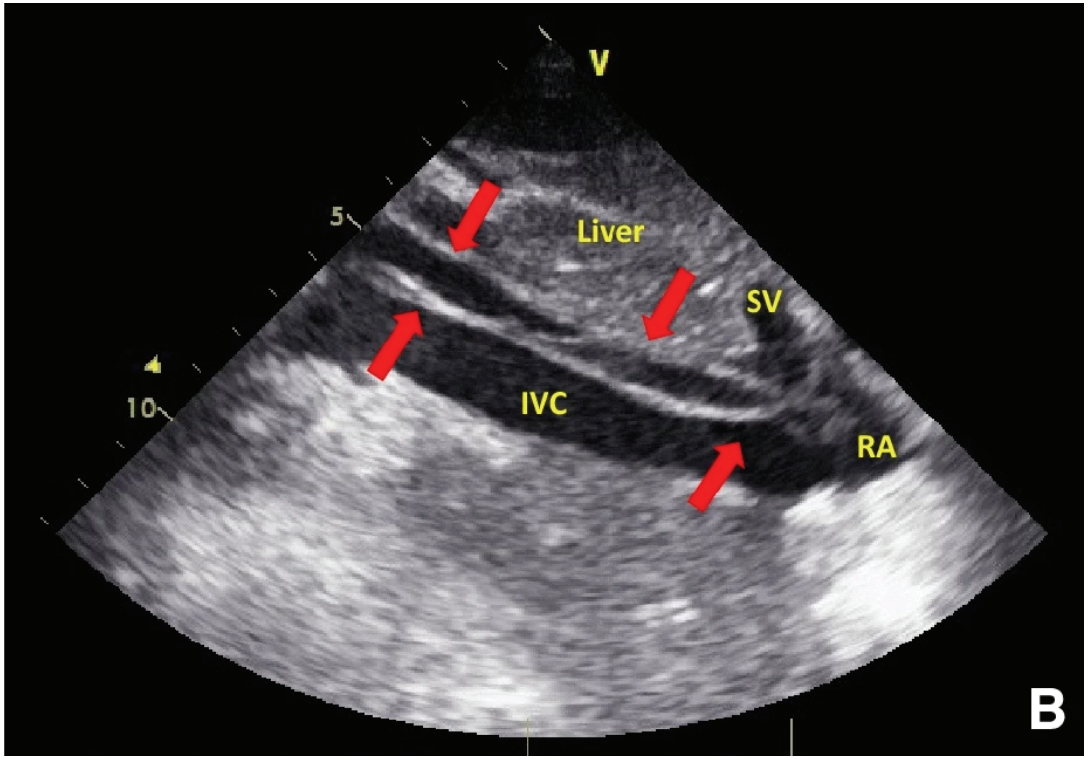





BLOOD OUT

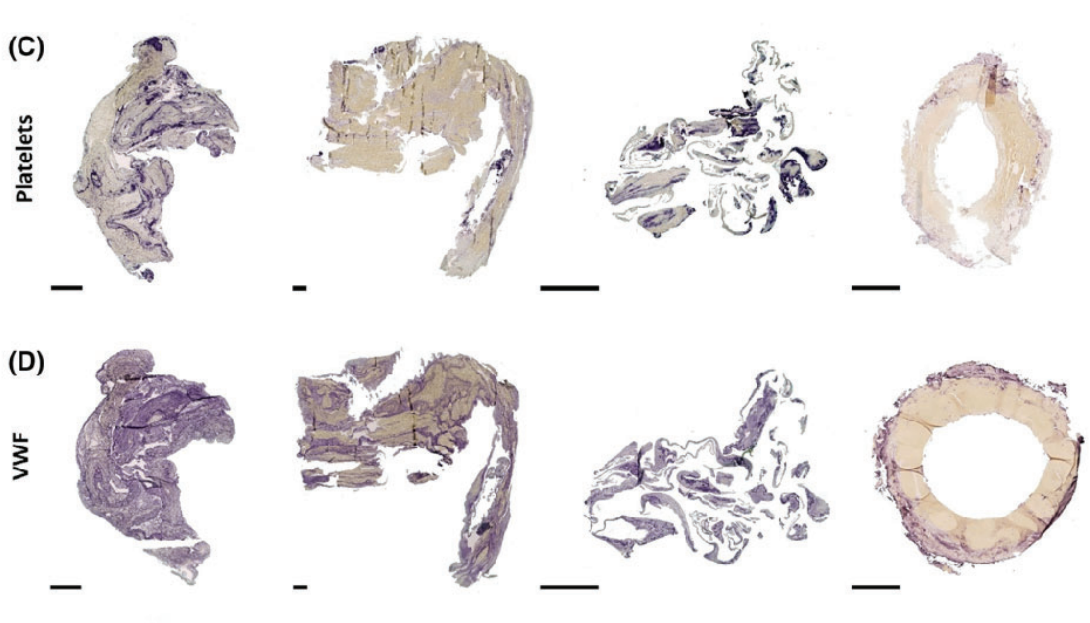
Thrombosis under ECMO

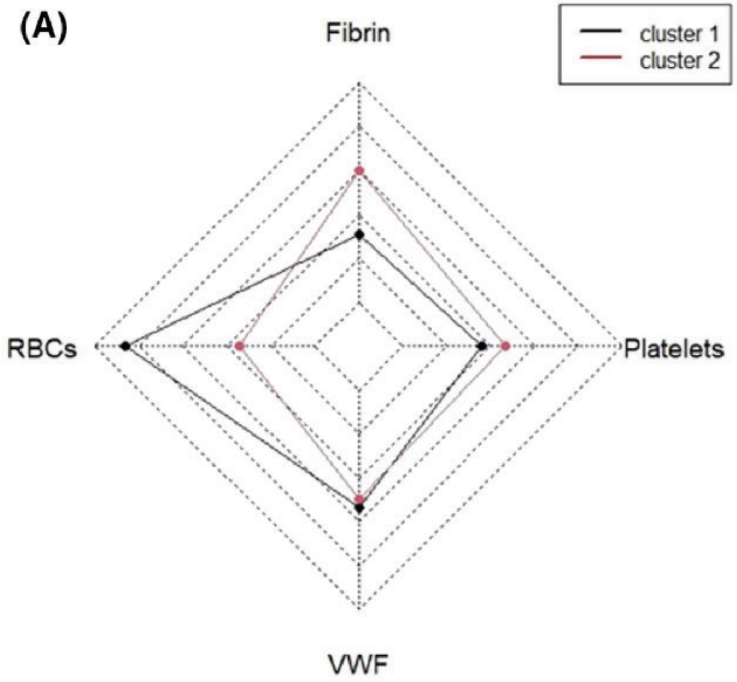




Dauwe et al. ICM 2020

Thrombose sous ECMO



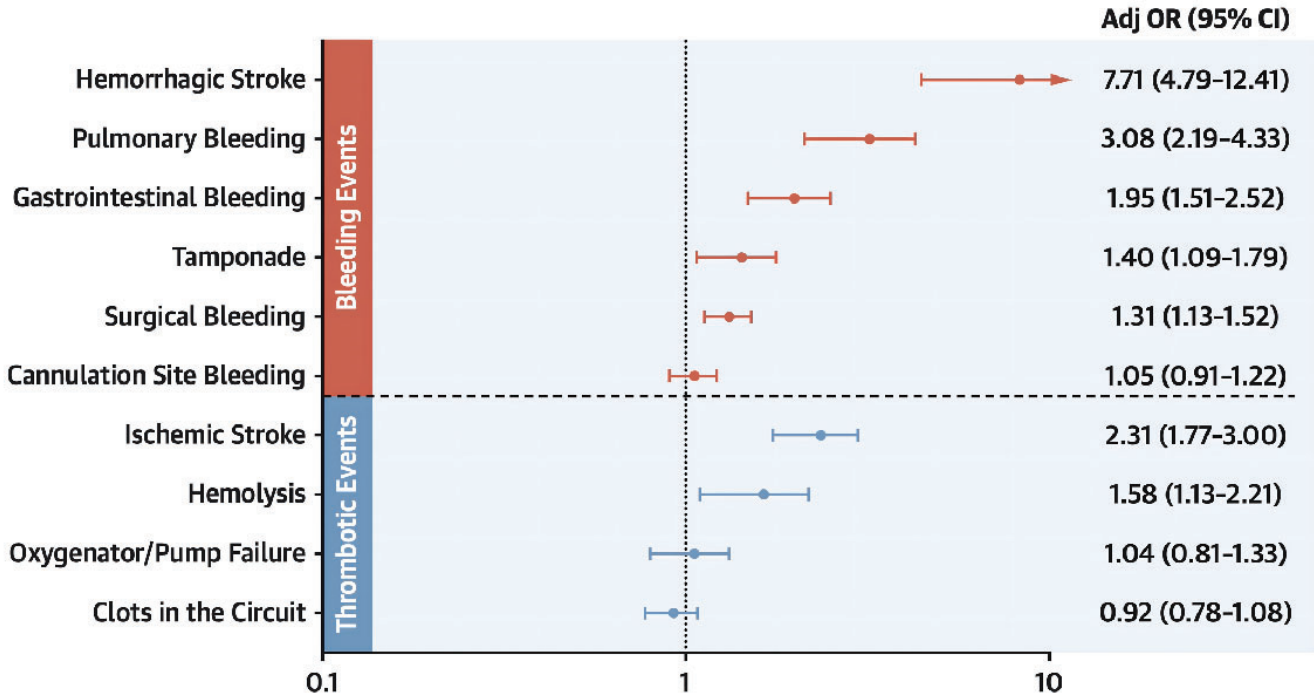


Staessens et al. JTH 2022

ELSO registry
11 984 VA-ECMO

BLEEDING
33% patients
5,254 events

THROMBOSIS
20% patients
3,203 events

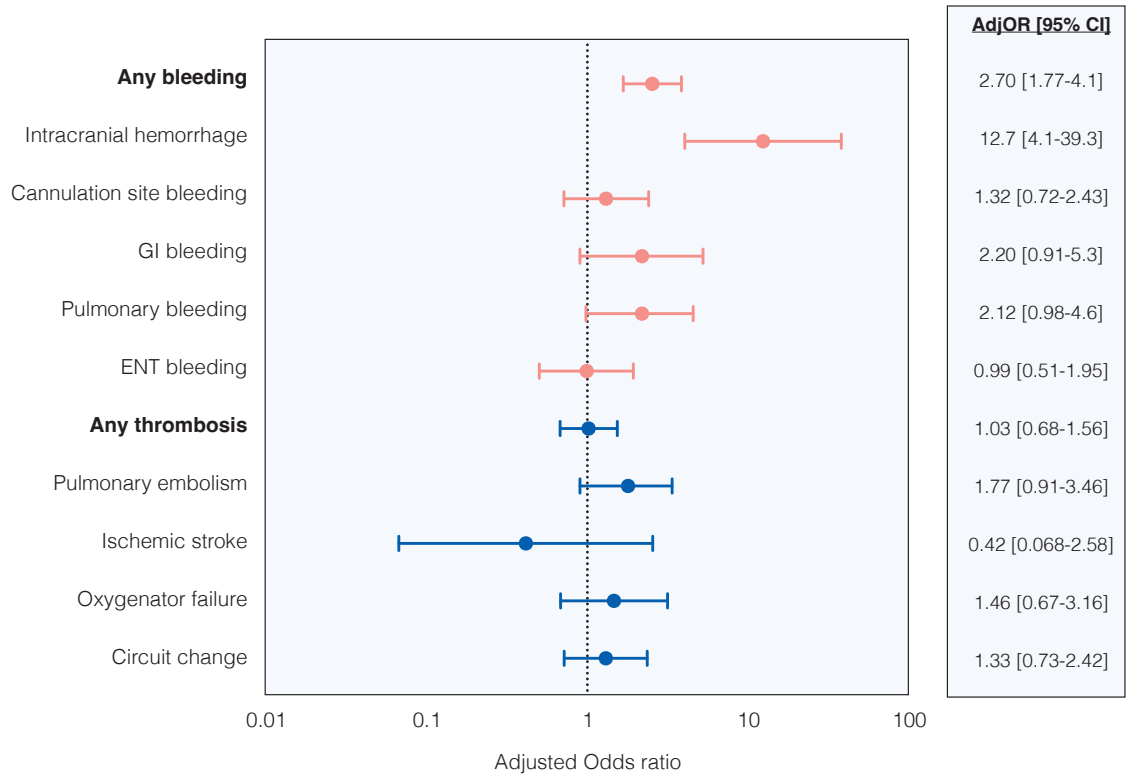


Chung et al. JACC Heart Failure 2020

ECMOSARS registry
620 ECMO COVID-19

BLEEDING
49% patients
382 events

THROMBOSIS
36% patients
343 events



Mansour et al. Intensive Care Med 2022

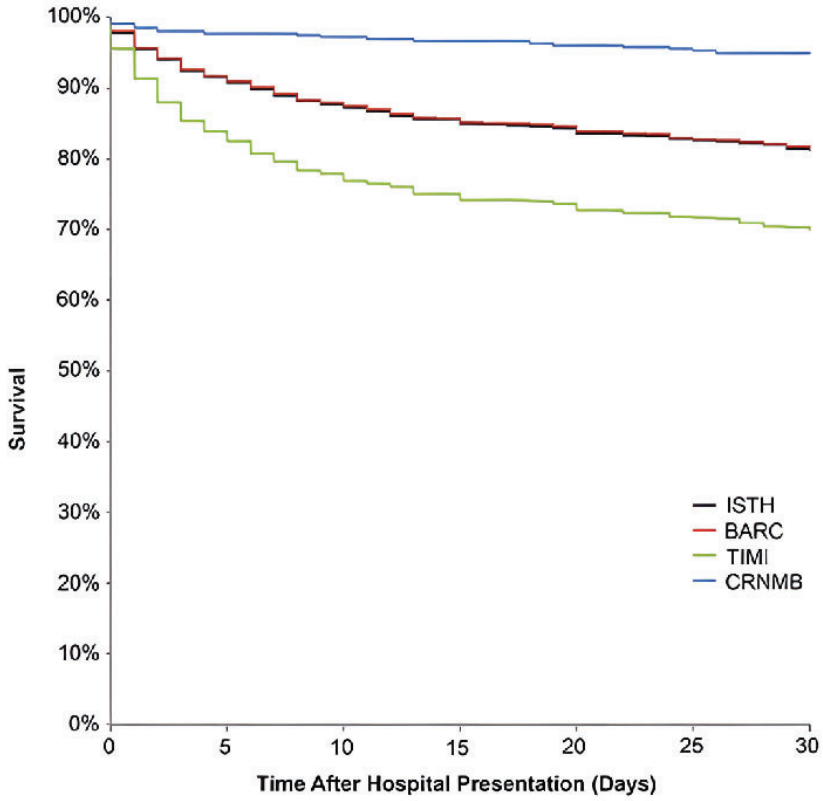
Patient Hemorrhagic Complications

Hemorrhagic complications requiring packed red blood cell or whole blood (PRBC) transfusion (>20ml/kg/calendar day of PRBCS or >3U PRBCs/calendar day in neonates and pediatrics and >3U PRBCS/calendar day in adults) or other intervention such as surgical or endoscopic intervention.

GI hemorrhage	Upper or lower GI hemorrhage requiring PRBC transfusion (>20ml/kg/24 hrs of PRBCS or ≥3U PRBCs/24 hrs in neonates and pediatrics or ≥3U PRBCS/24 hrs in adults), and/or, endoscopic intervention, and/or hemostatic agent deployment
Peripheral cannulation site bleeding	Select this complication if there is bleeding from a peripheral cannulation site such as the neck, groin, or axilla. Peripheral cannulation site bleeding requiring PRBC transfusion (>20ml/kg/24 hrs of PRBCS or ≥3U PRBCs/24 hrs in neonates and pediatrics or ≥3U PRBCS/24 hrs in adults) and/or, surgical intervention (includes intravascular hemostatic agent deployment). A reperfusion cannula is a type of peripheral cannulation site.
Mediastinal cannulation site bleeding	Select this complication if there is bleeding from cannulae that are placed across the mediastinum. Mediastinal cannulations are also referred to as central cannulations and are placed via their mediastinum. Mediastinal cannulation site bleeding requiring PRBC transfusion (>20ml/kg/24 hrs of PRBCS or ≥3U PRBCs/24 hrs in neonates and pediatrics or ≥3U PRBCS/24 hrs in adults, and/or surgical intervention.
Surgical site bleeding	Select this complication if there is bleeding from a surgical site other than mediastinal or peripheral cannulation site. Requiring PRBC transfusion (>20ml/kg/24 hrs of PRBCS or ≥3U PRBCs/24 hrs in neonates and pediatrics or ≥3U PRBCS/24 hrs in adults), and/or surgical intervention

Bleeding definitionS

	ISTH	BARC (Class IIIA-C, V)	TIMI
Mortality	Fatal bleeding[a]	Fatal bleeding[a]	Fatal bleeding[a]
Hemoglobin drop	≥2 g/dL	≥3 g/dL	≥5 g/dL
Site of bleed	• Intracranial • Tamponade • Intraocular • Intra-spinal • Intra-articular • Intra-muscular with compartment syndrome	• Intracranial • Tamponade • Intraocular	• Intracranial • Intraocular
Transfusion	≥2 packed red blood cells	Any transfusion	
Other		Surgical intervention Vasopressor requirement	



Xu et al. Thrombosis Research 213 (2022) 57–64

VA-ECMO // BARC bleeding

Type 2: Any overt, actionable sign of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that does not fit the criteria for Types 3, 4, or 5, but does meet at least one of the following criteria: (1) requiring non-surgical, medical intervention by a health care professional, (2) leading to hospitalization or increased level of care, (3) prompting evaluation

Type 3
- Type 3a
  - Overt bleeding plus haemoglobin drop of 3 to <5*g/dL (provided haemoglobin drop is related to bleed)
  - Any transfusion with overt bleeding
- Type 3b
  - Overt bleeding plus haemoglobin drop ≥ 5*g/dL (provided haemoglobin drop is related to bleed)
  - Cardiac tamponade
  - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid)
  - Bleeding requiring intravenous vasoactive drugs
- Type 3c
  - Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal)
  - Subcategories; confirmed by autopsy or imaging or LP
  - Intra-ocular bleed compromising vision

Type 4: CABG-related bleeding
- Perioperative intracranial bleeding within 48 h
- Reoperation following closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48 period**
- Chest tube output ≥ 2 L within a 24 h period

CHU LILLE

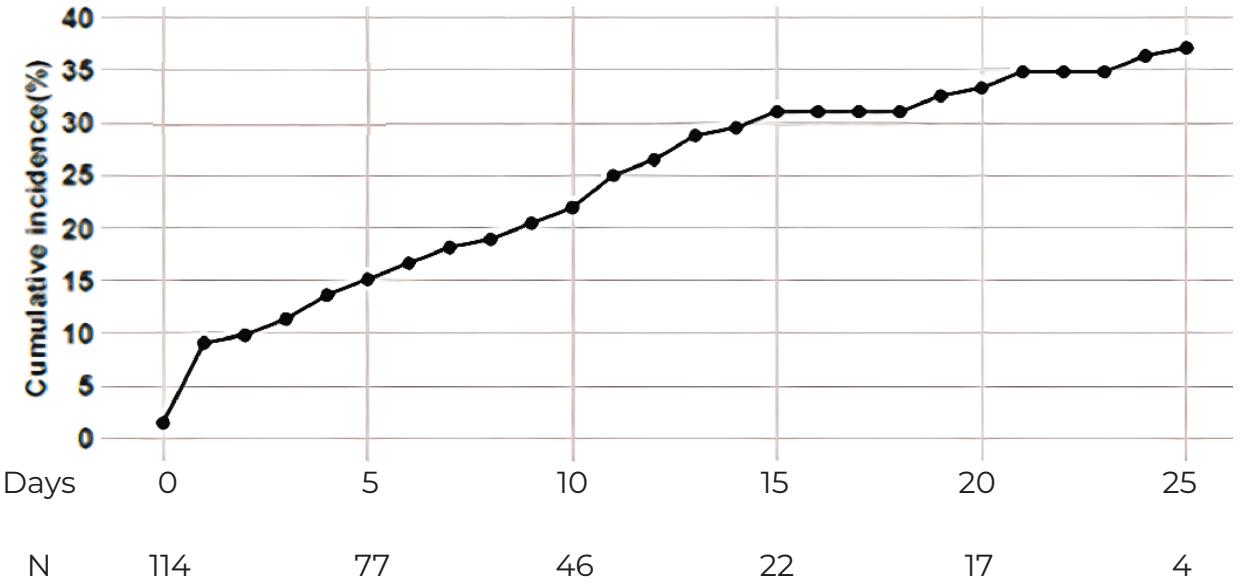
Observational single center
Non-ECPR VA-ECMO
N= 308
ECMO duration : **7 days**

BARC ≥3a : 39%

Moussa et al. Can J Anesth 2023

Observational single center (LPS)
VA-ECMO post-AMI
N= 132

BARC ≥3b 39%



Massi et al. Journal of Critical Care 82 (2024) 154771

Meta-analyse
159 études
N= 21 942

« No studies were at low risk of bias »
Définitions H/T

Major Bleeding Events

Subgroup	n	No. Events	Pooled Estimate (%)	95% CI	I^2 (%)
Overall population	12736	5006	40	36–44	97.12
Overall population by formal definitions*	4549	1863	44	39–48	90.66

Major Thrombosis

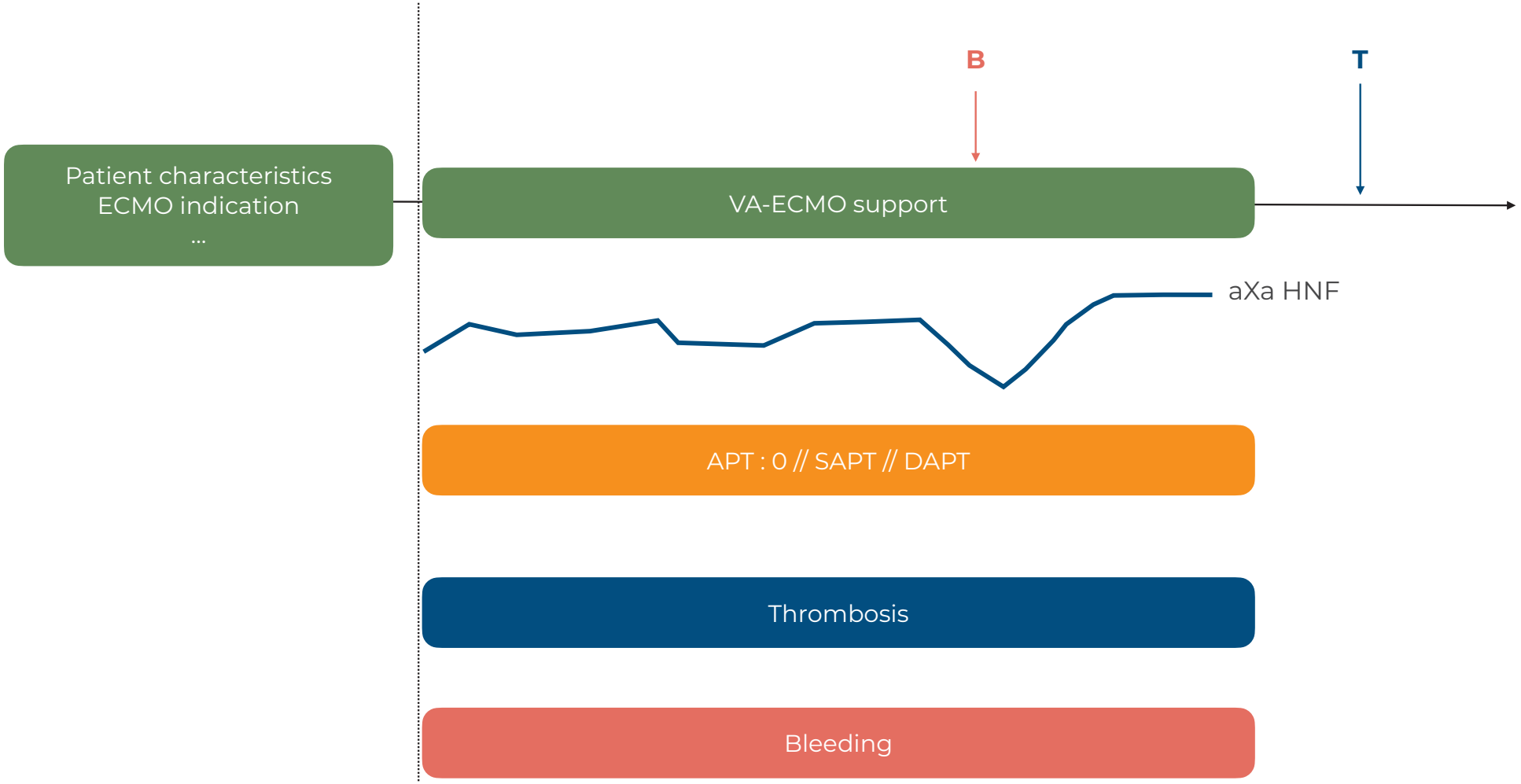
Subgroup	n	No. Events	Pooled Estimate (%)	95% CI	I^2 (%)
Overall population	6505	952	17	14–19	92.60

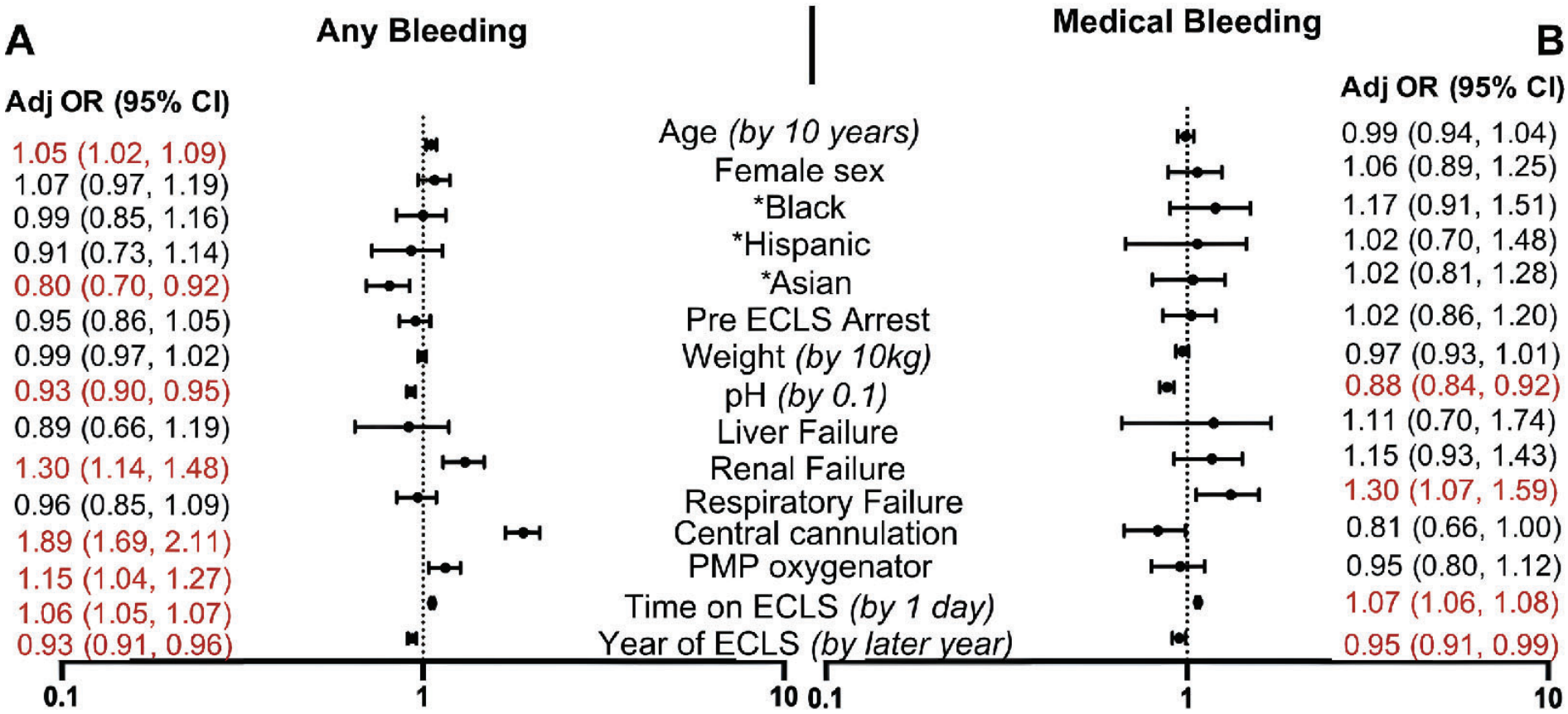
R. Vlok et al. Critical Care and Resuscitation 2024

Pourquoi les patients saignent sous ECMO ?

LE TERRAIN, L'ECMO OU L'ANTICOAGULATION ?

Statistical nightmare !




A
Any Bleeding
Adj OR (95% CI)
1.05 (1.02, 1.09)
1.07 (0.97, 1.19)
0.99 (0.85, 1.16)
0.91 (0.73, 1.14)
0.80 (0.70, 0.92)
0.95 (0.86, 1.05)
0.99 (0.97, 1.02)
0.93 (0.90, 0.95)
0.89 (0.66, 1.19)
1.30 (1.14, 1.48)
0.96 (0.85, 1.09)
1.89 (1.69, 2.11)
1.15 (1.04, 1.27)
1.06 (1.05, 1.07)
0.93 (0.91, 0.96)
0.1
1
10
Age (by 10 years)
Female sex
*Black
*Hispanic
*Asian
Pre ECLS Arrest
Weight (by 10kg)
pH (by 0.1)
Liver Failure
Renal Failure
Respiratory Failure
Central cannulation
PMP oxygenator
Time on ECLS (by 1 day)
Year of ECLS (by later year)
Medical Bleeding
B
Adj OR (95% CI)
0.99 (0.94, 1.04)
1.06 (0.89, 1.25)
1.17 (0.91, 1.51)
1.02 (0.70, 1.48)
1.02 (0.81, 1.28)
1.02 (0.86, 1.20)
0.97 (0.93, 1.01)
0.88 (0.84, 0.92)
1.11 (0.70, 1.74)
1.15 (0.93, 1.43)
1.30 (1.07, 1.59)
0.81 (0.66, 1.00)
0.95 (0.80, 1.12)
1.07 (1.06, 1.08)
0.95 (0.91, 0.99)
0.1
1
10

THE ANNALS OF THORACIC SURGERY

Risk Factors of Bleeding in Patients Undergoing Venoarterial Extracorporeal Membrane Oxygenation

Variables	OR	(95% CI)	*P* Value
Postcardiotomy	1.98	(1.08-3.62)	.02
pH	0.15	(0.02-1.04)	.05
Body mass index, $kg.m^{-2}$	0.91	(0.85-0.98)	.01
Hemoglobin, $g.dL^{-1}$	0.80	(0.70-0.92)	.02
Fibrinogen, $g.L^{-1}$	0.67	(0.52-0.85)	.01

243 VA-ECMO
UFH : anti-Xa 0.15-0.3
ELSO criteria
Major bleeding : 46%

Ellouze et al. Ann Thorac Surg 2021;111:623-8

Annals of Intensive Care

Ischemic and hemorrhagic brain injury during venoarterial-extracorporeal membrane oxygenation

Factor	Univariable analysis		Multivariable analysis	
	OR [95% CI]	*P* value	OR [95% CI]	*P* value
Age > 53 years	0.6 [0.2–1.5]	0.3		
Female sex	3 [1.2–7.3]	0.02	2.9 [1.1–7.5]	0.03
Previous history of stroke	3 [0.9–10.92]	0.1		
SAPS II at ICU admission ≥ 72	1.2 [0.5–2.8]	0.8		
Renal replacement therapy	2 [0.6–7]	0.3		
Intra-aortic balloon pump	0.5 [0.2–1.5]	0.3		
Central VA-ECMO	5.0 [2.0–12.2]	0.0007	3.8 [1.1–10.2]	0.008
Cardiac surgery	0.9 [0.4–2.3]	1		
Biology at ECMO onset				
Lactate > 6 mmol/L	2.7 [0.9–7.6]	0.06		
pH < 7.32	1.0 [0.4–2.6]	1		
Platelets < 100 giga/L	4.3 [1.7–11.3]	0.003	3.7 [1.4–9.7]	0.009
Bilirubin > 33 µmol/L	1.8 [0.7–4.8]	0.3		
Fibrinogen < 1.5 g/L	1.7 [0.5–6.2]	0.4		
Prothrombin time < 30%[a]	2.7 [1.0–7.7]	0.07		
aPTT, patient/normal-value ratio > 3	2.3 [0.8–6.7]	0.2		
Hemostasis disorders on ECMO[b]				
Platelets < 100 × giga/L	1.2 [0.4–4.3]	1		
Prothrombin time < 30%[a]	2.0 [0.8–5.0]	0.1		
Fibrinogen < 1.5 g/L	1.9 [0.7–4.9]	0.2		
aPTT, patient/normal-value ratio > 3	1.1 [0.4–3.1]	0.8		

878 VA-ECMO
UFH : aPTT-R 1.5-2
ICH : 2%
Hospital mortality : 90%

Le Guennec et al. Ann. Intensive Care 2018

Annals of Intensive Care

Predictive factors of bleeding events in adults undergoing extracorporeal membrane oxygenation

111 VA-ECMO + 38 VV-ECMO
UFH : aPTT 50-70s
ELSO criteria - Major bleeding : 60%
ICH: 2.2% - HR death : 2.17 (1.07-4.41)

Variable	Adjusted odds ratio	95 % confidence interval	*P*
Previous-day aPTT[a]			
≥46 and ≤55 s	1.35	0.73–2.49	0.33
≥56 and ≤69 s	1.45	0.75–2.82	0.26
≥70 s	3.00	1.64–5.47	<0.01
Previous-day anticoagulation	0.40	0.24–0.66	<0.01
APACHE III score	1.01	1.01–1.02	0.01
Post-surgical ECMO	3.04	1.62–5.69	<0.01

L’anticoagulation: coupable idéal ?

ASAIO Journal 2022

2021 ELSO Adult and Pediatric Anticoagulation Guidelines

Ali B.V. McMichael,* Lindsay M. Ryerson,† Damian Ratano,‡§ Eddy Fan,‡ David Faraoni,¶ and Gail M. Annich||

« Anticoagulation is necessary for most pediatric and adult extracorporeal membrane oxygenation (ECMO) patients to prevent circuit clotting »

Mc Michael et al. ASAIO Journal, March 2022 - Volume 68 - Issue 3 - p 303-310

Anticoagulation in adult patients supported with extracorporeal membrane oxygenation: guidance from the Scientific and Standardization Committees on Perioperative and Critical Care Haemostasis and Thrombosis of the International Society on Thrombosis and Haemostasis

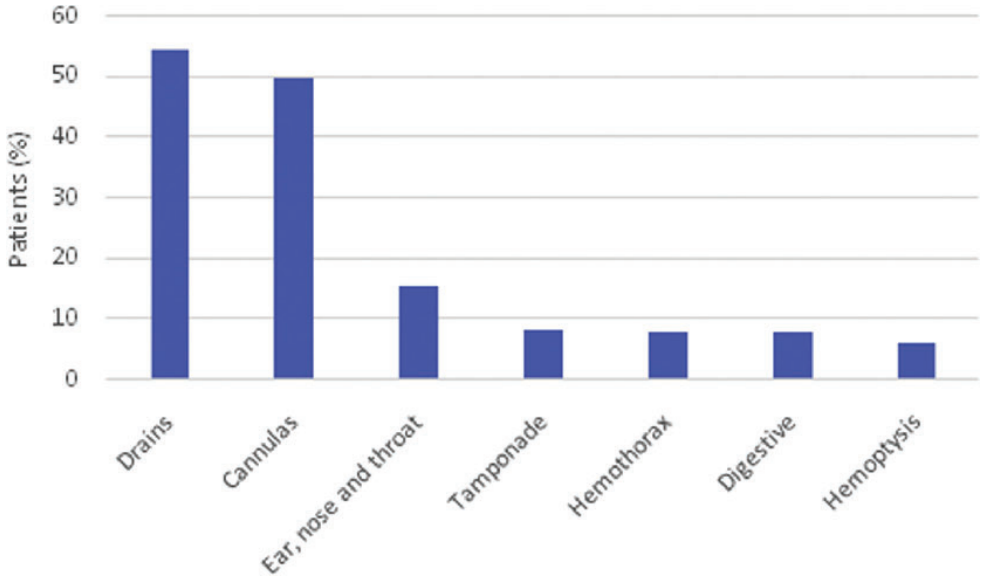
« We recommend the use of intravenous unfractionated heparin for anticoagulation during ECMO support »

« We suggest against the routine use of no anticoagulation for patients on ECMO »

Helms et al. J Thromb Haemost. 2023 Feb;21(2):373-396

THE ANNALS OF THORACIC SURGERY

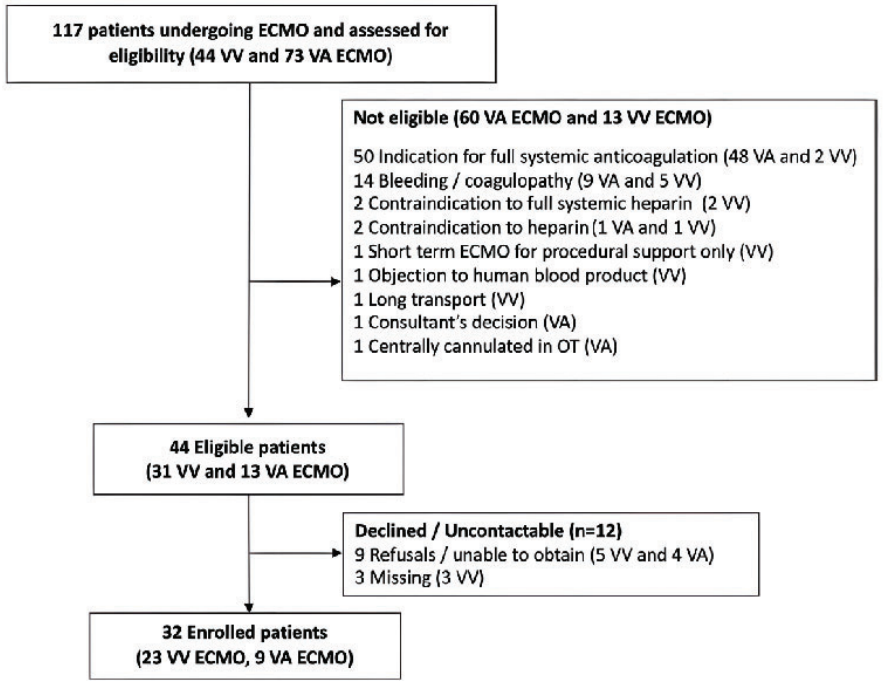
Risk Factors of Bleeding in Patients Undergoing Venoarterial Extracorporeal Membrane Oxygenation



243 VA-ECMO
UFH : anti-Xa 0.15-0.3
ELSO criteria
Major bleeding : 46%

Ellouze et al. Ann Thorac Surg 2021;111:623-8

Low-Dose Versus Therapeutic Anticoagulation in Patients on Extracorporeal Membrane Oxygenation: A Pilot Randomized Trial



Pilot RCT

Low dose UFH : aPTT <45s

Therapeutic UFH : aPTT 50-70s

	Low dose n=16	Therapeutic n=16	P-value
Bleeding	7 (43.8)	7 (43.8)	> 0.999
Patient thrombosis	3 (19)	4 (25)	0.67
Circuit thrombosis	4 (25%)	2 (13%)	0.37

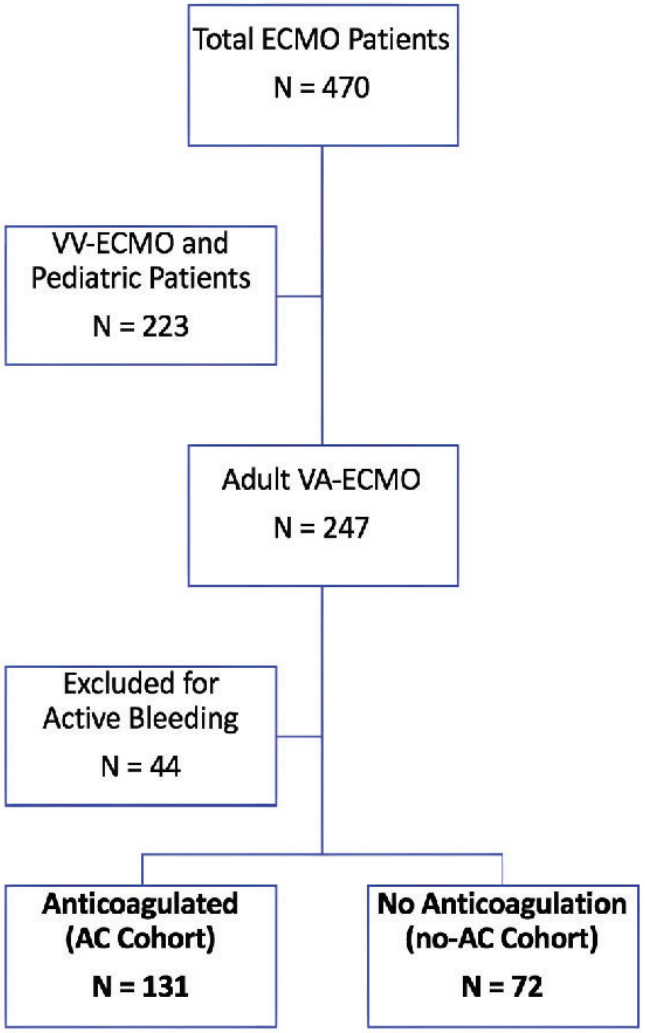
Aubron et al. Crit Care Med. 2019 Jul;47(7):e563-e571

Venoarterial-Extracorporeal Membrane Oxygenation Without Routine Systemic Anticoagulation Decreases Adverse Events

Katherine L. Wood, MD, Brian Ayers, MBA, Igor Gosev, MD, Neil Kumar, MD, Amber L. Melvin, MD, Bryan Barrus, MD, and Sunil Prasad, MD

Division of Cardiac Surgery, University of Rochester Medical Center, Rochester, New York

Since 2016 : no systematic anticoagulation
Except if circuit flow <2L/min



Wood et al. Ann Thorac Surg 2020

Variable[a]	Anticoagulated (N = 131)	Not Anticoagulated (N = 72)	*P* Value
Overall complication	99 (76)	41 (57)	.007
Hemorrhagic	83 (63)	38 (53)	.178
Cardiac tamponade	12 (9)	5 (7)	.792
Gastrointestinal	19 (15)	6 (8)	.266
Surgical site	11 (8)	4 (6)	.581
Cerebral	5 (4)	2 (3)	1.000
Pulmonary	8 (6)	3 (4)	.750
≥4 U PRBCs within 24 hours	31 (24)	15 (21)	.727
Other	3 (2)	1 (1)	1.000
Thrombotic	28 (21)	9 (13)	.132
Pump failure	0 (0)	0 (0)	1.000
Oxygenator failure	3 (2)	0 (0)	.554
Circuit clots	2 (2)	0 (0)	.540
Stroke	4 (3)	5 (7)	.285
Limb ischemia	16 (12)	4 (6)	.147
Pulmonary embolism	3 (2)	0 (0)	.554
Intracardiac	7 (5)	1 (1)	.264
Other	1 (1)	1 (1)	1.000
Heparin-induced thrombocytopenia	10 (8)	0 (0)	.015

Attention : median time on ECMO 160h vs 70h !

Wood et al. Ann Thorac Surg 2020

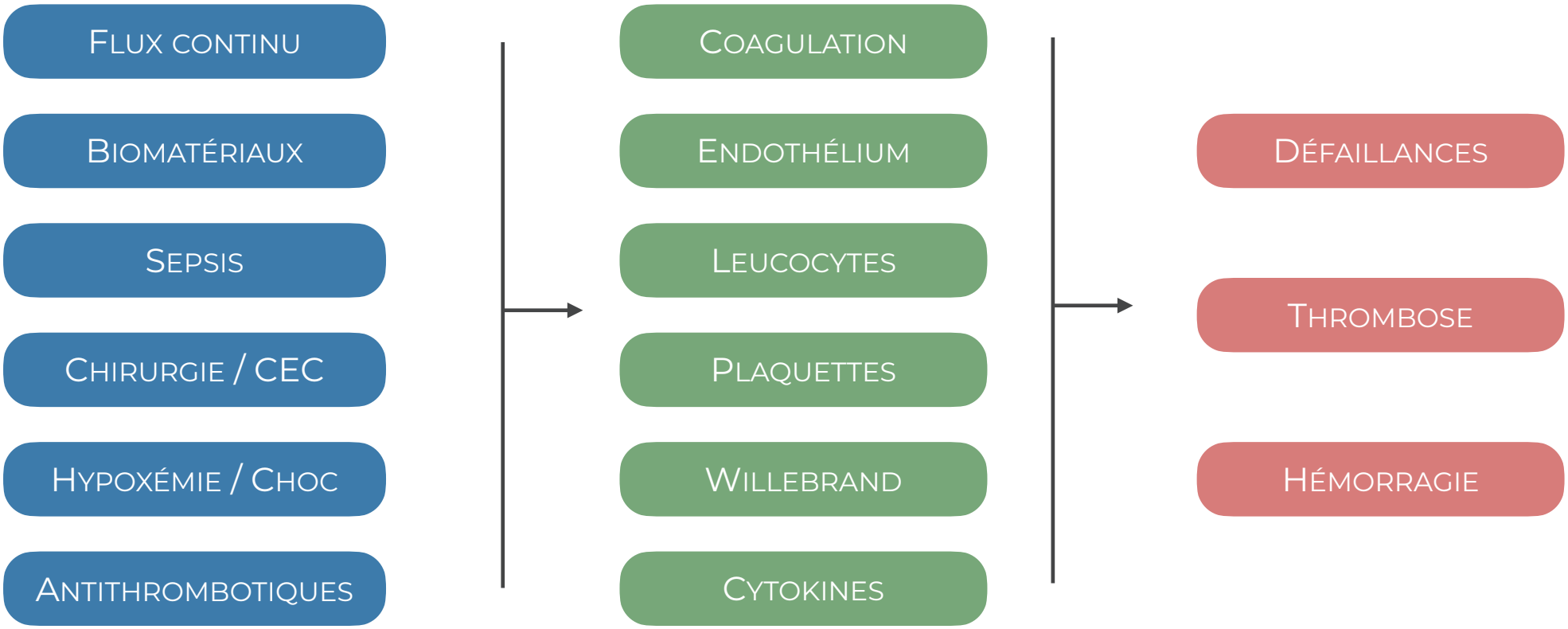
Meta-analyse
159 études
N= 21 942

Subgroup	n	No. Events	Pooled Estimate (%)	95% CI	I^2 (%)
Overall population	12736	5006	40	36–44	97.12
Overall population by formal definitions*	4549	1863	44	39–48	90.66
Heparin	12183	4848	41	36–46	97.39
Bivalirudin	130	51	43	28–58	64.50
No anticoagulation	251	84	38	18–58	93.56
Monitored by APTT†	5463	1716	48	39–58	89.43
Monitored by anti-Xa†	1051	483	48	39–58	89.43

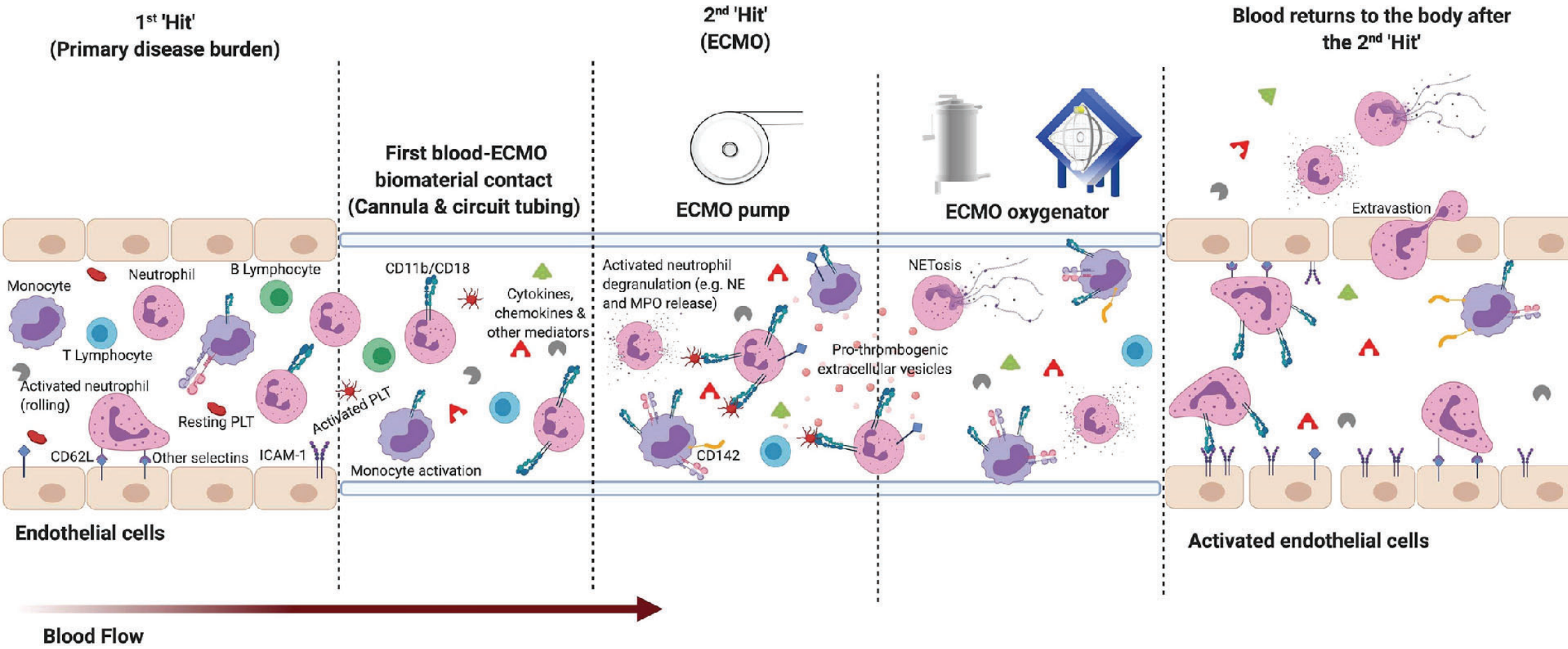
Subgroup	n	No. Events	Pooled Estimate (%)	95% CI	I^2 (%)
Overall population	6505	952	17	14–19	92.60
Heparin	5968	901	19	15–22	93.12
Bivalirudin	244	39	15	1–19	0.0
No anticoagulation	158	11	6	0–13	76.9
Monitored by APTT†	1621	326	22	16–29	90.74
Monitored by anti-Xa†	993	244	21	15–27	79.79

R. Vlok et al. Critical Care and Resuscitation 2024

UN PROBLÈME D'HÉMOCOMPATIBILITÉ !

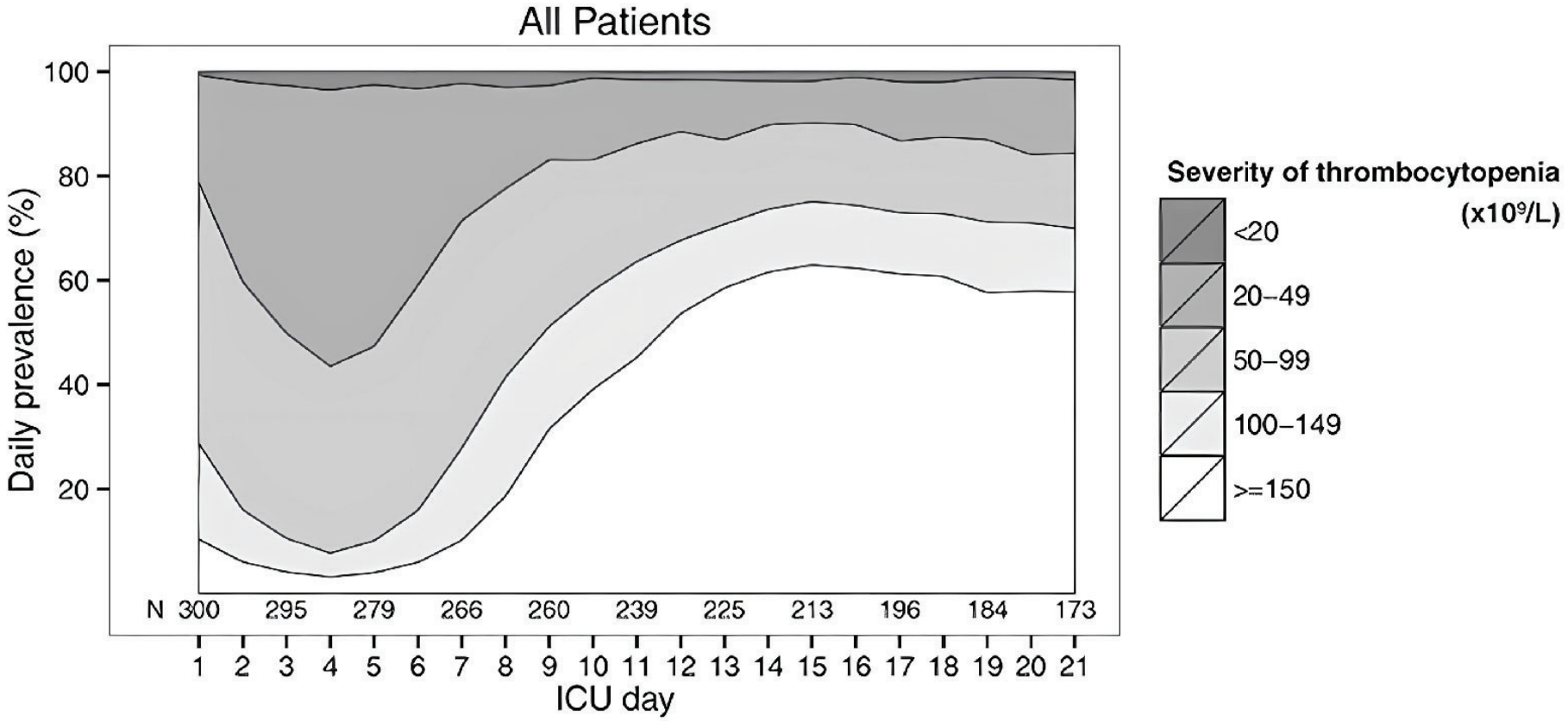


Doyle et al. Front. Med. 2018
Millar et al. Crit. Care 2016



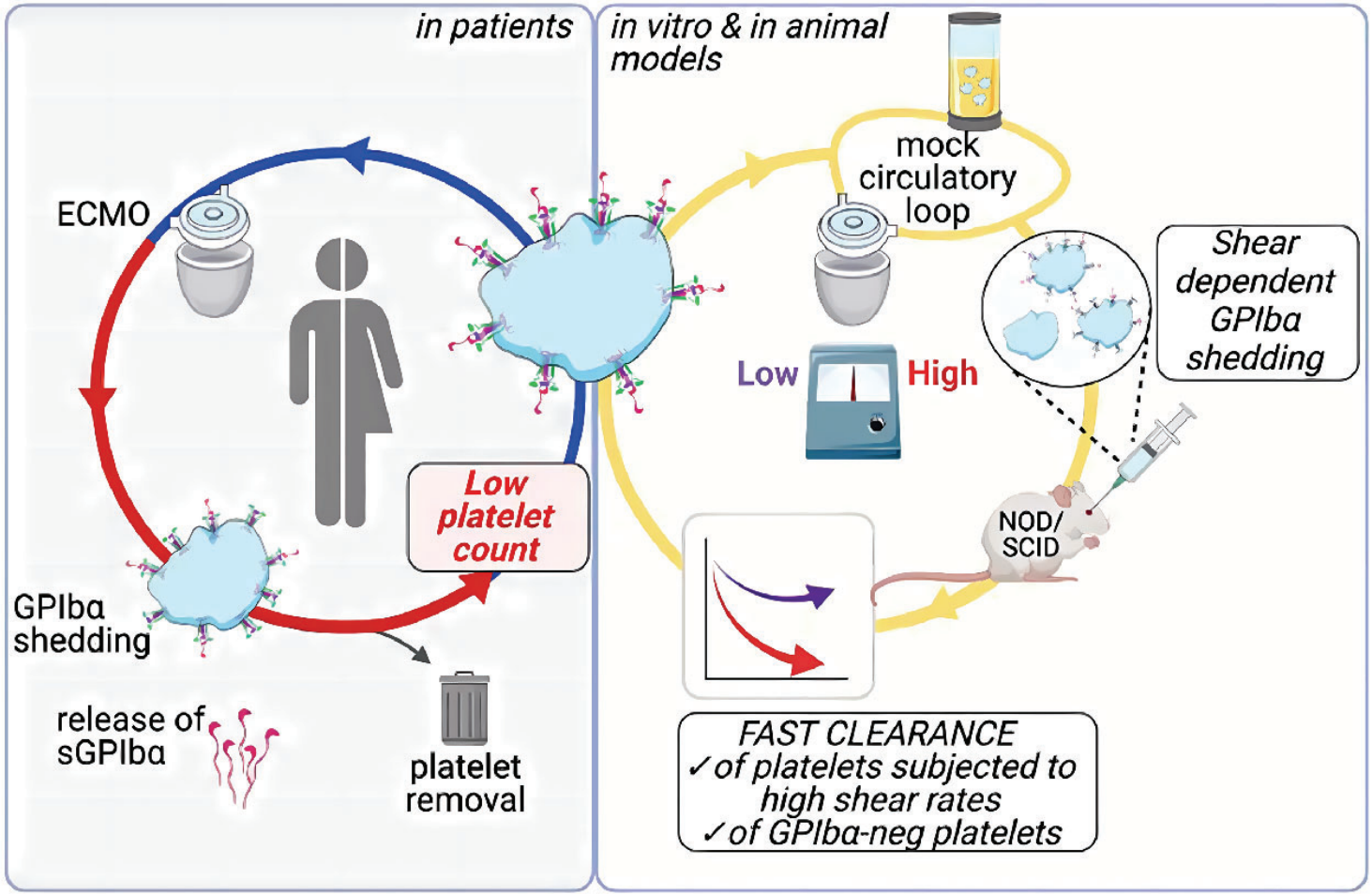
Ki et al. Front Immunol. 2021

ECMO et Plaquettes



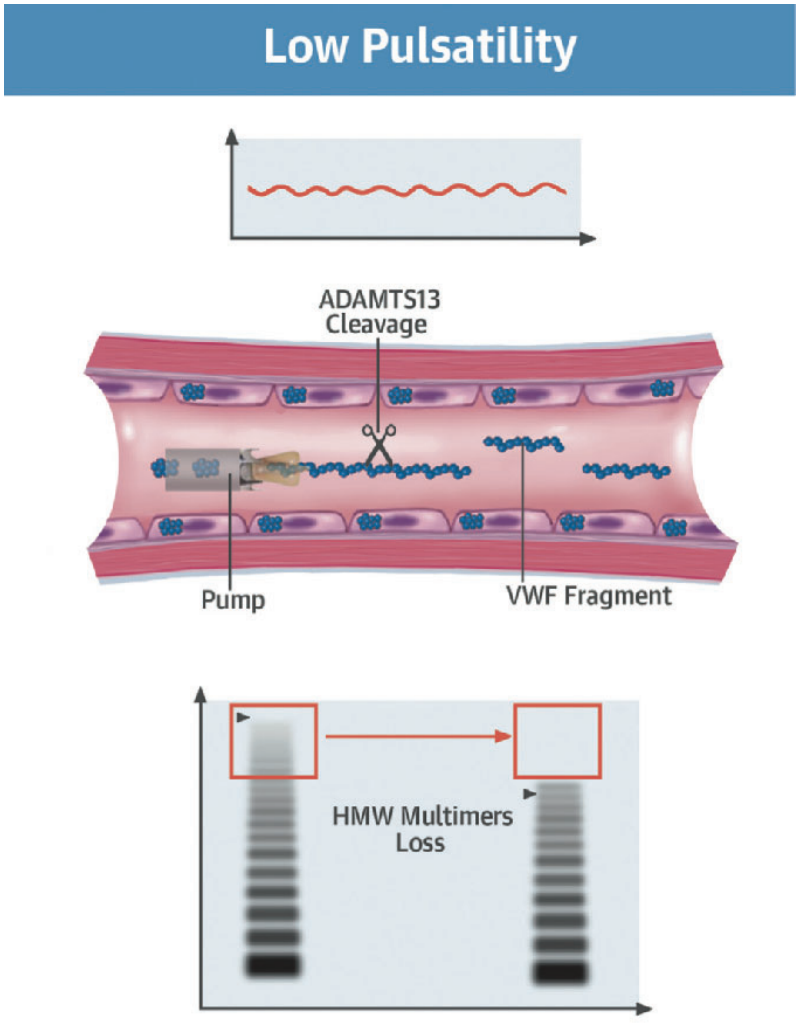
Opfermann et al. Crit Care Med 2016

ECMO et Plaquettes



Rauch et al. Circulation Research. 2023;133:826–841

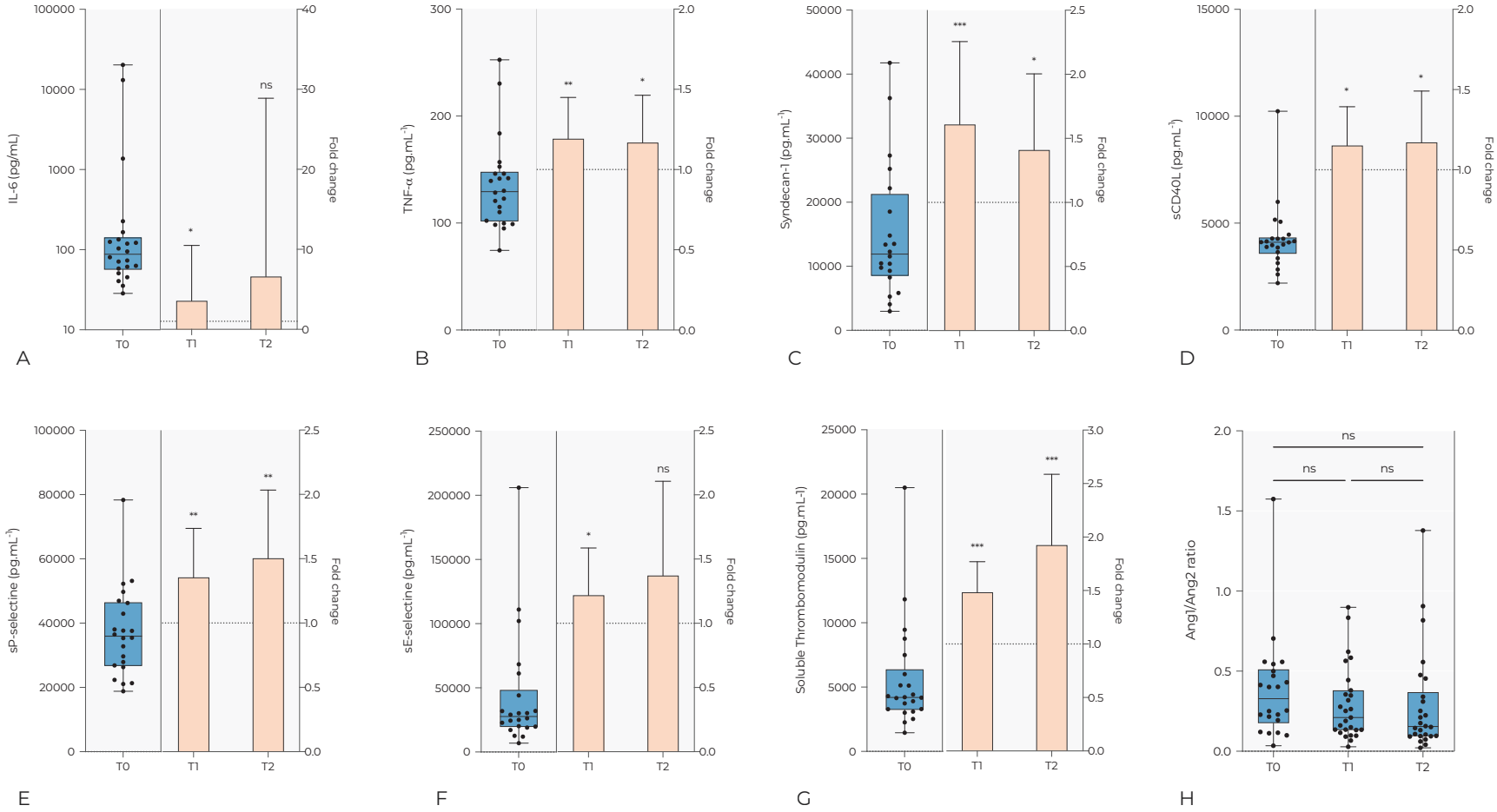
ECMO et Willebrand



Willebrand acquis sous ECMO : 100% !

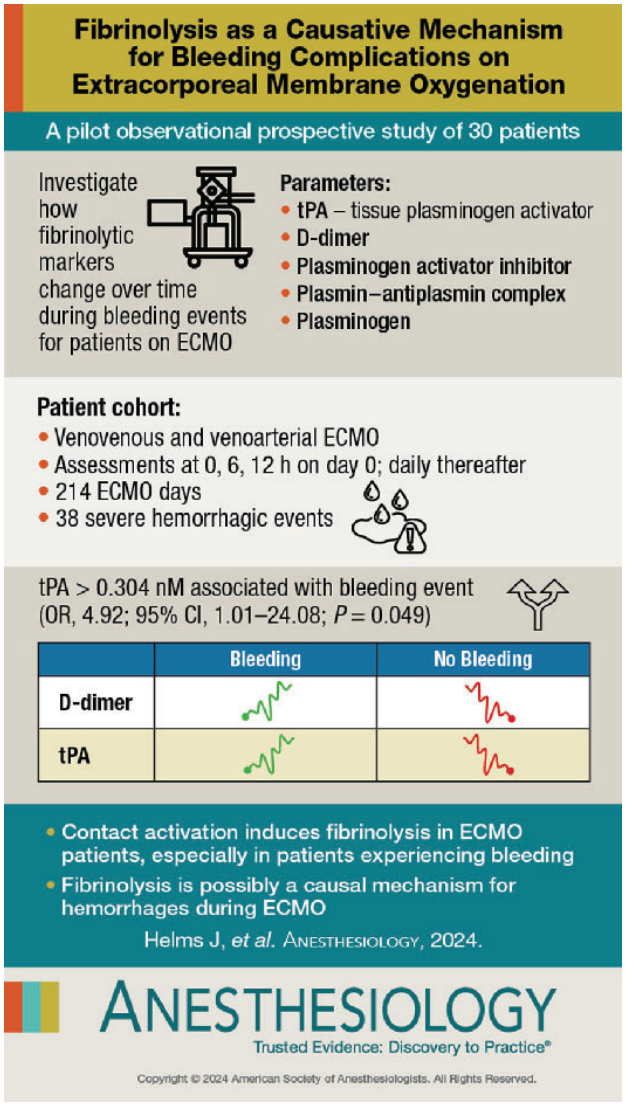
Vincent et al. JACC 2018

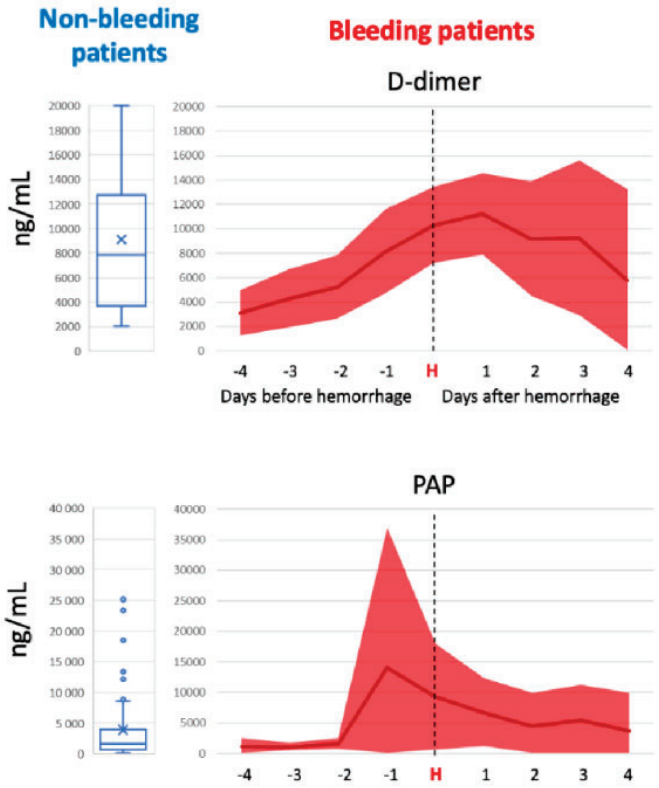
ECMO et endothélium



Nesseler et al. Intensive Care Med. 2024 Nov;50(11):1929-1930.

Un rôle de la fibrinolyse ?



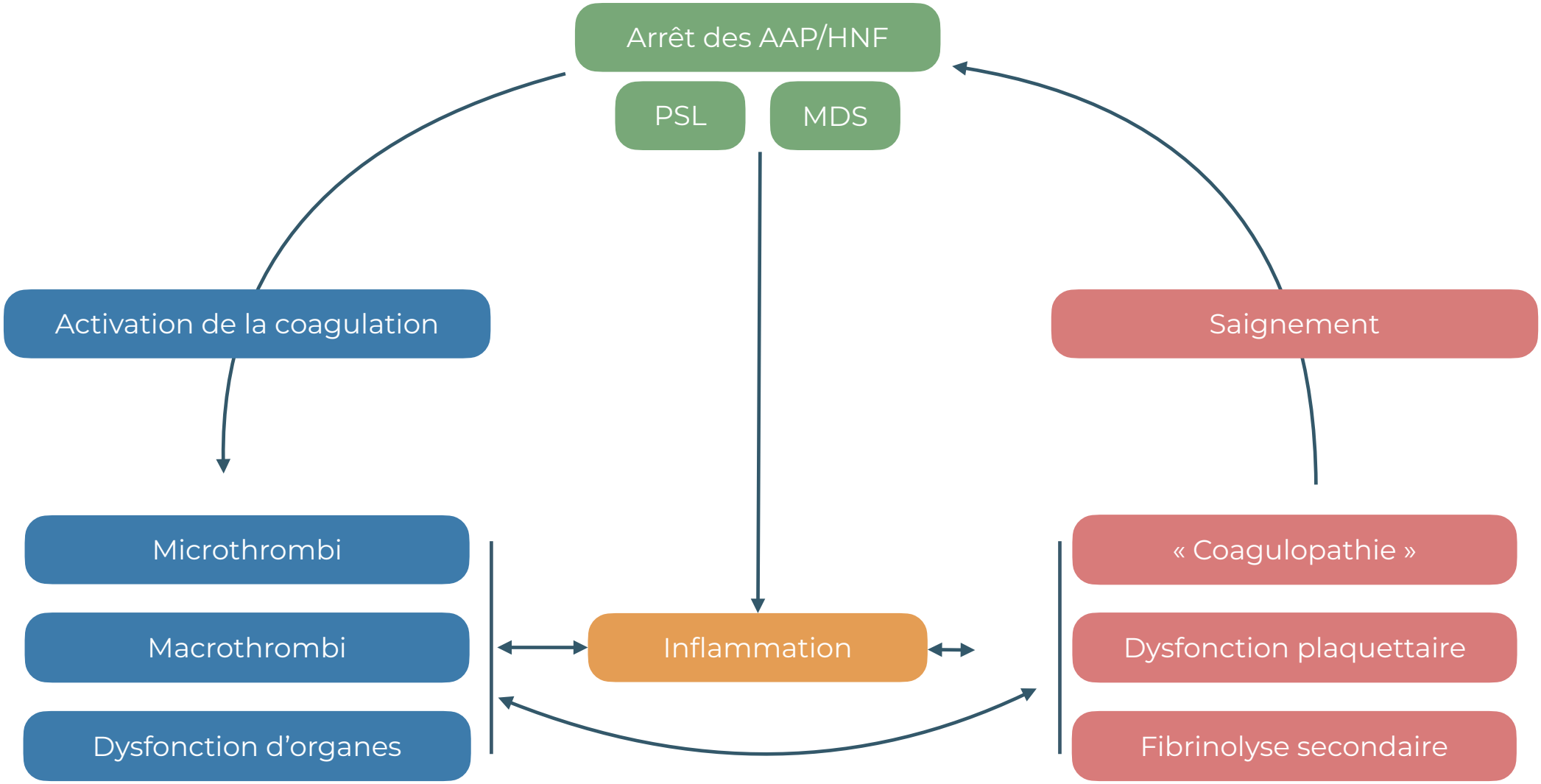


Helms et al. Anesthesiology 2024

VV et VA
Saignement précoces
Saignement canules ++

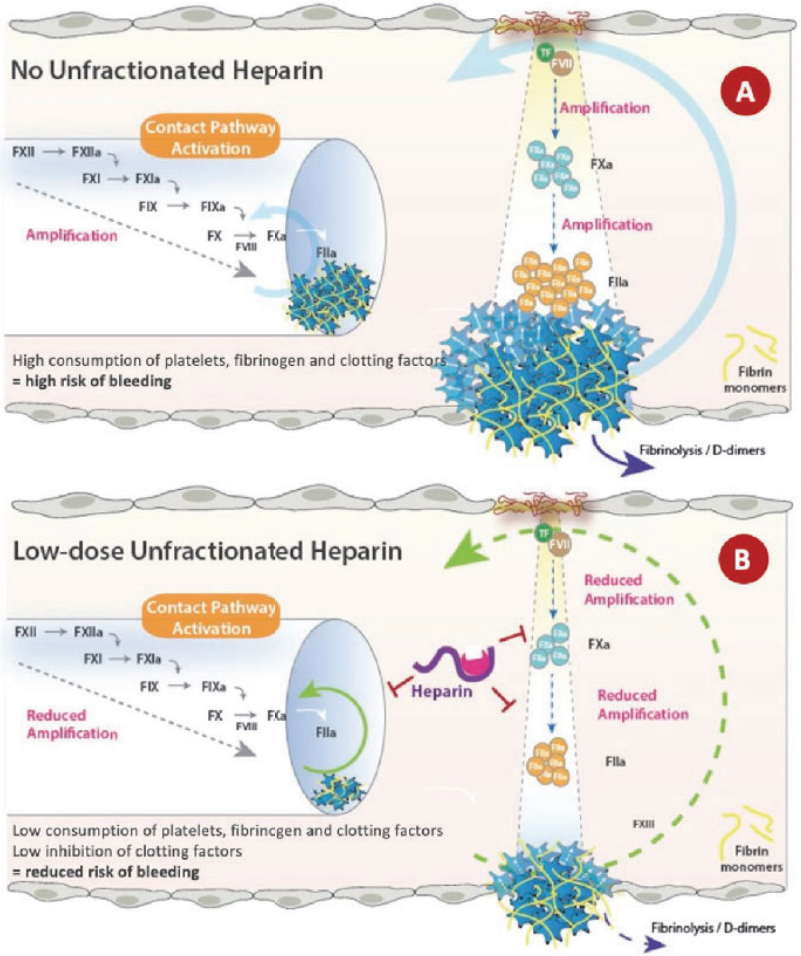
Causalité <u>non établie</u>
<u>Association vs causalité</u>

Fibrinolyse
primitive vs secondaire

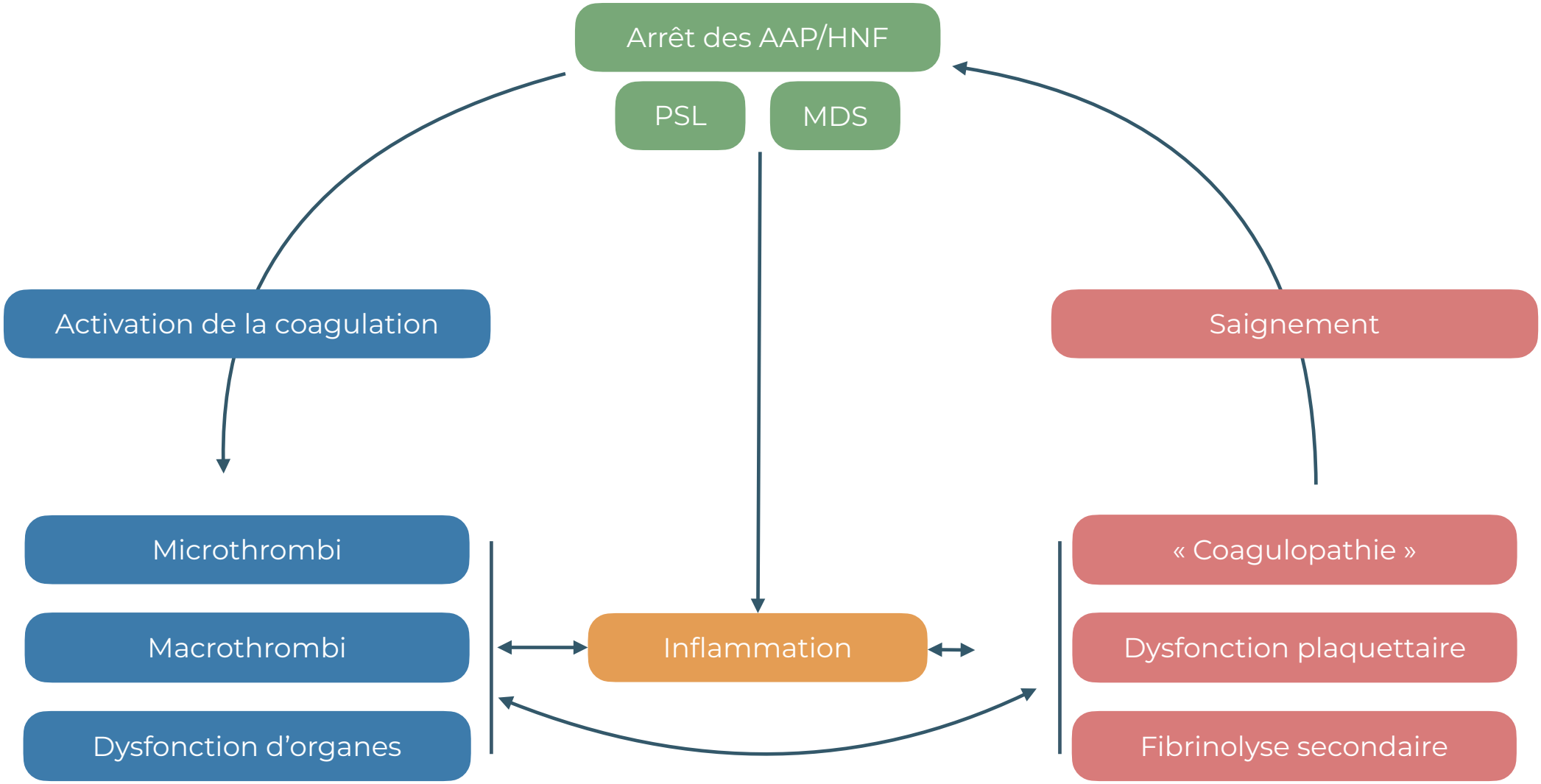

Arrêt des AAP/HNF
PSL
MDS
Activation de la coagulation
Saignement
Microthrombi
Macrothrombi
Dysfonction d'organes
Inflammation
« Coagulopathie »
Dysfonction plaquettaire
Fibrinolyse secondaire

Consumptive coagulopathy: how low-dose unfractionated heparin can prevent bleeding complications during extracorporeal life support

Christophe Vandenbriele[1,2,5*], Thomas Mueller[3] and Brijesh Patel[1,4]



	No UFH	Low-dose UFH	Therapeutic UFH
D-dimers	↑	=	↓ / =
Fibrinogen	↓	=	↑ / =
Platelets	↓	=	↑ / =
Clotting factors	↓	=	=
Anti-Xa	< 0,15 IU/ml	< 0,15 IU/ml	0,3-0,5 IU/ml
Bleeding	↑	↓	↑
Thrombosis	↑	=	↓


Arrêt des AAP/HNF
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Inflammation
« Coagulopathie »
Dysfonction plaquettaire
Fibrinolyse secondaire

COMMENT FAIRE EN PRATIQUE ?

2021 ELSO Adult and Pediatric Anticoagulation Guidelines

Ali B.V. McMichael,* Lindsay M. Ryerson,† Damian Ratano,‡§ Eddy Fan,‡ David Faraoni,¶ and Gail M. Annich||

AVIS D'EXPERT

niveau de preuve faible

HNF

anti-Xa 0.3-0.7 IU/mL

Mc Michael et al. ASAIO Journal, March 2022 - Volume 68 - Issue 3 - p 303-310

Anticoagulation in adult patients supported with extracorporeal membrane oxygenation: guidance from the Scientific and Standardization Committees on Perioperative and Critical Care Haemostasis and Thrombosis of the International Society on Thrombosis and Haemostasis

AVIS D'EXPERT

niveau de preuve faible

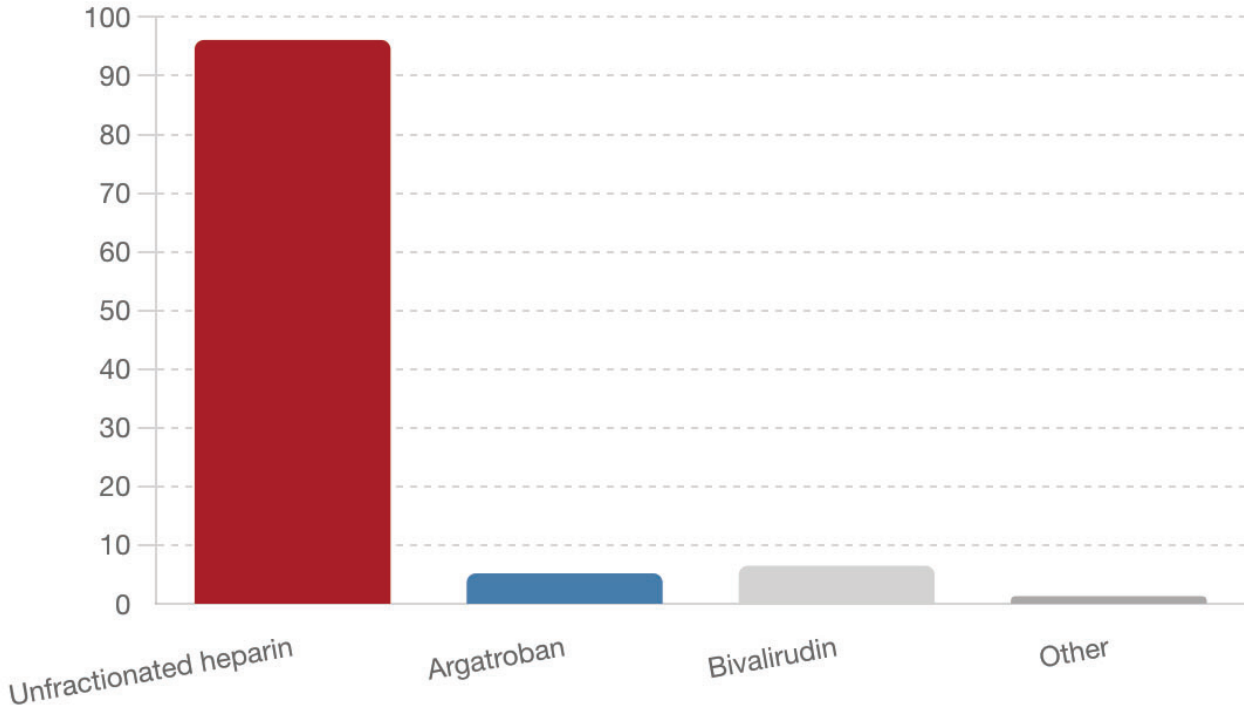
HNF

anti-Xa 0.3-0.5 IU/mL

Helms et al. J Thromb Haemost. 2023 Feb;21(2):373-396

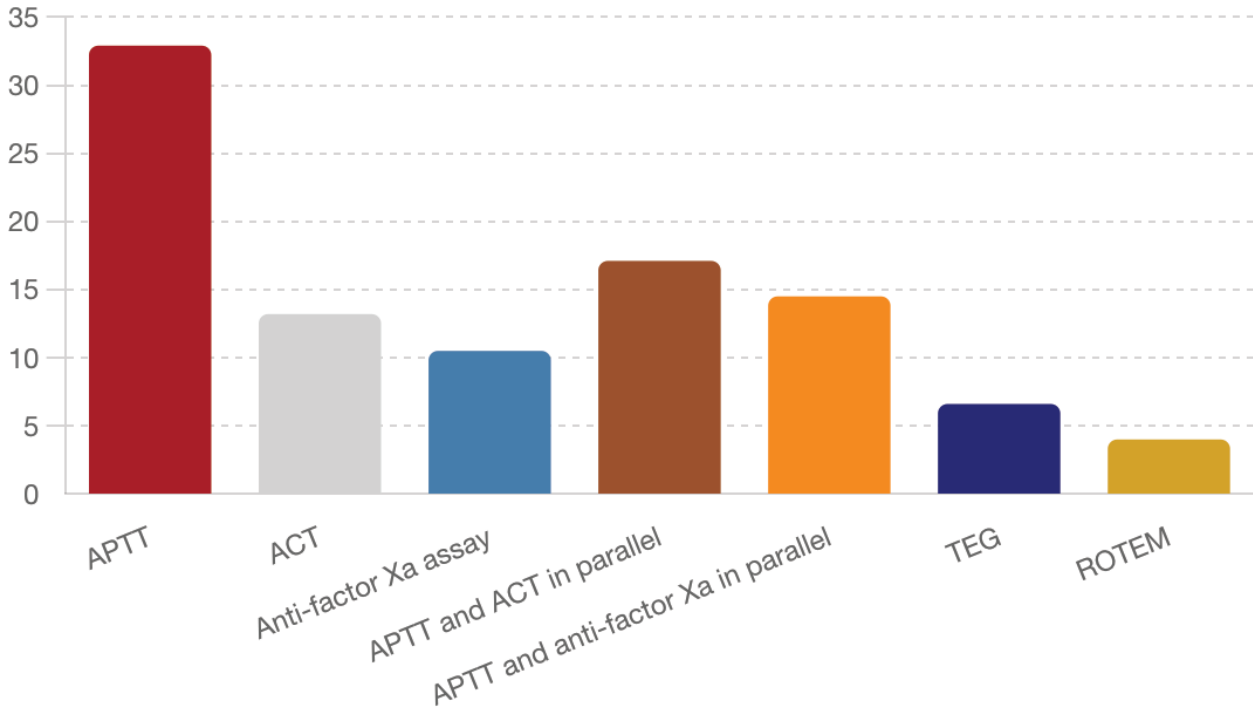
En pratique : quelle anticoagulation ?

Survey européen
26 pays - 99 centres



Van Edom et al. . Eur Heart J Acute Cardiovasc Care. 2024 Jun 30;13(6):458-469.

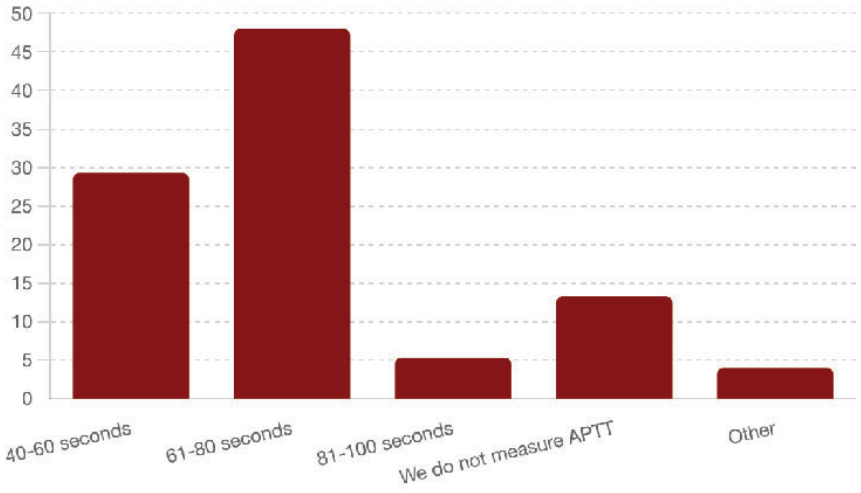
En pratique : quelle monitorage de l’HNF ?



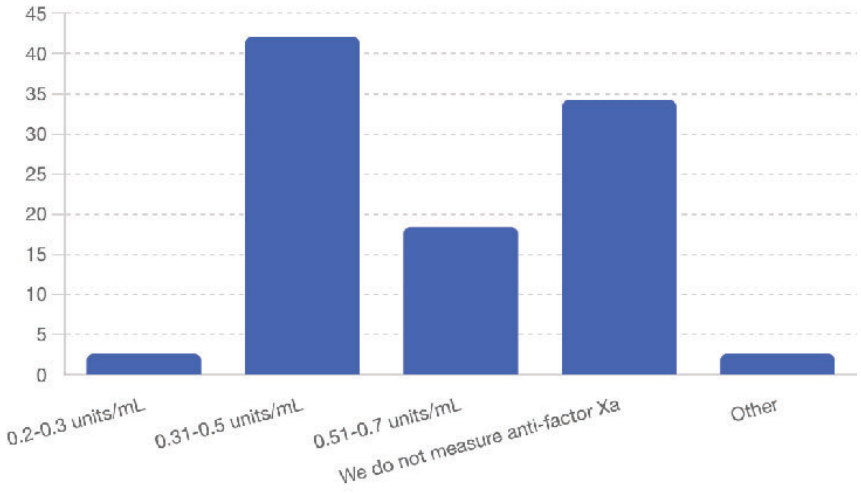
Van Edom et al. . Eur Heart J Acute Cardiovasc Care. 2024 Jun 30;13(6):458-469.

En pratique : quelle cible ?

TCA



anti-Xa



Van Edom et al. . Eur Heart J Acute Cardiovasc Care. 2024 Jun 30;13(6):458-469.

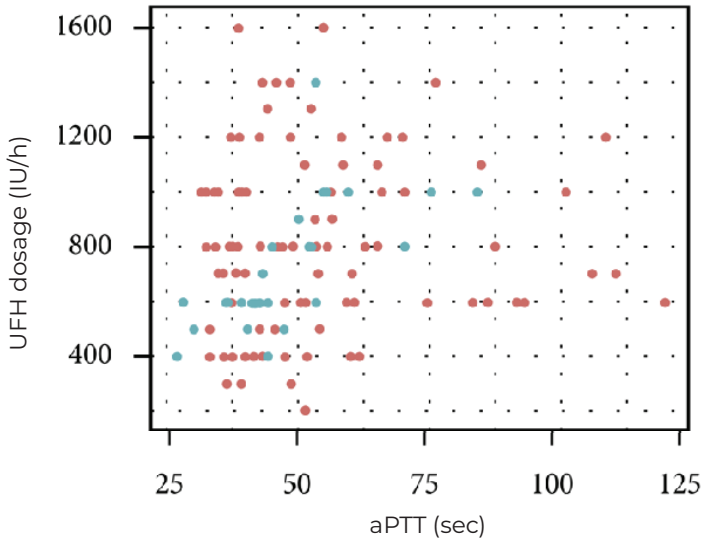
HNF sous ECMO-VA

Characteristics	All patients (n=50)	Postcardiotomy (n=21)	Non-postcardiotomy (n=29)	p-value
AT at H0 (%)	51 (40-64)	45 (34-55)	58 (44-73)	0.010
Time-weighted average of AT	63 (57-73)	62 (58-70)	66 (57-78)	0.387
Time spent <70%	71 (41-100)	78 (51-98)	60 (23-100)	0.321
Time spent <50%	11 (0-32)	13 (1-25)	10 (0-33)	0.550
Time to reach first anti-Xa ≥0.3 IU.mL^{-1} (h)	13 (5-31)	13 (5-25)	13 (4-32)	0.949
% of ECMO time spent in anti-Xa range				
Anti-Xa <0.30 IU.mL^{-1}	50 (31-74)	62 (34-78)	44 (29-66)	0.216
Anti-Xa [0.30 – 0.50] IU.mL^{-1}	38 (16-55)	29 (15-47)	46 (22-59)	0.307
Anti-Xa >0.50 IU.mL^{-1}	6 (2-16)	6 (1-14)	7 (4-17)	0.646
Anti-Xa >0.70 IU.mL^{-1}	0 (0-4)	0 (0-1)	0 (0-6)	0.197
Number of unfractionated heparin interruptions	1 (1-2)	1 (1-2)	1 (1-2)	0.636
Bleeding	36 (72%)	19 (90%)	17 (59%)	0.013
Thrombosis (without HIT- n=48)	22 (44%)	11 (52%)	11 (38%)	0.481

TCA : différents réactifs

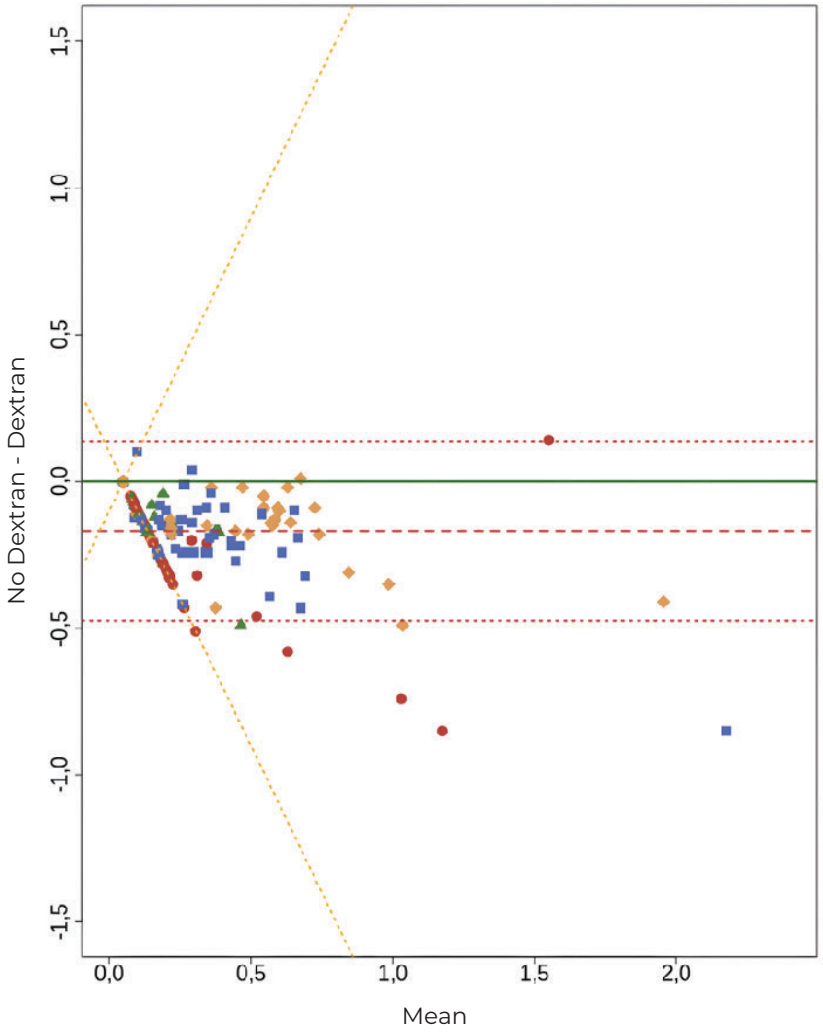
Reagent	Correlation curve		Bland Altman		aPTT ratios corresponding to 0.3-0.7 anti-Xa IU/mL
	R	slope	mean bias	+/− 1.96 SD	
Synthafax	0.85	2.7	0.59	−1.3/2.5	1.6-2.6
CK Prest	0.83	3.6	0.57	−0.6/2.1	1.6-3.0
Cephascreen	0.79	4.2	0.29	−0.8/1.4	1.8-3.5
Synthasil	0.85	5.2	0.15	−0.8/1.1	1.9-4.0
Automated APTT	0.83	6.5	-	-	2.1-4.7
APTT SP	0.85	6.6	0.05	0.4/-0.3	2.0-4.6
APTT HS	0.87	7	−0.05	−0.5/0.4	2.1-4.9
Cephen	0.78	8.5	−0.27	−2.1/1.6	2.1-5.5
Actin FSL	0.79	9	−0.22	−2.1/1.6	2.2-5.8
PTTA	0.82	9.2	−0.60	−2.1/0.9	2.6-6.2
APTT S	0.79	9.3	−0.31	−2.5/1.9	2.3-6.0
Actin FS	0.79	10.1	−0.31	−2.5/1.9	2.2-6.3
Actin	0.64	10.7	−0.29	−4.7/4.1	2.3-6.6
Cephen LS	0.78	12.3	−0.66	−4.3/3.0	2.6-7.5
Pathromtin	0.76	21	−1.99	−10.2/6.2	3.6-12

Gouin-Thibaut et al. Thromb Res. 2012;129(5):666-667.



Nguyen et al. Crit Care Res Pract. 2021 May 3;2021:5579936

anti-Xa vs anti-Xa



Sans Dextran
0.22 IU/mL (<LOQ – 1.84)

Avec Dextran
0.31 IU/mL (<LOQ – 2.60)

+53%
CI 95%: 31-80

Lasne et al. Thromb Haemost. 2023

Protocole d'anticoagulation CHU Rennes

IV UFH
Weight-based nomogram +++
anti-Xa UFH /4-6h

Very high bleeding risk
UFH interruption
ECMO Flow >2l/min

Bleeding risk = thrombotic risk
anti-Xa 0.15-0.3

Thrombotic risk > bleeding risk
anti-Xa 0.3-0.5

Quelle est votre attitude ?

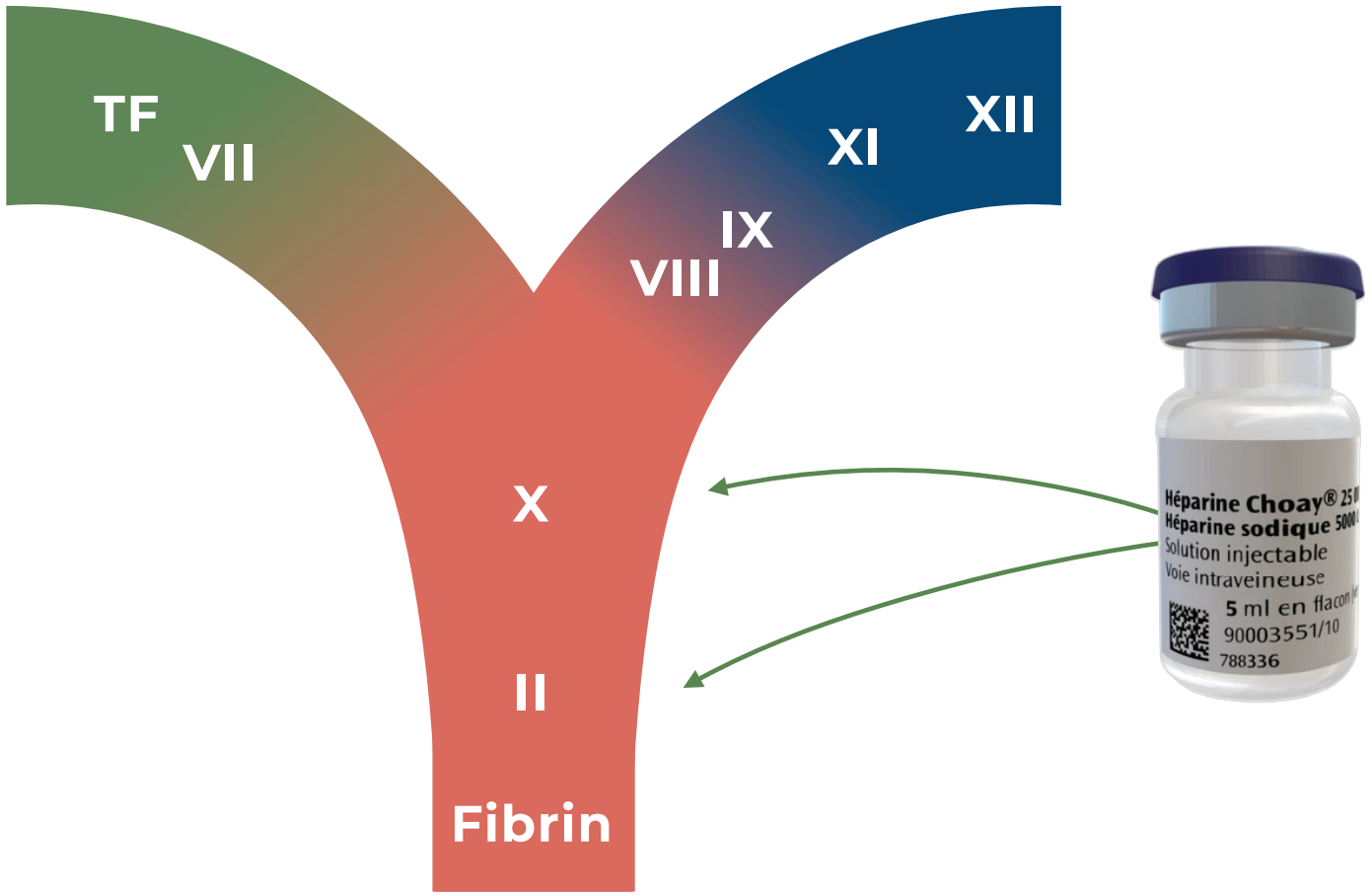
	J1	J2	J3	J4	J5
HNF UI/kg/h	10	22	26	39	39
Anti-Xa UI/mL	< 0,10	< 0,10	< 0,10	0,27	0,18
TCA ratio		0,96			2,29

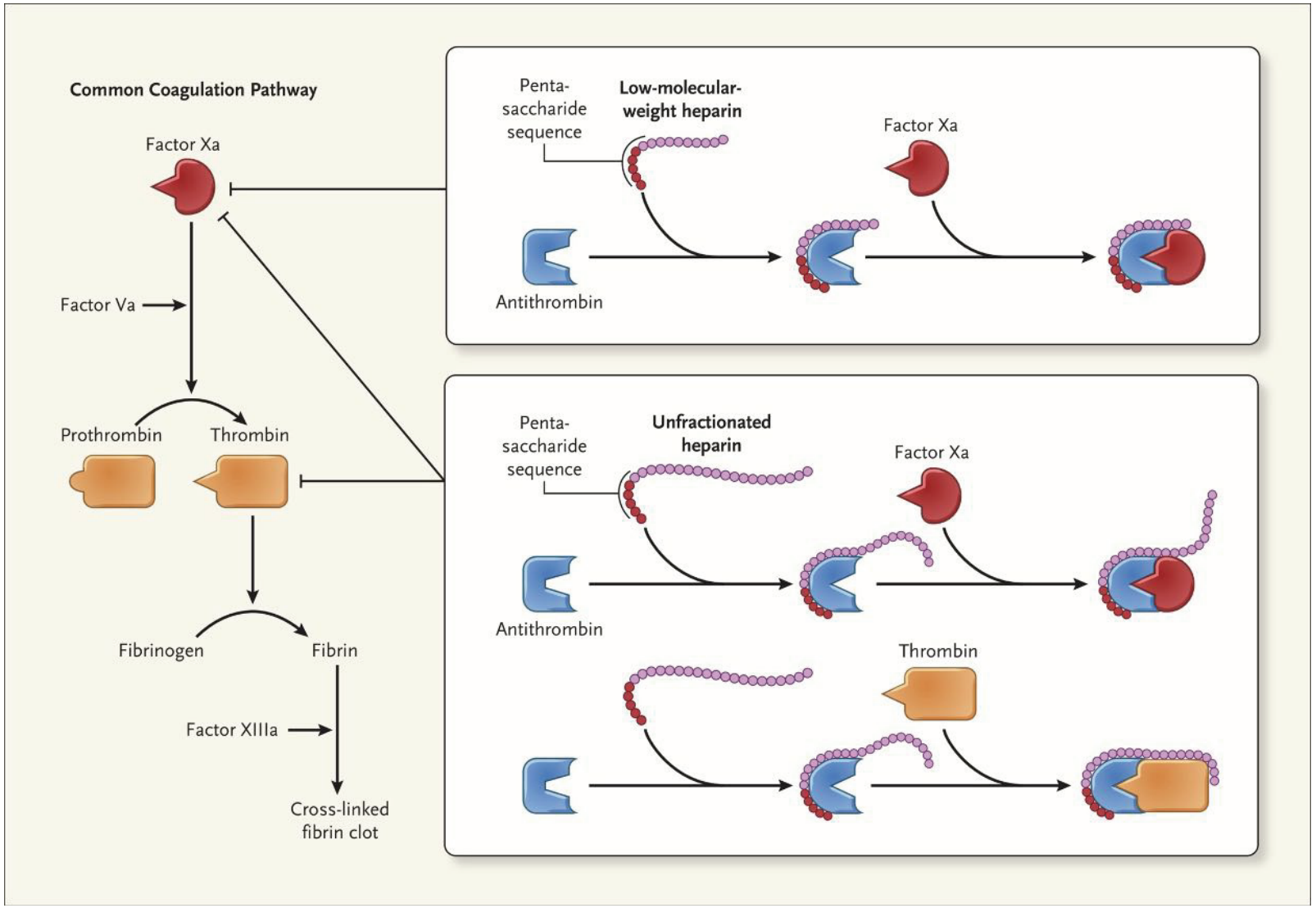
?

Quelle est votre attitude ?

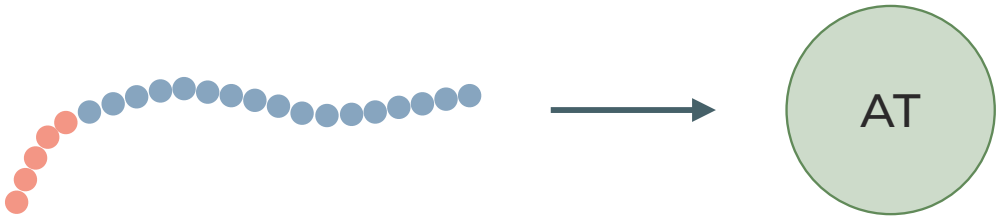
	J1	J2	J3	J4	J5
HNF UI/kg/h	10	22	26	39	39
Anti-Xa UI/mL	< 0,10	< 0,10	< 0,10	0,27	0,18
TCA ratio		0,96			2,29

Majorer l'HNF ?
Abandonner ?
PFC ?
Doser / Supplémenter en AT ?
Switcher : Argatroban / Bivalirudine ?

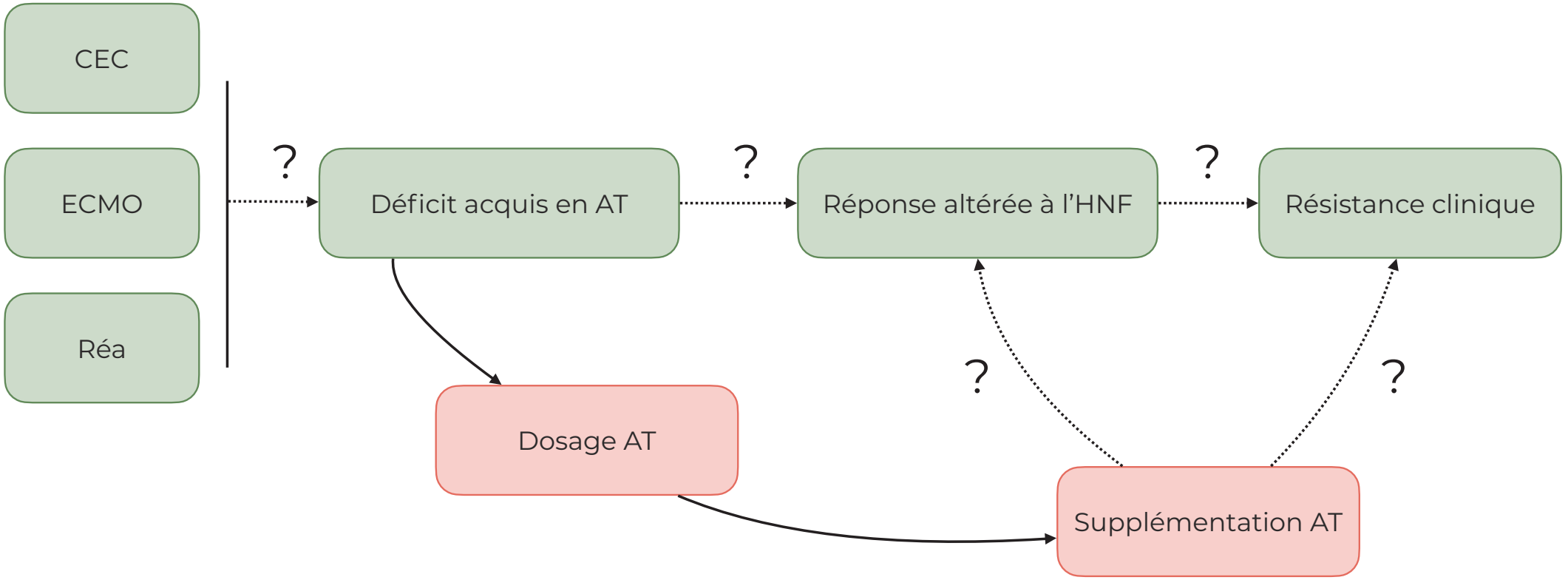

TF
VII
XII
XI
IX
VIII
X
II
Fibrin
Héparine Choay® 25
Héparine sodique 5000
Solution injectable
Voie intraveineuse
5 ml en flacon
90003551/10
788336



Levy et al. NEJM 2021


AT


Déficit **Héréditaire** en AT
Réponse altérée à l'HNF
Supplémentation


CEC
ECMO
Réa
?
Déficit acquis en AT
?
Réponse altérée à l'HNF
?
Résistance clinique
?
?
Dosage AT
Supplémentation AT

Déficit acquis en antithrombine

Consommation
Diminution ½ vie
Dilution

CIVD
Thrombose extensive, SAPL
CEC, ECMO

Défaut de synthèse

Ins. Hépato Cellulaire

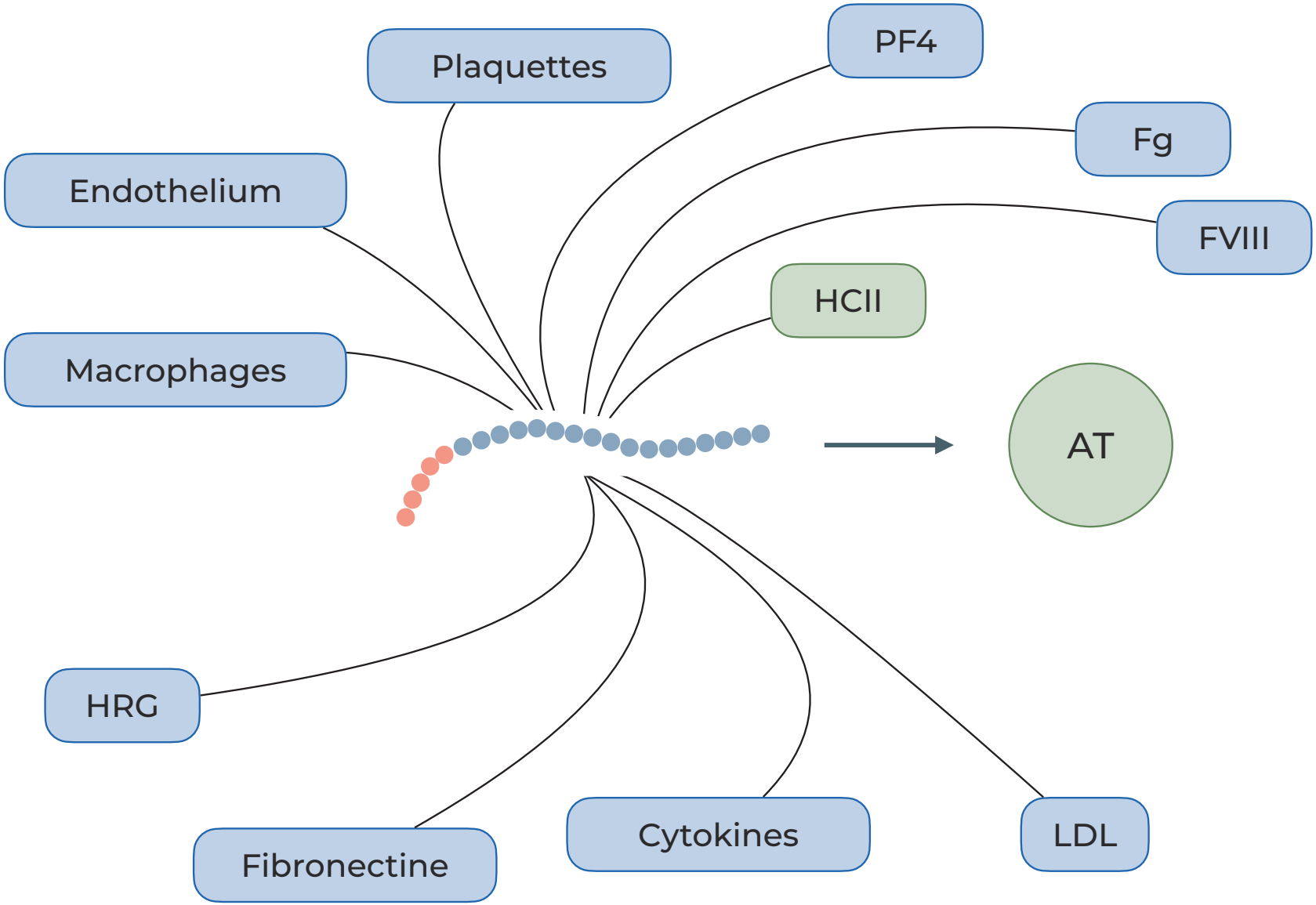
Excès d'élimination

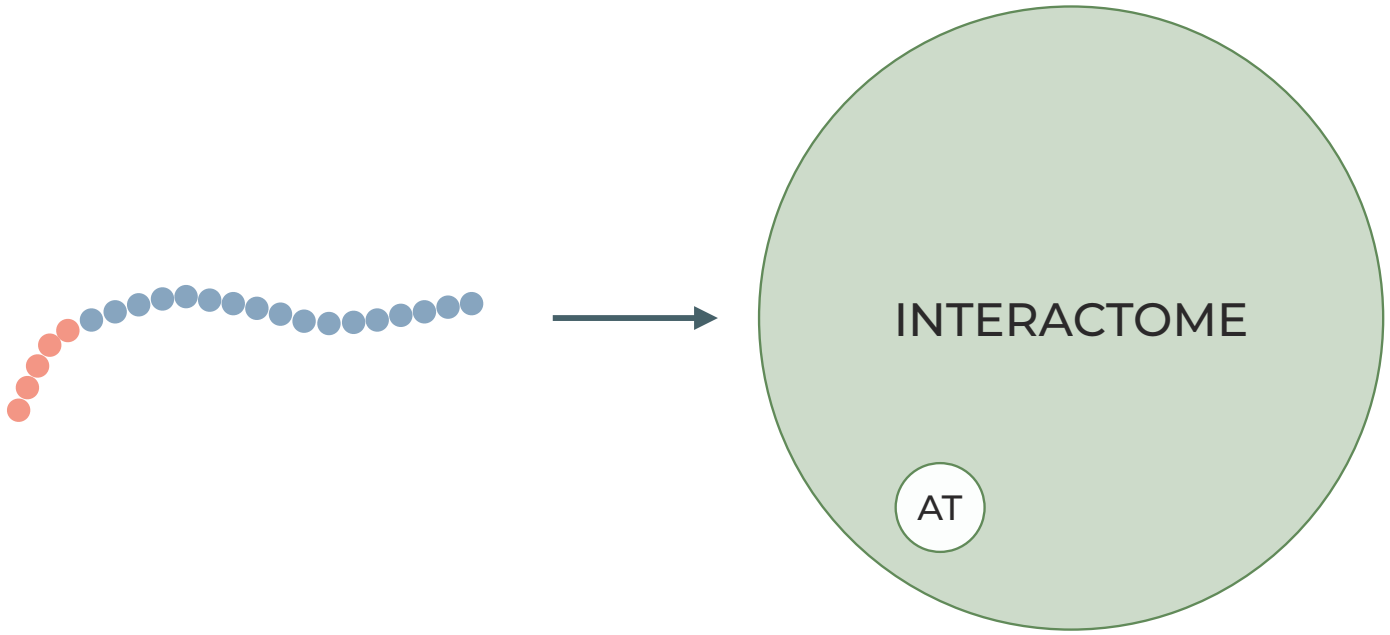
Syndrome néphrotique

Déficit combiné acquis ≠ 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


Plaquettes
PF4
Endothelium
Fg
FVIII
HCII
Macrophages
AT
HRG
Fibronectine
Cytokines
LDL


INTERACTOME
AT

HNF : utilisation d'algorithmes d'adaptation des doses

Posologies IV:

- Bolus initial : 80 UI/kg (max. 10 000 UI)
- Débit initial de perfusion : 18 UI/kg/h

Surveillance :

- Surveillance par la mesure de l'activité anti-Xa HNF, à effectuer 6 h après l'initiation de la perfusion et 6 h après tout changement de dose.
- La mesure de l'activité anti-Xa doit être effectuée au moins une fois par jour.

Garcia DA, Chest 2012; Raschke RA, Ann Intern Med 1993; Rosborough TK, Pharmacotherapy 1999; Smith ML, Am J Health-Syst Pharm 2010; Whitman-Purves E, Clin Appl Thromb 2018; Jimaja WE, BMJ open 2022; Lardinois B, J Clin Med 2022

HNF : utilisation d'algorithmes d'adaptation des doses

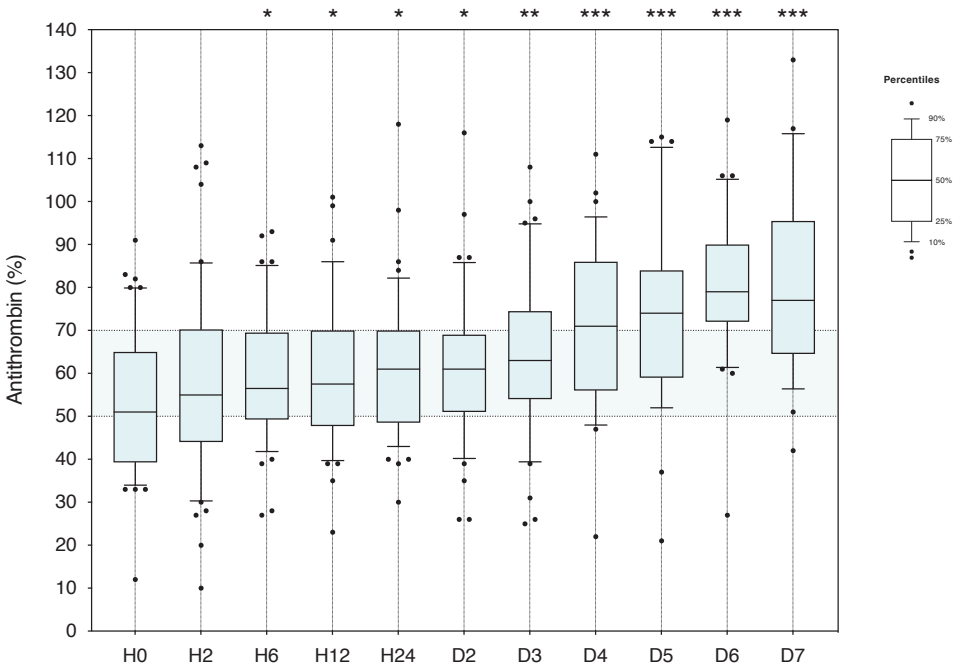
Zone thérapeutique, anti-Xa 0,3 à 0,5 UI/mL
Ajustements posologiques (4h après chaque modification)

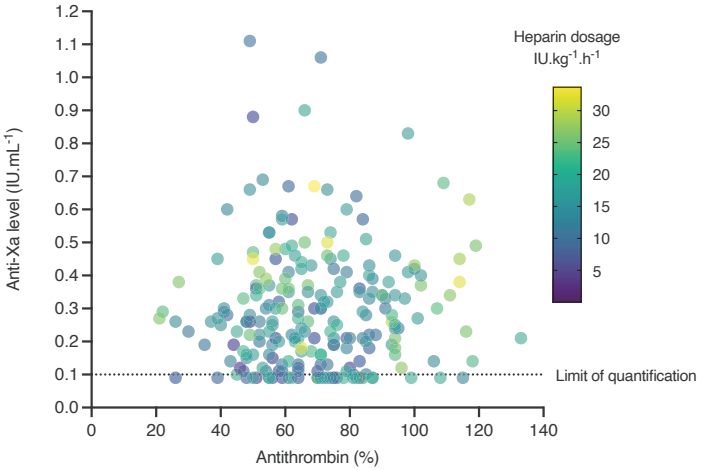
Activité anti-Xa HNF (UI/mL)	Bolus IVD	Ajustement de la dose
<0,10	50 UI/kg	+ 4 UI/kg/h
0,10 – 0,19	40 UI/kg	+ 3 UI/kg/h
0,20 – 0,29	20 UI/kg	+ 2 UI/kg/h
0,30 – 0,49	-	-
0,5 – 0,59	-	- 1 UI/kg/h
0,6 – 0,69	-	- 2 UI/kg/h
>0,7	Stop 1h	- 3 UI/kg/h

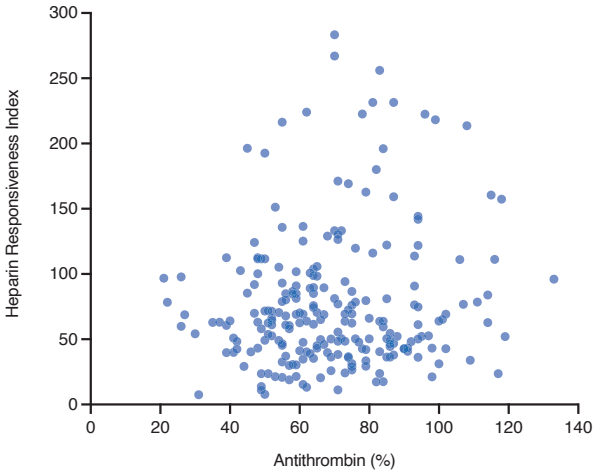
Anti-Xa : Liquid® Stago, sans dextran

ECMO-VA

Pas de lien entre AT et réponse à l'HNF







A Randomized Controlled Trial of Antithrombin Supplementation During Extracorporeal Membrane Oxygenation

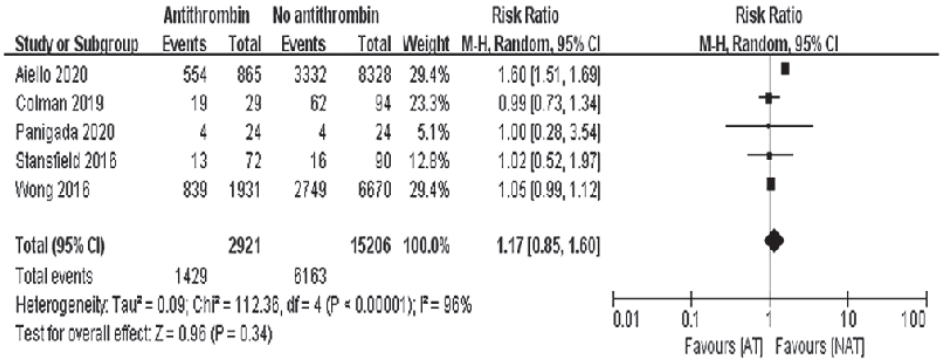
	Control ($n = 24$)	Treatment ($n = 24$)	Estimates	p^a
Primary endpoint				
Heparin infused (IU/kg/hr), median (IQR)	15.1 (10.7–18.3)	13.5 (9.6–17.9)	Mean difference = −1.2 (−3.7 to 1.2)	0.33
Person-days, *n*	403	305		
Secondary endpoints				
Anti-Factor Xa (IU/mL), median (IQR)	0.3 (0.2–0.5)	0.4 (0.3–0.5)	Mean difference = 0.02 (−0.07 to 0.11)	0.65
Person-days, *n*	170	135		
Any bleeding (cumulative incidence, %)	12 (50)	11 (45.8)	OR = 0.85 (0.28–2.59)	0.77
Bleeding categories[a], *n* (%)				0.10
0	7 (29.2)	8 (33.3)	Base	
1	4 (16.7)	7 (29.2)	RRR = 2.9 (0.44–19.02)	0.27
2	6 (25.0)	4 (16.7)	RRR = 0.19 (0.03–1.15)	0.07
3	5 (20.8)	4 (16.7)	RRR = 0.45 (0.05–4.15)	0.48
4	2 (8.3)	1 (4.2)	RRR = 0.35 (0.02–5.65)	0.46
Bleeding, first event (person-days, 95% CI)	0.06 (0.03–0.10)	0.04 (0.02–0.07)	IRR = 0.66 (0.29–1.51)	0.33
Blood products transfused per day, median (IQR)				
Packed RBCs (U)	0.6 (0.4–0.8)	0.7 (0.3–1.3)	Mean difference = −0.23 (−0.07 to 0.21)	0.30
Fresh frozen plasma (mL)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	Mean difference = 12.75 (−52.37 to 77.86)	0.69
Platelet pools (U)	0.0 (0.0–0.1)	0.0 (0.0–0.5)	Mean difference = −0.25 (−0.63 to 0.12)	0.18
Thrombosis[b], *n* (%)	3 (12.5)	4 (16.7)	OR = 1.4 (0.31–6.34)	0.68
Circuit change, first (person-days), median (IQR)	0.07 (0.04–0.12)	0.04 (0.02–0.08)	IRR = 0.50 (0.20–1.25)	0.14

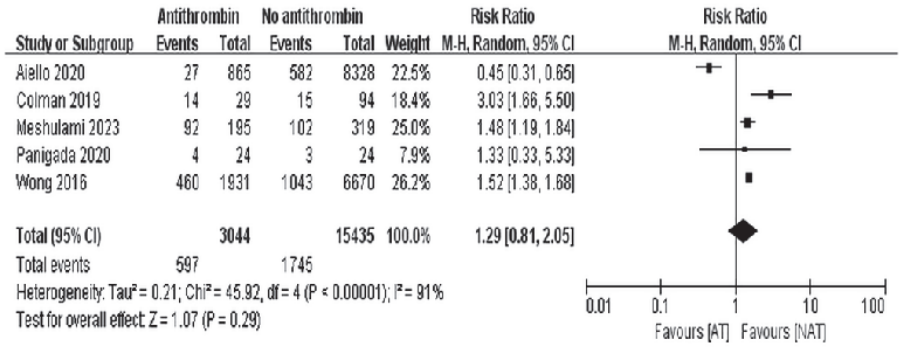
Pilot RCT
VV-ECMO
Treatment : AT obj 80-120%

Panigada et al. Crit Care Med. 2020 Nov;48(11):1636-1644.

Study	Study design	Multicenter study	Sample size	Age stratification	AT dose	AT type	indication of ECMO	bias risk
Aiello 2020	Cohort study	yes	9193	≤18 yr	NA	NA	Cardiac	Low
Colman 2019	Cohort study	no	123	>18 yr	NA	AT III	Other	Medium
Meshulami 2023	Cohort study	yes	514	≤18 yr	NA	AT III	Other	Medium
Panigada 2020	RCT	yes	48	>18 yr	2360 IU/d	AT III	respiratory	Low
Stansfield 2016	Cohort study	no	162	≤18 yr	125 IU/kg	AT III	respiratory	Low
Wong 2016	Cohort study	yes	8601	≤18 yr	NA	AT III	Other	Low

AT: antithrombin; ECMO: extracorporeal membrane oxygenation; RCT: randomized controlled trial.

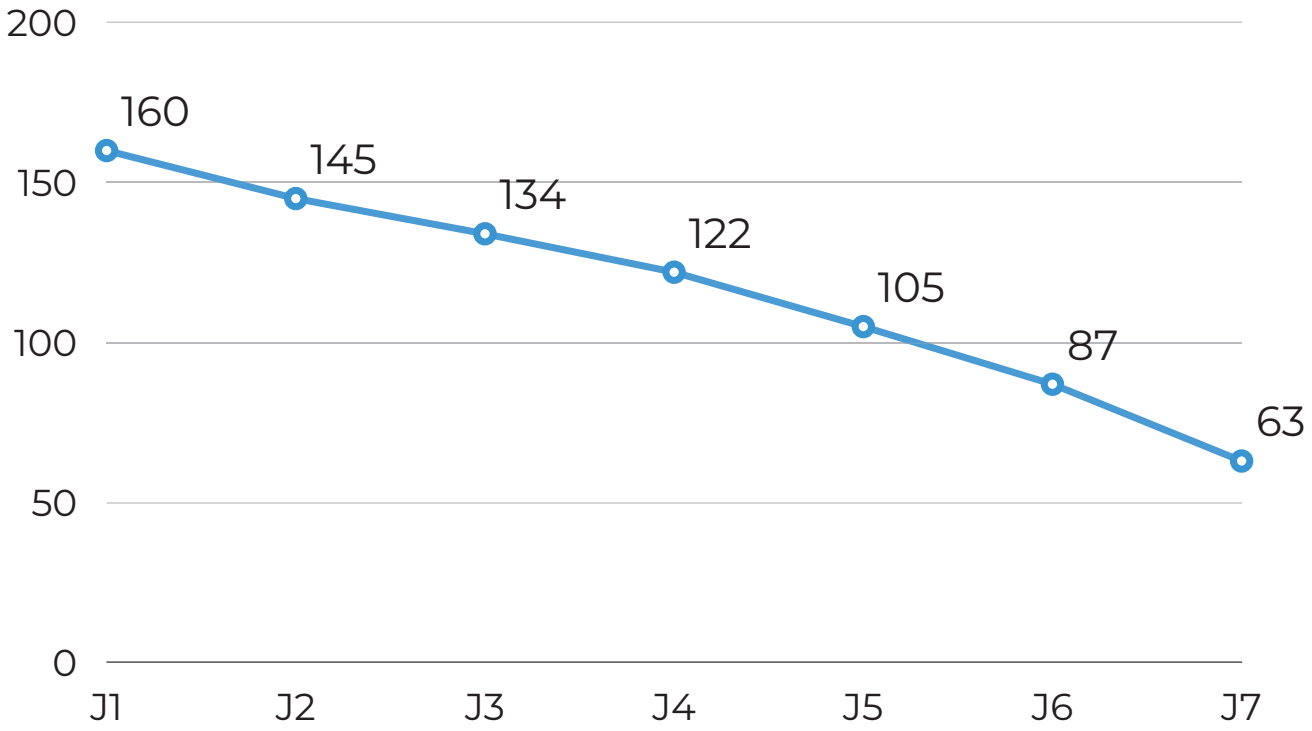




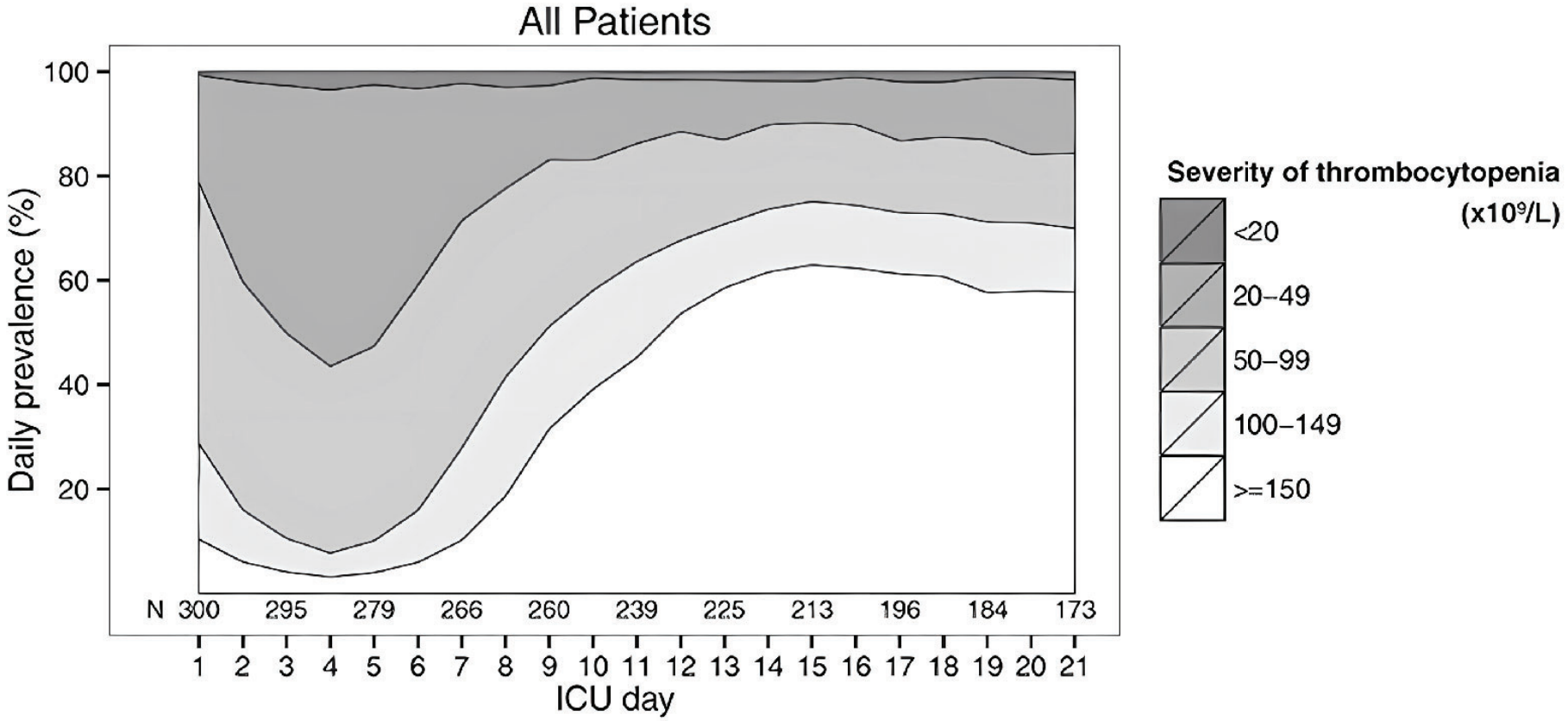
	J1	J2	J3	J4	J5	J6
HNF UI/kg/h	10	22	26	39	39	45
Anti-Xa UI/mL	< 0,10	< 0,10	< 0,10	0,27	0,18	0,38
TCA ratio		0,96			2,29	

AT 54%

A J7, l'IDE vous sollicite car la numération plaquettaire ce matin est à 63 G/L
Quelle votre attitude diagnostique et thérapeutique ?

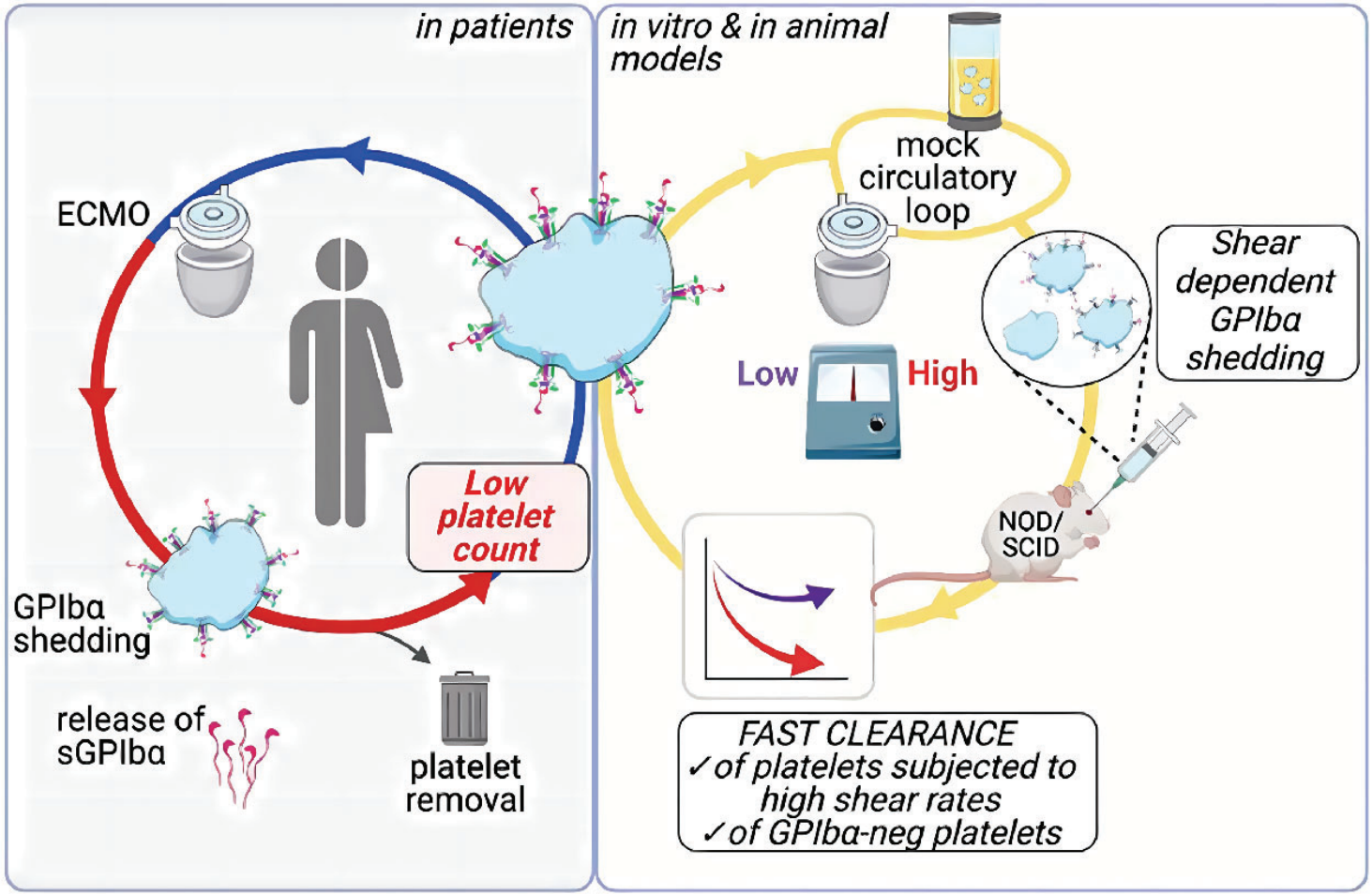


ECMO et Plaquettes



Opfermann et al. Crit Care Med 2016

ECMO et Plaquettes



Rauch et al. Circulation Research. 2023;133:826–841

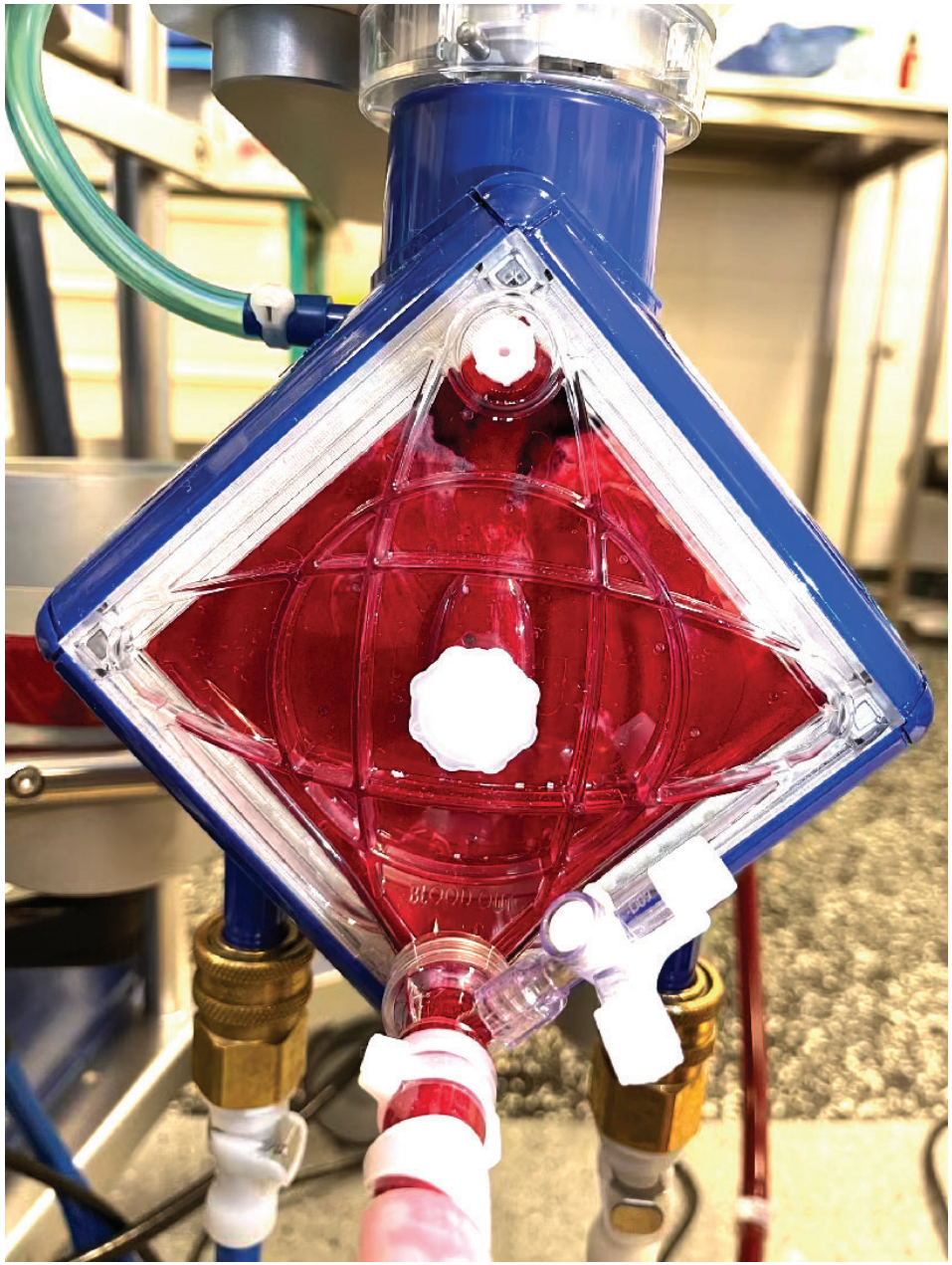
A J7, l'IDE vous sollicite car la numération plaquettaire ce matin est à 63 G/L
Quelle votre attitude diagnostique et thérapeutique ?

Y a t il une diathèse hémorragique clinique ? > NON

Dysfonction de membrane d'ECMO ? > FmO2 en hausse à 80%

Défibrination ? > Fg stable entre 3 et 4

Thrombose ? > pas de TVP clinique, plusieurs caillots sur la membrane


BLOOD OUT

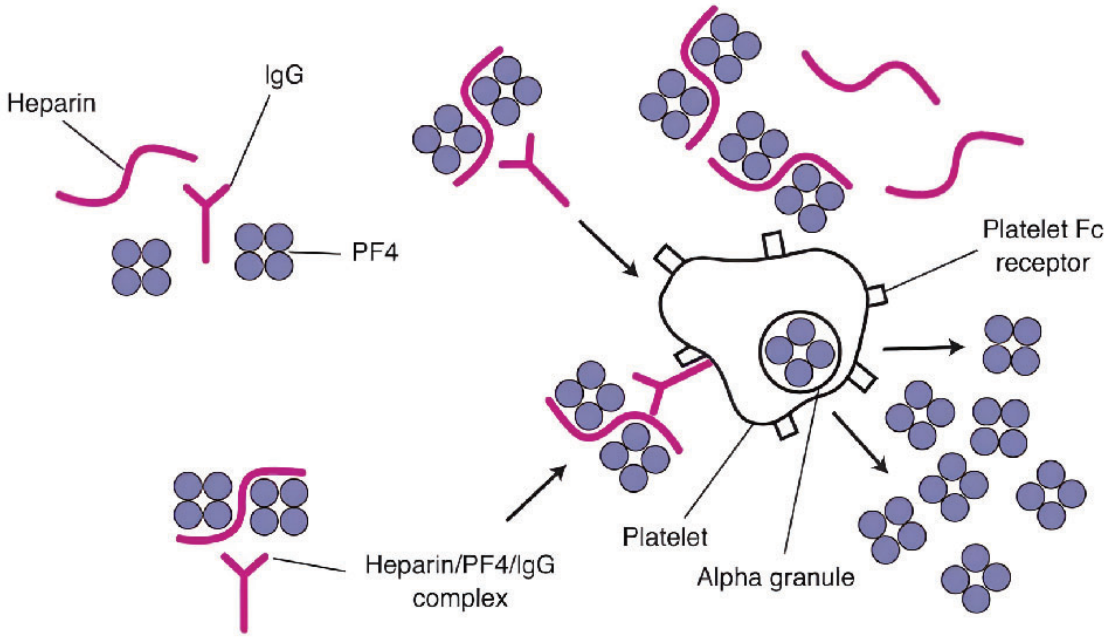
TIH ?

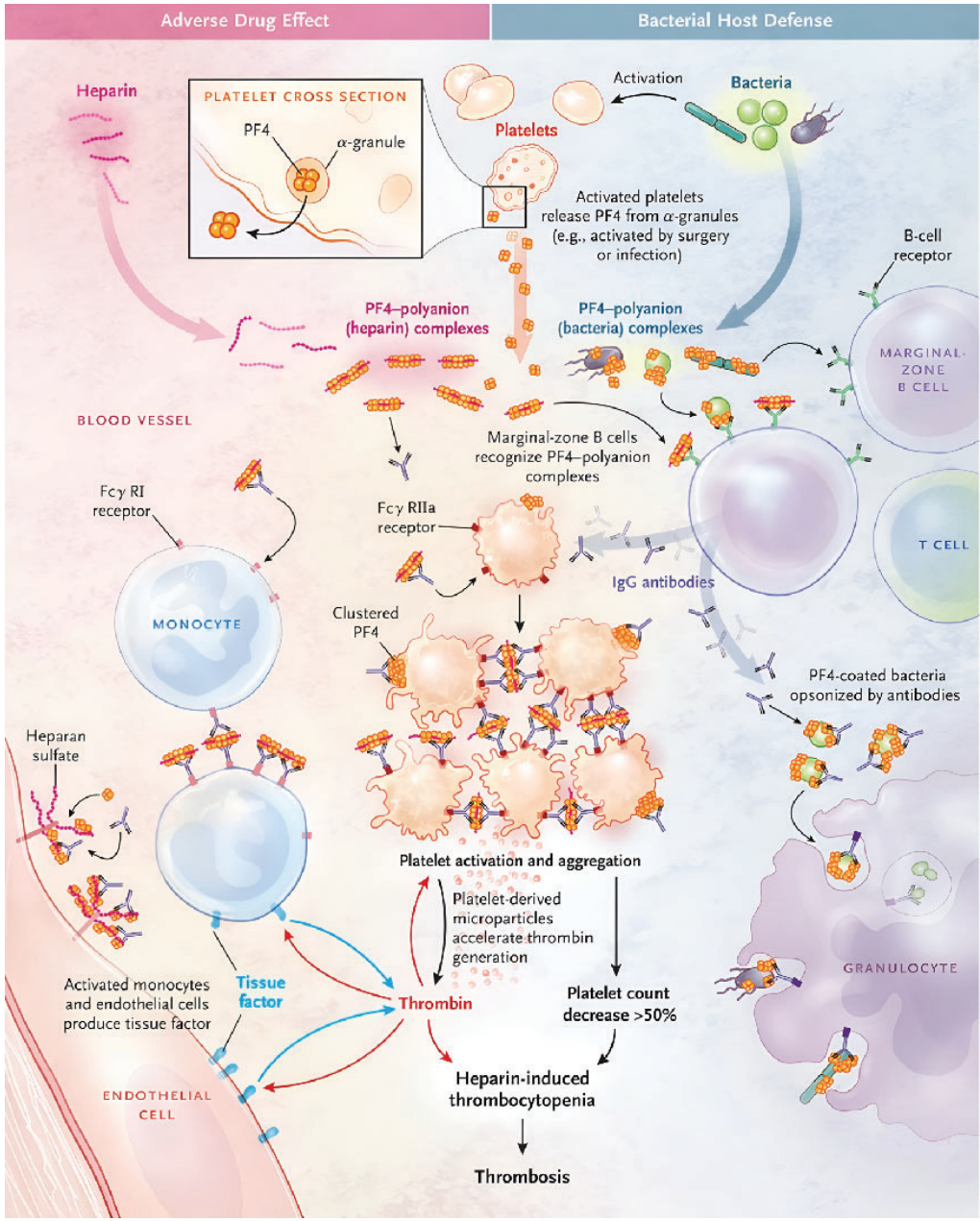
Diagnostic et prise en charge d'une thrombopénie induite par l'héparine

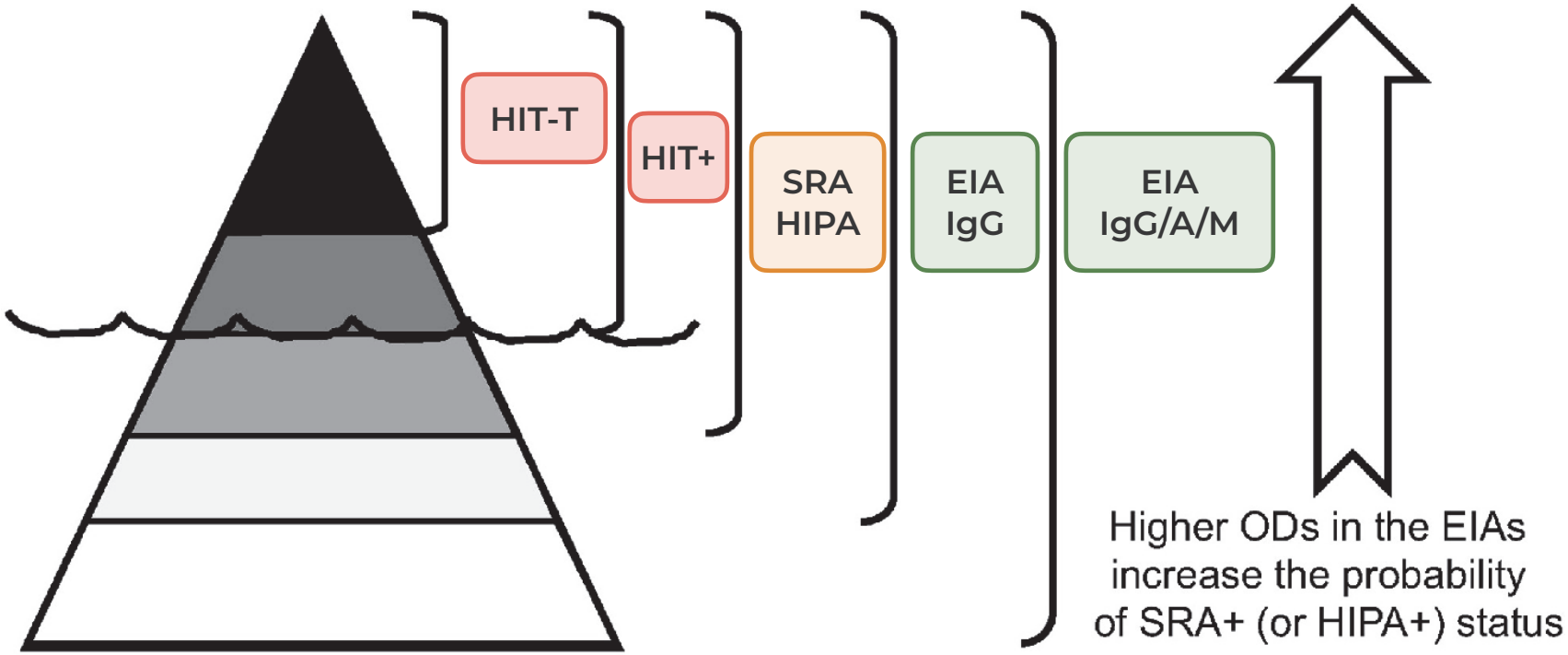
2019

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

www.gihp.org


Heparin
IgG
PF4
Platelet Fc receptor
Platelet
Alpha granule
Heparin/PF4/IgG complex


Adverse Drug Effect
Bacterial Host Defense
Heparin
PLATELET CROSS SECTION
PF4
α-granule
Platelets
Activation
Bacteria
Activated platelets release PF4 from α-granules (e.g., activated by surgery or infection)
B-cell receptor
PF4–polyanion (heparin) complexes
PF4–polyanion (bacteria) complexes
MARGINAL-ZONE B CELL
BLOOD VESSEL
Marginal-zone B cells recognize PF4–polyanion complexes
T CELL
Fcγ RI receptor
Fcγ RIIa receptor
IgG antibodies
MONOCYTE
Clustered PF4
PF4-coated bacteria opsonized by antibodies
Heparan sulfate
Platelet activation and aggregation
Platelet-derived microparticles accelerate thrombin generation
GRANULOCYTE
Activated monocytes and endothelial cells produce tissue factor
Tissue factor
Thrombin
Platelet count decrease >50%
ENDOTHELIAL CELL
Heparin-induced thrombocytopenia
Thrombosis



TIH = Thrombopénie + Ac anti-PFA/HNF IgG + + Test fonctionnel +

Warkentin et al. J Am J Med 2011

Quand suspecter une TIH ?

Thrombopénie*

J4- J14

diminution de la numération plaquettaire initiale > 50%

30-70 G/L

Complications thromboemboliques sous héparine

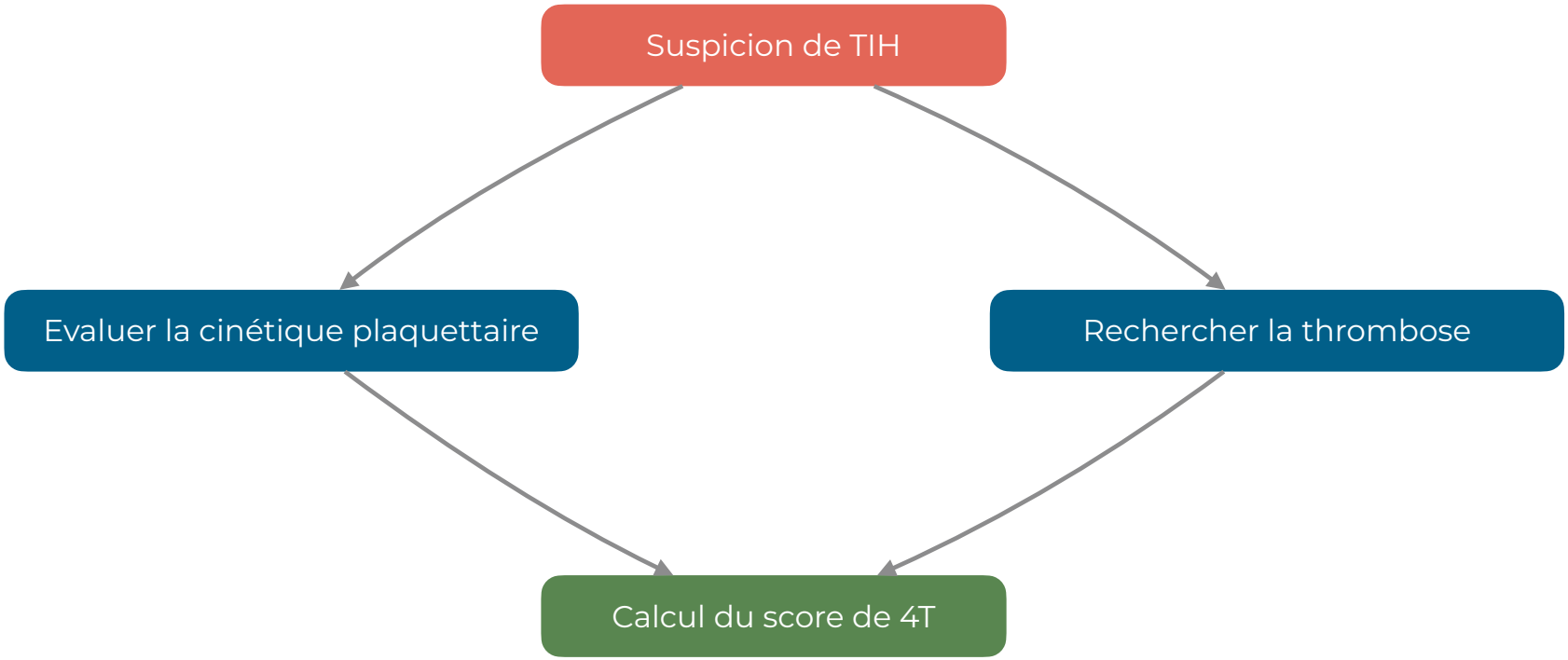
Thromboses veineuses des gros vaisseaux : membres inférieurs, embolie pulmonaire

Thromboses artérielles périphériques

AVC

Autres vaisseaux : sinus cérébral et veines splanchniques

* En l'absence de cinétique, éliminer une fausse thrombopénie



Diagnostic et prise en charge d'une thrombopénie induite par l'héparine
Propositions du Groupe d'Intérêt en Hémostase Périopératoire (GIHP) et du Groupe Français d'études sur l'Hémostase et la Thrombose (GFHT)

Suspicion de TIH

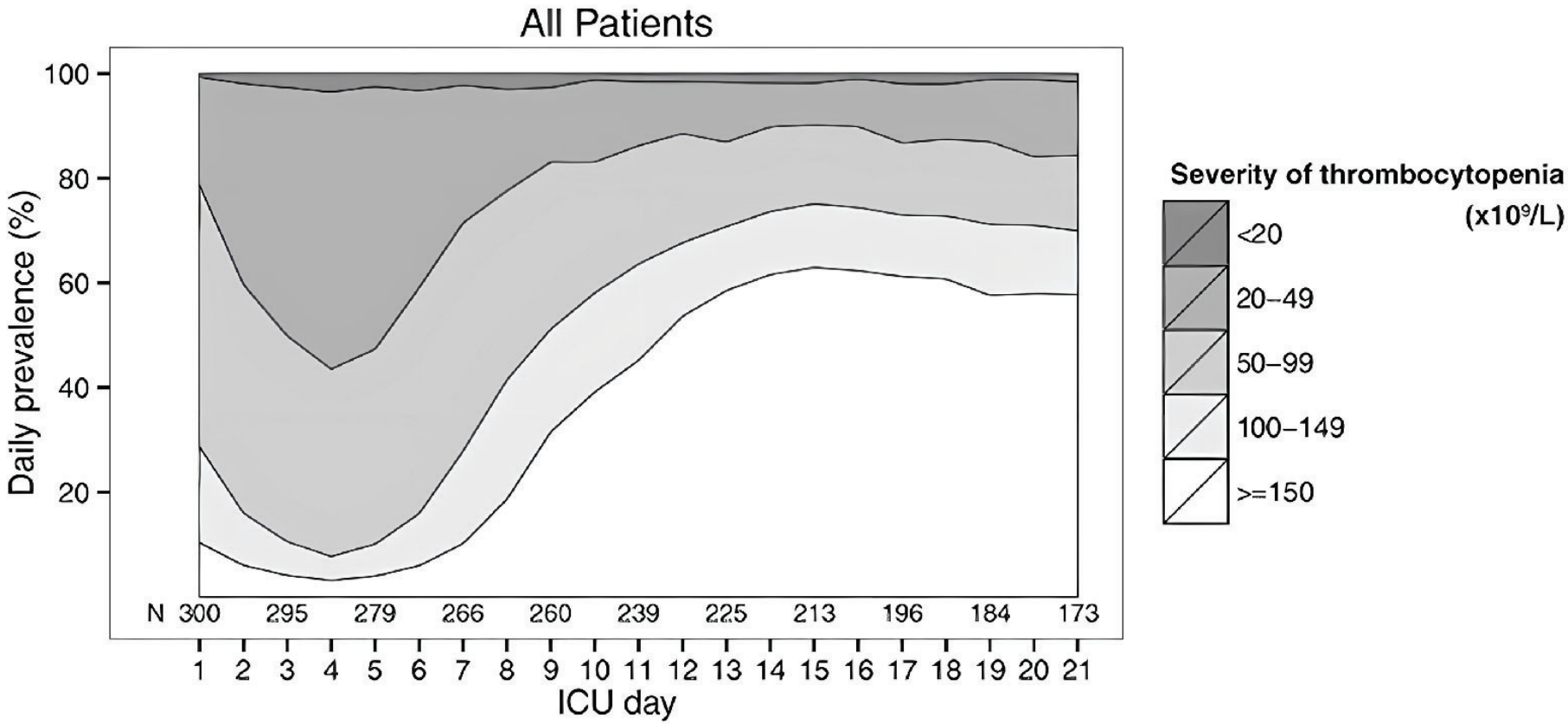
↓

Evaluation de la probabilité clinique

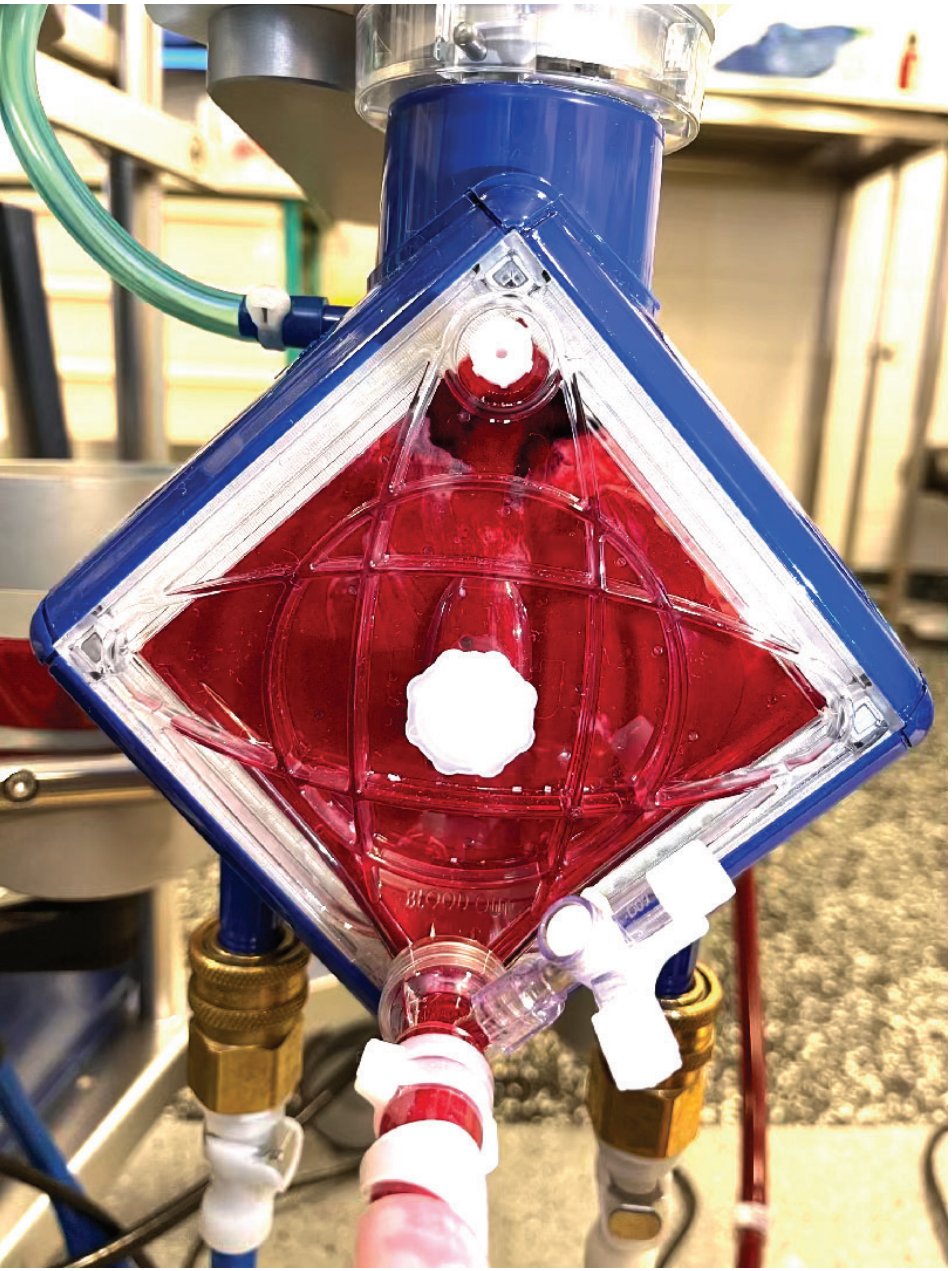
↓

IMPORTANCE DU BINÔME CLINICIEN-BIOLOGISTE

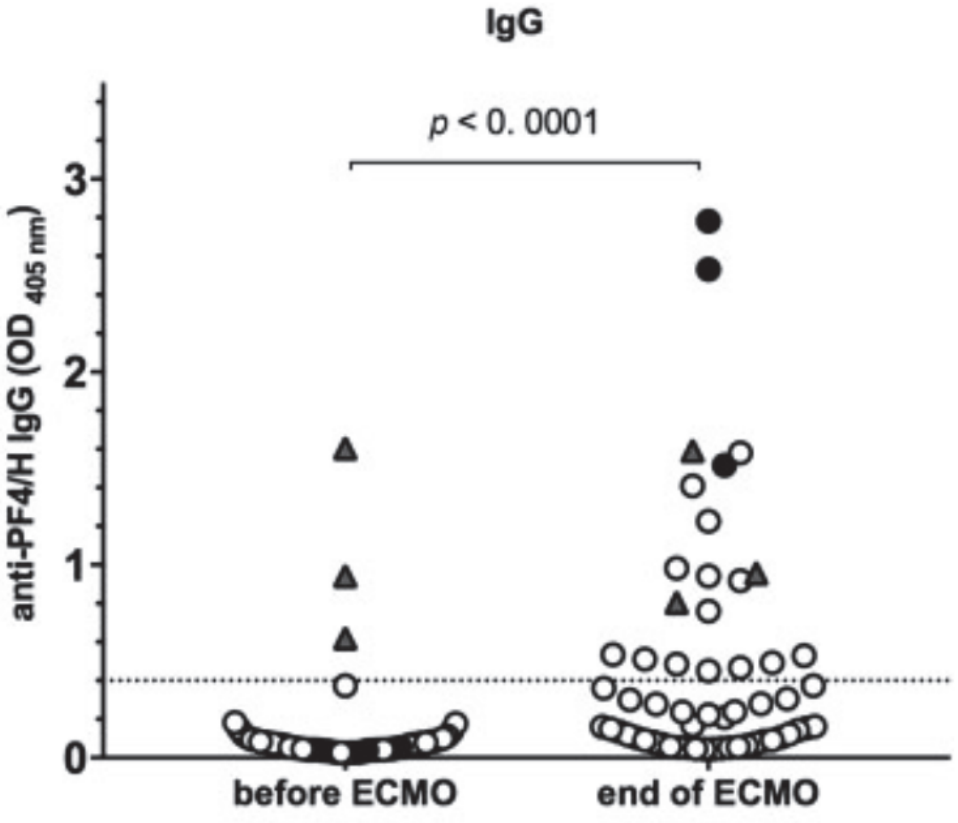
ECMO et Plaquettes

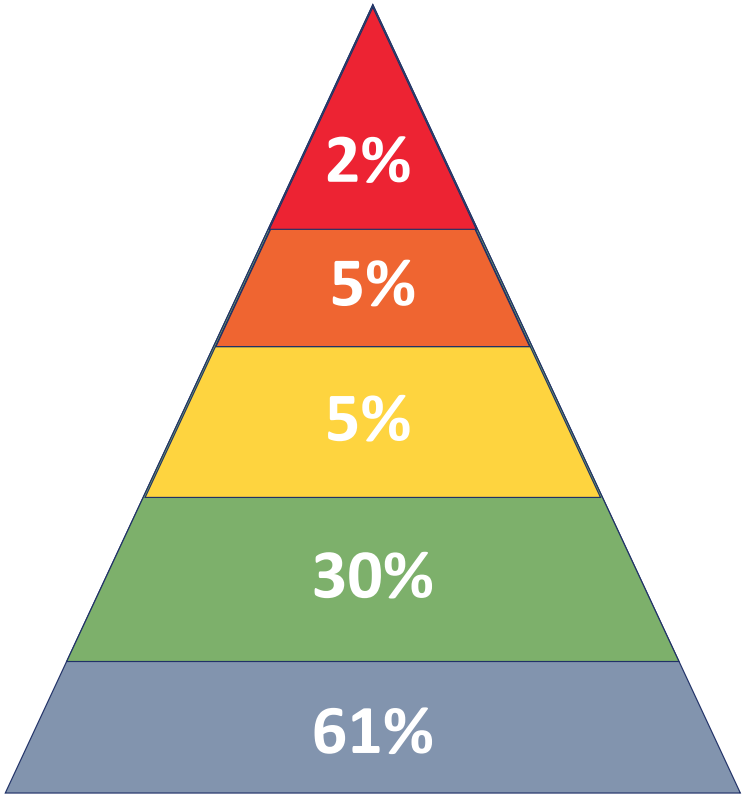


Opfermann et al. Crit Care Med 2016

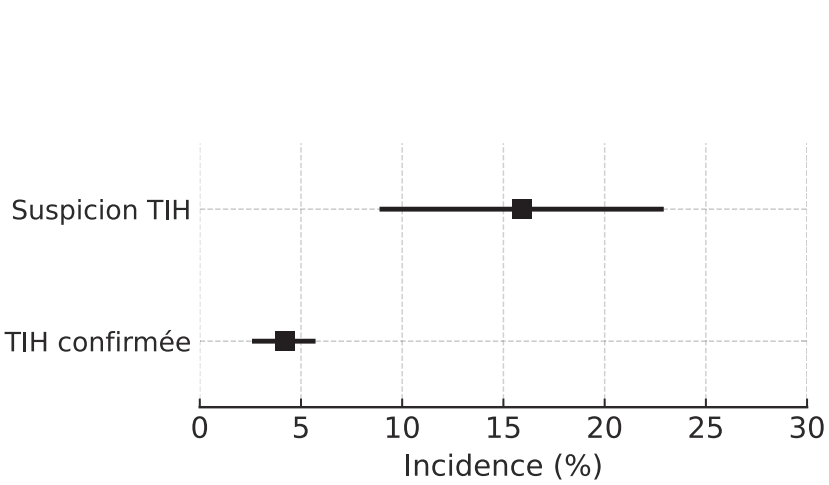


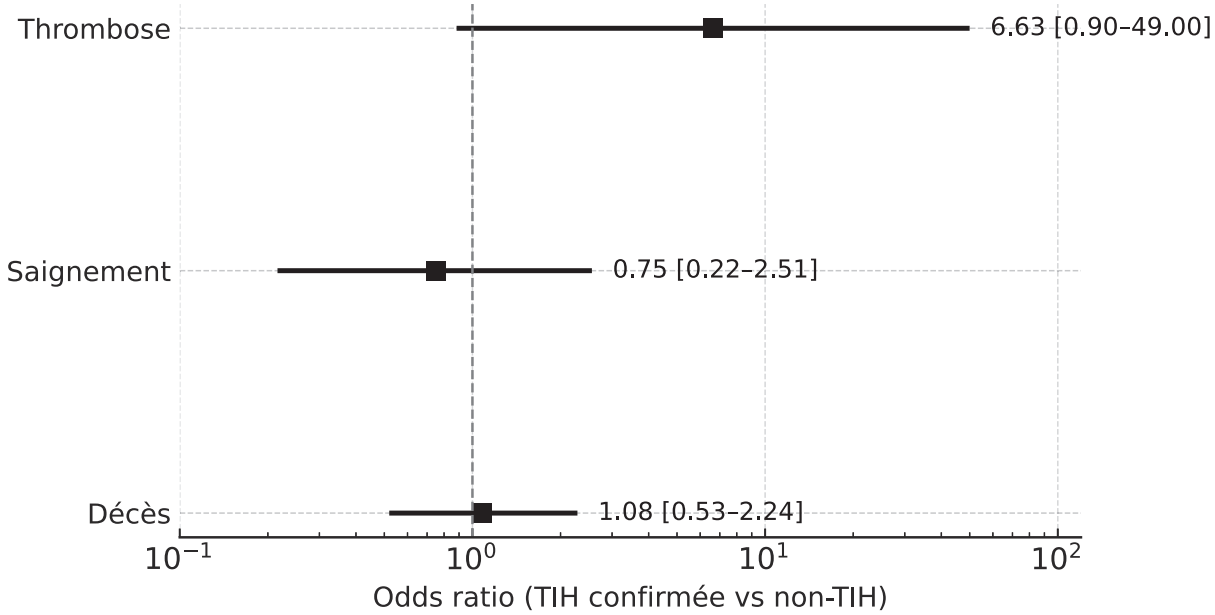
Est-ce une thrombose ?





Vayne et al. Thromb Haemost 2019





« Several studies confirmed that there was no significant difference in the PLT nadir or percentage of falls between patients who were confirmed to have HIT and patients who ultimately had HIT excluded by laboratory tests »

Song et al. Thrombosis Journal 2024

Quand suspecter, comment diagnostiquer ?

Suspicion fréquente

Un score 4T <4 et une DO EIA <0,4 permettent d’exclure la TIH

Confirmation fonctionnelle obligatoire : SRA / HIPA / agrégations

Place pour les tests rapides ?

Quelle prise en charge ?

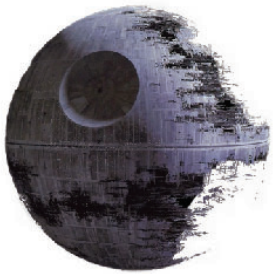
Arrêter HNF

Changer la canule/le circuit recouvert d’héparine (?)

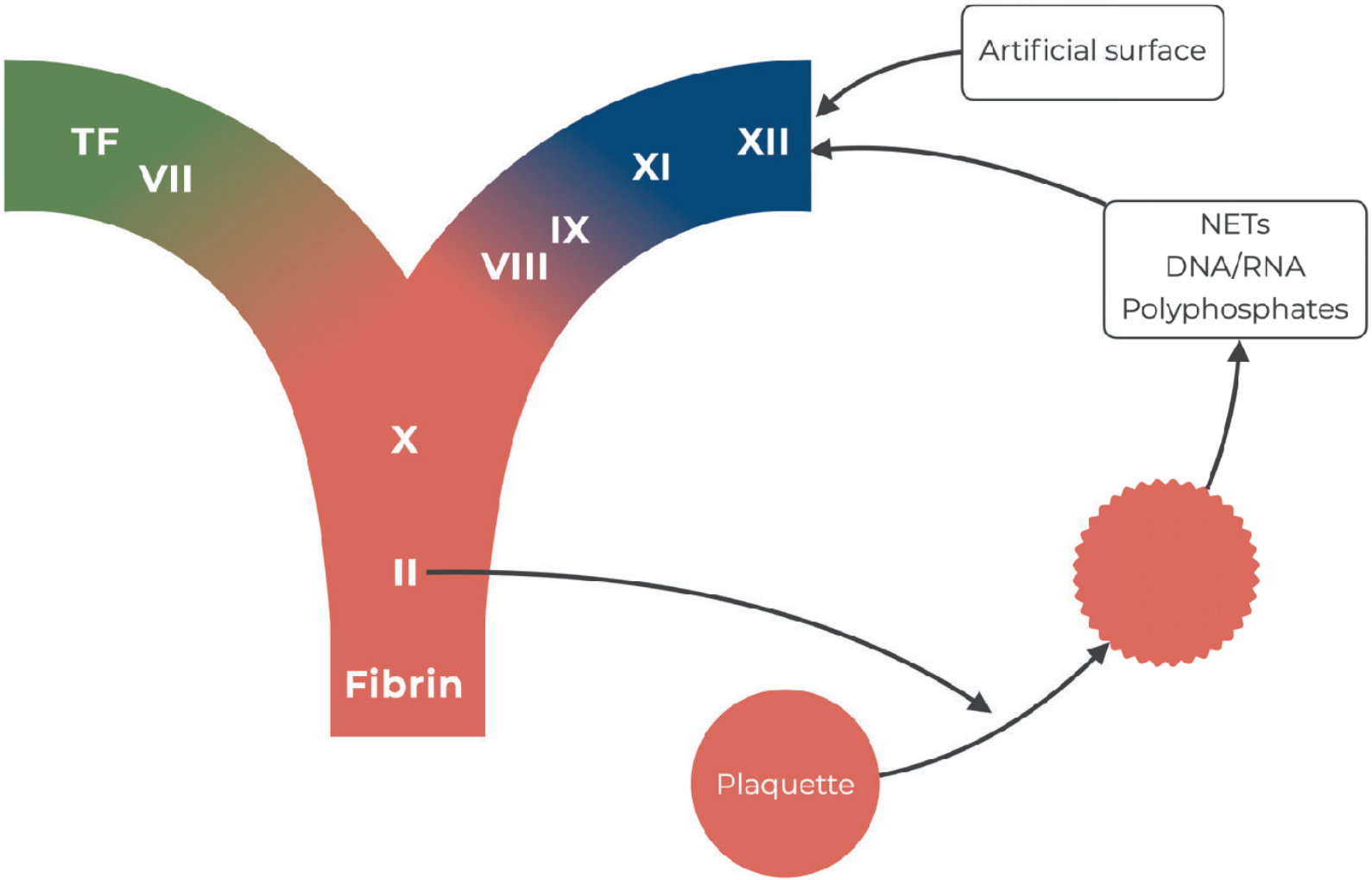
Passer à la BIVALIRUDINE ou l’ARGATROBAN

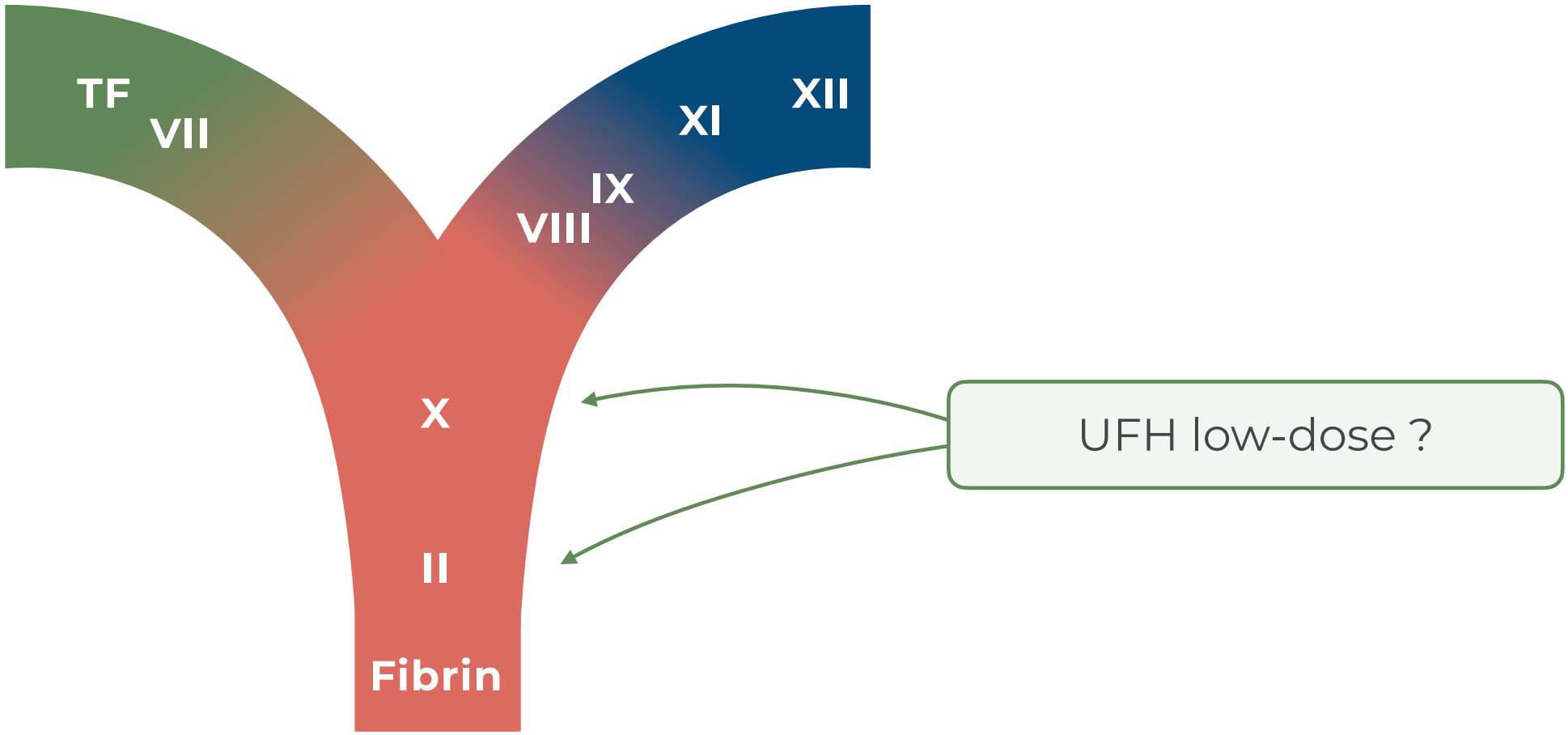
L’AVENIR ?

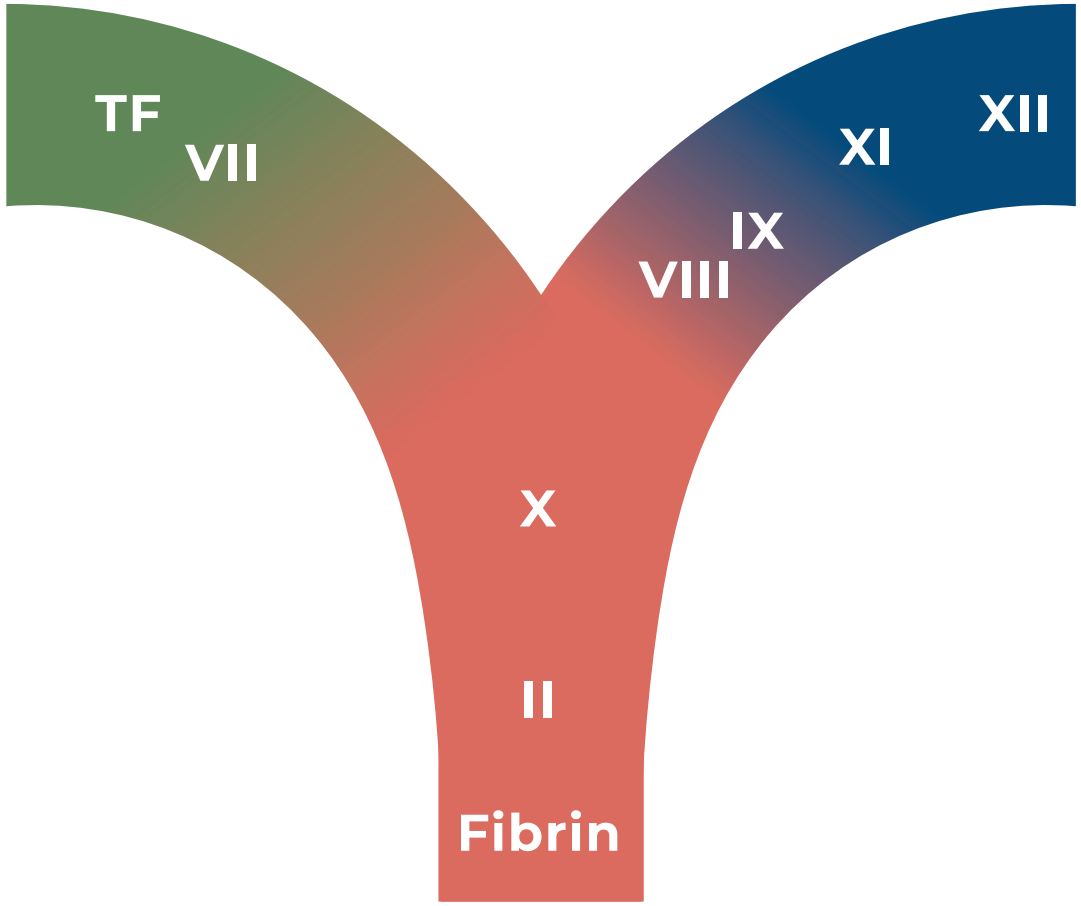
Surface modifications for better hemocompatibilty

	Bioactive Surfaces	Biopassive Surfaces	Endothelialization
Commercial	Heparin-Bound Circuit	Phosphorylcholine PMEA	
Under Development	Nitric Oxyde	Omniphobic	Pre-endothelialization Self-endothelialization

Ontaneda et al. Front. Med. 2018


Artificial surface
TF
VII
XI
XII
IX
VIII
NETs
DNA/RNA
Polyphosphates
X
II
Fibrin
Plaquette


TF
VII
XII
XI
IX
VIII
X
II
Fibrin
UFH low-dose ?



No anticoagulation ?

ECMO sans anti-coagulation ?

Feasibility of Venovenous Extracorporeal Membrane Oxygenation Without Systemic Anticoagulation

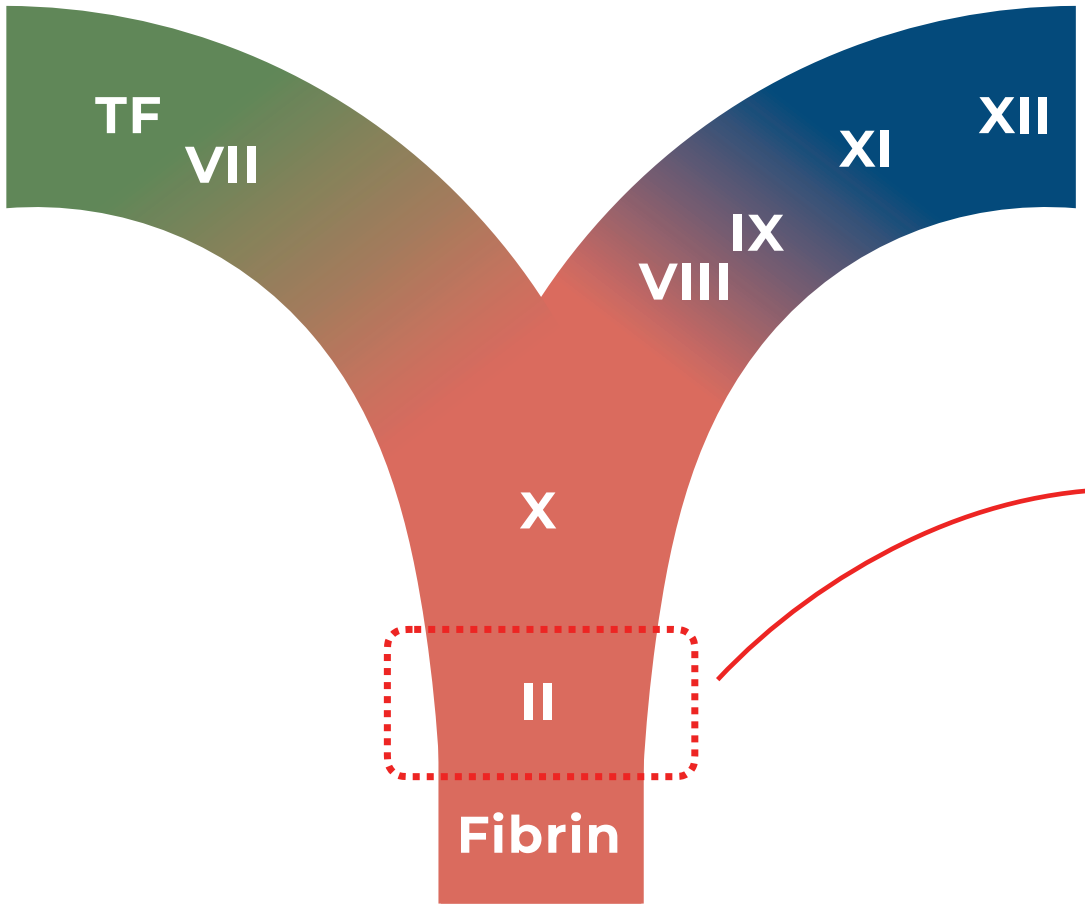
Chitaru Kurihara, MD, James M. Walter, MD, Azad Karim, MD, Sanket Thakkar, RRT-ACCS, Mark Saine, PA-C, David D. Odell, MD, Samuel Kim, MD, Rade Tomic, MD, Richard G. Wunderink, MD, G. R. Scott Budinger, MD, and Ankit Bharat, MD

Venoarterial-Extracorporeal Membrane Oxygenation Without Routine Systemic Anticoagulation Decreases Adverse Events

Katherine L. Wood, MD, Brian Ayers, MBA, Igor Gosev, MD, Neil Kumar, MD, Amber L. Melvin, MD, Bryan Barrus, MD, and Sunil Prasad, MD

Division of Cardiac Surgery, University of Rochester Medical Center, Rochester, New York

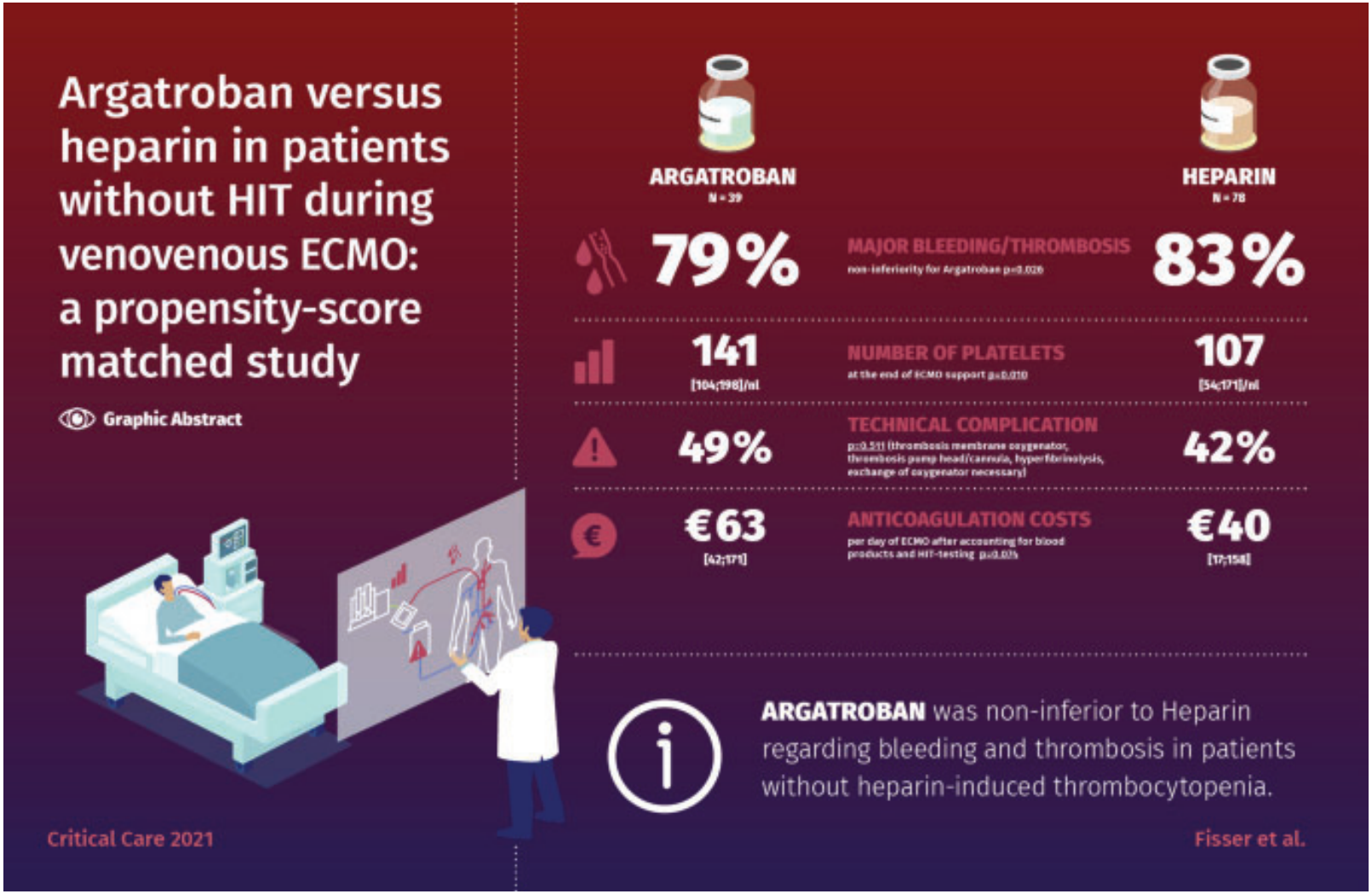
Wood et al. Ann Thorac Surg 2020
Kurihara et al. Ann Thorac Surg 2020



Direct Thrombin Inhibitors

Argatroban

Bivalirudin



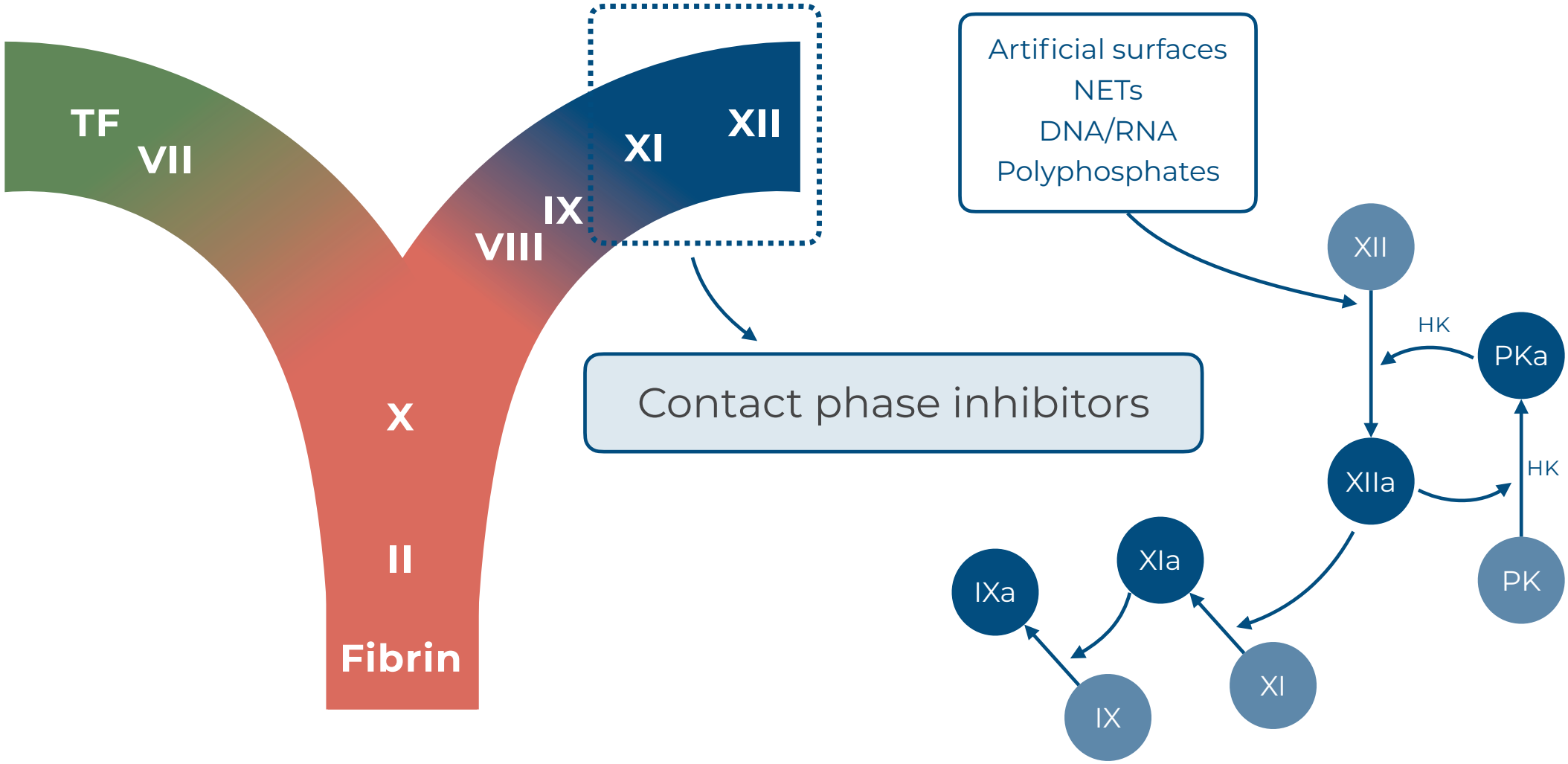
Fisser et al. Crit Care 2021

Comparison of Bivalirudin Versus Heparin for Maintenance Systemic Anticoagulation During Adult and Pediatric Extracorporeal Membrane Oxygenation

Comparison of Anticoagulation Strategies in Patients Requiring Venovenous Extracorporeal Membrane Oxygenation: Heparin Versus Bivalirudin*

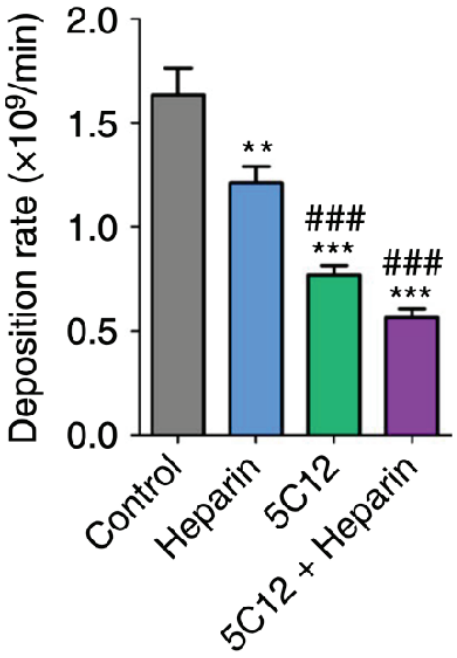
Rivosecchi et al. Crit Care Med 2021

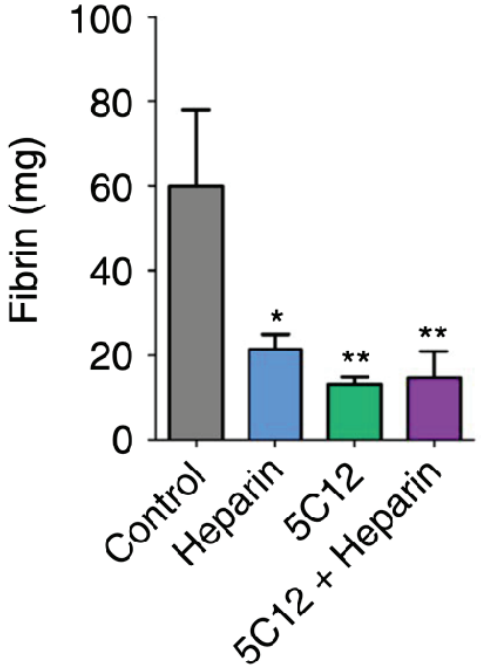
Seelhammer et al. Crit Care Med 2021

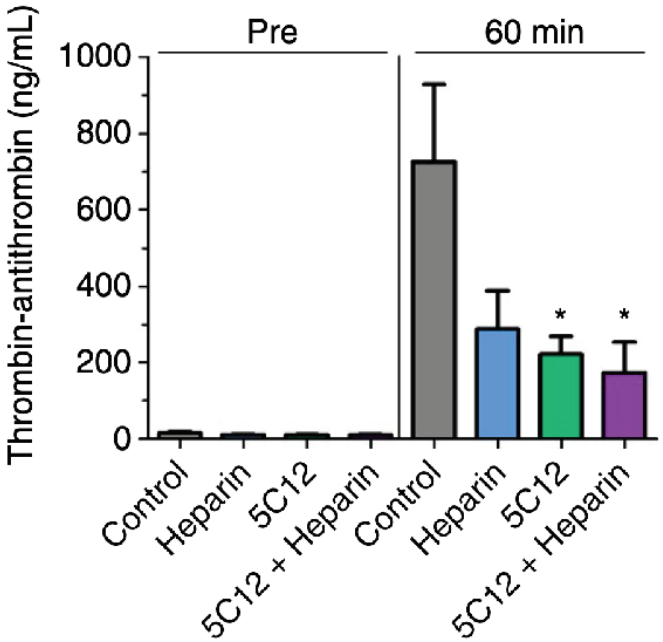

TF
VII
VIII
IX
XI
XII
X
II
Fibrin
Contact phase inhibitors
Artificial surfaces
NETs
DNA/RNA
Polyphosphates
XII
HK
PKa
XIIa
HK
PK
XIa
IXa
XI
IX

Antibody inhibition of contact factor XII reduces platelet deposition in a model of extracorporeal membrane oxygenator perfusion in nonhuman primates

5C12
Monoclonal antibody
FXII/FXIIa inhibitor



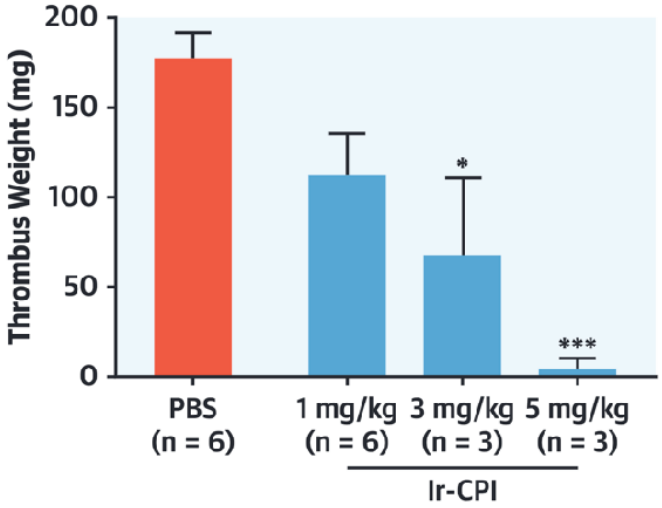


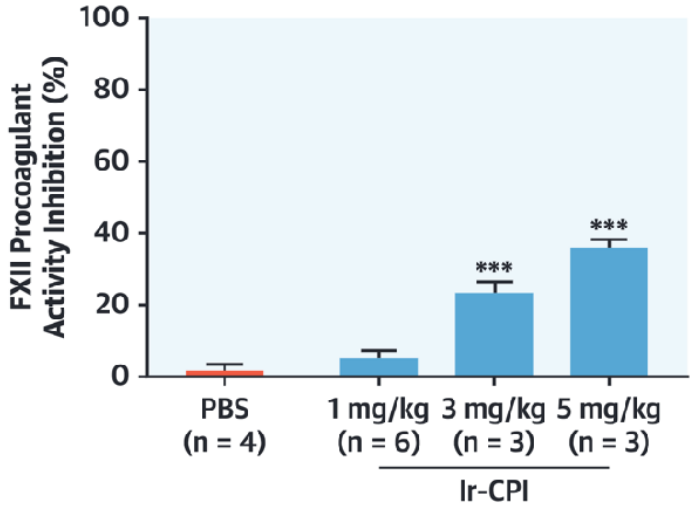


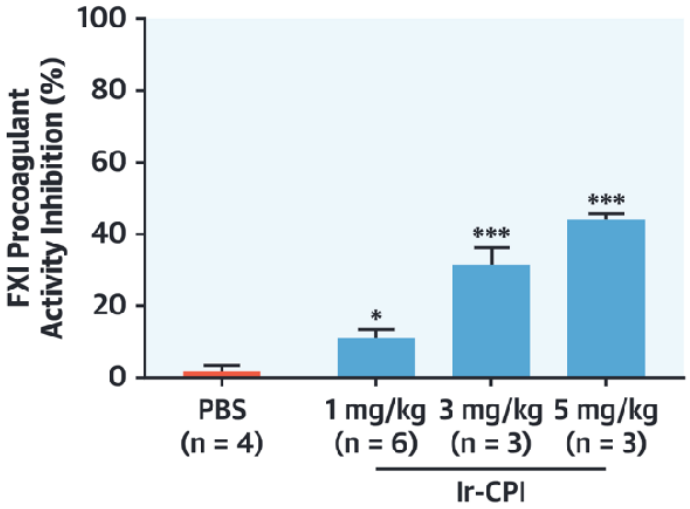
Wallis et al. RPTH 2019

Anticoagulation With an Inhibitor of Factors XIa and XIIa During Cardiopulmonary Bypass

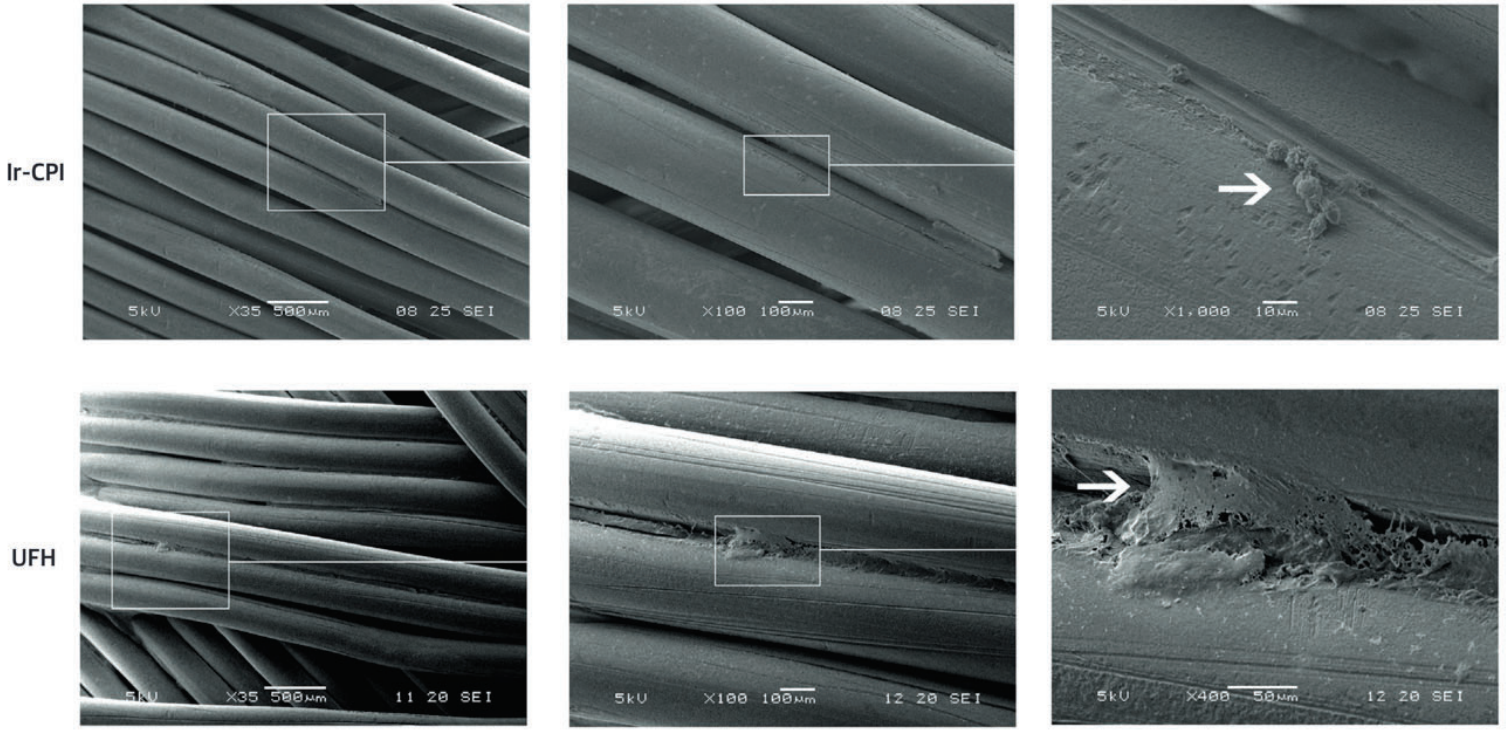
Ixodes ricinus contact phase inhibitor (Ir-CPI)
FXIa and FXIIa inhibitor
Intravenous

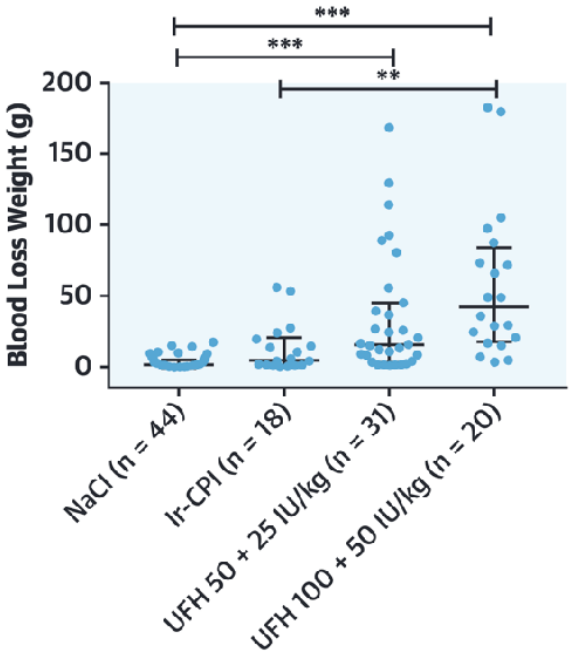






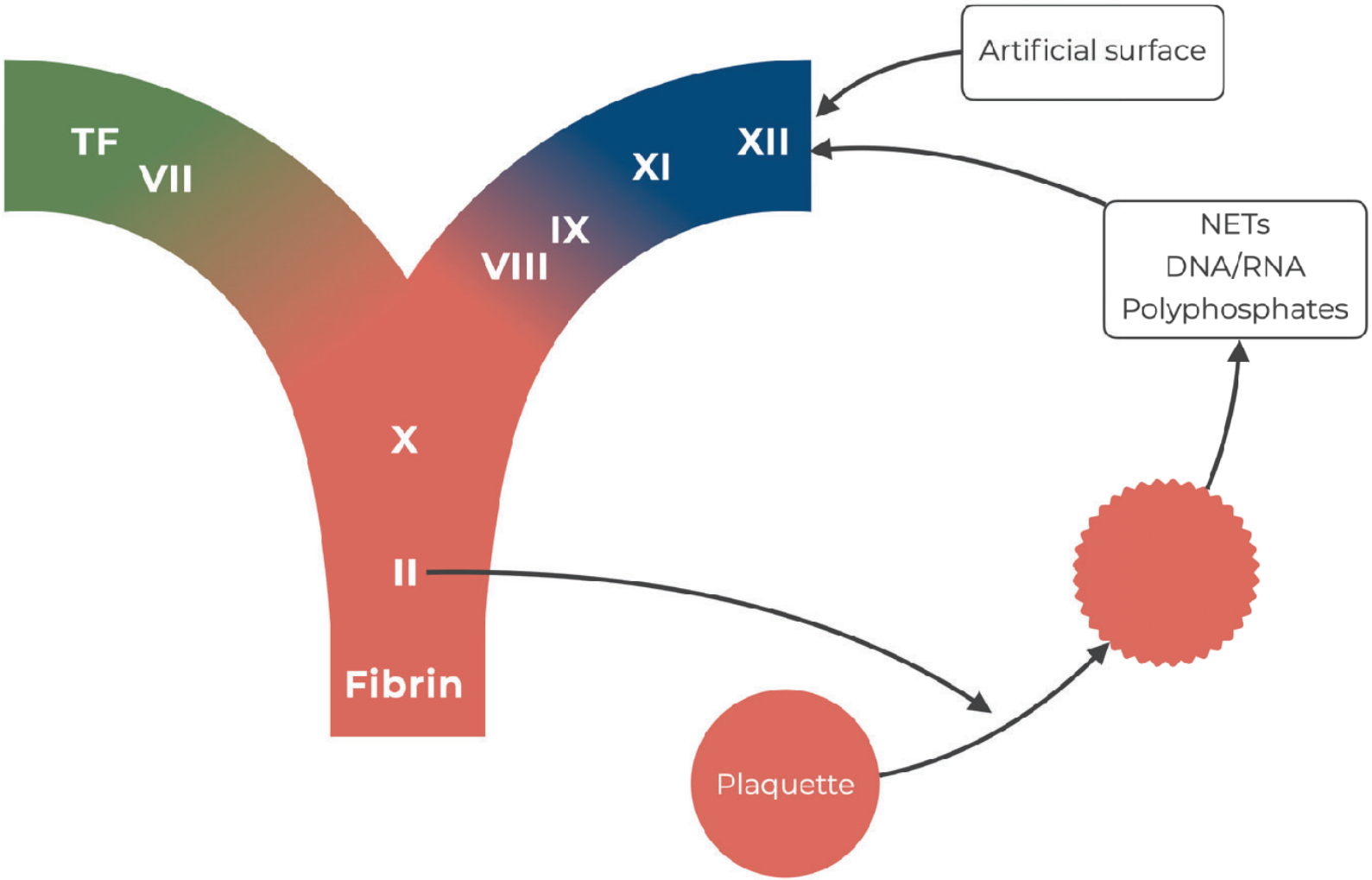
Pireaux et al. JACC 2019





Pireaux et al. JACC 2019

Agents antiplaquettaires ?



LETTER TO THE EDITOR

Artificial Organs

WILEY

Use of cangrelor during venoarterial extracorporeal membrane oxygenation following percutaneous coronary intervention

Clinical Use of Cangrelor After Percutaneous Coronary Intervention in Patients Requiring Mechanical Circulatory Support

Annals of Pharmacotherapy
1–8

DOI: 10.1177/1060028021994621
journals.sagepub.com/home/aop
SAGE

Katz et al. Annals of Pharmacotherapy, 55(10), 1215–1222
Ciolek, et al. Artificial Organs. doi:10.1111/aor.13563

PHRC-N IMPACT-VA

IMProving AntiCoagulation Therapy during VA-ECMO support

A prospective multicenter, three-arm, randomized, open-label, blinded end-point, superiority trial to assess the efficacy and safety of an anticoagulation strategy using low-dose of UFH or argatroban compared to therapeutic-dose of UFH in adult patients supported by venoarterial extracorporeal membrane oxygenation

HYPOTHESIS

Anticoagulation using argatroban or low-dose UFH during adult VA-ECMO could be associated with a reduced incidence of major bleeding complications without increasing thrombotic events, compared to therapeutic-dose UFH.

OBJECTIVE

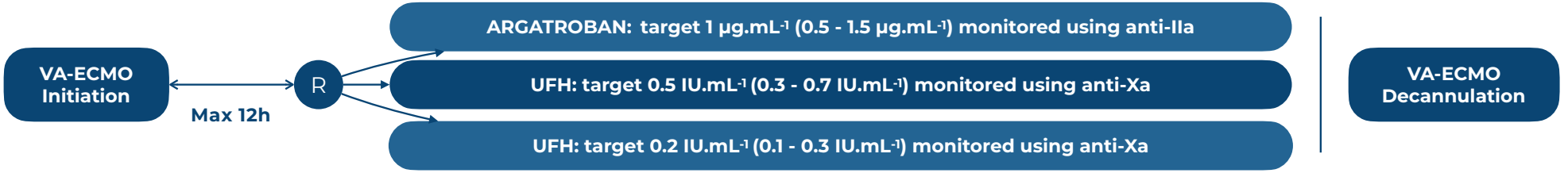
Evaluate the superiority of an anticoagulation strategy using low-dose UFH or argatroban compared to therapeutic-dose UFH on a composite ranked outcome including mortality, bleeding events and thrombotic events.

INCLUSION CRITERIA

Age ≥ 18-year-old
First VA-ECMO run
VA-ECMO cannulation for less than 12 hours

NON-INCLUSION CRITERIA

History of heparin-induced thrombocytopenia
Child-Pugh score C or ALF (AST/ALT > 20N and/or SOFA score liver ≥ 3)
ECMO for severe PE or ECPR (pre-hospital and/or CPR ≥ 30 min)
Contraindication for anticoagulation (e.g. overt bleeding, PLT <50G/L)
Formal indication of therapeutic anticoagulation
Moribund patient with expected life expectancy <24 hours



PRIMARY OUTCOME

Composite ranked outcome of: 30-day all-cause mortality (Rank 1); major bleeding (BARC≥ 3) or thrombotic events (Rank 2); non-major bleeding (BARC = 2) or thrombotic events (Rank 3)

SAMPLE SIZE

684 patients (228 in each arm)

Conlusions / Points Clés

- Très haut risque hémorragique / haut risque thrombotique
- Impact majeur morbidité / mortalité
- Partiellement dépendant du terrain et du niveau d'anticoagulation
- Coagulation / Plaquettes / Willebrand / Fibrinolyse / Endothelium …
- Recommendations actuelles : UFH, anti-Xa > TCA, cible curative 0.3-0.5

Besoin d'études prospectives +++

Avenir : UFH poso faible ? Pas d'AC ? DTI ? AAP ? Phase contact ?

DU CEC 2025

PHYSIOPATHOLOGIE DE L'HÉMOSTASE SOUS ECMO

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