Coagulation management during ECMO - the role of laboratory & POC testing

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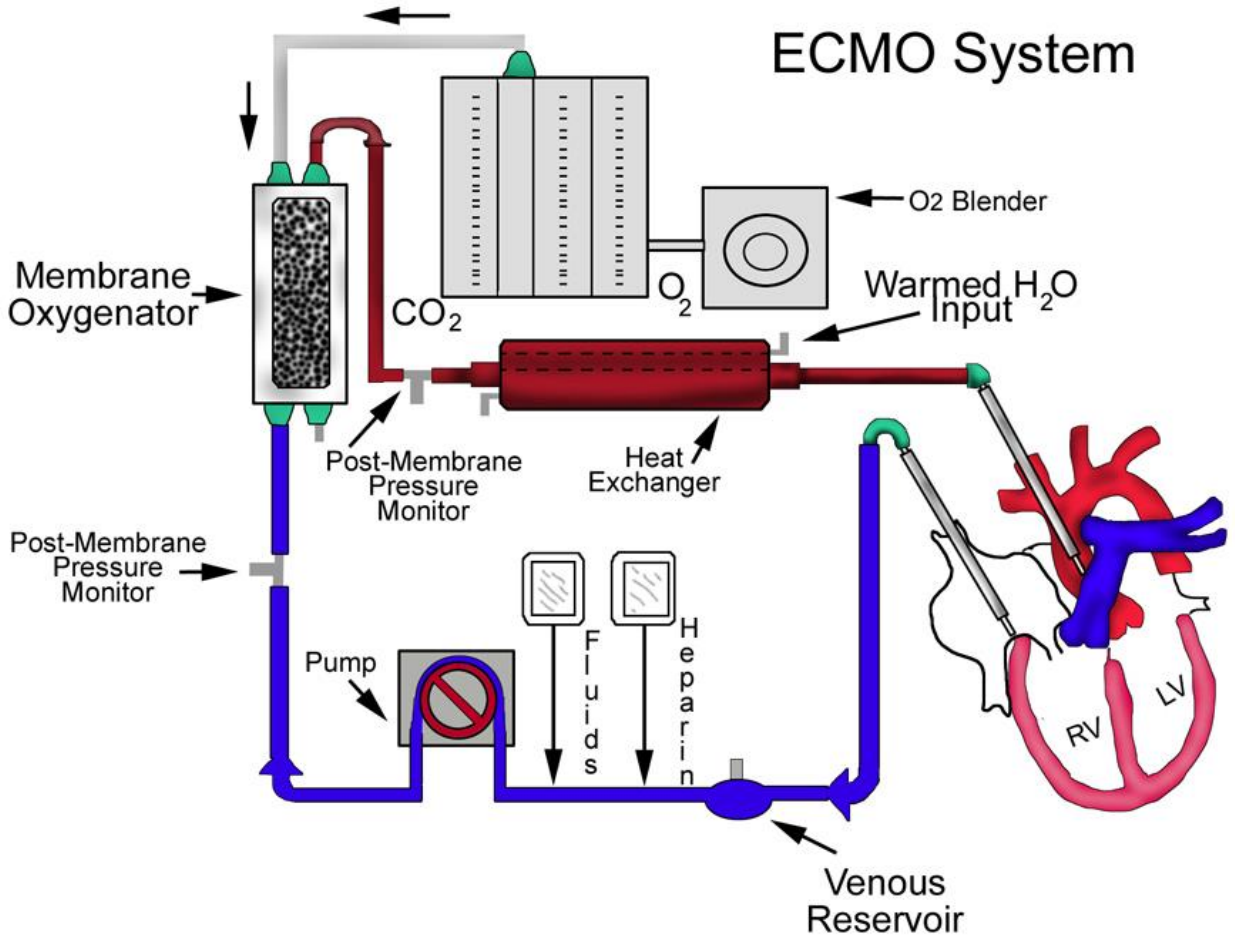
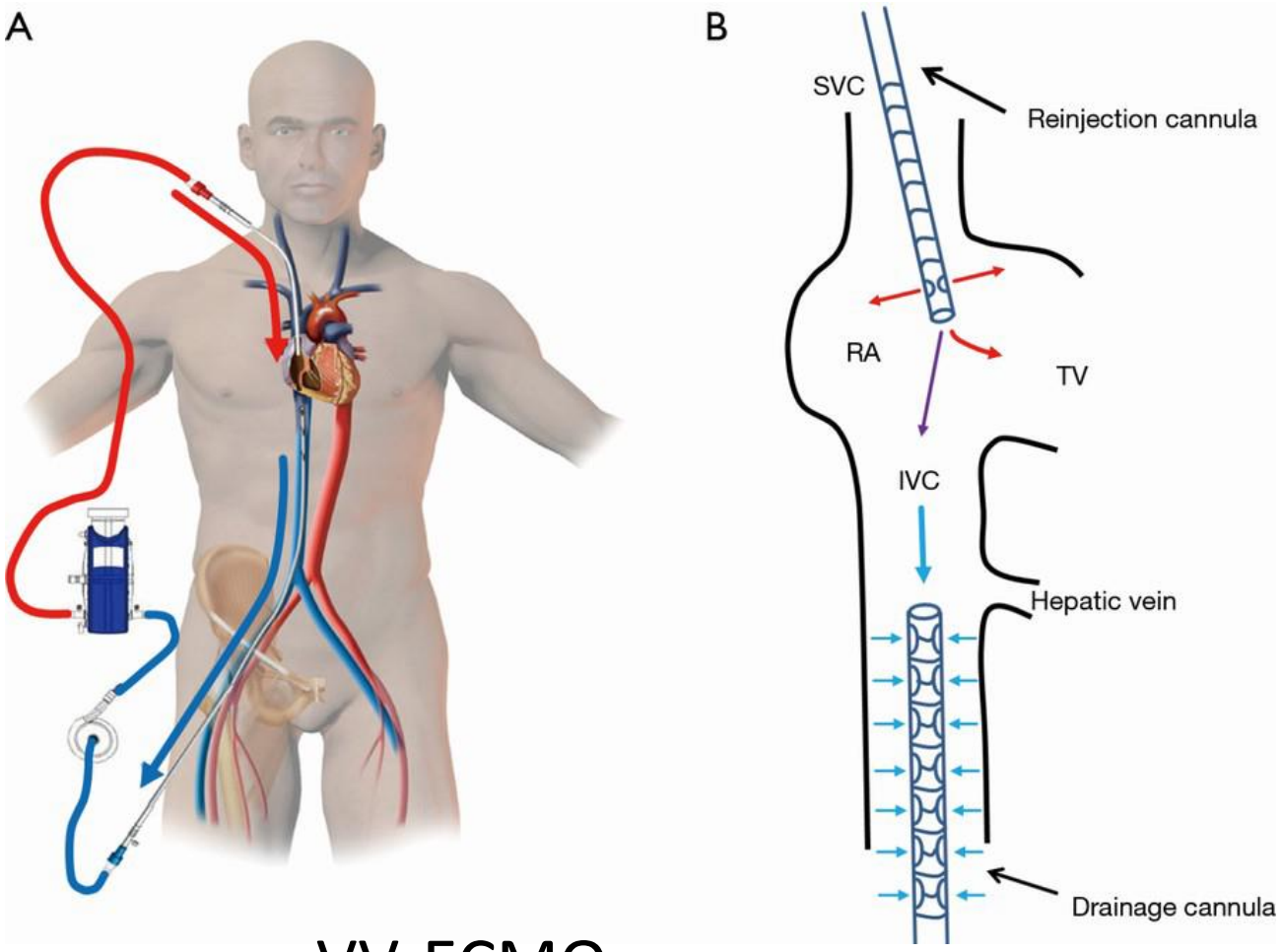
What is ECMO?

- Extra Corporeal Membrane Oxygenation
  - Pump
  - Oxygenator
  - Tubings
  - Gas-blender
  - Heat exchanger

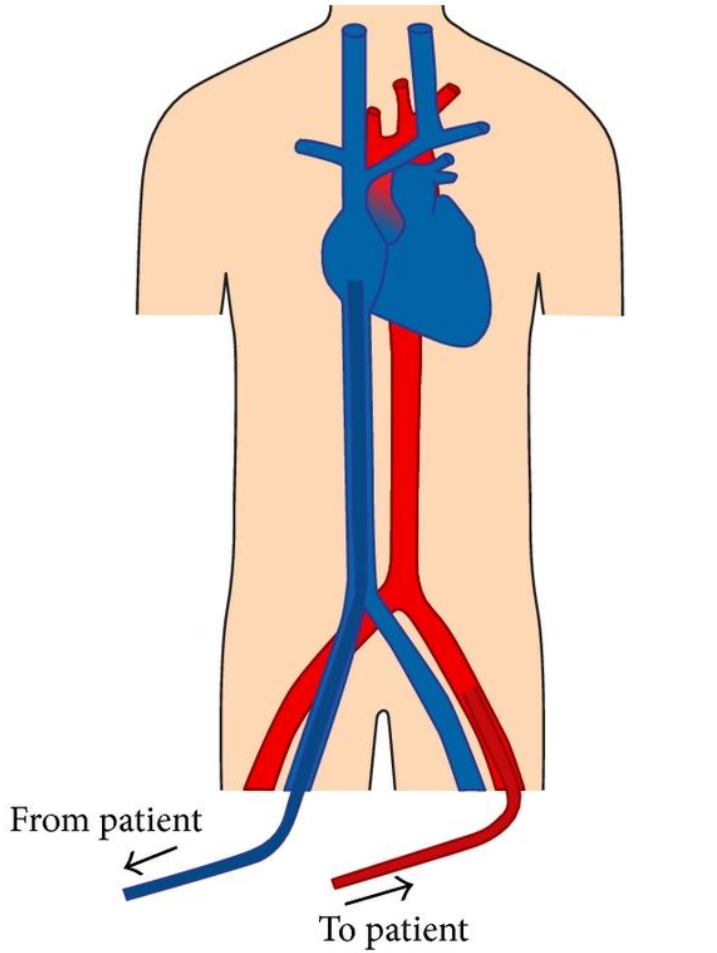


ECMO = ECMO?



VV-ECMO

VA-ECMO



Current indications

- Cardiac failure
  - After cardiac surgery
  - After cardiac arrest
  - Acute cardiac failure
  - Massive pulmonary embolism
- Respiratory failure despite optimized ventilator therapy
  - Hypoxemia (PaO_2/FiO_2 <100mmHg)
  - Hypercarbia pH <7.20

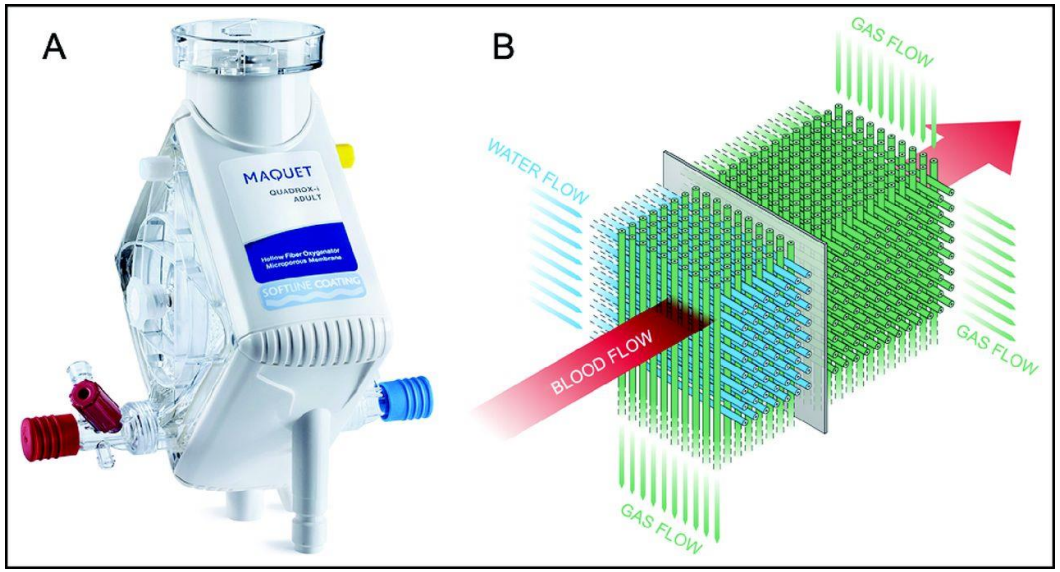
- Bridge to
  - Recovery
  - Transplantation
  - Destination
  - Bridge

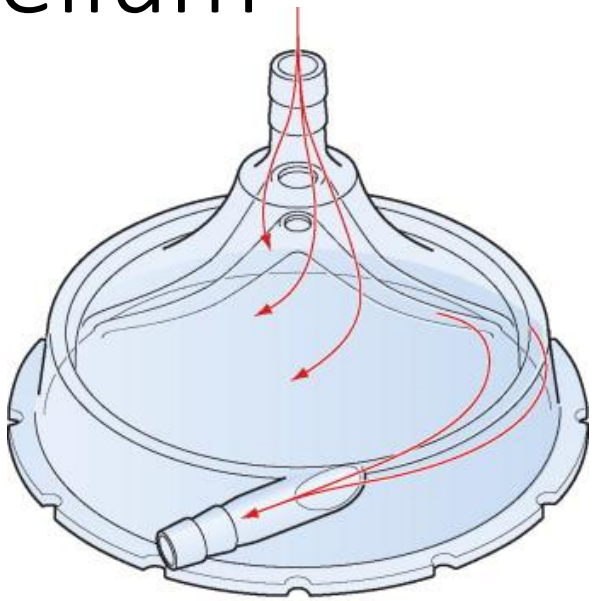
Evidence

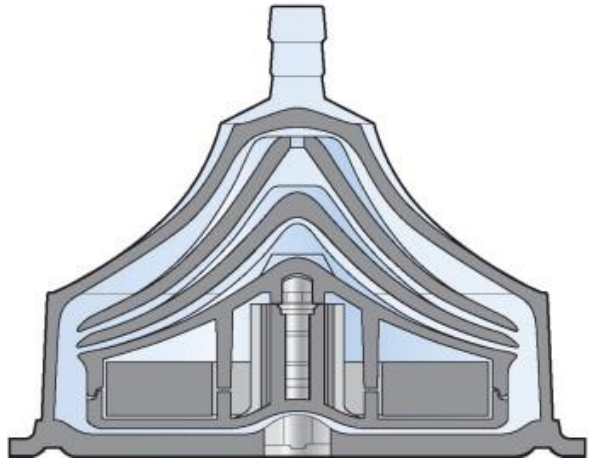
- Respiratory ECMO
  - ARDS
  - Infection (H1N1)
  - Survival of 60-70%
  - CESAR trial 2009, EOLIA trial 2018

- Cardiac ECMO
  - Post cardiotomy
  - Acute myocardial damage
  - E-CPR
  - Survival 20-50%

Artificial surface without endothelium

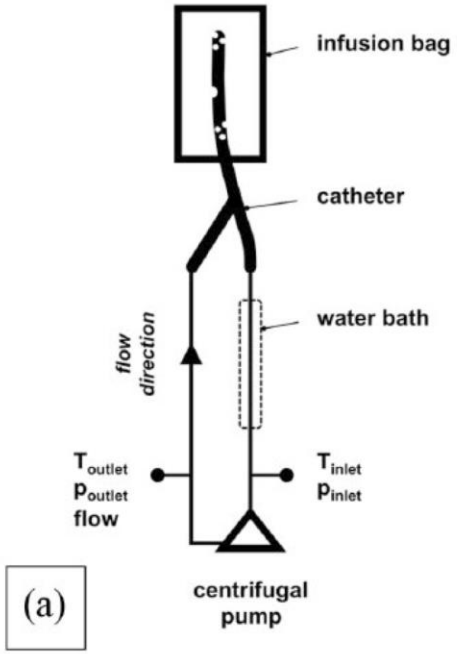


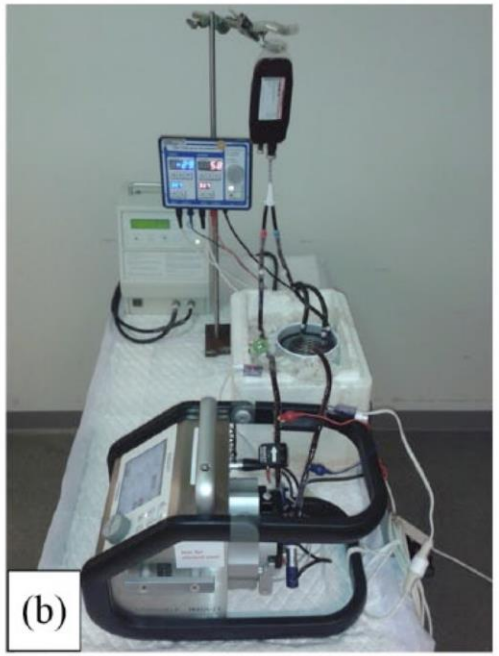


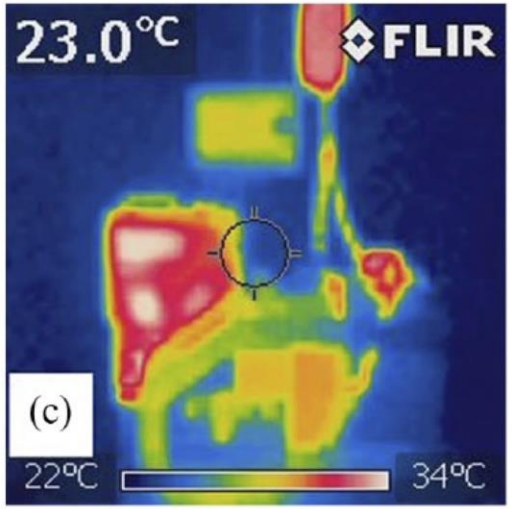


Abnormal blood flow

- Turbulent flow
- High shear rates
- Variability of flow speed
- High surface contact
- Friction & warming

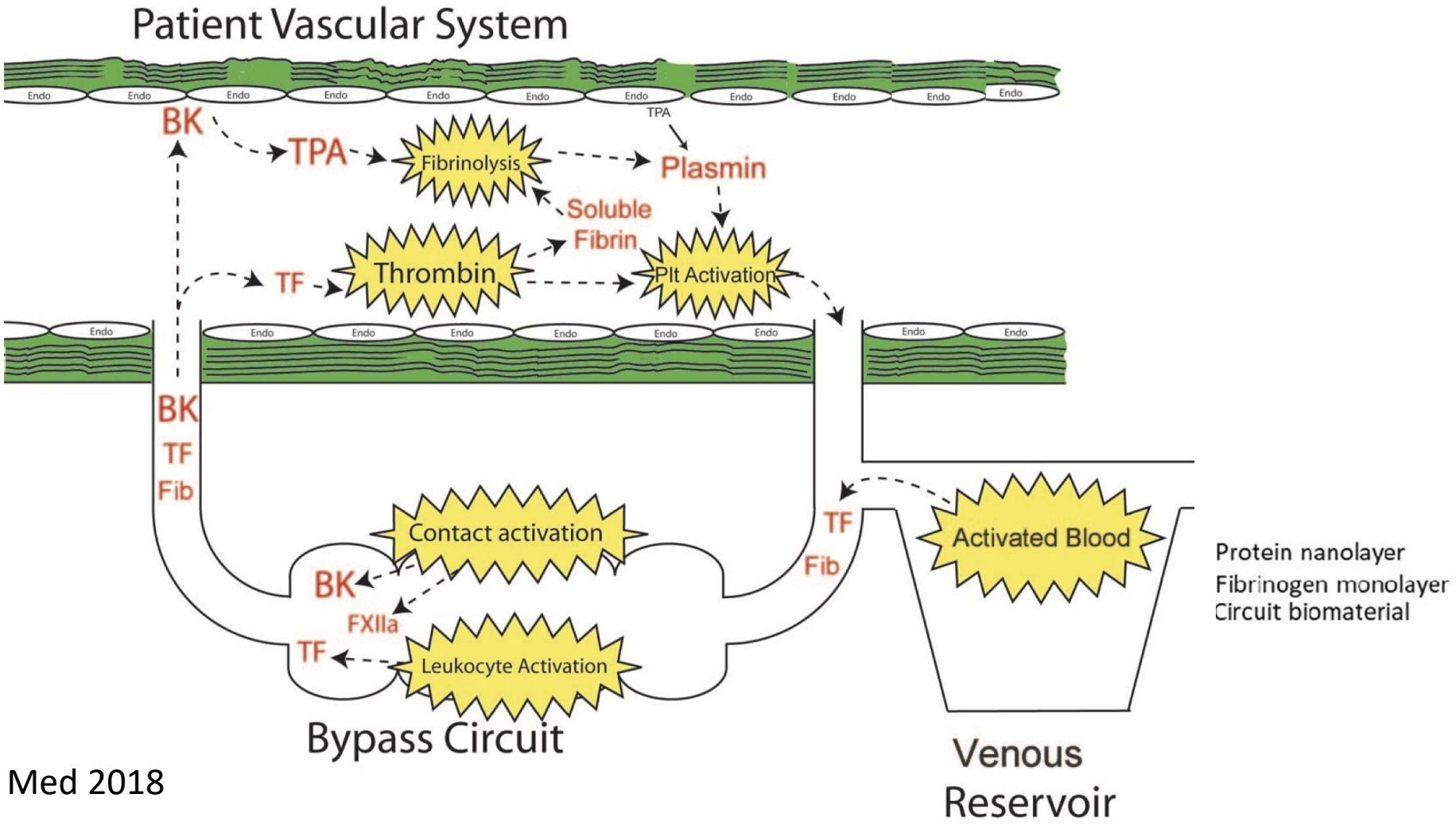






Kusters et al. Perfusion 2016

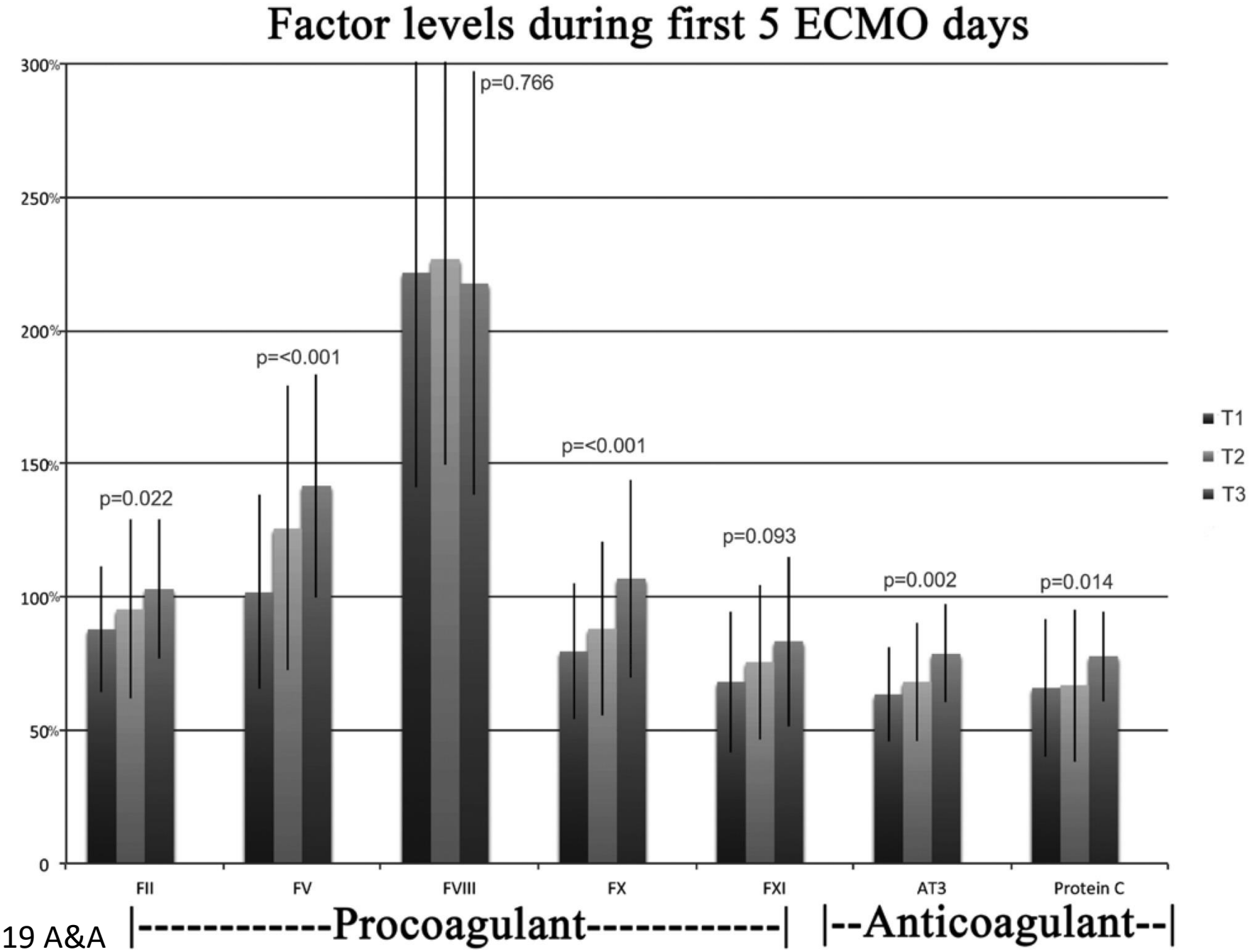
ECMO‘s effect on the coagulation system



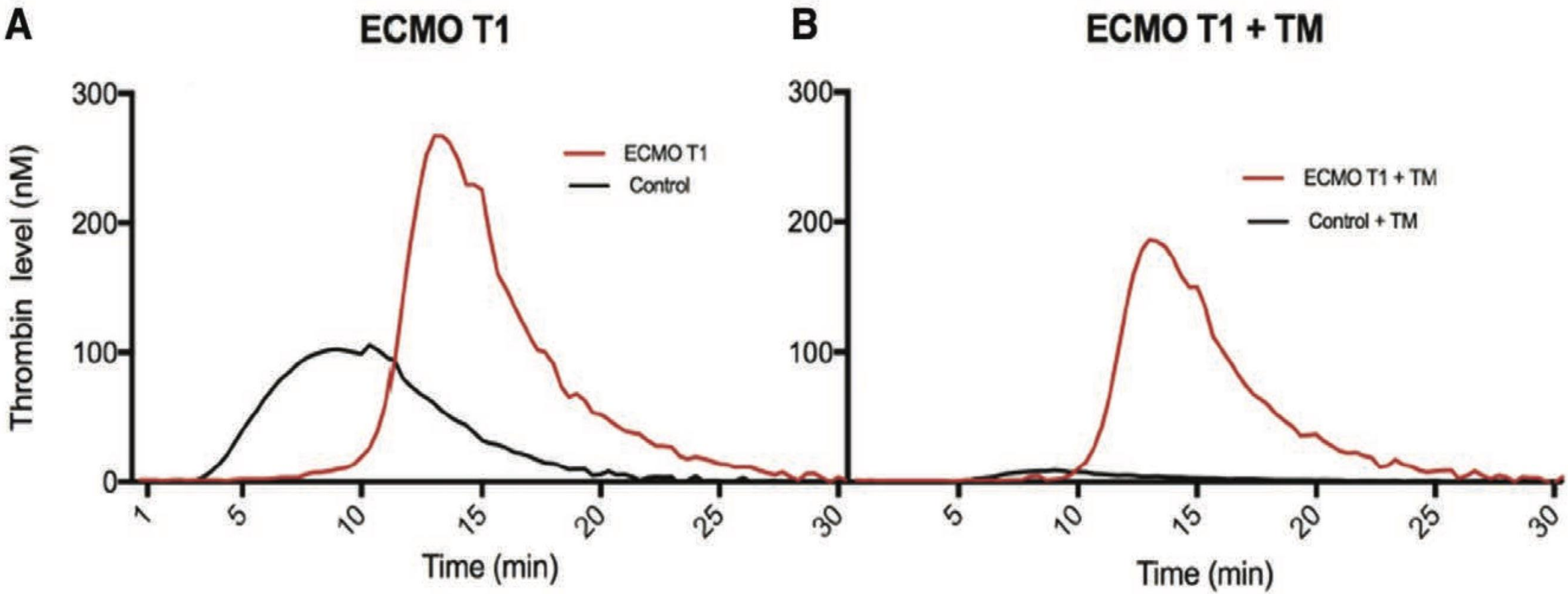
Doyle et al. Frontiers Med 2018
Sniecinski A&A 2011

CPB vs ECMO vs DIC?

	CPB	ECMO	DIC
Contact activation	+, short duration	++, prolonged	–
Consumptive coagulopathy	–	++	++
Dilutional coagulopathy	++	+	–
Fibrinogen levels	Often decreased (due to hemodilution)	High (acute phase reaction)	Low (due to fibrinolysis)
Fibrinolysis	+	+ to ++	++
Thrombin generation	Mildly decreased to normal (after CPB)	++ (limited by heparin)	++
Platelet count	Mild to moderately decreased	Low	Low
Platelet function	Mildly decreased	Activated	Activated



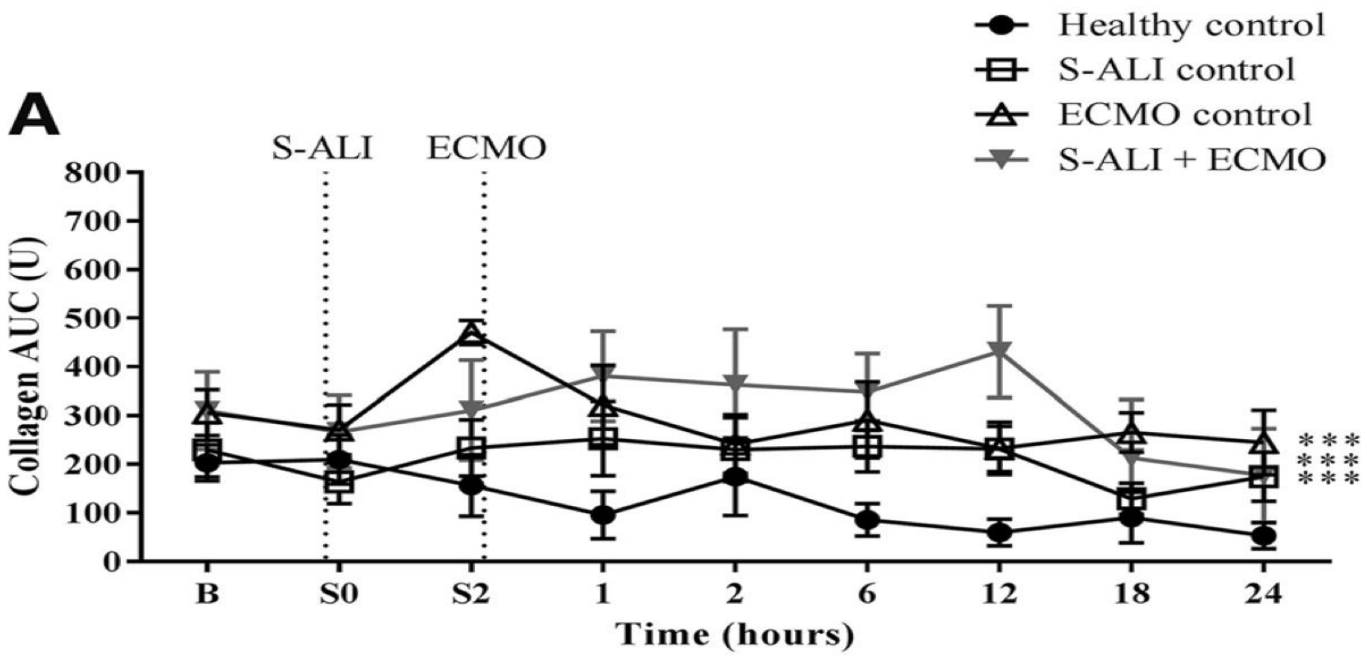
Mazzeffi et al. 2019 A&A

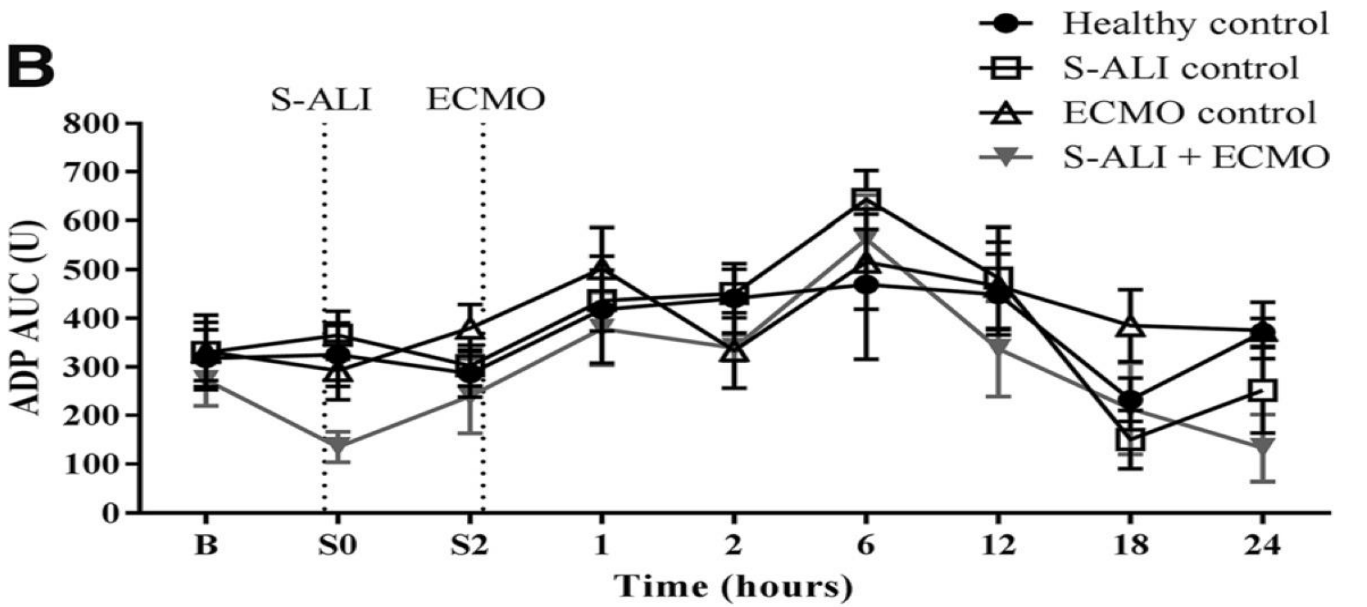


2 pM TF/ 5 nM TM

Mazzeffi et al. 2019 A&A

Table 1 Routine and specialised haemostatic parameters by experimental group at selected time points





ECMO control		S-ALI + ECMO	
B	24 h	B	24 h
7.0 (2.2)	7.9 (1.7)[a]	6.6 (1.2)	9.1 (3.8)[a]
8.0 (1.2)	4.8 (0.54)[a]	8.3 (0.87)	7.3 (1.2)
89.3 (12)	54.3 (5.4)[a]	93.4 (11)	83.5 (12)
0.26 (0.04)	0.16 (0.01)[a]	0.28 (0.03)	0.24 (0.04)
471 (95)	260 (80)	364 (140)	199 (60)
12.9 (0.6)	17.4 (2.1)	14.3 (0.9)	35 (6.7)[a]
26 (4.6)	122 (64)	30 (6)	158 (57)
2.9 (0.47)	2.6 (0.16)[a]	3.0 (0.97)	1.5 (0.5)[a]
435 (192)	343 (217)	406 (213)	213 (136)
12 (1)	156 (81)	13 (1)	44 (69)
891(235)	408 (51)[a]	904 (166)	531 (242)[a]
151 (37.7)	67 (12.4)	107 (20.2)	16 (6.7)[a]
55 (13.4)	50 (11.2)	46 (11.4)	14 (4.5)[a]
94 (47.6)	88 (10.9)[a]	129 (30)	96 (25.3)[a]
93.7 (8.8)	62.7 (6)	92.3 (1.9)	22 (4.3)[a]

Passmore et al. Crit Care 2017

	Clinical manifestations	Potential causative changes
Thrombosis Oxygenator 7-13% CNS 2-4.4%	Deep vein thrombosis Pulmonary embolism Oxygenator thrombosis Small vessel thrombosis	Increased coagulation factors Contact pathway activation Haemolysis and free hemoglobin Vessel injury at cannulae sites Microthrombi formation Circulating microparticles Pre-existing systemic inflammation in patients e.g. Monocytic tissue factor
Hemorrhage Cannula site 10-30% CNS 2.2-6%	Line and surgical site Pulmonary and upper airway Intracranial Abdominal	von Willebrand Factor dysfunction Increased fibrinolysis Thrombocytopenia Platelet dysfunction and damage Reduced coagulation factors Hypofibrinogenaemia Systemic anticoagulation
Inflammatory response	Systemic inflammatory response syndrome Capillary leak syndrome	Complement activation Neutrophil and monocyte activation Contact pathway activation

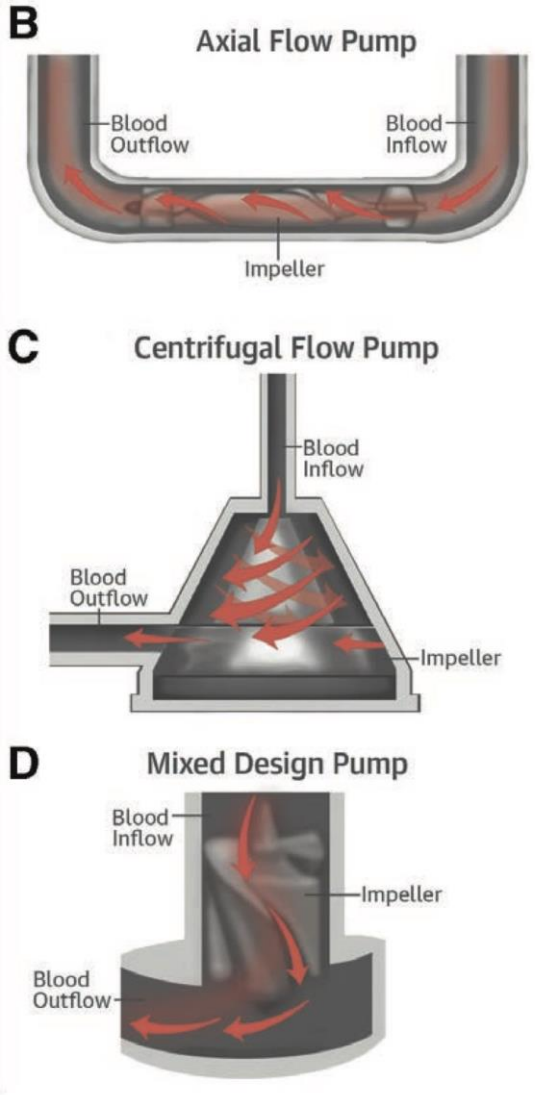
Pro & con anticoagulation

- To prevent thrombosis
- To prevent activation of inflammation
- To prevent platelet activation
- To prevent consumption of coagulation factors

- To prevent bleeding
- To prevent side effects of anticoagulation (HIT2)

Technical innovations to prevent clotting

- Bio-coating of the surfaces
- Reducing the size of the system
- Reducing the resistance of the system
- Avoiding areas of stasis
- Avoiding blood-air contact
- Keeping a “blood-flow” of >2L (avoiding hemostasis)
- New flow generators



Sladen et al.A&A 2017

References	Case no.	Combined injury besides pulmonary failure	Intervention	ECMO	Heparin	ECMO duration	Outcome
Madershahian et al. [2]	1, 19/F	Spleen, Liver	Laparotomy	v-a[5]	(+)	138 hours	Survived
		Right main bronchus	Thoracotomy				
	2, 48/M	Vertebra and long bone Fracture	Osteosynthesis	v-a	(+)	120 hours	Survived
	3, 26/M	Spleen	Splenectomy	v-va[6]	(+)	84 hours	Survived
		Brain					
Yuan et al. [5]	4, 18/M	Liver, Gr. III	Conservative	v-v	(+)	10 days	Survived
		Endobronchial hemorrhage					
	5, 38/M	Brain SDH[1]	Conservative	v-v	(+)	5 days	Survived
Campione et al. [4]	6, 14/M	Bronchial Disruption	Right bilobectomy of lung	v-v	(+)	3 days	Survived
Yen et al. [7]	7, 21/M	Brain EDH[2]	Decompressive craniotomy	v-a	(+)	49 hours	Survived
Friesenecker, et al. [8]	8, 34/M	Liver, Spleen	Laparotomy	v-v	(+)	17 days	Survived
		Brain ICH[3] with edema	Decompressive craniotomy				
Muellenbach et al. [9]	9, 53/M	Liver	Laparotomy	v-v	(–)	8 days	Survived
		Traumatic brain injury	ICP[4] Monitoring				
	10, 16/M	Traumatic brain injury		v-v	(–)	3 days	Survived
	11, 28/M	Spleen	Splenectomy	v-v	(–)	2 days	Survived
		Traumatic brain injury					
Arlt et al. [6]	10 Cases	Bleeding shock	-	7 v-v	All (–)	Mean 5 days	6/10 Survived
				3 v-a			

Chung et al. ASIAIO 2017

Wen et al WJES 2015

ECMO with low anticoagulation

			Bleeding complications	
Group	Weaned Off ECMO	Died	Minor	Major
Group 1 (control), No. (%)	18/50 (36)	35/50 (70)	21/50 (42)	16/50 (32)
Group 2 (low heparin), No. (%)	26/52 (50)	28/52 (53.8)	11/52 (21)	6/52 (11.5)
Total, No. (%)	44/102 (43)	63/102 (61.7)	32/102 (32)	22/102 (22)
p-value	0.050	0.050	0.017	0.012

Raman et al. JHLT 2019

Non-relevant clots
10 (20%) of group 1
8 (19%) of group 2

Choices for anticoagulation

- Unfractionated heparin (UFH) iv
- LMWH sc/iv
- DTI (argatroban/bivalirudin) iv
- Antiplatelet drugs
- Iloprost

International survey:

45/47 centers used UFH as primary drug

2/47 used bivalirudin

Esper et al. Vox Sang. 2017

Tools to assess anticoagulation

- SLT
  - aPTT or aPTT ratio
  - PT or PT ratio (INR)
  - AT
  - Fibrinogen
  - D-dimers
  - WBC
  - Anti Xa levels

- Bedside tests
  - ACT
  - VET's
  - Platelet function analysis
  - Hemochron (bedside SLT's)

What do we (traditionally) miss?

- Endothelium function
- vW-factor assessment (multimere)
- Factor XIII measurements

- Prot C
- Prot S

Clinical practice

• Heparin concentration	4%
• ACT	42%
• aPTT	42%
• Anti-FXa	10%
• TEG/ROTEM	8%
• PT/INR	2%
• Combination	8%

26 articles/1496 pts
24/1319 pts →heparin
3/50 pts →no anticoagulation
1/119 pts →bivalirudin

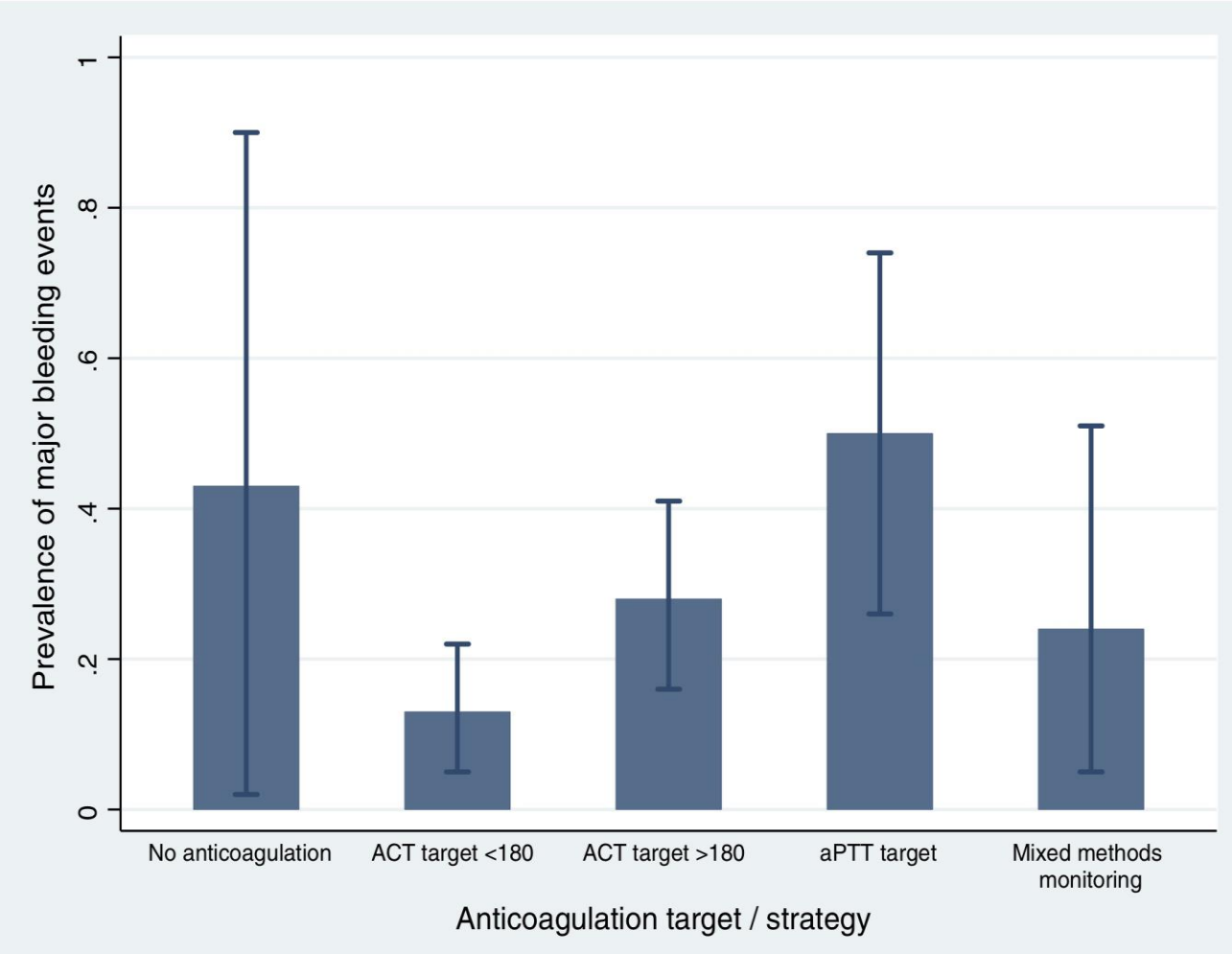
16 ACT
4 aPTT
4 combination

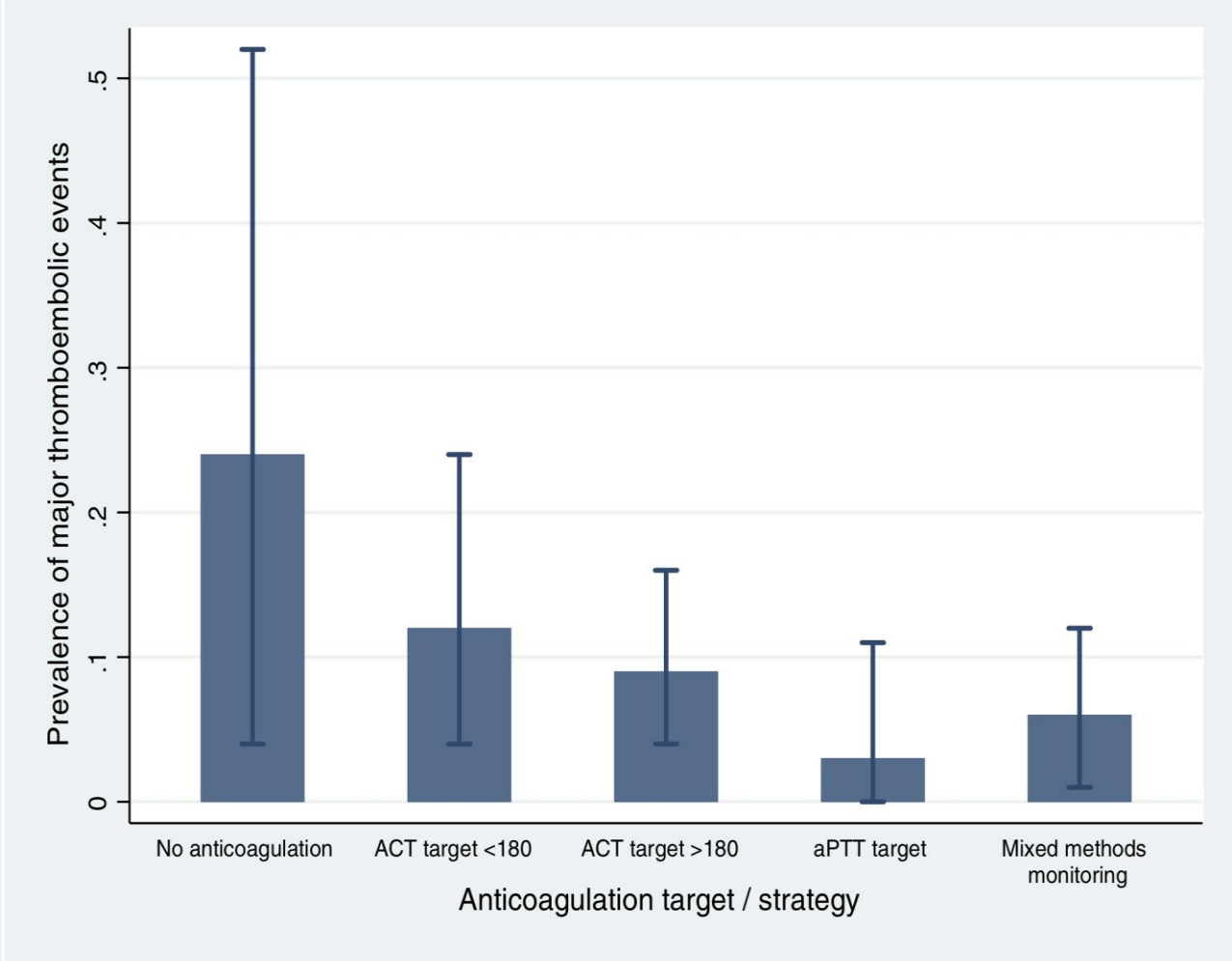
Esper et al. Vox Sang. 2017
Sy et al. J Crit Care 2017

What do we want to measure?

- Concentration of the drug?
- Laboratory reflection/effect of the drug?
- Clinical effect of the drug?
- Clinical effect of the artificial system on the clotting?
- Predict bleeding?
- Predict thrombosis?

Bleeding/thrombosis & monitoring





Sy et al. J Crit care 2017

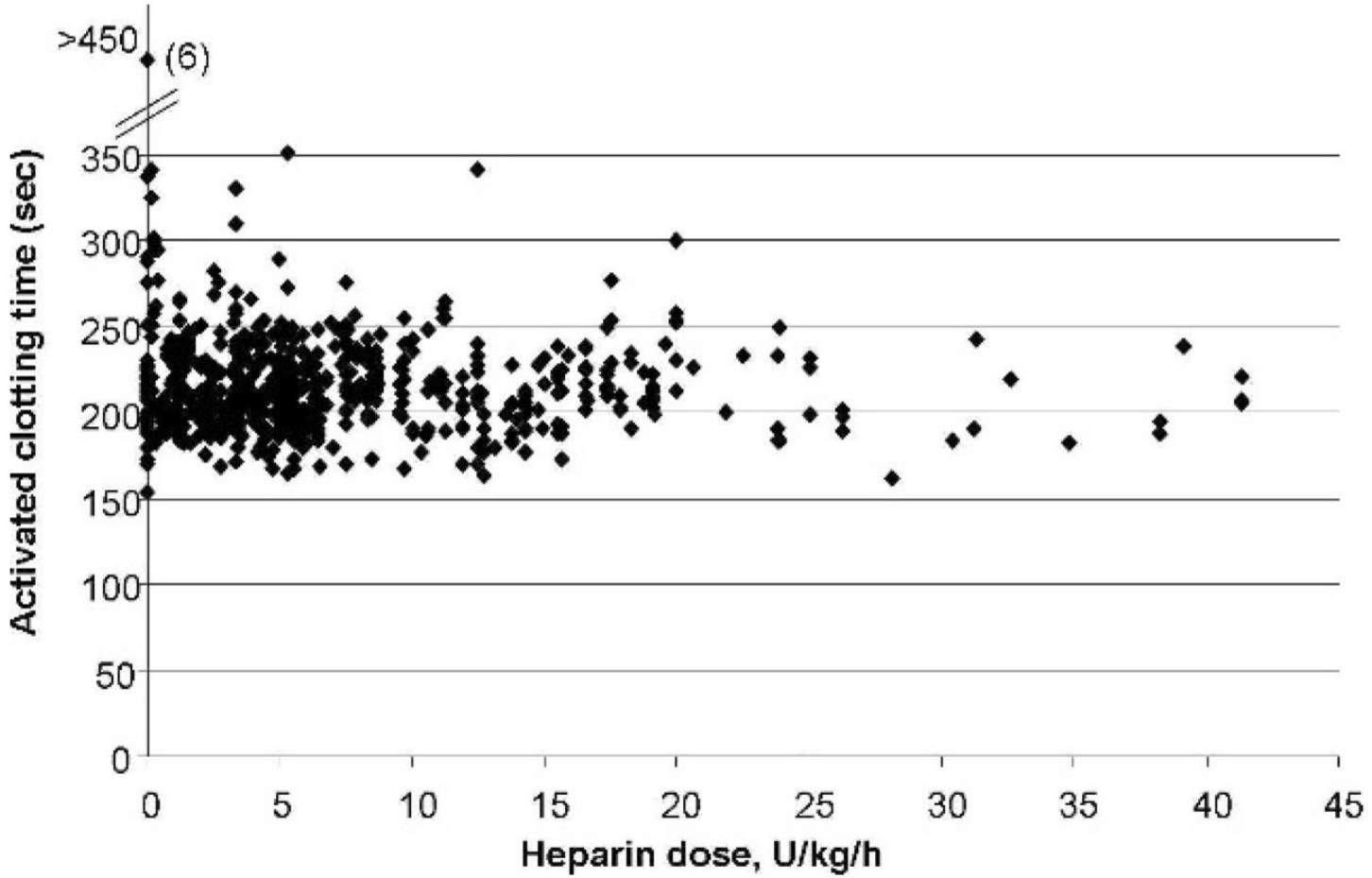
ACT

Assay range	Major bleeding (%)	Thrombosis (%)
ACT <180 seconds	13	12
ACT >180 seconds	28	9
aPTT	50	3

- Traditionally used (CPB & ECMO)
- Designed for high dose UFH monitoring
- Targets variable between 150-180 sec & up to 240 sec
- Advantage: bedside, well known (?), lesser bleeding complications
- Disadvantage:
  - Inaccurate in low dose UFH
  - High variability due to different assays (celite/kaolin/phospholopids)
  - Influenced by Hct, Platelet count/fibrinogen <100mg/dl/hemodilution

Koster et al. Ann Cardiothorac Surg 2019

ACT & heparin dose



Reed et al. Ped Devel Path 2010

aPTT-aPTT ratio

- Advantage:
  - Gold standard for UFH monitoring (?)
  - Good availability
  - Cheap
- Disadvantage:
  - TAT high
  - Different reagents- standardization?
  - AT sensitive (variable assays)
- Poor correlation with anti-Xa and heparin concentration

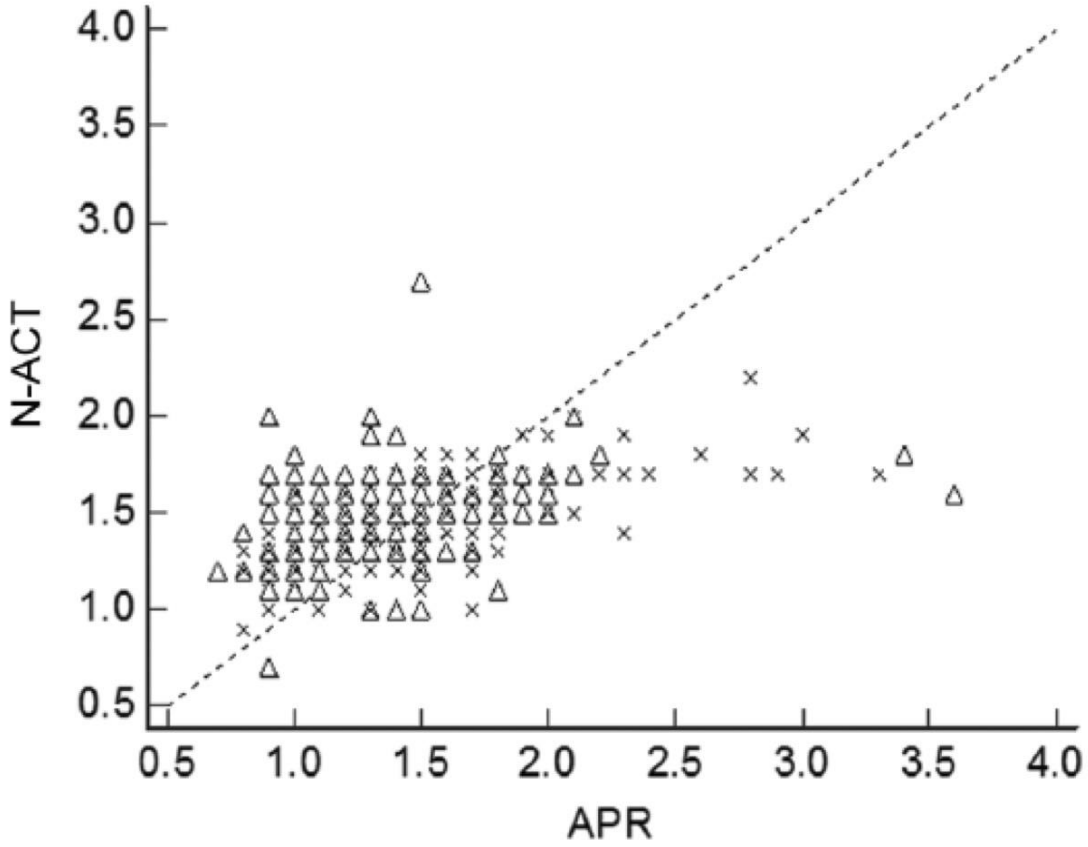
Annich et al. Am J Cardiovasc Drugs 2017

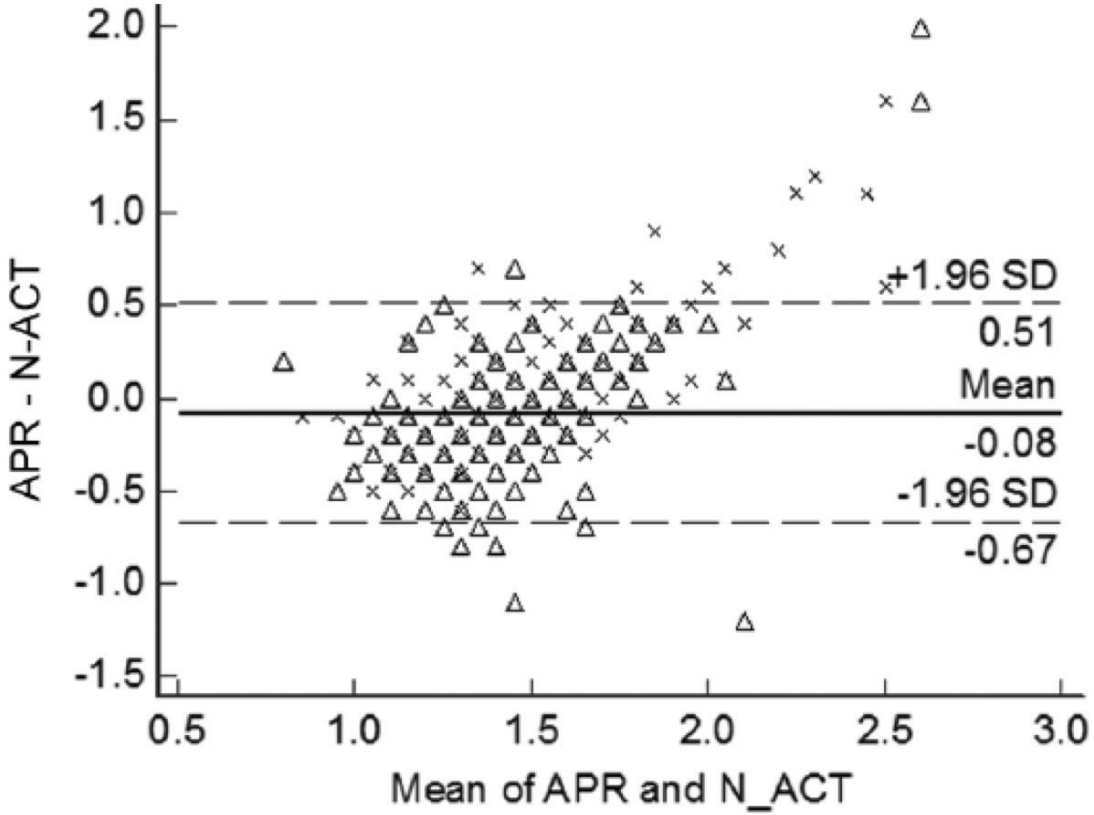
Prediction of bleeding

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

Aubron et al. Ann Intenisve Care 2016

ACT vs aPTT





Cunningham et al. Perfusion 2016

Anti Xa

- Advantage:
  - Better correlation with heparin concentration
  - Generally lesser transfusion than aPTT guided UFH therapy
  - Lesser thrombosis (ECMO)
- Disadvantage:
  - Not always available
  - Needs validation for each anticoagulant
  - Free Hb and bilirubin sensitive
- Therapeutic range wide between 0.5-0.7 IU/mL & <1.3 IU/mL

Annich et al. Am J Cardiovasc Drugs 2017
Koster et al. Ann Cardiothorac Surg 2019

Non-concordance with aPTT

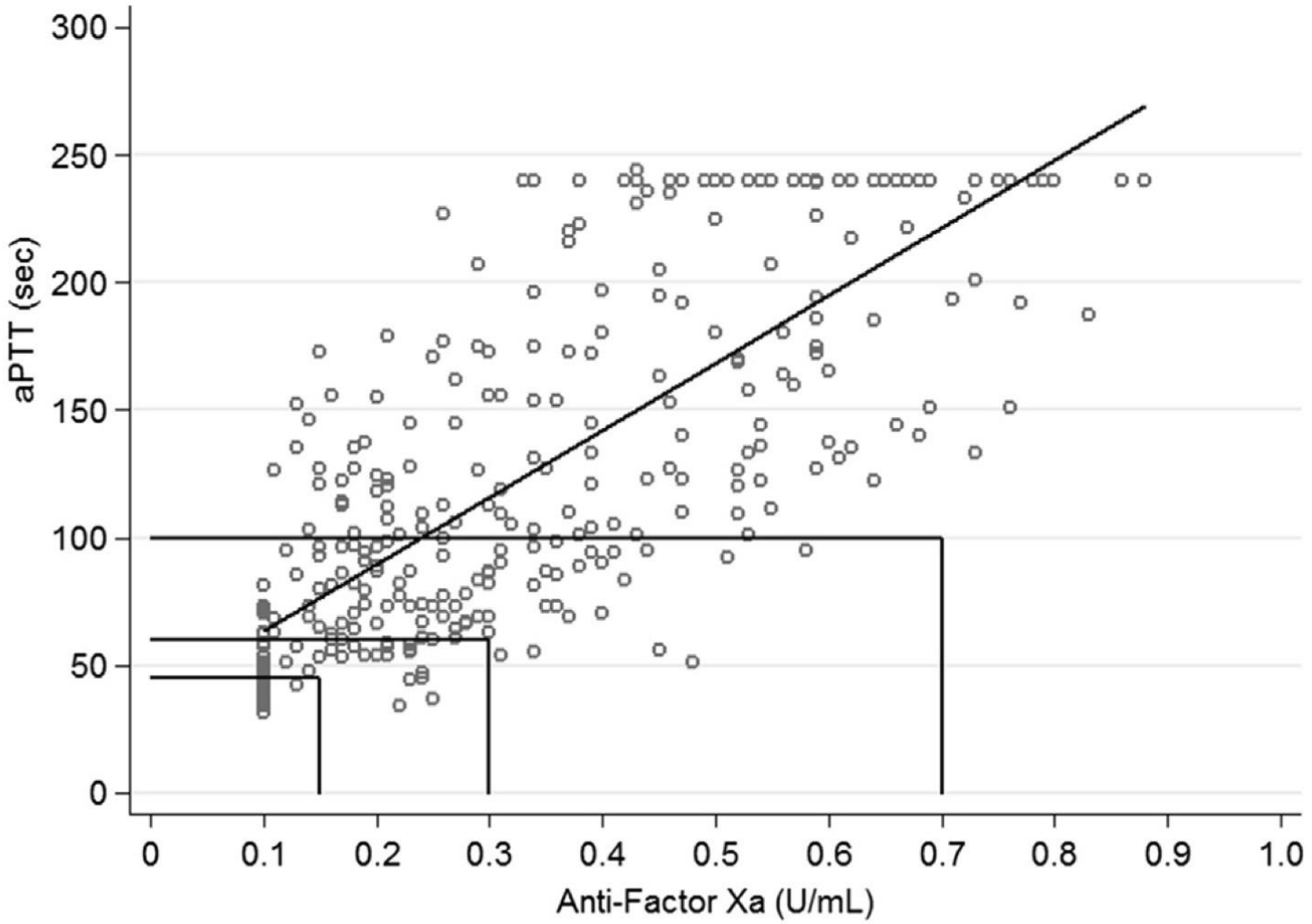
- 340 samples on 38 pts
- Anti-Xa UFH titrated
- 75% discordance between Anti-Xa & aPTT
- Most common pattern
  - aPTT supratherapeutic while anti-Xa in target

Adatya et al. JACC: heart failure 2015

TABLE 2 All CF-LVAD Patients (340 Samples From 38 Patients) According to aPPT Level

	Anti-Factor Xa, U/ml	Concordant, n (%)	Discordant, n (%)
<45 s	<0.15	22 (88.0)	0
	0.15-0.29	0	3 (12.0)
	0.3-0.7	0	0
	>0.7	0	0
45-60 s	<0.15	0	24 (46.2)
	0.15-0.29	23 (44.2)	0
	0.3-0.7	0	5 (9.6)
	>0.7	0	0
61-100 s	<0.15	0	10 (12.8)
	0.15-0.29	0	43 (55.1)
	0.3-0.7	25 (32.1)	0
	>0.7	0	0
>100s	<0.15	0	5 (2.7)
	0.15-0.29	0	38 (20.5)
	0.3-0.7	0	125 (67.6)
	>0.7	17 (9.2)	0
Total	—	87 (25.6)	253 (74.4)

FIGURE 1 Anti-FXa and aPTT Pairs in 38 Patients With CF-LVADs Treated With UFH



$r^2 = 0.57$. anti-FXa = anti-factor Xa; aPTT = activated partial thromboplastin time; CF-LVAD = continuous-flow left ventricular assist device; IV-UFH = intravenous unfractionated heparin.

Adatya et al. JACC: heart failure 2015

Hemostatic capacity & consumption

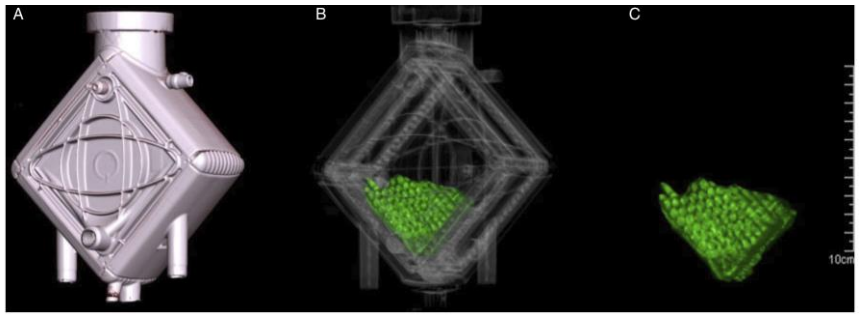
- PT-PT ratio
  - Not appropriate for guiding anticoagulation
  - Mainly used for global hemostatic capacity
  - Again different reagents
  - High variability
- Fibrinogen
  - Important factor in active bleeding
  - Acute phase protein
- Whole blood count
  - Simple measure in EDTA blood
  - Counting erythrocytes, white blood cells & platelets

Antithrombin (AT)

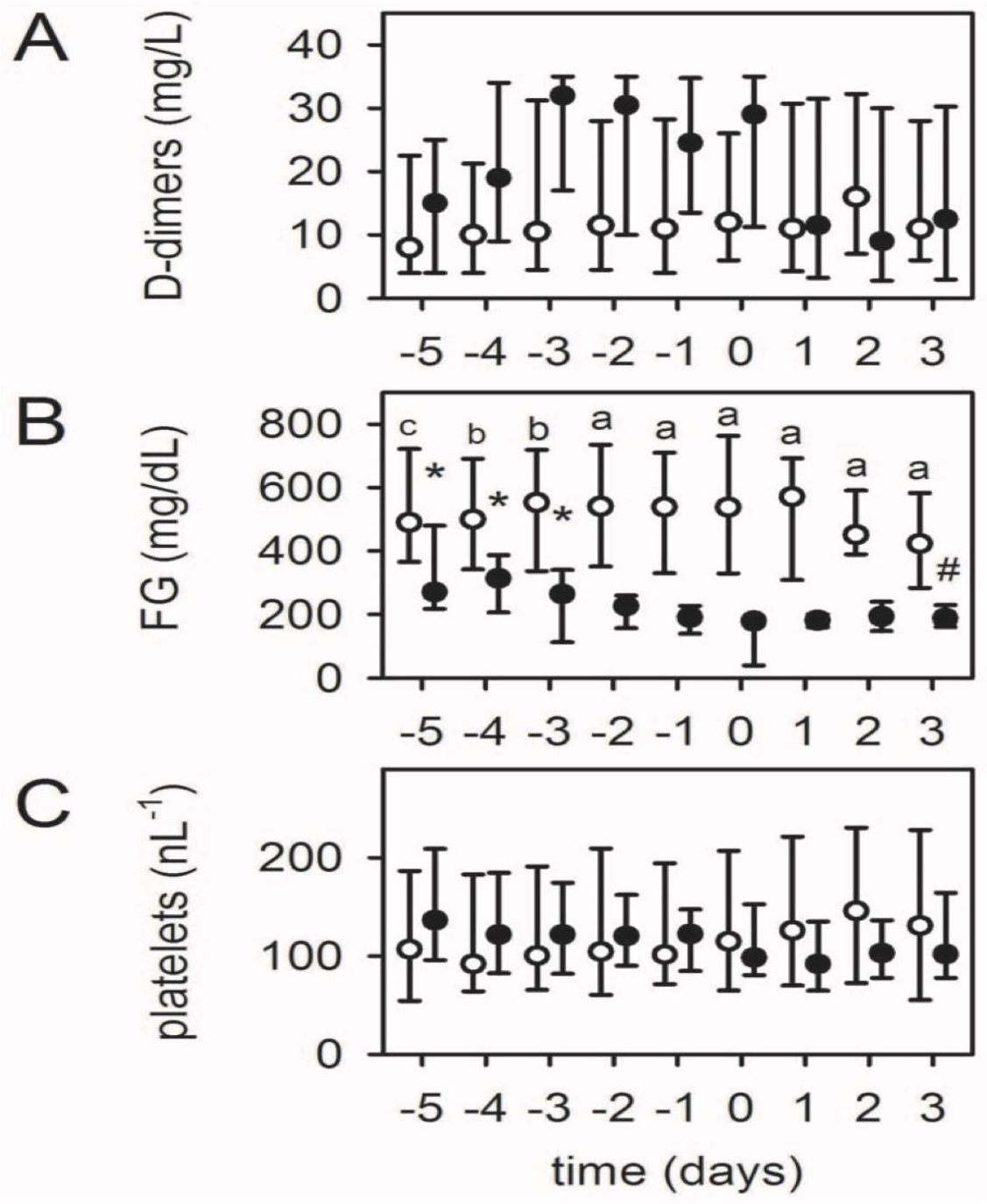
- Important amplifier of heparin & LMWH
- Consumption during heparin therapy
- Consumption in sepsis

D-dimers

- Good correlation with clotting in the system
- Predictor for oxygenator failure



Lubnow et al. PLOS 2014
Dornia et al. ASOI 2015



Viscoelastic tests ROTEM/TEG

- Advantage:
  - Fast
  - Well established

Balance between anticoagulation, fibrinolysis & global clot stability

		Dose Quartiles of heparin[a]				
		Very low dose	Low dose	Medium dose	High dose	*P*[e]
INTEM CT	% ≥ target range[b]	20.7%	43.9%	59.6%	71.4%	<0.001
	Median[c]	199 (177–234)	235 (191–291)	242 (224–266)	257 (228–290)	<0.001[d]
ACT	% ≥ target range[b]	53.6%	73.7%	88%	86%	<0.001
	Median[c]	174 (145–201)	189 (169–228)	199 (182–216)	204 (181–233)	<0.001
aPTT	% ≥ target range[b]	61.8%	89.3%	96.1%	95.2%	<0.001
	Median[c]	56(48–74)	63(53–75)	72(64–81)	78(64–94)	<0.001

Prakash et al. Anaesth Intensive Care 2016

VET's & transfusion

Interval	Parameter	Target	Intervention
Hourly	Haemoglobin	>10 g/dl	Red cell concentrate
Daily	Platelets (citrate)	>100 thousand/µl	Platelet concentrate
	INR	<1.35	PPSB
	aPTT	40 - 45 sec	Heparin reduction, Fresh frozen plasma
Monday + Thursday and when clinical bleeding signs are present	Factor VIII	>70 %	10 IU/kg Factor VIII concentrate i.v.
	Factor XIII	>50 %	1250 IU Factor XIII concentrate i.v.
	VWF:Ag VWF:RCo *since 10/2012*: VWF:A	VWF:RCo/VWF:Ag ratio >0.6 VWF:A/VWF:Ag ratio >0.73	0.2 µg/kg Desmopressin i.v. → if target value not reached, repetition of 0.2 µg/kg Desmopressin i.v. → if target value still not reached, administration of FVIII+VWF-C (10 IU/kg i.v.)
	RoTEM: Fibrinogen deficiency	FibTEM MCF <10 mm	2 g Fibrinogen i.v.

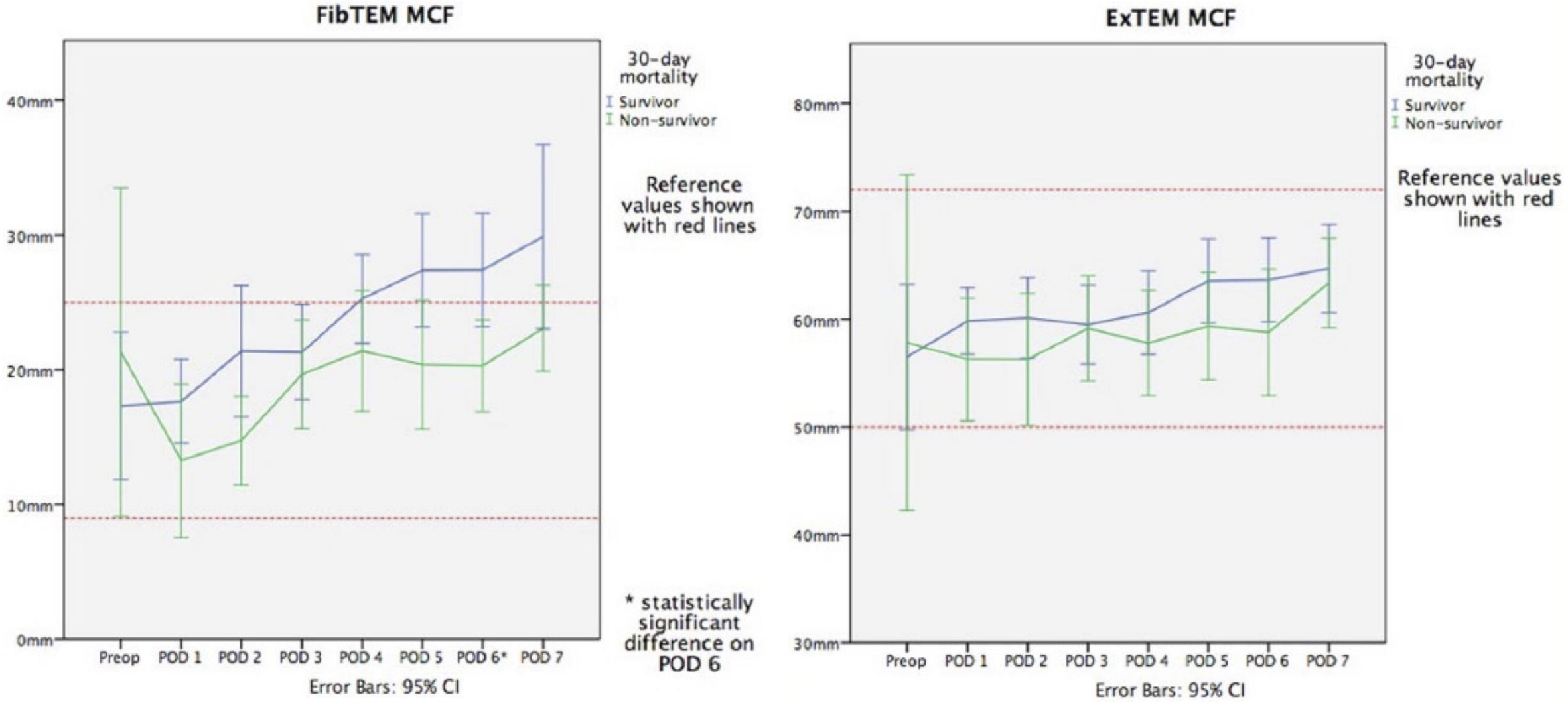
Kalbhenn et al. Perfusion 2016

VET's & transfusion

	Control group	Intervention group
	[ml/kgbw/ECMO days]	
Platelet concentrates		
Mean ± SEM	1.42 ± 0.37	3.15 ± 0.78
Red cell concentrates		
Mean ± SEM	8.97 ± 1.76	7.32 ± 1.60
Fresh frozen plasma		
Mean ± SEM	1.56 ± 0.54	3.59 ± 1.21
	[IU(mg)/kgbw/ECMO days]	
Coagulation factor concentrates		
– Factor VIII + VWF (IU) Mean ± SEM	0.35 ± 0.19	0.17 ± 0.10
– Factor XIII (IU) Mean ± SEM	1.32± 0.54	1.42 ± 0.42
– Fibrinogen (mg) Mean ± SEM	0.59 ± 0.0	2.81 ± 1.0
– PPSB (IU) Mean ± SEM	0 ± 0	0.07 ± 0.07

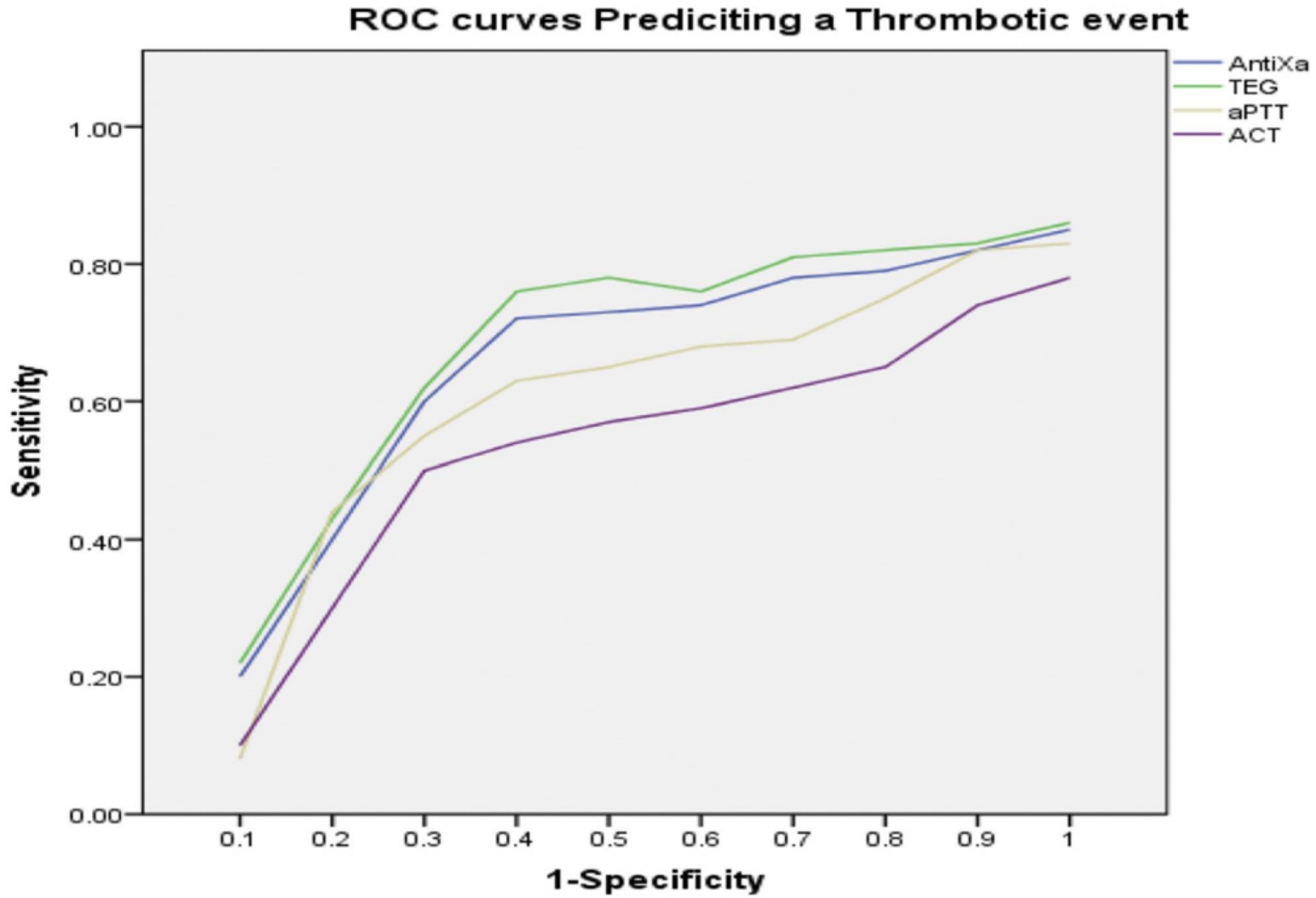
Kalbhenn et al. Perfusion 2016

ROTEM & outcome



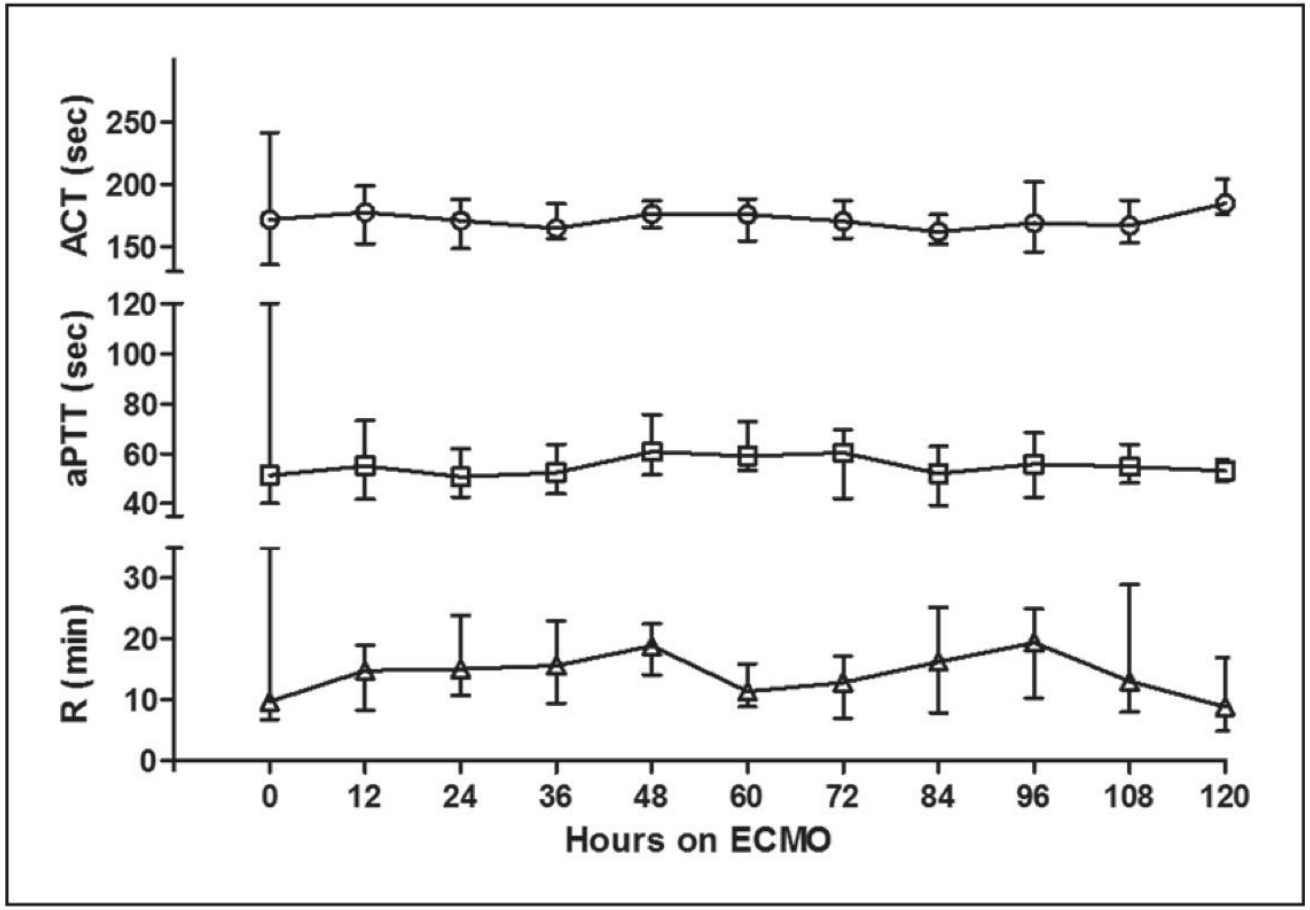
Laine et al. Perfusion 2016

VET & thrombosis



Henderson et al. J Extra Corpor Technol 2018

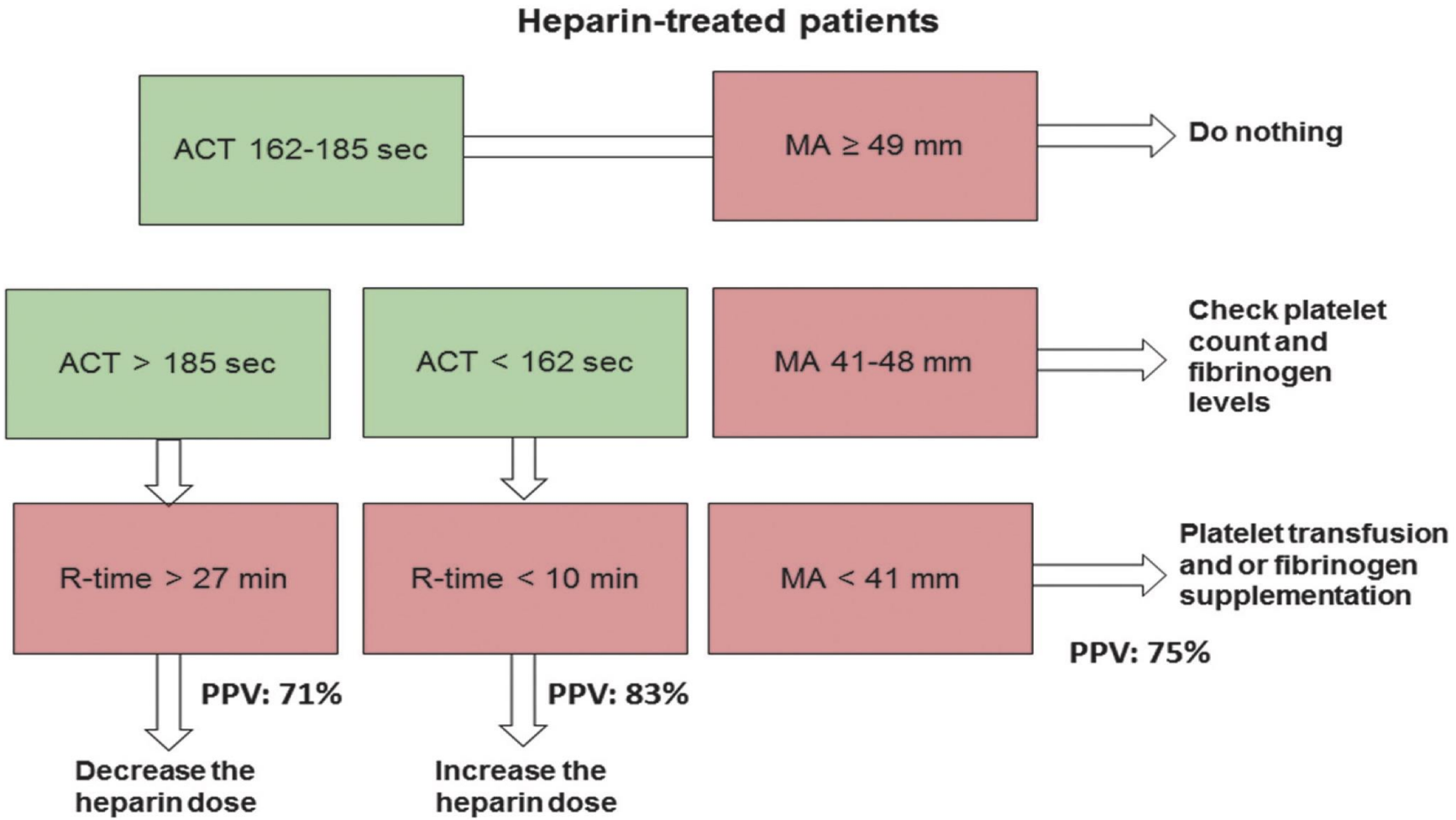
VET strategy



Point-of-care test values	PPV for short (<50 seconds) aPTT
ACT<162 seconds	64.8%
R-time<10 minutes	54.8%
ACT<162 seconds and R-time<10 minutes	82.6%
Point-of-care test values	**PPV for long (>70 seconds) aPTT**
ACT>185 seconds	50.7%
R-time>27 minutes	38.5%
ACT>185 seconds and R-time>27 minutes	71%

Ranucci et al. Minerva anesthesiol 2016

VET strategy



Ranucci et al. Minerva anesthesiol 2016

Monitoring scheme

Once daily	Twice daily	Thrice daily
Fibrinogen	Haemoglobin	aPTT combined with:
MA-TEG/MCF-ROTEM	Platelet count	ACT or
Lysis index		R-time TEG/CT-ROTEM
D-dimer		
AT%		

Mulder et al Neth J Crit Care 2018

Summary

- Specific, time dependent coagulation changes
- Mostly continuous iv. anticoagulation UFH
- Monitoring heterogeneous
- Targets should be clear
- POC tests may contribute if embedded in algorithm

Thank you

FIFA WORLD CUP
Qatar2022