ECMO: Der schmale Grat ...

ao. univ. Prof. Dr. Dietmar Fries; MSc

Trauma ICU

Department for Anaesthesia and Critical Care Medicine
Medical University Innsbruck, Austria

Financial disclosure:

Grants/scientific support/lecture fees

Astra Zeneca, Baxter, BBraun, Cytosorb, CSL Behring, LFB-France, Mitsubishi Pharma, Octapharm, Pfizer, Werfen.

Fallbericht:

- 58-y.o patient following CABG: open chest, av ECMO, ...
- Compartment syndrome, massive bleeding > 10 RBC per day

PT: 39%

pTT: 114 sec

Fibrinogen: 150 mg/dL

FXIII: 32%

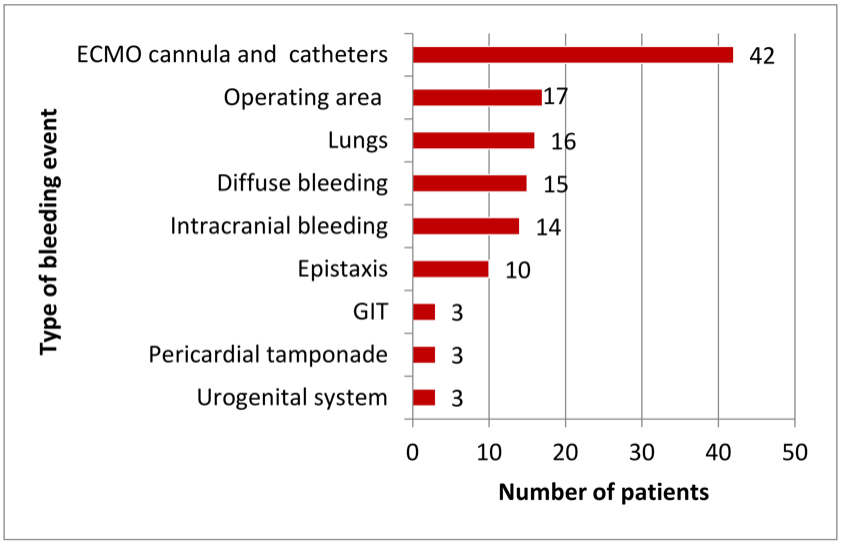
platelets: 49.000

1. **Protamin**
2. **FFP**
3. **platelets**
4. **Fibrinogen**
5. **FXIII concentrate**
6. **4F-PCC**
7. **Von Willebrand Konzentrat**
8. **All**

Der schmale Grat ...

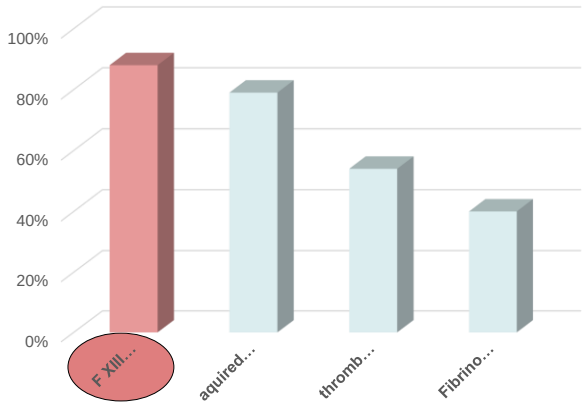
Cause of death	N = 145
Multi organ failure	72 (49,7 %)
Sepsis	34 (23,5 %)
Intracranial bleeding	**9 (6,2 %)**
Stroke	**7 (4,7 %)**
Bleeding	**6 (4,1 %)**
Pulmonary embolism	**3 (2,1 %)**
Necrotizing pancreatitis	3 (2,1 %)
Transplant rejection	3 (2,1 %)
Graft failure	2 (1,4 %)
Mediastinitis	1 (0,7 %)

Opfermann P, et al. Prognostic Impact of Persistent Thrombocytopenia During Extracorporeal Membrane Oxygenation Crit Care Med 2016; 44 (12) 1208-1218.



Rajsic et al. The Role of Excessive Anticoagulation and Missing Hyperinflammation in ECMO-Associated Bleeding. J Clin Med 2022, 11(9); 2314

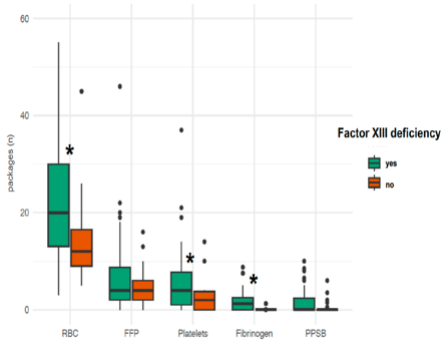
Acquired coagulation disorders on ECMO



Kalbhenn J, et al. Identification of acquired coagulation disorders and effects of target-controlled coagulation factor substitution on the incidence and severity of spontaneous intracranial bleeding during veno-venous ECMO therapy Perfusion 2015; 2015 Nov;30(8):675-82

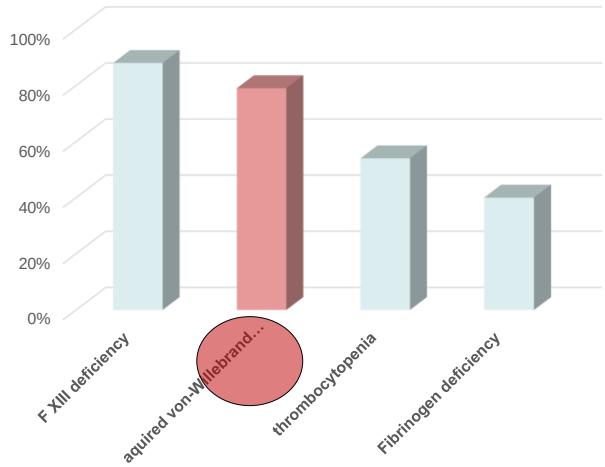
Acquired Factor XIII Deficiency Is Common during ECMO Therapy and Associated with Major Bleeding Events and Transfusion Requirements

	Factor XIII Deficiency	*No Factor XIII Deficiency*
n (%)	35 (%)	8 (%)
Haemopericardium	11 (25.6)	0
Haemothorax	10 (23.3)	2 (18.2)
Pulmonary	6 (14)	3 (27.3)
Ear/Nose/Throat	5 (11.6)	1 (9.1)
Cerebral	4 (9.3)	1 (9.1)
Gastrointestinal	3 (7)	2 (18.2)
Vascular	1 (2.3)	1 (9.1)
Abdominal/Pelvis	2 (4.7)	0
Others	**1 (2.3)**	**1 (9.1)**
Total	**43 (79,6 %)**	**11 (20,4 %)**



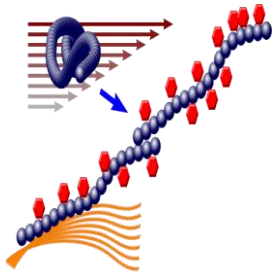
Noitz M et al. J. Clin. Med. 2023, 12, 4115.

Acquired coagulation disorders on ECMO



Kalbhenn J, et al. Identification of acquired coagulation disorders and effects of target-controlled coagulation factor substitution on the incidence and severity of spontaneous intracranial bleeding during veno-venous ECMO therapy Perfusion 2015; 2015 Nov;30(8):675-82

Extracorporeal membrane oxygenation induces short-term loss of high-molecular-weight von Willebrand factor multimers.

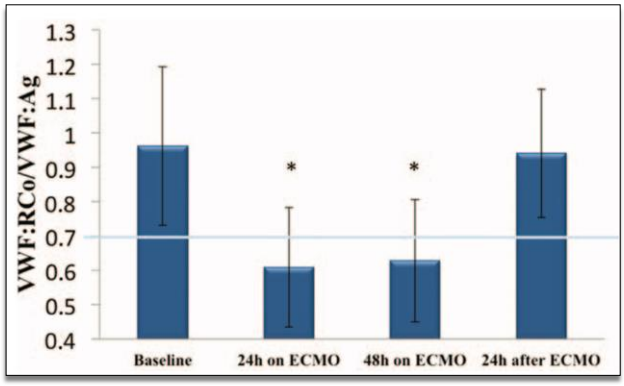


Loss of HMW vWF multimer bands occurre in patients undergoing ECMO support and resolve after termination of ECMO.

Although **not detectable** with coagulation screening tests, a **vWF:RCo/vWF:Ag ratio <0.7** during ECMO was highly indicative for loss of HMW vWF multimers.

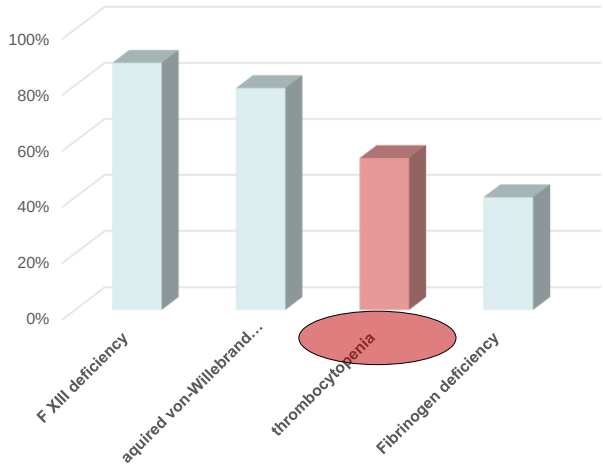
Tauber H et al. Extracorporeal membrane oxygenation induces short-term loss of high-molecular-weight von Willebrand factor multimer Anesth Analg. 2015 Apr;120(4):730-6.

Extracorporeal membrane oxygenation induces short-term loss of high-molecular-weight von Willebrand factor multimers.



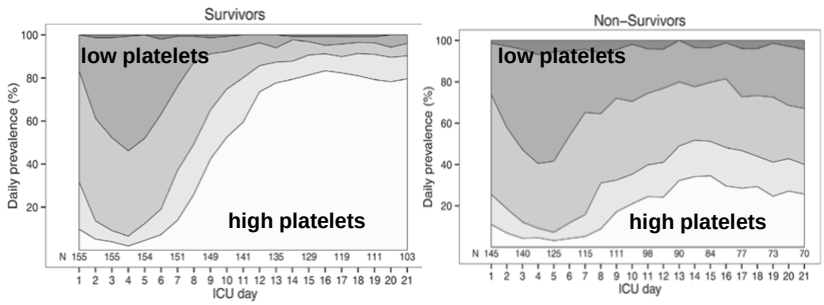
Tauber H et al. Extracorporeal membrane oxygenation induces short-term loss of high-molecular-weight von Willebrand factor multimer Anesth Analg. 2015 Apr;120(4):730-6.

Acquired coagulation disorders on ECMO



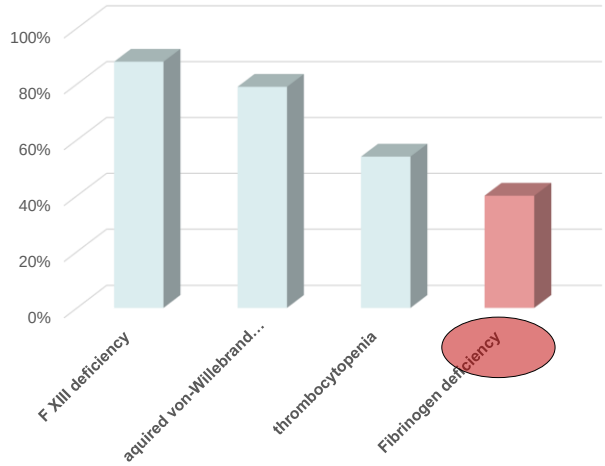
Kalbhenn J, et al. Identification of acquired coagulation disorders and effects of target-controlled coagulation factor substitution on the incidence and severity of spontaneous intracranial bleeding during veno-venous ECMO therapy Perfusion 2015; 2015 Nov;30(8):675-82

Persistence of thrombocytopenia during ECMO



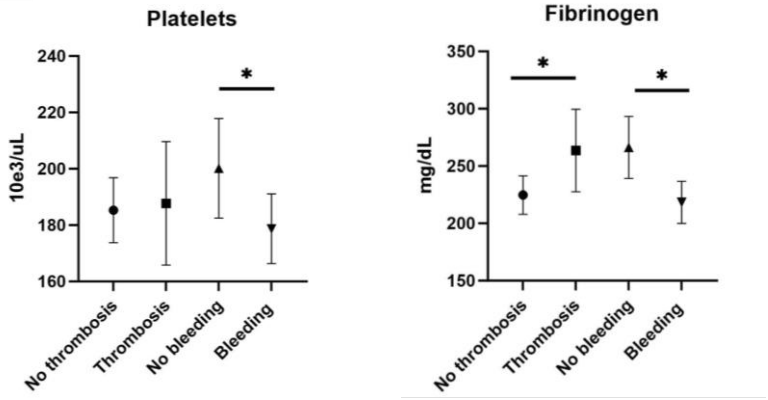
Opfermann P, et al. Prognostic Impact of Persistent Thrombocytopenia During Extracorporeal Membrane Oxygenation Crit Care Med 2016; 44 (12) 1208-1218.

Acquired coagulation disorders on ECMO



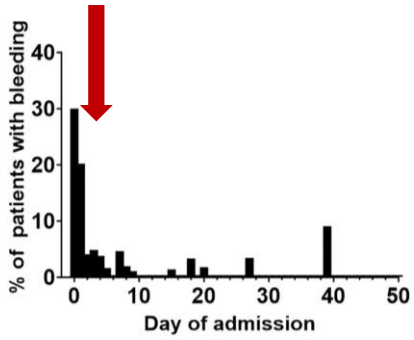
Kalbhenn J, et al. Identification of acquired coagulation disorders and effects of target-controlled coagulation factor substitution on the incidence and severity of spontaneous intracranial bleeding during veno-venous ECMO therapy Perfusion 2015; 2015 Nov;30(8):675-82

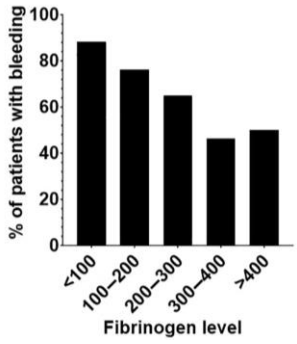
Platelets, fibrinogen and ECMO



Guitierrez A et al. Bleeding and Thrombosis in Patients With Out-of-Hospital Ventricular Tachycardia/Ventricular Fibrillation Arrest Treated With Extracorporeal Cardiopulmonary Resuscitation. Journal of the American Heart Association. 2024; Vol 13 (9)

Platelets, fibrinogen and ECMO





Guitierrez A et al. Bleeding and Thrombosis in Patients With Out-of-Hospital Ventricular Tachycardia/Ventricular Fibrillation Arrest Treated With Extracorporeal Cardiopulmonary Resuscitation. Journal of the American Heart Association. 2024; Vol 13 (9)

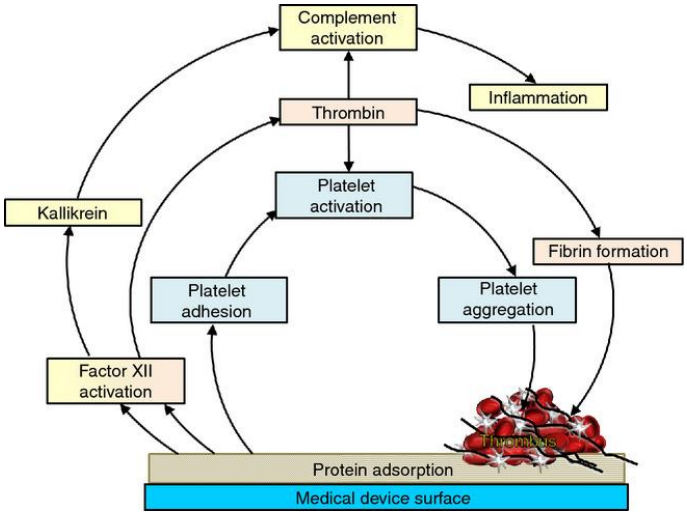
Summary (1): Escalation protocol for bleeding&coagulation management during ECMO therapy:

1. Exclude surgical bleeding (e.g. canula insertion site)
2. Local haemostasis
3. Check heparin/dti (anti-Xa UFH/LMWH/diluted thrombin time)
4. Platelet number > 50 G/L
5. Fibrinogen > 250 mg/dl
6. Factor XIII > 60%
7. von-Willebrand-Factor concentrate
8. **Stop ECMO therapy**

Der schmale Grat …

Cause of death	N = 145
Multi organ failure	72 (49,7 %)
Sepsis	34 (23,5 %)
Intracranial bleeding	**9 (6,2 %)**
Stroke	**7 (4,7 %)**
Bleeding	**6 (4,1 %)**
Pulmonary embolism	**3 (2,1 %)**
Necrotizing pancreatitis	3 (2,1 %)
Transplant rejection	3 (2,1 %)
Graft failure	2 (1,4 %)
Mediastinitis	1 (0,7 %)

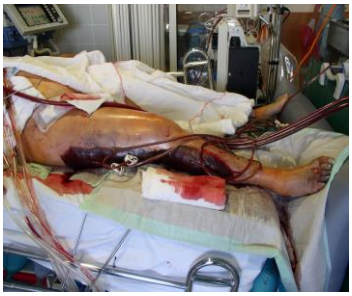
Opfermann P, et al. Prognostic Impact of Persistent Thrombocytopenia During Extracorporeal Membrane Oxygenation Crit Care Med 2016; 44 (12) 1208-1218.



Jaffer IH et al. Medical device-induced thrombosis: what causes it and how can we prevent it? Journal of Thrombosis and Haemostasis 13: 72 -81 (June 2015)

Case presentation (1):

- 58-y.o patient following CABG: open chest, av ECMO, ...
- Compartment syndrome, massive bleeding > 10 RBC per day



PT: 39%

pTT: 114 sec

Fibrinogen: 150 mg/dL

FXIII: 32%

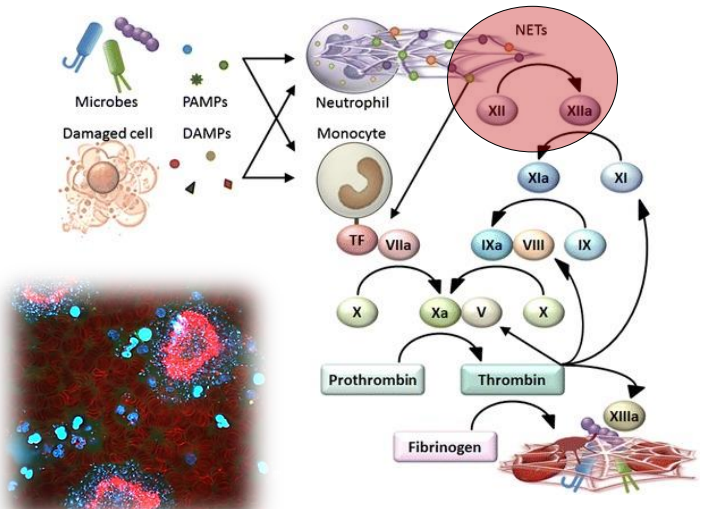
platelets: 49.000

antiXa (UFH): 0,15

FVIII: 79%, FIX: 50%

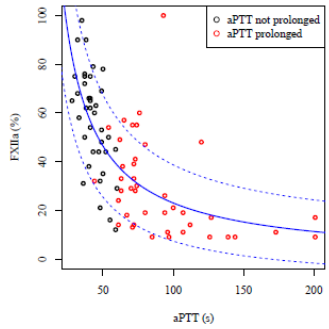
FXII: 13%

Inflammation & coagulation



Takashi L. J Intens Care. 2014; 2(1): 67

Influence of factor XII deficiency on aPTT in critically ill patients



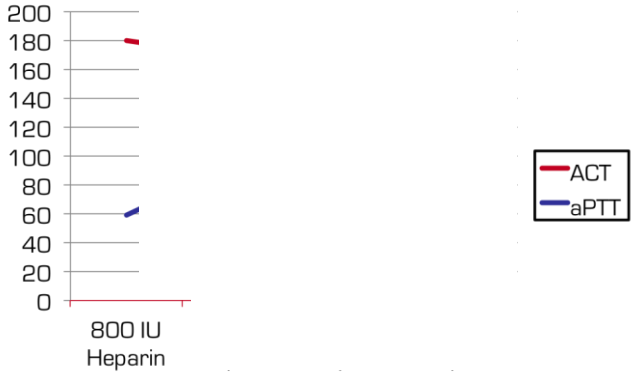
- threshold for a **FXIIa level** causing an aPTT-prolongation is: **42.5 %**
- **52%** of patients experience this FXIIa deficiency

Bachler M et al. Journal of Thrombosis and Thrombolysis (2019) 48:466–474

Standard coagulation tests: aPTT and ACT

Vv. ECMO in a patient with Bleomycin induced toxic lung failure …

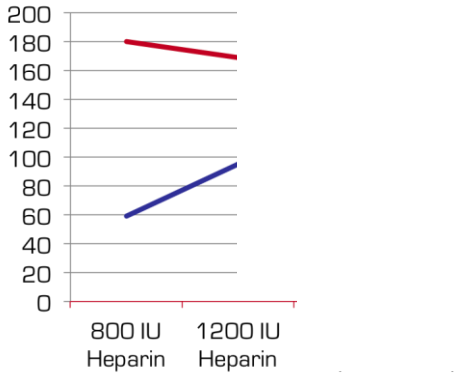
Anticoagulation: UF Heparin
Monitoring: ACT, aPTT



Standard coagulation tests: aPTT and ACT

Vv. ECMO in a patient with Bleomycin induced toxic lung failure …

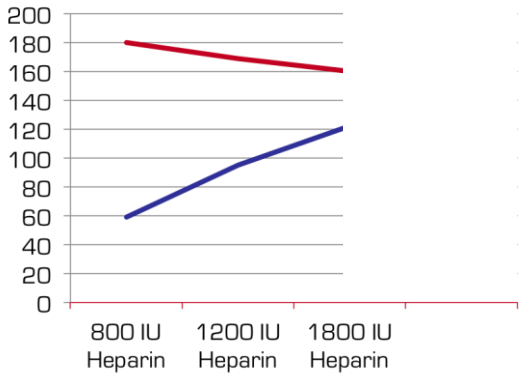
Anticoagulation: UF Heparin
Monitoring: ACT, aPTT



Standard coagulation tests: aPTT and ACT

Vv. ECMO in a patient with Bleomycin induced toxic lung failure …

Anticoagulation: UF Heparin
Monitoring: ACT, aPTT

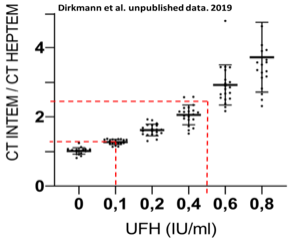


Standard coagulation tests: aPTT and ACT

Vv. ECMO in a patient with Bleomycin induced toxic lung failure …

Anticoagulation: UF Heparin
Monitoring: ACT, aPTT

CT InTEM 535 sec : HepTEM CT 180 sec: 2,97

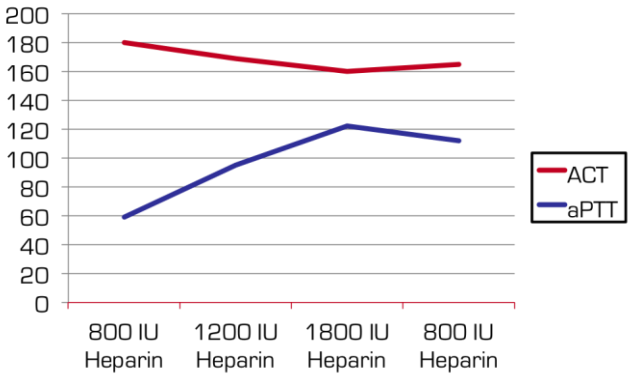


⇨ antiXa --- 0,6

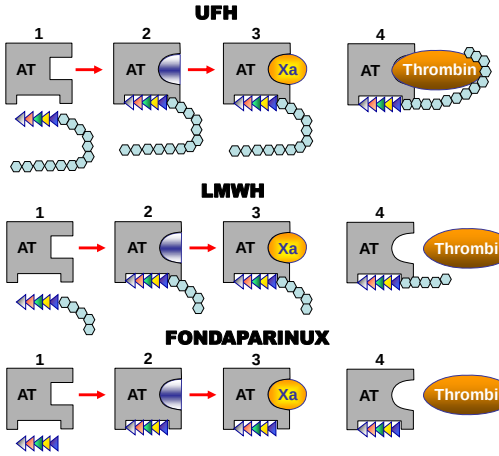
Standard coagulation tests: aPTT and ACT

Vv. ECMO in a patient with Bleomycin induced toxic lung failure …

Anticoagulation: UF Heparin
Monitoring: ACT, aPTT



Heparines: different mode of action

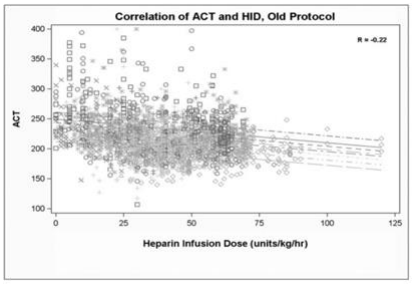


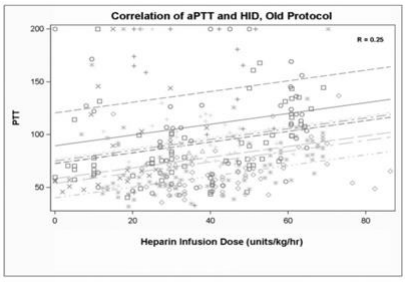
Inhibition of Factor Xa and Thrombin: ratio of 1:1

Inhibition of Factor Xa and Thrombin: ratio of 2-4:1

Inhibition of Factor Xa and Thrombin: ratio of 4:1

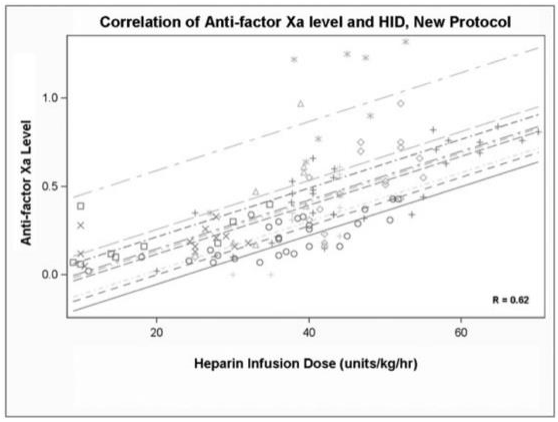
UF-Heparin monitoring: ACT < aPTT < antiXa (!)





Kessel A, J Int Care Med, 2015

Heparin monitoring: ... or anti-Xa (UFH)

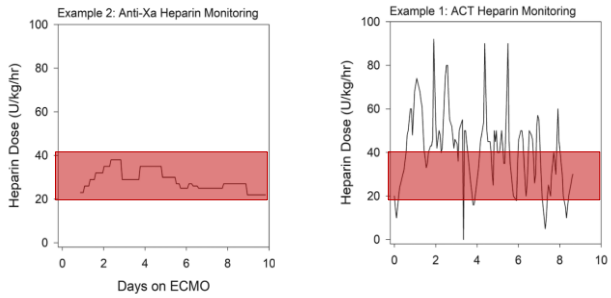


anti-Xa > apTT > ACT

Kessel A, J Int Care Med, 2015

Activated Clotting Time or anti-Xa Heparin Activity?

antiXa **ACT**



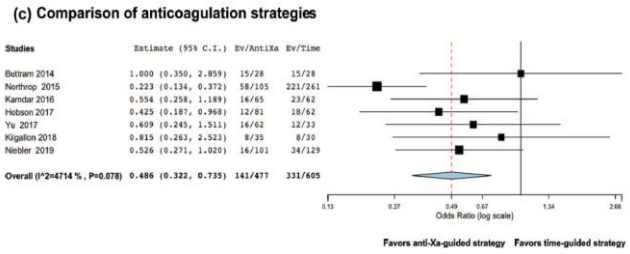
anti-Xa > 0,25: 50% reducion of circuit exchange
anti-Xa monitoring: reduction of bleeding episodes from 69% to 51%

Figueroa-Villalba et al. Conversion From Activated Clotting Time to Anti-Xa Heparin Activity Assay for Heparin Monitoring During Extracorporeal Membrane Oxygenation. Crit Care Med 2020; 48:e1179–e1184

Activated Clotting Time or anti-Xa Heparin Activity?

Anticoagulation with UFH to achieve (26/7 studies):

- **ACT time between 180 and 220 seconds**
- **anti-Xa of 0.3–0.7 IU/mL**



Wilms A et al. Anti-Xa versus time-guided anticoagulation strategies in extracorporeal membrane oxygenation: a systematic review and meta-analysis. Perfusion 2020 Aug 29

Anti-Xa versus time-guided anticoagulation strategies in extracorporeal membrane oxygenation: a systematic review and meta-analysis.

Anticoagulation with UFH to achieve (26/7 studies):

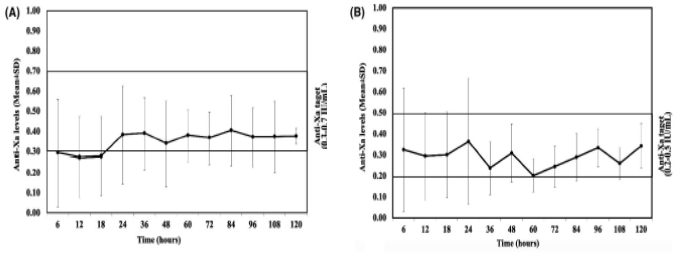
- **ACT time between 180 and 220 seconds**
- **anti-Xa of 0.3–0.7 IU/mL**

	anti-Xa	ACT/aPTT	P value
Bleeding	**34,2 %**	**41,6 %**	**0,001**
Thrombosis	**32,6 %**	**38,4 %**	**0.071**
Mortality	**35,4 %**	**42,9 %**	**0,3**

Meta-analysis of the **proportion of bleeding** according to the anticoagulation strategy

Wilms A et al. Anti-Xa versus time-guided anticoagulation strategies in extracorporeal membrane oxygenation: a systematic review and meta-analysis. Perfusion 2020 Aug 29

0.3–0.7 IU/ml versus restricted 0.2–0.5 IU/ml anti-factor Xa



restricted anti-Xa (0.2 – 0.5 IU/ml):

- **trend to less major bleeding**
- **significantly lower rate of pRBC transfusion**
- **no increase in thrombotic complications**

Alkazemi A et al. Conventional versus restricted anti-Xa-guided heparin protocol in adult patients undergoing extracorporeal membrane oxygenation. Artificial Organs 2022;46:128–137

Heparinresistance – an underestimated problem!

500 IU UFH bolus fail to prolong ACT ≥ 480 sec

Staples M et al. Heparin resistance after preoperative heparin therapy or intra-aortic balloon pumping.

Ann Thor Surg 1994

≥ 28.000 UFH/24h fail to prolong apTT

Maurin N. et al. Heparin resistance and antithrombin deficiency.

Med Klin (Munich). 2009;104(6):441-9.

Heparin dose: >35 000 U/d or > 30 U/kg/h

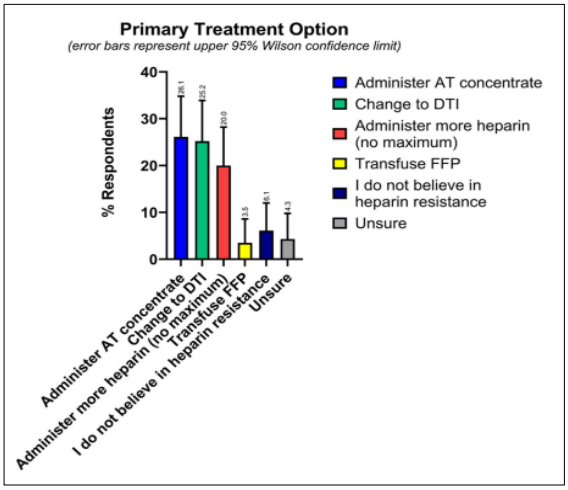
Levy J et al. J Thromb Haemost 2023; 21/12: 3649-3657

Levine MN et al. Arch Intern Med 1994; 1:49-56

How do you manage heparin resistance …

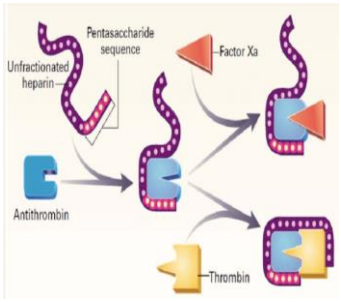
1. I make heparin dosage great again
2. LMWH instead of UF Heparin
3. Antithrombin substitution
4. Direct thrombin inhibitor (Bivalirudin or Argatroban)
5. I do not believe in heparin resistance

Heparinresistance – an underestimated problem!

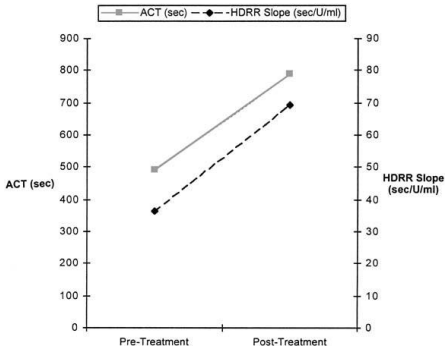


Levy JH et al. Defining heparin resistance: communication from the ISTH SSC Subcommittee of Perioperative and Critical Care Thrombosis and Hemostasis. JTH 2023; 21 812): 3649-365

Antithrombin and heparin resistance

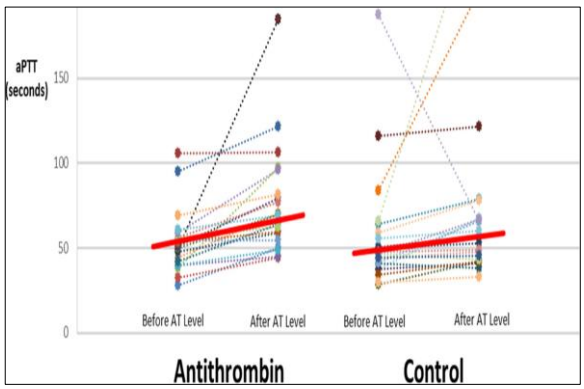


Catalysis of antithrombin-mediated inactivation of thrombin by heparin (Weitz 1997).



Lemmer HJ et al. Antithrombin III concentrate to treat heparin resistance in patients undergoing cardiac surgery. J of Thoracic and Cardiovascular Surgery 2002; 123(2): 213-221.

Antithrombin and heparin resistance



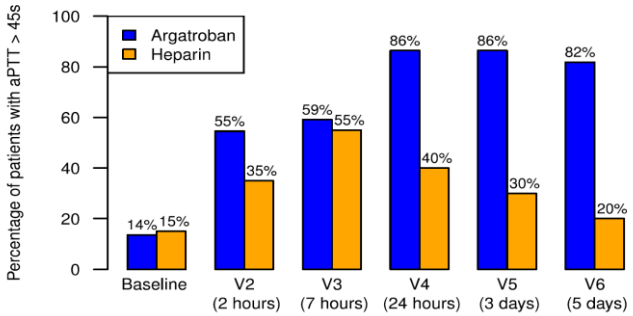
Beyer JT et al. Antithrombin Administration During Intravenous Heparin Anticoagulation in the Intensive Care Unit: A Single-Center Matched Retrospective Cohort StudClinical and Applied Thrombosis/Hemostasis 2018, Vol. 24(1) 145-150.

Journal of Clinical Medicine

MDPI

Article

A Prospective Pilot Trial to Assess the Efficacy of Argatroban (Argatra®) in Critically Ill Patients with Heparin Resistance †



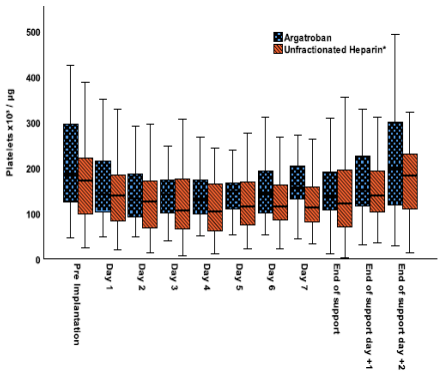
Bachler M et al. J. Clin. Med. 2020, 9, 963

Argatroban versus heparin in patients without heparin-induced thrombocytopenia during vv ECMO

Primary composite endpoint:

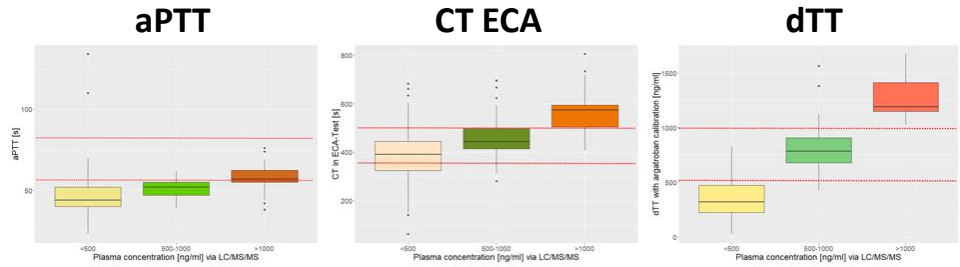
Bleeding/Thrombosis

83% UFH vs 78% Argatroban (p 0,026)



Fisser C et al. Crit Care. 2021 Apr 29;25(1):160.

Monitoring of argatroban in critically ill patients:
a prospective study comparing aPTT, point-of-care viscoelastic testing with ecarin clotting time and dTT to mass spectrometry



Target range 60-80 sec | Target range 350-500 s | Target range 500-1000 ng/ml

Heubner L et al. Anesthesiology Newly Published on October 3, 2023

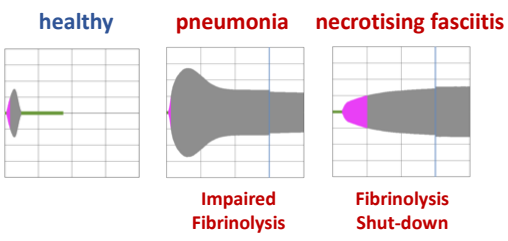
Fibrinolytic shut down

Impaired fibrinolysis in sepsis

Associated with poor outcome:

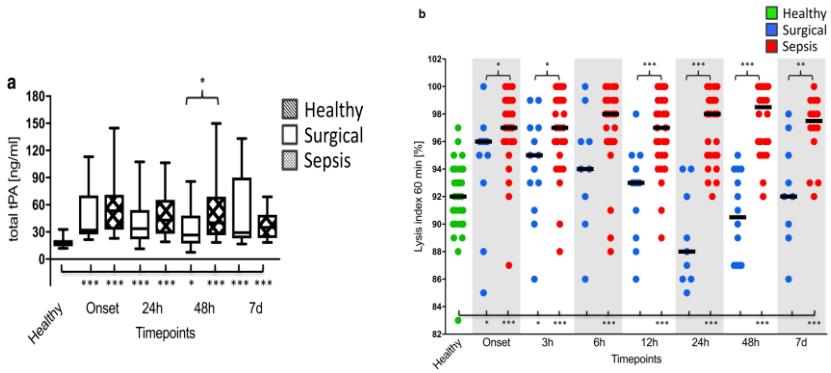
- → **Thrombosis**
- → **Organ failure**
- → **Mortality**

SEPSIS



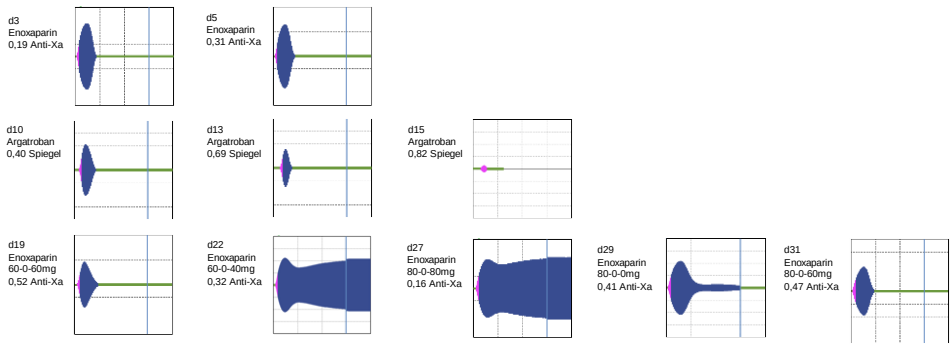
Nougier C, et al. Journal of thrombosis and haemostasis : JTH 2022
Kruse JM, et al. Crit Care. 2020; Zeerleder Set al.Thromb Res. 2006
Tipoe TL, et al. Front Immunol. 2018
Prakash S, et al. Journal of Critical Care. 2015

Acute fibrinolysis shutdown occurs **early in septic shock** and is associated with **increased morbidity and mortality**: results of an observational pilot study

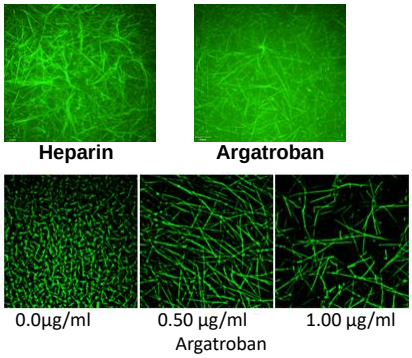


Schmitt et al. Ann. Intensive Care (2019) 9:19

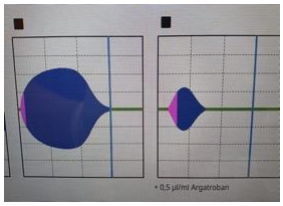
Enoxaparin → Argatroban (ECMO) → Enoxaparin; TPA-test (Clotpro)



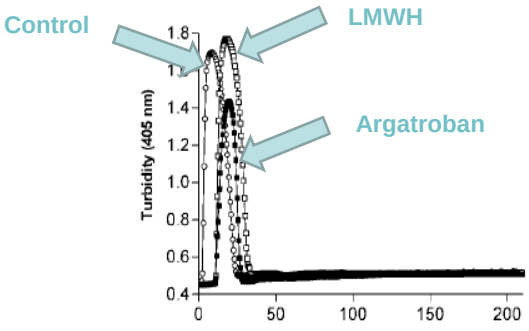
Influence of DTI on fibrinolysis in „sticky Covid-19 blood“



- can bind to already fibrin-bound thrombin and so can reduce clot size of an already formed clot
- influence on clot structure
- increases fibrin network porosity and thus facilitate fibrinolysis

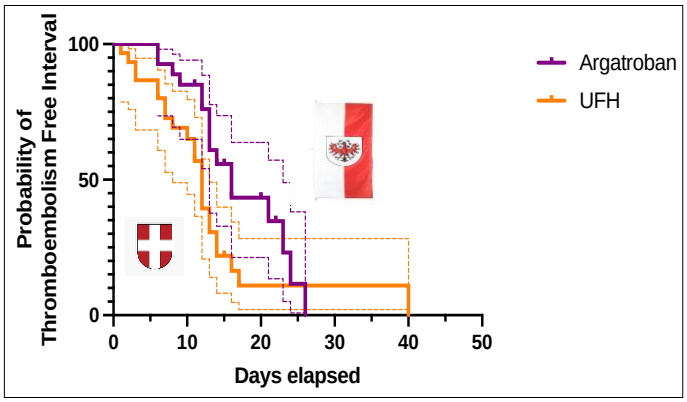


shut down lysis and COVID-19 ... Argatroban



LMWH could not influence clot lysis time

Argatroban (Hemoclot monitoring) vs LMWH (anti-XA monitoring)



Mayrhöfer T et al. Anticoagulation with argatroban using hemoclot™ targets is safe and effective in CARDS patients receiving venovenous extracorporeal membrane oxygenation: An exploratory bi-centric cohort study Thromb Res 2024; 236:161-166.

Summary (2): Anti-coagulation of ECMO: ICU Innsbruck

1. UFH Heparin:

- *Monitoring:* BB, pTT, antiXa-UFH (3x/d: 6:00, 14:00, 22:00)
- *Target values:* antiXa 0,2 – 0,5.
- Target AT levels in case of heparin resistance: 70% or in case you can not achieve anti Xa target.

2. LMWH *not* used for anticoagulation in Innsbruck, Medical University yet.

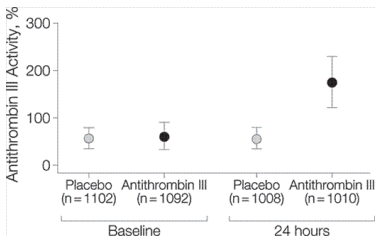
3. Argatroban after stabilisation of the patient (bleeding, organfunction, liverfunction) fast shift to Argatroban.

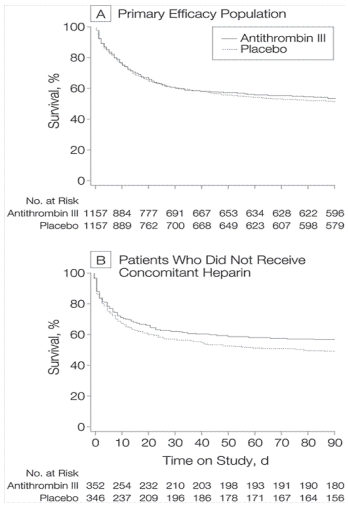
- *dosing:* depending on liver- and oragnfunction; best prediction with Bilirubin
- *monitoring:* diluted thrombintime
- *Target values* Argatratest: 0,2 – 0,5 (depending on individual situation/bleeding tendency, fibrinogen+platelets, etc.)
- *Antidot:* PCC 25IE (-50IE)/kg KG

Cause of death	N = 145
Multi organ failure	72 (49,7 %)
Sepsis	34 (23,5 %)
Intracranial bleeding	**9 (6,2 %)**
Stroke	**7 (4,7 %)**
Bleeding	**6 (4,1 %)**
Pulmonary embolism	**3 (2,1 %)**
Necrotizing pancreatitis	3 (2,1 %)
Transplant rejection	3 (2,1 %)
Graft failure	2 (1,4 %)
Mediastinitis	1 (0,7 %)

Opfermann P, et al. Prognostic Impact of Persistent Thrombocytopenia During Extracorporeal Membrane Oxygenation Crit Care Med 2016; 44 (12) 1208-1218.

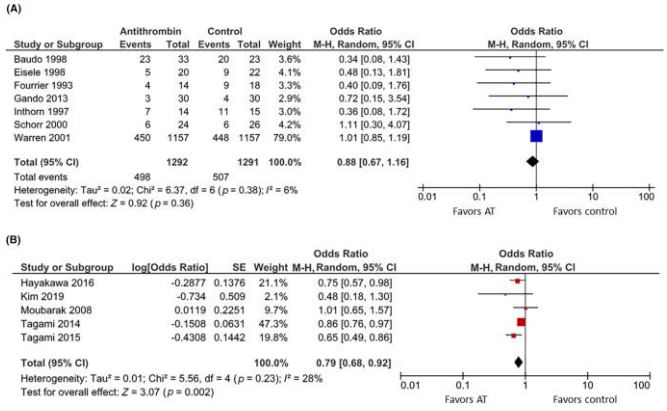
Antithrombin in sepsis …





Warren BL et al. High-Dose Antithrombin III in Severe Sepsis. A Randomized Controlled trial. JAMA 2001; 286:1869-1878.

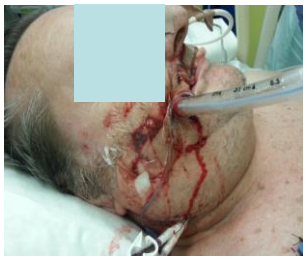
Antithrombin in sepsis …



Tsuchida T et al. Efficacy of antithrombin administration for patients with sepsis: A systematic review, meta-analysis, and meta-regression. Acute Med Surg 2024; 11(1).

Summary (3):

Coagulation management in severe septic shock/MOF

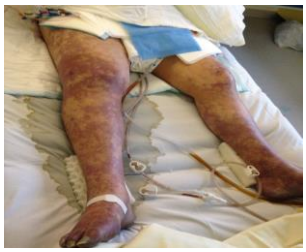


„Bleeding“ phenotype:

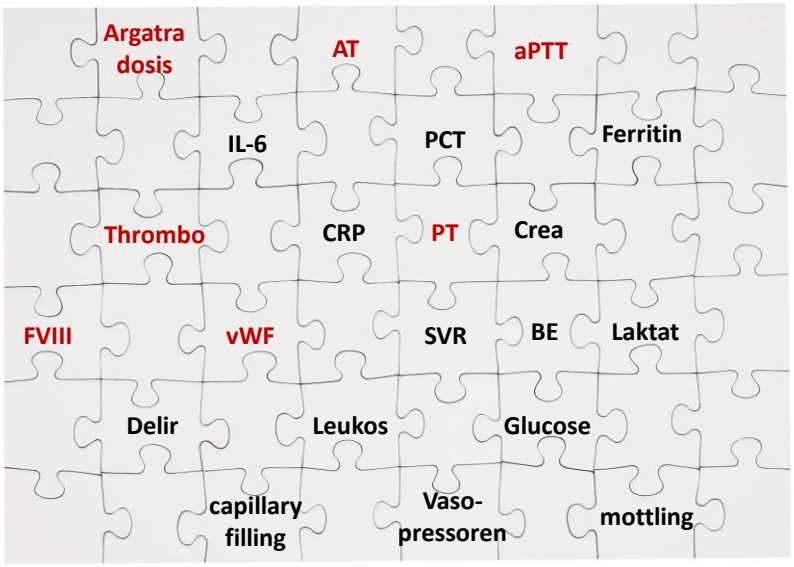
- maintain minimal number of platelets (e.g. 15-20 G/L)
- substitution according to VET results (except InTEM CT)
- in doubt: monitoring of FXIII, FXII, FVIII, ...

„impaired microcirculation“ phenotype:

- (cardiac output? volume status? vasopressor?...)
- AT substitution: bolus + continuous*
- no heparin, if AT substitution is conducted
- If basic liver function exists, Argatroban is considered*



**Not recommended in sepsis guideline*
**only registered for HIT2*



THANK YOU
for your
ATTENTION!