Hémorragie sous ECMO

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Conflicts of interest

Fabienne NEDELEC-GAC

1 – Titulaire de brevets/Porteur de parts sociales ou membre d'une structure de gouvernance ou salarié	Aucun
2 – Consultant ou membre d'un Conseil scientifique	Aucun
3 – Conférencier ou auteur/rédacteur rémunéré d'articles ou documents	Aucun
4 – Prise en charge de frais de voyages, d'hébergement ou d'inscription à des congrès ou autres manifestations	LFB
5 – Investigateur principal d'une recherche ou d'une étude clinique	Aucun
6 – Co-Investigateur d'une étude clinique	Aucun

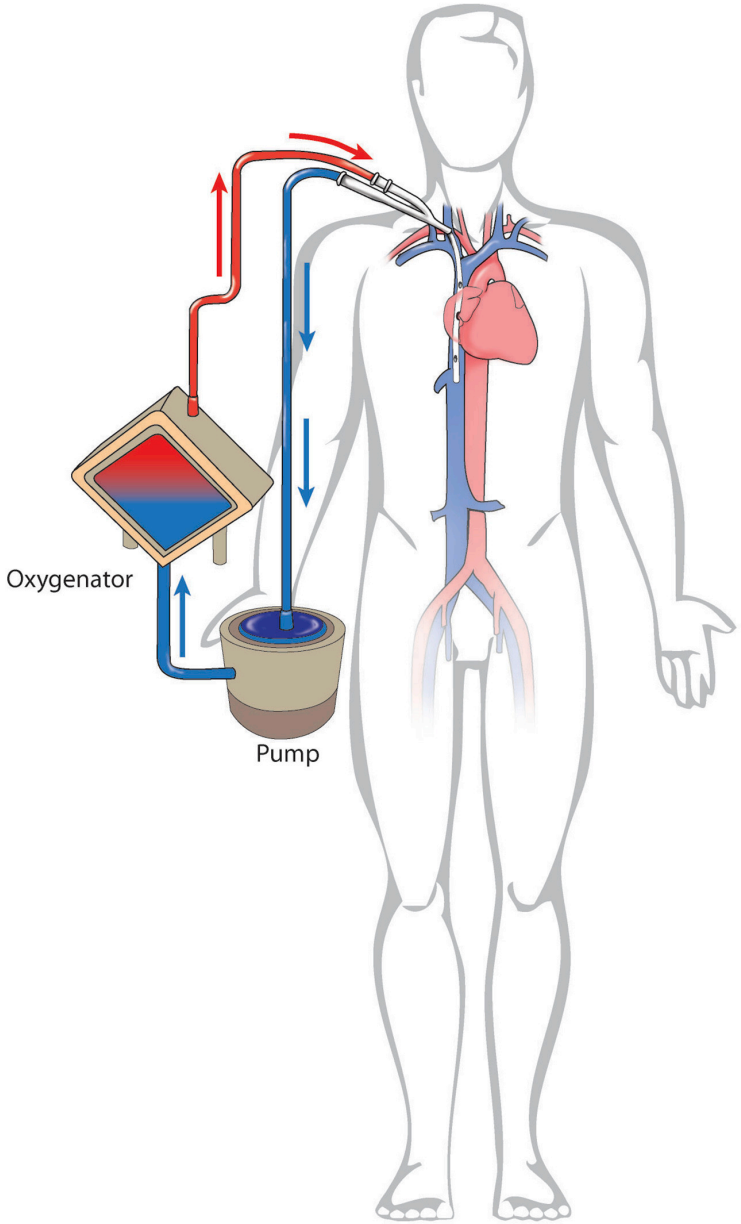
Conflicts of interest

Alexandre MANSOUR

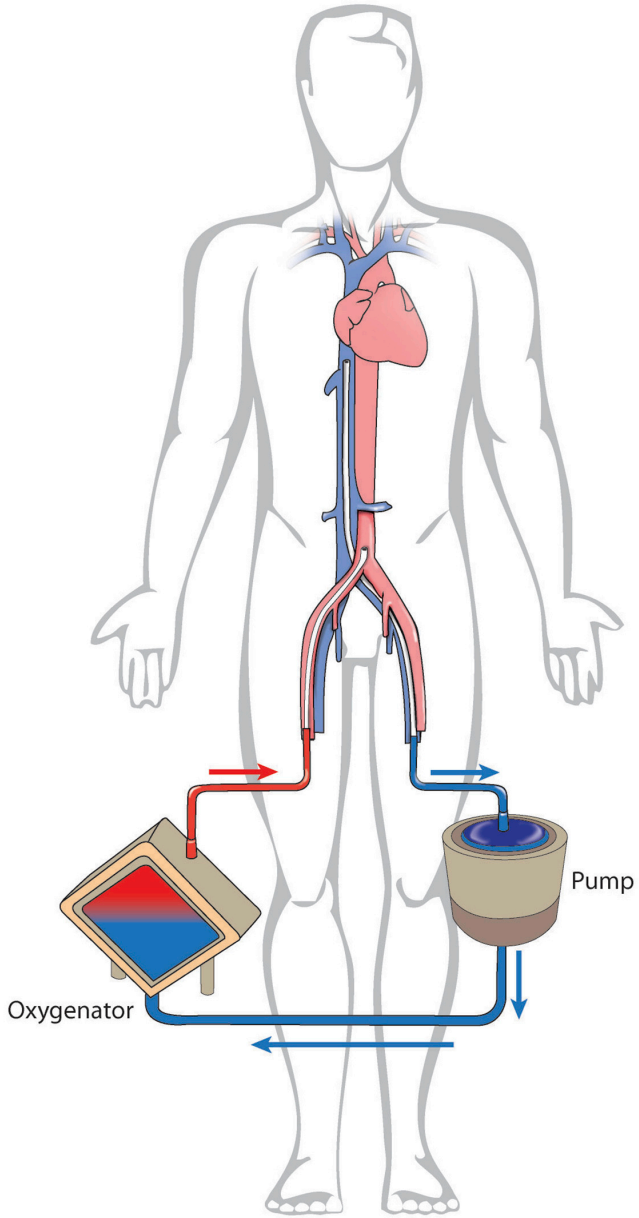
1 – Titulaire de brevets/Porteur de parts sociales ou membre d'une structure de gouvernance ou salarié	Aucun
2 – Consultant ou membre d'un Conseil scientifique	I-SEP
3 – Conférencier ou auteur/rédacteur rémunéré d'articles ou documents	Aucun
4 – Prise en charge de frais de voyages, d'hébergement ou d'inscription à des congrès ou autres manifestations	AbbVie, I-SEP, LFB
5 – Investigateur principal d'une recherche ou d'une étude clinique	I-SEP
6 – Co-Investigateur d'une étude clinique	Aucun

ECMO/ECLS

VV-ECMO



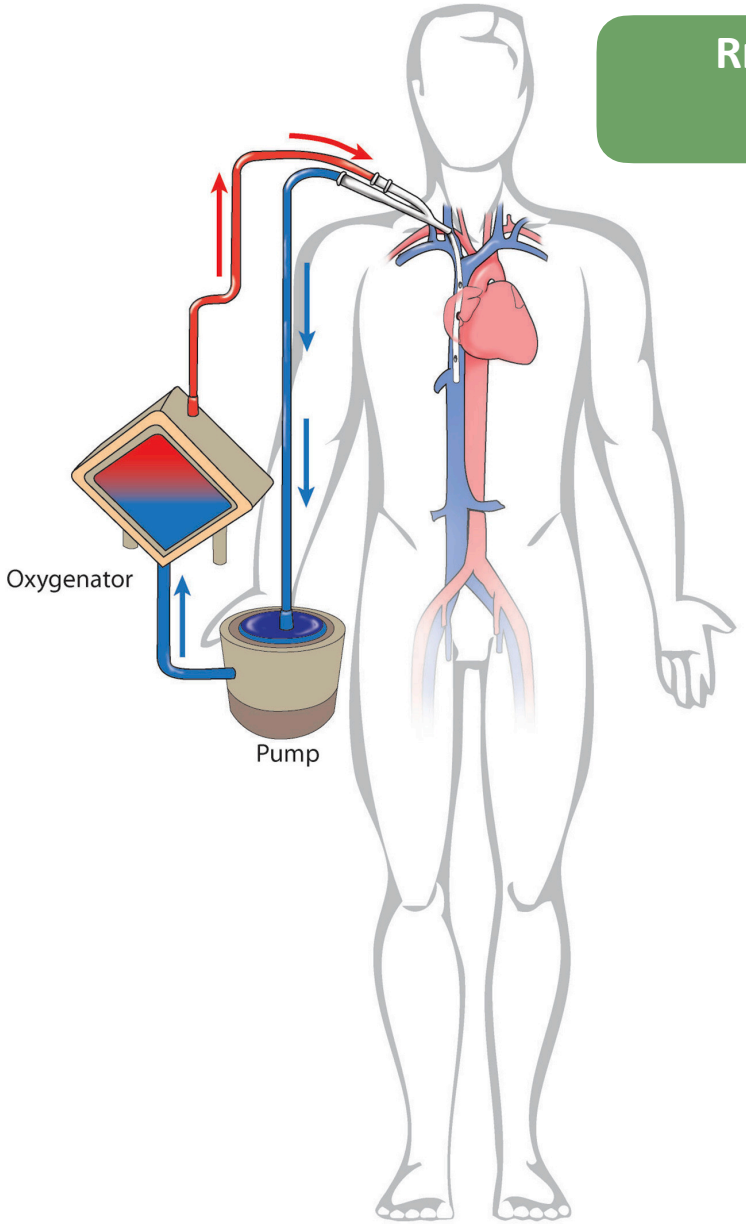
VA-ECMO



Squiers et al. JTCVS 2016

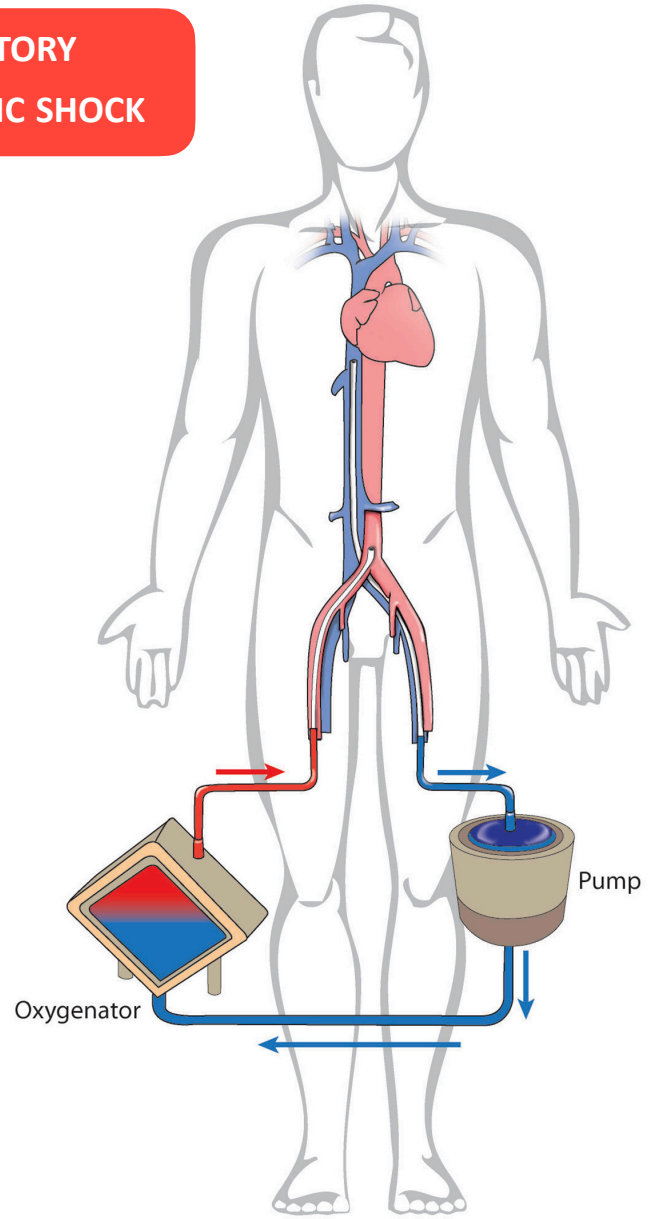
VV-ECMO

Refractory ARDS



VA-ECMO

Refractory Cardiogenic shock



Squiers et al. JTCVS 2016

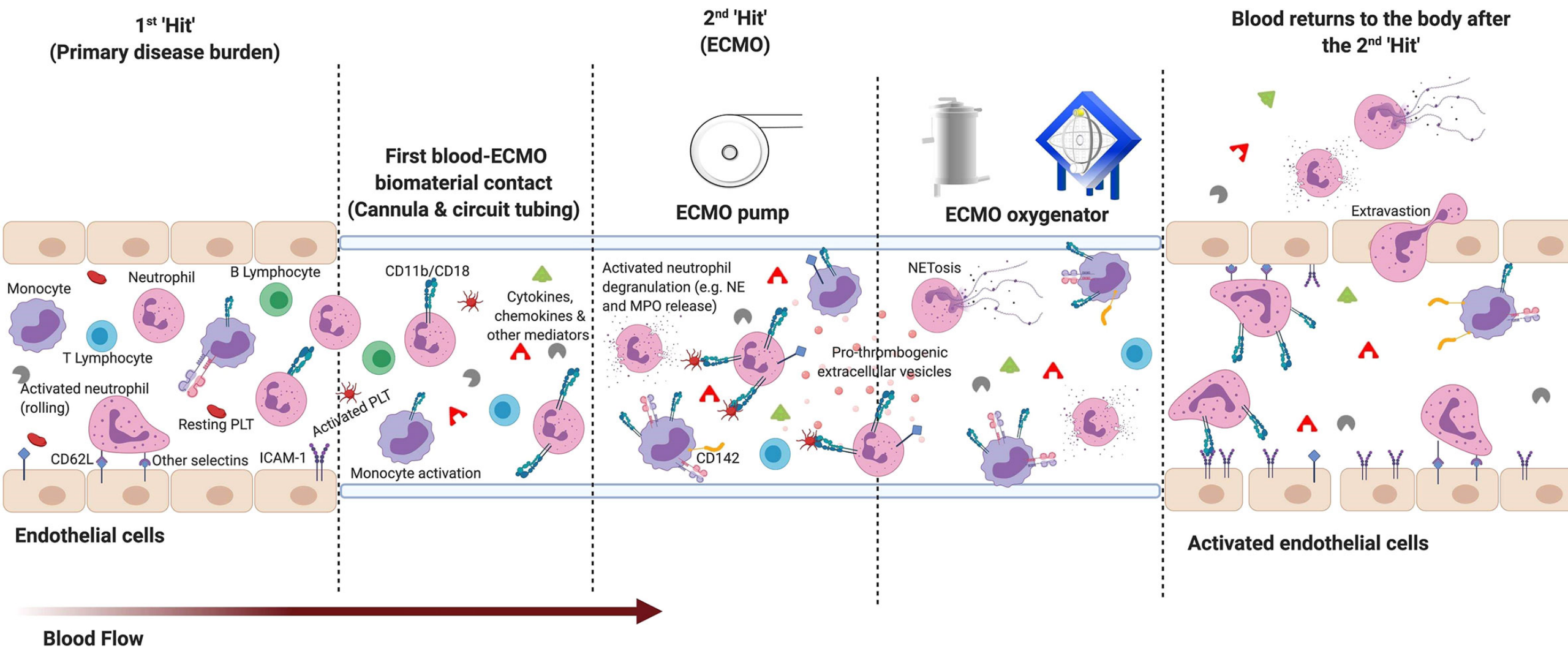
Inflammatory response to ECMO/ECLS

- Continuous flow
  Shear
- Blood-biomaterial interactions
- Sepsis
- Surgery
  CPB
- Hypoxemia
  shock

→

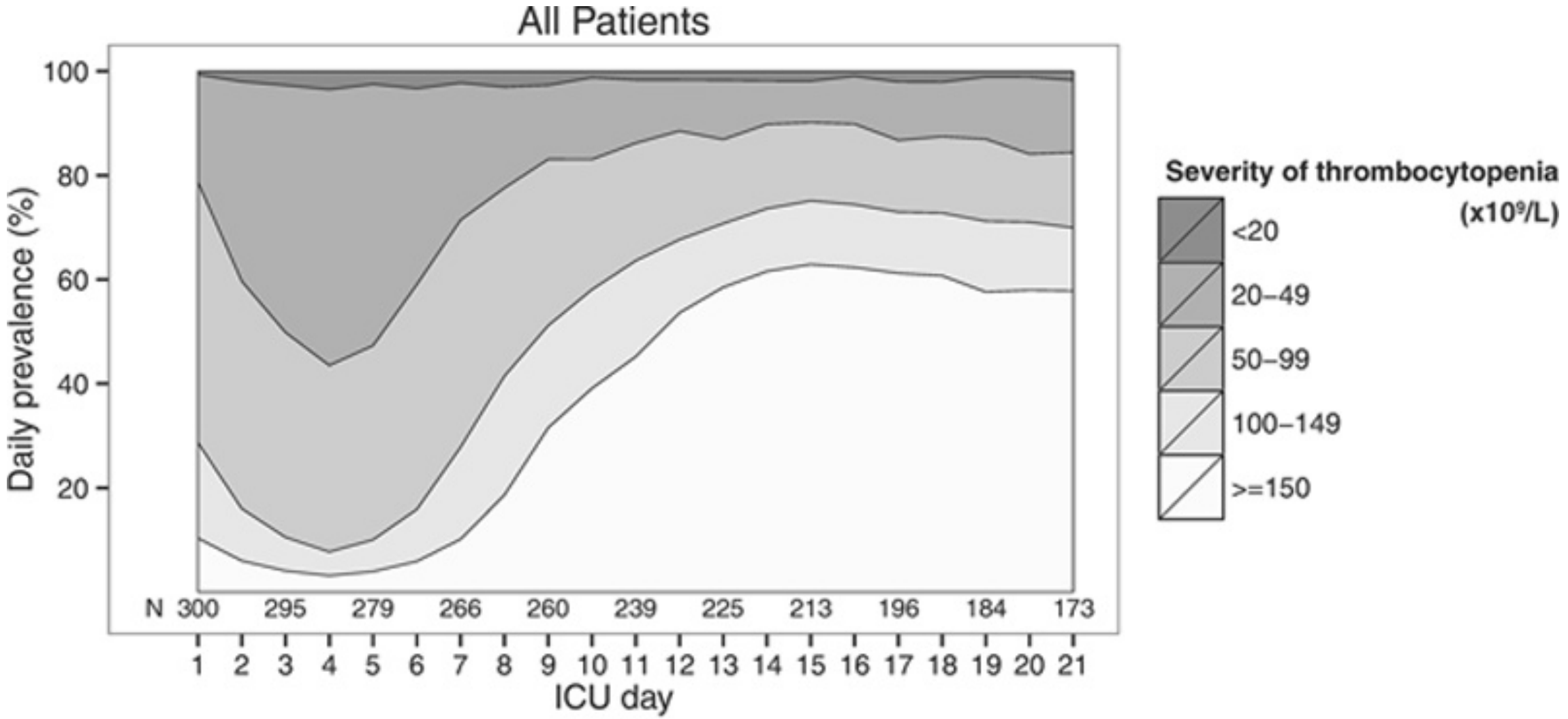
- Coagulation activation
- Complement activation
  Cytokines release
- Platelet activation
- Endothelial activation
- Leukocytes activation

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



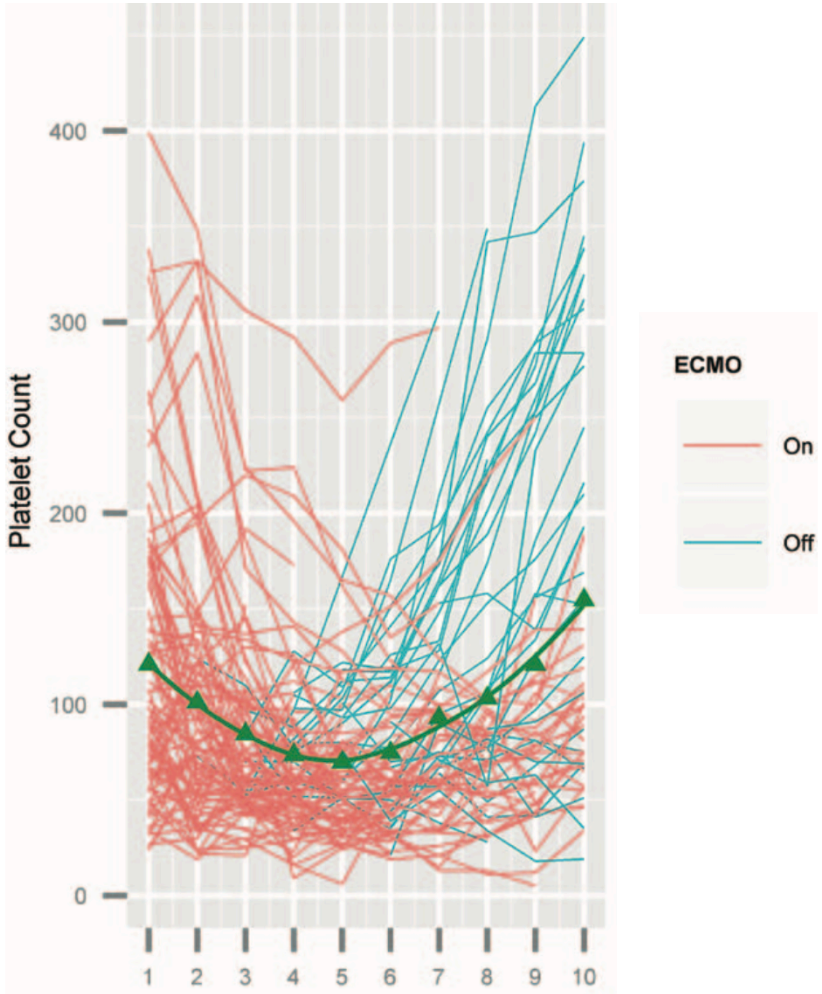
Ki et al. Front Immunol. 2021

Thrombocytopenia under ECMO



Opfermann et al. Crit Care Med 2016

Thrombocytopenia under ECMO



Sokolovic et al. CCM 2016

Systemic anticoagulation : Unfractionated Heparin !

Hemocompatibility-Related Adverse Events and Survival on Venoarterial Extracorporeal Life Support

An ELSO Registry Analysis

- ELSO registry
- 11 984 VA-ECMO
- Bleeding : 33% patients
- Thrombosis : 20% patients

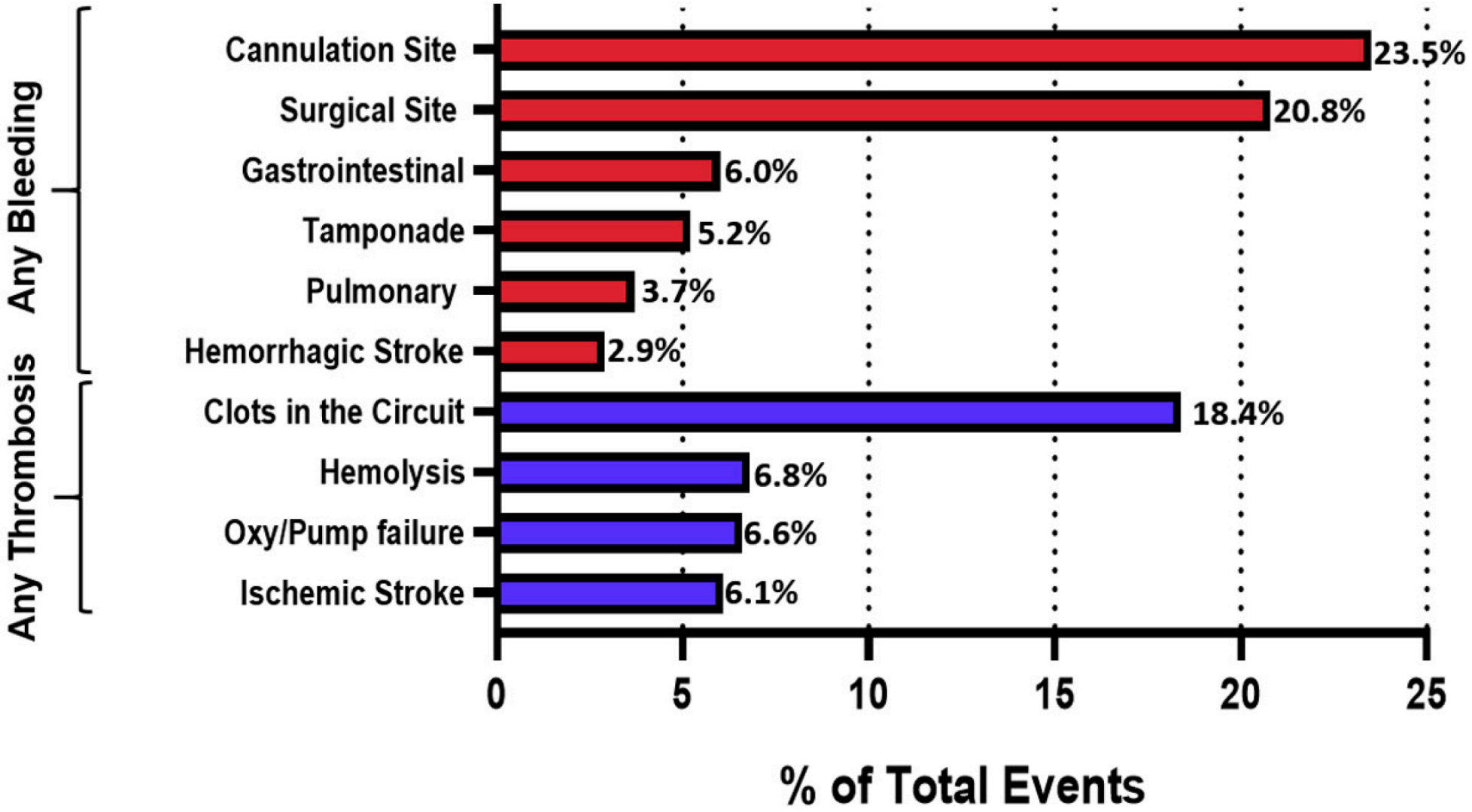
Chung et al. JACC Heart Failure 2020

Patient Hemorrhagic Complications

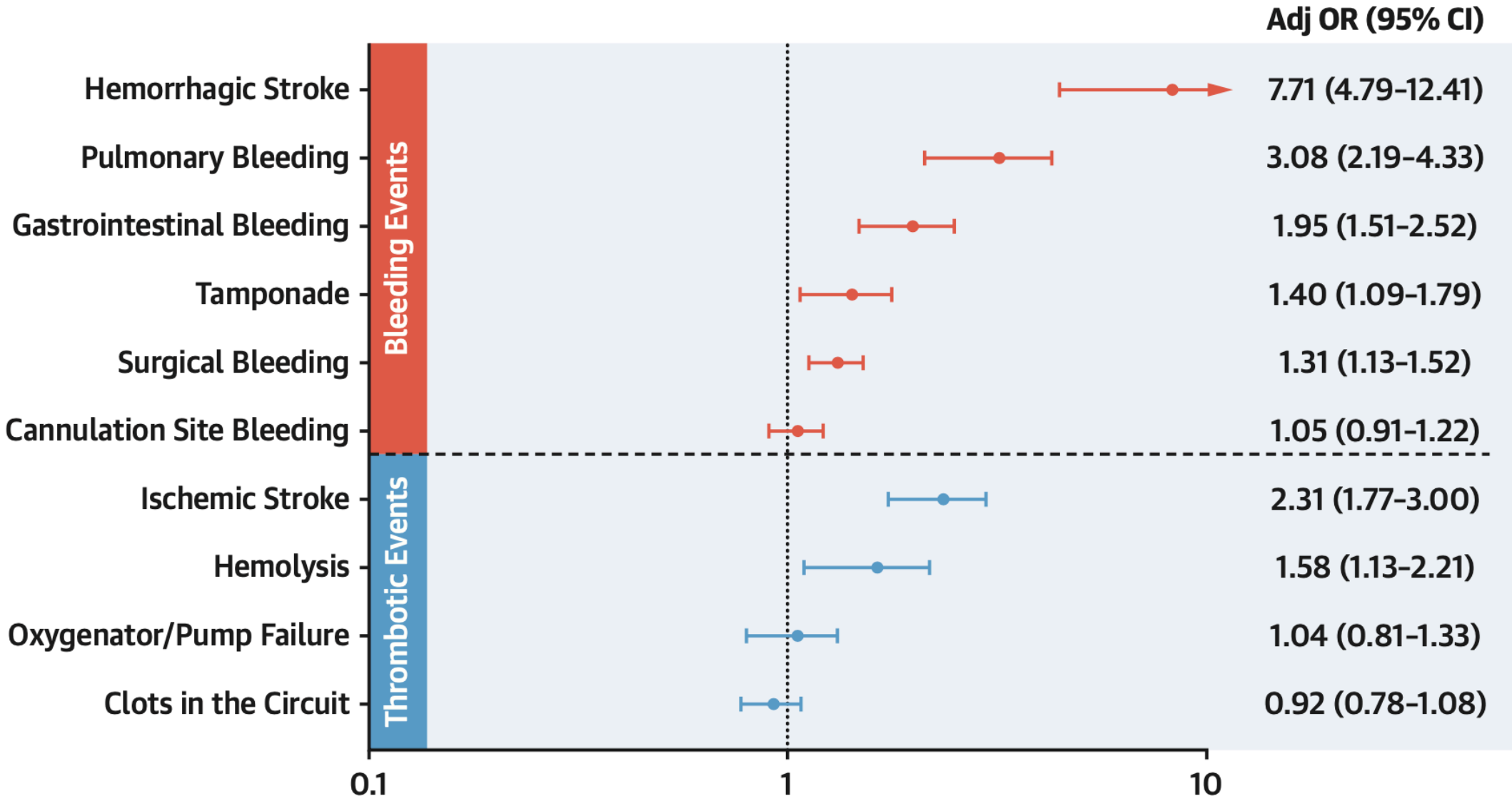
Hemorrhagic complications requiring packed red blood cell or whole blood (PRBC) transfusion (>20ml/kg/calendar day of PRBCS or >3U PRBCs/calendar day in neonates and pediatrics and >3U PRBCS/calendar day in adults) or other intervention such as surgical or endoscopic intervention.

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

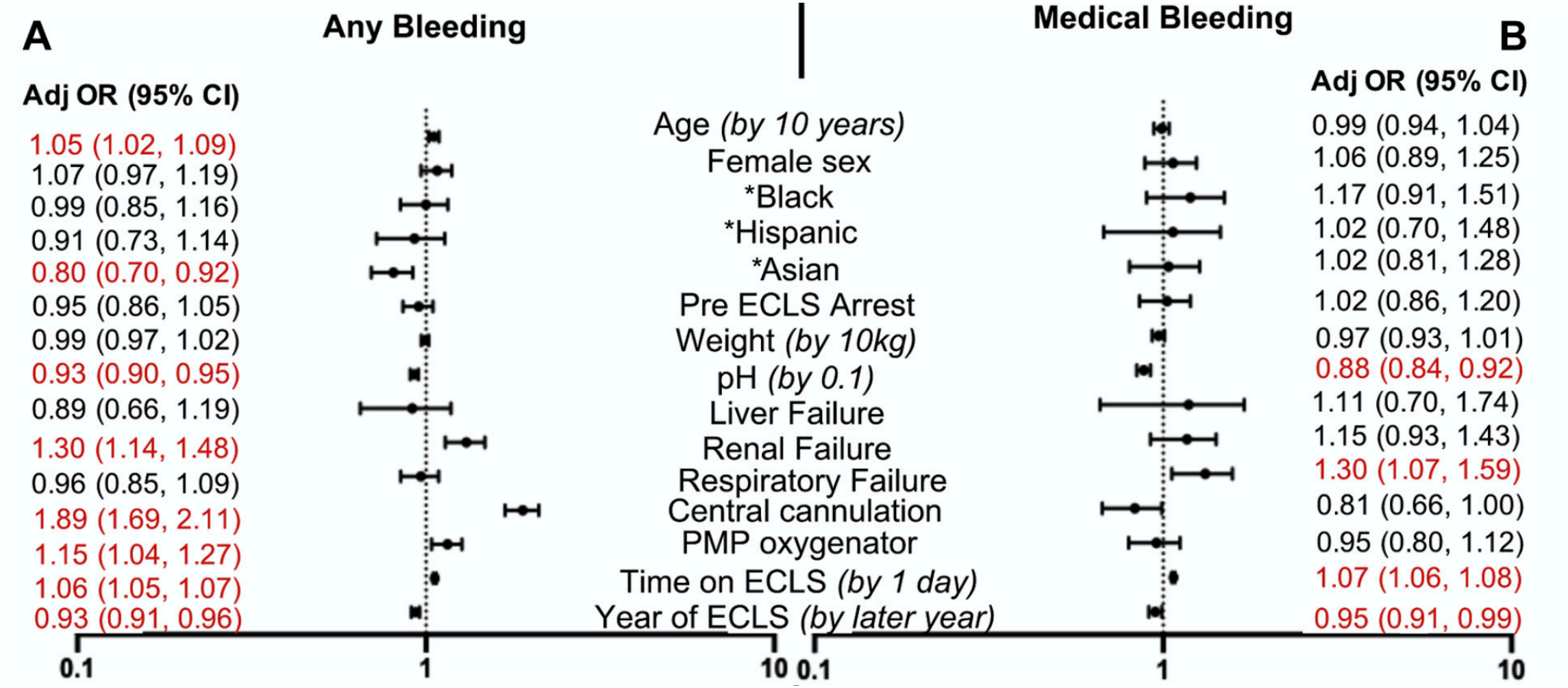
ELSO registry definition 02/2021



Chung et al. JACC Heart Failure 2020



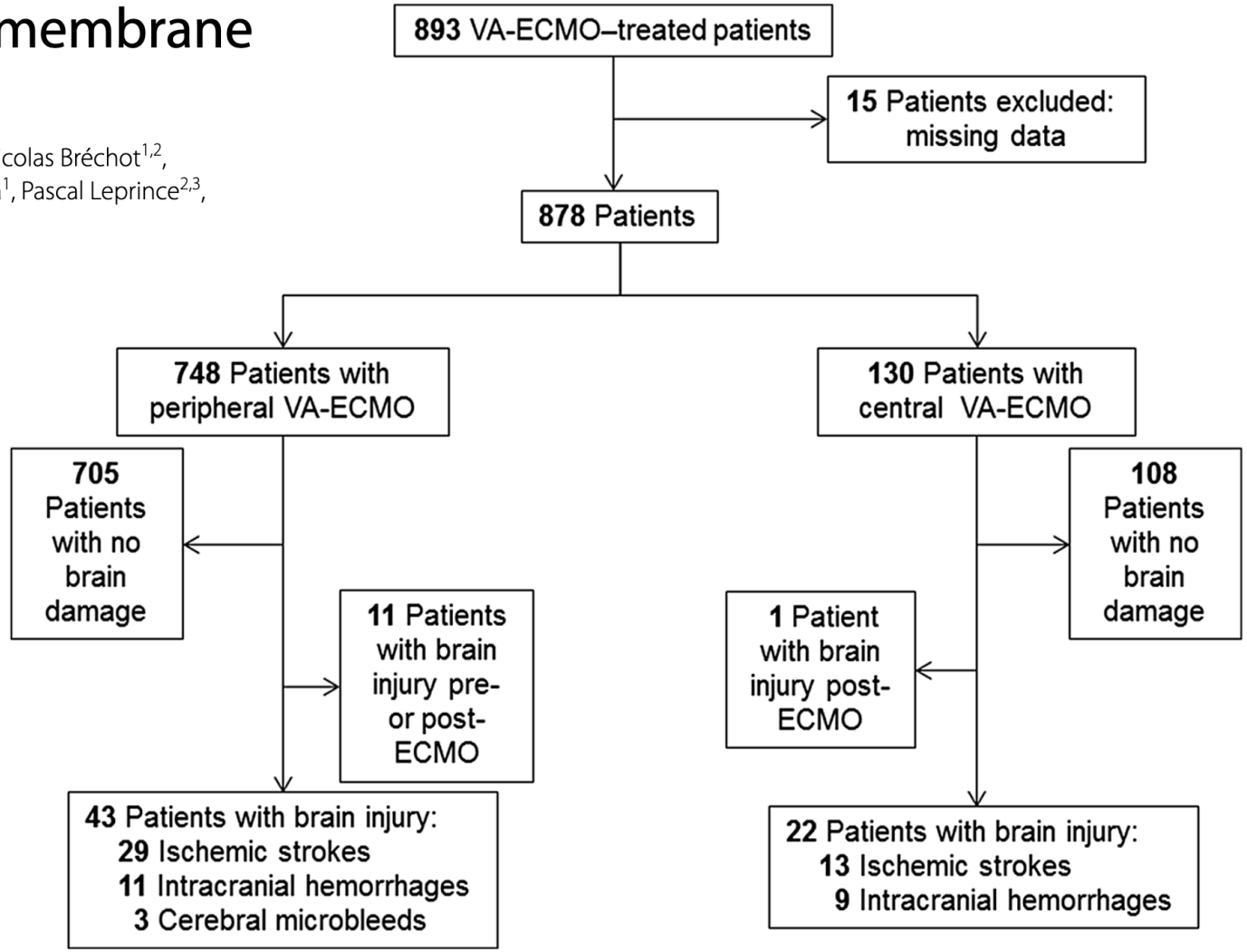
Chung et al. JACC Heart Failure 2020



Chung et al. JACC Heart Failure 2020

Ischemic and hemorrhagic brain injury during venoarterial-extracorporeal membrane oxygenation

Loïc Le Guennec[1*], Clémentine Cholet[1], Florent Huang[1], Matthieu Schmidt[1,2], Nicolas Bréchot[1,2], Guillaume Hékimian[1], Sébastien Besset[1], Guillaume Lebreton[2,3], Ania Nieszkowska[1], Pascal Leprince[2,3], Alain Combes[1,2] and Charles-Edouard Luyt[1,2]



Le Guennec et al. Ann. Intensive Care 2018

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		

Le Guennec et al. Ann. Intensive Care 2018

135 VV-ECMO
ICH : 7,5 %

Factor	Univariable analysis, OR [95 % CI]	Cox analysis, HR [95 % CI]
Age >46 years	1.91 [0.51–7.10]	
Female sex	2.02 [0.55–7.41]	
SAPS II score at ICU admission ≥70	1.16 [0.32–4.19]	
Body mass index >26	0.47 [0.1–1.96]	
McCabe and Jackson comorbidity score ≥2	0.46 [0.09–2.24]	
MV duration before ECMO >5 days	1.68 [0.45–6.24]	
Organ failure at ECMO initiation[a]		
Cardiovascular	0.73 [0.15–3.60]	
Hepatic	2.74 [0.69–10.95]	
Renal	5.80 [1.18–28.47]	6.13 [1.29–28.57]
Hematological	0.81 [0.09–6.83]	
Neurological	1.05 [0.21–5.25]	
Gas exchange change		
Arterial pH >0.2[b]	2.34 [0.61–8.89]	
PaO_2 >50 mmHg[b]	4.44 [1.16–17.03]	
$PaCO_2$ <–27 mmHg[b]	5.95 [1.20–29.52]	6.02 [1.28–28.57]
Renal replacement therapy	1.26 [0.34–4.68]	
Hemostasis disorders during ECMO		
Platelets <20 × 10^9/L	1.31 [0.26–6.62]	
Prothrombin time <30 %[c], *n* (%)	0.52 [0.06–4.33]	
Fibrinogen, <1.5 g/L	0.76 [0.15–3.76]	
Anticoagulant overdose	–	

Luyt et al. Intensive Care Med 2016

Impact of major bleeding and thrombosis on 180-day survival in patients with severe COVID-19 supported with veno-venous extracorporeal membrane oxygenation in the United Kingdom: a multicentre observational study

Complication	n = (152)	Alive (n = 107)	Dead (n = 45)	Crude time-adjusted HR (95% CI)	Time-adjusted HR* (95% CI)
Major bleeding	**47 (30·9%)**	**23 (48·9%)**	**24 (51·1%)**	**3·01 (1·63–5·51)**	**3·87 (2·10–7·23)**
ICH	**16 (34%)**	**6 (37·5%)**	**10 (62·5%)**	**3·30 (1·36–7·76)**	**5·97 (2·36–15·04)**
GI	5 (11%)	2 (40%)	3 (60%)		
Other	3 (6%)	2 (66%)	1 (33%)		
Pulmonary haemorrhage	12 (26%)	5 (41·7%)	7 (58·3%)		
>1 Bleeding site	11 (23%)	8 (72·7%)	3 (27·3%)		
Venous thrombosis	68 (44·7%)	48 (70·6%)	20 (29·4%)	1·14 (0·61–2·14)	1·63 (0·94–3·04)
PE	**45 (66·2%)**	**28 (26·2%)**	**17 (37·8%)**	**2·12 (1·19–3·76)**	**2·00 (1·09–3·56)**
DVT	13 (19·1%)	11 (84·6%)	2 (15·4%)		
PE and DVT	10 (14·7%)	9 (90%)	1 (10%)		
Arterial thrombosis	**13 (8·6%)**	**6 (46·2%)**	**7 (53·8%)**	**1·74 (1·24–6·14)**	**1·70 (0·71–3·92)**
ECMO circuit thrombosis	15 (9·9%)	12 (80·0%)	3 (20·0%)	0·92 (0·26–3·04)	0·79 (0·34–2·78)

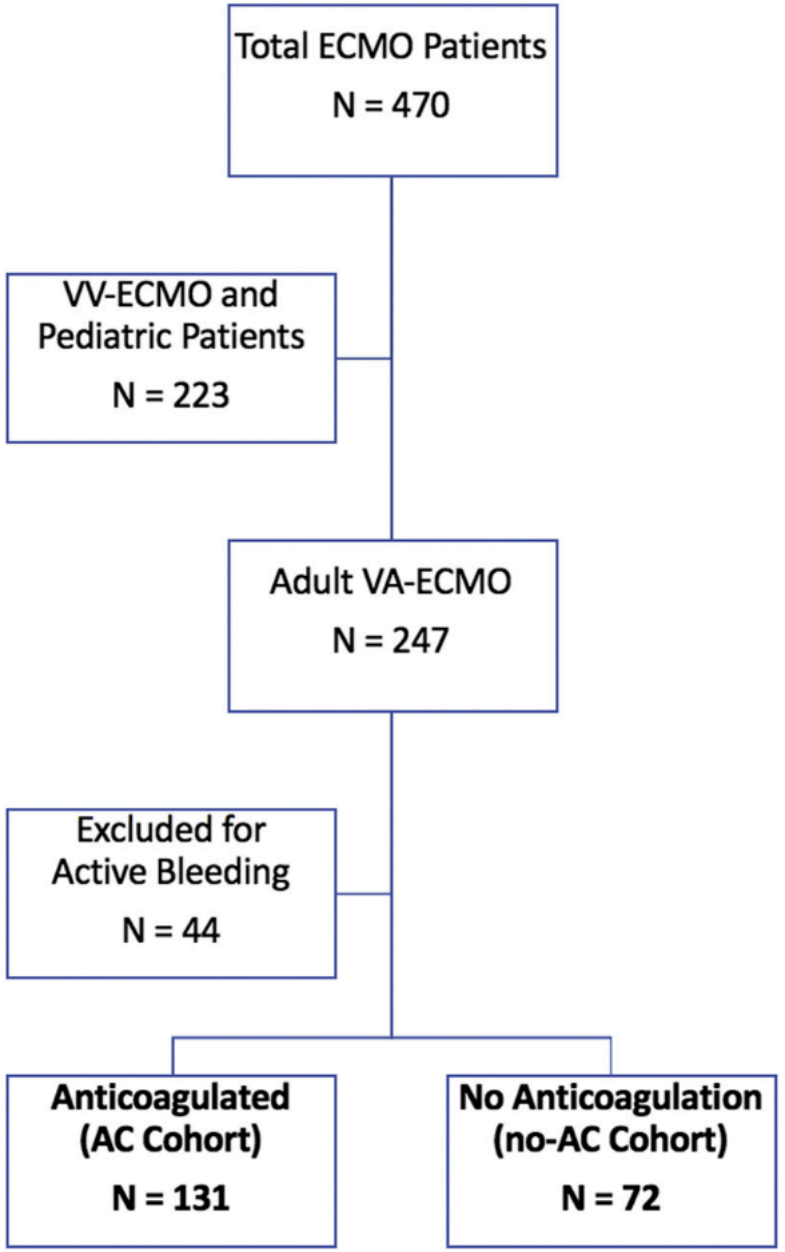
Arachchillage et al. BJH 2021

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

Wood et al. Ann Thorac Surg 2020

Anticoagulation Protocol CHU Rennes

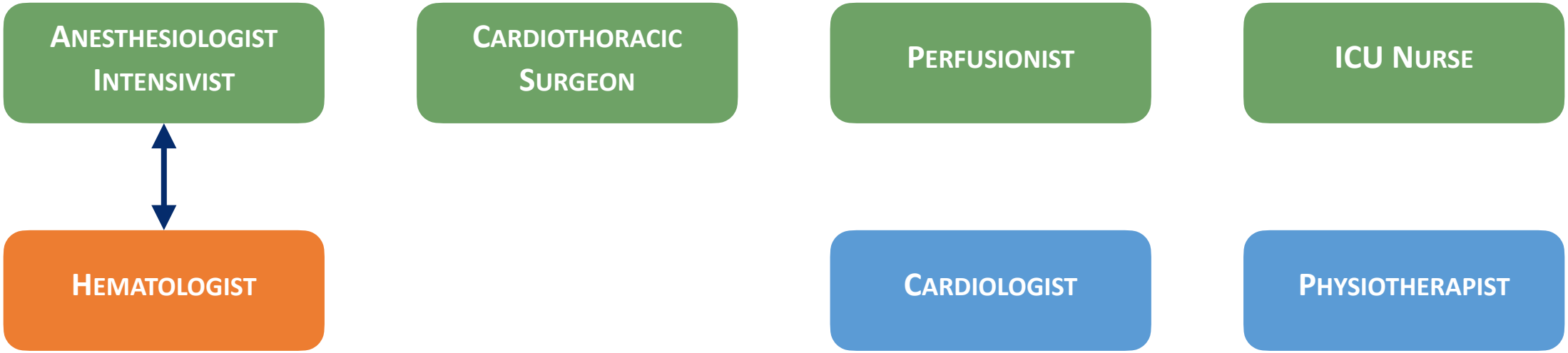
- IV UFH
- antiXa UFH /4h

- 3 clinical situations :
  - Very high bleeding risk : UFH suspension, ECMO Flow >2l/min
  - Bleeding risk = thrombotic risk : antiXa 0,15-0,3
  - Thrombotic risk > bleeding risk : antiXa 0,3-0,5

ECMO Team

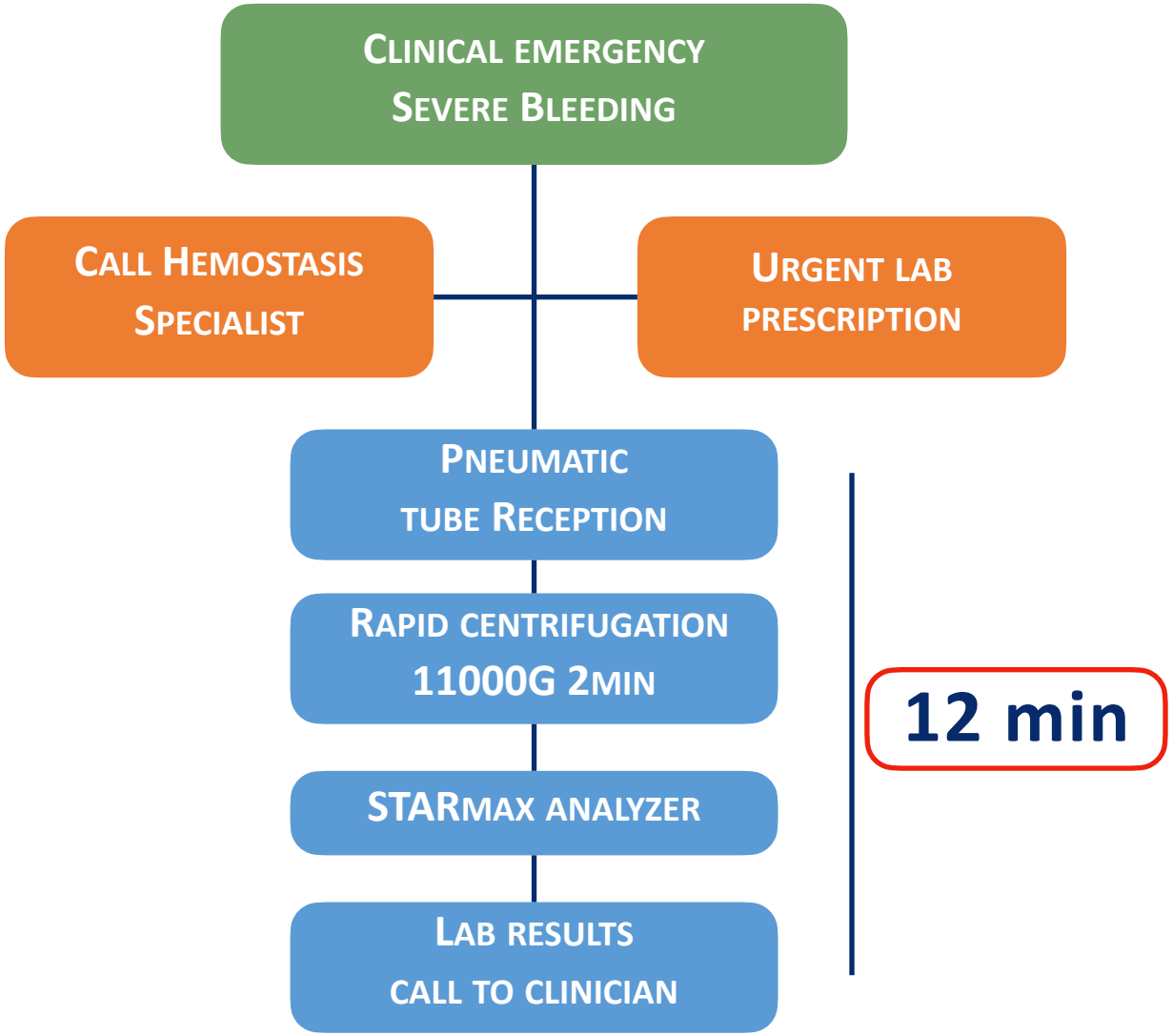
- Anesthesiologist Intensivist
- Cardiothoracic Surgeon
- Perfusionist
- ICU Nurse
- Cardiologist
- Physiotherapist

ECMO Team



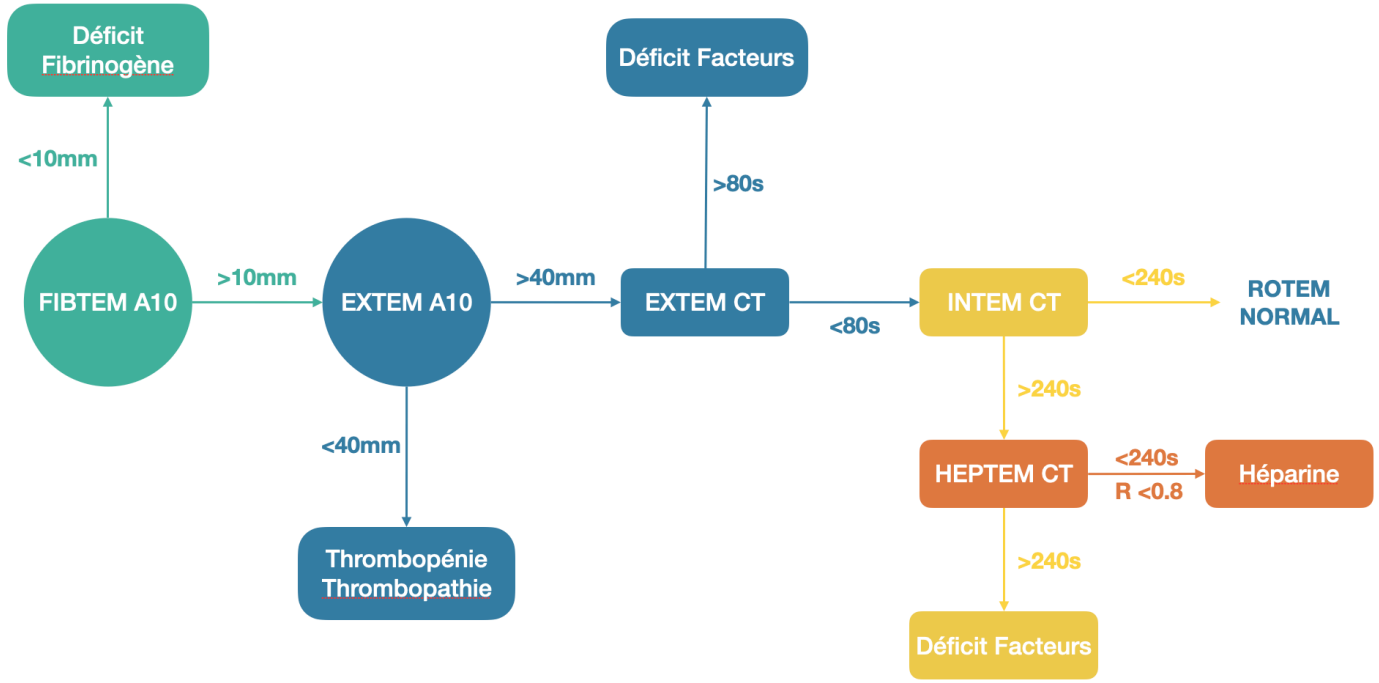
On-call duty 24h/7d

Fastrack coagulation test CHU RENNES



PT, APTT, Fg, antiXa, CBC

Viscoelastic Testing / ROTEM



Platelet function POC ?

Mild bleeding

- UFH : decrease antiXa target or suspension
- Search for surgical / cannula related bleeding
- Hemostasis lab tests

Severe bleeding

- Stop UFH
- Emergency coagulation test / POC
- TXA
- PLT < 100G/L => PC
- Fg <2 or FIBTEM A5/10 => Fg concentrate
- PT or EXTEM CT => FFP or PCC

Desmopressin ?

- VWF and FVIII secretion
- Platelet dependent thrombin generation

The effect of desmopressin on platelet function: a selective enhancement of procoagulant COAT platelets in patients with primary platelet function defects

Giuseppe Colucci, Monika Stutz, Sophie Rochat, Tiziana Conte, Marko Pavicic, Marianne Reusser, Evelyne Giabbani, Anh Huynh, Charles Thürlemann, Peter Keller, and Lorenzo Alberio

Colucci et al. Blood 2014

Desmopressin ?

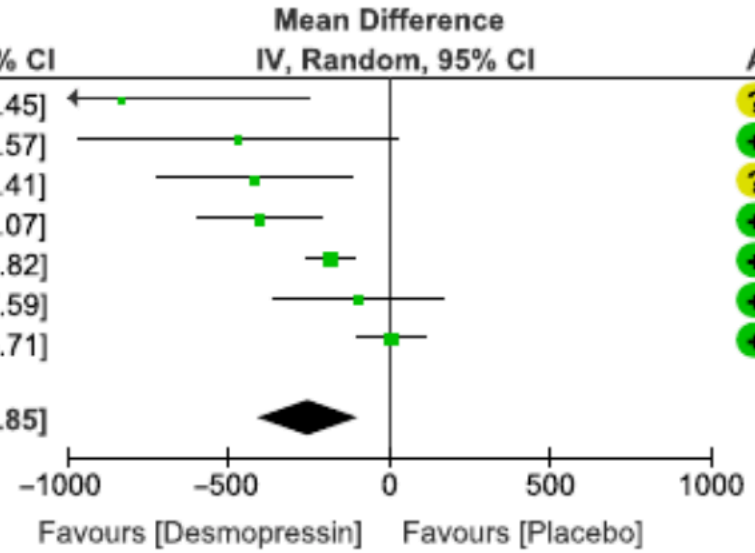
Beneficial effect on post CBP with platelet dysfunction

A

Study or Subgroup	Desmopressin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Sheridan 1994	1,543	626	20	2,376	1,293	24	5.4%	−833.00 [−1418.55,−247.45]
Mongan 1992	881.2	594.6	13	1,352.6	773.1	16	6.9%	−471.40 [−969.37, 26.57]
Gratz 1992	1,215	381	29	1,637	761	30	12.4%	−422.00 [−727.59,−116.41]
Despotis 1999	624	209	50	1,028	682	51	17.3%	−404.00 [−599.93,−208.07]
Steinlechner 2011	250	141	20	434	125	23	22.6%	−184.00 [−264.18,−103.82]
Bignami 2016	681.19	553.2	25	780.96	429.7	29	14.0%	−99.77 [−367.13, 167.59]
Pleym 2004	606	237	46	601	301	46	21.4%	5.00 [−105.71, 115.71]
Total (95% CI)			**203**			**219**	**100.0%**	**−253.93 [−408.01, −99.85]**

Heterogeneity: Tau² = 25629.83; Chi² = 24.39, df = 6 (P = 0.0004); I² = 75%

Test for overall effect: Z = 3.23 (P = 0.001)



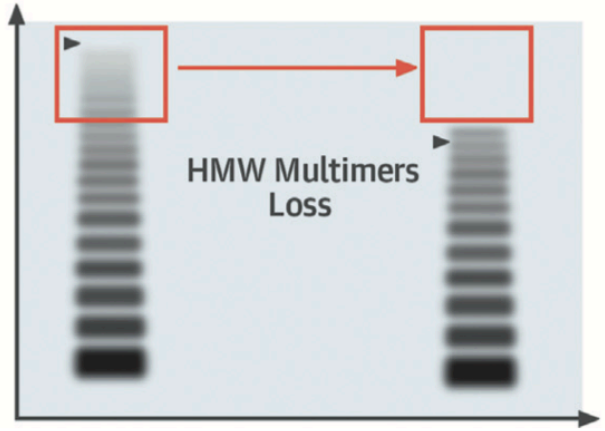
Desbourough et al. JTH 2016

Willebrand concentrate ?

- ECMO : 100% AVWS

- Willebrand lab testing ?
  - Only if VWF concentrate administration

- VWF concentrate administration ?
  - No prospective evaluation
  - Pharmacokinetics ?
  - Help for refractory bleeding ?

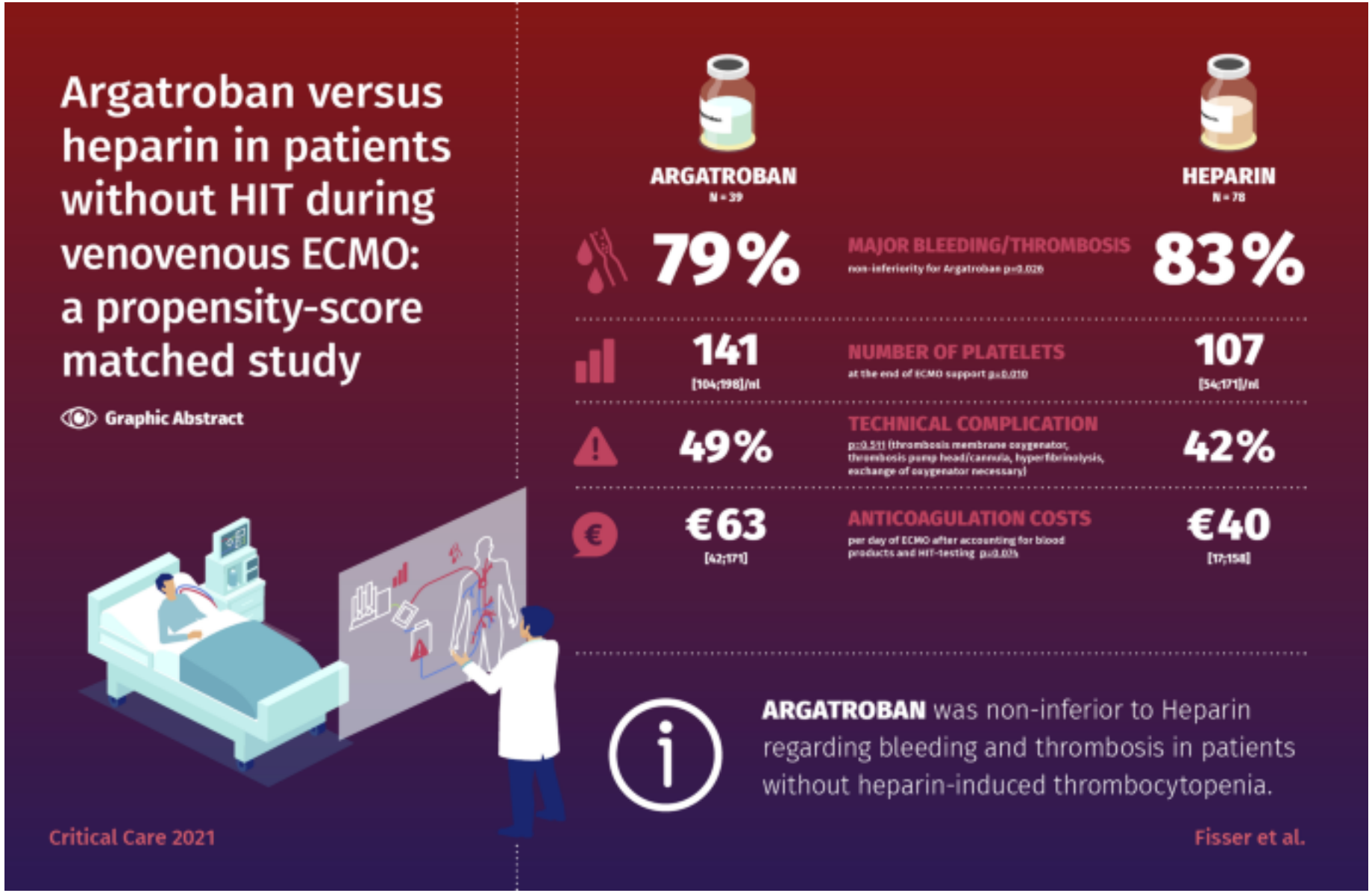


Heilmann et al. Intensive Care Medicine, 2012
Vincent et al. JACC 2018

Conclusion

- Bleeding on ECMO :
    - Frequent
    - Poor outcomes
- ECMO team
- Synergy clinician+hematologist

Merci pour votre attention



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

ETUDE CHU RENNES

- 31 patients sous ECMO (27 VA/4VV, 2 consoles Rotaflow-Maquet® et Medos- Xenios®AG)
- Objectif primaire : identifier paramètres qui peuvent influencer le degré de perte des HPM.

Factors associated with acquired von Willebrand syndrome severity

	Univariate analysis		Multivariate analysis	
	ß-coefficient (95% CI)	P-value	ß-coefficient (95% CI)	P-value
Blood group O (vs A, B, AB)	-0.031 (-0.168, 0,143)	0.870		
Rotational speed (10^3 rpm)	-0.059 (-0.094, -0.024)	0.002	-0.057 (-0.091, -0.023)	0.002
Apache II score	0.017 (-0.002, 0.035)	0.078	0.009 (-0.008, 0.027)	0.294
Time between ECMO initiation and blood sampling (days)	-0.014 (-0.040, 0.012)	0.284		
VA ECMO (vs VV ECMO)	0.029 (-0.201, 0.259)	0.799		

Consensus Recommendations for Hemostasis Primary Outcomes in Cardiac Surgery and Mechanical Circulatory Support (MCS)

	0 None	1 Mild	2 Moderate	3 Severe	4 Life-Threatening	5 Fatal
BLEEDING	None	No change to AC	Lower AC target	Stop AC	Acutely reverse AC or causing patient harm	Fatal bleed
		Transfuse up to 20cc/kg	Transfuse pRBC 21-40cc/kg	Ongoing bleeding (pRBC 41-80cc/kg)	Actively reverse with FEIBA,FVII, TXA, AMICAR pRBC>80cc/kg	
			Small SDH	Moderate SDH	Large SDH	
THROMBOSIS	None	No change to AC	Increase/ modify AC intensity	Circuit change or thrombectomy	Life-threatening or causing patient harm	Fatal thrombosis

Levy et al. Annals of Thoracic Surgery 2021

Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

Type 3a

Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)

Any transfusion with overt bleeding

Type 3b

Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)

Cardiac tamponade

Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)

Bleeding requiring intravenous vasoactive agents

Type 3c

Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)

Subcategories confirmed by autopsy or imaging or lumbar puncture

Intraocular bleed compromising vision

Type 4: CABG-related bleeding

Perioperative intracranial bleeding within 48 h

Reoperation after closure of sternotomy for the purpose of controlling bleeding

Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†

Chest tube output ≥2L within a 24-h period

Type 5: fatal bleeding

Mehran et al. Circulation 2011